

Pulmonary hyalinizing granuloma

Bilateral pulmonary nodules associated with chronic idiopathic thrombocytopenic purpura

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ABSTRACT

We report a case of a 30-year-old female who had been treated periodically with steroids for idiopathic thrombocytopenic purpura (ITP) over the last 10 years. Recently, during the course of investigation, she was found to have incidental asymptomatic multiple pulmonary nodules on chest CT. Following a needle biopsy to exclude malignancy, 2 nodules were excised and were histologically confirmed as pulmonary hyalinizing granuloma (PHG). The remaining 2 nodules regressed on increasing her dose of steroids. The case is discussed with emphasis on the histological and radiological differential diagnosis, in addition to including ITP among the spectrum of immunologic conditions associated with PHG.

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Pulmonary hyalinizing granuloma (PHG) is a rare disease characterized by bilateral or solitary fibrotic nodular lesions in the lungs, first described by Englemen et al.¹ The condition is rare and worth reporting as only under 100 cases are cited to date in the world literature.¹⁻¹³ Radiologically the lesions closely mimic metastatic carcinoma.^{1,4} The nodules were described as subpleural, well circumscribed, firm, varying in size from 0.5 – 9 cm.² The nodules are defined histologically by a central irregular, haphazard or whorl-like deposition of lamellar collagen surrounded peripherally by a perivascular lymphoplasmacytic infiltrate and myofibroblastic proliferation.^{2,4} Patients are usually adults, often presenting with pulmonary symptoms;^{1,2} however, rarely patients present with extrapulmonary

symptoms^{12,13} and approximately 25% are asymptomatic.^{1,2} The PHG is of unknown etiology. The condition has however, been linked to a number of infectious and non-infectious immune diseases including tuberculosis,² histoplasmosis,⁵ aspergillosis,⁶ retroperitoneal fibrosis,⁷ Castleman's disease,⁸ lymphoma⁹ and multiple sclerosis.¹⁰ Such associations may indicate a common immune mechanism for the pathogenesis of PHG.¹¹ Prognosis of PHG is excellent, most lesions regress or remain stable with or without steroid therapy.² The aim of this presentation is to bring awareness of PHG, to be included in the clinical and radiological differential diagnosis of multiple or solitary pulmonary nodules and to include ITP among its reported associated immunologic conditions.

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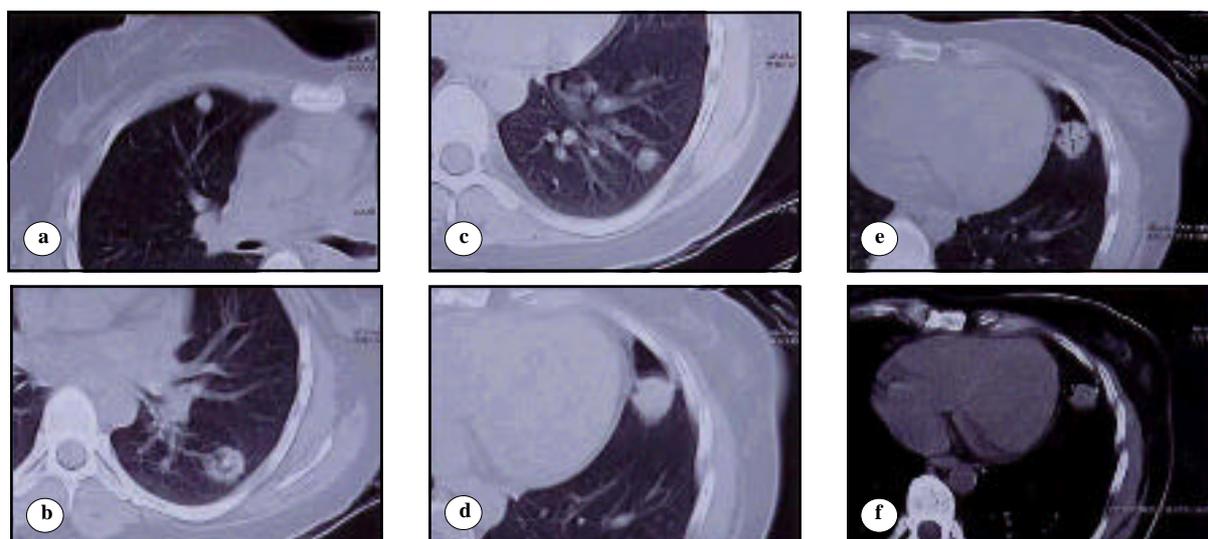


Figure 1 - Chest CT scans showing subpleural nodular lesions in right upper lobe anterior segment: (a) left lower lobe superior (b) and lateral (c) segments as well as inferior lingula (d). Images e & f showing measurements of dominant lingular nodule.

