CASE REPORT

Pulmonary Lymphomatoid Granulomatosis- a Case Report with Review of Literature

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Abstract Lymphomatoid granulomatosis is a rare, Epstein Barr Virus (EBV)-associated systemic angiodestructive disorder that may progress to a diffuse large B cell lymphoma. Pulmonary involvement occurs in over 90 % cases followed by kidney, skin and brain. WHO classifies lymphomatoid granulomatosis under the generic heading of B cell proliferations of uncertain malignant potential. Radiologically, pulmonary lymphomatoid granulomatosis (PLG) presents with non specific findings making histopathology the gold standard for diagnosis. The histological diagnosis of PLG includes a triad of polymorphic lymphoid infiltrates, transmural infiltration of arteries and veins by lymphoid cells (“angiitis”), and focal areas of necrosis within the lymphoid infiltrates. PLG should be distinguished from granulomatosis with polyangitis, as well as other forms of malignant lymphoma, like extranodal NK/T cell lymphoma, secondary diffuse large B-cell lymphoma and primary Non Hodgkin lymphomas of lung.

Keywords EBV · Immunohistochemistry · Grading · Rare · Lymphoproliferative disorder · Pulmonary involvement · Prognosis

Introduction

Pulmonary lymphomatoid granulomatosis (PLG) has always been an elusive lesion for pulmonary pathologist. It has existed in our glossary of rare clinicopathological entities

since 1972 when it was first described by Liebow [1]. Currently, it is known to represent an Epstein-Barr virus (EBV) associated lymphoproliferative disorder involving extranodal sites. The malignant potential of the disease correlates with the pathological grading. Patient presents with a waxing and waning clinical course finally progressing to an aggressive disease of high mortality. Non specific clinical, laboratory and imaging features makes this disease a perplexing entity.

Case Report

A 57 year old woman presented with 1 month history of cough and breathlessness. She was a known case of rheumatoid arthritis and was on methotrexate. No abnormality was detected on physical examination and there were no palpable lymph nodes. She was investigated for respiratory disorder. A Contrast Enhanced CT scan was done which showed a spiculated mass lesion in left upper lobe of lung. No lymphadenopathy was noted. Her PET NCCT scan revealed a FDG avid soft tissue nodular lesion with spiculated margins which was suspicious of mitotic etiology. A robotic left upper lobe lobectomy was performed. We received a lobectomy specimen alongwith hilar and lobular lymph nodes. Left lobe of lung measured $10 \times 7 \times 1.5$ cm. and serial slicing of the specimen revealed a well circumscribed nodule measuring 0.8 cm. Cut surface of nodule was yellow with areas of necrosis and congestion. Rest of the lung parenchyma was unremarkable.

The light microscopic examination of sections from the mass revealed a relatively well circumscribed lesion composed of polymorphous infiltrate. Large atypical lymphoid cells were seen interspersed with many mature lymphocytes, histiocytes and few plasma cells. Atypical cells were large

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with vesicular to coarse granular chromatin and conspicuous nucleoli. An occasional binucleate Reed Sternberg like cells was also noted. Both large and small caliber vessels showed lymphomononuclear infiltration of the wall resulting in subendothelial collections. Extensive destruction of the vessel wall by the infiltrating lymphocytes was seen (Fig. 1). Large areas of necrosis were also observed. No granulomas were seen.

On immunohistochemistry, background small lymphocytes stained positive with CD3 while histiocytes were CD68 positive. The atypical large cells were CD20 positive. These cells also stained strongly positive for Epstein Barr Virus (EBV). Most of the atypical cells were also positive for CD30. These cells were negative for CD15 and ALK 1 (Fig. 2).

Based on morphological and immunohistochemical features diagnosis of pulmonary lymphomatoid granulomatosis was made. Numerous large atypical lymphoid cells and EBV positive cells ranging from 15 to 20/HPF with extensive necrosis accounted for grade II/III according to the current grading system.

Patient was treated with four cycles of chemotherapy. She responded to therapy and is in remission after 4 years of completion of treatment.

Discussion

Pulmonary lymphomatoid granulomatosis is a rare lymphoproliferative disorder associated with EBV. The incidence is higher in patients with immunodeficiency disorder [1]. It

usually presents in adult life with median age of 48 years. It affects males more often than females (M: F ratio $\geq 2:1$). Lung is essentially always affected and in 90 % of patients respiratory symptoms are initial sign of manifestation. Major sites of extrapulmonary involvement include kidney (32 %), skin (29 %), liver (29 %) and CNS (26 %) [2]. Upper respiratory tract, gastrointestinal tract, spleen and lymph nodes are rarely affected [3].

