



Case report

Idiopathic eosinophilic pleurisy: A practical diagnostic approach

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ABSTRACT

A 37-year-old man with fever, cough, and dyspnea with no medical history developed an eosinophilic pleural effusion and blood eosinophilia. No evidence of malignancy or pathogens was detected in the pleural effusion, and the pleural specimen obtained by thoracoscopy showed eosinophilic infiltration with inflammatory granulation tissue without fibrinoid necrosis or malignant cells. Since a myeloproliferative disorder was also excluded, the diagnosis was idiopathic eosinophilic pleurisy. Corticosteroid treatment was started and then slowly tapered, and the eosinophilic pleural effusion resolved. Considering the various etiologies of eosinophilic pleurisy, a practical clinical approach to the investigation and diagnosis of eosinophilic pleurisy is presented.

1. Introduction

Eosinophilic pleurisy, which is defined as pleural inflammation with an eosinophilic pleural effusion, can be the result of a variety of differential etiologies, from benign to malignant diseases [1–3], and appropriate examinations are necessary to obtain the correct diagnosis. The case of a patient with idiopathic eosinophilic pleurisy with an eosinophilic pleural effusion as a diagnosis of exclusion based on various examinations focusing on the different etiologies is presented. In addition, an approach to the investigation and diagnosis of this condition based on the frequency and importance of the various etiologies, as well as the ease of performance and physical invasiveness of the examinations, is presented. Better understanding of the differential diagnosis of eosinophilic pleurisy with an eosinophilic pleural effusion and the role of investigations can facilitate rapid and accurate diagnosis, avoiding misdiagnosis of the underlying etiology, leading to the selection of appropriate treatment.

1.1. Case presentation

A 37-year-old Japanese man with a 4-month history of fever, cough, and dyspnea with abnormal chest X-ray findings was referred to a respirologist. He had no past history, including allergic diseases,

asbestos exposure or recent trauma, and was on no regular medications, including dietary supplements. He had never eaten raw meat or fresh-water fish. On physical examination, his temperature was 37.8 °C, and respiratory sounds were decreased on the left side, with no abnormal respiratory sounds. He had no skin rash, bruises, or sensorimotor disorders. Chest radiography showed decreased permeability in the left lower lung field (Fig. 1a), and dynamic chest computed tomography showed a pleural effusion with passive atelectasis and pleural thickening on the left side (Fig. 1b and c). Thrombosis in the pulmonary artery and other abnormalities were not observed. On laboratory examination of the pleural effusion, the white blood cell count was 3200/μL, with 68.0% eosinophils, and total protein was 4.8 g/dL, albumin was 2.8 g/dL, and lactate dehydrogenase was 796 IU/L, indicating an exudative pleural effusion with no malignant cells on cytology and no detection of pathogens, including tuberculosis. Adenosine deaminase was 26.8 IU/L. These results were the same on examination of his other pleural effusion specimen. Blood tests showed a white blood cell count of 14,900/μL, and eosinophils were 68.0%, with no abnormal lymphocytes or hemocytoblasts. Total IgE was 730 IU/mL, and C-reactive protein was 1.57 mg/dL. Other results including liver enzymes, rheumatoid factor, antinuclear antibody, anti-neutrophil cytoplasmic antibody, and urinalysis were normal. Parasite IgG in serum, and examinations for helminth eggs were negative in stool and the pleural effusion. A thoracoscopic pleural biopsy

