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CASE REPORT

Primary mediastinal large B-cell lymphoma and its mimickers: a rare case report with literature review

Thin Thin WIN *MMedSc (Pathology),* Zaleha KAMALUDIN *MD* and Azlan HUSIN* *MMed*

*Departments of Pathology and *Medicine, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia*

Abstract

Primary mediastinal large B-cell lymphoma (PMLBL) is an uncommon non-Hodgkin lymphoma with a distinct clinicopathological entity in the WHO classification of lymphoid malignancies. It is known to originate from B-cells of the thymus. It mimics thymic neoplasms and other lymphomas clinically and histopathologically. We reported a 33-year-old obese man who presented with shortness of breath off and on for 4 years. Radiologically, there was a huge anterior mediastinal mass. Tru-cut biopsy was initially diagnosed as type-A thymoma. Histopathological examination of the excised specimen revealed PMLBL with stromal fibrosis and sclerosis which created a diagnostic difficulty. The neoplastic cells varied from medium-sized to large pleomorphic cells, including mononuclear cells with centroblastic and immunoblastic features as well as bi-lobed Reed Sternberg (RS)-like cells and horse-shoe like hallmark cells. Some interlacing spindle cells and epithelioid cells were also present. Immunohistochemically, tumour cells expressed diffuse positivity for LCA, CD20, CD79a, CD23, Bcl2, MUM-1 and heterogenous positivity for CD30 and EMA, and were negative for CD10, CD15 and ALK. Ki67 scoring was very high. Tumour cells infiltrated into peri-thymic fat and pericardium. No malignant cells were detected in the pleural fluid and there was no bone marrow infiltration. The patient showed partial response to 6 cycles of RICE chemotherapy, and was planned for second line chemotherapy using hyper-CVAD regimen followed by autologous stem cell transplantation. This case illustrates the importance of thorough sampling and immunohistochemistry in differentiating PMLBL from its differential diagnoses.

Key words: Primary mediastinal large B-cell lymphoma, non-Hodgkin lymphoma, thymoma, immunohistochemical staining

INTRODUCTION

Primary mediastinal large B-cell lymphoma (PMLBL) is an uncommon entity in the WHO classification of lymphoid malignancies. It arises in the anterior mediastinum from B-cells of the thymus. It shows distinct clinical, pathological, and genetic features suggesting a unique histogenesis. It accounts for 2-4% of non-Hodgkin lymphoma (NHL) and occurs predominantly in young adults with a female predominance.[1]

Unlike most of the other large cell lymphomas, PMLBL rarely involves the bone marrow. It commonly presents with symptoms related to the mediastinal mass with or without lymph node involvement.[2] As it arises from the thymus and is locally infiltrative, thymic neoplasm is one of the differential diagnoses. It can also mimic nodular sclerosis type of Hodgkin lymphoma (HL) histopathologically and immunohistochemical stains are very important to differentiate them. We reported a case of PMLBL in a middle aged man, clinically and histopathologically mimicking thymic tumour and HL.

Case report

A 33-year-old obese man, who was a non-smoker, presented with shortness of breath off and on for the past 4 years. On examination, air entry was reduced in the left lung. No lymphadenopathy was detected. Palpation assessment of the liver and spleen was not impossible as the patient was very obese. Computerized tomography (CT) of the thorax showed a large anterior mediastinal

Address for correspondence: Dr. Thin Thin Win, Pathology Department, School of Medical Sciences, University Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia. Email: safiya@usm.my

mass (13x12x8 cm in greatest dimensions) which was lobular and extending to the left upper chest with left sided pleural effusion. A few discrete mediastinal lymph nodes and lung nodules were also found. The CT scan report was mediastinal tumour with a differential diagnoses of lymphoma, thymic neoplasm and teratoid tumor. CT guided Tru-cut biopsy was reported as type-A thymoma as the specimen was composed of spindle shaped cells separated by fibrous tissue admixed with lymphocytes. However, immunohistochemical stains were not performed on this biopsy. The case was then referred to our institution and with the plan to excise the anterior mediastinal tumour.