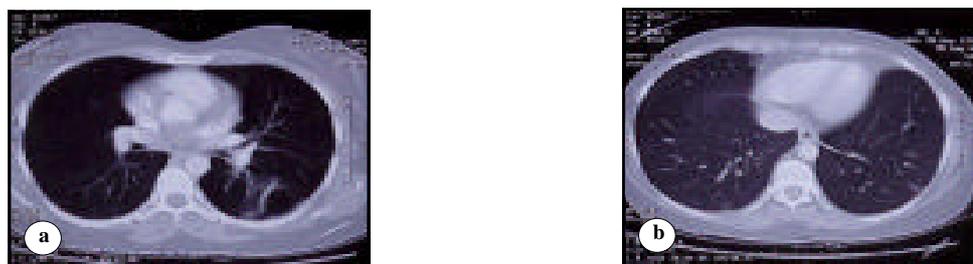


Figure 2 - Postoperative scans 6 weeks following prednisolone therapy through apical segment of lower lobes (a) showing only minimal scar and lingula (b) showing no residual lesion.

Case Report. A 20-year-old lady was diagnosed to have idiopathic thrombocytopenic purpura (ITP) following investigations of bleeding and easy bruising in 1993 and platelet count of $9 \times 10^9/L$. The patient was investigated for underlying causes of immune thrombocytopenia. However, the autoantibodies profile: antinuclear antibodies (ANA), ds-DNA, rheumatoid factor (RF) were negative. Antiphospholipid and anticardiolipin antibodies were also negative. The patient's serum was not reactive to hepatitis C or HIV antibodies. The patient was treated with standard dose of prednisolone 2 mg/kg/day. However, she failed to have a sustained rise of platelet count and remained to suffer from chronic ITP, mostly off steroids, with platelet count of $20-40 \times 10^9/L$ for years. Serial follow up investigations failed to reveal emergence of any of lymphoid or collagen disorders known to be

associated with ITP. However, in October 2003, almost 10 years after the diagnosis of ITP, the patient presented with loss of weight without constitutional symptoms. At the time, she was on prednisolone 5 mg/day. Physical examination was unremarkable. In view of suspicion of possible lymphoma, the patient had CT scan of the pelvis and abdomen, which were normal. The CT scan of chest (**Figure 1**) showed four subpleural nodules; one each in right upper lobe anterior segment, left lower lobe superior and lateral basal segments as well as one in inferior lingula. Nodules are well defined with no calcification or cavitation within. The nodule in superior segment of left lower lobe showed eccentric internal ground-glass density and a leading vessel. None of the nodules enhanced after contrast injection and they ranged in size between 1.5 - 2.1 cm. There was no evidence of lymphadenopathy and no pleural or pericardial

