CASE REPORT

Primary pulmonary Hodgkin's lymphoma and a review of the literature since 2006

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SUMMARY

A 28-year-old woman of Laotian origin presented with dry cough, fevers, night sweats and weight loss over the preceding 6 weeks. Radiological investigations revealed large complex cavitary lesions in the middle and lower lobes of the right lung, with no mediastinal lymph node enlargement. Bronchoscopic investigations did not yield a diagnosis. CT-guided fine-needle aspiration raised the possibility of Langerhans cell histiocytosis. Open lung biopsy initially supported this, but eventually a microscopic and immunohistochemical diagnosis of Hodgkin's lymphoma was made. The final diagnosis was primary pulmonary Hodgkin's lymphoma. We present a new case as well as a literature review of reported cases published since 2006.

BACKGROUND

Secondary pulmonary involvement occurring in the course of Hodgkin's lymphoma occurs in 12–40% of patients and usually indicates an extension of disease originating in mediastinal or hilar lymph nodes.[1 2] Primary pulmonary Hodgkin's lymphoma, on the other hand, is a rare and often misdiagnosed entity (table 1), and represents lymphoma arising directly from lung tissue. The clinical picture at presentation and radiological findings are often non-specific. Definitive diagnosis most often requires invasive open lung biopsy, and a long diagnostic process may risk delays in potentially curative treatment.

CASE PRESENTATION

A 28-year-old Australian-born woman of Laotian heritage presented with dry cough, fevers, night sweats and weight loss of 6 weeks' duration. She had no medical problems and was a non-smoker. Respiratory examination revealed coarse crackles over the right upper zone anteriorly and the right lower zone posteriorly. Physical examination did not reveal clubbing, peripheral lymphadenopathy or hepatosplenomegaly. No cutaneous signs were present; however, the patient later reported that she had noticed an intermittent pruritic rash which got worse after a hot shower.

INVESTIGATIONS

Laboratory investigations revealed a significant neutrophilia (16.43×10^9/L). The C reactive protein was 209 mg/L. There were no other haematological or biochemical abnormalities. Hydatid, HIV and hepatitis serologies were negative, as were autoimmune and vasculitic screens. Multiple sputum samples were sent for acid-fast bacilli (AFB), microscopy and culture, but failed to solve the diagnostic problem.

Chest X-ray revealed consolidation of the right middle lobe with multiple cavities containing air-fluid levels (figure 1). A CT of the chest showed almost complete replacement of the right middle lobe architecture by a large low-density mass with cavitation and mild bronchiectasis, and alveolar consolidation in the right lower lobe (figure 2). Nodules and multiple cavities of varying sizes and wall thicknesses were seen in the right upper lobe. There was no evidence of mediastinal or hilar lymphadenopathy.

At bronchoscopy, the macroscopic appearance of the airways was normal. Specimens obtained for cytology, microscopy, culture and sensitivity including AFB, along with fungal stains, were unremarkable.

CT-guided fine-needle aspiration cytology (FNA) was performed twice. Initially, it revealed intense non-specific acute inflammation. The second sample was reported as a lymphohistiocytic infiltrate with atypical histiocytes in aggregates and eosinophils raising the possibility of Langerhans cell histiocytosis. Supplementary immunohistochemistry was negative for CD1a and predominantly negative for S100, contrary to a diagnosis of Langerhans cell histiocytosis and therefore inconclusive.

Three months after presentation, the patient developed haemoptysis complicated by anaemia. She was treated with tranexamic acid and blood transfusion. This prompted a referral to the cardiothoracic unit for open lung biopsy. A lung Wedge resection was performed. The histopathology was initially reported as florid active Langerhans cell histiocytosis. However, a second pathology opinion with additional immunohistochemistry noted scattered large mononuclear Hodgkin cells and classic Reed-Sternberg cells (figure 3, CD30 and CD15, Pax5 weakly positive), on a predominant background of T cells (CD3), B cells (CD20), neutrophils and eosinophils, with background Langerhans cells (figure 4, S100 and CD1a) in the periphery of the mass. A final diagnosis of primary pulmonary classical Hodgkin's lymphoma (nodular sclerosis subtype) with reactive histiocytosis was made.

Bone marrow examination was performed and was normal. Epstein-Barr virus (EBV) serology was indicative of prior infection.

