

Mediastinal Gray Zone Lymphoma

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Abstract

A 50-year-old male presented with cough and breathlessness. A positron emission tomography scan revealed FDG (Fluorodeoxyglucose) avid mediastinal mass. Tru-cut biopsy showed fibrotic stromal tissue with cellular infiltrate consisting of abnormal lymphoid cells and few large cells with smudged nucleus. Immunohistochemistry revealed diffuse positivity with CD20, focal positivity for CD30 and rare CD15 positive cells. Histological picture and immune profile showed overlapping features of non-Hodgkin's as well as Hodgkin's lymphoma. A diagnosis of mediastinal gray zone lymphoma was made. The patient showed a complete metabolic response to six cycles of chemotherapy.

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Key words: Mediastinal gray zone lymphoma, Non-Hodgkin's large B-cell lymphoma, Hodgkin's lymphoma, Overlapping features.

Introduction

Lymphomas are classified on the basis of clinical features, morphology, immune phenotypic profile along with molecular genetic studies, whenever indicated. However, it has been observed that certain cases have overlapping features and it is not possible to assign them into a specific group. The term 'gray zone lymphoma', was first used in 1998, at a workshop on Hodgkin's disease and related disorders, to designate lymphomas at the border of classical Hodgkin's and other entities.¹

We describe a case of mediastinal mass with features between Hodgkin's and primary mediastinal large B-cell lymphoma.

Case Report

A 50-year-old male presented with a history of cough and breathlessness of four months duration. A positron emission tomography-computed tomography (PET-CT) scan revealed a large enhancing lobulated FDG (Fluorodeoxyglucose) avid anterior mediastinal mass measuring 10cmx7cmx6.5cm encasing the mediastinal vessels, infiltrating the pericardium and the left chest wall with extension till the supra-clavicular region along with FDG avid bilateral pulmonary nodules and pleural effusion (Figure 1A). Serum tumour markers, i.e. LDH (lactodehydrogenase), AFP (alpha-fetoprotein), β -HCG (beta-human chorionic gonadotropin) were normal. Pleural fluid cytology revealed blood and inflammatory cells. Bone marrow aspiration and biopsy showed a normal bone marrow.

On microscopic examination, the tru-cut biopsy from

the mediastinal mass showed cellular infiltrate in fibrotic stromal tissue. The cells were mildly pleomorphic and showed indentation of the nuclear membrane with minimal cytoplasm. Clear cytoplasm was seen in cells in focal areas. Few large cells with smudged nucleus or prominent nucleoli were also present (Figure 1B). Immunohistochemical staining revealed strong diffuse CD20 positivity (Figure 1C). Large cells showed positivity with CD30 as well as CD20 (Figure 1D). Rare CD15 positive cells were present. Few reactive CD3 positive cells were also seen. Staining for cytokeratin and CD10 was negative. Ki67 index was 15%.

The histological picture had overlapping features of Hodgkin's as well as non-Hodgkin's lymphoma. In view of the strong CD20 (B-cell marker) positivity along with CD30 positivity and rare cells showing CD15 positivity, a diagnosis of mediastinal gray zone lymphoma was made. The patient was subsequently treated with rituximab and CHOP based chemo-immunotherapy (rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m², prednisolone 40 mg/m²) and completed six cycles. He showed a complete metabolic response. He subsequently completed radiation therapy to the mediastinum.

Discussion

The World Health Organization 2008 classification introduced two new categories, i.e. (1) B-cell lymphoma, unclassifiable with features intermediate between diffuse large B-cell lymphoma (DLBCL) and classical