Operative findings showed a large thymic tumour infiltrating to the pericardium with left massive pleural effusion. The tumour was adhered to the inner surface of the sternum and left thoracic wall. The thymic tumour was excised together with a piece of pericardium and sent for histopathological examination. As there was no clear plane of separation between the tumour tissue and underlying structures, there was tumour tissue left over after surgery.

Pathology findings

Gross pathological examination of specimen (Fig. 1) showed enlarged thymus gland measuring 18x15x8 cm in greatest dimensions and weighing 517g. Anterior and posterior surfaces are nodular with adhesion to fibro-collagenous tissue (including pericardium). Serial sections showed solid tan white to brownish appearance with multiple areas of haemorrhage. Necrotic areas were also seen.

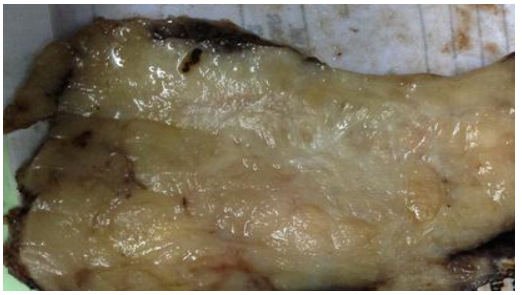

Fig. 1: Cut surface of the tumour showing nodular appearance grossly.

Histopathological findings from through sectioning and sampling of the specimen exhibited diffuse infiltrative lymphoid tumour composed of pleomorphic lymphoid cells admixed with non-neoplastic CD3 positive lymphocytes and numerous CD68 positive histiocytes. The neoplastic cells vary from medium-sized to large pleomorphic cells. Most of them were mononuclear cells with centroblastic and immunoblastic features as well as a few bi-lobed Reed Sternberg (RS)-like cells and horse-shoe like hallmark cells (Fig. 2a). 5-6 mitoses were seen in per 10 hpf. Marked stromal fibrosis with dense collagenization was seen within the tumour (Fig. 2b). Some of the tumour cells were spindle shape with an interlacing pattern of arrangement (Fig. 2c) and some exhibited an epithelioid appearance with moderate to marked pleomorphic nuclei, inconspicuous to prominent nucleoli and abundant eosinophilic cytoplasm. Tumour cells infiltrated into peri-thymic fat and pericardium. Residual non-neoplastic overlying and entrapped thymic epithelium (cytokeratin

