PCW Lui 呂智偉
WK Ng 吳偉權
LYC Yam 任燕珍
WWC Wong 黃慧中
YP Tai 戴玉平

Pyothorax-associated large B-cell lymphoma: case report with emphasis on the potential diagnostic challenge

與膿胸有關的巨大B細胞淋巴瘤：具潛在診斷挑戰的病例報告

A rare case of pyothorax-associated large B-cell lymphoma occurring in Hong Kong is reported. The patient was a 64-year-old Chinese male who presented with shortness of breath and pleuritic pain. Radiological examination revealed left pleural thickening associated with bilateral pleural effusion. Open biopsy of the thickened parietal pleura revealed occasional large malignant lymphoid cells of B lineage admixed with fibrin and hyalinised fibrous tissue. These lymphoma cells were shown to harbour both Epstein-Barr virus and human herpesvirus type 8 by in situ hybridisation and immunohistochemical study, respectively. There was no associated lymphadenopathy and hepatosplenomegaly. The clinicoradiological presentation and pathological findings thus fulfilled the criteria of the so-called pyothorax-associated large B-cell lymphoma. Awareness of this rare entity, together with diligent histological examination and proper application of ancillary investigative techniques, are essential for making a correct diagnosis. The co-infection with Epstein-Barr virus and human herpesvirus type 8 in this case also suggests a possible pathogenetic relationship between pyothorax-associated large B-cell lymphoma and primary effusion lymphoma.

本文報告了一宗在香港發生而又罕見的與膿胸有關的巨大B細胞淋巴瘤病例。患者是一名64歲的華裔男性。患者呈現氣短和胸膜痛，放射檢查顯示左胸膜增厚，並且胸膜兩面有積液情況。切片檢查增厚的胸膜發現少量巨大的惡性B淋巴瘤細胞，並混有纖維蛋白和纖維組織。原位雜交和免疫組化分別顯示這些淋巴瘤細胞聚集了愛—巴氏病毒和8型疱疹病毒。患者並沒有淋巴結病和肝脾腫大。臨床放射檢查結果和病理診斷均符合與膿胸有關的巨大B細胞淋巴瘤的定義。要作出正確的診斷，必需對這種罕見的腫瘤提高警覺，並要有仔細的組織學檢查和適當的輔助研究技術。在這病例中，愛—巴氏病毒和8型疱疹病毒的交叉感染也意味著，與膿胸有關的巨大 B 細胞淋巴瘤和原發性積液淋巴瘤之間可能有相互關係。

Key words:
Empyema, pleural;
Lymphoma, B-cell

關鍵詞：
膿胸；
B 細胞淋巴瘤

Hong Kong Med J 2002;8:359-62

Department of Pathology, United Christian Hospital, 130 Hip Wo Street, Kwun Tong, Hong Kong
PCW Lui, MB, BS
Pamela Youde Nethersole Eastern Hospital, 3 Lok Man Road, Chai Wan, Hong Kong:
Department of Clinical Pathology
WK Ng, FHKCPath, FHKAM (Pathology)
Department of Medicine
LYC Yam, FHKCP, FHKAM (Medicine)
Department of Diagnostic Radiology
WWC Wong, FHKCR, FHKAM (Radiology)
Department of Surgery
YP Tai, FCSHK, FHKAM (Surgery)

Correspondence to: Dr WK Ng

Introduction

Pleural thickening is often due to fibrous plaque, loculated suppuration, metastatic carcinoma, and malignant mesothelioma. Occasionally, solitary fibrous tumour, synovial sarcoma, and epithelioid haemangioendothelioma may present as a pleural mass. Primary pleural lymphoma, however, is rare. Although radiological examination may help to localise the pleural lesion and look for other associated conditions such as lung tumour, pathological examination remains the hallmark for definitive diagnosis. Often, however, the diagnostic cells are scanty and may not be sampled, especially if the biopsy is blindly carried out using Cope's or Abram's needles. In addition, there are many morphological mimickers in pleural pathology.

