

Primary Mediastinal Large B-Cell Lymphoma in A 26-Year Old Female

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Background --- Primary mediastinal large B-cell lymphoma (PMLBL) is a diffuse type of large B-cell lymphoma arising putatively from the thymus and is rare.

Case --- This is a case of a 26 year old with a chief complaint of easy fatigability. CT-scan revealed an anterior mediastinal mass in keeping with thymoma. Debulking procedure through sternotomy was done. Frozen section, routine histopathology and immunohistochemical studies were performed. Post-operative chemotherapy afforded resolution of the mass.

Results --- Histopathologic evaluation including a frozen section revealed a tumor composed of medium to large cells set in a fibrovascular stroma. It shows distinct fibrosis made up of an irregular broad collagen bands forming nodules, and within nodules, compartmentalized cellular areas are seen. The tumor cells overran adjacent fibrous tissues and adipose tissues. Cytoplasmic clearing is observed similar to cells in dysgerminoma. There were geographic areas of necrosis. The touch imprints favor features of lymphoid cells than epithelial cells. Immunohistochemistry (IHC) using LCA and CD20 showed intense reactivity in both the medium to large cells which were negative for cytokeratin, CD 30 and CD 15. This immunophenotype including the H&E and cytomorphology were in keeping with a primary mediastinal large B-cell lymphoma. Short of flow cytometry, the differential diagnosis is a diffuse large cell lymphoma arising from lymph nodes.

Conclusion --- Lymphoid malignancy in the anterior mediastinum may share radiologic findings similar with malignant thymoma. CT-guided FNA may obtain only necrotic and fibrotic material and a definite diagnosis may not be arrived at. Tissue confirmation thus would be crucial either through a mediastinoscopy or as is in this case, a debulking procedure. Differentiating a primary lymphoma arising from the thymus, from a lymphoma of nodal origin can be discerned if the morphology is classic and in the absence of lymphadenopathies as seen in our case. Immunophenotyping through flow cytometry will be confirmatory. *Phil Heart Center J 2008; 14(1):84-91.*

Key Words: Lymphoma, mediastinal tumors ■ Primary Mediastinal Large B Cell Lymphoma ■ lymphoid tumor cells, immunostaining

The principal primary neoplasms of the anterior mediastinum are thymoma, Hodgkin disease (50-70% of mediastinal lymphoma), and non-Hodgkin lymphomas (15-25% of mediastinal lymphoma) and germ cell tumors. Primary mediastinal large B-cell lymphoma (PMLBCL) has a relatively short history in the written literature. Its description appeared in the 1980's, and it was included in the Revised European-American Lymphoma (REAL) classification as PMLBL in 1994.¹ PMLBCL is a rare entity, accounting for 2-3% of non-Hodgkin's lymphoma (NHL) arising from thymic mature B cells.² It is thought by some to be a distinct disease entity, and it is reported to occur characteristically in young females with a bulky mediastinal mass and low-stage disease.

Clinical features that are associated with PMLBCL include pleural and pericardial effusions, superior vena cava syndrome, elevated serum lactate dehydrogenase level, and a tendency to relapse in unusual sites.³ The histologic features that have been associated with PMLBCL include (1) a diffuse proliferation of medium to large transformed B-cells, which are often devoid of surface immunoglobulin; (2) abundant clear cytoplasm; and (3) areas of sclerosis.⁴ However, the various reported series indicate that these histologic features are inconsistent and that PMLBCL actually consists of a group of lymphomas with rather heterogeneous morphology, including diffuse mixed-cell, diffuse large-cell, and immunoblastic types.⁵

When PMLBCL has an extensive involvement of

Accepted paper for PHC 16th Annual research Paper Competition 2008 and for 38th PHA Annual Convention held on May 2008 at Edsa Shangrila Hotel, Philippines

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mediastinal structures, it may be difficult to distinguish clinically from malignant thymomas. We report a case of an anterior mediastinal mass from a young female with no known lymphadenopathy elsewhere and have classic histologic and cytologic features of PMLBCL.

