Case Report

Recurrent Pleural Effusion and Lung Infiltrates Hide an Unexpected and Uncommon Lymphoproliferative Disorder

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Abstract

Angioimmunoblastic T Cell Lymphoma (AITL) is an aggressive subtype of Peripheral T Cell Lymphomas (PTCL) with a high mortality rate. AITL may present with a wide range of nonspecific symptoms and clinical findings for which reason it is difficult to diagnose. Rarely, patients present with lymphoproliferative lung involvement. We describe a case of a patient with recurrent pleural effusion masquerading a lymphoproliferative disorder.

Keywords: Angioimmunoblastic T cell lymphoma; Peripheral T cell lymphomas; T cell receptor

Introduction

Angioimmunoblastic T cell lymphoma is an unusual subtype of Peripheral T cell lymphomas with an aggressive disease course and high mortality rate with a median survival of less than 36 months [1-3]. It accounts for approximately 1% to 2% of non-hodgkin's lymphoma, with an annual incidence of 0.05 new cases per 100,000 people in the United States [2,3]. Interestingly, the incidence rate of AITL is more common in Europe than in Asia and North America [4-6]. AITL affects elderly patients at a median age ranging from 59 years to 65 years, and data suggest a male predominance [7]. AITL clinical presentation includes generalized lymphadenopathy (76% to 95%), systemic B symptoms including fever, night sweats or weight loss (70% to 85%), hepatosplenomegaly (50% to 70%), splenomegaly (70%), maculopapular pruritic rash (20% to 60%) and rarely lung involvement including pleural effusion (20% to 35%) [6,8].

Case Presentation

A 59-years-old nulliparous hispanic female with a medical history significant for hypothyroidism and endometriosis arrived at the emergency room complaining of worsening dysnea of approximately 4 months evolution. She described associated dry cough, generalized non-pruritic rash, unquantified fever, arthralgia, and 10 pounds unintentional weight loss within the above mention period. She denied previous history of similar symptoms or environmental exposure.

Upon arrival to the emergency clinic vital signs were significant for sustained tachycardia and pulse oximetry of 85% at ambient air. Initial physical examination revealed a diffused morbilliform rash involving face, trunk, upper and lower extremities (Figure 1A and 1B), and bilateral decreased breath sounds with dullness to percussion up to 2/3 lung fields.

Initial diagnostic workup including laboratory showed severe hypoxemia of 44.9 PO2, acute respiratory alkalosis and elevated inflammatory markers including CRP. Leukocytes and other laboratory parameters were within normal limits. Chest x-ray revealed large bilateral pleural effusion (more prominent at the right lung) and bilateral reticular infiltrates (Figure 1C). Diagnostic impression for admission was community acquired pneumonia and suspicion of para-pneumonic pleural effusion.

Within the first 24 hours of admission, thoracentesis was performed and fluid analysis was consistent with exudative effusion (glucose: 112, total protein: 5.3 and LDH: 208). Cultures and gram stain were negative, and no malignant cell was identified. Patient showed little to no clinical response with initial medical treatment which included intravenous antibiotic with levofloxacin 750 mg daily and supporting care. A second thoracentesis was performed due to re-accumulation of pleural fluid and worsening respiratory symptoms and yield similar results. Atypical etiologies including infectious, autoimmune and rheumatologic causes were also explored including: HIV, hepatitis, influenza A and B, Zika, Dengue, Chikungunya, CMV, EBV, rheumatic factor, ANA, ds-DNA, anti-Jo, anti-Sm, Anti-Sm/RNP, Anti-SSA and Anti-SSB all of which came negative. Skin lesion biopsy was also performed, results showed superficial perivascular dermatitis with mild spongiosis and eosinophilia; a non-specific finding. Pleural fluid continued to rapidly re-accumulate for which...
a third thoracentesis was performed. This time pleural fluid cytology was suggestive of a lymphoproliferative disorder.

Workup for underlying malignancy was then ordered including chest and abdominopelvic CT-scan with intravenous contrast. Imaging studies revealed mediastinal and extensive retroperitoneal lymph adenopathies, bilateral ground glass pulmonary opacities (Figure 1D), and associated pleural and ascites fluid. Due to the small size of accessible lymph nodes, excisional biopsy was unsuccessful. Bone biopsy was then performed giving the diagnosis of Angioimmunoblastic T cell lymphoma. These findings were based on the presence of diffuse effacement of the nodal architecture, vascular proliferation with prominent arborization of high endothelial venules, extra follicular meshwork of FDCs, atypical population of CD3+ T cells, and large CD20+ B cells. Patient was started on CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) (Figure 1E and 1F).

