Pulmonary infiltration with eosinophilia complicated with mucosa-associated lymphoid tissue lymphoma: A case report

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Abstract. Tissue eosinophilia is rarely observed in cases of non-Hodgkin's lymphoma of B cell origin. The present study describes a rare case of mucosa-associated lymphoid tissue (MALT) lymphoma, which was initially misdiagnosed as eosinophilic pneumonia. The initial diagnosis was formed based on the results of chest radiography, peripheral eosinophilia tests and bronchoalveolar lavage, and the clinical course of the patient. Following administration of methylprednisolone (40 mg/day) for 4 days and oral administration of prednisolone (30 mg/day), the clinical course rapidly improved and the eosinophil count immediately decreased a to normal level. However, abnormal shadows observed on computed tomography (CT) scans of the chest did not diminish. At 6 months after the initiation of treatment, CT-guided percutaneous lung biopsy was performed, and a final diagnosis of primary pulmonary mucosa-associated lymphoid tissue lymphoma was made based on immunohistochemical examination. Primary lung MALT lymphoma remains a rare entity, with an indolent course and a reasonably favorable prognosis, whose diagnosis may be challenging.

Introduction

Eosinophilic lung diseases, which comprise a varied group of pulmonary diseases, are characterized by eosinophilic infiltration of the interstitium of the lung, airways or alveoli (1). They were originally described as pulmonary infiltration with eosinophilia syndromes, and were classified by the observation of lung infiltrates associated with peripheral blood eosinophilia on chest radiographs (2). Currently, the detection of eosinophilic lung disease may be based on the observation of lung tissue eosinophilia on lung biopsy, bronchoalveolar lavage (BAL) eosinophilia or pulmonary disease with blood eosinophilia. Primary lung mucosa-associated lymphoid tissue (MALT) lymphoma is a rare distinct entity. The outcome is generally favourable in the majority of cases, with a 5-year overall survival of >80% or >10 years (3). Generally, these cases are difficult to diagnose accurately due to their nonspecific clinical and radiological presentation (3). The present study reports a rare case of MALT lymphoma, which was initially misdiagnosed as eosinophilic pneumonia.

Case report

A 49-year-old woman was referred to Drum Tower Hospital (Nanjing, China) in December 2012, presenting with a 2-month history of low-grade fever and a non-productive cough. The patient was a non-smoker, had not recently travelled abroad and did not own any domestic pets. The patient also denied any history of allergic conditions. Her vital signs were stable at initial examination; the patient was afebrile and oxygen saturation was 95% in ambient air. On physical examination, auscultation of the lungs detected slight coarse crackles at the right base. The remainder of the examination was unremarkable. Laboratory tests identified hypereosinophilia [white cell count: 7,200 cells/μl (normal range, 4,000-10,000 cells/μl), comprising 44.1% eosinophils (normal range, 0.5-5.0%), 33.3% neutrophils (normal range, 51.0-75.0%) and 15.6% lymphocytes (normal range, 20.0-40.0%)]. Blood chemistry analysis did not provide any remarkable data. The patient was negative for antinuclear, antineutrophil cytoplasmic and antiparasitic antibodies in immunofluorescence assays. A comprehensive metabolic profile was normal and urine analysis did not identify any sediment. Arterial blood gas analysis was as follows: pH, 7.444 (normal range, 7.350-7.450); PaO_2, 73 mmHg (normal range, 80-100 mmHg); and $PaCO_2$, 37.1 mmHg (normal range, 35.0-45.0 mmHg) in room air. High-resolution chest computed tomography (CT; LightSpeed; GE Healthcare Life Sciences, Chalfont, UK) revealed no pleural effusion or pulmonary edema, but did identify diffuse, non-segmental areas of patchy (or airspace) consolidation with peripheral predominance (Fig. 1A-C). Lung spirometry was performed and the forced expiratory volume of 1 sec (FEV1), forced vital capacity (FVC) and their ratio (FEV1/FVC) were determined to be 81.3, 84.3 and 96.9% of the predicted values,

