CASE REPORT

Eosinophilic Pleural Effusion as the First Presentation of Angioimmunoblastic T Cell Lymphoma

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Eosinophilic pleural effusion (EPE), defined as pleural effusion that contains at least 10% eosinophils among the leukocytes, can be a manifestation of a great variety of diseases. However, eosinophilia is a relatively rare finding in malignant pleural effusions, and it has been used as an indicator of good prognosis. In clinical experience, very few cases of malignant lymphomas accompanied by EPE have been reported. In this report, we present an 82-year-old otherwise healthy man with the initial presentation of left EPE. Pleural biopsy could not yield a definite diagnosis initially. Hookworm ova were also found in the stool and parasite associated with EPE was suspected. However, after anti-parasitic agent treatment with mebendazole, the pleural effusion did not improve. Six months later, bilateral neck, axillary and inguinal lymphadenopathy developed, and lymph node biopsy confirmed the diagnosis of angioimmunoblastic T cell lymphoma, with positive CD10 expression. Therefore, we retrospectively carried out CD10 staining of the sample obtained from pleural biopsy and the positive result confirmed that the etiology of EPE was due to malignant T cell lymphoma. The patient refused chemotherapy and he died 1 month later. [*J Formos Med Assoc* 2007;106(2):156–160]

Key Words: angioimmunoblastic T cell lymphoma, eosinophilic pleural effusion

Eosinophilic pleural effusion (EPE), first described by Harmsen in 1894, is defined as pleural effusion that contains at least 10% eosinophils among the leukocytes, and can be a manifestation of a great variety of diseases. However, eosinophilia is a relatively rare finding in malignant pleural effusions. Adelman et al concluded that the presence of pleural fluid eosinophilia reduces the probability of malignancy and denotes a benign underlying disorder.[1] That view has been challenged by three other studies.[2–4] In clinical experience, however, very few cases of malignant lymphomas accompanied by EPE have been reported.[5–8] Here, we report an unusual case of angioimmunoblastic T cell lymphoma (AITL) presenting initially with EPE.

Case Report

An 82-year-old man, a non-smoker, visited our chest outpatient department with the complaint of progressive dyspnea of 5 days' duration. The dyspnea was associated with fever, dry cough, and poor appetite. The patient was a farmer and denied any history of asthma or chronic obstructive

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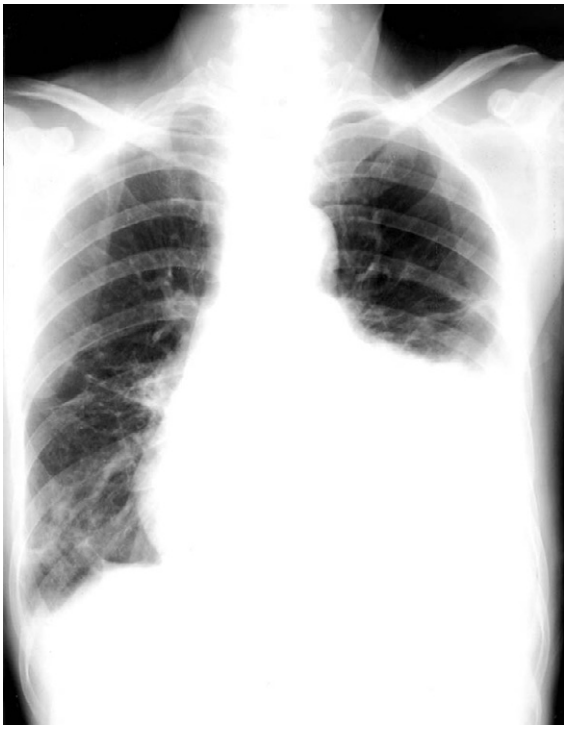

Figure 1. Chest radiography on admission shows left massive pleural effusion.

pulmonary disease; he had not taken any drug before this event. Chest radiography showed left massive pleural effusion and he was admitted for further evaluation.

