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Managing Lung Cancer in Developing Countries: Difficulties and Solutions

Lung cancer has been the most common cancer in the World since 1985, and by 2002, there were 1.35 million new cases, representing 12.4% of all new cancers. It was also the most common cause of death from cancer, with 1.18 million deaths, or 17.6% of the World total. Almost half (49.9%) of the cases occur in the developing countries of the World—a big change since 1980, when it was estimated that 69% were in developed countries. Worldwide, it is by far the most common cancer of men, with the highest rates observed in North America and Europe (especially Eastern Europe). Moderately high rates are also seen in Australia/New Zealand and Eastern Asia (China and Japan). In women, incidence rates are lower with a global rate of 12.1 per 100,000 women compared to 35.5 per 100,000 in men¹. Population-based as well as hospital-based data from the Cancer Registry of the Indian Council of Medical Research (ICMR) and the Cancer Atlas Programme of the ICMR revealed that lung cancer has increased in India during the last few years²⁻⁴. Of the 10 centers from which data was available, it was the most common form of malignancy in males in six centers, and 2nd and 3rd in order in two other centers. From many of the centers including one from a rural centre, lung cancer ranks among 10 cancer sites in women. The Cancer Atlas Programme revealed very interesting data²⁻⁴. Lung cancer is the commonest form of malignancy in the north-east region of the country—a hither-to-unknown fact. In fact, the region may be called as “hot-spot” for lung cancer and particularly in women of this region, which is akin to that seen in women in the Western World. Published clinical data from all regions of India also testifies the fact that cancer is increasing in our country⁵. Further, the assessment of risk factors in Indian patients revealed that *bidi* smoking is the major risk factor for lung cancer in India in contrast to the cigarette or cigar smoking in USA⁶. Further, in non-smoking Indian women indoor air pollution due to domestic cooking fuels particularly the biomass fuel is a significant risk factor⁷.

Lung cancer remains a highly lethal disease. Survival at five years in the United States is 15%, the best recorded at the population level. The average survival in Europe is 10%, not much better than the 8.9% observed in developing countries¹. The situation is similar in India. Published reports do not mention about the five-year survival rates. One-year survival has been reported as 9.8 percent⁸. Where should we go from here? Should we treat these patients? What are the problems in the management of lung cancer for Indian scenario? Who are all to be associated with the management of these cases? Unfortunately at the time of presentation, lung cancer presents at an advanced

stage⁹. Even diagnosis at earlier stages (where surgery could be offered) is possible only in about 80% of all lung cancer cases in the Western World. Unfortunately, only less than 5% of cases present in such stages in our country. However because of associated smoking, COPD and other cardio-vascular causes, some of them cannot be taken up for surgical treatment. Further, it is a fact that our country does not have sufficient number of thoracic surgeons who will be interested in thoracic oncology surgery as a matter of preference. This delay in diagnosis occurs because of the fact that most symptoms of lung cancer and pulmonary tuberculosis are similar and most patients receive anti-tubercular therapy for varying period of time before a definite diagnosis could be made. This is more so if the patient is below the age of 40 years. Diagnostic facilities like fiberoptic bronchoscopy and other invasive procedures like fine needle aspiration cytology/biopsy are not available uniformly throughout the country. Because of the advanced stage of the disease the only option is systemic chemotherapy. The radiotherapy can be used as an adjuvant and is a localised form of treatment. Moreover, radiotherapy facilities are not available at all medical colleges in our country. As regards chemotherapy there are a number of problems. It is well established that chemotherapy is better than best supportive care^{10,11}. Prolongation of life even for few weeks to months is important for many socio-economic reasons. Then should we give chemotherapy to all? These drugs are toxic, costly and we need expertise to deliver such therapy. All drugs used in lung cancer treatment are now available in India. The cost of drugs and administration of therapy will vary according to the set up where it is given. Whereas one of the best combinations of chemotherapy¹² will cost around Rs.15000 to Rs.20000 per cycle in a government hospital, but in other corporal and private settings the cost will be much more. Can we send all patients to medical oncologists? Again there are not enough medical oncologists in all the medical colleges in India. Thus, there may be a point where the chest physician came into the picture. He sees the patient, makes a diagnosis, manages the complications like pleurodesis, treatment of pneumonia and hemoptysis, etc. Then he should be able to deliver chemotherapy. However, to deliver chemotherapy also, the chest physician will need some specialised training in handling anti neoplastic drugs along with management of associated complications of such therapy. The current approach of lung cancer management has been directed towards molecular based targeted therapies^{13,14}. We should have more studies on the molecular and genetic aberrations in lung cancer in our population, although some information is

available from this country¹⁵⁻¹⁷. Such targeted therapy is also possible now in this country with benefit^{18, 19}.

While we are attempting to treat the disease, our efforts should be concentrated on the prevention of the lung cancer particularly with more aggressive and anti-smoking campaign and propaganda. Secondly, we should try to diagnose patients at an early stage, which can come with awareness and use of various diagnostic modalities.

D. Behera

Professor

Department of Pulmonary Medicine

PGI , Chandigarh-160012

Tele.: 91-172-2756822

E-mail: dbehera@glide.net.in

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The Challenges of Tuberculosis

According to the World Health Organization, India has more new tuberculosis cases annually than any other country. For the World as a whole, the biggest challenge of tuberculosis (TB) is its ability to survive in most countries and to flourish in Southern Countries even in the year 2006 of the Common Era (CE).

Challenges in Tuberculosis

There are other challenges as well. These are : (1) diagnostic difficulties, especially in children and those with sputum negative disease; (2) ability to team up with *Diabetes Mellitus*, silicosis and most recently with human immunodeficiency virus (HIV) infection and disease; (3) ability to lie dormant for many years in people, only to re-activate later, much later; and (4) ability to bounce back within weeks or months of apparent completion of treatment-relapses. These challenges and the versatile nature of the tubercular bacillus pose a great challenge in the successful control of tuberculosis and its eradication. It is estimated that by 2010, the World will see a mortality of 20 million and a case burden of 80 million!

History of Tuberculosis

How old is the life history of *Mycobacterium tuberculosis Hominis* (MTB)? It is estimated to be about 12 to 20,000 years old. It entered humans at least 7000 years ago, the spread was likely to have been from domesticated cattle, birds or other animals. Tuberculosis resembles cholera, small pox and HIV in spreading from animals to man.

The Europeans dreaded the “White Plague”, that was recognised as a major public health problem in the 14th to 18th centuries. The Captain amongst these men of death (John Bunyan) caused nearly 20% of all deaths in London around the year 1650 AD. Around 1820 AD, it caused nearly seven million deaths and in modern era in 2004, it caused 2.8 million deaths. This excludes deaths in association with HIV that would amplify the magnitude of the problem further.

Ethnic Differences

Are there Ethnic/Racial differences in ‘Catching TB’? People with no ancestral experiences with TB catch and suffer more easily. These include native American tribes who acquired it from white immigrants, land locked Nepalis who got it from British colonization, the AINU of Hokkaido and Shakalin Isles of Japan and the natives of Western Scottish Isles. These “virgin” populations suffered haematogenous TB spread (miliary) and often galloping disease. The Japanese considered TB as a “Death Sentence” in the first half of 20th Century. In

India the word TB carries a big social stigma. There is often ostracism and there is difficulty in arranging marriage for daughters.

Trends in Epidemiology

Is TB such a big killer now? Fortunately, no. It began to decline in the Western World from the mid to late 19th Century. However, the picture is turning dismal again. In the US the downward trend stalled and reversed in the 1980s. This is likely to have occurred because of dismantled social support system, immigration and the emerging epidemic of HIV. New York City alone had to spend over \$800 million to limp back from the mini surge of TB epidemic.

What caused the decline of TB in the West? There are several reasons for this: (1) rising standard of living reflected in improved nutrition, housing, water supply, sanitation and clean air; (2) segregation and eventual recovery/death of the more extensively affected; and (3) eradication of Bovine TB. It is noteworthy that drugs and chemotherapy (the magic bullets) played no part in this recorded decline. Waksman and streptomycin appear on stage only in 1944! It is, thus, clear that TB is no ordinary infectious epidemic but a sensitive index of socio-economic status. It may be called a “barometer of social condition” and is “an archetypal disease of poverty”.

Natural History

The natural history of TB starts with the droplet nuclei reaching the lungs of an uninfected person. As many as 70% of these exposed persons do not get infected. Only 30% develop infection. Amongst these exposed and infected 30%, about 5% develop early primary TB (early progression). However, almost 40% develop early primary TB, if they have concurrent HIV infection. Of the original 30%, another 5% develop late TB (late progression). Thus amongst those actually infected, 90% successfully contain the infection for life! They are just Tuberculin Positive-Period!. The estimated dose of bacilli required to cause infection is 10^3 to 10^4 while the estimated dose of bacilli required to cause disease is about 10^7 to 10^8 . A prolonged and close contact increases the chances of transmission. The estimated burden of bacilli in patients may be upto 10^{10} .

Are there natural variations in virulence? Yes. Group C drug susceptible outbreaks in Manhattan Shelters and the Group W or Beijing-HIV linked nosocomial outbreaks in NYC-MDRTB are examples of this. Group W grows 4-5 times faster inside macrophages than others which cause no secondary outbreaks. The basis of attenuation of BCG and H37Ra or the virulence of *M. Bovis* and H37Rv remain unclear.

Introduction of DOTS

How are we responding to the challenges? The New York resurgence of TB shook the Western World. WHO declared TB as a Global Health Emergency (1993) and offered 'DOTS' as the 'mantra' to contain and overcome TB! A large chunk of Africa-Sub-Saharan Africa (SSA)-suffered decimation on account of TB, and WHO declared TB as Regional Medical Emergency! Many in India play the same tune and sing "DOTS for all-all for DOTS"!

DOTS: A Reality Check

A reality check on DOTS is revealing. In Ethiopia, DOTS has performed below par. Reasons are the distance to the Health Centre, cost of transportation and poor awareness about the disease. In Pakistan, DOTS center attendance is reported to be irregular because of time and travel costs, ill health of the patients, need to pursue own occupation and the DOTS provider attitudes that are cynical and uncaring. DOTS centre timing and schedules more suited to provider than to the patient. There is more emphasis on "tablet watching" and no effort towards "patient support".

In India, in the city of New Delhi, patients in absolute poverty, socially marginalised, itinerant labourers and poorly integrated in the city are excluded from DOTS. The programme, thus, excludes the most vulnerable from the best available care (V. Singh, *et al. Trop Med Int Health* 2002; 7: 693-700). In Kerala 26.5% of patients who were recorded as having received DOTS did not actually receive it. (V.N. Balasubramanian, *et al. Int J Tuberc Lung Dis* 2002; 4: 409-13). In Tamil Nadu Tiruvallur programme of the Tuberculosis Research Centre, 74% patients were cured, 17% defaulted, 5% died and 4% failed. Amongst multidrug-resistant tuberculosis (MDR-TB), 33% patients failed. A higher death rate was recorded for body weight <35 kg, and a history of previous antituberculous therapy (T. Santha, *et al. Int J Tuberc Lung Dis* 2002; 6: 780-8). In Mumbai, at a Medical College in the year 2004, there were 673 smear positive, 71 HIV positive cases out of which only 72% were cured or declared "completed treatment".

Counterpoint: DOTS vs SAT (Indian Experience)

What is the Indian experience in comparing DOTS with SAT (self administered treatment)? In the Madurai randomised controlled trial carried out by the Tuberculosis Research Centre, Chennai, twice weekly DOTS (2HRZ/4HR) and daily SAT (6HR) were compared with a 36-month follow-up. Almost 87% improved in both the groups. There were three relapses in DOTS and two in SAT. There were 11% adverse reactions in DOTS and one percent in SAT. (M.S. Jawahar, *et al. Trop Med Int Health* 2005; 10: 1090-8.)

Counterpoint (World View)

There is a counter point in the world view too. According of Medicines Sans Frontiers (MSF), DOTS does not detect TB in paediatric age or in extra-pulmonary or smear negative cases. Sputum microscopy picks up only 45% of lung TB in non-HIV and only 38% of lung TB in HIV-positive patients and detects less than 5% of lung TB in children. DOTS excludes many people with active TB.

According to Social Scientists, simplifying policy approaches to "One-Size-fits-all" carries inherent risks and can be perceived to harm locally appropriate preferences. (J. Ogden, *et al. Social Sci Med* 2003; 57: 179-88). "The Chinese have done well with DOTS" is a common refrain. (*Comment in Lancet* 2004; 364: 391-2). The heretical notion "Strong health systems in the overall rich areas (of China) were responsible for effective TB control, not the DOTS strategy" is supported. Further, Shanghai has effectively controlled TB through strong health systems and does not use either free treatment or DOTS. (*Editorial comment by C.C. Whalen. Clin Infect Dis* 2006; 42: 1048-50).

There has been a failure of DOTS in Africa, and there has been a call for new approaches. In sub Saharan Africa, the TB incidence rates have surpassed 1000 cases/100000 in some areas. Near Cape Town, TB rates increased 2-5 fold amongst adolescents and 20-39 year olds despite a levelling off of HIV. Thus, DOTS is not optimally designed to interrupt the spread of TB and only alters the duration of treatment. It does not address the number and frequency of contacts or the likelihood of disease after infection.

Controlling TB in India

What about TB control efforts in India? Clearly the brand and mantra "DOTS" will not work in each and every region of India. The basic premise of DOTS "Persons with TB (read-mostly poor and disadvantaged) cannot be relied upon to take their medicines regularly" smacks of paternalism and pro-fascist ideas. All are born equal and the Government must treat them equally. The Constitution makers of India have rightly rejected votes only for those with property and/or education. We have Universal Franchise.

There is a need to change the approach to epidemic control: empower the people, make them strong. They will resist TB infection and disease effectively.

Suggestions

Urgent inputs are required. These should include the following:

1. Measures to reduce poverty and illiteracy. Extreme poverty is still found in rural areas of Bihar, Madhya Pradesh, Uttar Pradesh and West Bengal.

- Rural Employment Guarantee Scheme is a step in the right direction. Once the socio-economic status improves, TB declines.
2. Improve public sector clinics and hospitals—improve access and drugs availability.
 3. Individualise diagnosis and treatment approaches. Give back choice to the patients. If they want DOTS so be it! If they want SAT so be it!

4. Treat latent TB infection with INH for 9-12 months.

C.N. Deivanayagam

Member, National Council on AIDS
and
President, Health India Foundation
E-mail: cdeivanayagam@hotmail.com

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Is Routine Mediastinoscopy Indicated for Patients with T1 Non-small Cell Lung Cancer?

Seyyit Ibrahim Dincer, Adalet Demir, Hasan Akin, Mehmet Zeki Gunluoglu, Muzafer Metin, Huseyin Melek and Atilla Gurses

Department of Thoracic Surgery, Yedikule Teaching Hospital for Chest Diseases and Thoracic Surgery, Istanbul, Turkey

ABSTRACT

Objective. Mediastinoscopy is gold standard in the staging patients with non-small cell lung cancer (NSCLC) patients. Yet, its necessity in every patient is being questioned as new data is being collected. In the present study, we compared pathology reports of the cases with T1 NSCLC both after mediastinoscopy and thoracotomy, and discussed about the necessity of mediastinoscopy.

Methods. We retrospectively reviewed the records of 74 patients (73 patients with pathologic T1 NSCLC patients who underwent pulmonary resection and one patient clinically T1 who did not undergo pulmonary resection), between 1996 and 2002. Clinically 80% of the cases were at T1 stage, and the rest were at T2 stage. The distribution of clinical lymph node status was N0 in 85%, 15% N2.

Results. Fifty-three (71.6%) cases underwent mediastinoscopy. Mediastinoscopy showed that one patient had contralateral lymph node involvement and the remaining cases had no lymph node metastases. No mortality occurred and morbidity rate was 1.9%. Lobectomy was performed in 60 cases, pneumonectomy in seven, wedge resection in five, and segmentectomy in one. The histopathologic types were; squamous cancer in 40 (55%) cases, adenocarcinoma in 29 (40%), and large cell carcinoma in four (5%). Only two cases (2.7%) who had no detectable lymph node metastases at mediastinoscopy were found to have N2 disease after thoracotomy. In rest of the cases, N0 was observed in 48 (66%) and N1 in 23 (31.5%). Five-year survival of the cases was calculated to be 73%. The two cases with N2 disease are alive at seven and four years after the operation.

Conclusion. Routine mediastinoscopy does not appear to be necessary for patients with clinical T1 non-small cell carcinoma having no enlarged lymph nodes on computerised tomography. [Indian J Chest Dis Allied Sci 2006; 48: 249-252]

Key words: Mediastinoscopy, T1 non-small cell lung cancer.

INTRODUCTION

Surgical resection is still at top of treatment modalities of non-small cell lung cancer (NSCLC) to provide a good survival. Unfortunately this is only possible in patients with early stage tumours. The most important prognostic indicator of local dissemination is the status of the mediastinal lymph nodes which should be clarified before surgical resection¹⁻³. Many techniques including thorax computed tomography (CT), positron emission tomography (PET), ultrasonography-guided transesophageal biopsy, selective or routine mediastinoscopy, mediastinotomy, and video-assisted thoracoscopic (VATS) biopsy have been used to achieve this goal¹. In the last two decades, CT and (PET) received great interest because mediastinoscopy is an invasive procedure despite of its effectiveness and high accuracy. But, it is still be gold standard cited in the literature¹⁻⁴.

The chance of mediastinal lymph node metastasis of T1 NSCLC has been reported in a wide spectrum in different series. It is especially quite low if chest CT is negative for mediastinal lymphadenopathy. For this reason it has been questioned more frequently whether to perform routine mediastinoscopy in this group of patients^{3,4}. In this study we compared pathology reports of the cases with T1 NSCLC both after mediastinoscopy and thoracotomy, and discussed about the necessity of mediastinoscopy.

MATERIAL AND METHODS

Between 1996 and 2002, 758 patients with NSCLC were admitted to our clinic. Our current practice is to perform mediastinoscopy in all cases except in patients with T1 squamous carcinoma and no evidence of lymph nodes more than 1 cm size in diameter on CT scan of the chest. But before the year 2000 mediastinoscopy was routinely

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Correspondence and reprint requests: Dr Adalet Demir, Yuzyil mah. Kisla Cad. Yesil zengibar sitesi, A-3 Block, D-9 Bagcilar, Istanbul, Turkey; Tele.: 90 212 6641700; Telefax: 90 212 5472233; E-mail: dradalet@hotmail.com.

performed in all cases with NSCLC. Patients with no mediastinal nodal disease directly underwent thoracotomy and appropriate resection. When N2 or N3 disease was detected, the patients were referred to oncological therapy (n=104); but, after year 2000 patients with N2 disease of single station or without capsule involvement referred to oncology clinic for neoadjuvant therapy (n=72).

The remaining 582 cases underwent thoracotomy. When the tumour is localised to a single lobe with no sump involvement, lobectomy with systematic lymph node sampling was done. Should the tumour involves adjacent lobe or sump lymph nodes, bilobectomy or pneumonectomy and systematic lymph node sampling was performed.

Mediastinoscopy, as described by Carlens in 1959, was performed by either a consultant or a trainee under general anesthesia with a single lumen tracheal intubation in supine position with neck extension. All the lymph node stations that can be accessible by standard mediastinoscopy were sampled. The patients were extubated in the operating room at the end of the procedure.

The study population consisted of 74 patients who had T1 lung carcinoma at the final pathology report. One patient had N3 disease after mediastinoscopy and referred to oncology. We analysed the clinical data of 73 out of these 582 patients who had T1 tumour according to histopathology report.

All cases underwent chest CT, fiberoptic bronchoscopy, complete blood count, and routine biochemistry, electrocardiogram, and arterial blood gas analysis. Some had also undergone transthoracic needle aspiration biopsy. Cranial CT, abdominal ultrasound or radionuclide bone scanning were not performed unless the patient was symptomatic. No patient was evaluated with PET scanning.