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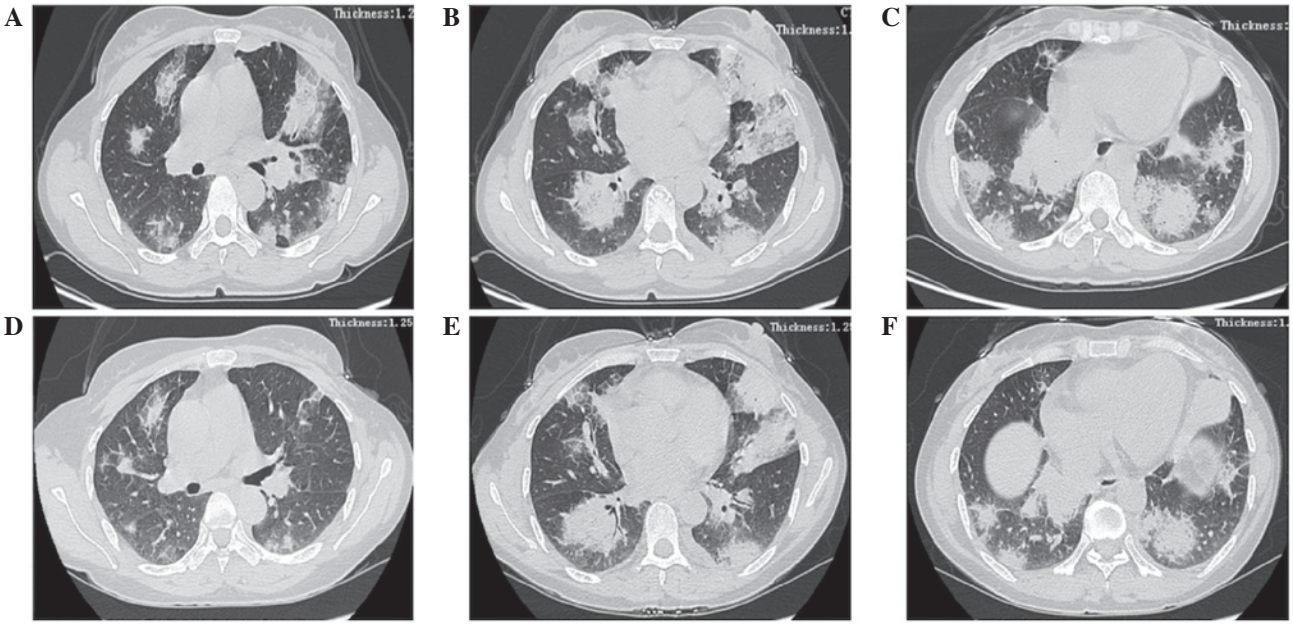

Figure 1. CT scans performed at initial presentation and 6 months post-steroid treatment. Initial CT scans showing (A) multifocal nodules with poorly-defined margins and ground-glass changes in the upper and middle lobes and (B) diffuse areas of patchy or airspace consolidation distributed along the broncho-vascular bundle or pleura in both middle and lower lobes. (C) Initial CT scans of the middle and lower lobes showing multiple peripheral lung nodules and consolidation distributed along the pleura prior to steroid treatment. Chest CT scans performed after 6 months of steroid treatment showing that (D) small areas of ground-glass change were partially absorbed, and (E) the patchy consolidation was not alleviated following treatment. (F) No changes in the peripheral lung nodules and consolidation were observed subsequent to steroid treatment CT, computed tomography.