These factors pose a diagnostic challenge to both clinicians and pathologists. The second patient with pyothorax-associated large B-cell lymphoma occurring in Hong Kong is reported here. Awareness of this rare entity, together with correct tissue sampling, diligent pathological examination, and application of ancillary investigations, are essential for a correct diagnosis.

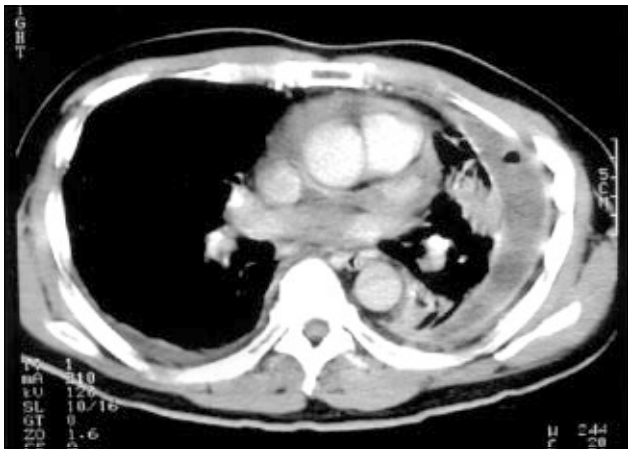

Fig 1. Computed tomography of the thorax showing thickened left parietal pleura associated with left lung collapse
The radiological features are indistinguishable from pleural plaque, mesothelioma, or metastatic malignancy

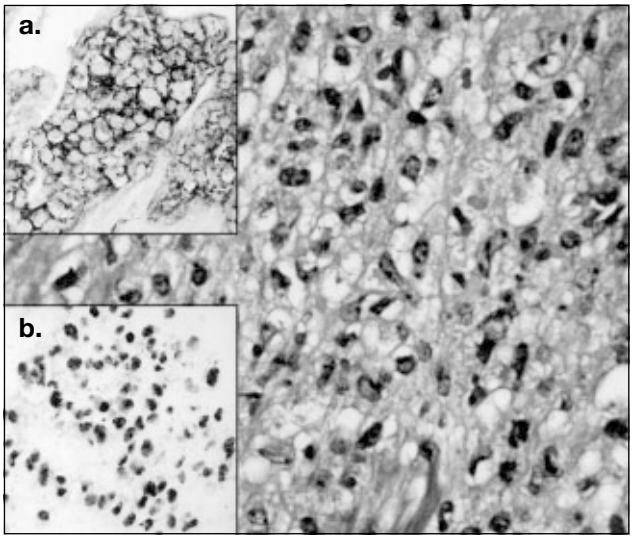

Fig 2. High-power photomicrograph of the pleural biopsy showing scattered medium-to-large lymphoid cells with irregular nuclei and occasional distinct nucleoli (H&E, x600)
These cells may mimic reactive lymphoid cells in pleural plaque: (a) immunostaining for B-cell marker, CD20, shows membranous positivity in most tumour cells (x300); (b) in situ hybridisation for Epstein-Barr virus–encoded RNA reveals positive nuclear signals (x300)

Case report

The patient was a 64-year-old Chinese man who frequently travelled by air. He presented with right-sided pleuritic pain 1 month before admission to hospital and dyspnoea for 3 months. He reported a similar pain in the left chest 1 year previously, for which he did not seek medical advice. Computed tomography of the thorax 1 month before admission confirmed right lower lobe segmental pulmonary embolism with bilateral pleural effusion, left-sided pleural thickening, and two ill-defined masses in the lingual and left lower lobe. He was given heparin. Fine needle aspiration biopsy of the lingular mass showed organising pneumonia. He was referred to the Pamela Youde Nethersole Eastern Hospital for pleurectomy.