In 46 patients (62%) the tumour was located on the right side. Clinically, 59 cases (80%) had T1 tumours and 63 of the cases had no detectable lymph node on thorax CT (cN0). Mediastinoscopy was performed in 53 patients (71.6%) and the remaining 21 cases (28.3%) underwent thoracotomy without mediastinoscopy. One patient who had been discovered to have N3 was referred to oncology. Resected specimens were examined histopathologically. Staging was performed according to the new international staging system for lung cancer⁵.

Data are presented as mean and percentages. Survival was estimated by the Kaplan-Meier method and differences in survival were determined by long-rank analysis.

RESULTS

Out of the 74 patients, there were 65 males and nine females. Their mean age was 59±9 years (range 32–76 years). Fifty-three (71.6%) cases underwent mediast-

inoscopy, but only one patient was found to have contralateral mediastinal lymph node involvement (N3) and was referred to oncology. No other mediastinal lymph node involvement was detected at mediastinoscopy. The clinical characteristics of these patients are shown in table 1. No mortality occurred. Only one patient had hoarseness of voice (1.9%).

Table 1. Clinical characteristics of 74 patients with non-small cell lung cancer

Characteristics	No. (%)
Age (years)*	59±9 (32-76)
Sex	
Male	65 (88%)
Female	9 (12%)
Location of tumour	
Right	46 (62%)
Left	28 (38%)
Clinical T status	
T1	59 (80%)
T2	15 (20%)
Clinical N status	
N0	63 (85%)
N2	11 (15%)
Mediastinoscopy	
Yes	53 (71.6%)
No	21 (28.3%)

*=Mean ± SD (range).

The preferred type of resection (Table 2) was lobectomy which was performed in 60 cases (80.8%). Five cases underwent wedge resection and one underwent segmentectomy due to insufficient pulmonary capacity. Seven patients underwent pneumonectomy. This included four cases with upper lobe tumour invading lymphatic sump detected intraoperatively with frozen section, and three cases with severe hilar adhesions (which caused pulmonary hemorrhage in two of them). For mediastinal lymph nodes either systematic sampling (n=41) or random sampling (n=32) was performed at the discretion of the

Table 2. Characteristics of 73 patients with non-small cell lung cancer who underwent pulmonary resection

Variable	No. (%)
Surgical procedure	
Lobectomy	60 (82%)
Pneumonectomy	7 (9%)
Segmentectomy	1 (2%)
Wedge resection	5 (7%)
Mediastinal dissection	
Systematic	41 (56%)
Random sampling	32 (44%)
Average tumour size	2.2 cm
Histologic type	
Squamous cell carcinoma	40 (55%)
Adenocarcinoma	29 (40%)
Large cell	4 (5%)
Nodal status (postoperative)	
N0	48 (66%)
N1	23 (31.5%)
N2	2 (2.7%)

surgeon. The mean diameter of the tumour was 2.2 cm. The most common histologic type was squamous cell carcinoma (55%). Postoperative pathology report revealed that 48 of the cases had N0, 23 had N1, and only two had N2 disease.

Two patients had mediastinal lymph node metastases after thoracotomy. Both of these cases had undergone mediastinoscopy before thoracotomy, but no metastasis was found at that time. One of them with squamous cell carcinoma in the right upper lobe was found to have right lower paratracheal lymph node metastases. The patient was staged clinically T1N2 and underwent right upper lobectomy. Thus, the rate of mediastinal lymph node metastases in cN2 group was one in 11 cases (9%). Another patient with squamous cell carcinoma in the left lower lobe had subcarinal lymph node metastases. He was staged T1N0 clinically and underwent left lower lobectomy. In contrast to high rate lymph node metastases in cN2 group, the rate of lymph node metastases in cN0 group was 1.6%. Both of them were referred to oncology for adjuvant therapy.

Five-year survival was found in 73% of cases (Figure 1). The case with positive right lower paratracheal and the other with subcarinal lymph nodes are both alive and disease free at 7th and 4th year respectively. Comparison of the N status in the present study with observations from other published studies is shown in table 3.

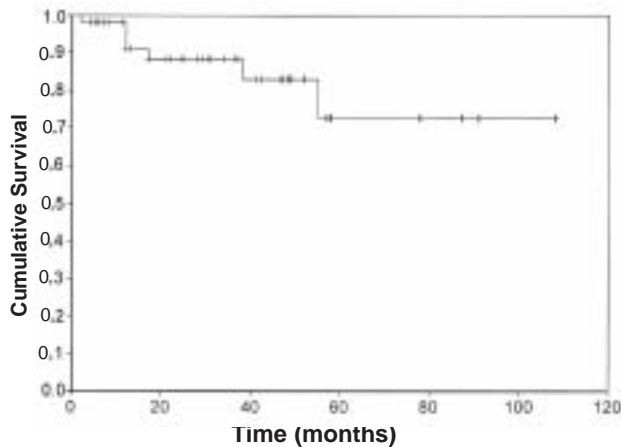


Figure 1. Cumulative survival of all resected pathological T1 non-small cell lung cancer patients.

Table 3. N status of previous studies with pathological T1 tumours

Study (year)	No. of Cases	N0 No.	N1 No. (%)	N2 No. (%)	N3 No. (%)
Coughlin <i>et al</i> (1985) ⁷	202	-	-	30 (14.9)	-
Jolly <i>et al</i> (1991) ⁸	145	-	-	15 (10)	-
Funatsu <i>et al</i> (1994) ¹	164	125	16	20 (12)	3 (2)
Mountain <i>et al</i> (1997) ⁵	640	511	76 (11.8)	53 (8.3)	-
van Rens <i>et al</i> (2000) ⁹	513	416	84 (16.3)	13 (2.5)	-
Tahara <i>et al</i> (2000) ¹²	17	13	1	3 (8)	-
Sakao <i>et al</i> (2003) ¹¹	54	43	2	9 (17)	-
Lardinois <i>et al</i> (2003) ¹³	23	-	-	2 (9)	5 (22)
Current series	74	48	23 (31.5)	2 (2.7)	1 (1.3)

DISCUSSION

In lung cancer many procedures have been used to explore mediastinum for staging but mediastinoscopy remains to be the gold standard. Recently, it has been used routinely in patients with NSCLC. We had performed preoperative mediastinoscopy in almost all patients who were eligible for surgical operation, to assess N factors before the operation. But after the year 2000 we did not perform mediastinoscopy if the patient had T1, epidermoid type NSCLC and with no detectable lymph nodes on CT scan of the chest.

Though mediastinoscopy is considered a minimally invasive technique, it is not totally safe because it carries a certain morbidity and mortality. In published literature the morbidity and mortality of mediastinoscopy has been reported to be 0.03% to 2.3%^{3,4,6}. We recently reported our experience with mediastinoscopy⁶. Our mortality and morbidity rates were 0.3% and 1.7% respectively. For this reason it becomes a dilemma whether to perform mediastinoscopy routinely, especially in clinical T1 cases in whom the incidence of mediastinal metastases is very low.

Many reports have presented the results of mediastinoscopy in patients with lung cancer^{4-8, 14-16}, whereas detailed analysis of the results of mediastinoscopy by N factors, in particular those of T1 cases, has been limited^{1,7,8,10}. It has been reported that the rate of mediastinal lymph node metastases in pathological T1 cases can increase up to 18%, whereas when published series with more than 100 cases are considered the rate decreases to as low as 2.5%^{1, 5, 7-13} (Table 3). The source of different rates in the literature originates from the variations of the patients' characteristics. Some studies included clinical or radiological N2 cases and some included only certain histopathologic types. In Sakao *et al*¹¹ series all cases had adenocarcinoma, while Funatsu *et al*¹ had observed adenocarcinoma in most of the cases.

In the present series N2 rate is quite low when compared to some series in the literature^{1,5,7-13}. A possible explanation of this low rate could be relatively high rate of squamous cell carcinoma in our series (Table 3). Interestingly this series had relatively higher rate of N1 disease compared to literature^{1, 5, 7-13}.

Only one patient was found to have contralateral mediastinal lymph node involvement (N3 disease) (1.7%) at mediastinoscopy. After thoracotomy two cases had N2 disease; one at right paratracheal station (number 4R) and the other subcarinal area (number 7). Resection was possible in both cases and they were referred to oncology for adjuvant therapy. The patient with right upper lobe tumour was clinically T1N2 and underwent mediastinoscopy. Right lower paratracheal station was sampled and no disease was detected in four lymph nodes. After thoracotomy only one out of six lymph nodes contained metastasis (minimal N2). The other patient with positive subcarinal lymph node was clinically T1N0 and also underwent mediastinoscopy. At thoracotomy two out of seven lymph nodes contain metastasis and the lymph node was located at posterior subcarinal area.

A striking finding is that mediastinal lymph node metastases in clinical N2 group was found to be 9%, whereas in clinical N0 group the rate of metastases was only 1.6%. A recent study from our center⁴ reported that the chance of detecting mediastinal lymph node metastases among all clinically N0 patients was 7.6% after mediastinoscopy and 5% after thoracotomy in patients found having no N2 disease with mediastinoscopy.

In the literature, 5-year survival of T1 stage ranged between 54% and 82%¹⁴⁻¹⁹. Five-year survival of T1N2 patients was reported to be between 20% and 41%¹⁴⁻¹⁹. Recent reviews reported 5-year survival of T1N2, T2N2 and T3N2 cases to 41%, 22% and 13% respectively^{20, 21}. Overall, 5-year survival in this series was 73%. The case with positive right lower paratracheal and the other with subcarinal lymph nodes are both alive and disease free at 7th and 4th year.

In our hospital, mediastinoscopy costs the patients approximately 800€. Mediastinoscopy revealed only one patient with contralateral lymph node involvement, and two patients had minimal N2 disease which could not be detected at mediastinoscopy. No unnecessary thoracotomy was performed in this series.

As a result, in patients with clinical T1 disease especially with negative chest CT for mediastinal lymphadenopathy, routine mediastinoscopy should be used cautiously in order to prevent unnecessary complications, to save time, and to decrease the cost of treatment because the rate-mediastinal involvement is extremely low in these patients.

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A Five-Year Review of Tuberculosis Mortality Amongst Hospitalised Patients in Ile-Ife

G.E. Erhabor, O.O. Adewole and O. Ogunlade

Department of Medicine, Obafemi Awolowo University Teaching Hospital Complex, Ile-Ife, Osun State, Nigeria

ABSTRACT

Background. Death from tuberculosis (TB) is the longest recorded indicator of the TB epidemic in industrialised countries. This study aims at investigating into various factors associated with death in hospitalised patients with tuberculosis in Ile-Ife, Nigeria.

Methods. A retrospective study of all admissions into the medical wards, total number of deaths and number of cases of deaths due to TB during the period 1998-2000 was done.

Results. Tuberculosis represented 8% (268) of all admissions (n=3464). The overall hospital mortality during the period under review was 1030 (30%). Tuberculosis was responsible for 5% of all deaths while TB specific mortality was 18.3 percent. The highest mortality was observed among patients between the 3rd and 4th decade of life with a male to female ratio 1.3 : 1. About 70% of the patients died within a week of admission. Pulmonary TB was responsible for 69% of deaths followed by tuberculous meningitis (14%), retroviral illness (24%), anaemia (60%). Delayed presentation and diagnosis were identified as factors commonly associated with death rate.

Conclusions. Delayed presentation and diagnosis were commonly associated with death. There is a need for more awareness among patients and health care providers about tuberculosis. [Indian J Chest Dis Allied Sci 2006; 48: 253-256]

Key words: Tuberculosis, Human immunodeficiency virus, Anaemia, Hypertension.

INTRODUCTION

Morbidity and mortality from tuberculosis (TB) have been on the increase in spite of increased understanding of its natural history and advances in therapy. Indeed *Mycobacterium tuberculosis* remains a leading cause of death from a single infectious disease world over.

Every year about eight million people develop this disease and some three million die of it, over 95% of these from developing countries¹⁻⁴. Projections suggest that by the year 2050, annual death rate will exceed five million a year. Majority of the deaths due to TB in Africa occur between the age group of 15 and 59 years, making TB a leading cause of a treatable disease within the economically productive age group in the world^{5,6}. Tuberculosis is responsible for 26% of avoidable adult deaths in the developing world⁷. Although the TB case rate has declined during the past few years, there remains a huge reservoir of individual infected with *M. tuberculosis*⁸.

We undertook this study as a follow-up evaluation, basing on our experience with previous studies, to identify the risk factors associated with death in patients with TB.

MATERIAL AND METHODS

This study covers a period of five years (1998-2002) and the following inclusion criteria were applied: presence of constitutional symptoms (fever, weight loss and fatigue); chronic cough; and or pulmonary infiltrates on chest radiograph which were consistent with the diagnosis of TB; proven cases of TB by positive Ziehl-Neelsen (ZN) stain of a diagnostic specimen such sputum smears or smear of tissue [e.g., lymph node biopsy, ascitic fluid, cerebrospinal fluid (CSF) and histological or cytological diagnosis of TB in tissue biopsy and ZN staining of aspirates]. Tuberculosis patients who were seen only at out-patient clinics and who were never admitted during the period under review were not included in this study.

Each patient was assessed to determine the form of TB, degree of delay due to patient, general practitioner (GP) or a specialist hospital. They were also assessed to determine if they were new or re-treatment cases by questioning and by review of case-notes. Intervals from admission to death were obtained by case-notes review and admission records. Post-mortem reports were obtained and reviewed in TB cases wherever possible.

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Correspondence and reprint requests: Dr G.E. Erhabor, Department of Medicine, Obafemi Awolowo University Teaching Hospital Complex, PMB 5538, Ile-Ife, Osun State, Nigeria; E-mail: gregerhabor@yahoo.com.

Additionally, patients were assessed to determine whether the diagnosis of TB had been established, what part TB played in the death of the patients and whether there were any potential error in the management of these cases.

Patients' delay was defined as the presence of symptoms for more than four weeks before presentation at a formal health center. Delay due to GP or specialist hospital was defined as the delay in referring patients to chest clinic after three visits or commencing treatment after more than one week of admission. Diagnosis of TB was said to be never established when TB was considered as a diagnosis but patients were not started on treatment and diagnosis was confirmed at autopsy. The diagnosis of TB meningitis, abdominal TB, TB spine, renal TB and others were made on clinical grounds supported by appropriate laboratory investigations, such as CSF stain for acid-fast bacilli (AFB), cytology, and biochemistry, ascitic fluid for cytology and AFB. Abdominal scan was done in patients with TB abdomen and renal TB. Thoracolumbar x-rays were done in suspected cases of TB spine. The abdominal scans and radiographs were reviewed with radiologists. Cytology reports showing lymphocytes, giant cells were taken as suggestive of TB, even if ZN stain was negative for AFB.

RESULTS

There were 3464 admission in the medical wards over the five-year period, of which 268 admissions were TB. Overall 1030 patients (30%) died; 49 of the 268 patients (18.3%) admitted with TB died. Forty-nine patients died from TB giving a mortality rate of 18.3 percent. Tuberculosis deaths represented 5% of all mortality.

The age of patients ranged from 9-79 years (mean age 42 years). The highest mortality was recorded between the 3rd and 4th decades of life. Socio-demographic characteristics of TB patients who died are shown in table 1. Mortality was also high among the married patients and unskilled workers (Table 1).

Table 2 shows the interval between admission and death, 51% of the deaths occurred within the first week of admission while only 4.1% died after four weeks. The average number of months the patients had TB was 5.5 months. Majority of deaths occurred in patients already or supposed to be on continuation phase of treatment. Seven patients were on re-treatment while the remaining 42 were new patients.

As shown in table 3, majority of the mortality was due to TB with active disease contributing 59.2% of the mortality. Also shown is that TB was a contributing factor in 20.4%, while the diagnosis of TB was not established in nine patients.

Majority of patients (69.4%) died due to pulmonary TB while miliary TB and tuberculosis meningitis contributed to 14.3% and 10.2% deaths, respectively.

Table 1. Socio-demographic characteristics of 49 patients who died due to tuberculosis

Variable	No. (%)
Sex	
Male	28 (57.1)
Female	21 (42.9)
Age (years)	
0-9	2 (4.1)
10-19	5 (10.5)
20-29	7 (14.2)
30-39	10 (20.4)
40-49	9 (18.4)
50-59	4 (8.2)
60-69	9 (18.4)
70-79	3 (6.1)
Marital Status	
Married	37 (75.5)
Single	12 (24.5)
Occupation	
Skilled	5 (10.2)
Unskilled	31 (63.3)
Unemployed	13 (26.5)
Religion	
Christianity	39 (79.6)
Islam	10 (20.4)

Table 2. Time interval between admission and death

Time interval (weeks)	No. (%)
<1	25 (51.0)
2-4	22 (44.9)
>4	02 (4.1)
Total	49 (100)

Table 3. Classification of patients certified as having died due to tuberculosis

Assessor's Classification	No. (%)
Died due to tuberculosis	
Active disease	29 (59.2)
Late effects of inactive disease	1 (2.0)
Died with tuberculosis as a contributing factor	
Active disease	6 (12.2)
Late effects of inactive disease	4 (8.2)
Tuberculosis present but irrelevant	-
Diagnosis of TB never established	9 (18.4)
Total	49 (100.0)

There was no recorded death due to renal TB.

Table 4 shows associated co-morbid factors. Human immunodeficiency virus (HIV) topped the list with 16.3%, coming close to it were anaemia and hypertension accounting for 14.3% and 12.2%, respectively. In 22.4%, there were no identifiable co-morbid condition.

Table 5 shows that diagnosis delay by patients was responsible for about two-thirds of deaths, while delay caused by general practitioners and specialist hospital contributed 6.1% and 14.5%, respectively. Poor drug compliance was identified as the main management shortcoming in 12.2% of deaths.

Table 4. Associated medical conditions in patients who died due to tuberculosis

Medical Condition	No. (%)
Nil	11 (22.4)
HIV	8 (16.3)
Anaemia	7 (14.3)
Hypertension	6 (12.2)
Heart failure	4 (8.2)
Malnutrition	2 (4.1)
Chronic renal failure	2 (4.1)
Chronic liver disease	1 (2.0)

HIV = human immunodeficiency virus

Table 5. Factors associated with death in 49 patients who died due to tuberculosis

Factor	No. (%)
Diagnostic delay caused by patient	32 (65.3)
Diagnostic delay in specialist hospital	7 (14.3)
Patient management shortcomings	6 (12.2)
Diagnostic delay caused by general practitioners	3 (6.1)
Management shortcomings in specialist hospital	1 (2.0)

DISCUSSION

Our study corroborates previous studies on TB in developing countries, in which mortality was mainly in the second and third decades of life¹¹. Published data suggests that 80% of those infected in industrialised nations are aged 50 years and above, while 75% of those in developing countries are less than 50 years¹. This finding contrasted with earlier study by Bandele *et al*¹² on TB mortality in Nigeria. In that study¹² conducted about two decades ago, 240 deaths were recorded due to TB. Active immunization with Bacille Calmette-Gurin (BCG) vaccine and improve nutrition and emphasis on child health may have tilted the balance towards the adult age group as seen in our study. Moreover, HIV would have lead to reactivation of TB in patients who were previously infected and have gone into dormant phase. In our study, 16.3% deaths were associated with HIV. Of all the risk factors for the development of TB, HIV is by far the most potent with a relative risk of 6 to 100 when compared with HIV-negative individuals¹³.