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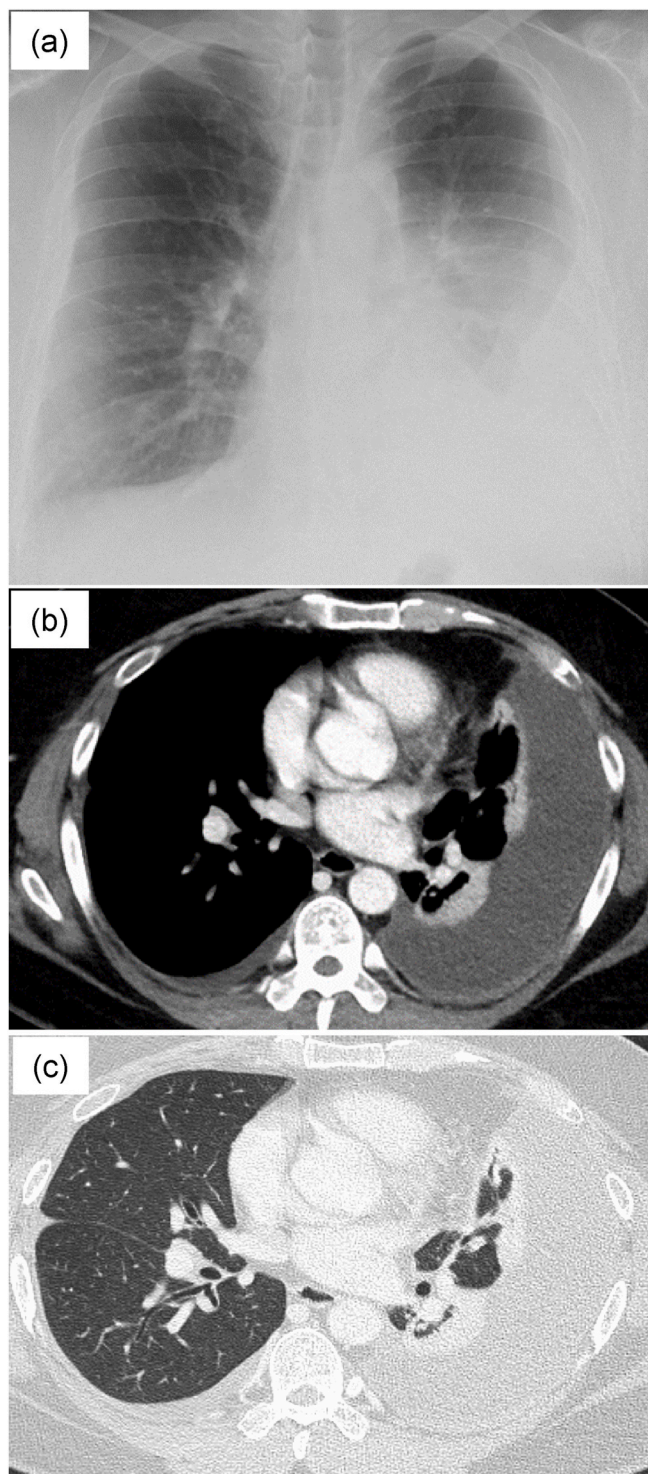


Fig. 1. Findings on chest X-ray and dynamic computed tomography (CT) before corticosteroid treatment. (a) Chest radiography shows reduced permeability in the left lower lung field. (b, c) Dynamic chest CT shows a pleural effusion with passive atelectasis and pleural thickness on the left side.

was performed, and eosinophilic infiltration with inflammatory granulation tissue was seen without fibrinoid necrosis or malignant cells (Fig. 2a). To rule out a myeloproliferative disorder, a bone marrow biopsy was performed, and normocellular marrow with 10% eosinophils