Physical examination of the patient showed left pleural effusion but no lymphadenopathy or organomegaly. Complete blood cell count was normal. Computed tomography of the thorax showed resolution of pulmonary embolism, persistent left pleural thickening and bilateral pleural effusion, ill-defined left lung masses, and scanty pericardial effusion (Fig 1). The pleural fluid cytology was negative. Sputum and pleural fluid specimens did not grow any acid-fast bacilli. The patient then underwent left thoracotomy. Intra-operatively, pleurectomy was not possible since the parietal pleura was markedly thickened, with complete encasement of the left lung. Consequently, the left lung was almost entirely collapsed. Histological examination of a small left pleural biopsy revealed high-grade malignant B-lymphoid cells which were co-infected by Epstein-Barr virus (EBV) and human herpesvirus type 8 (HHV-8). Subsequent serology for anti–human immunodeficiency virus was negative. The picture was thus consistent with pyothorax-associated large B-cell lymphoma.

Pathological findings

Histology showed occasional medium-to-large lymphoid cells (Fig 2, main picture) admixed with hyalinised fibrous tissue. These cells were moderately pleomorphic and discohesive. They contained vesicular nuclei, irregular nuclear outline, distinct basophilic nucleoli, and scanty amphophilic cytoplasm. Immunohistochemistry using Streptavidin-biotin complex technique (DAKO, Glostrup, Denmark) showed that the tumour cells expressed B-cell markers CD20 (Fig 2a). The staining for T-cell marker CD3 (DAKO), epithelial marker AE1/3 (Biogenex, San Ramon, US), and mesothelial marker calretinin (Swiss Antibodies, Bellinzona, Switzerland) was negative. There was also no expression of epithelial membrane antigen (DAKO)—a marker commonly positive in epithelial cells and plasma cells—and CD15 (DAKO)—a marker positive in Reed-Sternberg cells of Hodgkin's lymphoma. Occasional tumour cells showed membranous and paranuclear positivity for activation marker CD30 (DAKO). A high proliferation index was also demonstrated by Ki67 immunostain (Zymed, San Francisco, US). In situ hybridisation for EBV-encoded RNA revealed positive nuclear signals (Fig 2b). The picture was that of EBV-related pyothorax-associated large B-cell lymphoma. In addition, further immunohistochemistry showed that the lymphoma cells were reactive to HHV-8 ORF-73 antibody. In conclusion, the pleura was populated by a large B-cell lymphoma which was EBV-positive and HHV-8–positive.

Discussion

Pyothorax-associated lymphoma is a rare form of aggressive B-cell non-Hodgkin's lymphoma complicating long-standing pyothorax or chronic pleuritis.[1] Provided that there is a background of pleural fibrosis and chronic inflammation, this diagnosis can be made even in the absence of clinically manifested pyothorax. Most reported cases are from

Japan[2] and the pleural inflammation is mainly due to previous artificial pneumothorax for treatment of pulmonary tuberculosis or tuberculous pleuritis.[3] According to the literature,[2] pyothorax-associated lymphoma occurs between 22 and 55 years after the onset of tuberculosis. The patients are adults, with a mean age of 63 years and a male-to-female ratio of 5:1. The patients present with chest pain, pleural effusion, and pleural thickening. An association with EBV is consistently demonstrated.[4-6] In contrast, the lymphoma cells are not always infected by HHV-8.[6,7] There is no evidence of plasmacytic differentiation, as illustrated by epithelial membrane antigen–negativity. Some forms of p53 gene mutation have been demonstrated in 71% of cases.[8] In general, pyothorax-associated lymphoma has an aggressive clinical course and the prognosis is worse for patients with a poor performance status.[9]

An unusual finding associated with this patient was the presence of HHV-8 in tumour cells in addition to infection by EBV. Human herpesvirus type 8 is a member of the Rhadinovirus family and often seen in Kaposi's sarcoma, Castleman's disease, and acquired immunodeficiency syndrome (AIDS)–related lymphoma of the central nervous system. This co-infection with EBV and HHV-8 is typically found in a distinctive type of body cavity–based lymphoma called primary effusion lymphoma,[10] which is clinically and pathologically different from pyothorax-associated lymphoma.