Case History

A 26-year old female was admitted to a tertiary hospital due to shortness of breath. The condition started one month prior to admission (PTA), when patient had experienced easy fatigability on ordinary physical activity. No consultation or medication was taken. Three weeks PTA, the condition persisted, this time with associated non-productive cough, low grade fever, upper back pain and two-pillow orthopnea. The patient self-medicated with a single dose of azithromycin, but noted no improvement of her condition. One week PTA, she experienced severe shortness of breath. She was brought to a tertiary hospital where patient was admitted. Chest CT-scan showed a largely lobulated, heterogeneously contrast-enhancing mediastinal mass that is in keeping with thymoma, with features favoring locally invasive behavior. There was no noted enlarged lymph nodes but there was moderate left sided pleural effusion (Figure 1). CT-scan guided fine needle aspiration biopsy showed necrosis, fibrous tissue, a few round and spindle cells, and was signed out as suggestive of thymoma. She was then referred to this institution. Upon admission, patient was conscious, coherent, not in distress with the following vital signs: BP=110/70; CR=78/min; RR=18/min; T=37.5C. The rest of her physical examination was unremarkable. Due to her symptoms, a debulking procedure was in order. Intraoperatively, the tumor was described to surround the great vessels, involved the entire pericardium and infiltrated the anterior chest wall structures. There was moderate pericardial effusion amounting to about 50 ml of serous fluid. Through a sternotomy, debulking of the mediastinal mass was done on the third hospital day with an uneventful post-operative course. One-fifth of the tumor mass was removed and was sent for frozen section, routine histopathology and immunohistochemistry. Frozen section diagnosis was small round cell tumor, lymphoma versus malignant thymoma. Post-operatively, she responded to chemotherapy. Repeat CT-scan of the chest and whole abdomen after 4 cycles of chemotherapy showed a significant regression in the size and mass effect of the mediastinal mass measuring 7.5 cm from a previous 12 cm. Currently, there is very minimal evidence of the mass radiographically.

Histopathologic Evaluation Gross Examination

The specimen was submitted in several parts and consisted of fragments of tan-yellow to brown, soft to fleshy, irregular tissue entirely measuring 25.2 x 16.8 x 6.0 cm. Cut section shows tan-yellow to brown, soft, homogenous tissue with vague nodularity (Figure 2).

Microscopic Examination

The specimen shows distinct fibrosis made up of an irregular collagen bands compartmentalizing cellular areas (Figure 3). The tumor is composed of medium to large lymphoid cells set in a fibrovascular stroma (Figure 4). The lymphoid tumor cells overrun adjacent fibrous tissue and adipose tissue in places thereby forming nodules. Touch imprint stained with Diff Quik shows numerous medium to large hematopoietic cells with many degenerated cells and karyoexesis (Figure 5). The individual cells have abundant clear cytoplasm & pleomorphic round or ovoid nuclei with inconspicuous nucleoli. Abundant necrosis and mitotic figures are noted.

Immunohistochemistry

This is a method for localizing specific antigens in tissues or cells based on antigen-antibody recognition; it seeks to exploit the specificity provided by the binding of an antibody with its antigen at light microscopic level.[6] In this study, IHS were undertaken to further confirm the diagnosis. The following were requested: LCA (CD45) and CK (Figure 6); CD20 and CD3 (Figure 7); CD30 and CD15(Figure 8).

Leukocyte Common Antigen (LCA/CD45)

It is useful in identifying most lymphomas, except roughly 30% of Anaplastic Large Cell Lymphoma (ALCL). CD45 is a membrane protein tyrosine phosphatase found in all leukocytes (white blood cells) in a number of isoforms.