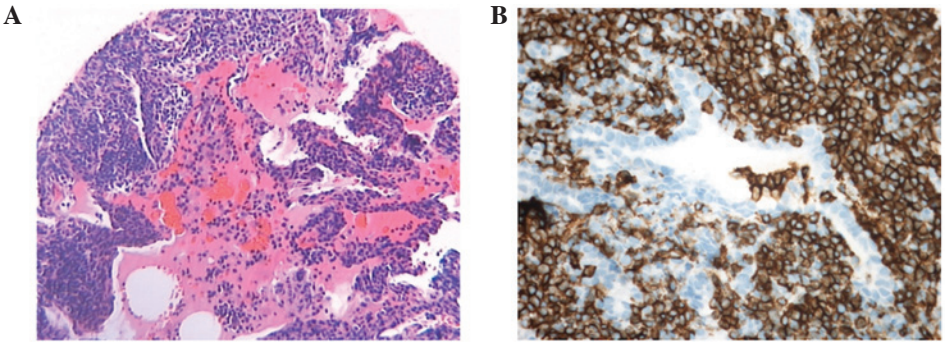

Figure 2. (A) Diffuse, severe lymphoid cell infiltration with a few plasma cells in the interstitium and alveolar walls (hematoxylin and eosin staining; magnification, x100). (B) Lymphoid cells were evenly admixed with B lymphocytes, which were immunoreactive for cluster of differentiation 20 (immunostaining with polymer/multimer 3,3'-diaminobenzidine detection system on paraffin embedded sections; magnification, x200).

respectively. In addition, carbon monoxide diffusion was 57.7% of the predicted value.

On day 4 of hospitalization, bronchoscopy with a trans-bronchial lung biopsy (TBLB) was performed from the left lingular lobe and the right middle lobe spur. In addition, BAL was performed on the right middle lobe. The percentage of eosinophils observed in the fluid obtained from BAL was 64%. Based on these observations, the patient was diagnosed with eosinophilic pneumonia. Corticosteroids (40 mg/day methyl-prednisolone) were administered for 3 days, followed by oral administration of prednisolone (30 mg/day), which resulted in immediate improvement, with the eosinophil count rapidly decreasing from 44.1% to a normal level within 3 days. The patient was discharged and instructed to gradually reduce the dose of prednisolone to 20 mg. However, 6 months after the initiation of treatment, the abnormal shadow observed on CT scans of the chest had not diminished (Fig. 1D-F). CT-guided needle biopsy of the lung was performed. Tissue samples were fixed in 10% neutral formaldehyde solution (Sigma-Aldrich China, Inc., Shanghai, China), dehydrated, embedded in paraffin (Leica Biosystems, Shanghai, China), and conventionally stained with hematoxylin and eosin. Microscopic examination (BX41; Olympus Corporation, Tokyo, Japan) of the specimen revealed an intense lymphoid infiltrate, which primarily consisted of B cells (Fig. 2A). Deparaffinized sections of patient tissue samples were washed with phosphate-buffered saline (PBS) three times for 5 min each. In order to block the endogenous peroxidase activity, the sections were incubated in PBS that contained 3% H_2O_2 for 10 min, and then immersed in 10% sheep serum for 30 min, prior to be incubated overnight with specific antibodies against cluster of differentiation (CD)3 (clone PS1; mouse anti-human monoclonal antibody; dilution, 1:100; PA0553; Novo castra; Leica Biosystems), CD5 (clone 4C7; mouse anti-human monoclonal antibody; dilution, 1:100; M3641; Dako, Glostrup,

Denmark), CD20 (clone L26; mouse anti-human monoclonal antibody; dilution, 1:500; M0755; Dako) and CD79a (clone JCB117; mouse anti-human monoclonal antibody; dilution, 1:150; M7050; Dako). The sections were washed and stained according to the manufacturer's protocol. Immunohistochemical analysis demonstrated that the lesion was positive for B cell markers, including cluster of differentiation (CD)20, CD79a and B cell lymphoma 2, and negative for T cell markers, including CD5 and CD3 (Fig. 2B). These findings were consistent with a diagnosis of MALT lymphoma. Thus, the patient was referred to the Department of Hematology of Drum Tower Hospital, where the patient was treated with 6 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone). The patient was followed up 30 months, and continues to be stable at present.