In contrast with pyothorax-associated lymphoma, primary effusion lymphoma usually occurs in patients with advanced AIDS, especially in homosexual males. The clinical presentation is massive effusion in the body cavities not associated with any tumoural mass. Histologically, the large lymphoma cells contain abundant basophilic cytoplasm and prominent perinuclear hof, compatible with a tendency for plasmacytic differentiation. The cells do not express B-cell markers at immunohistochemistry. Instead, activation markers and plasma cell markers are often positive. The B-lineage of the lymphoma cells is confirmed only by demonstration of clonal immunoglobulin gene rearrangement with molecular study. Primary effusion lymphoma is highly aggressive and the prognosis is worse than that of pyothorax-associated lymphoma. On the other hand, in view of their similar topographical distribution, a possible pathogenetic relationship has been suggested. Recently, O'Donovan et al[11] reported the presence of HHV-8 in occasional patients with pyothorax-associated lymphoma and demonstrated a similar HHV-8–encoded gene expression. As the majority of patients with pyothorax-associated lymphoma do not have HHV-8, HHV-8 infection is probably not essential in the pathogenesis of pyothorax-associated lymphoma. Its presence may contribute to the effusion phenotype. The findings in this case are in agreement with the suggestion of a possible link between pyothorax-associated lymphoma and primary effusion lymphoma.

The diagnostic dilemma in this situation is not limited to the viral association. The scantiness of tumour cells in certain pleura-based malignancies may pose diagnostic problems to pathologists. Classical examples include pyothorax-associated lymphoma and desmoplastic mesothelioma. This is in contrast with metastatic carcinoma, which often produces cellular specimens. Obtaining larger samples by thoracoscopic biopsy or even thoracotomy with biopsy under direct vision, together with diligent histological assessment and correct application of ancillary investigations including immunohistochemistry and molecular study, are crucial for diagnosis. If one does not pay attention to high-power cytology of the lymphoma cells, these cells may easily be misinterpreted as reactive follicular centre cells in lymphoid aggregates of pleural plaque. Sometimes, even molecular methods such as immunoglobulin gene rearrangement study may fail simply due to the paucity of tumour cells. The picture is further complicated by the presence of morphologic mimickers. Examples include desmoplastic mesothelioma in which the spindly tumour cells may be mistaken as reactive fibroblasts of pleural plaque. Similarly, the lymphoma cells in pyothorax-associated lymphoma may mimic poorly differentiated carcinoma or mesothelioma cells, which may also fail to express epithelial/mesothelial markers. The confirmation of the lymphoma diagnosis, however, is not difficult with immunohistochemistry, if one has taken this rare possibility into consideration.

The pathogenesis of pyothorax-associated lymphoma is still controversial. Danbara et al[12] investigated the development of pyothorax-associated lymphoma in relation to focal cytokinemic milieu and EBV infection. They proposed that scanty immortalised EBV-transformed B cells populated the pleura where tuberculous inflammation persisted. These B cells escaped from the attack of cytotoxic T lymphocytes because of attenuated host immune response and interleukin-6 produced at the site of chronic inflammation. Interleukin-6 had been shown to stimulate the growth of EBV-activated human B cells in vitro by acting as a paracrine and/or autocrine growth factor. The impaired immune responses to EBV-latent antigens caused by some immunosuppressive factors such as interleukin-10 and mutations in cytotoxic T lymphocyte epitopes for EBV-latent antigens might further support the progression.[13] In this example, the patient did not have a history of clinically manifested pyothorax or tuberculosis requiring artificial pneumothorax. Instead, as a frequent flyer, he was prone to recurrent pulmonary thromboembolism. In view of the history of left-sided pleuritic pain 1 year previously, he may have had a left-sided pulmonary embolism at that time, which resulted in persistent effusion and pleural thickening thereafter. In any case, he did have a proven right-sided pulmonary embolism before admission. The subsequent pleural inflammation and thickening from recurrent pulmonary embolism may have had a role in the development of pyothorax-associated lymphoma. This postulation, however, still requires further validation by large-scale

studies. Other unknown cofactors were also crucial, especially in view of the common occurrence of 'frequent flyer' pulmonary embolism in Caucasians but the relative rarity of pyothorax-associated lymphoma worldwide.