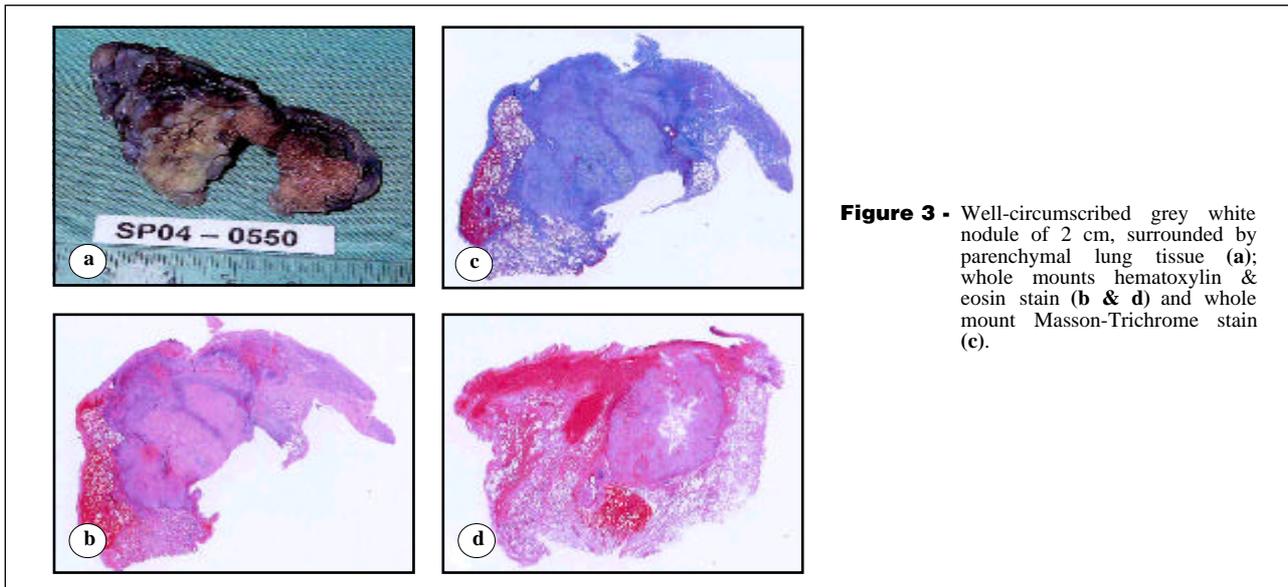


Figure 3 - Well-circumscribed grey white nodule of 2 cm, surrounded by parenchymal lung tissue (a); whole mounts hematoxylin & eosin stain (b & d) and whole mount Masson-Trichrome stain (c).

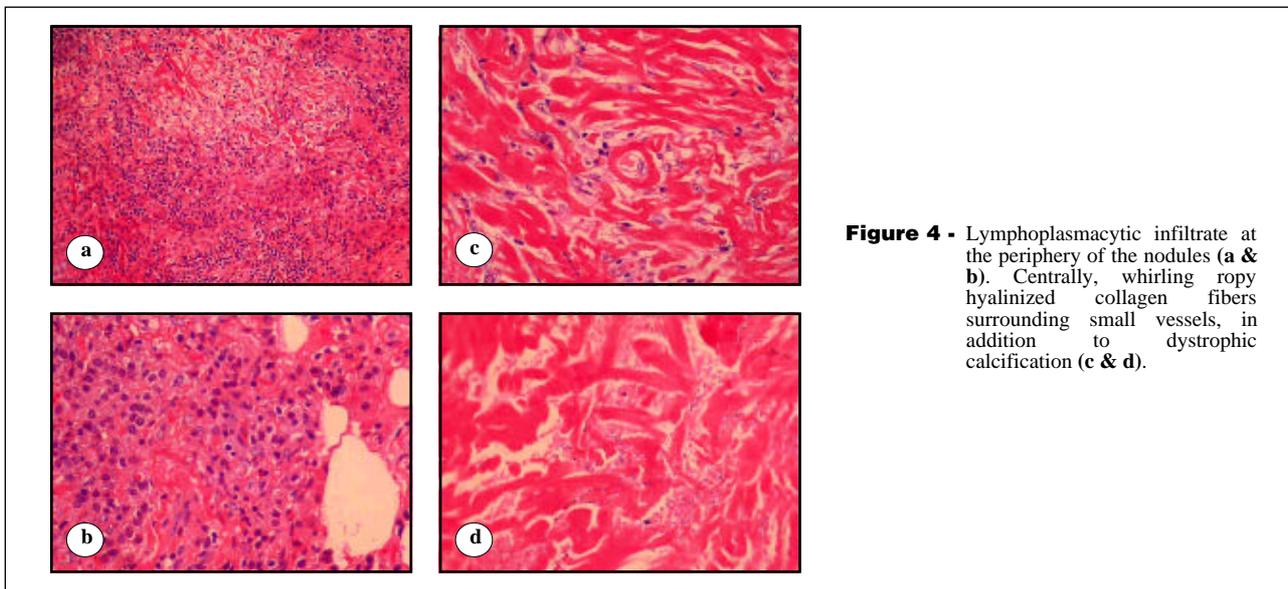


Figure 4 - Lymphoplasmacytic infiltrate at the periphery of the nodules (a & b). Centrally, whirling rosy hyalinized collagen fibers surrounding small vessels, in addition to dystrophic calcification (c & d).