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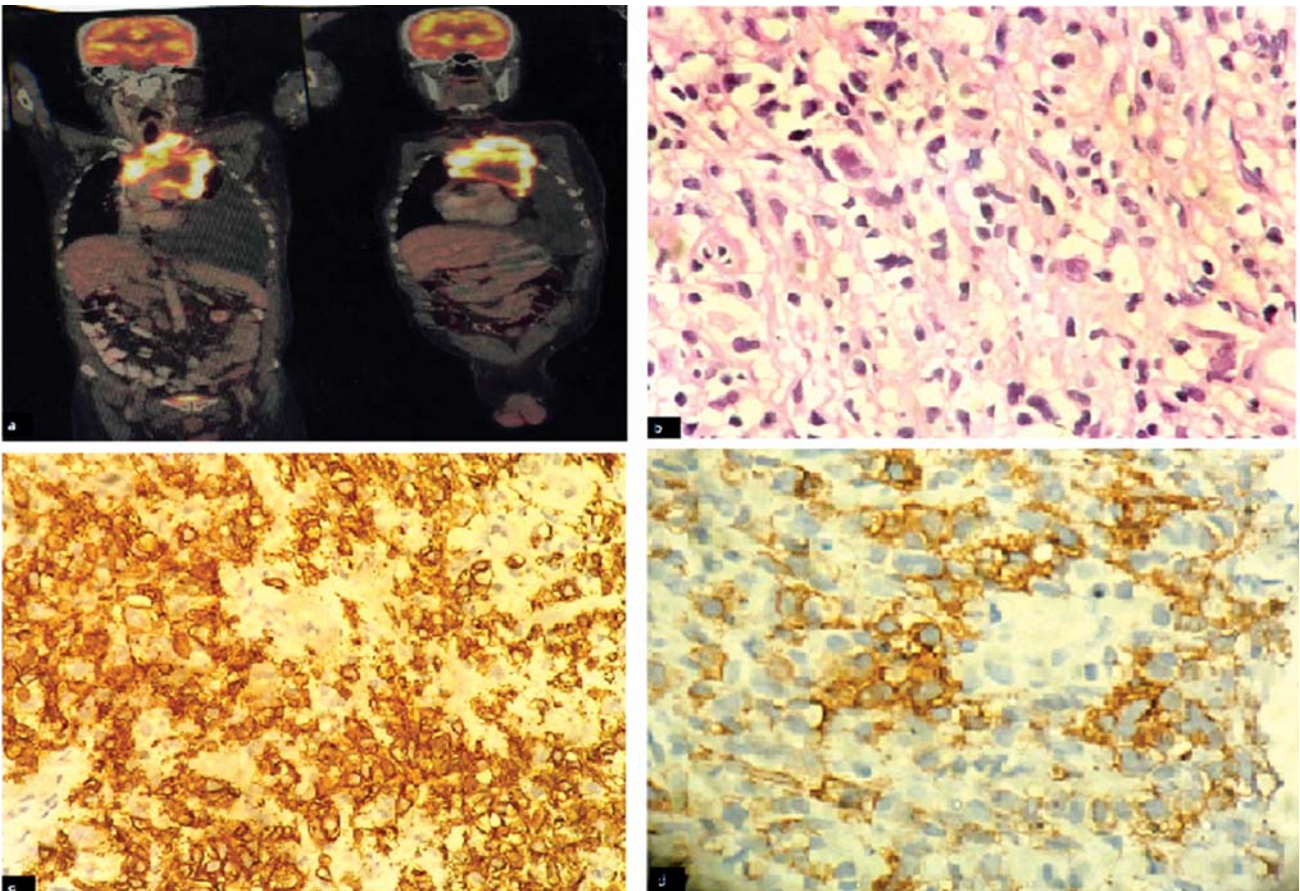


Figure 1. (A) PET scan showing FDG avid lesion in anterior mediastinum; (B) Cellular infiltrate showing lymphoid cells with convoluted nucleus and large abnormal cells with prominent nucleolus in dense sclerotic tissue (Haematoxylin and Eosin, $\times 400$); (C) Diffuse CD20 positivity seen in cells (Immunohistochemistry, $\times 400$) and (D) CD30 positivity in large cells (Immunohistochemistry, $\times 200$)

Hodgkin's lymphoma (CHL); and (2) B-cell lymphoma unclassifiable with features between Burkitt's lymphoma and DLBCL.² The term gray zone lymphoma (GZL) has been applied to tumours that demonstrate transitional morphology between CHL and DLBCL, especially primary mediastinal large B-cell lymphoma (PMBL).³