DIFFERENTIAL DIAGNOSIS

The initial clinical presentation and a history of frequent travel to Laos led to a provisional diagnosis

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Table 1 Reported cases of primary pulmonary Hodgkin's lymphoma since 2006

Author	Year	Country	Gender	Age	Radiological appearance	Initial clinical diagnosis	Confirmatory investigation	HL type	CD15	CD30	Pax5	CD3	CD20	LCA
Pai *et al*[23]	2006	India	Female	28	Solid mass	Round pneumonia, tuberculosis	Wedge biopsy	NS	+	+	NA	NA	NA	NA
Zhang *et al*[36]	2006	China*	NA	NA	NA	NA	NA	MC	NA	NA	NA	NA	NA	NA
Zhang *et al*[36]	2006	China*	NA	NA	NA	NA	NA	MC	NA	NA	NA	NA	NA	NA
Bakan *et al*[6]	2007	Turkey	Male	21	Multiple cavitations with air-fluid level	Hydatid disease, suppurative pulmonary abscess, actinomycosis	Wedge biopsy	NA	NA	NA	NA	NA	NA	NA
Nakachi *et al*[35]	2007	Japan	NA	NA	NA	NA	Lymph node biopsy	NS	NA	NA	NA	NA	NA	NA
Nakachi *et al*[35]	2007	Japan	NA	NA	NA	NA	Lymph node biopsy	NLP	NA	NA	NA	NA	NA	NA
Tillawi[17]	2007	Saudi Arabia	Male	19	Pulmonary parenchymal mass	Langerhans cell histiocytosis, Wegener's granulomatosis	Wedge biopsy	NS	+	+	NA	–	–	NA
Tillawi[17]	2007	Saudi Arabia	Female	32	Pulmonary parenchymal mass with mediastinal mass	Pneumonia	CT-guided fine-needle aspiration suggestive wedge biopsy confirmatory	NS	+	+	NA	–	–	NA
Saad *et al*[25]	2007	USA	Female	21	Dense lobar air-space consolidation	Pneumonia, Pulmonary embolism	Wedge biopsy	NS	+	+	NA	NA	–	NA
Kumar *et al*[5]	2008	India	Male	36	Solid mass	Non-small cell lung carcinoma	Fine-needle aspiration	NS	+	+	NA	–	–	–
Malur *et al*[16]	2009	India	Female	43	Pulmonary parenchymal mass	NA	Wedge biopsy	n/a	+	+	NA	+	NA	NA
Lluch-Garcia *et al*[18]	2010	Spain	Male	21	Three cavitations with air-fluid level, ground glass appearance and air bronchograms	Pulmonary abscess	Wedge biopsy	NS	+	+	NA	+	+	NA
Homma *et al*[26]	2010	Japan	Female	58	Pulmonary parenchymal mass with cavitation	Lung adenocarcinoma, malignant lymphoma	Complete excision	NS	+	+	+ (weak)	–	–	–
Oka *et al*[31]	2010	Japan	Female	66	NA	NA	NA	NS	+	+	NA	NA	+	NA
Binesh *et al*[19]	2011	Iran	Female	54	Multiple bilateral nodules	NA	Wedge biopsy	NS	NA	–	NA	NA	–	–
Valizadeh *et al*[37]	2012	Iran	Male	28	Air-space consolidation	Tuberculosis	Wedge biopsy	NA	+	+	NA	N/A	–	–
Simon *et al*[38]	2012	Hungary	Male	30	Air-space consolidation	Atypical pneumonia, Tuberculosis, Wegener's granulomatosis, Malignancy	Complete excision	LR	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ezzine-Baccari *et al*[39]	2012	Tunisia	Female	23	Air-space consolidation with cavitation and micronodules	Tuberculosis	Wedge biopsy	MC	+	+	NA	NA	–	NA
McElnay *et al*[40]	2013	UK	Female	61	Pulmonary parenchymal mass	Solitary fibrous tumour	Complete excision	NS	NA	+	+	–	–	NA
Fratoni *et al*[41]	2013	Italy	Female	27	Pulmonary parenchymal mass	Mediastinal malignancy	Video-assisted thoracoscopy (VATS) with wedge biopsy	NS	+	+	+ (weak)	–	–	–

*Zhang *et al*[36] reported two cases of PPHL, both of mixed cellularity subtype; however, no other characteristics were provided. Li *et al*[42] reported nine cases of PPHL; however, no other characteristics were provided.
LR, lymphocyte-rich; MC, mixed cellularity; NS, nodular sclerosis; NLP, nodular lymphocyte predominant; NA, data not available.