Another major cause of increasing mortality from TB-HIV co-infection is the problem of drug resistance. Drug resistance (either mono or multidrug-resistance) is increasing rapidly in under privileged, non-compliant, and minority groups in developed countries in whom it is fatal^{14, 15}. Africa in particular is experiencing a major resurgence in TB mainly as a consequence of the overlap between increasing levels of latent TB and increasing levels of HIV infections¹⁶, with the prevalence of HIV-TB co-infection ranging from 20 percent to 65 percent. However, mortality rate is higher in patients with HIV/AIDS and TB^{17, 19}.

Mortality is highest among those who presented within one week of admission. This high figure of patients dying within one week could be attributed to

delay in presentation. Delay in presentation is a major problem in most parts of the world, especially in our environment. The frequency of patient delay is lower than the 29% found in India and 44% found in Ghana^{20, 21}. In the earlier study referred to done in Lagos¹², 45.6% of delay in diagnosis were due to patients delay. In this study, about 56% of deaths were associated with delay in diagnosis due to patient factors. In another 22%, compliance with clinic attendance and medication were sub-optimal. This is reflected by the fact that majority of the patients had a mean delay of 5.5 months.

Delays are often multi-factorial; they may occur as a result of patient's perceptions of the disease, fear of stigma or difficult access to health facilities. In certain cases some patients may prefer seeking treatment in the traditional or private sector. Delay in diagnosis of TB is unacceptable as it may compromise the chance of a successful outcome, and lead to increase transmission of TB both in the household and in the community. Delay is also costly both to the patients and to health facilities. It strains already weak health system especially in developing countries as more resources will have to be allocated to take care of the complications that could develop from delay. As shown in this study, considerable delay occurred due to general practitioner or specialist hospitals. This is a reflection of poor awareness of diagnostic practices about TB in our environment.

Pulmonary TB, especially smear negative TB, was the most common form of lesion in this study associated with the highest death rate. It was responsible for death in 69.4% followed by miliary TB (14.3%). The pulmonary TB is of great importance, as sputum smear-positive TB has a much higher fatality than sputum smear-negative TB²³. This is exemplified in a long-term follow-up study of TB patients to Swiss Sanatorium between 1912 and 1927 where case fatality approached 60% in open TB compared to 10% to 15% in smear-negative TB²². Though there have been no recent follow up studies, mortality from pulmonary TB is still highest in Nigeria irrespective of the sputum AFB status. This might not be unconnected with the fact that pulmonary TB is the most common lesion generally in Nigeria, accounting more than 80% of cases²³.

Anaemia was associated with death in 14.3% of the cases. In a recent review of clinico-radiological presentation of 340 adults with TB in the Gambia over a third of the patients, were found to be anaemic²⁴. This was corroborated by other studies from India²⁵ and Hungary²⁶ where the prevalence of anaemia was 84% to 86% and 32%, respectively. The presence of anaemia could be considered a bad prognostic index. The causes of anaemia in these patients could be multi-factorial and could be due to causes, such as chronic malnutrition and haemoptysis. Co-morbid medical conditions, like chronic renal disease and chronic liver disease as seen in this study, could also be contributory. Also, bone

marrows findings in patients with TB in a study done in Ibadan²⁷ revealed that there were depressed erythroid activity in 69% of the patients, micronormoblastic changes in 18% and megaloblastic changes in 16.6%, while stainable iron in the marrow was found to be low or negative in 88.8% of the patients²⁸.

Tuberculosis may be missed as a primary diagnosis in most groups of patients who are not producing sputum and especially in patients with extra-pulmonary TB. There is, therefore, increased index of suspicion is required in an environment where TB is endemic and improved diagnostic methods are not routinely available. This underscores the importance of detecting patients with latent TB infection.

Within the limit of retrospective analysis one would say that a typical patient likely to die of TB will be a young male, presenting late and poorly compliant to therapy. The presence of HIV infection and anaemia would lead to further deterioration of the patient's condition. The challenge is to diagnose patients early and to ensure prompt treatment. Directly observed treatment, short-course (DOTS) has helped to improve compliance in our environment, however, it is still to be universally applied in Nigeria. Our study is limited by the fact that we do not study the role of drug resistance. This could not be done as drug susceptibility is not routinely done in our environment.

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Pleurocutaneous Flap: How Useful It is in Management of Chronic Empyema

Arvind Kohli, Gurjit Singh, Anita Vig, Kavi Raj Dubey and Rajinder Singh

Cardiothoracic and Vascular Surgery Unit, Government Medical College, Jammu, India

ABSTRACT

Background. Definitive surgical treatment of chronic empyema is associated with considerable morbidity and mortality.

Methods. Retrospective study of 50 patients with chronic empyema who underwent pleurocutaneous flap procedure during the period 1994 to 2003.

Results. Their age ranged from 14 to 70 years; there were 32 males. Thirty-seven (74%) patients were on intercostal tube drainage; nine (18%) presented with bronchopleural fistula; and four (8%) had past-pneumonectomy empyema. Following pleurocutaneous flap procedure, 28 (56%) responded with re-expansion of the lung; 15 (30%) had persistence of pus discharge and air-leak suggestive of bronchopleural fistula. Definitive surgery could be undertaken in nine of the 15 patients.

Conclusions. Pleurocutaneous flap procedure renders the patient ambulatory, facilitates re-expansion of the lung and helps as a tide-over procedure before definitive surgery in patients with chronic empyema. [Indian J Chest Dis Allied Sci 2006; 48: 257-259]

Key words: Chronic empyema, Pleurocutaneous flap procedure.

INTRODUCTION

The diagnosis and treatment of empyema was first described by Hippocrates over 2000 years ago. Virtually nothing else pertaining to this disease was recorded until the early 18th Century. Since that time, numerous treatments have been described including open and closed tube drainage, thoracentesis and thoracoplasty¹.

Open drainage was often successful and did not result in pneumothorax, because most cases of empyema were associated with adhesions and thickened visceral pleura that prevented the lung from collapsing. The epidemic of group A streptococcal pneumonia in military camps in 1917-1918 was associated with the rapid and early accumulation of empyema fluid and was the catalyst renewed study of empyema. Use of open drainage to manage this illness resulted in a high immediate mortality rate, probably because patients developed pneumothorax. The work of Graham² and the Empyema Commission married the physiological understanding of pleural mechanics with rational clinical treatment and paved the way for further advances in thoracic surgery.

Eloesser³ observed that the cure of empyema is made difficult by the tenacity with which the underlying lung resists expansion. Furthermore, it is made difficult by the unfavourable effect of an in-dwelling drainage tube of any kind leading to sepsis. The desire to obviate the

drainage lead to this operation in which a pleurocutaneous flap is created leading to open drainage of pleural space. We report our experience with this procedure.

MATERIAL AND METHODS

Fifty patients presenting with chronic empyema who underwent pleurocutaneous flap formation at our unit from 1994 to 2003 were studied. The diagnosis of chronic empyema was clinical and patients were not fit for undergoing definitive surgery at the outset.

The patients included in the study were not having desired response to conservative management. In addition to this, most of the patients were unable to undergo decortication because of the poor general condition. Posteriorly placed empyema which was unsuitable for tube placement and patients having mental illness not cooperating with prolonged tube drainage were also given the benefit of this procedure.

A detailed history was obtained and a thorough clinical examination was done. Chest radiograph in postero-anterior and lateral views were done in all the patients. The procedure was conducted under local anesthesia.

A U-shaped flap of skin and subcutaneous tissue was outlined anterior to posterior axillary line and inferior scapular angle. However, the exact placement of

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Correspondence and reprint requests: Dr Arvind Kohli, 39B/D, Gandhi Nagar, Jammu Tawi - 180004 (J & K), India; E-mail: Drarvind7@sancharnet.in.

formation of flap was thought of after assessing the site of loculation or the site of an already introduced intercostal tube. The flap had a base of two inches width and was about two-and-a-half inch long to reach the pleural cavity without tension. The rib underlying the flap was resected, amount resected equaling the width of the flap. The tip of the flap was turned into the chest and tacked to parietal pleura with one or two sutures and this kept the window open allowing the lung to re-expand after which it closes spontaneously and automatically (Figure 1). Adequate drainage of pus was the criterion for a good pleurocutaneous window. Patient himself or his attendant could change the dressing.

Although we did not refuse this procedure to any patient, the contraindications kept in mind were in patients in whom the lung was so badly affected that expansion to any degree did not seem possible, patients who had persistence of bacilli bearing sputum with large cavities and extensive parenchymal damage in whom definitive procedure in the form of thoracoplasty was thought to be safer.

Post-operative follow-up carried at one, three and six months and at one year intervals. Clinical examination, daily pus discharge and airleak, culture sensitivity of pus, chest radiograph indicating the re-expansion of the lung were assessed during follow-up visits.

RESULTS

Their age ranged from 14 to 70 years, there were 32 males. Majority of the patients (n=21) were in their third decade of life. Thirty-seven patients (74%) presented had already undergone tube thoracostomy and were on intercostal tube drainage; nine (18%) with bronchopleural fistula; and four 8% had post-pneumonectomy empyema. Thirty-eight (76%) patients were already receiving antituberculosis treatment.

The response was in the form of re-expansion of lung in 28 (56%) patients which occurred 3 to 24 months after the formation of the flap (Figures 1, 2 and 3). The majority of these patients had presented with complete collapse of the lung against the mediastinum despite a functional pleural drainage tube, and a few of them had minimal re-expansion of the lung with persisting pus discharge. Along with the re-expansion there was cessation of pus discharge, as well as spontaneous closure of the flap in these patients. Fifteen (30%) patients had persistence of pus discharge and prolonged air-leak, suggestive of bronchopleural fistula and re-expansion could not be achieved in them. Nine of them were taken up for definitive surgery. The procedures conducted were decortication in six cases, pneumonectomy in one and lobectomy in two cases. One patient died following definitive surgery. Pus culture was positive in 22 (44%) patients. This included *S. aureus* (n=13), *S. pneumoniae* (n=7) and *P. aeruginosa*



Figure 1. Pleurocutaneous flap in a male patient with chronic empyema formed on the right side.



Figure 2. Chest radiograph (postero-anterior view) of the same patient at the time of formation of the flap.



Figure 3. Chest radiograph (postero-anterior view) of the same patient after six months showing progressive expansion of the lung.

(n=2). They were treated with appropriate antibiotics as per culture sensitivity. Seven (14%) patients were lost to follow-up.

DISCUSSION

This study highlights the usefulness of pleurocutaneous flap in three ways; the patient become free from the intercostal tube, become ambulatory and can undergo domiciliary treatment. It also helps in achieving re-expansion of the lung obviating any major definitive surgical procedure and finally in sick patients, it can act as tide-over procedure, which subsequently can be complemented with a definitive procedure.

Wilcox⁴ described a modification of the original technique by Eloesser in which a rectangular flap of skin and subcutaneous tissue is elevated along the line of the rib to be removed with its base lateral or medial. After excision of the long segment of the rib, the skin flap is tacked lightly to the parietal pleura and periosteum creating a tract lined on one aspect with epidermis.

Galvin *et al*⁵ described the procedure of triangular window thoracostomy for management of empyema with bronchopleural fistula. They recommended its use either as a permanent stoma or as an interim measure before definitive surgical treatment.

Ali *et al*⁶ presented a series of 47 patients managed for primary mixed tuberculosis empyema with near or

total lung collapse over a period of seven years. In this study⁶, 28 patients achieved complete re-expansion the lung after 4 to 30 months of drainage and were completely cured, 11 were in the stage of re-expansion and in eight patients there was no-expansion. In their study⁶, irrigation of the cavity was performed after creating a pleurocutaneous window. Re-expansion was gradual, progressive and dependent upon improved compliance, clearing of bronchial inflammation and obstruction and pleural cleansing, as was observed in our study. In cases with bronchopleural fistula, the closure is accomplished by sealing the granulation tissue against the chest wall.

Kasturagi *et al*⁷ presented a retrospective analysis of 33 cases who underwent open window thoracostomy for chronic tuberculosis empyema with bronchopleural fistula. They concluded that in elderly with severe impairment of the pulmonary function, open window thoracostomy does not control the empyema well and has a high rate of mortality.

Graham³ described the mechanism of lung re-expansion in patients with open drainage for bacterial empyema and attributed this re-expansion to the gradual pull of adhesions between the lungs and the chest wall. Such has not been the experience with tuberculosis empyema (which was frequently encountered in our series), where lack of expansion necessitated decortication, lung resection and thoracoplasty in the past. However with the advent of modern-day antituberculosis treatment, the pulmonary and bronchial components are controlled and lung becomes capable of re-expansion. Only nine (18%) patients had to undergo decortication/lung resection in our series.

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Aetiology and Clinical Profile of Spontaneous Pneumothorax in Adults

Dheeraj Gupta, Sanjay Mishra, Shoaib Faruqi and Ashutosh N. Aggarwal

Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India

ABSTRACT

Background. Limited information is available on epidemiology of spontaneous pneumothorax (SP) from India. The present study was aimed at studying aetiology and clinical profile of patients with SP.

Methods. All patients admitted at a tertiary care hospital with the diagnosis of SP between January 2001 and March 2002 were prospectively studied. Detailed demographic and clinical data were recorded. Patients were divided into two groups—primary spontaneous pneumothorax (PSP), if no underlying aetiology for pneumothorax was found, and secondary spontaneous pneumothorax (SSP), when an underlying respiratory disorder could be identified. The clinical features were compared between the two groups.

Results. Sixty patients (12 with PSP and 48 with SSP) were included in the study. Annual incidence of SP was calculated as 99.9 per 100,000 hospital admissions. Annual incidence figures for PSP and SSP were 20.0 and 80.0 per 100,000 hospital admissions respectively. Age distribution showed a biphasic pattern and the overall male to female ratio was 5 : 1. The most common cause of SSP was found to be pulmonary tuberculosis (41.7%).

Conclusions. Pneumothorax is more common among men. In India, SSP is far more common than PSP, and the predominant underlying cause is pulmonary tuberculosis. [Indian J Chest Dis Allied Sci 2006; 48: 261-264]

Key words: Spontaneous pneumothorax, Epidemiology.

INTRODUCTION

Pneumothorax is defined as the presence of air in the pleural cavity. It is usually classified into spontaneous, occurring without a preceding cause, and traumatic which follows penetrating, blunt or barometric trauma to the chest. Spontaneous pneumothorax (SP) is subdivided into primary spontaneous pneumothorax (PSP), occurring in otherwise healthy individuals and secondary spontaneous pneumothorax (SSP), which occurs in patients with an underlying lung disease¹.

The aetiology and clinical spectrum of pneumothorax have undergone a marked change in the recent years. For example, pulmonary manifestations of acquired immunodeficiency syndrome (AIDS) have emerged as important cause of SSP². Data regarding epidemiology and clinical profile of SP are limited, especially so from the Indian subcontinent. Besides several case reports focusing on pneumothorax, there are few studies dealing with diagnosis and treatment of SP in India³⁻⁵. Occasional studies have also dealt with aetiology and clinical profile of SP in Indian adults and

children⁶⁻⁸. The present paper describes the aetiology and clinical profile of adult patients admitted with SP to a large tertiary care hospital.

MATERIAL AND METHODS

This was a prospective descriptive study conducted at a tertiary care institute in North India between January 2001 and March 2002. All the patients admitted to the hospital with a diagnosis of SP were included. A pre-designed structured performa that had sections on demographic details (age, gender, residence, smoking habit), anthropometry [height, weight, body mass index (BMI), upper segment to lower segment ratio], clinical presentation (pre-existing known cardiopulmonary disease or other comorbid conditions, respiratory and other symptoms at presentation, findings on general, respiratory and systemic examination), chest radiography, and details of other relevant investigations, was used to collect information. Depending on results of initial clinical evaluation and chest radiography, all patients underwent additional

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Correspondence and reprint requests: Dr Dheeraj Gupta, Additional Professor, Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh-160012, India; Tele.: 91-172-2756823; Telefax: 91-172-2745959; E-mail: dheeraj@indiachest.org.

detailed investigations to ascertain the underlying cause for SP. The tests carried out for individual patients included a variable combination of radiologic (e.g., thoracic CT scan), microbiological (e.g., sputum culture and examination for acid-fast bacilli), serological (e.g., antibodies to bacteria, fungi, human immunodeficiency virus), physiological (e.g., spirometry, static lung volumes, diffusion capacity), and other investigations. The patients were classified as having PSP if routine clinical and radiologic evaluation, as well as results of relevant additional investigations, failed to reveal a disease process that could potentially explain the occurrence of pneumothorax. All patients, in whom an underlying pulmonary disorder that could be linked to pneumothorax was detected, were categorized as having SSP. Patients were treated with simple needle aspiration or intercostal chest tube drainage as per the standard practice at our institute⁴.

Group comparisons were made between patients with PSP and SSP. Risk factor analysis for PSP was done for variables like age, sex, smoking, BMI, height, upper to lower segment ratio, and presence of exertion at the onset, using patients with SSP as controls.

Results are described in a descriptive fashion using percentage, mean and median. Statistical significance was determined using Chi-square test, unpaired t-test and Mann-Whitney test, and p value <0.05 was considered significant. The study did not require any intervention and was cleared by the ethics committee of the hospital. Written informed consent was obtained from all the patients before enrolment in the study.

RESULTS

Of the 60 patients included in the study, 12 (20%) had PSP while 48 (80%) had SSP. Based on the total number of admissions to our hospital during the study period, the annual incidence of SP was calculated as 99.9 per 100,000 hospital admissions. Annual incidence figures for PSP and SSP were similarly calculated as 20.0 and 80.0 per 100,000 hospital admissions respectively.

The patients studied had a mean age of 34.5 years (range 13-74). Patients with PSP were significantly younger as compared to patients with SSP (mean age 26.0 years vs 36.8 years, $p < 0.05$). Majority of patients included in the study were men, with an overall male to female ratio of 5 : 1. The male preponderance was even more dominant in PSP as compared to SSP (male to female ratio 11:1 and 4.3 : 1 respectively). The age distribution of patients showed a biphasic pattern. The first peak occurred between 20 and 30 years of age, and was mainly contributed by PSP, while the second occurred between 40 and 50 years, and was mainly contributed by SSP. Nearly half the patients (29 out of 60) had smoked tobacco, of whom four had PSP and 25 had SSP. Patients with PSP were significantly taller than those with SSP. However, weight and BMI were lower

in patients with SSP. There were no significant differences in the upper/lower segment ratio between patients in the two groups (Table 1).

Table 1. Anthropometric data in patients presenting with spontaneous pneumothorax

	SP	PSP	SSP	p value
Height (cm)				
Range	130-185	157-185	130-183	
Mean	164.2	171.0	162.5	<0.01
Weight (kg)				
Range	25-80	45-80	25-75	
Mean	51.3	58.5	49.5	<0.05
Body mass index (kg/m ²)				
Range	11-29.5	14-29	11-27	
Mean	18.9	20.2	18.6	>0.10
Upper/Lower segment ratio				
Mean	0.93	0.94	0.93	>0.10

SP=Spontaneous pneumothorax; PSP=Primary spontaneous pneumothorax; SSP=Secondary spontaneous pneumothorax.

The clinical presentation was largely similar irrespective of the category of SP. Dyspnoea was the commonest symptom at presentation in 56 (93%) patients, and was associated with pleuritic chest pain in 50 (83%) patients. In addition, 41 (68.3%) patients reported cough. No patient had a family history of pneumothorax. More patients (60%) had a right sided pneumothorax, and three (5%) patients presented with simultaneous bilateral pneumothoraces. A definite history of exertion at the onset of pneumothorax was elicited in only four patients.

The commonest aetiology for SSP was identified as pulmonary tuberculosis (in 41% patients with SSP) followed by chronic obstructive pulmonary disease (COPD) and pyogenic infections. AIDS associated pulmonary infections were seen in four (8.3%) patients with SSP (Table 2).

