Pulmonary hyalinizing granuloma: Atypical presentation☆

Dear Editor,

In 1977, Engleman et al. described pulmonary hyalinizing granuloma (PHG) as a separate entity.[1] This disease is rare and is radiologically characterized by multiple and often bilateral nodules with no preferential localization.[1,2] Its etiology and pathogenesis remain unclear, and a definitive diagnosis is provided by histopathological study of the lesions describing hyalinized lamellar collagen bundles surrounded by plasma cells, lymphocytes, and histiocytes. This disease usually evolves with a benign course with nodules slowly increasing in size over years. Specific treatment is

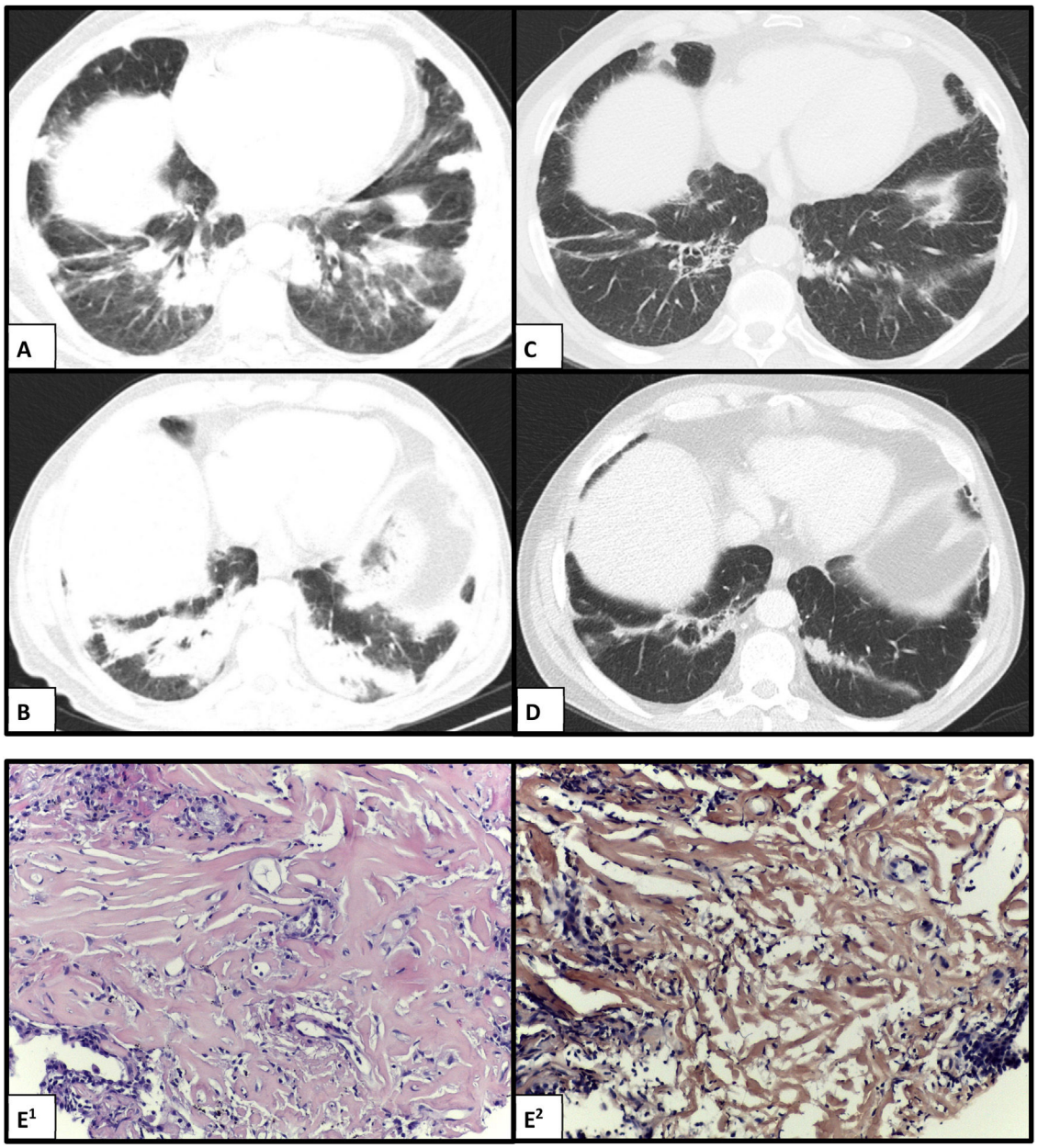

Figure 1 Chest CT scan showing bilateral peripheral consolidation areas in the lower lobes before (A and B) and after (C and D) complete chemotherapy scheme. (E^1) Histology showing hyalinized lamellar collagen tissue surrounded by lymphoplasmacytic infiltrates (hematoxylin and eosin, ×200); and (E^2) negative Congo red stain (CR, ×200).

☆ The authors present a clinical case of a rare disease with atypical radiological presentation, and an uncommon association between Pulmonary Hyalinizing Granuloma and a lymphoproliferative disorder.

not usually required, although corticosteroids have demonstrated some efficacy.[1–3]

The etiology of PHG is not well established, and no relation to occupational exposure has been identified. Due to the frequent association with infectious, autoimmune, and tumoral diseases, an abnormal immune reaction has been proposed to explain the development of PHG.[1,3,4] In the case in the present report, we describe an uncommon association between PHG and a lymphoproliferative disorder. We found only four similar reports of associations with multicentric Castleman disease[5,6]; diffuse lymphocytic lymphoma of the abdomen[7]; and pulmonary small lymphocytic lymphoma[8]. The ages of these patients ranged between 43 and 50 years, and the patients were predominantly male (3 males/1 female). All patients presented with multiple and bilateral pulmonary nodules, and diagnosis was made through video-assisted thoracoscopic lung biopsy in three cases and by post-mortem examination in one case. Chemotherapy schemes targeted at lymphoproliferative disease which included corticosteroid were initiated in three cases. In two of these cases, there was a reduction in the lung nodule dimensions.

