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CASE STUDY

A case of steroid responsive pulmonary hyalinising granuloma: complicated by deep venous thrombosis

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A case of steroid responsive pulmonary hyalinising granuloma: complicated by deep venous thrombosis. K.M.A. O'Reilly, J.A. Boscia, K.L. Kaplan, P.J. Sime. ©ERS Journals Ltd 2004.

ABSTRACT: A case of pulmonary hyalinising granuloma (PHG) complicated by deep venous thrombosis (DVT) is presented.

The DVT was associated with the presence of a lupus anticoagulant. In the past PHG has been linked to various auto-antibodies, but to the best of the authors' knowledge, this is the first case reporting PHG in association with a lupus anticoagulant and clinically significant venous thrombosis. Historically, PHG has been regarded as poorly corticosteroid responsive. However, the patient in this case study responded dramatically to prednisone.

This case study suggests that in selected patients with pulmonary hyalinising granuloma experiencing disabling symptoms and worsening pulmonary function, a trial of corticosteroids may be warranted.

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Pulmonary hyalinising granuloma (PHG) is an unusual inflammatory respiratory disease which causes pulmonary parenchymal nodules that may mimic bronchogenic carcinoma and tuberculosis (TB). These are usually multiple, bilateral and may occur in any lobe [1–3]. The aetiology is unclear but there is some evidence that it may represent an abnormal immunological reaction to an unknown antigen. In the past, PHG has been associated with various auto-antibodies and certain disease states, including tuberculosis and histoplasmosis [2, 3].

The course is generally benign but the lesions do grow progressively larger, albeit at a slow rate. Reports to date suggest that PHG is poorly corticosteroid responsive [2]. Here the authors present an interesting case of PHG which was complicated by an extensive deep venous thrombosis (DVT), and a lupus anticoagulant.

Case Report

A 60-yr-old Jamaican male initially presented to a hospital in Florida with complaints of dyspnoea, cough, weight loss and fatigue. A chest radiograph revealed bilateral nodular infiltrates. The patient was admitted, underwent bronchoscopy and was empirically started on anti-tuberculous therapy with rifampin, isoniazid, pyrazinamide and ethambutol. A purified protein derivative test (PPD) was performed and subsequently read as 0 mm of induration (a negative result for TB).

Two months later the patient moved to Rochester and was referred to the current authors' medical centre by his GP. At that time, his cough had improved on anti-tuberculous therapy. However, he reported continued weight loss, dyspnoea on exertion and vague chest discomfort. He denied pyrexia, chills, or haemoptysis, but had noted some right leg swelling and discomfort. The patient had lived in the USA for 14 yrs during which time he had worked as a migrant farmer. There was a 50-pack year history of cigarette smoking. Past medical history was noncontributory; HIV status was negative. There was no history of significant occupational exposures and no family history of thrombosis.

Physical examination revealed a thin man with swelling of the right leg. There was symmetrical expansion of the chest and the breath sounds were of decreased intensity bilaterally. No crackles or wheezes were auscultated. Pulmonary function testing revealed a forced expiratory volume in one second (FEV_1) of 1.71 L (53% of predicted) and a forced vital capacity (FVC) of 2.31 L (55% pred), the FEV_1/FVC ratio was preserved. The chest radiograph showed bilateral upper lobe reticulonodular infiltrates (fig. 1a). A chest computed tomography (CT) scan revealed extensive bilateral apical nodular areas of airspace opacification associated with small emphysematous cysts (fig. 1b). All acid fast and fungal cultures from Florida were negative so the anti-tuberculous therapy was discontinued. A bronchoscopy with transbronchial biopsies was performed 2 months after the patients' initial presentation and this was nondiagnostic. The patient was found to have an extensive right leg DVT which extended into the pelvic veins. No risk factors for DVT except cigarette smoking were identified. Anticoagulation was subsequently begun. Given the concern for possible bronchogenic carcinoma he underwent a limited right thoracotomy with lung biopsy. The pathology revealed replacement of the parenchyma with eosinophilic collections of hyalinised collagen, numerous lymphocytes and plasma cells (fig. 2a, b) with occasional germinal centres observed (fig. 2c). There was no evidence of neoplastic cells, and acid-fast, fungal and Congo red stains were all negative, similarly all cultures were