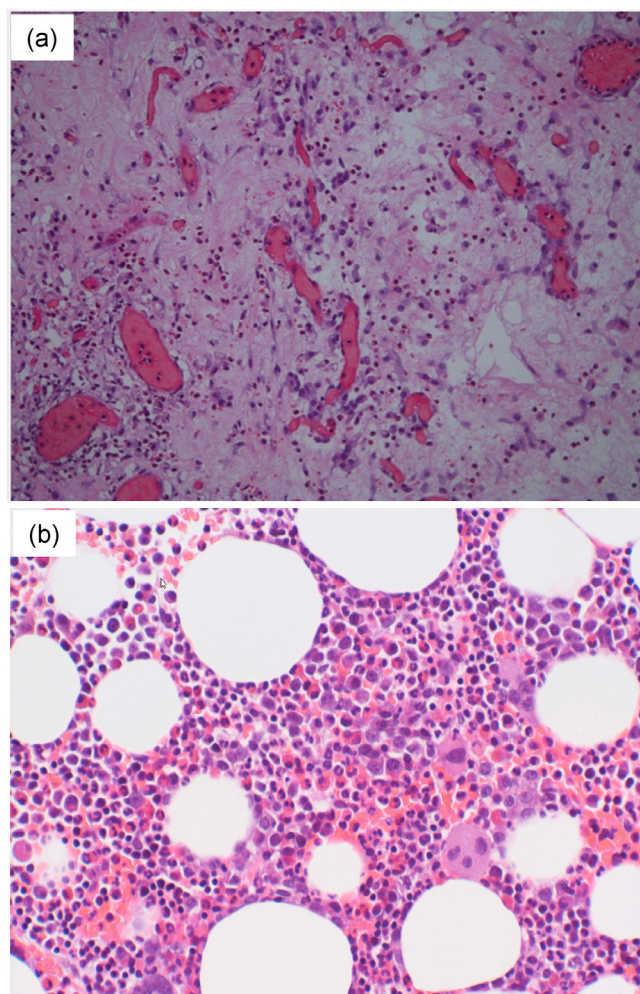


Fig. 2. Histological findings of the pleural specimen and bone marrow. (a) Histological examination of the pleural specimen shows eosinophilic infiltration with inflammatory granulation tissue without fibrinoid necrosis or malignant cells (x200). (b) Histological examination of the bone marrow shows normocellular marrow with 10% eosinophils in nucleated cells, with no maturity disorder of granulocytes and no increase of hemocytoblasts (x200).

in nucleated cells, with no maturity disorder of granulocytes and no increase of hemocytoblasts, was seen (Fig. 2b). Philadelphia chromosome, FIP1-like-1 (FIP1L1) – platelet derived growth factor receptor alpha (PDGFRA) fusion gene, platelet derived growth factor receptor beta (PDGFRB), and fibroblast growth factor receptor 1 (FGFR1) were not detected. A diagnosis of idiopathic eosinophilic pleurisy was made, and the patient was treated with prednisolone 0.5 mg/kg/day with gradual tapering. After treatment, the fever, cough, and dyspnea resolved along with a decrease of blood eosinophils. His pleural effusion disappeared 3 months after treatment (Fig. 3a). Currently, he has had no recurrence for 10 months on treatment with 5 mg/day of prednisolone.

2. Discussion

Eosinophilic pleurisy is defined as pleural inflammation with an eosinophilic pleural effusion. An eosinophilic pleural effusion, which is the most frequent manifestation of eosinophilic pleurisy, is defined as a pleural effusion with eosinophils accounting for more than 10% of the white blood cells [4]. Although the incidence rate of eosinophilic pleural effusion differs depending on the report, it is estimated that 5–9% [3–5]

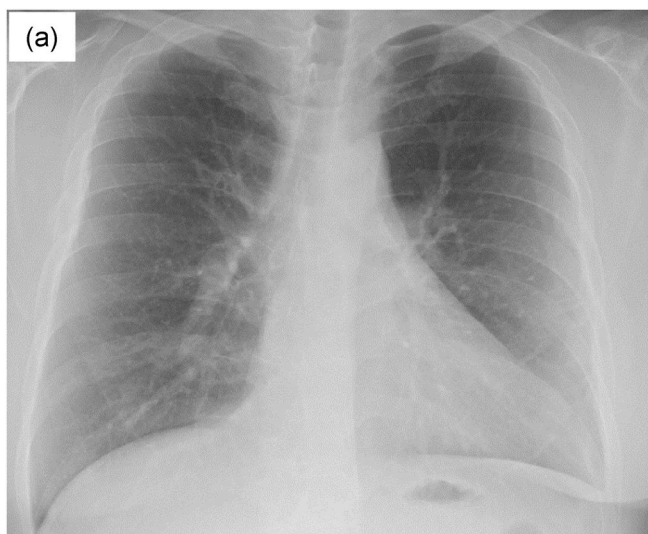


Fig. 3. Findings on chest X-ray after 3 months of corticosteroid treatment. (a) Chest radiography shows that the pleural effusion on the left side has disappeared after treatment.

of exudative pleural effusions are eosinophilic pleural effusions, suggesting that they are certainly not rare in daily clinical practice. A prospective cohort study of 476 patients whose pleural effusions were analyzed showed that the cumulative survival was significantly better in patients with eosinophilic pleural effusions than in those with non-eosinophilic pleural effusions [3], but the rate of malignant etiology was not significantly different between them [3].

