Lymphomatoid Granulomatosis: a Case Report with Unique Clinical and Histopathologic Features

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Abstract. Lymphomatoid granulomatosis is a rare lymphoproliferative disorder composed of rare-to-abundant atypical Epstein Barr virus infected B-cells admixed with numerous reactive T-cells. We report a case of a 42-year-old man presenting with fevers of unknown origin and acute renal failure. CT scan demonstrated lung opacities which progressed to numerous nodules throughout both lungs without any cavitations. Wedge lung biopsy showed nodular polymorphous mononuclear infiltrates containing scattered atypical large Epstein Barr virus positive B-cells consistent with lymphomatoid granulomatosis. The patient responded to chemotherapy, but later underwent relapse and transformation to diffuse large B-cell lymphoma. The clinical and histological features of lymphomatoid granulomatosis and differential diagnoses as related to this case are discussed.

Key words: Lymphomatoid granulomatosis; Lymphoma

Introduction

Lymphomatoid granulomatosis (LYG) is a rare angiocentric and angiodestructive B cell lymphoproliferative disease associated with Epstein Barr virus (EBV) infection [1]. It was first described in 1972 by Liebow et al as “the presence within the lung of more or less massive proliferation of atypical cellular derivatives of the reticuloendothelial system, often plasmacytoid, about and within the walls of blood vessels as well as within the parenchyma, with necrosis and ultimately fibrosis” [2]. The disease has been found to present in a wide variety of ways but most often clinically with symptoms associated with pulmonary involvement and radiographically with multiple lung nodules [3]. Histological diagnosis can pose a challenge to general surgical pathologists due to overlapping features of LYG with inflammatory lesions and other lymphoproliferative disorders [4]. Due to its rarity and the fact that many pathologists are not familiar with its histologic features, LYG is often not included in the initial differential diagnoses of a necroinflammatory lung lesion. We herein report a case of a 42-year-old male presenting with fever of unknown origin and acute renal failure.

Materials and Methods

Immunohistochemical (IHC) studies for CD3, CD5, CD10, CD20, MIB-1, and MUM-1 and special stains for PAS, AFB, and Grocott were performed on formalin fixed, paraffin embedded tissue sections (4-5 μm). IHC stains were performed on either DACO stainer using DACO DAB Detection System (Carpinteria, California) or Ventana BenchMark XT using iView/DAB detection system with commercially available antibodies according to standard manufacturing protocols (Table 1). All negative and positive controls demonstrated appropriate immunostaining. In-situ hybridization study for Epstein-Bar Virus (EBV)-Encoded RNA (EBER) was performed on Ventana BenchMark XT using iView/DAB detection system (Tucson, Arizona) with commercially available antibodies according to standard manufacturing protocols (Table 1). All negative and positive controls demonstrated appropriate labeling.

Case Report

The patient was a 42-year-old male who was transferred to our hospital from an outside hospital with fevers of unknown origin and worsening acute renal failure. He had recently been treated for a herpes zoster-like rash and meningencephalitis. The rash and encephalitis resolved; however, the patient
had fevers during the meningoencephalitis, which had not resolved. The fevers continued along with acute worsening renal failure. Renal biopsy showed tubulointerstitial disease without immune complex deposits. The patient had no previous medical history except for recurrent sinusitis.

A CT scan was performed and showed two vague opacities in the left upper lobe of lung. One month later, after extensive microbiology workup the only positive finding was an EBV PCR of the CSF (300 copies) while the patient continued to have fevers. Serum levels of cytoplasmic and perinuclear anti-neutrophil cytoplasmic antibodies (c-ANCA, p-ANCA) and antinuclear antibody (ANA) were within reference range. Approximately 2 months after the initial onset of fevers, a repeat CT scan of the chest showed the lung opacities to be worsening with numerous pulmonary nodules throughout both lungs without any cavitations noted. No lymphadenopathy was visualized. A wedge biopsy of the lung was performed with clinical differential diagnoses including pulmonary vasculitis, adult onset Still’s disease, and sarcoidosis.