On physical examination, his temperature was 38.1°C, pulse rate was 102/minute, respiratory rate was 22/minute, and blood pressure was 178/84 mmHg. The neck was supple and no lymphadenopathy was found. Chest examination revealed diminished breath sounds on the left side. No hepatosplenomegaly was noted. Hematologic study showed: red blood cell count, $4.32 \times 10^6/\mu L$; hemoglobin, 10.7 g/dL; white blood cell count, 9910/μL; neutrophils, 65.8%; lymphocytes, 14.2%; eosinophils, 12%; platelets, 277,000/μL. Serum biochemistries were all within normal limits except albumin (2.6 g/dL) and globulin (3.7 g/dL).

Chest radiography revealed left large pleural effusion (Figure 1). Diagnostic thoracentesis yielded an exudative pleural effusion (total protein, 3.9 g/dL; lactate dehydrogenase, 288 IU/L) with eosinophilia (white blood cell count, 890/μL; neutrophils, 27%; lymphocytes, 53%; eosinophils, 17%; monocytes, 3%). Cytologic examinations of

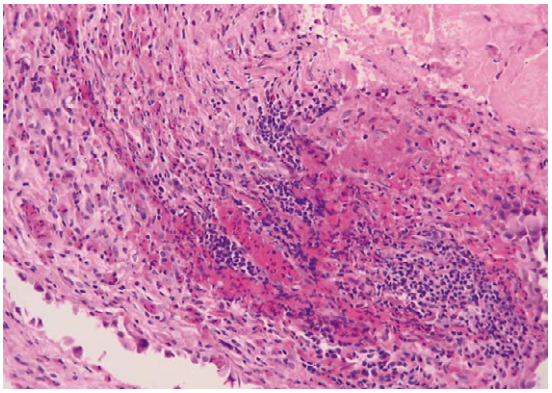

Figure 2. Pleural biopsy revealed patchy lymphocytic collections and dense eosinophilic infiltrate (hematoxylin & eosin, 200×).

pleural effusion and sputum were negative for malignancy. Chest computed tomography did not reveal additional information, and there was no pericardial fluid seen on the examination.

Pathologic examination of the pleural biopsy specimen revealed patchy lymphocytic collections and dense eosinophilic infiltrate (Figure 2), but a definite diagnosis could not be made initially. As the symptoms were relieved by thoracentesis, the patient refused further examination and he was discharged. Subsequently, he experienced dyspnea 3 weeks later and bilateral pleural effusion developed. He was readmitted; pleural fluid was re-examined and showed exudative effusion with eosinophilia (21%), a similar result as that obtained previously. However, hookworm ova were found in the stool. Parasite associated with EPE was suspected and mebendazole was prescribed. After a complete treatment course, stool examination was negative for hookworm ova. However, pleural effusion continued to progress. Fiberoptic bronchoscopy with bronchoalveolar lavage showed negative findings, including for parasite.

After admission, he was followed-up regularly in our outpatient clinic and frequent thoracenteses for symptom relief were needed. Six months later, bilateral neck, axillary and inguinal lymphadenopathy developed. Pathologic examination of the lymph node specimen allowed a definite diagnosis to be made of AITL with positive CD10 expression (Figure 3). Therefore, we retrospectively