Primary mediastinal large B-cell lymphoma has certain characteristics that differ from DLBCL and are closer to CHL. Morphological features of PMBL similar to CHL include broad band of fibrosis, presence of Sternberg like cells and CD30 positivity, although weak.^{4,5} However, strong and uniform B-cell associated antigens positivity is seen in PMBL indicative of its being a B-cell lymphoma. Unlike DLBCL, surface immunoglobulins are not expressed in PMBL and these are also absent in CHL. Immunoglobulin transcription factor OCT2 and BOB1 are maintained in PMBL and may be absent in CHL.⁴ Molecular signature of PMBL differs from DLBCL and shares features with CHL. These include gain a 2p15 (REL locus) and 9p24.1 (JAK2 locus), activation of cytokine JAK-STAT pathway and rearrangement of (CIITA locus).^{4,6} Primary mediastinal large B-cell lymphoma is

associated with favourable survival as compared to DLBCL.⁵

Primary mediastinal large B-cell lymphoma and CHL nodular sclerosis subtype have a number of clinical characteristics in common. Both tend to present anterior mediastinal mass in the third to fourth decade of life with a female predominance. Superior vena cava syndrome is seen frequently in PMBL, but it is much less common in CHL.

A small proportion of mediastinal lymphomas can not be classified and have characteristics of both PMBL and CHL. These are termed as mediastinal gray zone lymphomas (MGZL). Cases morphologically resembling CHL with strong positivity for B-cell markers or cases with morphology of PMBL and strong expression for CD15 or the presence of Epstein-Barr Virus (EBV) are included in this group.² Gray zone lymphoma usually present with mediastinal manifestations, but also include occasional cases involving non-mediastinal lymph node sites. Involvement of lung, spleen and bone marrow is documented.⁶ Mediastinal GZL are more frequent in young men, have more aggressive clinical course and poor outcome than CHL or PMBL.⁶ The tru-cut biopsy of

mediastinal mass in our patient had overlapping histological features. Strong CD20 positivity and CD30 positivity along with occasional large cells with CD15 positivity favoured a diagnosis of mediastinal GZL.

Holler *et al*⁷ have suggested high sensitivity of positive staining with p63 for PMBL and cyclinE for CHL. However, Eberle *et al*³ concluded that p63 and cyclinE do not help to differentiating GZL into well-defined categories, such as PMBL and CHL.³

Cases with intermediate features between PMBCL and CHL support a possible continuum spectrum between PMBL and CHL. Deoxyribonucleic acid methylation studies of micro-dissected tumour cells from MGZL showed distinct epigenetic profile intermediate between CHL and PMBCL but markedly different from DLBCL validating its inclusion as separate disease.⁸

Therapeutic management for these cases is difficult as CHL and PMBL require different therapies. A prospective study of 16 patients with GZL treated with the DA-EPOCH-R regimen (Dose-adjusted etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone, rituximab), despite clinical characteristics similar to those of the PMBL cohort had a significantly inferior event-free survival (45%) and overall survival 75% at a median follow-up of four years, and 37% required consolidation mediastinal radiation. In comparison in PMBL, the event-free survival was 95% and overall survival was 100%. Only two patients required consolidation radiation treatment, and none of the patients had relapsed.⁹ The inferior response of GZL may be due to bulky disease at presentation with extensive necrosis and poor vascularisation.¹⁰

Currently for MGZL, DA-EPOCH-R (continuous infusion etoposide, vincristine and doxorubicin for four days along with rituximab on day 1 and cyclophosphamide on day 5) regimen followed by radiation is the most reasonable treatment strategy in CD20 positive as well as CD20 negative cases.^{9,10} The autologous stem cell therapy aims at stimulating yield of stem cell in peripheral blood by granulocyte colony stimulating factor at times with plerixafer.¹¹ The autologous stem cells are given to the patients along with high doses of chemotherapy to achieve complete cancer cell kill to minimise unwanted effects of high dose therapy.¹² Relapse of the disease is generally seen at 6-12 months and is extremely rare after two years. Autologous stem cell transplant is generally employed on relapse of the disease. The chemoresponsiveness to salvage regimens predicts the overall outcome after autologous stem cell transplant. Our patient was treated with R-CHOP followed by radiation therapy and has showed a good response.

Diagnostic criteria and therapeutic response in large series of such patients needs documentation for establishing therapeutic management of these cases.

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