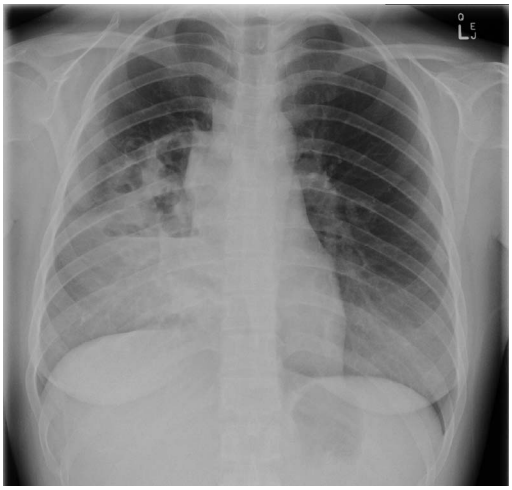

Figure 1 Chest roenterogram demonstrating consolidation and cavitation.

of pulmonary tuberculosis. Subsequent bronchoscopic and radiological evaluation broadened the differential to include congenital cystic adenoid malformation. Fine-needle aspiration further complicated the diagnosis, with a suggestion of Langerhans cell histiocytosis. Histological analysis of specimens taken at open biopsy also initially supported the diagnosis of Langerhans cell histiocytosis; however, review by a second pathologist and full immunohistochemistry led to the diagnosis being revised as classical Hodgkin's lymphoma.

TREATMENT

The patient was initially treated empirically for presumed *Mycobacterium tuberculosis* infection with the WHO standard four-drug regimen.[3] Failure to respond to antituberculous chemotherapy, deterioration in clinical state and suspicion of lung abscess prompted referral for cardiothoracic surgery. An open lung biopsy allowed definitive diagnosis and treatment.

OUTCOME AND FOLLOW-UP

The patient is currently undergoing chemotherapy with etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone, procarbazine (modified BEACOPP regimen) and the lung mass has shown rapid early regression.

DISCUSSION

The criteria for the diagnosis of PPHL include: (1) histological features of Hodgkin's lymphoma, (2) restriction of the disease

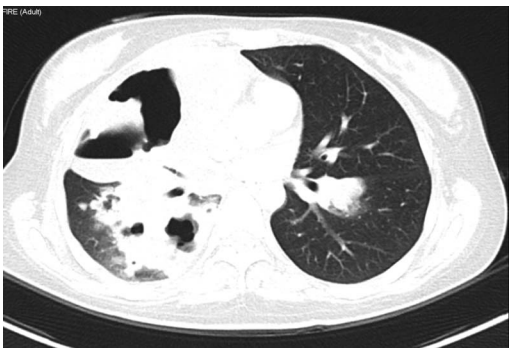

Figure 2 Chest CT demonstrating consolidation, cavitation and nodules.

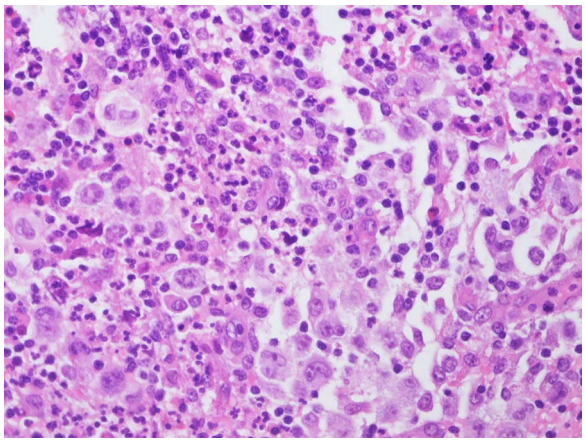

Figure 3 Periodic acid-Schiff stain demonstrating binucleate Reed-Sternberg cells and mononuclear Hodgkin's cells.

to the lung with or without minimal hilar lymph node involvement and (3) adequate clinical and/or pathological exclusion of the disease at distant sites.[4–6] Our case meets these criteria.

In 2006, fewer than 80 cases of PPHL without lymph node involvement had been reported.[7] We performed a literature review using the PubMed database, employing the search terms 'pulmonary lymphoma', 'Hodgkin's lymphoma', 'Hodgkin's disease' and 'primary pulmonary Hodgkin's lymphoma'. Reference lists were also reviewed to obtain further articles. Articles published in 2006 and thereafter, full text articles published in English and abstracts published in English were included. Since the 2006 review of Rodriguez and colleagues, 20 new cases have been reported in the literature, and are summarised in table 1.

Primary pulmonary lymphomas originate from mucosa-associated lymphoid tissue arising from lymphoid follicles or peribronchial lymph nodes and extending to the parenchyma, and are therefore described as separate entities from peripheral nodal lymphomas and from lymphomas affecting the lungs secondarily.[2] These tumours may be a type of Hodgkin's (PPHL) or non-Hodgkin's lymphoma (NHL).[8] Primary pulmonary lymphomas are rare entities,[9] and of these, only 1.5–2.4% are attributable to PPHL.[10]

In the largest report, PPHL showed a slight female preponderance (1.4 : 1 F:M), with a bimodal age distribution (<35 and

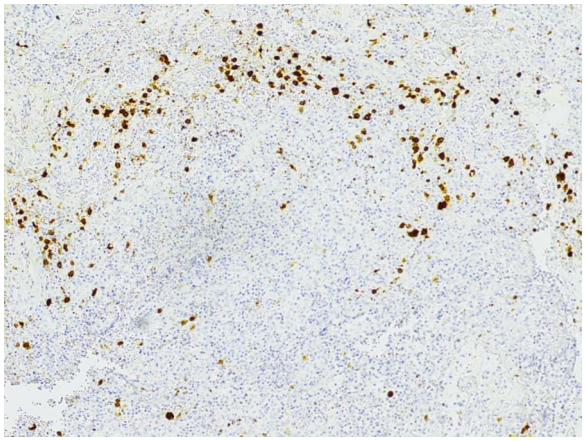

Figure 4 Histiocytes staining positive for S100 in the periphery of the mass.

