Pulmonary hyalinizing granuloma: Atypical presentation

Dear Editor,

In 1977, Engleman et al. described pulmonary hyalinizing granuloma (PHG) as a separate entity. This disease is rare and is radiologically characterized by multiple and often bilateral nodules with no preferential localization. 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 needed.

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. (E1) Histology showing hyalinized lamellar collagen tissue surrounded by lymphoplasmacytic infiltrates (hematoxylin and eosin, ×200); and (E2) 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.\textsuperscript{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.\textsuperscript{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\textsuperscript{1,4} and diffuse lymphocytic lymphoma of the abdomen\textsuperscript{1}; and pulmonary small lymphocytic lymphoma.\textsuperscript{5} 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). No evidence of neoplastic cells was found, and acid-fast, fungal, and Congo red stains were all negative (Fig. 1E). 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 occasionally appear as lung parenchymal infiltration or consolidation with irregular or indistinct borders, such as in this case.\textsuperscript{1} 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).

**Funding**

No funding.

**Conflicts of interests**

The authors have no conflicts of interest to declare.

**References**

and corticosteroid. BMJ Case Rep. 2013;2013(September),
http://dx.doi.org/10.1136/bcr-2013-010233.
7. Drasin H, Blume MR, Rosenbaum EH, Klein HZ. Pulmonary
hyalinizing granulomas in a patient with malignant lymph-
phoma, with development nine years later of multiple
myeloma and systemic amyloidosis. Cancer. 1979;44:215-20,
http://dx.doi.org/10.1002/1097-0142(197907)44:1-215::aid-
cncr2820440135-3.0.co;2-g.
8. Ren Y, Raitz EAN, Lee KR, Pingleton SK, Tawfik O.
Pulmonary small lymphocytic lymphoma (Mucosa-
Associated Lymphoid Tissue Type) associated with
pulmonary hyalinizing granuloma. Chest. 2001;120:1027-30,
http://dx.doi.org/10.1378/chest.120.3.1027.

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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 pred-
nisolone 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 dis-
ease 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 innumer-
able 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 tuberculo-
sis (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 con-
stitutional symptoms, negative sputum culture results and
resolved pulmonary miliary nodules (Fig. 1D). 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 initi-
ated 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 immu-

ity under the prescription of immunosuppressive agents.1,2
TNF blocker administration has been recognized as a risk
for TB reactivation in various autoimmune-mediated inflam-

matory 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 recep-
tor 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 antibo-

ies.