Owing to the rarity of cases, the treatment of pyothorax-associated lymphoma has not yet been standardised. Occasional reports of treatment outcomes are on record.[14,15] Various combinations of chemotherapy and radiotherapy regimens have been used. In general, most authors believe that local irradiation plays an important role in controlling this pleura-based lymphoma.

Acknowledgements

The authors would like to thank Dr JKC Chan of Queen Elizabeth Hospital, Hong Kong, and Professor K Aozasa of Osaka University, Japan, for their expert comments on this case.

References

1. Aozasa K, Ohsawa M, Kanno H. Pyothorax-associated lymphoma: a distinctive type of lymphoma strongly associated with Epstein-Barr virus. Adv Anat Pathol 1997;4:58-63.
2. Iuchi K, Aozasa K, Yamamoto S, et al. Non-Hodgkin's lymphoma of the pleural cavity developing from long-standing pyothorax. Summary of clinical and pathological findings in thirty-seven cases. Jpn J Clin Oncol 1989;19:249-57.
3. Aozasa K, Ohsawa M, Iuchi K, Tajima K, Komatsu H, Shimoyama M. Artificial pneumothorax as a risk factor for development of pleural lymphoma. Jpn J Cancer Res 1993;84:55-7.
4. Fukayama M, Ibuka T, Hayashi Y, Ooba T, Koike M, Mizutani S. Epstein-Barr virus in pyothorax-associated pleural lymphoma. Am J Pathol 1993;143:1044-9.
5. Ohsawa M, Tomita Y, Kanno H, et al. Role of Epstein-Barr virus in pleural lymphomagenesis. Mod Pathol 1995;8:848-53.
6. Copie-Bergman C, Niedobitek G, Mangham DC, et al. Epstein-Barr virus in B-cell lymphomas associated with chronic suppurative inflammation. J Pathol 1997;183:287-92.
7. Taniere P, Manai A, Charpentier R, et al. Pyothorax-associated lymphoma: relationship with Epstein-Barr virus, human herpes virus-8 and body cavity-based high grade lymphomas. Eur Respir J 1998;11:779-83.
8. Hongyo T, Kurooka M, Taniguchi E, et al. Frequent p53 mutations at dipyrimidine sites in patients with pyothorax-associated lymphoma. Cancer Res 1998;58:1105-7.
9. Aozasa K, Ohsawa M, Iuchi K, et al. Prognostic factors for pleural lymphoma patients. Jpn J Clin Oncol 1991;21:417-21.
10. Said JW. Body cavity-based (primary effusion) lymphoma: a new lymphoma subtype associated with Kaposi's sarcoma herpesvirus (human herpesvirus 8). Adv Anat Pathol 1996;3:254-8.
11. O'Donovan M, Silva I, Uhlmann V, et al. Expression profile of human herpesvirus 8 (HHV-8) in pyothorax associated lymphoma and in effusion lymphoma. Mol Pathol 2001;54:80-5.
12. Danbara M, Takano Y, Fujino Y, Okayasu I, Shionoya S. Development of pyothorax-associated pleural lymphoma in relation to focal cytokinemic condition and Epstein-Barr virus infection. Acta Haematol 1998;99:41-4.
13. Kanno H, Naka N, Yasunaga Y, et al. Production of the immunosuppressive cytokine interleukin-10 by Epstein-Barr-virus-expressing pyothorax-associated lymphoma: possible role in the development of overt lymphoma in immunocompetent hosts. Am J Pathol 1997;150:349-57.
14. Sumi M, Satoh H, Ohtsuka M, Hasegawa S, Fujiwara M, Kamma H. Long-term cure of a malignant lymphoma of the pleural cavity treated by irradiation. Oncol Rep 1998;5:1439-40.
15. Aruga T, Itami J, Nakajima K, et al. Treatment for pyothorax-associated lymphoma. Radiother Oncol 2000;56:59-63.