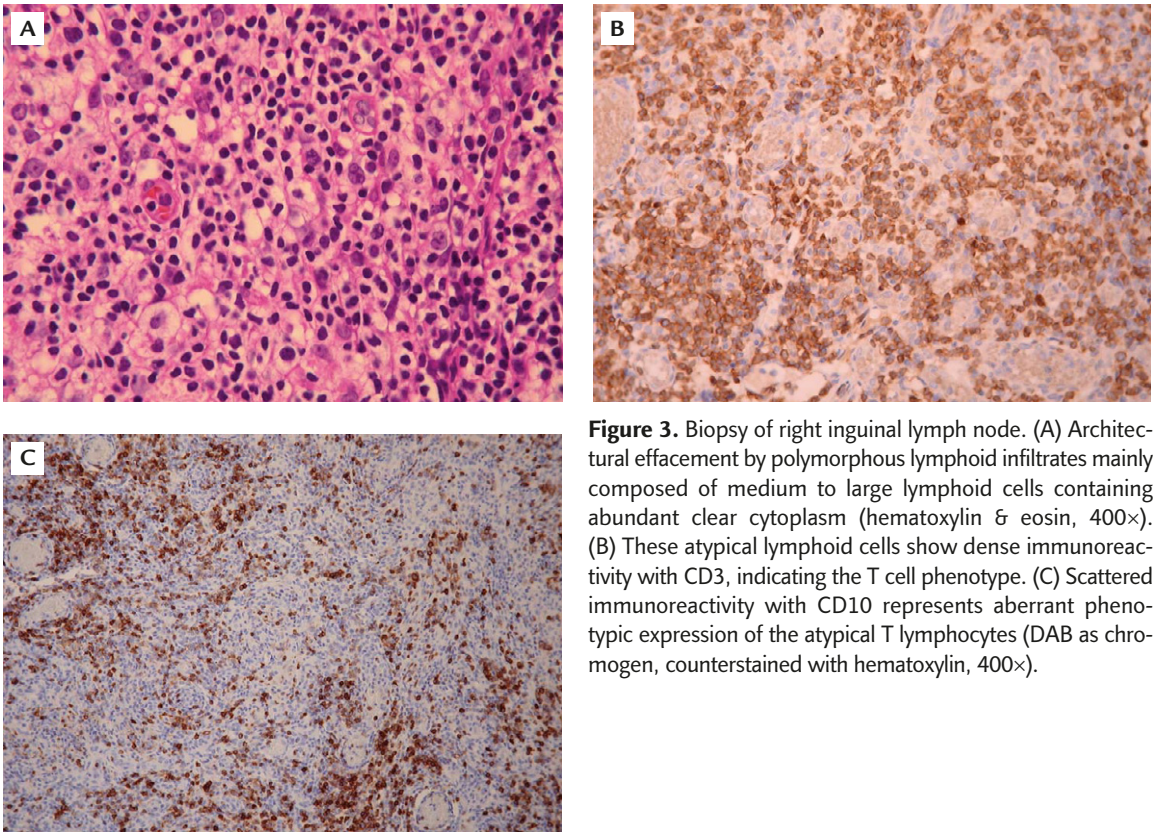

Figure 3. Biopsy of right inguinal lymph node. (A) Architectural effacement by polymorphous lymphoid infiltrates mainly composed of medium to large lymphoid cells containing abundant clear cytoplasm (hematoxylin & eosin, 400×). (B) These atypical lymphoid cells show dense immunoreactivity with CD3, indicating the T cell phenotype. (C) Scattered immunoreactivity with CD10 represents aberrant phenotypic expression of the atypical T lymphocytes (DAB as chromogen, counterstained with hematoxylin, 400×).