With respect to the clinical manifestations of patients with eosinophilic pleural effusions, the blood eosinophil level depends on the etiology of the eosinophilic pleural effusion, since it is higher in patients with non-malignant eosinophilic pleural effusions than in those with malignant eosinophilic pleural effusions [1], which is supported by the current case. In addition, the probability of patients having malignancy is inversely related to the percentage of eosinophils in the pleural effusion, and the sensitivity and specificity of differentiation between malignant versus non-malignant etiologies of eosinophilic pleural effusion is estimated as 85.1% and 34.3% respectively, if the cut-off level is defined as 40% [1,2], which is also consistent with the current case.

There are very many different causes of eosinophilic pleural effusion, as previously reported [1,3,6,7], and making the correct diagnosis in an individual case is vital for providing appropriate treatment. In transudative pleural effusions defined by the criteria of Light, the etiologies of eosinophilic pleural effusion include congestive heart failure, nephrotic syndrome, and hepatic hydrothorax, although they are not normally causes of pleurisy [1,7]. In exudative pleural effusion, malignancy, such as lung cancer, mesothelioma, and other sites of cancers, is the most critical etiology that cannot be missed, accounting for approximately 17% of cases of eosinophilic pleural effusion [1,6]. In addition, respiratory infections including parapneumonic effusion and tuberculosis are also important etiologies, accounting for 10% each [1, 8]. As for other etiologies of eosinophilic pleural effusion, connective tissue diseases including rheumatoid arthritis and ulcerative colitis, pulmonary embolism, benign asbestos pleural effusion and pancreatic diseases including acute pancreatitis account for a few percent of the etiologies of eosinophilic pleural effusions [1,9–11]. Importantly, in previous studies, around 20% of the cases were of unknown etiology, some of which might have been occult, rare differential diagnoses including hypereosinophilic syndrome, eosinophilic granulomatous polyangiitis, chronic eosinophilic pneumonia, chronic myeloid

leukemia, human T-cell leukemia virus type 1 infection, drug-induced pleuritis, and parasitic infestations [1,12–18], although they should be diagnosed because they require specific treatments. Thus, it is necessary to have an approach to the investigation of the different causal etiologies of eosinophilic pleurisy taking into account their frequency, importance, and the ease of performance and invasiveness of the examinations.

Recently, Luo et al. reported a diagnostic procedure for idiopathic eosinophilic pleural effusion [19]. Because we focused on the different causal etiologies of eosinophilic pleurisy including malignancy, we propose an approach to investigation with more detailed context of the examinations (Fig. 4). After confirmation of the presence of an eosinophilic pleural effusion that contains more than 10% eosinophils on the cell differential count, a history of the progression of the pleural effusion, trauma, and drugs should be confirmed because such benign etiologies might be controlled without any additional treatment. Comorbidities including malignancy, connective tissue diseases, and others are also important when considering the etiologies of eosinophilic pleurisy. In the next step, dynamic CT is performed to detect abnormalities in addition to pleural effusions, including malignancy, embolism, and lung infiltrates. In addition, repeated analyses of cytology and staining and cultures for infections of pleural effusions should be performed to increase the sensitivity of the examinations and avoid misdiagnosis [20,21]. Blood examinations including smears to evaluate the forms of blood cells, eosinophil count, biochemistry, tumor markers, and autoantibodies are also useful, without being severely physically invasive, to differentiate the etiologies mentioned above. If the above examinations are negative, examinations for parasitic infestations, such as parasite IgG in serum and/or examinations for helminth eggs in stool and the pleural effusion are considered. After confirmation of negative findings from these examinations, with an increasing amount of eosinophilic pleural effusion, thoracoscopy can be performed to make a diagnosis of malignancy and infections such as tuberculosis, as reported previously [4,22,23], although its use may be limited, because thoracoscopy can be performed in few institutions, and it is an invasive examination for the patient.

Finally, corticosteroid treatment could be considered for idiopathic eosinophilic pleurisy if no other etiology were found, but bone marrow biopsy and gene analysis of FIP1L1/PDGFR α , PDGFR β , and FGFR1 are considered in cases of massive blood eosinophilia to make the diagnosis of chronic myeloid leukemia and hypereosinophilic syndrome, such as in the current case, or in cases with no known etiology that are refractory to corticosteroid treatment. Notably, a recent report suggested that mepolizumab, a targeted humanized monoclonal antibody of interleukin-5, might be effective for certain cases, such as the present case, of eosinophilic pleurisy with blood eosinophilia as hypereosinophilic syndrome [24].