We report a case of a 69-year-old man, former smoker (70 pack-years), with occupational exposure to dust and fumes from metallurgical casting and contact with birds, who presented to the emergency department with a 6-month history of progressive dyspnea. He reported mild fever, anorexia, and weight loss (10 kg over the prior 3 months). A physical examination revealed inspiratory crackles in the lower lungs. Chest computed tomography (CT) scan showed bilateral peripheral consolidation areas, mainly in the lower lobes but also involving the middle lobe and lingula (Fig. 1 — A and B); the CT also revealed hepatosplenomegaly. Laboratory data demonstrated normocytic and normochromic anemia, and elevated levels of C-reactive protein and erythrocyte sedimentation rate. An autoimmunity study was negative. No endobronchial lesions were detected in the bronchoscopy. In the bronchoalveolar lavage, the total and differential cell counts revealed lymphocytic (47%) and neutrophilic (7.4%) alveolitis, which was negative for microorganisms and malignant cells. An initial pulmonary function test revealed moderate restrictive ventilatory alteration with a forced expiratory volume in one second (FEV1) 2.06 L (72.8% of the predicted value), forced vital capacity (FVC) 2.42 L (65.6%), preserved FEV1/FVC ratio, a total lung capacity (TLC) 4.51 L (68.5%), and carbon monoxide transfer factor (TLCO) 52%. A CT-guided transthoracic core biopsy was subsequently performed, and hyalinized lamellar collagen tissue surrounded by lymphoplasmacytic infiltrates was reported on histological examination (Fig. 1E[1]). No evidence of neoplastic cells was found, and acid-fast, fungal, and Congo red stains were all negative (Fig. 1E[2]). These findings were consistent with a diagnosis of PHG. The patient was started on oral corticosteroid therapy (deflazacort in an equivalent dose of 0.5 mg/kg/day of prednisolone, within a weaning scheme) and demonstrated partial clinical and functional but not radiological improvement.

Throughout the investigation, an indolent non-Hodgkin's lymphoma (NHL) was incidentally diagnosed, supported by a bone marrow biopsy. The clinical case was, therefore, discussed in a multidisciplinary team, and with PHG hypothesized as a paraneoplastic manifestation of hematological disease, a decision to start NHL treatment was made. After completing eight cycles of chemotherapy (rituximab, cyclophosphamide, vincristine, and prednisolone), the patient had significant clinical, functional, and radiological improvement (Fig. 1 — B and D). At the time this report was written, the patient was asymptomatic and functional with FEV1 2.88 L (106.5%), FVC 3.66 L (103.1%), TLC 5.83 L (89.7%), and TLCO 68%. No residual disease was found on further bone marrow tests.