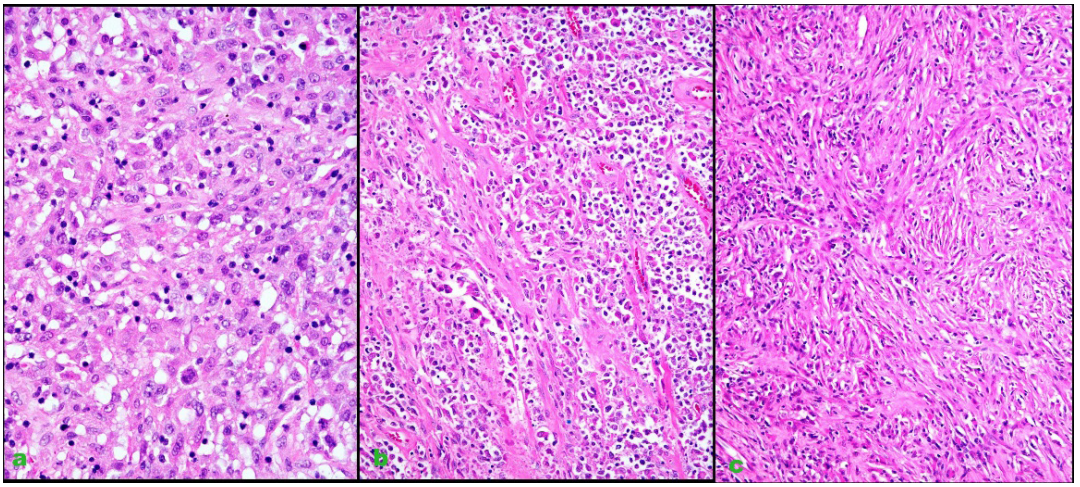

Fig. 2: (H&E) (a) Pleomorphic tumour cells & some bi-lobed RS-like cells (X400). (b) Tumour cells with marked stromal fibrosis (X200). (c) Spindle shaped tumour cells mimicking thymoma. (X200).

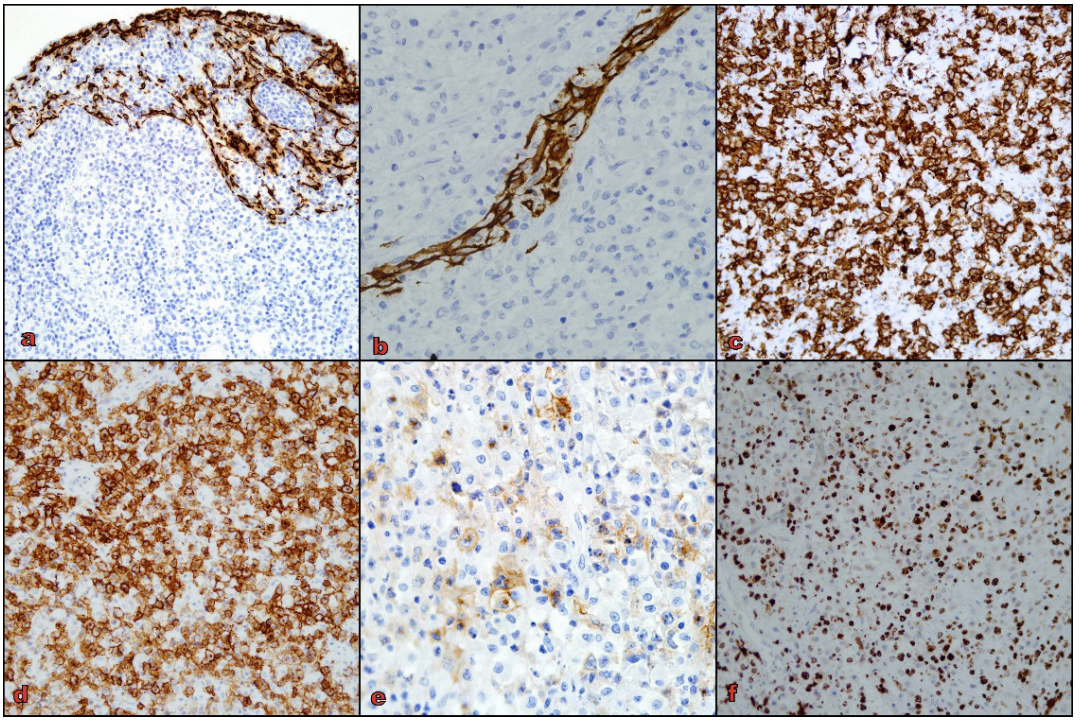

Fig. 3: (Immunohistochemical stains) (a) & (b) Residual overlying and entrapped thymic epithelium expressing CKAE1&3 (X200). (c)& (d): Diffuse positivity for CD20 and CD23 (X200). (e): Heterogonous positivity for CD30 (X400). (f): Very high Ki67 expression of tumour cells (X200).