On gross examination, the right upper lung wedge biopsy contained a 0.7 x 0.6 x 0.5 cm yellow tan lung nodule and scattered dense areas. Histological sections showed nodular collections of lymphohistiocytic infiltrates with focal areas of necrosis (Figure 1A). A high-power view demonstrated a mixed cell population of small lymphocytes, histiocytes, plasma cells, and scattered large atypical cells, admixed with fibrinoid necrosis (Figure 1B). The large atypical cells resembled immunoblasts and had vesicular chromatin and prominent nucleoli (Figure 1C). Vascular infiltration by dense small lymphocytes was also identified (Figure 1D). The initial differential diagnosis included infection, vasculitis, and a lymphomatous process. Special stains were all negative for fungal organisms and acid fast bacilli. Immunohistochemical staining performed showed the large atypical cells to be CD20 positive B-cells (Figure 2A) with a background of reactive T-cells (CD3 and CD5 positive). In-situ hybridization for EBV RNA was also performed and showed focal clustered positivity in the large atypical B-cells (Figure 2B). Based on the above histologic features and staining patterns, the diagnosis of lymphomatoid granulomatosis lymphoma, grade 3 was made.

The patient was treated with six cycles of cyclophosphamide, vincristine, prednisone, and rituximab (R-CVP), and went into remission with complete resolution of lung nodules. Approximately one year later, lung nodules were noted on follow-up imaging with surrounding hilar lymphadenopathy. A lung biopsy was performed again at this time and showed sheets of large cells with necrosis (Figure 3A). The large cells stained positive for CD20 (Figure 3B), MUM-1, EBER (near 100%) (Figure 3C), and MIB-1 (near 100%) (Figure 3D). The cells were negative for CD3, CD5, and CD10. Diffuse large B cell lymphoma non-germinal center

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**Table 1. Immunohistochemistry and In-situ hybridization Antibody Information**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Clone</th>
<th>Dilution</th>
<th>Vendor</th>
<th>Location</th>
<th>Pretreatment</th>
</tr>
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<tbody>
<tr>
<td>CD3</td>
<td>2GV6</td>
<td>Predilute</td>
<td>Ventana</td>
<td>Tucson, Arizona</td>
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<tr>
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<td>SP19</td>
<td>Predilute</td>
<td>Cell Marque</td>
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</tr>
<tr>
<td>CD10</td>
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<tr>
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<td>L26</td>
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<td>Ventana</td>
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</tr>
<tr>
<td>Ki-67</td>
<td>MIB-1</td>
<td>Predilute</td>
<td>DakoNorth</td>
<td>Carpinteria, California</td>
<td>FLEX TRS Low</td>
</tr>
<tr>
<td>MUM-1</td>
<td>MUM1p</td>
<td>Predilute</td>
<td>DakoNorth</td>
<td>Carpinteria, California</td>
<td>FLEX TRS Low</td>
</tr>
<tr>
<td>EBER</td>
<td>EBER1</td>
<td>Predilute</td>
<td>Ventana</td>
<td>Tucson, Arizona</td>
<td>ISH Open DNP probes probe Chromogenic V3</td>
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Lymphomatoid granulomatosis: a unique case was diagnosed. The patient was subsequently treated with 4 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Following the R-CHOP chemotherapy, the patient is currently 6 months out of treatment and is disease free.

Discussion

Lymphomatoid granulomatous is a rare EBV-associated lymphoproliferative disease that most often affects the lung. It occurs most frequently in middle aged adults and is more prevalent among males and immunocompromised individuals [5]. In reported cases, the most common symptoms patients present with are signs of lung involvement (cough, hemoptysis, chest pain) and fever. Although renal lesions have been found in patients with lymphomatoid granulomatosis, they are usually clinically silent and only identified at the time of autopsy [6]. Glomerulonephritis has not been found as a symptom of lymphomatoid granulomatosis [4, 6]. Radiographically, the disease ordinarily presents as multiple discrete nodular lesions throughout the lungs [7]. Histologically, lymphomatoid granulomatosis is an angiocentric, angiodestructive lymphoproliferative disease with a polymorphous mononuclear infiltrate that contains abundant reactive T-cells admixed with atypical B-cells infected with the Epstein Barr virus [7]. Typically, the disease shows nodular replacement of lung parenchyma with vascular invasion and variable amounts of necrosis [4]. Grading of lymphomatoid granulomatosis is based upon the number of atypical EBV infected B-cells [1,8,9].