Table 2. Etiologic distribution of secondary spontaneous pneumothorax

Diagnosis	Number (%)
Pulmonary tuberculosis	20 (41.7)
Chronic obstructive pulmonary disease	12 (25.0)
Pneumonia	7 (14.6)
Human immunodeficiency virus (HIV) associated	
Pulmonary tuberculosis	3 (6.2)
<i>P. Jiroveci</i> pneumonia	1 (2.1)
Miscellaneous	5 (10.1)
Lung malignancy	1 (2.1)
Esophageal tear	1 (2.1)
Bullous lung disease	1 (2.1)
Pulmonary thromboembolism	1 (2.1)
Systemic lupus erythematosus	1 (2.1)

All patients with SSP were managed with intercostal chest tube drainage. All patients with PSP were initially managed with simple needle aspiration. The outcome of

this procedure was universally good, except in one patient with PSP who required placement of intercostal chest tube following failed needle aspiration. No treatment related complications were recorded in patients with PSP. However, one patient with SSP had developed empyema after intercostal tube placement.

DISCUSSION

Although the entity of pneumothorax has been well recognized since the beginning of 19th century, very few studies are available regarding its epidemiology, particularly from India. The most widely quoted study on the incidence of SP was conducted in Olmsted County, Minnesota⁹. In this study, the incidence of PSP was 7.2 per 100,000 per year among men and 1.2 per 100,000 per year among women, while the incidence of SSP was 6.3 per 100,000 per year and 2.0 per 100,000 per year for men and women respectively. Recently, large quantitative data from national databases in UK have been presented¹⁰. The overall person consulting rate for pneumothorax (primary and secondary combined) in the general practice was 24.0 per 100,000 each year for males and 9.8 per 100,000 each year for females. Hospital admissions for pneumothorax as a primary diagnosis occurred at an overall incidence of 16.7 per 100,000 per year and 5.8 per 100,000 per year for males and females respectively. In the present study, the incidence of SP was calculated to be 99.9 per year per 100,000 hospital admissions (~0.1%). This figure does not reflect the true incidence of SP in the general population and is not strictly comparable to the figures quoted in Western studies, since our study is from a tertiary care institute wherein the denominator comprises of patients predominantly referred hospital admissions.

The reported incidence of PSP among all patients presenting with SP have been widely variable in the few studies available from India, and has ranged from 12.5% in a study from Jaipur⁷ to 25% from Rohtak³ and 64% from Srinagar⁶. In the present study, the underlying aetiology could be found in 48 patients (80%), leaving only 12 (20%) in the PSP group. This high relative incidence of SSP could partly be related to the fact that most patients of PSP are managed at the primary and secondary health care hospitals, while several patients of SSP, who have associated co-morbidities, are referred to tertiary care hospitals.

Similar to other reports from the Western world, age distribution in our study also showed a biphasic distribution. Classically, these two age peaks correspond to PSP and SSP respectively, where PSP is predominantly a disease of younger men. In our study, the second age peak occurred a little earlier (40-50 years) as compared to the 60-65 years range reported in the other Western studies^{9,10}. The likely explanation for an

earlier occurrence of the second peak is that a large number of the cases of SSP in this study were secondary to tuberculosis and not COPD, which is the leading cause of SSP in the West and occurs relatively later. The sex ratio showed male predominance with male to female ratio of 5 : 1. This is in keeping with previously published studies. The higher incidence in men has been attributed to higher rates of smoking, body habitus and different mechanical properties of the lungs¹¹.

Patients with PSP were relatively taller (mean height 171 cm), which is a well-known observation¹¹. The higher incidence in tall people is possible due to greater pleural pressure gradient at the lung apex than at the base¹². Weight and BMI however, were lower in patients with SSP, which may be explained by the nature of chronic illnesses they suffered from.

Smoking is known to be an important risk factor for development of PSP. In fact, a study from Sweden even established that incidence of PSP was significantly affected by the sale of cigarettes¹³. History of smoking was obtained in only four out of 12 patients with PSP. This could be related to the small number of patients with PSP. Another commonly held belief is that exertion could promote the onset of SP. This hypothesis, though seemingly attractive, has never been proven in any study¹⁴. We also could not demonstrate any such significant association.

Until the description of PSP by Kjaegard¹⁵ more than 70 years ago, tuberculosis was thought to be the leading cause of SP. The scenario has changed over the years, and COPD has now emerged as the leading cause of SSP in the literature from the West^{1,16}. We found tuberculosis to be still the commonest aetiology for SSP, while COPD accounted for only 25% cases of SSP. Pulmonary infections other than tuberculosis, such as pneumonia or lung abscess, were responsible for SP in 14.6% instances. Thus, pulmonary infections seem to account for most SSPs in India. Similar results were earlier reported in children, in whom pyogenic infections and tuberculosis accounted for 75% and 21% cases of spontaneous pneumothorax respectively⁸. Tuberculosis has remained the dominant cause for SSP in all studies in adults from India^{6,7,17,18}. AIDS was responsible for 12.5% of cases of SSP in this study. Much higher figures are reported from the Western countries, with some studies reporting AIDS related pulmonary disorders in as high as 26% of patients with SSP². Majority of patients with AIDS in this study had either *P. Jiroveci* pneumonia or mycobacterial infection.

In summary, spontaneous pneumothorax in India is more often secondary to an underlying lung disease. Pulmonary tuberculosis remains the commonest cause of SSP, followed by COPD and other lung infections. PSP occurs more commonly in tall young men. Spontaneous pneumothorax has a good clinical outcome.

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Role of Bronchoscopy in Early Diagnosis of Lung Cancer

Ajay V. Kamath and Prashant N. Chhajed¹

Respiratory Medicine, Norfolk and Norwich University Hospital, Norwich, UK and Pulmonary Medicine¹, University Hospital Basel, Switzerland

ABSTRACT

Lung cancer is a leading cause of cancer deaths and the incidence is rising. Most patients with lung cancer present to the clinician in a fairly advanced stage and at best only 25-30% of patients can be offered curative resection. Screening tests using sputum cytology and chest radiograph have been used with limited success. Value of low dose spiral CT scan as screening tool for lung cancer is being evaluated and its limitations include high costs, need for repeated scanning and necessity to obtain histological confirmation with additional procedures. There have been significant advances in the early diagnosis of lung cancer in high risk patient groups using bronchoscopic methods such as white light bronchoscopy, autofluorescence bronchoscopy, high magnification bronchoscopy, narrow band imaging and endobronchial ultrasound. These techniques appear to be promising tools as they might allow to visualise changes of early lung cancer and also permit sampling for histological confirmation. [Indian J Chest Dis Allied Sci 2006; 48: 265-269]

Key words: Bronchoscopy, Lung cancer, Autofluorescence bronchoscopy, Endobronchial ultrasound, High magnification broncho- videoscopy.

INTRODUCTION

Lung cancer is a leading cause of cancer deaths and the incidence is rising¹. By the time patients present to clinicians the condition is fairly advanced and at best only 25-30% of patients can be offered curative resection²⁻⁴. There has been a lot of interest in screening tests for detection of early lung cancer. Screening tests using sputum cytology and chest radiograph have been used with limited success and a recent meta-analysis⁵ has shown that these strategies are not very useful and newer strategies need to be evaluated. Low dose spiral computerised tomographic scan (CT Scan) has also been explored as screening tool for lung cancer. A study by Henschke *et al*⁶ detected 27 lung cancers using spiral CT whereas only seven of these were visible on chest radiographs which were obtained at the same time. Another study⁷ looked at chest radiograph retrospectively in 44 cases of lung cancer diagnosed by using low-dose spiral CT as a screening tool and found that chest radiograph failed to detect 79% of lesions which were less than or equal to 2 cm. This highlights the importance of spiral CT in detecting small lesions in asymptomatic patients. However spiral CT is not yet the perfect tool for lung cancer screening due to the high cost of scanning and need for follow-up scans, small risk of cancer associated with multiple follow-up scans and the inability to do biopsies at the same sitting.

Bronchoscopic techniques for early detection of lung cancer are a promising tool as they might allow to visualise changes of early lung cancer and also permit sampling for histological confirmation. It is important to detect bronchial carcinoma *in situ* (CIS) since over 40% of these can develop into invasive cancer⁸. There is strong evidence from the treatment of cervical dysplasia or CIS, resulting in reduction in the incidence and mortality of invasive cervical cancer⁹, suggesting that a similar strategy may be useful in lung cancer. The role of conventional fiberoptic bronchoscopy in the diagnosis and management of lung cancer has been well established over the past few decades. There have been exciting innovations in the last decade in this field which can help with the goal of early detection of lung cancer by bronchoscopic techniques and coupled with new modalities of treatment such as chemoprevention and endobronchial therapies, the prognosis and outcome of these patients can potentially be altered in the near future.

Autofluorescence Bronchoscopy

The need to look for superficial bronchial mucosa malignancy was first addressed by Kato and Cortese¹⁰ using porphyrin injection, followed by bronchoscopic observation using a laser monochromatic light source. Tumour drug fluorescence was detected at 630 nm wavelength which was quite distinct from normal

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Correspondence and reprint requests: Dr Prashant N. Chhajed, Pulmonary Medicine, University Hospital Basel, Petersgraben 4, CH-4031, Basel, Switzerland; Tele.: 41-61-3286339 (office direct); 41-76-3419917; Telefax: 41-61-2654587; E-mail: PChhajed@uhbs.ch.

fluorescence at 500-580 nm. Though this technology improved sensitivity, the prohibitive cost and photosensitivity reaction meant that it could not be applied in routine screening. Subsequent research by a group in Canada^{11,12} led to the development of the LIFE (light imaging fluorescence endoscope). This technology uses blue light at 442 nm from a laser light source. Autofluorescence distinctions between normal and malignant mucosa can be made using image intensified cameras in real time. Bronchial epithelial fluorescence is measured in red (>630 nm) and green (520 nm). For the diagnosis of early lung cancer, the findings at white light bronchoscopy (WLB) are classified as (1) normal (2) abnormal - areas with increased redness and hypervascularity, swelling or thickening of the bronchial mucosa, focal thickening of subcarina (3) suspicious - nodular or polypoid lesions, irregularity of bronchial mucosa. On autofluorescence, normal bronchial mucosa appears green, abnormal lesions appear slight brown with ill defined margins and areas suspicious for high grade dysplasia or cancer appear brown or brownish-red¹³⁻¹⁵.

In a multicentre study Lam *et al*¹³ used LIFE as an adjunct to WLB to detect and perform biopsies from areas suspicious of intraepithelial neoplasia as compared to WLB alone. This study involved 173 patients and 700 biopsies were examined. This study showed that LIFE together with WLB had a relative sensitivity of 6.3 for detecting intraepithelial neoplastic lesions and 2.7 when invasive carcinomas were included, as compared to WLB alone. This set the stage

for the use of LIFE for detecting early stage lung cancer. However, another smaller study by Kurie *et al*¹⁶ involving 53 patients did not show any additional benefit of using LIFE. One of the reasons for the difference between the two studies might have been that the study by Lam *et al*¹³ included patients with known or suspected lung cancer whereas the study by Kurie *et al*¹⁶ included patients with heavy smoking history (>20 pack years) but free of active cancer.

A D-Light fluorescence-reflectance system has been developed. This uses noncoherent ultraviolet to blue 300W xenon filtered lamp (380-460 nm) to excite broad emission spectra of the different chromophores in tissue. Using this system the normal tissues appear bluish and the areas with high grade dysplasia and CIS give darker images. The LIFE system is somewhat bulky and does not allow direct and immediate comparison of white light and autofluorescence images. The D-Light system allows direct comparison of images between the two modalities. A study by Herth *et al*¹⁷ compared the D-Light system with the LIFE system in 332 patients and included 1,117 biopsies. Differences between the two systems were observed only in five biopsies which was not statistically significant ($p=0.3$). This study demonstrates that the D-Light and LIFE are comparable. The examination time by the D-Light system was much less (7.4 vs 11.4 mins, $p<0.001$) probably due to direct switch between white light and autofluorescence imaging.

Other systems being used are the system of autofluorescence endoscopy (SAFE) 1000 auto-

White Light Bronchoscopy

Light Imaging Fluorescence Endoscopy

LtB1+2b/c biopsy revealed severe dysplasia

Figure. Comparison of white light bronchoscopy and light imaging fluorescence endoscopy (LIFE). White light bronchoscopy is normal and autofluorescence bronchoscopy revealed a suspicious lesion.

fluorescence system using a xenon-lamp (420–480 nm) and a camera with a fluorescence filter and an image intensifier¹⁸. Another new fluorescence–reflectance imaging system is the ONCO-LIFE with a view to reduce equipment costs and to make the autofluorescence bronchoscopy much easier.

All the above studies have used fibreoptic bronchoscopes for the WLB. However, fibreoptic systems are now being replaced by flexible videobronchoscopy (FVB) where the images are clearer and sharper. A study comparing FVB and LIFE in patients at high risk of lung cancer¹⁹ showed that the sensitivity was 72% and 96% and the specificity was 53% and 23% respectively. The relative sensitivity of LIFE over FVB was 1.33. This is in striking contrast to the study by Lam *et al*¹³ which showed a relative sensitivity of 6.3 of LIFE over WLB using fibreoptic bronchoscopy and most likely attributable to better quality of images obtained using FVB.

High Magnification Bronchovideoscopy and Narrow Band Imaging

Conventional WLB is not as sensitive as autofluorescence bronchoscopy at detecting the early stages of dysplasia or CIS. The only findings of note using WLB with a bronchovideoscope are swelling and redness at bronchial bifurcations in contrast to the LIFE system²⁰. A high magnification bronchovideoscope combining two systems — a video observation system for high magnification observation and a fibre observation system for orientation of the bronchoscope tip, has been reported²¹. Using this system the magnification obtained is four times that of a standard bronchovideoscope. The scope is inserted like a normal bronchovideoscope into the tracheobronchial system using the fibre orientation system until the target area of suspicious mucosa is reached and then the mucosa is observed at high magnification on a television monitor. Areas of bronchial dysplasia, detected by autofluorescence bronchoscopy, are characterised by increased thickening of bronchial epithelium and vessel growth implying that neovascularisation might have a role in the development of bronchial dysplasia. High magnification bronchovideoscopy helps in observing the mucosa closely and pick up these lesions. Shibuya *et al*²¹ conducted a study in which they did autofluorescence bronchoscopy in high risk patients for lung cancer followed by high magnification bronchovideoscopy and observed vascular patterns in areas of normal and abnormal fluorescence and biopsies were performed at normal and abnormal sites. The areas with increased vessel growth and complex network of tortuous vessels of various sizes on high magnification bronchovideoscopy were assumed to be positive for dysplasia and areas with vascular networks with a regular pattern were assumed to be negative for dysplasia. The sensitivity and specificity using this

criterion were 71.4% and 90.9% respectively as confirmed by histology.

As a further improvisation high magnification bronchovideoscopy was combined with narrow band imaging (NBI)²². In this system the normal red, green, blue (RGB) broadband filter was changed to the new NBI filter. The NBI filter used wavelengths of B1 : 400-430 nm, B2: 420-470 nm and G: 560-590 nm. This contrasts with the conventional RGB filters using B: 400-500 nm, G: 500-600 nm and R: 600-700 nm. Of particular note is the fact that the NBI filter includes the NBI-B1 (400-430 nm) filter which includes the 410 nm absorption wavelengths for haemoglobin with perhaps more accurate detection of vessel structures. This would allow focused and detailed observation of bronchial vascular patterns. The optical absorption and scattering properties for tissues are strongly wavelength dependent²³. Blue light, which has a shorter wavelength than visible light, reaches into shallow surfaces²⁴ which is helpful for detecting the submucosal vessels and patterns of vascularisation. With conventional RGB light delivered through an endoscope, some of the light is reflected from the tissue, some is scattered or absorbed within the tissue and little is detected to form an image viewed on the monitor. However, with the NBI there is less scattering of light and clearer images are viewed on the television monitor.

It is important to note that areas with abnormal appearance on autofluorescence bronchoscopy may show inflammation on histology as opposed to dysplasia. A new morphological entity named angiogenic squamous dysplasia (ASD) was detected in the large central airways on autofluorescence bronchoscopy. This consisted of network of capillary blood vessels closely juxtaposed to and projecting into dysplastic bronchial epithelium^{25,26}. Bronchial squamous dysplasia often has increased vessel density in the submucosa^{27,28} implying that angiogenesis is a relatively early event in lung cancer pathogenesis²⁹. It is difficult to distinguish conventional squamous dysplasia from ASD using white light or fluorescence bronchoscopy. Shibuya *et al*²² have reported that high magnification bronchovideoscopy combined with narrow band imaging to be useful in the detection of capillary blood vessels in angiogenic squamous dysplasia lesions at sites of abnormal fluorescence. This might enable the discrimination between angiogenic squamous dysplasia and other pre-invasive bronchial lesions. A future prospect for detecting angiogenic squamous dysplasia may be quantitative fluorescence imaging combined with fluorescence reflectance imaging and spectrofluorometry^{30,31}.

Endobronchial Ultrasound (EBUS)

Endobronchial application of ultrasound³² using a miniature probe introduced *via* a fibreoptic bronchoscope channel was first described in 1992 and

over the last decade huge strides have been made in its applications. EBUS has been widely used for sampling mediastinal lymph nodes, endobronchial ultrasound - transbronchial needle aspiration (EBUS-TBNA) using both the radial probe as well as the convex probe^{33, 34} and for peripheral lung lesions by transbronchial biopsies (EBUS-TBB)³⁵.

EBUS can be performed using a radial probe introduced through the working channel of a flexible bronchoscope. The working channel needs to be 2.8 mm or more in diameter. A balloon sheath filled with saline is inflated and the transducer is rotated through 360° within this balloon window to form an image of the airway and its surrounding structures. The 20 MHz EBUS probe has a penetration depth of 2 cm, which provides optimum resolution with sufficient airway-wall image penetration³⁶. A new technique utilising flexible bronchoscope equipped with a 7.5 MHz convex probe for endobronchial ultrasound (CP-EBUS) that scans parallel to the insertion direction of the bronchoscope has also been developed³⁷.

On the basis of EBUS *in vitro* studies a seven layer ultrasound structure of the cartilaginous portions of trachea or extra/intrapulmonary airways has been described^{38,39}. The layers from the lumina outwards are:

1. Mucosa: hyperechoic – this appears as very bright enhanced by the adjacent balloon (first),
2. Submucosa: hypoechoic – clearly distinguishable from the other structures of the bronchial wall (second),
3. Cartilage: appears as three layers;
 - (a) hyperechoic – endochondrium (third),
 - (b) hypoechoic – internal layer (fourth),
 - (c) hyperechoic – perichondrium (fifth),
4. Supporting connective tissue – hypoechoic (sixth),
5. Adventitia – hyperechoic (seventh).

The three-layer structure of the membranous portion of the extra-pulmonary bronchi is:

- First layer – hyperechoic – epithelium and initial part of submucosa,
- Second layer – hypoechoic – smooth muscle and
- Third layer – hyperechoic – adventitia.

Kurimoto *et al*⁴⁰ performed EBUS in 45 specimens of normal human trachea or bronchi that had previously been excised for non-neoplastic indications and corroborated them with microscopic findings on histology. They found a good correlation between microscopy and EBUS images and on this basis proposed a five layer EBUS appearance for the tracheobronchial wall. In a further 24 lung cancer resected specimens, comparison of the determination of the depth of tumour invasion on the basis of EBUS and histopathologic findings showed that the findings were the same in 23 lesions (95.8%) and different in only one lesion (4.2%), in which lymphocytic infiltration protruding between the cartilages was misinterpreted by EBUS as tumour invasion. A number of other studies^{14,42} have shown that there is good correlation

between EBUS findings and histology.