In 1979 Katzenstein et al. studied 152 cases of lymphomatoid granulomatosis and their association with various clinical and pathological features. This is the largest study so far where they suggested increased prevalence of disease in patients on immunosuppressants, transplant patients and those with already existing autoimmune disorders. Hence, the role of B cell immune dysfunction and the atypical cell belonging to B cell lineage was proposed [3]. In 1990, in another study EBV genome was detected in 29 cases by polymerase chain reaction [4]. Later, Jaffe et al. have demonstrated Epstein Barr virus in CD20 positive B cells and atypical large cells by immunohistochemistry and in situ hybridization techniques [5]. Approximately 60 % cases contain clonal rearrangements as studied by polymerase chain reaction. EBV sequences can be localized to B cells and are clonal in most cases [6]. According to 2001 WHO classification PLG is a lymphoproliferative disorder of indeterminate potential [5, 6].

Prognosis correlates with the grading system for the disease. Various grading systems have been proposed [7]. Currently, a three tiered system is in use. Grade I lesions show scant necrosis with only rare EBV positive in situ cells. Atypical lymphoid cells are absent. Grade II lesions show

Fig. 1 **a** Photomicrograph showing angiodestructive and angioinvasive pattern of infiltrate. **b** areas of necrosis. **c** polymorphic infiltrate comprising mature lymphocytes, plasma cells, histiocytes and atypical large lymphoid cells. **d** Reed-Sternberg like cell is seen in the centre of the field

Fig. 2 **a** Large atypical cells stain positive for EBV. **b** CD 20 positive in atypical large cells. **c** CD3 positive in background lymphocytes. **d** CD 68 positive in histiocytes. **e** CD 30 positive in atypical large cells. ALK1 and CD15 were negative

moderate necrosis with occasional large atypical cells. EBV positive cells are 5–20/HPF. Grade III patients show predominant population of large atypical cells associated with extensive necrosis and EBV positive cells are >20/HPF. Grade I and II patients may undergo spontaneous remission. In contrast grade III lesions are considered equivalent to diffuse large B cell lymphoma, lymphomatoid granulomatosis variant. [2, 8, 9] The treatment options are not well defined for PLG patients and vary from observation to use of steroids and chemotherapy. Interferon alfa-2b in combination with Rituximab has been shown to be highly effective in grade I/II disease and leads to long term remissions and potential cures. Patients with grade III disease are treated as high grade lymphoma with RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone). However, grade I/II disease may progress to grade III disease or there may be a recurrence following chemotherapy-rituximab. More than 50 % patients respond to treatment while 13–47 % patients develop lymphoma [9].

The main differential diagnoses are granulomatous polyangiitis (GPA), extranodal lymphomas and primary lymphoma of the lung. Angiocentric polymorphous infiltrate and large areas of necrosis are the features that resemble GPA but absence of multinucleated giant cells, neutrophilic microabscesses, palisading epithelioid cells and negative EBV differentiate it from the PLG. Post transplant lymphoproliferative disorder cases show T cell poor infiltrate which is not angiocentric and patients are by definition post transplant [10]. Similarly patients with EBV associated B cell lymphoma

present with a history of immunosuppression. Histological features include absence of angiocentricity and angioinvasion and infiltrate comprising predominant population of B cell. Angiocentricity and association with EBV make it difficult to differentiate extranodal T cell lymphoma, nasal type from PLG [11]. Pattern of necrosis with numerous apoptotic bodies which is not seen in PLG alongwith immunostaining of atypical lymphoid cells with CD56 can serve little help. Other studies including immunoglobulin rearrangement and identification of EBV positive cells can help to reach the final diagnosis. Primary non-Hodkin's lymphoma (NHL) is a very rare entity accounting for only 0.4 % of extranodal NHL. The most common primary pulmonary NHL is represented by marginal zone lymphoma (low grade MALT-lymphoma) arising in the main bronchus. In a study by Kim et al., marginal zone lymphoma accounted for 54 % of primary pulmonary NHL followed by DLBCL comprising 28 % cases [11]. Histologically these cases show monomorphic neoplastic B cell population and characteristic immunoprofiles. Thus primary pulmonary NHL can be easily differentiated from PLG.

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Compliance with Ethical Standards

Final Approval of Manuscript All authors.

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