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Pyothorax-associated lymphoma – the first reported case in the UK

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ABSTRACT An 84-year-old man presented with dyspnoea and chest pain, together with a chest X-ray demonstrating a complete white-out of the left hemithorax. Four decades earlier he had been treated for tuberculosis with an artificial pneumothorax. A diagnosis of pyothorax-associated lymphoma (exclusively B-cell non-Hodgkin's type) was made. Strongly associated with Epstein-Barr virus infection, pyothorax-associated lymphoma is known to develop in the chronic inflammatory environment of a pleural cavity in patients with a long-standing history of pyothorax. Although the condition is responsive to chemo-radiotherapy, overall prognosis is poor (five-year survival of 21.6%). Our patient has demonstrated a remarkable response to surgical decortication and resection with adjuvant rituximab – cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP) chemotherapy – and makes a case for routine debulking as part of the multimodality treatment of this unusual malignant complication of tuberculosis therapy.

KEYWORDS Artificial pneumothorax, empyema, non-Hodgkin's lymphoma, tuberculosis

DECLARATION OF INTERESTS No conflict of interests declared.

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CASE REPORT

An 84-year-old Caucasian male retired medical practitioner presented with a four-month history of dyspnoea and increasingly intense left-sided back pain, without any other associated constitutional symptoms. This occurred on a background of pulmonary tuberculosis (TB) in the late 1940s to early 1950s, which had been treated with a left-sided artificial pneumothorax without anti-tuberculous chemotherapy. He had never smoked.

A large left-sided pleural effusion with mediastinal shift was confirmed on chest X-ray (Figure 1) and subsequent computed tomography (Figure 2). A turbid, aseptic exudative (lactate dehydrogenase [LDH] 4488 iu/L) pleural aspirate negative for cytology was initially treated with anti-tuberculous therapy, given the small chance that the patient's symptoms represented a relapse of his old TB. However, there was no evidence of an improvement. Bronchoscopy and left thoracotomy revealed a large blood-stained encysted tuberculous empyema cavity, with granulation tissue invading the adjacent intercostal spaces. This was resected and decorticated. The histopathological analysis of the surgical specimens was negative for all epithelial and mesothelial markers but consistent with an atypical non-Hodgkin's anaplastic large B-cell CD79a positive malignant lymphoma 1, termed pyothorax-associated lymphoma (PAL), which unusually was CD20 negative but CD30 positive. In situ hybridisation revealed the cells to be Epstein-Barr virus nuclear antigen (EBNA)-1 positive and latent membrane protein (LMP)-1 negative.[1] His human immunodeficiency virus (HIV) serology and human herpes virus 8 (HHV8) tumour status were not established.

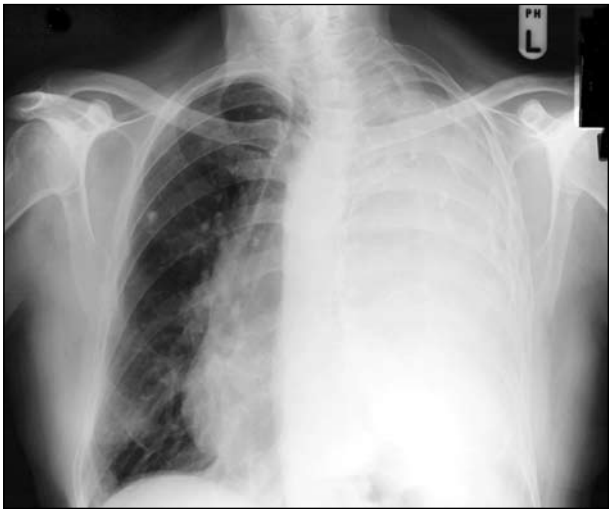

FIGURE 1 An 84-year-old male with a history of tuberculosis, treated 40 years ago with an artificial pneumothorax, presented with a four-month history of increasing dyspnoea and left-sided chest pain. His initial chest X-ray demonstrated a complete white-out of the lung with mediastinal shift and a small right upper lobe calcified granuloma consistent with his history of previous tuberculosis therapy. There was no evidence of active rib pathology to explain his chest discomfort. A diagnostic aspirate demonstrated a sterile exudative effusion, negative for inflammatory or malignant cytology.

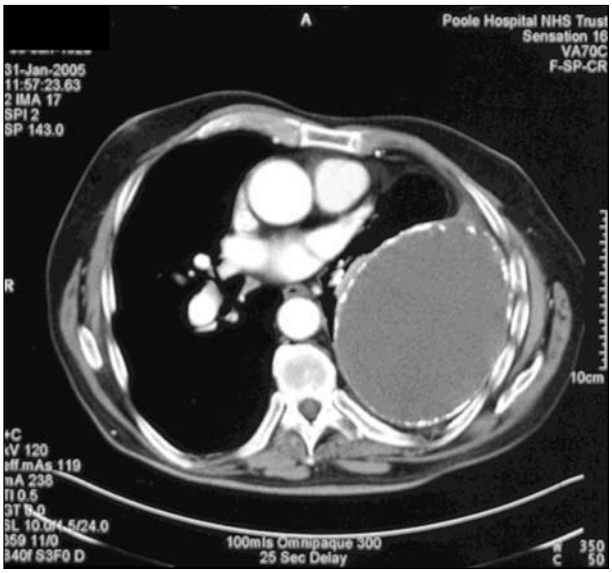

FIGURE 2 Selected image from staging computed tomography of chest and abdomen (mediastinal windows). This shows a tense collection with a calcified wall occupying the majority of the left hemithorax. The absence of systemic symptoms, significant nodes or disease below the hemi-diaphragm was consistent with stage Ie. The patient underwent rigid bronchoscopy, left thoracotomy and decortication of a huge tuberculous empyema cavity. No masses were found within the space, and intercostal ingrowing granulation tissue was resected and sent for microscopy, culture and histopathology. No acid fast bacilli were isolated or latterly cultured, and the histopathology was consistent with a pyothorax-associated B cell non-Hodgkin's lymphoma.