Treatment of Early Stage Lung Cancer

One of the contentious issues in detecting early cancer is whether or not they would ultimately progress to invasive carcinoma and how to manage them. A follow-up study using AFB-LIFE at regular intervals showed that CIS ultimately progressed to squamous cell carcinoma⁴³, indicating that CIS is the point of no return. Photodynamic therapy (PDT) is a modality which uses photosensitisers, combined with laser illumination of the tumour area to obtain selective necrosis. This is a modality which is the treatment of choice for early stage cancer⁴⁴⁻⁴⁶ and a significant proportion may be spared surgery after initial PDT. This may be a prudent approach to preserve healthy lung tissue and quality of life^{45, 47, 48}. Chemoprevention strategies might be used in treating patients with early lung cancer⁴⁹.

To summarise, there have been significant advances in the early diagnosis of lung cancer in high risk patient groups using bronchoscopic methods. Success of a screening or diagnostic program will rely on a diagnostic tool that is routinely available and not expensive. A more proactive role is needed to detect lung cancer at CIS stage, so that best chance of cure can be offered to the patients.

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RADIOLOGY FORUM

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- (d) the chest radiograph is accompanied by brief clinical account, not exceeding one page typescript.

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Editor-in-Chief

High Intensity Exercise Training Programme Following Cardiac Transplant

A.J. Rajendran, U.M. Pandurangi, A.S. Mulasari, S. Gomathy, K.V. Kuppu Rao¹ and V.K. Vijayan²

Institute of Cardio-vascular Diseases, Chennai, Cardio-pulmonary Medicine Unit¹, Tuberculosis Research Centre, Indian Council of Medical Research, Chennai, and Vallabhbhai Patel Chest Institute², University of Delhi, Delhi; India

ABSTRACT

A 26-year-old male patient who presented with symptoms of end stage cardiac failure as a result of dilated cardiomyopathy, had an orthotopic cardiac transplantation. A comprehensive cardiac rehabilitation programme was provided to him and he was introduced to a sport (tennis). The exercise training programme progressed from low intensity training to high intensity programme over a period of 15 months. A cardio-pulmonary exercise test done 22 months after surgery suggested that he was able to achieve the aerobic capacity comparable to that of a normal South Indian subject. He participated successfully in the World Transplant Games in Sydney and returned safely. This suggests that after a proper cardiac rehabilitation programme, patients undergoing heart transplantation can achieve normal physiological responses to lead a normal active life. [Indian J Chest Dis Allied Sci 2006; 48: 271-273]

Key words: Cardio-pulmonary exercise testing, Cardiac transplantation, Cardiac rehabilitation.

INTRODUCTION

Orthotopic heart transplantation is an established therapeutic procedure for end stage heart failure patients¹. The haemodynamic responses following transplant during exercise in the supine and in the upright posture have been well documented^{2,3}. In general, less than normal increase in cardiac output at more than normal ventricular filling pressures is noted during exercise in a transplant recipient. These observations have been attributed among many reasons, mainly to the effects of cardiac denervation, a mismatch of donor and recipient cardiac size, myocardial fibrosis resulting from rejection and graft vascular disease^{4,5}. The beneficial effects of exercise training programme for transplant recipients are well known^{6,7}.

CASE REPORT

A 26-year-old male patient, who presented at our Institute of Cardio-vascular Diseases, Chennai, with end stage cardiac failure as a result of dilated cardiomyopathy, underwent orthotopic cardiac transplantation on 5th December 1995. The post-operative course was uneventful, leading to a complete recovery. Regular follow up including endomyocardial

biopsies, coronary angiograms, 2D echocardiograms and clinical assessments were done periodically to assess rejection episodes and improvement in his physical endurance according to the protocol⁸. His aptitude to learn tennis and his zeal to participate in World Transplant Games (WTG), Sydney, Australia were identified and encouraged. A comprehensive rehabilitation programme⁹ was offered to him to re-develop his exercise tolerance. After six months of transplantation, he was constantly motivated to ensure compliance and was guided through the exercise programme, which progressed from a low intensity training to a high intensity training programme for a period of 15 months. At the beginning of the exercise programme, patient had dyspnea (class II), no evidence of clinical congestive cardiac failure, normal chamber dimensions and normal ejection fraction by 2D echocardiogram. Towards the end of this training programme, his rating of perceived exertion was in the range of 16-17¹⁰. One week before his departure to participate in WTG, a graded exercise test was done in September 1997 in the Cardio-pulmonary Medicine Unit of the Tuberculosis Research Centre (ICMR) using a motorised treadmill and with a metabolic cart which analysed respiratory gases (Morgan, Chatham, UK). The Bruce protocol was used for the exercise testing^{11,12}. Analyzers were calibrated with gases of known concentrations before each session. The participants

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Correspondence and reprint requests: Dr V.K. Vijayan, Director, V. P. Chest Institute, University of Delhi, Delhi – 110 007
E-mail: vijayanvk@hotmail.com.

breathed through a mouth piece and wore nose clips throughout. Expired gas collection was performed with a low resistance, small dead space Rudolph valve. Ventilatory parameters were measured with an intake turbine ventilometer. Expired O_2 content was determined with a model QA 500 paramagnetic analyzer and carbon dioxide content was measured by a model 901 infrared CO_2 analyzer (PK Morgan Instruments Inc.). Data were supplied to a Magna 88 computer, which provided 15-second averages of oxygen consumption, minute ventilation, tidal volume, respiratory rate, respiratory exchange ratio and ventilatory equivalent for oxygen and carbon dioxide. Heart rate and arterial oxygen saturation were measured by a pulse oximeter (Ohmeda model IV A) continuously during the exercise test. Data were

initially obtained for three minutes at rest. Maximal exercise effort was defined by fatigue, facial flushing, dyspnoea and unsteady gait in conjunction with respiratory exchange ratio over 1.0 or achieving maximal heart rate (% predicted $\pm 5\%$). Maximal oxygen consumption and ventilatory parameters were taken as the highest achieved during exercise. Basic gas and flow measurements were corrected for ambient temperature, barometric pressure and water vapour. Anaerobic threshold was defined as $\dot{V}O_2$ at which expired carbon dioxide increased non-linearly relative to oxygen consumption (v-slope).

On treadmill, our subject could perform Bruce stage IV attaining appropriate blood pressure response. Patient could attain 70% of control $\dot{V}O_2$ max and 93% of maximal control heart rate. There were no arrhythmias and ST-T changes. The cause of termination of test was fatigue. Cardio-pulmonary exercise data compared with age- and sex-matched control South Indian subjects are given in table. The data suggest that, if a properly structured Comprehensive Rehabilitation Programme is offered to a cardiac transplant patient, he can achieve the aerobic capacity of a normal person, and this has helped our patient to participate in an enduring sport competition like lawn tennis at WTG held at Sydney, Australia in 1997. He successfully participated in the WTG and returned safely. The last follow up in January 2004 revealed that his physical endurance is maintained and he achieved 10 metabolic equivalents (METs) on treadmill test by Bruce Protocol and one metabolic equivalent is equal to 3.5 ml O_2 /kg/min.

Table. Cardio-pulmonary exercise test parameters

Parameters	Patient	Control	% of Control
(a) Metabolic Parameters			
1. $\dot{V}O_2$ (ml/min)			
Rest	335	380	88
Maximal Exercise	1600	2300	70
2. $\dot{V}O_2$ /kg (ml/min/kg)			
Rest	5.2	5.9	88
Maximal Exercise	24.6	35.9	69
3. $\dot{V}O_2$ at AT (ml/min)			
	1320	1935	-
(% of $\dot{V}O_2$ max)	(82.5%)	(84%)	-
(b) Gas Exchange Parameters			
1. $\dot{V}E/\dot{V}O_2$ (ml/min)			
Rest	33.8	32.4	104
Maximal Exercise	41.3	38.7	107
2. $\dot{V}E/\dot{V}CO_2$ (ml/min)			
Rest	31.5	32.4	97
Maximal Exercise	30.2	32.7	92
3. Respiratory Exchange Ratio			
Rest	0.9	0.9	100
Maximal Exercise	1.4	1.2	117
(c) Ventilatory Parameters			
1. Respiratory Rate (/min)			
Rest	21	19	111
Maximal Exercise	44	44	100
2. Tidal Volume (ml)			
Rest	546	634	86
Maximal Exercise	1457	2374	61
3. Ventilation (L/min)			
Rest	11.4	12.3	93
Maximal Exercise	71.5	90.7	79
(d) Cardiovascular Parameters			
1. Pulse (beats/min)			
Rest	100	75	133
Maximal Exercise	172	184	93
2. O_2 -Pulse (ml/min)			
Rest	3.4	5.1	67
Maximal Exercise	9.3	12.5	74
3. O_2 Saturation (%)			
Rest	96	98	98
Maximal Exercise	97	97	100

$\dot{V}O_2$ =Oxygen consumption; AT=Anaerobic threshold;
 $\dot{V}E/\dot{V}O_2$ =Ventilatory equivalent for oxygen;
 $\dot{V}E/\dot{V}CO_2$ =Ventilatory equivalent for carbon dioxide.

DISCUSSION

The denervated donor heart has a higher resting heart rate and smaller resting stroke volume¹³. The peak heart rate achieved during exercise is lower. Inappropriate response to circulating catecholamine leads to reduced stroke volume during exercise and thereby, limiting the exercise tolerance¹⁴. Another potential cause is altered muscle metabolism secondary to immunosuppressive therapy¹⁵. Cyclosporine A, the common immunosuppressive agent used to treat post transplant patients has been shown to affect muscle metabolism. Cyclosporine A significantly reduces muscle mitochondrial respiration and therefore result in sub maximal exercise endurance¹⁵. Lean tissue loss following major surgery is common and is exacerbated by steroid administration. This is also the result of prolonged, preoperative physical inactivity due to cardiac illness. This reduction in muscle mass plays a major role in limiting maximum exercise performance. Because of low peak oxygen uptake, exercise is quickly halted by fatigue. Anxiety and postoperative debility can also significantly limit exercise tolerance. Several studies have shown that a constructive rehabilitation programme involving multidisciplinary efforts would

enable the heart transplant recipients to improve exercise tolerance significantly¹⁶⁻¹⁸.

Our subject was able to achieve normal physiological responses to exercise after the cardiac transplantation. This was possible by the right motivation and the excellent cardiac rehabilitation programme provided to the patient. This emphasizes that individuals with end stage cardiac failure who had undergone successful cardiac transplant and had appropriate and sustained cardiac rehabilitation can lead a normal active life. We believe that our case is the first report of an Indian Cardiac Transplant recipient undergoing supervised high intensity exercise programme to achieve normal physical endurance. The fact that he was able to achieve 10 METs on treadmill test by Bruce Protocol eight years after the transplantation was an indication that he was maintaining his physical endurance at least eight years following the transplant.

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Superior Vena Cava Syndrome Caused by Pulmonary Amoebic Abscess

K.B. Gupta, Manav Manchanda, Uma Chaudhary¹ and Manish Verma

Departments of Tuberculosis and Chest Diseases and Microbiology¹, Pt. B.D. Sharma Postgraduate Institute of Medical Sciences, Rohtak, India

ABSTRACT

Isolated pulmonary amoebiasis without involvement of liver and other systems is extremely rare. Its presentation with superior vena cava (SVC) syndrome is not well documented. The case of 38-year-old male who developed SVC syndrome due to a large pulmonary amoebic abscess, which initially mimicked a pulmonary neoplasm with distal lung abscess is presented here. Subsequent bacteriological examination of the aspirated pus and the sputum along with suggestive serology confirmed the diagnosis of pulmonary amoebic abscess. [Indian J Chest Dis Allied Sci 2006; 48: 275-277]

Key words: Superior vena cava syndrome, Abscess, Pulmonary, Amoebic.

INTRODUCTION

Amoebiasis is a protozoan infection caused by *Entamoeba histolytica*. Prevalence of amoebic colitis and liver abscess is high in developing regions than the industrialised world¹.

Pleuropulmonary amoebiasis occurs in 2%-3% of patients with invasive amoebiasis and is frequently associated with liver abscess. Lung disease without liver involvement is exceptional and it is believed that infection of the lung is a result of haematogenous spread from a primary site, usually colon².

Superior vena cava (SVC) obstruction is oftenly caused by malignant process, such as bronchogenic carcinoma or lymphoma. However, in a small number of patients the obstruction results from a benign, non-malignant process which includes mediastinitis, mediastinal tumours, cardiac and vascular causes, trauma among others. Of these, tuberculosis, retrosternal thyroid, aortic aneurysm and thymoma are common. Among pulmonary causes, mediastinal emphysema and pneumothorax have also been reported³. Few cases of severe pulmonary infection by *Escherichia coli* and *Klebsiella*⁴ have been reported. Lichtenstein *et al*⁵ reported a case of pulmonary abscess due to *E. histolytica* causing SVC obstruction along with cerebral and intestinal involvement. We report an unusual case of large pulmonary amoebic abscess that presented as SVC syndrome without extra-pulmonary involvement.

CASE REPORT

A 38-year-old male presented with progressive swelling of his face and neck for 10 days. He also complained of progressively increasing breathlessness on exertion, cough with expectoration of brown thick sputum and mild chest pain on right side. There was no history of fever, gastrointestinal symptoms, abdominal pain, hoarseness of voice or weight loss. He denied any past illness of chronic bloody diarrhea. He had a history of *bidi* smoking for 13 years. The patient was a truck-driver by occupation, unmarried and a chronic alcoholic. History of poor food hygiene was also present.

Physical examination showed the patient in mild dyspnea. He was anemic. There was no evidence of pedal edema. Blood pressure was 116/80 mmHg, pulse was 84 per minute, respirations was 20 per minute and temperature was 98.4 °F. He had swelling of face and neck along with marked periobital oedema and collateral circulation on face, neck, anterior chest wall and abdominal wall. Neck veins were distended and non-pulsatile. Clubbing of digits was present. On chest percussion, a dull note was found in the areas corresponding to right upper lobe. Decreased breath sounds and succussion splash were found in right axillary region on auscultation. There was no organomegaly or peripheral lymphadenopathy.

Chest radiograph (Figure 1) showed a large abscess with air fluid level in right upper lung field with rest of lung field looking apparently normal. Laboratory investigations revealed haemoglobin: 6.5 gm/dl, total

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Correspondence and reprint requests: Dr K.B. Gupta, 18/6J, Medical Enclave, Pt. B.D. Sharma PGIMS, Rohtak-124001 (Haryana), India; Tele.: 91-01262-213837.

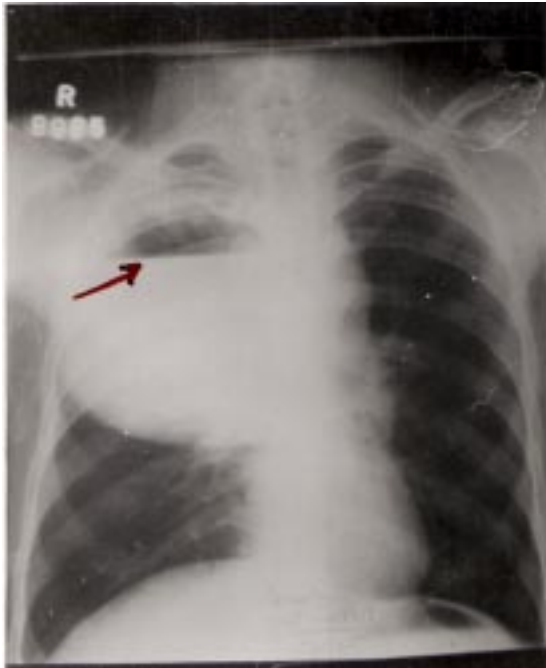


Figure 1. Chest radiograph (postero-anterior view) showing lung abscess on the right side with air-fluid level (arrow).

leukocyte count: 9500 per mm^3 , with a differential leukocyte count of neutrophils: 75%, lymphocytes: 15%, monocytes: 2% and eosinophils: 8%. Arterial blood gas analysis showed pH: 7.414, PaCO_2 : 33.4 mmHg, PaO_2 : 56.9 mmHg, bicarbonate: 20.7 mEq/l, base excess: 2.1 mEq/l and oxygen saturation: 90.3%. Sputum was negative for acid-fast bacilli (AFB) on direct and concentrated smears. Serological testing for human immunodeficiency virus (HIV) was negative. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) levels were within normal limits. Stool examination for ova cysts of *E. histolytica* was negative on three occasions. In view of short history, rapidly progressive SVC obstruction syndrome and absence of signs of infective pathology, an initial presumptive diagnosis of a neoplasm causing distal lung abscess with SVC syndrome was made.

Ultrasonography of thorax and abdomen was performed which revealed a thick-walled cystic area of size 10.6 cm \times 11 cm with internal echoes in the right upper zone. Liver was normal. Contrast enhanced computerised tomographic (CECT) scan of the chest showed a peripherally enhancing cystic lesion with air-fluid level in the right upper lobe which was compressing superior vena cava leading to obliteration of lumen of SVC (Figure 2).

Diagnostic tap was done and about 200 ml of brown coloured turbid fluid was aspirated from the right axillary region. Aspirated fluid was negative for AFB and malignant cells and was sterile for pyogenic culture. Biochemical examination showed protein level greater than 6.0 g/dl. In view of young age and brown coloured fluid, we also suspected pulmonary

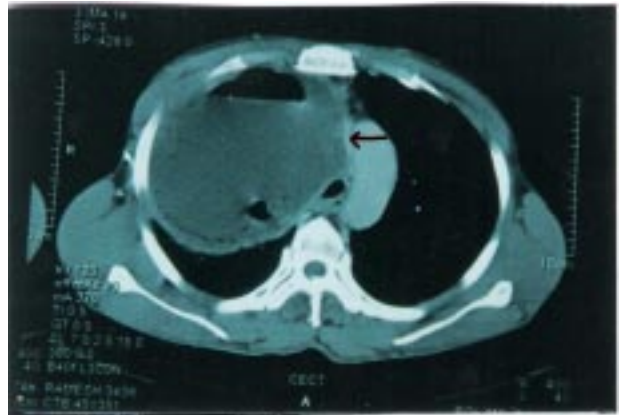


Figure 2. Computed tomographic scan of the chest (mediastinal window) showing lung abscess in right upper zone with compression of superior vena cava (arrow).

amoebiasis and fluid was also examined for trophozoites of *E. histolytica*. Wet mount preparation and hematoxylin and eosin staining of fluid revealed *E. histolytica* trophozoites with RBCs. Subsequently, *E. histolytica* trophozoites were also found in the sputum. Later on, enzyme-linked immunosorbent assay (ELISA) further supported the diagnosis of amoebiasis (value = 1.2 units in our patient, normal value < 0.4 units). During initial stage, treatment with broad-spectrum antibiotics for one week did not show any response and chest radiograph showed increase in size of the lung abscess. After confirmation of diagnosis of amoebic pathology, patient was treated with metronidazole (800 mg thrice a day) and chloroquine (300 mg twice a day for two days and 150 mg twice a day for 19 days). Repeated therapeutic aspirations of fluid were also done. After two weeks of treatment patient showed marked clinical improvement with disappearance of facial oedema and significant decrease in size of lung abscess (Figure 3).



Figure 3. Chest radiograph (postero-anterior view) showing significant decrease in the size of the abscess.

DISCUSSION

The syndrome of SVC compression is not an uncommon entity⁶. The SVC syndrome is usually related to malignant process, but frequently benign causes have also been described. Mediastinitis caused by various granulomatous processes is probably the most common cause of the benign SVC syndrome³. There has been reports of SVC obstruction caused by pulmonary and mediastinal infection caused by tuberculosis⁷, histoplasmosis⁸, and nocardiosis⁹, *E. coli* and *Klebsiella*⁴. A case of pulmonary abscess due to *E. histolytica* causing SVC obstruction along with cerebral and intestinal involvement has been reported⁵. In this report⁵, liver enzymes of the patient were within normal range and no abnormality of liver was found on ultrasonography. Histological examination of the excised tissue (after right pneumonectomy), immunofluorescence using anti-entamoeba histolytica antibodies and serology confirmed the diagnosis of amoebiasis. The patient improved on treatment with cytrioxone and metronidazole⁵. However, isolated pulmonary involvement in amoebiasis without evidence of involvement of extra-pulmonary site along with SVC has not been documented previously.