Discussion

Angioimmunoblastic T cell lymphoma was initially described in the 1970s as a non-neoplastic lymphoproliferative disease and believed to represent an abnormal “hyperimmune” reaction of the B-cell system or an atypical lymphoid process [1]. Subsequently, the neoplastic nature ofAITL and its classification as a type of PTCL were definitively established due to its morphological features of malignancy and the identification of clonal cytogenetic abnormalities including clonal T Cell Receptor (TCR) gene rearrangements by the World Health Organization in 1980 [2-4]. Recent data points toward AITL being the second most common type of PTCL second to not-otherwise-specified-PTCL; incidence varies significantly according to geographic location [4]. Europe has the highest incidence (29%), while Asia and North America have lower incidence (17% and 15% respectively) [4-6]. The reason for the difference in geographic distribution of AITL has not been well established but maybe related to the lower prevalence of genotype mutations associated with T cell neoplasm in western countries [6].

AITL mostly affects elderly population (ranging from 20 years to 86 years, median age of 65 years) with slightly greater incidence in males [7]. Most patients present with symptoms associated with advanced-stage disease (Stage III to Stage IV) but some may present with asymptomatic lymphadenopathy [7,8]. Symptoms frequently include: generalized lymphadenopathy (76% to 95%), systemic B symptoms including fever, night sweats or weight loss (70% to 85%), hepatosplenomegaly (50% to 70%), splenomegaly (70%), cutaneous lesions which can vary from maculopapular rash to nodular purpura (20% to 60%) and rarely lung involvement including pleural effusion (20% to 35%) [7-9]. Bone marrow is involved in 30% to 60% of cases [7]. In some instances associated autoimmune diseases such as vasculitis, hypo- or hyperthyroidism, arthritis with or without a detectable rheumatoid factor, immune thrombocytopenic purpura, and hemolytic anemia have been described [10].

Given the lack of clinical and histological diagnostic criteria the diagnosis of AITL is challenging [7,11]. Excisional biopsy for histology and immunophenotype assessment is still the gold standard diagnostic test. In difficult to diagnose scenarios, PCR-based tests for clonal T cell receptor can aid in the diagnosis. The lymph node morphologic assessment usually reveals obliteration of the normal architecture with diffuse infiltration of atypical large lymphocytes including immunoblasts, lymphocytes, histiocytes, and plasma cells, along with several endothelial venules that are surrounded by a network of follicular dendritic cells. On immunohistochemical
staining, the malignant cells express CD3, and CD4, and less frequently BCL-6 and CD10 [11].

The prognosis of AITL is poor with an overall survival at 5 years of 30% to 35% and a median survival of 36 months [12]. Spontaneous remission is rare but has been reported [13]. The optimal management of the disease has not been well defined. Current standard treatment options include combination chemotherapeutic regimens, CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; or COPBLAM/IMVP-16: cyclophosphamide, vincristine, prednisolone, bleomycin, doxorubicin, procarbazine, ifosfamide, methotrexate and etoposide with a reported three-year event free survival and overall survival rate of 50% and 68% respectively [14]. Promising result has been reported in recent retrospective studies which suggest high survival rates with autologous hematopoietic cell transplantation [15-17].

Conclusion

Although malignant pleural effusion has already been reported as a complication of AITL, little data is available describing the diagnostic yield of pleural fluid cytology analysis. Cross reference data suggests that the diagnostic yield of pleural fluid analysis depends on factors such as extent of disease and the nature of the primary malignancy. It is estimated that the rate of diagnosis increases with repeated thoracentesis. Within the first thoracentesis, the success rate of cytological diagnosis is 65% and the second thoracentesis adds 27% to the success rate, while the third thoracentesis only adds 5%. Although we could not identify the tumor cell population in the pleural fluid analysis, it did reveal the presence of lymphocytic pleural effusion in our patient guiding further diagnostic workup which included bone marrow biopsy.

Considering the wide variety of unspecific clinical findings, it is of much importance to raise awareness concerning AITL diagnosis due to its highly aggressive course and poor prognosis. A careful review of the patient symptoms with the prompt histological examination is essential for an accurate diagnosis and treatment management which may improve patient survival.

References