In summary, PHG is a rare entity with nonspecific symptoms and slow progression. Although isolated or multiple nodular lesions are the most frequent findings, PHG can occaisonally appear as lung parenchymal infiltration or consolidation with irregular or indistinct borders, such as in this case.[3] In patients showing a rapid course and significant functional impairment, corticosteroid treatment may be attempted, despite the unclear efficacy of this approach. Due to the frequent association with underlying diseases, a careful investigation should be performed for therapeutic and prognostic implications.

Ethical disclosures

There are no personal details of patient in any part of the paper and in any supplementary materials (including illustrations).

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Conflicts of interests

The authors have no conflicts of interest to declare.

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Miliary tuberculosis in a rheumatoid arthritis patient receiving long-term tumor necrosis factor monoclonal antibody therapy

Dear Editor,

A 51-year-old woman had a diagnosis of seropositive rheumatoid arthritis (RA) with polyarthritis involving bilateral elbow, small joints of hand and knee areas on March 12, 2004. Owing to refractory therapeutic responses with a DAS28 score of 6.16 under methotrexate 15 mg/week, hydroxychloroquine 400 mg/day and prednisolone 10 mg/day, she started to receive regular biweekly 40 mg subcutaneous injection of adalimumab, a tumor necrosis factor (TNF) monoclonal antibody (mAb) since June 17, 2011. She had no history of lung diseases with a clear chest X-ray (Fig. 1A). There was a negative QuantiFERON test before initiating anti-TNF therapy. She had reduced disease activity after treatment without further prescription of hydroxychloroquine and prednisolone. Owing to productive cough with intermittent fever and weight loss for 3 weeks, the use of TNF mAb was discontinued on February 20, 2018, 80 months after initiating such a treatment. However, she did not receive follow-up QuantiFERON test during her long-term anti-TNF therapy. Chest images including X-ray (Fig. 1B) and computed tomography (Fig. 1C) showed bilateral diffuse miliary lesions characterized by innumerable micronodular opacities. She had no exposure to fine mineral or chemical dust, and her malignancy survey and human immunodeficiency virus examination were negative results. Sputum cultures were positive for *Mycobacterium tuberculosis*. There was no recent household tuberculosis (TB) contact history. She received anti-TB medications with daily dosages of rifampicin 480 mg, isoniazid 320 mg, pyrazinamide 1000 mg and ethambutol 800 mg for 9 months from April 12, 2018 (drug-susceptibility testing in TB with resistance to streptomycin and sensitive to others). After antibiotic therapy, there were no more respiratory or constitutional symptoms, negative sputum culture results and resolved pulmonary miliary nodules (Fig. 1 D). For her arthritis flare-up after discontinuing TNF mAb injection, rituximab, a B-cell depleting mAb, under a regimen of 1 g × two fortnightly infusions every 6 months was initiated on February 7, 2020 with improved disease activity (DAS 28 score 5.34 to 2.70) after 4 infusions at the end of 2020.

Miliary TB, a rare fatal presentation of mycobacterial infection, can occur in the presence of impaired host immunity under the prescription of immunosuppressive agents.[1,2] TNF blocker administration has been recognized as a risk for TB reactivation in various autoimmune-mediated inflammatory disorders,[3] especially when anti-TNF treatment is combined with the use of immunosuppressive agents like methotrexate.[4] Greater incidences are found during the first year of treatment than afterwards, while there are higher occurrences with mAb than with recombinant soluble receptor fusion protein therapy. Despite an additional risk of having been born in an area of endemic TB,[5] the reported case raises a potential infection hazard under the long-term TNF mAb treatment.

In conclusion, we reported miliary TB in a RA patient receiving long-period TNF blocker therapy. In addition to the initial QuantiFERON survey, periodic latent TB testing should be carried out in patients receiving the long-term immunosuppressive agents like TNF monoclonal antibodies.