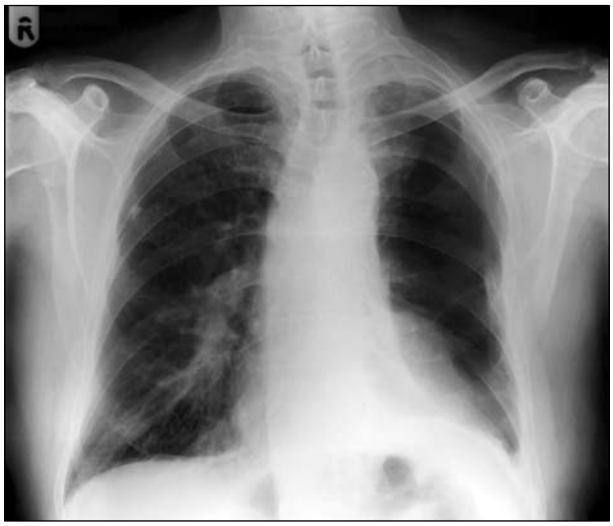

FIGURE 3 Following the completion of six cycles of well-tolerated R-CHOP adjuvant chemotherapy six months previously, this follow-up chest X-ray demonstrates this patient's impressive response to combination therapy. There is evidence of persistent circumfrential calcified pleural thickening and volume loss within the left hemithorax but no reaccumulation of the effusion. The patient was discharged from further follow-up in October 2006 and remains well.

Following a good recovery from surgery and the resolution of his pain, his performance status was assessed and he was accepted for six cycles of R-CHOP (rituximab – cyclophosphamide, doxorubicin, vincristine, pred-nisolone) chemotherapy that he completed successfully. The patient currently remains well, 40 months after treatment (Figure 3). There is limited experience of this condition in Europe and, to our knowledge, this is the first case of PAL to be reported in the UK.

DISCUSSION

Case control studies have previously demonstrated artificial pneumothorax to be the only significant risk factor for the development of PAL in patients with a long-standing pyothorax.[2] The mechanism is thought to result from long-term exposure to the reactive oxygen species present in the chronic immunosuppressive inflammatory cytokine microenvironment, causing genetic abnormalities[3] with the possible contribution of repetitive radiological inspection.[4] Histology is usually of a diffuse proliferation of large cells of B-cell type (CD20, CD79a, CD45 positive) (88%), with in situ hybridisation studies demonstrating a strong association (70%) with Epstein-Barr virus positivity and expression of latency genes LMP-1, EBNA-1 and -2. EBNA-2 transcript-negative tumours are associated with worse prognosis.[1,5] Despite the absence of data regarding the patient's HIV and HHV8 status, his presentation and clinical course made the differential diagnosis of primary effusion lymphoma (PEL) very unlikely. [6]

The Japanese experience[5] is of the development of PAL in patients with a median age of 64 years, a 12.3:1 male/female ratio and a 37-median-year history of pyothorax resulting from artificial pneumothorax treatment for pulmonary TB or TB pleuritis. The most common presentation is chest or back pain and fever. Pyothorax-associated lymphoma has been found to be responsive to chemotherapy (CHOP, VEPA – vincristine, cyclo-phosphamide, doxorubicin, prednisolone) and radiotherapy (median 48 Gy) with a 57% complete or partial response, but with an overall poor prognosis (five-year survival of 21.6%). The Japanese data suggest that the increased incidence seen in the Far East might result from the greater frequency of artificial pneumothorax therapy or, perhaps, genetic factors. Shortened survival is correlated with a poor performance status, high serum levels of alanine transaminase (ALT) and urea.[7]

The debulking of our patient's early-stage disease prior to adjuvant chemotherapy, with neither of his CT scans demonstrating evidence of extra nodal disease and his reasonable performance status may have been the favourable prognostic features in this case. Certainly there is case report evidence to suggest that this multimodality approach to isolated chest wall lymphoma results in long-term survival.[8] Given the CD20-negative status of the tumour in this case, the inclusion of rituximab was not warranted and there are no trials regarding its specific use in PAL. However, it should be noted that there is convincing evidence that rituximab administered as

induction or maintenance with CHOP chemotherapy has been shown to significantly prolong failure-free survival in older patients with diffuse large B-cell lymphoma.[9,10]

CONCLUSION

Pyothorax-associated lymphoma is a relatively unusual condition that should be considered in patients in whom TB has been treated with an artificial pneumothorax. It is possible that a combined approach with surgery and adjuvant chemotherapy may improve long-term outcomes in this form of B-cell non-Hodgkin's lymphoma. Establishing patients' HIV and HHV8 status, more in keeping with primary effusion lymphoma, should be considered. The addition of rituximab was well tolerated and should be contemplated in CD20-positive tumours.

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