CLINICAL VIGNETTE

Pulmonary Hyalinizing Granuloma in a Veteran with Latent Tuberculosis and Agent Orange Exposure

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Introduction

Pulmonary hyalinizing granuloma (PHG) is a rare, self-limited process first described in 1977[1]. Clinical presentation is variable. Symptoms may include nonspecific respiratory complaints or the patient may be asymptomatic. Recurrent, multiple, and often bilateral pulmonary nodules are a characteristic finding. However, presentation as a solitary pulmonary nodule has been described. PHG is often an incidental finding and has been associated with autoimmune, infectious, and neoplastic diseases. A relationship between Agent Orange exposure and PHG has not previously been described. There is currently no effective treatment for PHG, but significant response to corticosteroids has been reported[2]. We report a case of PHG in a U.S. Veteran with latent tuberculosis (TB) and Agent Orange exposure.

Case Report

A 57-year-old male veteran was found to have an incidental right upper lobe soft tissue density on a pre-operative chest radiograph done in preparation for surgical repair of a tendon laceration of his left hand. He was an active thirty-nine pack-year smoker. He reported a five-year history of a productive cough with brown/black sputum and an unintentional 5.4-kg weight loss over the previous month. There was no history of fever, night sweats or hemoptysis. The remainder of his medical and family history was unremarkable. Previous employment included multiple jobs in the construction, machinery, carpentry, and agriculture industries. He also reported a history of Agent Orange exposure during his service in the Vietnam War.

The chest radiograph demonstrated interval development of a soft tissue density in the right upper lung zone not seen on imaging three years prior (Fig. 1). Computerized tomography (CT) of the chest demonstrated a non-calcified 3.3 cm lobulated soft tissue mass in the apical segment of the right upper lung lobe with numerous smaller satellite lesions (Fig. 2). There were additional small clusters of micronodules in the superior segments of bilateral lower lobes. 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) demonstrated mild FDG avidity isolated to the mass (Fig. 3). Pulmonary function tests were normal. Serologies for Histoplasmosis and Coccidiomycosis were negative. Sputum cultures were negative for mycobacteria, but QuantiFERON-TB Gold assay returned positive. The airway was normal on flexible fiberoptic bronchoscopy. Microbiologic stains and cultures from bronchoalveolar lavage samples were negative for bacterial, mycobacterial and fungal pathogens. A CT guided core biopsy of the apical lung mass demonstrated haphazard hyalinized collagen lamellae with chronic inflammatory cells consistent with PHG (Fig. 4).

A nine-month course of Isoniazid with B6 supplementation was completed for latent TB. No specific therapy was initiated for PHG. At one-year follow-up, the right upper lobe mass slightly decreased in size with interval development of a necrotic center. There was also partial resolution of several of the micronodules. The original productive cough improved but persisted, and his weight stabilized. He remained otherwise asymptomatic and continues to be followed with serial imaging.

Figure 1. Chest radiograph revealed a soft tissue density in right upper lung zone.

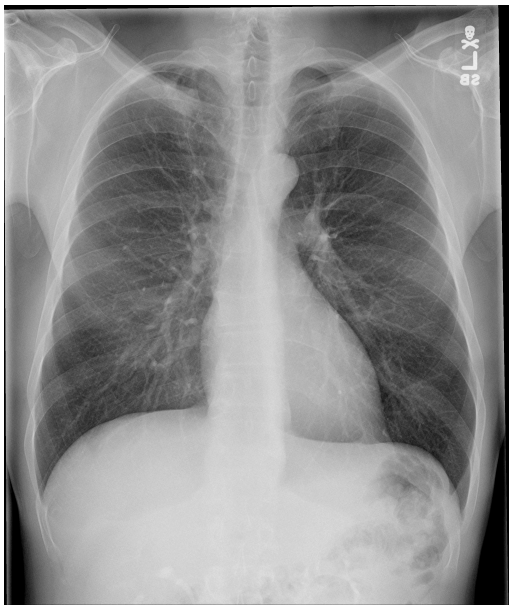


Figure 2. CT of the chest demonstrated a lobulated mass with satellite lesions in right upper lobe.

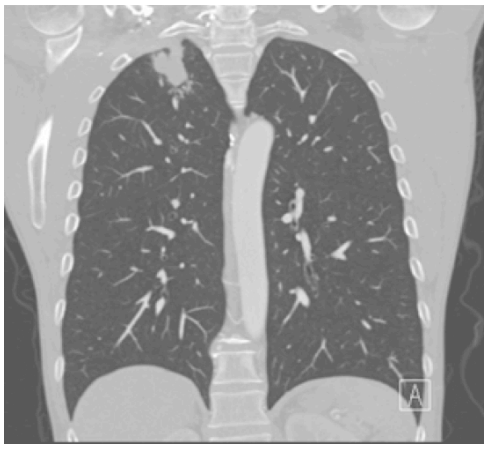


Figure 3. FDG-PET exhibited mild metabolic activity in the right upper lobe lung mass.