CKAE1/3 positive) were seen at the periphery and also within the tumour (Fig. 3a&b). Immunohistochemically, tumour cells expressed diffuse positivity for leucocyte common antigen (LCA), CD20 (Fig. 3c), CD79a, CD23 (Fig. 3d), Bcl2, MUM-1 and heterogenous positivity for CD30 (Fig. 3e) and epithelial membrane antigen (EMA). Ki67 scoring was very high (Fig. 3f). However, staining for CD10, CD15, anaplastic lymphoma kinase (ALK) was negative in the tumour cells. With the above histopathological findings and immunophenotyping, a diagnosis of PMLBL was confirmed. Cytological examination of fluid from left pleural cavity was blood stained; however it was negative for malignant cells.

Clinical course

After the histopathological diagnosis of PMLBL was made, bone marrow trephine biopsy was done and there was no evidence of bone marrow infiltration by the primary tumour. RICE (Rituximab, Ifosfamide, Carboplatin and Etoposide) chemotherapy regimen was started. After 6 cycle of chemotherapy, patient was well and shortness of breath was reducing. Serum lactate dehydrogenase enzyme (LDH) was high with 973 U/L before chemotherapy and reduced to 282 U/L after 6 cycles of chemotherapy. However, repeat CT scan showed only 65% (estimated) reduction of the residual tumour compared to the pre-operative CT scan and patient was planned for second line chemotherapy using the hyper-CVAD regimen (Cyclophosphamide, Vincristine, Adriamycin and Dexamethazone) followed by autologous stem cell transplantation.

DISCUSSION

PMLBL is a rare type of NHL arising in the mediastinum from putative thymic B-cells with distinct clinical, pathological, and genetic features. It predominantly occurs in young adults with a female predominance.[1] In this case, the patient was young adult male. PMLBL also can occur in children and adolescents; and the response to chemotherapy and overall survival is excellent in that age group.[3,4]

PMLBL typically presents as a large, fast-growing tumour with invasion usually limited to the anterior-upper mediastinum although it tends to infiltrate adjacent thoracic structures like the chest wall, pleura, lungs, pericardium

and heart causing pleural/pericardial effusion in approximately 30–50% of cases.[5] The mass tends to be confined to the thorax without involvement of lymph nodes or other lymphoid organs at initial diagnosis. Extra-thoracic or extra-nodal involvement is more frequent at relapse. Bone marrow involvement is extremely rare, even in cases of recurrence.[6] This case had left lung nodules suggestive of pulmonary dissemination. Although PMLBL is a fast growing tumour, this case was slow growing as the symptoms started 4 years ago with shortness of the breath off and on.

PMLBL harbors distinctive chromosomal aberrations, including consistent gains in chromosome 9p and 2p corresponding with Janus kinase (*JAK*)-2 and c-Rel, respectively. That genetic expression is also seen in the nodular sclerosis type of HL.[7,8] However, genetic study was not performed in our case.

Histopathologically, PMLBL has a wide morphological spectrum with a common feature of marked stromal fibrosis.[1,9] The infiltrating cells are often entrapped in compartments surrounded by collagenous fibrosis, forming so-called compartmentalizing alveolar fibrosis.[10] Tumour cells are medium to large size with abundant pale cytoplasm and regular round or ovoid nuclei. Pleomorphic and /or multilobated nuclei which may resemble RS cells are also seen.[1] Immunophenotypically, apart from B-cell antigens, tumour cells of PMLBL express CD30 (>80%), CD23 (70%), MUM1 (75%), Bcl2 (55 – 80%) and Bcl6 (45 – 100%).[1] They are usually CD15 negative.[9]