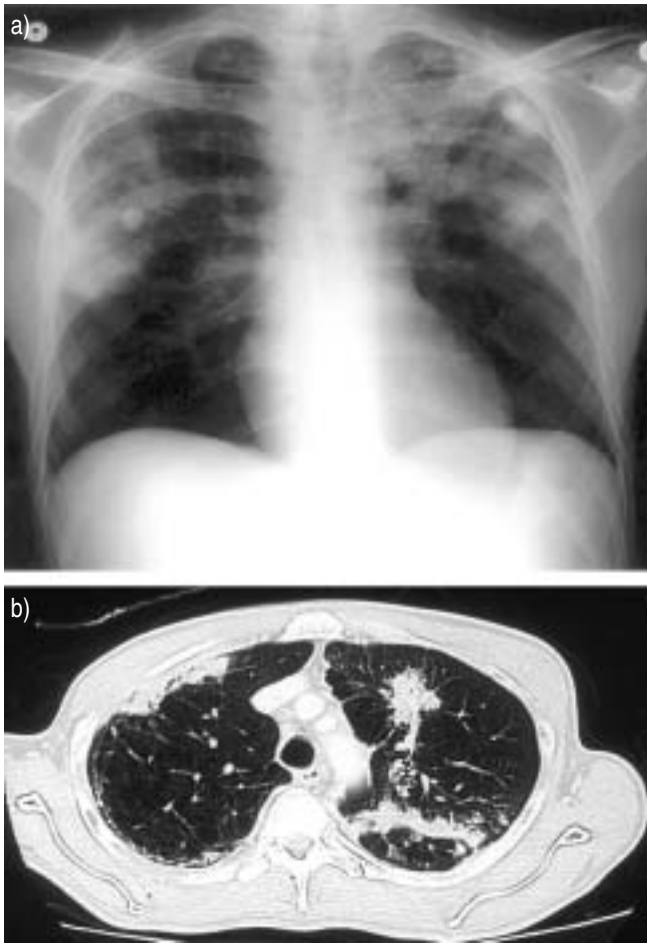

Fig. 1. – a) Chest radiograph demonstrating bilateral upper lobe nodular densities. b) A computed tomography of the thorax showing multiple areas of patchy nodular densities; there is significant scarring in the upper lobes with focal emphysematous changes.

negative. The findings were consistent with a diagnosis of pulmonary hyalinising granuloma.

The patient was then lost to follow-up for >1 yr, but returned with complaints of increasing dyspnoea and chest discomfort. A chest radiograph and CT scan showed progression of the upper lobe nodular infiltrates. The FVC had dropped to 1.47 L (34% pred). The patient had completed 6 months of anticoagulation therapy, and there were no signs or symptoms from his previous DVT. A hypercoagulability screen revealed a lupus anticoagulant, but no anti-cardiolipin antibody. The patient was treated with long-term anticoagulation and a steroid trial (prednisone 60 $mg \cdot day^{-1}$) was instituted to see if the disease progression could be slowed. This resulted in a dramatic improvement in his FVC, which rose to 2.82 L (65% pred), and corresponded to a marked improvement in his exercise tolerance. However, the dense infiltrates did not change appreciably on radiograph. In the subsequent months, two separate attempts were made to decrease the steroid dose, on each occasion this led to a marked reduction in his FVC and worsening exercise tolerance (fig. 3). He had no further episodes of thrombosis while on warfarin.

Discussion

PHG is an unusual cause of pulmonary parenchymal infiltrates that may mimic such diverse diseases as bronchogenic carcinoma, metastatic neoplasm, TB, Wegener's granulomatosis, sarcoidosis and amyloidosis. To date there have been <70 cases reported in the English-language literature. PHG appears to affect young to middle-aged adults (range 24–77 yrs), but no sex or race predilection has been noted. Common presenting complaints include cough, dyspnoea and chest pain (which may be pleuritic in nature), and less frequently, fatigue and haemoptysis. However, certain patients may be entirely asymptomatic and come to attention only when the lesions are detected on routine chest radiography.