CD20

It is strongly positive on approximately half of lymphoblastic lymphoma-leukemias, almost all mature B-cell lymphomas (except plasma cell lesions), Reed-Sternberg cells in roughly one quarter of the cases of classic Hodgkin disease and almost no T-cell lymphomas. The CD20 epitope is acquired late in the pre-B cell stage of maturation & remains on cells throughout most of their differentiation, although it is lost at the plasma cell stage.

CD3

It is very specific for T-cell derivation. The T-cell antigen receptor binds to the CD3 protein complex at

the cell membrane.

Cytokeratin

This family of intermediate filaments is crucial in diagnostic IHS for the identification of specific carcinoma subtypes.

CD15

It is a marker for the Reed-Sternberg cells of classic Hodgkin disease. It is negative in most non-Hodgkin's lymphomas, with the exception of some primary cutaneous ALCLs & other peripheral T-cell lymphomas. The pattern of staining is typically membranous, with a paranuclear dot-like, Golgi localization.

CD30

It is present in ALCL and lymphomatoid papulosis and is seen in 95% of classic Hodgkin's cases in some Reed-Sternberg cells. It is neither tumor-specific nor lymphoma-specific. The CD30 antigen is part of the tumor-specific factor receptor superfamily and has a pleiotropic on cells carrying it. The staining pattern is membranous or paranuclear dot-like. ⁷ RESULT In our case, the tumor cells are LCA-positive and cytokeratin-negative. CD 20 is strongly reactive in both medium and large cells indicative of B-cell lineage, There are a few CD3 positive T-cells scattered. The large cells are CD30 and CD15 negative. This immunophenotype is compatible with a primary mediastinal large B-cell lymphoma.

Result

In our case, the tumor cells are LCA-positive and cytokeratin-negative. CD 20 is strongly reactive in both medium and large cells indicative of B-cell lineage, There are a few CD3 positive T-cells scattered. The large cells are CD30 and CD15 negative. This immunophenotype is compatible with a primary mediastinal large B-cell lymphoma.

Discussion

Among non-Hodgkin lymphomas, PMLBCL has been considered a separate entity that has specific clinical and histological aspects. [8] Primary mediastinal large B-cell lymphoma accounts for 2-3% of non-Hodgkin lymphomas and occurs predominantly in young adults (third & fourth decade), with a slight female predominance. It is unrelated to Epstein-Barr viruses or other known tumor viruses. It might be driven by a still elusive oncogene, probably located on chromosome. [9] At presentation, the disease affects the antero-superior area of the mediastinum without superficial lymphadenopathy or hepatosplenomegaly. The thymus is typically

involved. The mass is often "bulky" (>10cm in diameter), and is often locally invasive. At progression, it disseminates predominantly to extranodal sites. Signs and symptoms are related to the mediastinal mass: superior vena cava syndrome (most frequently), airway obstruction, pleural and/or pericardial effusion. B symptoms may be present.

The cut-surface of these tumors has a fleshy appearance often with necrotic areas. Thymic cysts may be present.

The growth pattern is diffuse. PMLBCL has a broad range of cytomorphology, however, individual cases tend to be monomorphic. The cell range from medium-sized to large (2-5x the size of a small lymphocyte), have abundant, frequently clear cytoplasm & irregularly round or ovoid (occasionally multilobated) nuclei, usually with small nucleoli. Some cases may have more pleomorphic nuclei & abundant amophilic cytoplasm and may resemble Hodgkin lymphoma or nonlymphoid tumors. Mitotic activity is high, similar to other large cell lymphomas. The center of the lesion contains predominantly neoplastic cells. However, at the periphery of the mass, a variable number of reactive cells such as lymphocytes, macrophages & granulocytes may be present. A frequent but not consistent feature is a distinctive fibrosis made up of irregular collagen bands compartmentalizing cellular areas of varying size.

The combination of different architectural patterns & cellular morphology might raise the differential diagnosis of thymoma, seminoma or Hodgkin lymphoma.