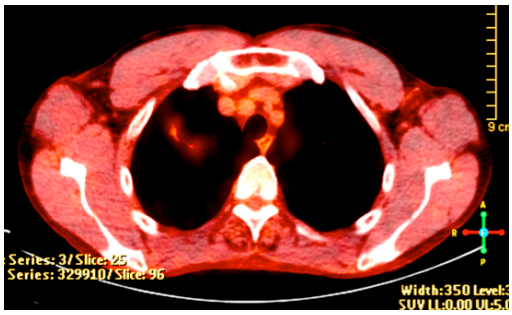
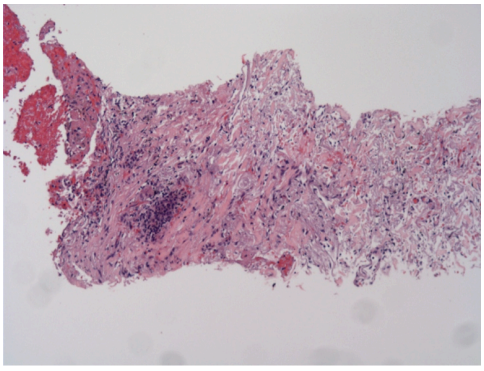


Figure 4. Biopsy of the right upper lobe lung mass demonstrated haphazard hyalinized collagen lamellae with chronic inflammatory cells consistent with PHG (magnified 4x).



Discussion

PHG is a rare fibronodular condition that affects individuals between the age of 19 and 77. There is no gender, racial or ethnic predilection[3]. The symptoms of PHG are non-specific and often mimic more common respiratory conditions such as a respiratory infection or obstructive lung disease. Symptoms include cough, pleuritic chest pain and dyspnea in addition to constitutional symptoms such as fatigue, fever, chills and night sweats. However, patients with PHG may also be asymptomatic. Most cases of PHG are discovered incidentally during routine examinations or during peri-procedural chest imaging, as was the case in our patient[4].

A number of cases have associated PHG with infectious processes (e.g. tuberculosis and histoplasmosis), autoimmune conditions (e.g. abnormally elevated rheumatoid factor, antinuclear antibodies, positive antiglobulin, Sjogren's, and hemolytic anemia), and neoplastic phenomena (e.g lymphoma and Castleman's)[5]. Latent tuberculosis has been associated with PHG, but a causal role is challenging to confirm[6]. It has been suggested, however, that PHG is the consequence of an exaggerated immune response to an underlying inflammatory process.

The lesions of PHG are variable but are often well demarcated. They may be solitary or multiple, unilateral or bilateral, and calcified or acalculous. Their size may vary in diameter from sub-centimeter to as large as 15.0 cm, with an average of approximately 2.0 cm[7]. The cavitation seen in this case is an atypical finding, but has been reported[8]. Increased metabolic activity can be detected with

FDG-PET and requires the exclusion of malignancy. Diagnosis of PHG is confirmed by histology demonstrating a perivascular lymphoplasmacytic infiltrate flanking a gradient of concentric hyalinized collagen[9]. Most cases of PHG are generally benign. However, 30% of patients may exhibit progressive growth of pulmonary lesions resulting in dyspnea[8].

Agent Orange and other dioxin-containing compounds used during the Vietnam War are associated with numerous diseases including respiratory cancers, soft-tissue sarcomas and primary amyloidosis. They have not been associated with the development of PHG[10]. Agent Orange has been shown to promote derangements in translation[11]. Kuwatsuka et al recently reported markedly increased concentrations of pro-inflammatory cytokines (e.g. IL-17, IL-23, IL-1β, TNF-α) and decreased concentrations of the anti-inflammatory IL-22 in a patient population that experienced the Yusho Poisoning Incident over 40 years ago[12]. Peltier et al also described a similar phenomena, in which *E. coli* pretreated with dioxin-containing chemicals were measured to have increased concentrations of pro-inflammatory cytokines (e.g. TNFα, PGE2, and COX2), while simultaneously having decreased levels of anti-inflammatory cytokines, such as IL-10[13]. Collectively, these findings suggest individuals exposed to Agent Orange and other dioxin-containing chemicals may be biochemically predisposed to more vigorous inflammatory responses that may favor the development of PHG.

In conclusion, we report a case of PHG in a male veteran with latent TB and environmental exposures, including Agent Orange. He was treated for latent TB with interval partial resolution on serial imaging and remains clinically stable without other PHG-specific therapy. The association between the development of PHG and Agent Orange exposure is novel. The pro-inflammatory biochemical derangements reported to occur as a result of exposure to such chemicals may predispose an individual to develop PHG. PHG should be considered in the differential diagnosis for nodular pulmonary disease, and requires a biopsy for diagnosis with exclusion of associated diseases including malignancy, infection, and an underlying connective tissue disorder. There is no specific therapy, but cases of steroid responsive disease have been reported.

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