The typical radiographic appearance is of multiple bilateral, well-circumscribed nodules which can occur throughout

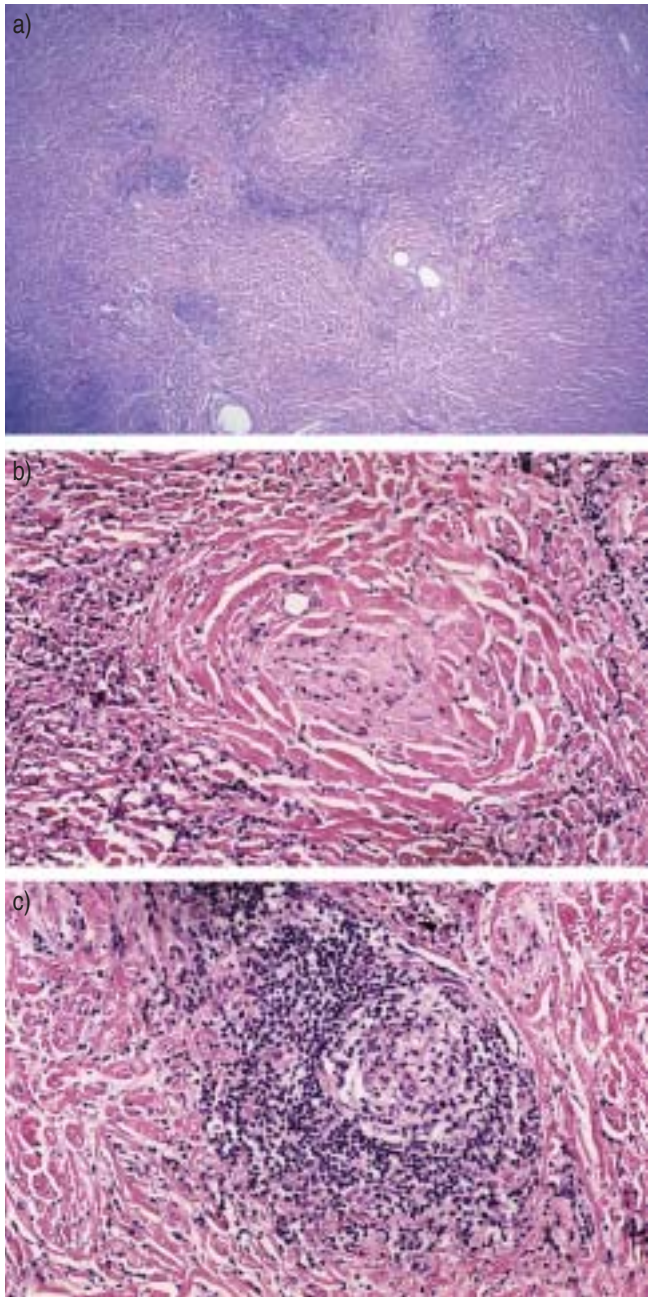

Fig. 2. – a) A low power photomicrograph of excised tissue illustrating the key features of pulmonary hyalinising granuloma. Well-defined acellular nodules are seen to replace the normal lung parenchyma. b) Photomicrograph showing bundles of eosinophilic hyaline lamellae with scant inflammatory cells. c) Photomicrograph of a germinal centre adjacent to the collagen bundles.