PMLBCL expresses B-cell lineage-specific surface molecules such as CD19, CD20, CD22, and the immunoglobulin-associated CD79a molecule, but not lineage-restricted T-cell antigens, except for MAL, which is regarded as T-cell restricted and is not observed in other diffuse large B-cell lymphomas. CD10 has been detected in some studies in 20-25%. CD15 and CD21 are always negative. The majority do not express Immunoglobulin. CD30 expression, often weak and restricted to a subset of the tumor cells, is often observed, especially when antigen retrieval techniques are used. CD30 expression is typically low compared with the strong CD30 expression in neoplastic cells of classic Hodgkin lymphoma (HL) or in diffuse large B-cell lymphoma (DLBCL) of anaplastic type. This may result in differential diagnostic problems between PMLBCL, Hodgkin disease and the so-called "grey zone" lymphomas of the mediastinum, which have features intermediate between HL & DLBCL. In our case, the tumor cells are LCA-positive and cytokeratin-negative. CD 20 is strongly reactive in both medium and large

cells indicative of B-cell lineage, There are a few CD3 positive T-cells scattered. The large cells are CD30 and CD15 negative. This immunophenotype is compatible with a primary mediastinal large B-cell lymphoma.

Histologically, PMLBCL has been attributed to the asteroid variant of thymic medullary B-cells. Genetically, PMLBCL seems to be derived from B-cells that have been activated by a specific antigen, passed through the germinal centre & have shut down their mutational machinery before neoplastic transformation is completed. Immunophenotypically, PMLBCL are at post-germinal centre stage.

There are no histological, immunophenotypic or genotypic features that have prognostic potential. Similarly to other DLBCL, response to initial therapy is similar.⁹ Compared to DLBCL, EBV reactivity and surface and/ or cytoplasmic immunoglobulins are not usually associated or demonstrated with PMLBCL.

In our case, the clinical features as well as the histology were very characteristic of PMLBCL. The CT-guided FNA was non-contributory in the pre-operative diagnosis due to the nature of the tumor given the extent of necrosis and fibrosis. The tissue sampling was well beyond adequate and good viable tissue was obtained. The immunophenotype was compatible without the aid of flow cytometry.

Conclusion

Lymphoid malignancy in the anterior mediastinum may share radiologic findings similar with malignant thymoma. CT-guided FNA may obtain only necrotic and fibrotic material and a definite diagnosis may not be arrived at. Tissue confirmation thus would be crucial either through a mediastinoscopy or as is in this case, a debulking procedure. Differentiating a primary lymphoma arising from the thymus, from a lymphoma of nodal origin can be discerned if the morphology is classic and in the absence of lymphadenopathies as seen in our case. Immunophenotyping through flow cytometry will be confirmatory and ideal.



Figure 1. Chest CT Scan with contrast shows a largely lobulated, heterogeneously enhancing mediastinal mass



Figure 2 .Gross picture showing tan-yellow to brown, soft, homogenous tissue on cut section

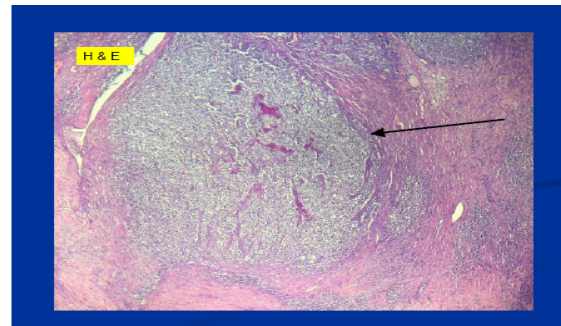


Figure 3. Distinctive fibrosis compartmentalizing cellular areas (H&E,x10)