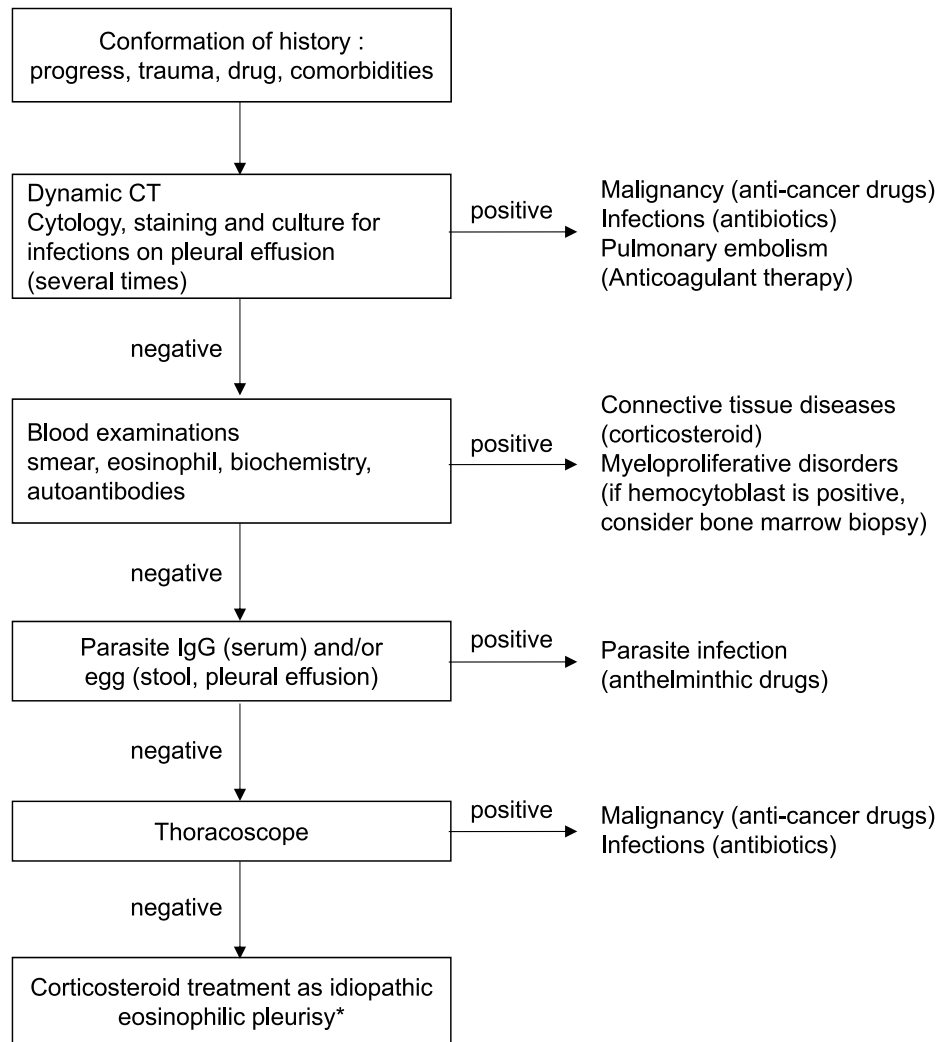
3. Conclusion

The case of a patient with idiopathic eosinophilic pleurisy diagnosed by various examinations focusing on the different etiologies was reported. In addition, an approach to investigation that contributes to better understanding of the differential diagnoses of eosinophilic pleurisy, avoiding misdiagnosis of the etiologies, leading to accurate selection of the treatment was presented.

Declaration of competing interest

The authors declare that they have no competing interests.

Eosinophilic pleural effusion containing more than 10% of eosinophils



*Consider bone marrow biopsy and gene analysis in case of massive blood eosinophilia and/or refractory for corticosteroid with unknown etiology

Fig. 4. Flow chart of investigations for eosinophilic pleurisy considering the different etiologies.

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