

Plasma Cell Granuloma of the Lung in the Differential Diagnosis of Pulmonary Nodules in a Child with Acute Lymphoblastic Leukemia

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Citation

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Abstract

Plasma Cell Granuloma (PCG) is the most common lung tumor in children, usually presenting with respiratory symptoms such as cough, fever, chest pain and dyspnea. It can be confused with pneumonia or fungal infection and is difficult to be diagnosed without surgical biopsy. The etiology is unknown, but some reports consider infectious agents as a trigger including Epstein-Barr virus (EBV) and Human herpes virus 8 (HHV8). Others consider it a result of dysregulation of cytokine production. We present a case of PCG in patient with ALL. We believe that PCG should be considered in the deferential diagnosis of pulmonary nodules in immunocompromised patient especially if antimicrobial therapy does not lead to resolution of the pulmonary nodules.

INTRODUCTION

Plasma Cell Granuloma (PCG) is the most common primary tumor of the lung in children. It is also known as inflammatory pseudotumor, fibroxanthoma, xanthogranuloma, xanthofibroma, and histiocytoma. This is a heterogenous group of lesions that occur mostly in the lung as a solitary nodule. It can also appear in many other organs including orbit, thyroid, liver and others (1). PCG can present at any age group, but is most common in childhood and early adulthood. Plasma cell granuloma of the lung is recognized as a benign lesion, but aggressive behavior including rapid growth, local invasion, and recurrence has been documented (1, 2).

CASE REPORT

A 7 year old girl with standard risk acute lymphoblastic leukemia (ALL), received induction therapy with dexamethasone, vincristine, asparaginase along with intrathecal methotrexate, followed by consolidation therapy with mercaptopurine, methotrexate, vincristine, dexamethasone and intrathecal Methotrexate. Initial pneumocystis prophylaxis consisted of trimethoprim/sulfamethoxazole, which was replaced later by dapson because of severe myelosuppression. During her maintenance therapy the patient started to have a dry cough, without fever, upper respiratory symptoms, hemoptysis or

shortness of breath. She was treated with albuterol and inhaled steroids with mild improvement. Few days later she developed left sided chest pain. A chest radiograph showed right lower lobe and left upper lobe opacities. She was treated with azithromycin and ceftazidime for multifocal pneumonia. Blood and comprehensive viral cultures were negative, mycoplasma IgM titer was negative, sputum culture grew only normal flora, seven days after antibiotics, minimal improvement was seen, and thus she underwent a bronchoalveolar lavage from right lower lobe directed by bronchoscopy which showed only inflammatory cells, all cultures including viral, bacterial and fungal were negative. Further work up included a chest CT scan which revealed several bilateral scattered solid pulmonary nodules (figure, 1). The most dominant one was in right lower lobe measuring approximately 2 cm x 1.8 cm. No associated calcification or mediastinal adenopathy were present. Pleural based opacities were also seen in the most inferior aspect of both bases. Under the clinical suspicion of fungal infection supported by the radiologic finding, she was started on fluconazole with mild improvement. \

Three months after antifungal therapy, a chest radiograph and a chest CT scan showed many pulmonary nodules again at the same size. Eventually the patient underwent a surgical biopsy by thoracoscopy.

A 5 x 4 x 2 cm wedge-shaped, 12 gm portion of lung was resected. Cut section revealed a well demarcated firm mass. Histologic evaluation revealed an exuberant bronchocentric inflammatory infiltrate, predominantly composed of plasma cells, immunoblasts and lymphocytes (figure 2). The immunoblasts stained positive for Epstein-Barr encoded RNAs (EBER) immunostain. The infiltrate showed a polyclonal B cell population by flow cytometry and was negative for Terminal Deoxynucleotidyl Transferase (TDT) and CD34 antigens. Anaplastic lymphoma kinase (ALK) was negative by both immunostain and Fluorescent in situ hybridization (FISH). All histochemical stains as well as cultures for bacteria, protozoa, fungus and virus were negative. The lesion was diagnosed as an EBV-driven plasma cell granuloma.

After surgical resection, dapsone was stopped and patient was treated with oral corticosteroids (2mg/kg/d) for almost five weeks. The patient showed gradual improvement in her clinical situation. No lesions were seen on the further chest radiographs. The patient is currently doing well (in remission) without any pulmonary issues five years after the completion of the chemotherapy.