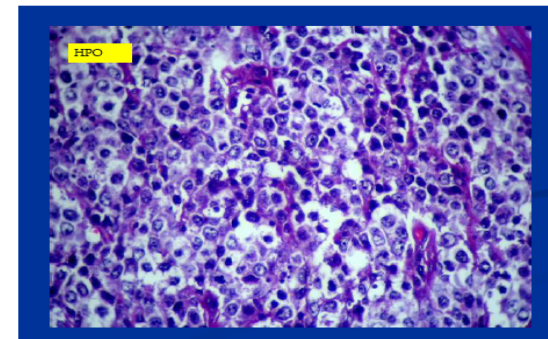


Figure 4. Tumor composed of medium to large lymphoid cells in a fibrovascular stroma (H&E,x40) TOUCH IMPRINT

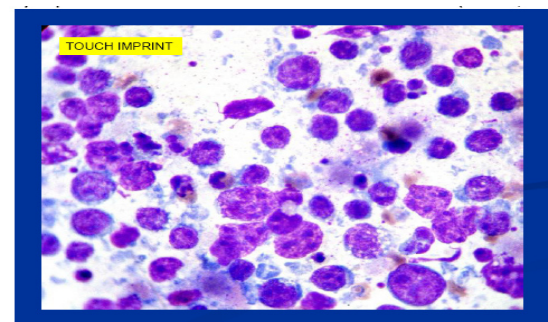


Figure 5. Touch imprints show numerous medium to large hematopoietic cells with many degenerated cells & karyohexis (Diff Quick, x100)

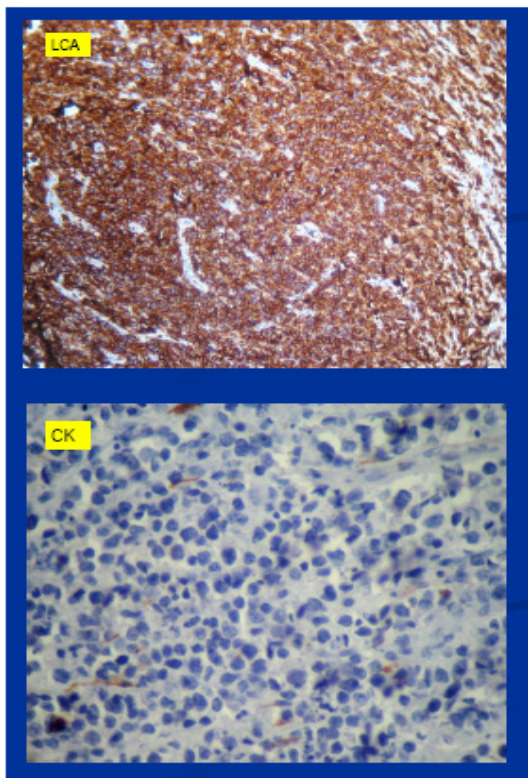


Figure 6. Immunostaining with LCA showed intense reactivity in both medium to large cells; CK is negative

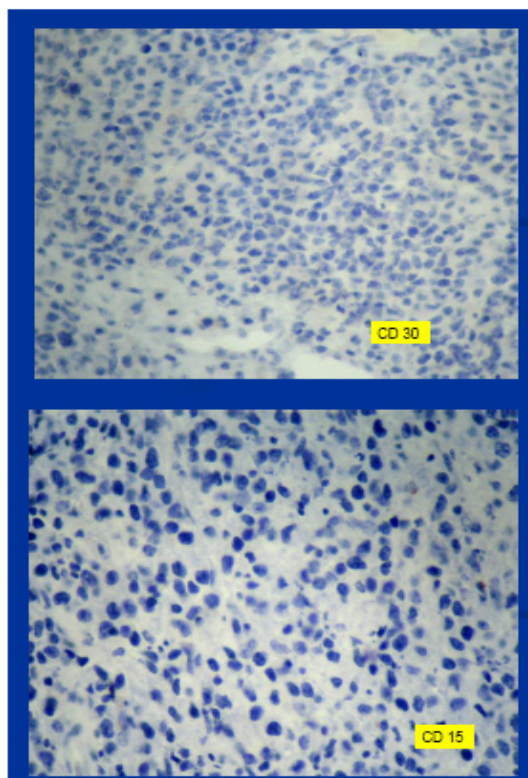


Figure 8. Immunostains with CD30 & CD15 are negative including the large lymphoid cells