>60 years).[11] A review of cases from 2006 did not replicate these observations; however, the incidence was highest in 21–30-year-olds (table 1). The most common presenting symptoms are weight loss, fever, night sweats and dry cough. Dyspnoea and haemoptysis are also common, as noted in this case.[11]

Radiologically, PPHL typically involves the superior portions of the lungs, whereas secondary pulmonary involvement from Hodgkin's lymphoma shows a more random miliary distribution without zonal predilection.[7 11 12] Many present as a solitary mass, alveolar consolidation or multiple nodules (table 1).[11 12] Cavitary pulmonary lesions have a wide differential diagnosis.[13] The present case emphasises that no radiological appearance is pathognomic for PPHL.

Bronchoscopic evaluation is warranted to exclude other pathologies, although endobronchial lesions are rare,[14–16] and bronchial cytology often fails to yield Reed-Sternberg cells.[12 15] Diagnosis usually requires an open thoracotomy and lung biopsy (table 1).[6 12 17–19]

Hodgkin's lymphoma is divided into either the nodular lymphocyte predominant type or into one of four classical subtypes: nodular sclerosing, mixed cellularity, lymphocyte rich and lymphocyte depleted.[20] In PPHL, the nodular sclerosing histological type is most common, as was our case, followed by the mixed cellularity type.[7 21 22] Initial misdiagnosis based on histological appearance, as occurred in the present case, has been reported previously.[23 24] Immunohistochemistry provides the definitive diagnosis in histopathologically indistinct cases.[25] PPHL tumour cells are positive for CD15, CD30, Pax5 and rarely CD20, and negative for T-cell markers.[26 27] The most considered diagnoses in the current case were tuberculosis, congenital adenoid cystic malformation on the basis of radiology and Langerhans histiocytosis on the basis of the initial histopathology. Immunohistochemistry staining for CD3 and CD15 and lack of predominant staining for CD1a and S100 were instrumental in ruling out the latter possibility, although cases of Langerhans histiocytosis with concurrent pulmonary Hodgkin's lymphoma have been described.[28 29]

This case shows serologi evidence of prior EBV infection, although the lung biopsy was not analysed for EBV-encoded small RNA. The true contribution of EBV to Hodgkin's lymphoma remains unknown.[30] There are only a few reports of PPHL associated with EBV infection.[24 26 31] Prior infection with EBV is reported in 33–50% of all cases of Hodgkin's lymphoma.[24 30] It has been suggested that EBV infection may be present in all patients with Hodgkin's lymphoma, but that in immunocompetent patients the EBV genome may persist as integrated fragments or as a defective genome with absent viral gene expression, and therefore may not be diagnosed as EBV positive using conventional techniques.[32] EBV has been associated with a survival disadvantage in several population-based series, although perhaps not in women aged between 19 and 44 years.[30]

Owing to the lack of survival data, prognostic factors affecting survival of PPHL are not well defined,[10] but several factors have been suggested: 'B' symptoms, bilateral disease, multilobar involvement, penetration of the pleura with or without associated pleural effusion, cavitation, age greater than 60 years and clinical relapses.[12 33 34] Nakachi *et al*[35] found that 14 of 23 patients with PPHL survived and four relapsed or died, which suggests that the prognosis for PPHL is not as poor as previously reported.[12 26]

Management plans vary in the literature. Although surgical biopsy is required in most cases for diagnosis, the indications for surgical treatment are poorly defined.[10 36] It has been generally accepted that, for diffuse and bilateral lesions, the combination of multiple-agent chemotherapy and radiotherapy is required.[12 17 34] Recent authors have recommended chemotherapy over radiotherapy due to the risk of radiation pneumonitis.[27 35]

Learning points

- Primary pulmonary Hodgkin's lymphoma is a rare disease and is distinct from Hodgkin's lymphoma affecting the lungs secondarily.
- The clinical presentation and the radiological and histological appearances are non-specific.
- Immunohistochemical evaluation of open lung specimens is in most cases required to make the diagnosis.
- The challenges of the diagnostic process can delay potentially curative therapy.

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Patient consent Obtained.

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