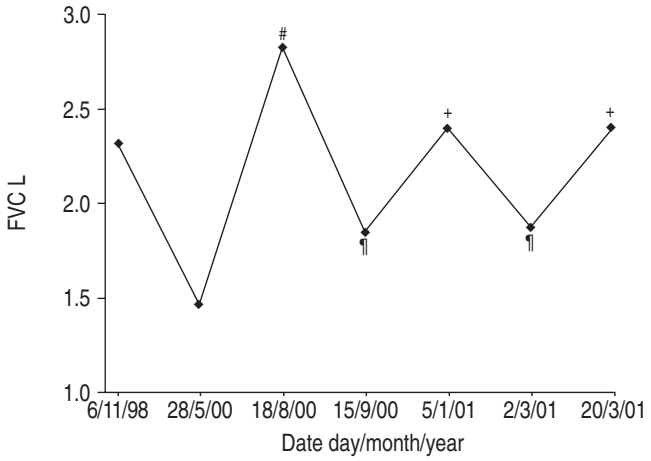

Fig. 3. – Change in forced vital capacity (FVC) over time. The patient's FVC dropped by ~1 L between 06/11/1998 and 26/05/2000. Steroid therapy was initiated ($^{\#}$: prednisone 60 mg·day^{-1}) and the FVC improved dramatically, reaching 2.82 L by 18/08/2000. Subsequently two attempts to decrease the dose (¶: prednisone 15 mg·day^{-1}) resulted in a rapid drop in FVC; on each occasion reinstitution of the maintenance dose ($^{+}$: prednisone 30 mg·day^{-1}) resulted in a return to baseline values.

both lungs. However, this may vary considerably; there have been reports of unilateral, poorly defined or spiculated nodules [1, 2]. The radiographic appearance is not diagnostic. A tissue diagnosis is thus required to exclude malignancy and to confirm a diagnosis of PHG.

In general, the pathology is very characteristic: the centre of the lesion consists of extracellular, eosinophilic hyalinised collagen usually arranged in parallel lamellae, but it may be quite disorganised. The peripheral areas tend to be more cellular with clusters of lymphocytes, histiocytes and plasma cells; germinal centres may be seen. The appearance is easily confused with nodular amyloid. KATZENSTEIN and ASKIN [3] feel that cases resembling PHG, but exhibiting a positive Congo red stain, should be considered nodular pulmonary amyloidosis. However, GUCCION *et al.* [4] have reported a case where Congo red and crystal violet stains were focally positive for amyloid. However, electron microscopy ruled out this diagnosis. The histological appearance of PHG is identical to that of sclerosing mediastinitis, a more commonly encountered condition [3]. This is characterised by the development of thick fibrous tissue which encases, and may compress mediastinal structures. One recognised complication of PHG is the development of sclerosing mediastinitis which presumably arises by extension of a fibrotic focus from the parenchyma into the adjacent hilum or mediastinum.

The aetiology of PHG is uncertain, however, it has been proposed that it represents an abnormal immune reaction to an infectious agent, possibly histoplasmosis or TB [1, 2]. There is evidence that sclerosing mediastinitis may also be related to previous fungal or tuberculosis infections. Support for this hypothesis has come from the demonstration of a variety of auto-antibodies in sera of patients with PHG. To date, there have been reports of anti-antinuclear antibodies, rheumatoid factor, anti-neutrophil cytoplasmic antibodies, anti-smooth muscle antibodies, anti-microsomal antibodies and Coomb's-positive haemolytic anaemia [2, 5]. In addition, circulating immune complexes have been demonstrated.

To the best of the authors' knowledge this is the first report of a lupus anticoagulant or any acquired thrombophilic disorder in association with PHG. This lends further support to the theory that PHG is associated with abnormal immune activation. It is especially significant given the association with extensive venous thrombosis in the current study patient. Based on this finding, it would be valuable to examine patients presenting with PHG and venous thrombosis for the presence of a lupus anticoagulant.

Another particularly interesting feature of this case is the degree of corticosteroid responsiveness demonstrated. Prior to institution of corticosteroid therapy the progression of this patients' disease radiologically did not appear to exceed that reported in the literature [1]. However, the decline in lung function was marked, associated with debilitating symptoms and necessitated intervention. Reports to date have suggested that pulmonary hyalinising granuloma is difficult to treat effectively, a conclusion that seems to have been reached due to the lack of efficacy achieved with corticosteroids. However, some authors have reported success in treating pulmonary hyalinising granuloma with chemotherapy, instituted for an alternate diagnosis [6]. The experience of the current authors suggests that certain cases of pulmonary hyalinising granuloma can be treated quite effectively with corticosteroids and would argue that a therapeutic trial is indicated in cases where the disease has become significantly disabling, as was the case for the patient of the present study.

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