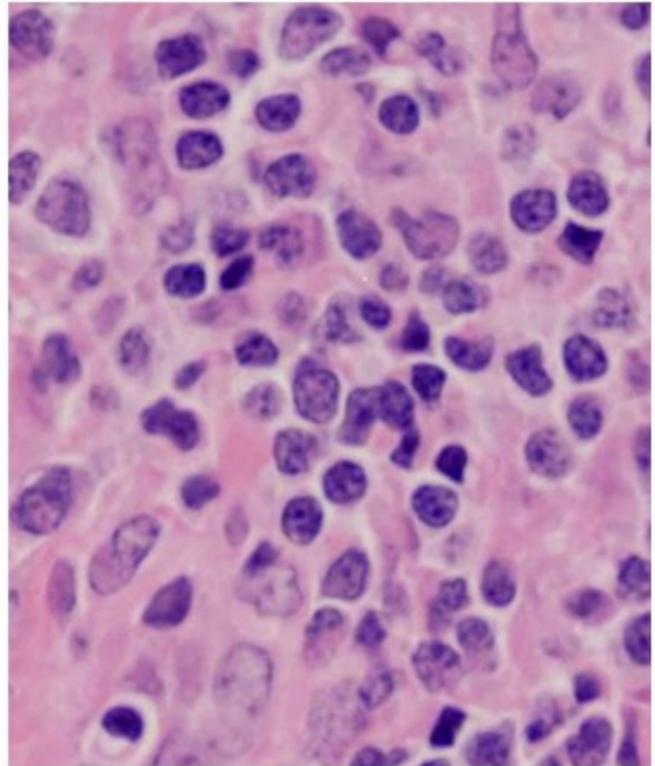
Figure 1

Chest CT scan, pulmonary nodule in the right lower lobe.



Figure 2

Microscopic appearance of plasma cell granuloma. Mature plasma cells are the major component (High power 400x)



DISCUSSION

Plasma Cell Granuloma (PCG) is also known as inflammatory pseudotumor, fibroxanthoma, xanthogranuloma, xanthofibroma, and histiocytoma. The lung is the most common site of localization, accounting for 0.7% of all thoracic tumors in children aged less than 16 years (3). PCG is the most frequent primary pulmonary tumor. However, it is not limited to the lung and can grow in other organ systems such as the brain, liver, larynx, retroperitoneum, orbit and abdomen (1, 2).

The etiology of PCG is unknown; theories regarding pathogenesis include an inflammatory reaction to an infection or to an underlying low grade malignancy (4, 5). Several infectious agents have been associated with the occurrence of PCG in specific patients, but these findings have not been noted universally. Some investigators have identified clonal DNA expression of EBV in PCG (5). Similarly, human herpes virus (HHV-8) DNA was identified in few cases (4,6). Increased serum levels and increased local production of the cytokines interleukin-1 and interleukin-6 was documented in one case (7). This finding supports the theory that this disease is initiated by

dysregulation of cytokine production. Another hypothesis considers plasma cell granulomas as low-grade mesenchymal neoplasms with a secondary inflammatory component. This is supported by the presence of a chromosomal rearrangement at band 2p23 in some cases (8).

Morphologically PCG is well circumscribed, unencapsulated and a vascularized lesion, that can have irregular cavities. It usually consists of spindle cells with features of fibroblasts and myofibroblasts with inflammatory cells consisting of lymphocytes, plasma cells, histiocytes and few eosinophils (9). The inflammatory cells might be dense enough to obscure the spindle cells. Immunohistochemical staining of PCG lesions reveals the presence of IgG predominant, polyclonal plasma cells (10). This finding supports the theory that PCG is a reactive inflammatory process especially that upper respiratory infection precipitates 30% of cases (9).

PCG of the lung is characterized by variable clinical presentations that range from incidental findings revealed by systematic chest radiography to aggressive presentation, similar to neoplasms. Common clinical characteristics include cough, chest pain, dyspnea, hemoptysis, fever, malaise and weight loss (11). Also nail clubbing and hypertrophic osteoarthropathy have been reported. Up to one-third of patients report a previous history of lower respiratory tract infections, but a clear chronology has not been shown. The laboratory tests are normal or have non-specific alterations (12).

Imaging is nonspecific and often shows a solitary, well-circumscribed peripheral mass usually in the lower lobes. Pathologically, these tumors are composed of a heterogeneous population of inflammatory and mesenchymal cells. Therefore, Definitive diagnosis of PCG may prove to be very difficult and often only possible after resection of the tumor and immunohistochemical investigation. Important differential diagnostic considerations include sarcoma, malignant fibrous histiocytoma and lymphoma (13).

Early and complete surgical resection of the PCG remains the best treatment option to exclude malignancy and to achieve cure. Delay in diagnosis and treatment may increase considerably the magnitude of the surgical intervention required (14). Steroid therapy presents varying effects, from complete resolution to utter ineffectiveness. There are several cases with good results when it is used as a primary

treatment. Thus, it may have a place in the setting of incomplete surgical resection, multifocal disease, postoperative tumor recurrence, or contraindications to lung resection (12, 15,16).

Other nonsurgical treatment modalities including Methotrexate and radiotherapy may be considered for some cases (17).

There can be recurrence after surgery or steroid treatment (18). However, it has been documented that lesions confined to the lung rarely recur in children, whereas those extending beyond the lung or affecting other organ systems have a 30-fold increase in recurrence rates and a poor prognosis (13). Some cases may show spontaneous resolution without any treatment (5).

CONCLUSION

This case should alert the physician to consider PCG in the differential diagnosis of single or multiple pulmonary nodules in a child receiving immunosuppressive chemotherapy. A surgical biopsy should be considered when the prolonged antimicrobial treatment does not lead to resolution of pulmonary nodules.

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