Our case illustrates a unique and challenging diagnostic example from both clinical and pathological aspects. The patient presented clinically with the unique picture of fever and worsening acute renal failure in the background of a treated herpes zoster-like rash and meningoencephalitis with no significant previous medical history. Although fever has been reported as one the most common presenting symptoms in lymphomatoid granulomatosis, acute renal failure has not been reported as an associated symptom [4, 6]. In our case, the patient’s renal failure was actually not associated with the disease but related to the anti-viral treatment and other pre-renal causes. Our patient initially presented with

Figure 1. A. Low power view of the lung wedge biopsy shows a nodular collection of lymphohistiocytic cells with areas of necrosis (x40). B. Intermediate power demonstrates mixed populations of small mature lymphocytes, histiocytes and scattered large atypical cells (x200). C. The large atypical cells (arrows) have vesicular chromatin and prominent nucleoli (x400). D. There is lymphocytic infiltration of the blood vessel wall in the lesion (x200).
Figure 2. A. Immunohistochemical stain for CD20 is positive in the large atypical cells (x400). B. In-situ hybridization for EBV demonstrates positivity in the same CD20-positive large atypical cells (x400).

Figure 3. A. The second lung biopsy after relapse shows large areas of necrosis rimmed by sheet of large atypical cells (x40). B. The sheets of large cells are positive for CD20 immunohistochemical stain (x400). C. In-situ hybridization for EBV shows diffuse positivity in the large cells (x400). D. Immunohistochemical stain for Ki-67 shows near 100% positivity in the large cells (x400).
vague bilateral lung opacities that only progressed into discrete lung nodules late in the clinical picture, an atypical presentation for lymphomatoid granulomatosis. Most of the reported cases have been found to present with discrete lung nodules [6].

The histological diagnosis of this case also offered a challenge. There was not a well-demarcated nodule with a large central area of necrosis rimmed by lymphoid cells. Instead, the lesion was composed of nodular lymphohistiocytic infiltrate with spotty areas of necrosis. The vascular infiltration by lymphocytes was also focal and at the periphery of the lesion. On H&E examinations, the differential diagnoses included infectious etiologies, vasculitis, and a lymphomatoid process. An infectious etiology was considered as both tuberculosis and histoplasmosis can show a lymphohistiocytic infiltrate with necrosis on histological examination. AFB, PAS, and Grocott staining were negative for fungal organisms and acid-fast bacilli. The vascular infiltration by lymphocytes and areas of necrosis placed vasculitis high in the differential diagnosis, especially Wegener’s granulomatosis. However, necrotizing granulomas and necrotizing vasculitis characteristic of Wegener’s granulomatosis were not seen in this case. The infiltration of the blood vessels was by lymphoid cells rather than neutrophils. The serum c-ANCA testing was also negative. A lymphomatous process was placed at the top of the differential diagnosis after immunohistochemical staining for CD3 and CD20 were performed, which showed abundant CD3 positive T cells with scattered atypical CD20 positive cells. The final diagnosis was confirmed when in-situ hybridization for EBV RNA showed a diffuse positive staining pattern involving the large atypical CD20 positive cells.

Another unique feature of this case is the clinical course of the patient. The clinical course of lymphomatoid granulomatosis can be variable [10]. However, many cases, especially grade 3, are found to be an aggressive disease with the mortality rate between 30% and 70% and a median survival of 2 years [7, 11]. Our patient was treated with six cycles of R-CVP and found to be in complete remission before relapsing with transformation to diffuse large B cell lymphoma. After treatment with R-CHOP, the patient is now once again in complete remission and disease free with no complaints for two year from his original presentation. This case demonstrates that the clinical course of lymphomatoid granulomatosis can be variable even when it is grade 3 or after transforming to diffuse large B cell lymphoma. Grade 3 lesions can show good response to aggressive chemotherapy. It has been reported that grade 1 or 2 lesions may respond to interferon alpha 2b therapy [12].

In summary, although a rare entity, lymphomatoid granulomatosis should be included in the differential diagnosis when faced with the histological picture of a polymorphous mononuclear nodular infiltrate of the lung in the background of a non-specific clinical presentation.

References