effusions. The radiological differential diagnosis included metastatic lung disease, granuloma, bronchiolitis obliterans organizing pneumonia (BOOP) and intrapulmonary lymphoid nodules. The patient was referred to the respiratory clinic for further evaluation. Her ANA, RF, anti-neutrophil cytoplasmic antibody (ANCA) were all negative and her angiotensin converting enzyme (ACE) level was normal. She was admitted for CT scan guided biopsy. The histology revealed a fibro-inflammatory lesion with no evidence of malignancy. Accordingly, it was decided to proceed with thoracoscopic surgical biopsy. Two nodules were removed and sent to histopathology.

Histopathological examination. Two nodules received, one from the left lower lobe 1.5 cm in diameter and one from lingula 2 cm in greatest diameter, both well-circumscribed, grayish-white and firm, gritty on sectioning (Figures 3 a-d). Histologically, sections from both show similar features. Both lesions are hyalinized in the center showing minimal dystrophic calcification and discrete tiny foci of punctate necrosis. Centrally, the collagen fibers are thick, whirling, rosy and surround small and large vascular channels (Figures 4 c & d). The hyalinized foci are surrounded at the periphery by chronic inflammatory bland cellular infiltrate and fibroblastic proliferation containing

prominent endothelial cells (**Figures 4 a & b**). The infiltrate is lymphoplasmacytic with no atypical features and included T and B-lymphocytes, histiocytes, eosinophils and neutrophil polymorphs. The mononuclear cells are seen in vascular intima associated with prominent vascular occlusion but no fibrinoid necrosis noted. No epithelioid granuloma or multinucleated giant cells are identified. The surrounding lung tissue showed collapse, exudation, foamy macrophage infiltration and obstructive changes. No microorganisms or evidence of malignancy seen and no evidence of Amyloid. The final diagnosis for both nodules was PHG.

Further management and follow-up of the patient had an uneventful postoperative course and was discharged in good condition. The dose of prednisolone was increased to 40 mg/day for 4 weeks and then tailed down gradually to a maintenance dose of 5 mg per day. Repeat CT scan 6 weeks later showed minimal scar in the apical segment of left lower lobe (**Figure 2a**) and no residual lesion in the lingula (**Figure 2b**). She remained asymptomatic and with platelets count $57 \times 10^9/l$, hemoglobin 12 gm/dl, and white blood cell $6.4 \times 10^9/l$.

Discussion. Pulmonary hyalinizing granuloma is a condition of undetermined etiology first reported by Engleman in 1977.¹ It is rare with less than 100 cases reported to date in the world literature.¹⁻¹³ The defining feature of the lesion is the histological hallmark of the nodule composed centrally of a distinctive whorled array of thickened hyalinized collagen fibers arranged in a ropy fashion around small vascular channels, surrounded by a perivascular lymphoplasmacytic infiltrate and fibroblastic proliferation.¹⁻⁴ Other cells including macrophages, neutrophils and eosinophils may be seen. Although occasional multinucleated giant cells have been noted, well-formed granulomas are not a feature. Spotty dystrophic calcification may rarely be noted in the center of the lesion. Necrosis is not a prominent feature and if it is dominant, associated infection should be sought.^{2,5,6} Patients usually are adults with a mean age of 45 years, often presenting with cough, dyspnea and chest pain. Over 25% of patients, however are asymptomatic.^{1,2}

Although no direct etiologic agents are known, the lesions are reportedly associated with sclerosing mediastinitis, retroperitoneal fibrosis,^{1-3,7} fungal histoplasmosis,^{4,5} aspergillus fumigatus,⁶ tuberculosis,² Castleman's disease,⁸ lymphoma⁹ and multiple sclerosis.¹⁰