The most frequent extra-intestinal site of involvement in amoebiasis is the liver (3–9% of all cases). The lung is invaded far less often, being affected usually by the extension of liver abscess (6–40% of patients with amoebic liver abscess)¹⁰. The lower and middle lobes of the right lung are mostly affected in form of empyema, abscess and hepatobronchial fistula. Isolated upper lobe involvement without pleural and hepatic involvement is extremely rare.

In our patient, poor hygiene of food can be related as source of infection and lung involvement may be secondary to haematogenous spread from the colon, but we did not find evidence of intestinal involvement either in history or during investigation. There have been sporadic case reports showing appearance of amoebic lung diseases without liver involvement¹¹. In our patient, large pulmonary amoebic abscess was causing SVC syndrome. Adequate treatment with metronidazole and chloroquine along with aspiration of pus caused improvement in symptoms and decrease in size of abscess.

In the present case, SVC obstruction might have been caused by an inflammatory exudate and oedema. Benign type of SVC is usually compatible with long life without complications. Treatment in such cases is variable. Several surgical procedures have been used to relieve the obstruction, but majority of experts did not advocate surgical intervention when clinical history is suggestive of benign SVC obstruction, especially of infective and inflammatory in origin. In fact, during surgery to control bleeding, sometimes important venous collaterals may be ligated leading to much hemorrhage³.

Most cases of SVC syndrome have a malignant aetiology and work up to rule it out should be aggressive. We recommend that *E. histolytica* should be included as a possible cause in differential diagnosis of lung lesions in young patients, especially in countries where amoebiasis is endemic because lung amoebiasis is a life threatening but treatable condition.

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Uncommon Parathyroid Mediastinal Cyst Compressing the Trachea

D. Agrawal, T.K. Lahiri, Anshu Agrawal¹ and Manish Kumar Singh¹

Department of Cardiothoracic Surgery and General Surgery¹, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

ABSTRACT

Mediastinal parathyroid cyst is a rare cause of space occupying lesion in the mediastinum. No specific symptomatology may be attributed to the non-functioning parathyroid cyst. The diagnosis is rarely made before exploration. The cysts are thin walled, smooth, of varying sizes and contained clear, opalescent or haemorrhagic fluid. Histopathological examination reveals clusters of parathyroid cells dispersed in the wall of the cyst. Surgical removal is the treatment of choice and can be performed with minimal morbidity. [Indian J Chest Dis Allied Sci 2006; 48: 279-281]

Key words: Mediastinal cyst, Parathyroid cyst, Sub-total resection.

INTRODUCTION

Mediastinal parathyroid cysts are embryologic aberration. They may be incidental, accidental, functional or non-functional¹. Due to asymptomatic presentation of the non-functional cyst, diagnosis is seldom made before the operation. Compression of the trachea by the non-functional parathyroid cyst is a rare presentation. Paucity of cases in the literature promoted us to report this case.

CASE REPORT

A 62-year-old female presented with a four months history of swelling of left lower neck along with dull aching pain. Fine needle aspiration from the swelling on the left supraclavicular area, which was nonpulsatile, compressible, globular, nontender, partially mobile and approximately 5 cm in diameter, revealed clear fluid only. There were no symptoms referable to the chest. Coughing with small quantities of sputum in the morning was admitted by the patient. She had no dyspnoea, dysphagia or weight loss. There were no signs or symptoms of hyperthyroidism. On physical examination fullness was present at left root of the neck. General physical and systemic examinations were unremarkable. Laboratory tests were in indexed range including serum T₃, T₄ thyroid stimulating hormone (TSH) levels. Routine chest radiograph showed a large mass on the left upper mediastinum along with

encroachment to the left upper lung field. This also revealed shifting of the trachea towards the right along with indentation (Figure 1). Contrast enhanced computed tomographic (CT) scan confirmed a mass (10.3 cm × 8.1 cm) in the superior mediastinum to the



Figure 1. Chest radiograph (postero-anterior view) showing a large left superior mediastinal mass with displacement, and indentation on the left side of the trachea.

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Correspondence and reprint requests: Dr D. Agrawal, Reader and Head, Department of Cardiothoracic Surgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005, (U.P.), India; Tele.: 91-0542-2307530, 2309484.

radiograph still showed indentation over the trachea.

DISCUSSION

Tumours and cysts occur in the mediastinum. Uncommon causes are thyroid cysts, parathyroid cysts and thoracic duct cysts. De Quervain first operated a case of mediastinal parathyroid cyst in 1925². Enlarged superior parathyroid cyst tends to locate in the tracheoesophageal groove, in the middle mediastinum, or else can be in retropharyngeal space. The inferior parathyroid cysts are found under the thyroid capsule, frankly intrathyroidal, within the thymus in the anterior mediastinum, or when undescended at the carotid bulb². The missing parathyroid cysts are located in the neck in approximately 50% of the cases. The places are medial to the upper pole of the thyroid, superior mediastinum in the thymic capsule, retroesophageal, in the carotid sheath and when undescended upto the hyoid bone (para-pharyngeous). Mediastinal locations are anterior superior, posterior mediastinum and aorto pulmonary window³. Mediastinal parathyroid cysts are rare and 94 cases have been collected until 1999⁴. The location of the cysts are anterosuperior (the pretracheal portion of the visceral compartment of the mediastinum) in 56 patients, in the middle region (retrotracheal upto thoracic spine) of the mediastinum in 26, and in the anterior, prevascular region in 12 patients. In our case the parathyroid cyst was compressing the trachea, left subclavian artery and arch of the aorta.

Parathyroid cysts present as functional or non-functional. Functional cysts present as symptoms of hyperparathyroidism with hypercalcaemia (99%), renal impairment (nephrolithiasis, nephrocalcinosis, impaired glomerular filtration rate) in 32%–84%, and skeletal manifestation (osteitis fibrosa cystica, absent lamina dura, diffuse spinal osteopenia, subperiosteal bone reabsorption, salt-and-pepper skull) in 41%–91%. Non-functional cyst is usually asymptomatic, or may present as a neck mass with symptoms of hoarseness, dysphagia, tracheal compression, recurrent laryngeal nerve palsy or innominate vein compression, predominantly in the females and attains a large size^{1,5,10}.

Parathyroid cysts are thought to arise from cystic degeneration in a parathyroid adenoma or hyperplastic gland. Other possibilities are remnants of vestigial pharyngobranchial ducts and Kursteiner canals, coalescence of the clefts, retention of secretion in the microcysts, and presence of foetal remnants of the third and fourth branchial clefts^{3,8}.

The diagnosis of mediastinal parathyroid cyst is seldom made before operation. Functional cysts are diagnosed with serum calcium level, PTH assay and Sestamibi parathyroid imaging scan with single photon emission CT imaging, and gamma camera during

operation^{2,6}. Non-functional cyst usually diagnosed as incidental. Clear, colourless watery fluid with high level of PTH (600 to 600,000 pg/ml) strongly suggestive of parathyroid cyst⁷. Definite diagnosis is made only by histopathologic examination. Grossly transparent cyst wall with clear low specific gravity fluid is detected. Microscopically cyst is lined by solitary layer of compressed cuboidal low columnar epithelium and contains eosinophilic colloid material, and stain positive for glycogen². Immunocytochemistry positivity for pancytokeratin, (thyroid epithelium), and weakly positive Factor VIII (for endothelial cells) can be detected.

Surgical removal of the cyst is indicated in symptomatic patients. The approaches are cervical approach, through posterolateral thoracotomy, occasionally median sternotomy, and now minimally invasive surgery^{1,2}. Recently pure closed endoscopic parathyroidectomy or video-assisted gasless parathyroidectomy through the axillary, anterior chest, lateral neck, and anterior neck approach have been advocated⁹. In the indexed case left posterolateral thoracotomy and subtotal excision of the mass has been performed.

In conclusion, non-functional mediastinal parathyroid cysts are rare causes of space occupying lesions to be dealt with by the clinician. The cysts produce symptoms due to compression on adjacent structures. They should be considered in the differential diagnosis of space occupying cystic lesion of the mediastinum. The presence of parathyroid cells in the lining of the cyst wall proves the diagnosis.

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Pulmonary Hyalinizing Granuloma with Ureteric Fibrosis: A Case Report and Review of Relevant Literature

D. Agrawal, R. Deshpande, S. Maheshwari, A. Patel and Z.F. Udwadia

Departments of Pulmonology, Pathology and Radiology, P.D. Hinduja Hospital and Medical Research Centre, Mumbai, India

ABSTRACT

A 52-year-old, asymptomatic patient presented with bilateral lung nodules on chest radiograph. She was diagnosed to have "pulmonary hyalinizing granuloma" on an open lung biopsy. We review the clinical features of this rare disease. [Indian J Chest Dis Allied Sci 2006; 48: 283-285]

Key words: Bilateral pulmonary nodules, Pulmonary hyalinizing granuloma, Ureteric fibrosis.

INTRODUCTION

Pulmonary hyalinizing granuloma is a rare, non-infectious disease of the lung, of unknown aetiology. It is usually diagnosed on open lung biopsy or after resection of nodules noted on chest radiography^{1,2}. We report one such case of this rare entity, as there is a paucity of Indian data on this condition.

CASE REPORT

A 52-year-old housewife from Surat came to our Hospital in Mumbai in June 2004 for evaluation of bilateral lung nodules on chest radiograph. In 1996 she was admitted at a private hospital in Surat with complaints of dry cough and low grade fever. She was then diagnosed to have right lung opacity on the chest radiograph for which she was treated with a 10-day course of antibiotics. Her routine haematological and biochemical tests were normal. Antinuclear antibody (ANA) test, antineutrophilic cytoplasmic antibody (ANCA) and rheumatoid factor (RF) were negative. Two months later she was empirically started on antituberculosis treatment in addition to 30 mg of prednisolone daily.

In view of persistent radiological features, computerised tomographic (CT) scan of chest and bronchoscopy were done. Transbronchial lung biopsy and CT-guided percutaneous transthoracic fine needle aspiration cytology (FNAC) were non-diagnostic. Antituberculosis treatment was discontinued as mycobacterial and fungal cultures of bronchoalveolar lavage fluid were negative. She was then lost to follow-up.

In 2004, she was re-admitted at Surat for abdominal pain. Routine chest radiograph and CT-scan during this admission showed bilateral lung nodules (Figures 1 & 2) and she was referred to our centre for further evaluation.



Figure 1. Chest radiograph (postero-anterior view) of 2004 showing a large irregular opacity in the right mid zone and opacities in the left upper zone.

She was asymptomatic at presentation to us. No crackles or wheeze were auscultated. Pulmonary function testing revealed forced expiratory volume in the first second (FEV₁) – 68% of predicted and the ratio of FEV₁ and forced vital capacity (%) [FEV₁/FVC – 80 percent. All routine haematological and biochemical tests were normal. Erythrocyte sedimentation rate (ESR) rate was 8 mm at the end of first hour. Repeat (ANA) and ANCA tests were negative. An open lung biopsy was done as it was considered mandatory to rule out malignancy. Histopathology showed well-defined

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Correspondence and reprint requests: Dr Z.F. Udwadia, Consultant Pulmonologist, P.D. Hinduja Hospital, Veer Savarkar Marg, Mahim, Mumbai-400016, India; Tele.: 91-22-24451515.

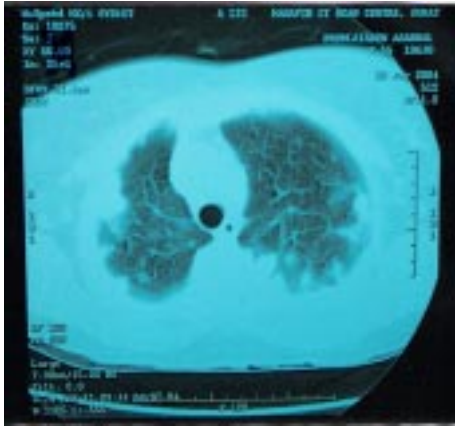


Figure 2. CT scan of chest of 2004 showing multiple subpleural nodules.

nodules of dense collagen arranged in a storiform pattern and in whorls (Figure 3), which confirmed pulmonary hyalinizing granuloma. CT scan of the abdomen was reviewed at our hospital and the cause of her abdominal pain was believed to be secondary to ureteric and retroperitoneal fibrosis as shown in figure 4 with soft tissue encasing the right proximal ureter.

Figure 3. Photomicrograph of the open lung biopsy specimen's, microscopy showing dense collagenous bands arranged in storiform pattern and in whorls. Lung periphery showing interstitial fibrosis and nodular aggregates of lymphocytes (H & E \times 400).



Figure 4. Contrast enhanced CT-scan of abdomen showing enhancing soft tissue encasing right proximal ureter.

DISCUSSION

The term "Pulmonary hyalinizing granuloma" was introduced by Engleman *et al*³ in 1977 to describe multiple bilateral pulmonary nodules. It is a rare fibrosing nodular disease of the lung which is usually discovered incidentally on chest radiograph and poses diagnostic difficulties but has excellent prognosis¹. A detailed medline search revealed only one other case report from India².

Age range of patients reported in two large series by Engleman *et al*³ and Yousem *et al*⁴ of 20 and 2 patients respectively was 24 to 77 years with a mean age of 42.3 years. The sex distribution reported by them was equal with no racial predominance. Our patient was slightly older than the average age mentioned. However, her radiographic abnormality had been there for eight years prior to the diagnosis.

Size of the tumours in above series varied from several millimeters to 15 cm in greatest dimension; 73% of their patients had multiple lesions^{3,4}. Multiple symptoms have been reported in different series and case reports^{3,4}. These include cough, dyspnea, weight loss and pleuritic chest pain. Many patients are asymptomatic with lesions being seen on routine health screening examinations^{3,4}. Cases complicated with sclerosing mediastinitis, retroperitoneal fibrosis and amyloidosis have also been reported³. Our patient had abdominal complaints and on further evaluation of this complaint was noted to have right ureteric fibrosis.

Pulmonary hyalinising granuloma can also present as dysphagia due to either direct involvement of the esophagus or due to tight stricture from associated mediastinal fibrosis^{2,5}. Neoplastic diseases have rarely been reported with pulmonary hyalinizing granuloma. These include abdominal lymphoma, multiple myeloma, Paget's disease of the breast and astrocytoma of the brain^{6,7}.

The aetiology of pulmonary hyalinizing granuloma is uncertain; however it has been proposed that it represents an abnormal immune reaction to tuberculous bacilli, histoplasma organisms or other infectious agents⁸. Autoimmune mechanism has also been suggested supported by the association of many immune-mediated diseases like rheumatoid arthritis, uveitis and retroperitoneal fibrosis². Microscopically the disease is characterised by a dense network of concentric hyalinized collagen in the center surrounded by perivascular lymphoplasmacytic infiltrate that rarifies in the center of the nodule³. Although pulmonary hyalinizing granuloma is a benign entity, 30% of patients may have progressive disease manifested by enlarging nodules and increasing dyspnea⁴.

Isolated lesions are often resected with resultant cure. No definite treatment is available for multiple lesions but the prognosis is good with no significant impact on

longevity⁸. In selected patients with pulmonary hyalinizing granuloma who experience disabling symptoms and worsening pulmonary function, a trial of corticosteroids is warranted⁷.

In summary, pulmonary hyalinizing granuloma should be considered in the differential diagnosis of pulmonary nodules. A high index of suspicion with use of lung biopsy would achieve the diagnosis.

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Life Threatening Exacerbation in Idiopathic Pulmonary Hemosiderosis Salvaged by Cyclophosphamide Infusion

Rahul Naithani, Jagdish Chandra, Varinder Singh, Veerendra Kumar and N.K. Dubey

Pulmonary and Critical Care Division, Kalawati Saran Children's Hospital and Lady Hardinge Medical College, New Delhi, India

ABSTRACT

A seven-year-old girl presented with frequent fever, cough and shortness of breath of three months duration. On the basis of her clinical features, peripheral blood and sputum findings, she was diagnosed as a case of idiopathic pulmonary hemosiderosis. After initial stabilisation with steroids and chloroquine, she presented four years later with massive pulmonary hemorrhage and respiratory failure, which responded dramatically to cyclophosphamide infusion. The rare occurrence of pulmonary hemosiderosis and different treatment regimens is discussed. [Indian J Chest Dis Allied Sci 2006; 48: 287-289]

Key words: Hemosiderosis, Exacerbation, Cyclophosphamide, Immunosuppression.

INTRODUCTION

The term pulmonary hemosiderosis describes a number of rare conditions characterised by abnormal accumulation of hemosiderin in lungs. Hemosiderin deposits follow diffuse alveolar hemorrhage and may occur either as primary disease of lung or secondary to cardiac or systemic vascular diseases^{1,2}. Mortality rate for this disease can be as high as 50 percent. Exact etiology is unknown, although it may be associated with immune-mediated mechanisms¹⁻³.

Although high-dose corticosteroids had been the treatment of choice during the acute stage of idiopathic pulmonary hemosiderosis (IPH) to decrease the frequency of pulmonary hemorrhage; the long-term benefit of this treatment is still in doubt^{3,4}. Long-term treatment with steroids, azathioprine, chloroquine and cyclophosphamide, have been instituted in a small number of cases, which have resulted in subsequent remissions³⁻¹¹.

We report a case of IPH with acute severe exacerbation, which was salvaged by cyclophosphamide infusion on two occasions.

CASE REPORT

A seven-year-old girl, who had experienced frequent fever, cough and shortness of breath for three months, was admitted to our hospital in November 1997. She had earlier received three blood transfusions. On

examination, she had pallor, tachypnoea, tachycardia and bilateral diffuse coarse crepitations. Rest of general physical or systemic examination was normal. Laboratory investigations revealed a haemoglobin of 5.6 g/dl; reticulocyte count of 7%, total leukocyte count of 11500/mm³ and a platelet count of 189 × 10³/mm³, normal liver and renal function tests, serum iron 53 µg/dl, total iron binding capacity 310 µg/dl, serum ferritin 108 ng/ml. Peripheral smear showed a dimorphic anemia. Coagulation profile was normal. Stool was negative for occult blood. Mantoux test was negative.

Chest radiograph showed bilateral diffuse alveolar infiltrates with consolidations in the right middle lobe. Electrocardiogram (ECG) showed sinus tachycardia but echocardiography was normal. Computed tomographic (CT) scan of the thorax revealed bilateral diffuse ground glass attenuation, diffuse hazy nodular pattern and patches of consolidation associated with early fibrotic changes (Figure). Microscopic examination of gastric aspirate showed hemosiderin-laden macrophages and was negative for acid-fast bacilli by Ziehl-Neelsen stain.

She was started empirically on antibiotics, hematinics and supportive therapy. After one week of treatment marked improvement was observed and her chest radiograph improved too, but she continued to have mild cough and pigment-laden macrophages persisted in gastric aspirates even after three months. Antinuclear antibody (ANA) was negative and C₃ and C₄ were normal. She was diagnosed as a case of idiopathic pulmonary hemosiderosis. She was started on oral prednisolone (2 mg/kg) and discharged.

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Correspondence and reprint requests: Dr Rahul Naithani, Department of Hematology, First Floor, IRCH Building, All India Institute of Medical Sciences, New Delhi-110029, India; Tele.: 91-11-261915694; Telefax: 91-11-23365792; E-mail: dr_rahul6@hotmail.com.