The differential diagnoses of PMBCL include other types of lymphomas with mediastinal localization and mediastinal tumours such as thymoma, germ cell tumours, and metastatic carcinomas. Other types of lymphomas with mediastinal localization includes gray zone lymphoma with features intermediate between diffuse large B-cell lymphoma (DLBCL) and classical HL, composite lymphoma, DLBCL with anterior mediastinum involvement, nodular sclerosis type of classical HL and mediastinal sequential lymphomas which is PMBCL relapsing as HL.[5] The most mimicking tumour of PMLBL is thymic neoplasm (thymoma and thymic carcinoma). The pattern of pan-cytokeratin expression is useful to differentiate them and it highlights overlying and entrapped thymic epithelium in thymic tumour. In this case, the tru-cut biosy was reported as type-A thymoma as the biopsy was composed of spindle shape cells. However, the biopsy was reported in an outside centre without the benefit of immunohistochemical stains and the diagnosis was only based on haematoxylin and eosin (H&E) stained sections. When we received the excised specimen, based on findings in H&E stained morphology before immunohistochemical stains were performed, the differential diagnoses included thymoma, thymic carcinoma, mediastinal lymphoma and nodular sclerosis type of HL. However, pan-CK and LCA staining pattern confirmed lymphoma and excluded thymic neoplasms. In germ cell tumour, β-HCG and α-fetoprotein are increased serologically and positive immunohistochemically.[2] At this point, an important lesson is that the diagnosis of thymoma in tru-cut biopsy requires immunohistochemical stains to differentiate it from its differential diagnoses.

Once lymphoma was confirmed, the next step was to classify the type of lymphoma. It is known that molecular characterization of PMBCL highlights an overlap with the nodular sclerosis subtype of classic HL sharing a number of genetic and gene expression features.[11] Marked stromal fibrosis and the presence of tumour cells which looked like Reed-Sternberg cells with bilobed nuclei mandate the exclusion of HL. In this case, although CD30 was heterogeneously positive in the tumour cells, CD15 negativity can exclude HL. Both will be positive in HL. CD30 and CD23 positivity in this case excludes diffuse large B-cell lymphoma which does not express it. CD23 is also reported to be useful in indistinguishing PMBL from classical HL and DLBCL.[12] The vast majority (70%) of mediastinal lymphomas strongly express CD23 whilst it is expressed in only 15% of non-mediastinal nodal DLBCLs and 9% of non-mediastinal extranodal DLBCLs.[13] Anaplastic large cell lymphoma which also occurs in younger persons is also one of the differentials and the component cells may be similarly large, with pleomorphic nuclei. However, sclerosis is not a feature; CD30 and ALK are positive in anaplastic lymphoma. Composite lymphoma is two or more histologically distinct types of lymphoma involving the same anatomical site; combined two different types of NHL of the same lineage or combined NHL and HL or combined two different types of NHL of different lineage.[2]

Mediastinal gray zone lymphoma is another differential diagnosis to be excluded in this case, as it has male preponderance and the patient

in this case was male. It has features of both classical HL and DLBCL, particularly nodular sclerosis type of HL of the mediastinum and PMLBL.[9] In this case, CD23 positivity and CD15 negativity excludes gray zone lymphoma.

Regarding prognosis of PMBCL, it has a favourable outcome, with those who survive beyond 2 years very unlikely to relapse, further highlighting it as a distinct entity from DLBCL.[13] Extension into adjacent thoracic viscera, pleural or pericardial effusion and poor performance status are associated with a poor prognosis.[1] Some studies found that the outcome of PMLBL is at least equivalent to or superior to that of other DLBCL.[1,14] A study of MYC protein expression in PMLBL cases found that MYC expression is seen in most PMLBL cases (94%) and increased expression is seen in one-third of the cases; however, it does not correlate with genetic abnormalities and there is no significant impact of MYC protein expression on clinical outcomes.[15] In this case, although the pericardium was locally invaded by tumour, pleural fluid cytology was negative for malignant cells.

In conclusion, PMLBL is an uncommon NHL. Distinction of PMBCL from classical HL, DLBCL and mediastinal gray zone lymphoma are important for prognostic and therapeutic reasons. Judicious immunophenotyping with careful and systematic selection of markers is necessary for definitive diagnosis. Through sampling of the specimen and immunohistochemical staining are also important in differentiating PMLBL from thymic neoplasm.

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