The finding of asymptomatic pulmonary nodules on CT in our patient was alarming, raising the possibility of lymphoid malignancy as an underlying cause of long-standing thrombocytopenia. The radiologic differential diagnosis

included metastatic malignancy, granuloma, BOOP and intrapulmonary lymphoid nodules. Radiologically, PHG are usually bilateral, multilobar, ill-defined homogeneous nodules that most typically resemble metastatic carcinoma.^{1,4} Cavitation and calcification are considered unusual features,^{1,2,4} but has recently been reported.⁵ Unlike metastatic malignancy, PHG nodules either remain stable in size or slowly enlarge with progressive respiratory symptoms.²

The histopathologic findings of the needle biopsy were exclusive of malignancy and suggestive of plasma cell granuloma (inflammatory pseudotumor). Such a diagnosis is the most difficult to differentiate from PHG especially on needle biopsies. This is due to the periphery of PHG, which is composed of a lymphoplasmacytic infiltrate. Moreover, sclerosed inflammatory pseudotumors may closely resemble PHG to the point that some PHG were thought of as the end stage of inflammatory pseudotumor.² However, plasma cell granulomas (inflammatory pseudotumor), unlike PHG are usually solitary and lack the characteristic whorled lamellar hyalinized collagen of PHG.

Histopathologic examination of both resected nodules was confirmatory, showing the typical features of PHG with the characteristic central whorled, ropy, hyalinized collagen fibers, surrounding the small blood vessels (**Figure 4**). The peripheral zones showed perivascular polymorphic lymphoplasmacytic infiltrate including macrophages, eosinophils and few neutrophil polymorphs. The differential diagnosis included infectious granulomas of tuberculosis and fungal histoplasmosis, Wegener's granulomatosis, lymphomatoid granulomatosis, sclerosed inflammatory pseudotumor (plasma cell granuloma), rheumatoid nodules, nodular amyloidosis and Hodgkin's lymphoma.² Lymphomatoid granulomatosis was ruled out by the lack of cytologic atypia. No granulomatous reaction and no vasculitis were seen excluding Wegener's granulomatosis. Although punctate necrosis was noted, Gomori-Methenamine Silver (GMS) and Ziehl-Neelsen (ZN) stains ruled out respectively fungal and tuberculous infections. No amyloid was seen on Congo-Red stain.

Differentiation from lymphoid tumors particularly sclerosing malignant lymphoma and Hodgkin's lymphoma is of utmost practical importance. The polymorphic lymphoplasmacytic infiltrate formed of T and B cells as well as histiocytes and the lack of cytologic atypia argue against a diagnosis of lymphoma in our patient. In this respect, PHG has been reported in a patient with plasma cell variant of Castleman's disease⁸ and in association with pulmonary B cell lymphoma.⁹ Apart from the long-standing thrombocytopenia, our patient did not have any extrapulmonary symptoms.

This is relevant as some patients may have symptoms related to sclerosing mediastinitis,^{1,4} retroperitoneal fibrosis^{7,14} and cervicofacial and orbital involvement¹² and dysphagia.¹³ Our patient with ITP, had a negative autoimmune profile; serologic evidence of autoimmune phenomena being identified in 2 patients with PHG¹¹ and in 6 of 10 patients of an original series including Coomb's positive hemolytic anemia.²

Patients may be asymptomatic or have pulmonary symptoms of cough, shortness of breath or chest pain.^{2,4} Weight loss, the only noted symptom in our patient, was reported in 4 of 24 patients with PHG.²

Follow up information of patients with solitary lesions is usually favorable; all 6 patients reported in a large series had no evidence of disease with a mean follow-up of 48 months.² In patients with bilateral disease the nodules may remain stable in size or show symptomatic progressive enlargement.² Apart from surgical excision, no specific therapy is curative for PHG,^{1,2,4} although steroids have been tried with some success.^{7,12} Following the surgical excision of 2 nodules in our patient, the increased dose of steroids has resulted in stabilizing the size of other nodules.

In conclusion, this case illustrates the typical clinical, radiologic and morphologic features of PHG in a patient with long-standing chronic ITP. Association with ITP, may be coincidental but does support the view of an underlying immunologic pathogenesis held for PHG.

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