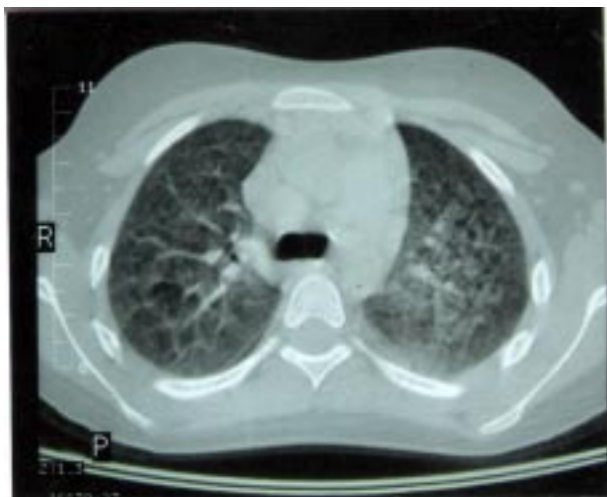


Figure. CT thorax showing bilateral diffuse ground glass attenuation and patches of consolidation with early fibrotic changes.

Her hemoglobin dropped from 13.1g/dl at discharge to 7.5 g/dl in four months. Prednisolone was then stopped and chloroquine, as an immunosuppressant in the dose of 50 mg/day was started. She continued on chloroquine for four years and her average haemoglobin during this period was 9.1 g/dl (7.1–11.9 g/dl). The drug was discontinued for about eight weeks due to deranged liver function tests, which improved to baseline in the said period. During these four years the patient was admitted on three occasions for similar symptoms of cough, shortness of breath, and respiratory distress.

In January 2002 she developed fever and progressive dyspnea. Chest radiograph revealed diffuse bilateral alveolar infiltrates. She was put on oxygen, steroids, intravenous fluids and antibiotics and transfused packed red blood cells but her condition continued to deteriorate. Seventeen hours later she was shifted to intensive care unit and mechanical ventilation was started. Her ventilatory requirements kept on increasing for the next 24 hours and she experienced a bout of pulmonary haemorrhage when it was decided to institute cyclophosphamide infusion in a dose of 2 mg/kg body-weight over one hour. Her condition stabilised in next 28 hours when we started reducing ventilatory settings. She continued to show gradual improvement and could be weaned off the ventilator in next 88 hours and started on supplemental oxygen and saline nebulisation. Pulmonary haemorrhage resolved by third day of cyclophosphamide infusion. She developed spiking fevers after extubation. Tracheal aspirate grew *Klebsiella spp* that was sensitive to ceftazidime; she recovered after institution of appropriate antibiotics. Cyclophosphamide infusion was continued for three days after ventilatory support and later switched to oral cyclophosphamide with prednisolone (2 mg/kg/day). She was discharged on oral antibiotics and alternate day cyclophosphamide (2 mg/kg/day).

She had regular follow-up visits at our hospital. Three weeks later she presented with a low platelet count of 25000/mm³. However, no evidence of petechiae or spontaneous bleeding was found. Platelet counts showed prompt recovery to stoppage of cyclophosphamide for 14 days after which it was reinstated in the same dosage. She was eventually weaned off from both cyclophosphamide and steroid therapy in next nine months.

After 18 months of event-free period, she developed hemoptysis and shortness of breath for which she was re-admitted. At this time the chest radiograph showed diffuse pulmonary infiltrates. During this acute episode cyclophosphamide intravenous infusion (2 mg/kg/day) along with prednisolone was administered from the beginning and her condition was immediately controlled. This time ventilatory support was not required. Cyclophosphamide infusion was continued for eight days. She was discharged on oral cyclophosphamide (2 mg/kg/day) but continued to have mild cough. Three months later chloroquine 150 mg per day was re-started.

During the subsequent year, the disease has stabilised without evidence of progression (e.g., hemoptysis or pulmonary infiltrates). Because of the patient's good response to cyclophosphamide and the chronic course of pulmonary hemosiderosis, we continued with cyclophosphamide (2 mg/kg given every other day) and chloroquine; and closely monitor the disease progression as well as the possible adverse effects of the treatment.

DISCUSSION

In children, the estimated incidence of idiopathic pulmonary hemosiderosis (IPH) is 0.24–1.23 cases per million². It is characterised by accumulation of hemosiderin in lungs following diffuse alveolar hemorrhage. An absolute requirement for the diagnosis is identification of hemosiderin-laden macrophages in sputum or confirmed by flexible fiberoptic bronchoscopy with a bronchoalveolar lavage (BAL) study².

Most therapeutic efforts institute immunosuppressive agents in an attempt to impede the immune responses, however, long-term benefits of such treatments are still debatable. Initial use of high-dose corticosteroids in acute episodes of IPH has proven to decrease the frequency of pulmonary haemorrhage, and is considered the treatment of choice^{1,2}. One series of 23 patients with IPH on long-term, low-dose steroid treatment showed that half of the patients had no relapse after discontinuation of steroids and the remaining cases continued normal life on a low-dose steroid regimen⁹.

Other forms of immunosuppression, such as azathioprine, chloroquine, or cyclophosphamide has been used in patients who fail to respond to steroids or develop unacceptable adverse effects^{3,9}. A 22-year-old

man with a life-threatening IPH experienced prompt and lasting remission of his disease with institution of azathioprine³. After discontinuation of this drug, the patient remained well. Another 8-year-old girl with IPH was successfully treated with prednisolone 1.5 mg/kg/day for 14 years, although her symptoms re-appeared when the dosage of both drugs were tapered⁴. Chloroquine has been shown to have some benefit in two earlier reports^{5, 6}. Our patient also remained in remission for four years with chloroquine after failing to respond to prednisolone before the exacerbation when cyclophosphamide infusion was required.

Cyclophosphamide possesses potent anti-inflammatory and immunosuppressive action. It inhibits both humoral and cell-mediated reactions through unknown mechanisms⁷. Notable advantages of this drug are the availability of oral route of administration and the possibility of giving fractionated doses over a period of time. Cyclophosphamide in IPH has been used in three cases and had been efficacious in controlling the disease with a decreased number of crises⁷. Another series reported beneficial effect in three patients⁸ with cyclophosphamide and prednisone^{7,9}.

Rarity of the disease makes the appropriate dosing regimen difficult. Clinical status and deteriorating ventilatory requirements that improved with cyclophosphamide infusion in our case suggest a beneficial response to drug. Second episode that occurred nine months after stopping the drug suggests prolonged continuation and gradual tapering over a period of time. Although the efficacy of these immunosuppressive agents is important but adverse effects may develop on long-term usage. Various side-effects of cyclophosphamide reported include thrombocytopenia⁹, alopecia, mucosal ulceration, second malignancy, haemorrhagic cystitis, interstitial pulmonary fibrosis, cumulative hepatotoxicity and ovarian

and testicular dysfunction^{7,10}. Fortunately for the patient thrombocytopenia was noticed when it was asymptomatic and improved after temporary discontinuation of drug. A long-term follow-up is required to fully understand the natural history of this disease.

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Book Review

Practical Approach to Critical Respiratory Medicine: Sleep Disorders and Fiberoptic Bronchoscopy

Editor: V.K. Arora; Associate Editor: Raksha Arora; Published by: Jaypee Brothers Medical Publishers Pvt Ltd, New Delhi; Edition: 2006; Paperback; Pages: xx+750+27 colour photograph pages; Price: Rs.995-00; ISBN 81-8061-731-9

The book is aimed mainly at the post-graduate students of pulmonary and critical care medicine and also at busy clinicians. Critical care has evolved into an inseparable part of pulmonary medicine today and there is always a need for compilations that are practically oriented rather than being too theoretical and full of technical jargon. This is the biggest plus point of this book. Further, the addition of sections on sleep disorders and fiberoptic bronchoscopy may be looked upon as a bonus. Inclusion of BTS guidelines on fiberoptic bronchoscopy and ACCP guidelines on interventional pulmonary procedures further strengthens the book.

The book is divided in three sections, covering Critical Respiratory Medicine, Sleep Disorders and Fiberoptic Bronchoscopy. The chapters on critical care medicine cover clinical presentations, diagnostic procedures in ICU, noninvasive and mechanical ventilation and management of specific problems including infection, shock, arrhythmias, ARDS and respiratory failure in asthma and COPD. Several chapters have described the practical aspects of patient monitoring. Problems specific to pediatric population have also been well discussed. The sections on sleep disorders discuss the technical aspects of polysomnography and management of these conditions. The section on bronchoscopy is very informative covering diagnostic as well as interventional aspects. While not forgetting rigid bronchoscopy, newer approaches including virtual bronchoscopy as well as pediatric bronchoscopy have also been presented.

The book draws on the clinical experience of several well-known workers in the field of pulmonary medicine in India. Illustrating the theoretical aspects with clinical case studies is an excellent approach to put across the point. The quality of printing is very good and the illustrations have come out very nicely. Radiographs have been excellently reproduced. The chapters have been well edited to ensure a uniform format that highlights key points through bullets, numbered lists and tables. The book is accompanied by a CD comprising video shots of fiberoptic bronchoscopy, procedures and pictures of various pathological conditions diagnosed on bronchoscopy. This interactive CD will no doubt be appreciated by the computer savvy physicians.

The book aims to familiarize the post-graduate students with the complexities of critical care medicine through an easily readable and informative text. Given that it is a multi-author book, some overlap between chapters was perhaps unavoidable, and also, the depth to which individual topics are covered was bound to be variable. One missed discussion of nutrition, and common medical problems in the ICU such as renal failure, hepatic failure and gastrointestinal hemorrhage. It is hoped that future editions will widen the scope of the book and include all the major problems a pulmonary "intensivist" is likely to come across. The post-graduate students should find the book a very useful introduction to the difficult and challenging area of critical care medicine.

S.K. Chhabra
Associate Editor

Some Forthcoming Scientific Events

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[Venue and Date]

National Conference on Pulmonary Diseases
NAPCON 2006

8th Joint Conference of National College of Chest Physicians (I)
and Indian Chest Society
[Shri Vasant Rao Deshpande Hall, Nagpur:
November 1-5, 2006]

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Scoring System and Clinical Application of COPD Diagnostic Questionnaires

David B. Price, David G. Tinkelman, Robert J. Nordyke, Sharon Isonaka, and R.J. Halbert for the COPD Questionnaire Study Group

Chest 2006; 129: 1531-1539

Objectives. In most primary care settings, spirometric screening of all patients at risk is not practical. In prior work, we developed questionnaires to help identify COPD in two risk groups: (1) persons with a positive smoking history but no history of obstructive lung disease (case finding), and (2) patients with prior evidence of obstructive lung disease (differential diagnosis). For these questionnaires, we now present a scoring system for use in primary care.

Methods. Scores for individual questions were based on the regression coefficients from logistic regression models using a spirometry-based diagnosis of obstruction as the reference outcome. Receiver operator characteristic analysis was used to determine performance characteristics for each questionnaire. Several simplified scoring systems were developed and tested.

Results. For both scenarios, we created a scoring system with two cut points intended to place subjects within one of three zones: persons with a high likelihood of having obstruction (high predictive value of a positive test result); persons with a low likelihood of obstruction (high predictive value of a negative test result); and an intermediate zone. Using these scoring systems, we achieved sensitivities of 54 to 82%, specificities of 58 to 88%, positive predictive values of 30 to 78%, and negative predictive values of 71 to 93%.

Conclusions. These questionnaires can be used to help identify persons likely to have COPD among specific risk groups. The use of a simplified scoring system makes these tools beneficial in the primary care setting. Used in conjunction with spirometry, these tools can help improve the efficiency and accuracy of COPD diagnosis in primary care.

Post-Bronchodilator Spirometry Reference Values in Adults and Implications for Disease Management

Ane Johannessen, Severre Lehmann, Ernst R. Omenaas, Geir Egil Eide, Per S. Bakke, and Amund Gulsvik

The American Journal of Respiratory and Critical Care Medicine 2006; 173: 1316-1325

Rationale. International guidelines promote the use of post-bronchodilator spirometry values in the definition and severity classification of chronic obstructive pulmonary disease. However, post-bronchodilator reference values have not yet been developed.

Objectives. To derive reference values for post-bronchodilator forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC , and to compare these reference values with locally derived and existing pre-bronchodilator reference values.

Methods. Based on a random sample of a general adult population, 2,235 subjects (70% of invited subjects) performed spirometry with reversibility testing. A reference population of healthy never-smokers constituted 23% of the study population (n=515). Reference values for median and lower-limit-of-normal pre- and post-bronchodilator lung function and bronchodilator response were modeled using quantile regression analyses.

Main Results. The reference population had equal proportions of men and women in the age range 26–82 yr. Both FEV_1 and FVC decreased with age and increased with height. FEV_1/FVC decreased with age, although this trend was not statistically significant for men after bronchodilatation. Linear models gave the best overall fit. Lower-limit-of-normal post-bronchodilator FEV_1/FVC exceeded 0.7 for both sexes. Post-bronchodilator prediction equations gave higher predicted FEV_1 and FEV_1/FVC than both locally derived and existing pre-bronchodilator equations. The bronchodilator response decreased with age.

Conclusions. The present study is the first to develop reference values for post-bronchodilator lung function. Post-bronchodilator prediction equations can facilitate better management of patients with chronic obstructive pulmonary disease by avoiding falsely high $FEV_1\%$ predicted with a subsequent underestimation of disease severity.

Effects of Early Intervention with Inhaled Budesonide on Lung Function in Newly Diagnosed Asthma

Paul M. O'Byrne, Soren Pedersen, William W. Busse, Wan C. Tan, Yu-Zhi Chen, Stefan V. Ohlsson, Anders Ullman, Carl Johan Lamm, and Romain A. Pauwels

Chest 2006; 129: 1478-1485

Study Objectives. Asthmatic patients lose lung function faster than normal subjects. The effectiveness of early intervention with inhaled corticosteroids on this decline in lung function is not established in recent-onset disease.

Design. The Inhaled Steroid Treatment as Regular Therapy in Early Asthma study was a randomized, double-blind study in 7,165 patients (5 to 66 years old), with persistent asthma for < 2 years to determine whether early intervention with low-dose inhaled budesonide prevents severe asthma-related events and the decline in lung function. Patients received budesonide (200 µg qd for children < 11 years old and 400 µg qd for others) or placebo for 3 years in addition to usual asthma medications.

Results. Treatment with budesonide significantly improved prebronchodilator and postbronchodilator FEV₁ percentage of predicted and reduced the mean declines from baseline for postbronchodilator FEV₁ at 1 year and 3 years: -0.62% and -1.79% for budesonide and -2.11% and -2.68% for placebo, respectively (p<0.001). The decline was more marked for male patients, active smokers, and patients > 18 years old, and the smallest treatment effects were in adolescents.

Conclusions. Long-term, once-daily treatment with low-dose budesonide improved both prebronchodilator and postbronchodilator FEV₁ in patients with recent-onset, persistent asthma, and reduced the loss of lung function over time.

Carbon in Airway Macrophages and Lung Function in Children

Neeta Kulkarni, Nevil Pierse, Lesley Rushton and Jonathan Grigg

The New England Journal of Medicine 2006; 355: 21-30

Background. Epidemiologic studies indirectly suggest that the inhalation of carbonaceous particulate matter impairs lung function in children. Using the carbon content of airway macrophages as a marker of individual exposure to particulate matter derived from fossil fuel, we sought direct evidence of this association.

Methods. Airway macrophages were obtained from healthy children through sputum induction, and the area of airway macrophages occupied by carbon was measured. Lung function was measured with the use of spirometry. We modeled the exposure to primary particulate matter (PM) that is less than 10 µm in aerodynamic diameter (PM₁₀) at or near each child's home address. Linear regression was used to evaluate associations between carbon content of alveolar macrophages and variables that may affect individual exposure. To determine whether lung function that is reduced for other reasons is associated with an increase in the carbon content of airway macrophages, we also studied children with severe asthma.

Results. We were able to assess the carbon content of airway macrophages in 64 of 114 healthy children (56 percent). Each increase in primary PM₁₀ of 1.0 µg per cubic meter was associated with an increase of 0.10 µm² (95 percent confidence interval, 0.01 to 0.18) in the carbon content of airway macrophages, and each increase of 1.0 µm² in carbon content was associated with a reduction of 17 percent (95 percent confidence interval, 5.6 to 28.4 percent) in forced expiratory volume in one second, of 12.9 percent (95 percent confidence interval, 0.9 to 24.8 percent) in forced vital capacity, and of 34.7 percent (95 percent confidence interval, 11.3 to 58.1 percent) in the forced expiratory flow between 25 and 75 percent of the forced vital capacity. The carbon content of airway macrophages was lower in children with asthma than in healthy children.

Conclusions. There is a dose-dependent inverse association between the carbon content of airway macrophages and lung function in children. We found no evidence that reduced lung function itself causes an increase in carbon content.

Up-Regulated Membrane and Nuclear Leukotriene B4 Receptors in COPD

Emanuela Marian, Simonetta Baraldo, Annalisa Visentin, Alberto Papi, Marina Saetta, Leonardo M. Fabbri and Piero Maestrelli

Chest 2006; 129: 1523-1530

Study Objectives. We investigated the role of two leukotriene B4 (LTB4) receptors, BLT1 and peroxisome proliferator-activated receptor (PPAR)- α , in conferring the susceptibility to develop COPD in smokers. Proinflammatory LTB4 activities are mediated by BLT1, while the inactivation of LTB4 is promoted by PPAR α .

Patients and Methods. BLT1 and PPAR α proteins were quantified by immunohistochemistry in specimens obtained during lung surgery from 19 smokers with or without COPD and from 7 nonsmoking subjects.

Results. We have shown that the percentages of PPAR α -positive alveolar macrophages and PPAR α -positive cells in the alveolar wall were increased in COPD patients compared with control subjects. Moreover, the patients with COPD exhibited a significant increase of BLT1-positive alveolar macrophages compared with nonsmokers and an increased number of BLT1-positive cells in the alveolar

walls compared with non-COPD smokers. In contrast, BLT1 and PPAR α immunoreactivity did not differ significantly between nonsmokers and non-COPD smokers. Most of BLT1-positive cells in the alveolar walls were neutrophils and CD8 cells. While the number of neutrophils infiltrating the lung parenchyma was similar among the three groups, the number of CD8 T cells was increased in COPD patients, but there was no evidence that BLT1 was up-regulated specifically on these cells in COPD patients.

Conclusions. The results demonstrated that BLT1 and PPAR α are detectable in alveolar macrophages and CD8 T cells in human lung tissue, and suggest that the dual LTB4 receptor system is up-regulated in the peripheral lungs of smokers who are susceptible to the development of COPD. This system might represent a novel target for therapeutic intervention in COPD patients.

The Role of Abrams Percutaneous Pleural Biopsy in the Investigation of Exudative Pleural Effusions

Biswajit Chakrabarti, Ida Ryland, John Sheard, Christopher J. Warburton and John E. Earis

Chest 2006; 129: 1549-1555

Introduction. Blind percutaneous pleural biopsy has traditionally been performed to investigate the etiology of exudative pleural effusion in which the initial thoracentesis has been nondiagnostic. In view of the increasing use of image-guided and thoracoscopic pleural biopsies, this study examines the role of blind Abrams pleural biopsy in the investigation of pleural effusion in a large urban hospital.

Methods. Patients undergoing blind Abrams needle biopsy between January 1997 and 2003 were identified from the hospital pathology database. The case notes and pathology records of these patients were analyzed retrospectively. All patients had presented to respiratory teams with an exudative pleural effusion and had initial nondiagnostic thoracentesis.