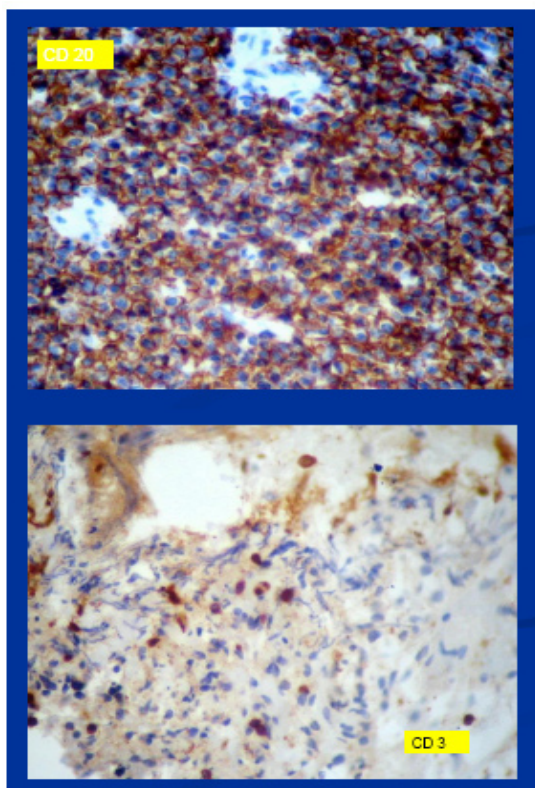


Figure 7. CD20 is positive in both medium & large lymphoid cells. CD3 with few positive lymphoid cells are sprinkled throughout. Non-specific background staining is observed.

Reference

1. Ergul S, Lal A, Afrin L, Frei-Lahr D. Primary Mediastinal Large B-cell Lymphoma. Southern Med J 95(9): 1005-1007, 2002
2. Siedemann K, Tiemann M, Lauterbach I et al. Primary mediastinal large B-cell lymphoma with sclerosis in pediatric & adolescent patients: treatment and results from three therapeutic studies of the Berlin-Frankfurt-Munster Group. J Clin Oncol 21(9):1782-9, 2003
3. Perrone T, Trizzera G, Rosai J. Mediastinal diffuse large cell lymphoma with sclerosis: A clinicopathologic study of 60 cases. Am J Surg Pathol 103:176-191, 1996
4. Lazzarino M, Orlandi B, Paulli M, et al. Primary mediastinal B-cell lymphoma with sclerosis: An aggressive tumor with distinctive clinical & pathologic features. J Clin Oncol 11:2306-2313, 1993
5. Yousem SA, Weiss LM, Warnke RA. Primary mediastinal non-Hodgkin's lymphomas: A morphologic and immunologic study of 19 cases. Am L Clin Pathol 3:676-680, 1985
6. Dabbs D. Introduction. Diagnostic Immunohistochemistry. 1:1, 2002
7. Dabbs D. Non-Hodgkin's Lymphoma. Diagnostic Immunohistochemistry. 1:114-118, 2002
8. Cazals-Hatem D, Lepage E, Brice P, et al. Primary mediastinal large B-cell lymphoma. A clinicopathologic study of 141 cases compared with 916 nonmediastinal large B-cell lymphomas, a GELA. Am J Surg Pathol. Jul;20(7):877-88, 1996
9. Travis W, Brambilla E, Muller-Hermelink H, Harris C. Pathology & Genetics Tumours of the Lung, Pleura, Thymus & Heart (WHO Classification of Tumours). 1.222-224, 2000