Discussion

Pulmonary eosinophilic infiltrates are a heterogeneous group of pulmonary disorders that are accompanied by characteristics of eosinophilia and lung disease in the peripheral blood, pulmonary interstitium or BAL fluid. Radiological and clinical presentations of these disorders may include chronic or acute eosinophilic pneumonia, allergic bronchopulmonary aspergillosis, simple pulmonary eosinophilia and pulmonary eosinophilia associated with a systemic disease, such as hypereosinophilic syndrome or Churg-Strauss syndrome (1). A diagnosis of eosinophilic lung disease may be determined by the identification of any of the following: Tissue eosinophilia confirmed at open biopsy or TBLB, increased eosinophils in BAL fluid, or pulmonary opacities with peripheral eosinophilia (4).

In the present case, a CT scan of the chest at admission demonstrated infiltrations in each lung with blood eosinophilia, and BAL fluid analysis identified a significant increase in the percentage of eosinophils. At admission, the clinical course of the patient and the BAL fluid results corresponded with a diagnosis of chronic eosinophilic pneumonia; thus, video-assisted thoracoscopic (VATS) lung biopsy or CT-guided percutaneous lung biopsy were not performed. As it is not possible to diagnose malignant lymphoma from BAL fluid analysis (3), this disease may have gone undetected at the time of referral.

Eosinophilic pneumonia may present as an early manifestation of lymphoma (4); thus, patients must be carefully monitored for any signs of deterioration in their clinical condition. Tissue eosinophilia is often observed in Hodgkin's disease and non-Hodgkin's lymphoma of T cell origin (5,6). However, eosinophilia is rarely observed in non-Hodgkin's lymphoma of B cell origin (3). There have been a limited number of cases of chronic eosinophilic pneumonia occurring prior to lymphoma (histiocytic type) and malignant histiocytosis (7,8), and pulmonary MALT lymphoma is extremely rare (3).

The physical signs and symptoms of pulmonary MALT lymphoma are highly heterogeneous. Symptomatic patients may present with hemoptysis, a cough, chest pain, sputum and/or moderate fever (3). The disease is characterized by indolent lesions, and patients often have a good prognosis (3). Additionally, the radiographical appearance of pulmonary MALT lymphoma is highly diverse (9). McCulloch *et al* (10) observed that MALT lymphoma lesions were typically multifocal and composed of poorly-defined nodules containing air bronchograms. The same study also reported the presence of focal lobar consolidation (10). Mediastinal lymphadenopathy and pleural reaction are uncommon (10). Bae *et al* (11) assessed the radiological appearance of 21 cases of MALT lymphoma. It was determined that multiple or single nodules, or areas of consolidation were the predominant radiographical abnormalities observed (11). In the current case, the major radiographical abnormality observed was described as multiple, patchy (or airspace) consolidations. Due to the poorly-defined clinical and imaging features of this disease, the majority of cases are initially misdiagnosed as pneumonia, pulmonary tuberculosis, organizing pneumonia or interstitial lung disease, and the diagnosis of primary pulmonary lymphoma is a common clinical challenge (11).

A diagnosis of pulmonary MALT lymphoma may only be confirmed by pathological methods. Open thoracotomy, or CT-guided percutaneous or VATS lung biopsies are the most commonly used methods to obtain samples. CT-guided percutaneous needle biopsy minimizes the requirement for open biopsy, and has therefore become an important diagnostic tool (3). A final diagnosis of primary pulmonary lymphoma requires a tissue sample obtained through invasive procedures. CT-guided core-needle biopsy is also widely used in the classification and diagnosis of malignant lymphomas.

In conclusion, the present study described an extremely rare case of malignant lymphoma, which was initially misdiagnosed as eosinophilic pneumonia. If a patient is not responsive to treatment, an alternative diagnosis should be considered and invasive procedures, including CT-guided percutaneous lung biopsies, open thoracotomy or a VATS lung biopsy, should be performed to provide an accurate diagnosis.

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