Results. Seventy-five patients undergoing blind biopsy were identified. Pleural tissue was obtained in 59 biopsies (79%), with no statistically significant difference in pleural yield between respiratory specialist registrars (equivalent to pulmonary fellows in training) and senior house officers/preregistration house officers

(equivalent to junior residents and interns, respectively) performing the biopsy (χ^2 test, $p=0.43$). When up to three samples were obtained per episode, sufficient pleural tissue was obtained in 18 of 25 patients (72%) compared to 80% (32 of 40 patients) in whom four to six samples were taken (χ^2 test, $p=0.55$ [not significant]). For all diagnoses, blind biopsy had a sensitivity of 38%, which rose to 43% when reviewing patients in whom sufficient pleural tissue was obtained (for malignant diagnosis alone, sensitivity values were 43% and 51%, respectively; specificity, 100% negative and positive predictive values, 51%). No fatalities were reported, and pneumothorax was seen in eight patients (11%), with only two patients requiring specific intervention.

Conclusions. Blind Abrams needle biopsy obtaining pleural tissue was diagnostic in approximately 50% of patients presenting with malignant effusion in the sample, and can be performed safely by all grades of medical staff with due attention to technique and supervision. The data support the continued use of the Abrams needle in the investigation of malignant pleural disease.

Cyclophosphamide *versus* Placebo in Scleroderma Lung Disease

Donald P. Tashkin, Robert Elashoff, Philip J. Clements, Jonathan Goldin, Michael D. Roth, Daniel E. Furst, Edgar Arriola, Richard Silver, Charlie Strange, Marcy Bolster, James R. Seibold, David J. Riley, Vivien M. Hsu, John Varga, Dean E. Schraufnagel, Arthur Theodore, Robert Simms, Robert Wise, Fredrick Wigley, Barbara White, Virginia Steen, Charles Read, Maureen Mayes, Kamal Mubarak, M. Kari Connolly, Jeffrey Golden, Mitchell Olman, Barri Fessler, Naomi Rothfield, and Mark Metersky, for the Scleroderma Lung Study Research Group

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Background. We conducted a double-blind, randomized, placebo-controlled trial to determine the effects of oral cyclophosphamide on lung function and health-related symptoms in patients with evidence of active alveolitis and scleroderma-related interstitial lung disease.

Methods. At 13 clinical centers throughout the United States, we enrolled 158 patients with scleroderma, restrictive lung physiology, dyspnea, and evidence of inflammatory interstitial disease on examination of bronchoalveolar-lavage fluid, thoracic high-resolution computed tomography, or both. Patients received oral cyclophosphamide (≤ 2 mg per kilogram of body weight per day) or matching placebo for one year and were followed for an additional year. Pulmonary function was assessed every three months during the first year, and the primary end point was the forced vital capacity (FVC, expressed as a percentage of the predicted value) at 12 months, after adjustment for the baseline FVC.

Results. Of 158 patients, 145 completed at least six months of treatment and were included in the analysis. The mean absolute difference in adjusted 12-month FVC percent predicted between the cyclophosphamide and placebo groups was 2.53 percent (95 percent confidence interval, 0.28 to 4.79 percent), favoring cyclophosphamide ($P < 0.03$). There were also treatment-related differences in physiological and symptom outcomes, and the difference in FVC was maintained at 24 months. There was a greater frequency of adverse events in the cyclophosphamide group, but the difference between the two groups in the number of serious adverse events was not significant.

Conclusions. One year of oral cyclophosphamide in patients with symptomatic scleroderma-related interstitial lung disease had a significant but modest beneficial effect on lung function, dyspnea, thickening of the skin, and the health-related quality of life. The effects on lung function were maintained through the 24 months of the study.

Prospective Study of the Diagnostic Accuracy of the Simplify D-dimer Assay for Pulmonary Embolism in Emergency Department Patients

Jeffrey A. Kline, Michael S. Runyon, William B. Webb, Alan E. Jones, and Alice M. Mitchell

Chest 2006; 129: 1417-1423

Objective. To determine if a d-dimer assay (Simplify D-dimer; Agen Biomedical; Brisbane, Australia) can reliably exclude pulmonary embolism (PE) by producing a posttest probability of PE $< 1\%$ in low-risk, symptomatic emergency department (ED) patients.

Methods. Hemodynamically stable patients were evaluated for PE using a structured d-dimer centered protocol; d-dimer testing was performed prior to imaging. Prior to testing, physicians completed an electronic data form that included their unstructured clinical estimate for the pretest probability of PE ($< 15\%$, 15 to 40%, or $> 40\%$) and the elements of the Charlotte

rule and Canadian score for PE. Criterion standard was selective use of pulmonary vascular imaging and 90-day follow-up.

Results. We enrolled 2,302 patients (mean age, 45 ± 16 years [\pm SD]; 31% male); 108 patients received a diagnosis of PE (4.7%; 95% confidence interval [CI], 3.6 to 5.6%). The overall sensitivity and specificity of the d-dimer assay were 80.6% (95% CI, 71.8 to 87.5%) and 72.5% (95% CI, 70.6 to 74.4%), respectively. The negative likelihood ratio and negative predictive value were 0.27 (95% CI, 0.18 to 0.39) and 98.7% (95% CI, 98.0 to 99.1%), respectively. The posttest prevalence of PE among low-

risk patients with negative d-dimer results was 0.7% (95% CI, 0.3 to 1.4%) for the unstructured estimate, 1.2% (95% CI, 0.7 to 2.0%) for the Canadian score, and 1.1% (95% CI, 0.6 to 1.7%) for the Charlotte rule.

Conclusions. The simplify d-dimer assay had moderate

sensitivity and relatively high specificity for PE in low-risk ED patients. The combination of a physician's unstructured estimate of pretest probability of PE of < 15% and a negative d-dimer result produced a posttest probability of PE of 0.7% (95% CI, 0.3 to 1.4%).

Multidetector Computed Tomography for Acute Pulmonary Embolism

Paul D. Stein, Sarah E. Fowler, Lawrence R. Goodman, Alexander Gottschalk, Charles A. Hales, Russell D. Hull, Kenneth V. Leeper Jr, John Popovich Jr, Deborah A. Quinn, Thomas A. Sos, Dirk Sostman, Victor F. Tapson, Thomas W. Wakefield, John G. Weg, and Pamela K. Woodard, for the PIOPED II Investigators

The New England Journal of Medicine 2006; 354: 2317-27

Background. The accuracy of multidetector computed tomographic angiography (CTA) for the diagnosis of acute pulmonary embolism has not been determined conclusively.

Methods. The Prospective Investigation of Pulmonary Embolism Diagnosis II trial was a prospective, multicenter investigation of the accuracy of multidetector CTA alone and combined with venous-phase imaging (CTA-CTV) for the diagnosis of acute pulmonary embolism. We used a composite reference test to confirm or rule out the diagnosis of pulmonary embolism.

Results. Among 824 patients with a reference diagnosis and a completed CT study, CTA was inconclusive in 51 because of poor image quality. Excluding such inconclusive studies, the sensitivity of CTA was 83 percent and the specificity was 96 percent. Positive

predictive values were 96 percent with a concordantly high or low probability on clinical assessment, 92 percent with an intermediate probability on clinical assessment, and nondiagnostic if clinical probability was discordant. CTA-CTV was inconclusive in 87 of 824 patients because the image quality of either CTA or CTV was poor. The sensitivity of CTA-CTV for pulmonary embolism was 90 percent, and specificity was 95 percent. CTA-CTV was also nondiagnostic with a discordant clinical probability.

Conclusions. In patients with suspected pulmonary embolism, multidetector CTA-CTV has a higher diagnostic sensitivity than does CTA alone, with similar specificity. The predictive value of either CTA or CTA-CTV is high with a concordant clinical assessment, but additional testing is necessary when the clinical probability is inconsistent with the imaging results.

Major Congenital Malformations after First-Trimester Exposure to ACE Inhibitors

William O. Cooper, Sonia Hernandez-Diaz, Patrick G. Arbogast, Judith A. Dudley, Shannon Dyer, Patricia S. Gideon, Kathi Hall, and Wayne A. Ray

The New England Journal of Medicine 2006; 354: 2443-51

Background. Use of angiotensin-converting-enzyme (ACE) inhibitors during the second and third trimesters of pregnancy is contraindicated because of their association with an increased risk of fetopathy. In contrast, first-trimester use of ACE inhibitors has not been linked to adverse fetal outcomes. We conducted a study to assess the association between exposure to ACE inhibitors during the first trimester of pregnancy only and the risk of congenital malformations.

Methods. We studied a cohort of 29,507 infants enrolled in Tennessee Medicaid and born between 1985 and 2000 for whom there was no evidence of maternal diabetes. We identified 209 infants with exposure to ACE inhibitors in the first trimester alone, 202 infants with exposure to other antihypertensive medications in the first trimester alone, and 29,096 infants with no exposure to antihypertensive drugs at any time during gestation. Major congenital malformations were

identified from linked vital records and hospitalization claims during the first year of life and confirmed by review of medical records.

Results. Infants with only first-trimester exposure to ACE inhibitors had an increased risk of major congenital malformations (risk ratio, 2.71; 95 percent confidence interval, 1.72 to 4.27) as compared with infants who had no exposure to antihypertensive medications. In contrast, fetal exposure to other antihypertensive medications during only the first

trimester did not confer an increased risk (risk ratio, 0.66; 95 percent confidence interval, 0.25 to 1.75). Infants exposed to ACE inhibitors were at increased risk for malformations of the cardiovascular system (risk ratio, 3.72; 95 percent confidence interval, 1.89 to 7.30) and the central nervous system (risk ratio, 4.39; 95 percent confidence interval, 1.37 to 14.02).

Conclusions. Exposure to ACE inhibitors during the first trimester cannot be considered safe and should be avoided.

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begin on a new page: title page; abstract; introduction; references; legends; tables.

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VII. *Acknowledgements.* Acknowledgement should be brief and made specific for scientific/technical assistance and financial supports in the form of grants/drugs/equipment only and for not providing routine departmental facilities and for help in the preparation of manuscript (including typing/secretarial assistance).

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Articles in Journals

1. *Standard journal article*

Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. *N Engl J Med* 2002; 347: 284-7.

More than six authors:

Rose ME, Huerbin MB, Melick J, Marion DW, Palmer AM, Schiding JK, *et al*. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. *Brain Res* 2002; 935 (1-2): 40-6.

2. *Article published electronically ahead of the print version*

Yu WM, Hawley TS, Hawley RG, Qu CK. Immortalization of yolk sac-derived precursor cells. *Blood* 2002 Nov 15; 100(10): 3828-31. Epub 2002 July 5.

3. *Volume with supplement*

Geraud G, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short-and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; 42 Suppl 2: S93-9.

4. *Issue with supplement*

Glauser TA. Integrating clinical trial data into clinical practice. *Neurology* 2002; 58 (12 Suppl 7): S6-12.

5. *Type of article indicated as needed*

Tor M, Turker H. International approaches to the prescription of long-term oxygen therapy [letter]. *Eur Respir J* 2002; 20(1): 242.

Lofwall MR, Strain EC, Brooner RK, Kindbom KA, Bigelow GE. Characteristics of older methadone maintenance (MM) patients [abstract]. *Drug Alcohol Depend* 2002; 66 Suppl 1: S105.

6. *Volume with part*

Abend SM, Kulish N. The psychoanalytic method from an epistemological viewpoint. *Int J Psychoanal* 2002; 83 (Pt 2): 491-5.

7. *Issue with part*

Ahrar K, Madoff DC, Gupta S, Wallace MJ, Price RE, Wright KC. Development of a large animal model for lung tumours. *J Vasc Interv Radiol.* 2002; 13(9 Pt 1): 923-8.

8. *Issue with no volume*

Banit DM, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop* 2002; (401): 230-8.

9. *No volume or issue*

Outreach: bringing HIV-positive individuals into care. *HRSA Careaction* 2002 Jun: 1-6.

10. *Pagination in roman numerals*

Chadwick R, Schuklenk U. The politics of ethical consensus finding. *Bioethics* 2002; 16(2): iii-v.

11. *Organization as author*

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; 40(5): 679-86.

12. *Both personal authors and an organization as author* (This example does not conform to NISO standards).

Vallancien G, Emberton M, Harving N, van Moorselaar RJ, Alf-One Study Group. Sexual dysfunction in 1,274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; 169(6): 2257-61.

13. *No author given*

21st century heart solution may have a sting in the tail. *BMJ* 2002; 325(7357): 184.

14. *Article containing retraction*

Feifel D, Moutier CY, Perry W. Safety and tolerability of a rapidly escalating dose-loading regimen for risperidone. *J Clin Psychiatry* 2002; 63(2): 169. Retraction of: Feifel D, Moutier CY, Perry W. *J Clin Psychiatry* 2000; 61(12): 909-11.

15. *Article retracted*

Feifel D, Moutier CY, Perry W. Safety and tolerability of a rapidly escalating dose-loading regimen for risperidone. *J Clin Psychiatry* 2000; 61(12): 909-11. Retraction in: Feifel D, Moutier CY, Perry W. *J Clin Psychiatry* 2002; 63(2): 169.

16. *Article republished with corrections*

Mansharamani M, Chilton BS. The reproductive importance of P-type ATPases. *Mol Cell Endocrinol* 2002; 188(1-2): 22-5. Corrected and republished from: *Mol Cell Endocrinol* 2001; 183(1-2): 123-6.

17. *Article with published erratum*

Malinowski JM, Bolesta S. Rosiglitazone in the treatment of type 2 diabetes mellitus: a critical review. *Clin Ther* 2000; 22(10): 1151-68; discussion 1149-50. Erratum in : *Clin Ther* 2001; 23(2): 309.

18. *Article not in English*

(Note: NLM translates the title into English, encloses the translation in square brackets, and adds an abbreviated language designator.)

Ellingsen AE, Wilhelmsen I. *Sykdomsangst blant medisiner- og jusstudenter. Tidsskr Nor Laegeforen* 2002; 122(8): 785-7.

Personal Communication

Name of the person and date of communication should be cited in parentheses in the text. For scientific articles, authors should obtain written permission and confirmation of accuracy from the source of a personal communication.

Unpublished Material19. *In press*

(Note: NLM prefers "forthcoming" because not all items will be printed.)

Tian D, Araki H, Stahl E, Bergelson J, Kreitman M. Significance of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA*. In press 2002.

Books and Other Monographs20. *Chapter in a book*

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumours. In: Vogelstein B, Kinzler KW, editors. *The Genetic Basis of Human Cancer*. New York: McGraw-Hill. 2002; pp 93-113.

21. *Conference paper*

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In : Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: *Proceedings of the 5th European Conference on Genetic Programming*; 2002 Apr 3-5; Kinsdale Ireland. Berlin: Springer.

2002; pp 182-91.

22. *Personal author(s)*

Murray PR, Rosenthal KS, Kobayashi GS, Pfaffler MA. *Medical Microbiology*; 4th ed. St. Louis: Mosby. 2002.

23. *Editor(s), compiler(s) as author*

Gilstrap LC (3rd), Cunningham FG, VanDorsten JP, editors. *Operative Obstetrics*. 2nd ed. New York: McGraw-Hill. 2002.

24. *Author(s) and editor(s)*

Breedlove GK, Schorfheide AM. *Adolescent Pregnancy*. 2nd ed. Wicczorek RR, editor. White Plains (NY): March of Dimes Education Services; 2001.

25. *Organization(s) as author*

Royal Adelaide Hospital; University of Adelaide, Department of Clinical Nursing. *Compendium of Nursing Research and Practice Development, 1999-2000*. Adelaide (Australia): Adelaide University; 2001.

26. *Conference proceedings*

Harnden P, Joffe JK, Jones WG, editors. Germ cell tumours V. *Proceedings of the 5th Germ Cell Tumour Conference*; 2001 Sep 13-15; Leeds, UK. New York: Springer; 2002.

27. *Scientific or technical report*

Issued by funding/sponsoring agency:

Yen GG (Oklahoma State University, School of Electrical and Computer Engineering, Stillwater, OK). Health monitoring on vibration signatures. Final report. Arlington (VA): Air Force Office of Scientific Research (US), Air Force Research Laboratory; 2002 Feb. Report No.: AFRLSRBLTR020123. Contract No.: F496209810049.

Issued by performing agency:

Russell ML, Goth-Goldstein R, Apte MG, Fisk WJ. Method for measuring the size distribution of airborne Rhinovirus. Berkeley (CA): Lawrence Berkeley National Laboratory, Environmental Energy Technologies Division; 2002 Jan. Report No.: LBNL49574. Contract No.: DEAC0376SF00098. Sponsored by the Department of Energy.

28. *Dissertation*

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

29. *Patent*

Pegedas AC, inventor; Ancel Surgical R& D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1.

Other Published Material

30. Newspaper article

Tynan T. Medical improvements lower homicide rate: study sees drop in assault rate. *The Washington Post*. 2002 Aug 12; Sect. A:2 (col. 4).

31. Audiovisual material

Chason KW, Sallustio S. Hospital preparedness for bioterrorism [videocassette]. Secaucus (NJ): Network for Continuing Medical Education; 2002.

32. Legal Material

Public law:

Veterans Hearing Loss Compensation Act of 2002, Pub.L.No. 107-9, 115 Stat. 11 (May 24, 2001).

Unenacted bill:

Healthy Children Learn Act, S. 1012, 107th Cong., 1st Sess. (2001).

Code of Federal Regulations:

Cardiopulmonary Bypass Intracardiac Suction Control, 21 C.F.R. Sect. 870.4430 (2002).

Hearing:

Arsenic in Drinking Water: An Update on the Science, Benefits and Cost: Hearing Before the Subcomm. on Environment, Technology and Standards of the House Comm. on Science, 107th Cong., 1st Sess. (Oct. 4, 2001).

33. Map

Pratt B, Flick, P, Vynne C, cartographers. Biodiversity hotspots [map]. Washington: Conservation International; 2000.

34. Dictionary and similar references

Dorland's Illustrated Medical Dictionary. 29th ed. Philadelphia: W.B. Saunders; 2000. Filamin; p. 675.

Electronic Material

35. CD-ROM

Anderson SC, Poulsen KB. *Anderson's Electronic Atlas of Hematology* [CD-ROM]. Philadelphia: Lippincott Williams & Wilkins; 2002.

36. Journal article on the Internet

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. *Am J Nurs* [serial on the Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6) : [about 3 p.]. Available from: <http://www.nursingworld.org/AJN/2002/june/Wawatch.htm>

37. Monograph on the Internet

Foley KM, Gelband H, editors. Improving palliative care for cancer [monograph on the Internet]. Washington: National Academy Press; 2001 [cited 2002 Jul 9]. Available from: <http://www.nap.edu/books/0309074029/html/>.

38. Homepage/Web site

Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: <http://www.cancer-pain.org/>.

39. Part of a homepage/Web site

American Medical Association [homepage on the Internet]. Chicago: The Association; c1995-2002 [updated 2001 Aug 23; cited 2002 Aug 12]. AMA Office of Group Practice Liaison; [about 2 screens]. Available from: <http://www.ama-assn.org/ama/pub/category1736.html>.

40. Database on the Internet

Open database:

Who's Certified [database on the Internet]. Evanston (IL): The American Board of Medical Specialists. c2000- [cited 2001 Mar 8]. Available from: <http://www.abms.org/newsearch.asp>

Closed database:

Jablonski S. Online Multiple Congenital Anomaly/Mental Retardation (MCA/MR) Syndromes [database on the Internet]. Bethesda (MD): National Library of Medicine (US). c1999 [updated 2001 Nov 20; cited 2002 Aug 12]. Available from: http://www.nlm.nih.gov/mesh/jablonski/syndrome_title.html

41. Part of a database on the Internet

MeSH Browser [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2002 - [cited 2003 Jun 10]. Meta-analysis; unique ID: D015201; [about 3 p.]. Available from: <http://www.nlm.nih.gov/mesh/MBrowser.html> Files updated weekly.

MeSH Browser [database on the Internet]. Bethesda (MD): National Library of Medicine (US); 2002 - [cited 2003 Jun 10]. Meta-analysis; unique ID: D015201; [about 3 p.]. Available from: <http://www.nlm.nih.gov/mesh/MBrowser.html> Files updated weekly.

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