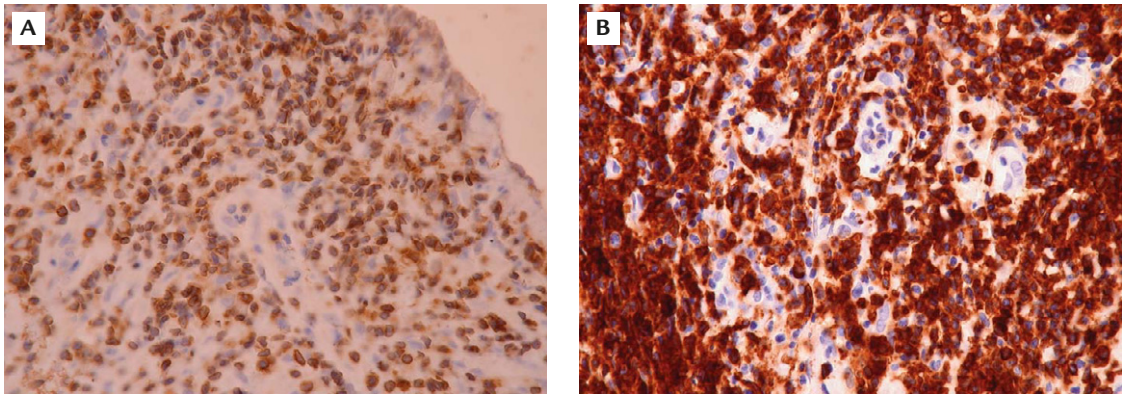

Figure 4. Retrospective immunohistochemistry of pleural biopsy. (A) Extensive CD3 staining, indicating a predominant T cell phenotype. (B) Dense immunoreactivity with CD10 represents aberrant phenotypic expression of T lymphocytes (DAB as chromogen, counterstained with hematoxylin, 400×).

carried out CD10 staining of the sample obtained from the pleural biopsy (Figure 4) and the positive result confirmed that the etiology of the EPE was due to malignant lymphoma. As the patient refused chemotherapy, supportive care was the principal treatment and he died 1 month after diagnosis.

Discussion

EPE accounts for 5–16% of exudative pleural effusion.[1–4] Most information about EPE comes from small series and case reports.[9] A considerable proportion of these patients (343 cases of EPE reported in the English literature up to 1983) have

been summarized previously by Adelman et al.[1] Since then, most of the information has come from four studies.[2–4,10] EPE occurs most commonly during conditions associated with the presence of blood or air in the pleural space, infections and malignancy. Drug-induced pleural effusion, pleural effusion accompanying pulmonary embolism, and benign asbestos pleural effusion are also common causes of EPE. Air/blood was the most common cause of EPE in the studies reviewed by Adelman et al (29%)[1] and Spriggs and Boddington (64%).[11]

Parasites are also etiologies of EPE. Among parasites that cause EPE, the most frequent is *Paragonimus* spp.,[9] which is endemic in Eastern and Southeastern Asia. Other parasitic diseases associated with EPE are sparganosis, toxocariasis, cutaneous myiasis, loiasis, strongyloidiasis, echinococcosis, lymphatic filariasis, ascariasis, and amebiasis.[9] In this patient, hookworm ova was found in the stool. Although hookworm-associated EPE has not been previously reported, that was the rational first impression because no evidence of other EPE-causing etiology could be found at the time.

AITL is a rare subtype of lymphoma, making up only 1–2% of non-Hodgkin lymphomas.[12] Patients with AITL are mostly elderly. Although generalized lymphadenopathy is the main presenting sign, many patients have evidence of extranodal involvement at the time of diagnosis.[13] The most frequently involved extranodal sites include the bone marrow, spleen, skin and lungs. Among the commonly reported presenting symptoms and signs, ascites/effusion account for 23–37%.[13] In our patient, pleural involvement was the first presenting sign and no lymphadenopathy could be found at that time. Histologic appearance in extranodal sites is usually nonspecific and cytologic features of malignancy can rarely be identified.[13] This explained why the initial pleural biopsy and cytology could not yield a definite diagnosis in this patient.

The relationship between EPE and malignancy is controversial. The frequency of malignancy in EPE varied between 6% and 40% in different studies.[1–4,9,10,14,15] The prevalence of EPE in malignant pleural effusion varied between 2.3% and 11.6%.[1–4,16–18] Adelman et al concluded that the presence of pleural fluid eosinophilia decreased the likelihood that a pleural effusion is malignant.[1] However, that view was challenged by the three more recent studies[2–4] that included 1058 patients in total (111 with EPE). According to those three studies, malignancy was as prevalent among EPE as among non-EPE. Overall, 27% of the patients with EPE and 29.8% of those with no EPE had malignant pleural effusion.

Pleural effusion is a relatively common finding in patients with non-Hodgkin lymphoma, with a frequency of up to 20%.[19] However, very few cases of malignant lymphomas accompanied by EPE have been reported.[5–8] In these reports, malignant cells were not detected in the pleural effusion, but spotted lesions were found on the pleural surface at autopsy in one report.[5] In our case, malignant cells were not detected in the pleural effusion and pleural biopsy could not yield a definitive diagnosis initially. But retrospective CD10 staining of the sample obtained from pleural biopsy proved the malignant cell invasion. The treatment of AITL consists of combination chemotherapy.[14] Although a complete remission rate of 50% can be achieved, relapse rates remain high. The prognosis for AITL patients is poor, with a median survival < 3 years.[12]

In conclusion, we found that EPE may not always indicate a benign disease. It could be an initial sign that develops up to several months before the full presentation of malignant T cell lymphoma.

References

1. Adelman M, Albelda SM, Gottlieb J, et al. Diagnostic utility of pleural fluid eosinophilia. *Am J Med* 1984;77:915–20.
2. Rubins JB, Rubins HB. Etiology and prognostic significance of eosinophilic pleural effusions. A prospective study. *Chest* 1996;110:1271–4.
3. Martinez-Garcia MA, Cases-Viedma E, Cordero-Rodriguez PJ, et al. Diagnostic utility of eosinophils in the pleural fluid. *Eur Respir J* 2000;15:166–9.
4. Kuhn M, Fitting JW, Leuenberger P. Probability of malignancy in pleural fluid eosinophilia. *Chest* 1989;9:992–4.

5. Kawasaki A, Mizushima Y, Matsui S, et al. A case of T cell lymphoma accompanying marked eosinophilia, chronic eosinophilic pneumonia and eosinophilic pleural effusion. A case report. *Tumori* 1991;77:527–30.
6. Farah MG, Nassar VH, Shahid M. Marked eosinophilia and eosinophilic pleural effusion in Hodgkin's disease. Report of a case with review of literature. *J Med Leban* 1973;26:513–21.
7. Henderson AH, Mejia G. Malignant lymphoma presenting with a high eosinophilia, eosinophilic pleurisy, and pericarditis. *Thorax* 1969;24:124–5.
8. MacMurray FG, Katz S, Zimmerman HJ. Pleural fluid eosinophilia. *N Engl J Med* 1950;243:330–4.
9. Kalomenidis I, Light RW. Eosinophilic pleural effusions. *Curr Opin Pulm Med* 2003;9:254–60.
10. Wysenbeek AJ, Lahav M, Aelion JA, et al. Eosinophilic pleural effusion: a review of 36 cases. *Respiration* 1985; 48:73–6.
11. Spriggs AI, Boddington MM (eds). *The Cytology of Effusions: Pleural, Pericardial and Peritoneal and of Cerebrospinal Fluid*, 2nd edition. London: Heinemann, 1968.
12. Ferry JA. Angioimmunoblastic T cell lymphoma. *Adv Anat Pathol* 2002;9:273–9.
13. Dogan A, Attygalle AD, Kyriakou C. Angioimmunoblastic T cell lymphoma: review. *Br J Haematol* 2003;121:681–91.
14. Bower G. Eosinophilic pleural effusion. A condition with multiple causes. *Am Rev Respir Dis* 1967;95:746–51.
15. Campbell GD, Webb WR. Eosinophilic pleural effusion. *Am Rev Respir Dis* 1964;90:194–8.
16. Light RW, Erozan YS, Ball YC. Cells in the pleural fluid: their value in differential diagnosis. *Arch Intern Med* 1973; 132:854–60.
17. Hirsch A, Ruffie P, Nebut M, et al. Pleural effusion: laboratory tests in 300 cases. *Thorax* 1979;34:106–12.
18. Pettersson T, Riska H. Diagnostic value of total and differential leukocyte counts in pleural effusions. *Acta Med Scand* 1981;210:129–35.
19. Berkman N, Breuer R, Kramer MR, et al. Pulmonary involvement in lymphoma. *Leuk Lymphoma* 1996;20:229–37.