CASE REPORT

Pulmonary alveolar proteinosis following cryptococcal meningitis: a possible cause?

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SUMMARY

Autoimmune pulmonary alveolar proteinosis (PAP) is a rare interstitial lung disease characterised by the presence of granulocyte macrophage colony-stimulating factor (GM-CSF) autoantibodies. A man with no history of infection developed cryptococcal meningitis and a right parahilar cryptococcal mass. Antifungal treatment led to infection control, although there was presence of neurological sequelae. After 3 years, thoracic CT revealed bilateral ground glass opacities and a crazy paving pattern. Transparietal needle biopsy showed proteinaceous alveolar deposits, confirming the diagnosis of PAP. A high titre of serum anti-GM-CSF autoantibodies was found. No specific treatment was started, and radiological lesions decreased progressively. Cryptococcal infection may occur in PAP and in patients with anti-GM-CSF antibodies without PAP. These antibodies dysregulate phagocytosis in monocytes and macrophages, possibly leading to opportunistic infections in previously healthy subjects.

BACKGROUND

Autoimmune pulmonary alveolar proteinosis (PAP) is a rare lung disease characterised by the accumulation of the lipoproteinaceous components of surfactant in the alveolar airspace.[1] It is due to granulocyte macrophage colony-stimulating factor (GM-CSF) autoantibodies.[1] We report the case of an immunocompetent patient who developed cryptococcal infection of the central nervous system and of the lungs, followed by autoimmune PAP. The hypothetical mechanisms of this rare association are discussed, with particular focus on the relationship between infection, autoimmunity and GM-CSF autoantibodies.

CASE PRESENTATION

A 42-year-old man presented with fever, headache, weight loss and peripheral facial paralysis. His medical history included a 20 pack-years, weaned smoking habit.

INVESTIGATIONS

Brain MRI showed multiple grey matter cyst-like lesions with postcontrast enhancement. Lumbar puncture found a lymphocytic hypercellular cerebrospinal fluid with increased protein level and decreased glucose level. The cerebrospinal fluid cryptococcal antigen was positive and the culture was positive for *Cryptococcus gattii*. Chest CT scan showed a right parahilar mass. Needle biopsy cultures confirmed cryptococcal growth. No cellular or humoral immunodeficiency was found.

TREATMENT

The patient was treated with multiple antifungal regimens including fluconazole, liposomal amphotericin B and voriconazole for nearly 5 years.

OUTCOME AND FOLLOW-UP

The general outcome was favourable, but the patient had neurological sequelae with hearing loss, anosmia and blindness. Three years after cryptococcal meningitis (CM), follow-up chest CT revealed bilateral ground glass opacities and a 'crazy paving' pattern with superimposed intralobular reticular thickening (figure 1). The patient had no respiratory symptoms. Microbial cultures of bronchoalveolar lavage were negative. Pathological examination of transthoracic needle biopsy showed granular eosinophilic deposits in alveolar spaces, along with foamy macrophages and positive staining for periodic acid-Schiff. Testing for anti-GM-CSF autoantibodies was positive at a high titre (1700 ng/mL), and the diagnosis of autoimmune PAP was made. No treatment was initiated. Three years after the diagnosis of PAP, the patient remains asymptomatic, with near-complete regression of radiological lesions (figure 1) and decrease in the anti-GM-CSF antibody titre (1260 ng/mL).

DISCUSSION

We report a case of autoimmune PAP that followed CM. Although it is well established that PAP may be associated with opportunistic infections,[2] the mechanism of this association is not precisely known, and infection generally follows the diagnosis of PAP. However, most of the reports were published before the identification of anti-GM-CSF autoantibodies.[3 4] Here, fungal infection occurred before autoimmune PAP.

The level of anti-GM-CSF antibodies was measured using a functional test based on the ability of serum antibodies to neutralise the activity of GM-CSF on erythroblasts as compared with negative and positive controls. The titre of antibodies was expressed by the reciprocal of the dilution, which inhibits 50% of the cells. A level greater than 19 ng/mL has a specificity of 100% and a sensitivity of 92%–98% for autoimmune PAP.

The presence of anti-GM-CSF antibodies hinders the phagocytic properties of monocytes, macrophages and neutrophils,[5] which constitute the

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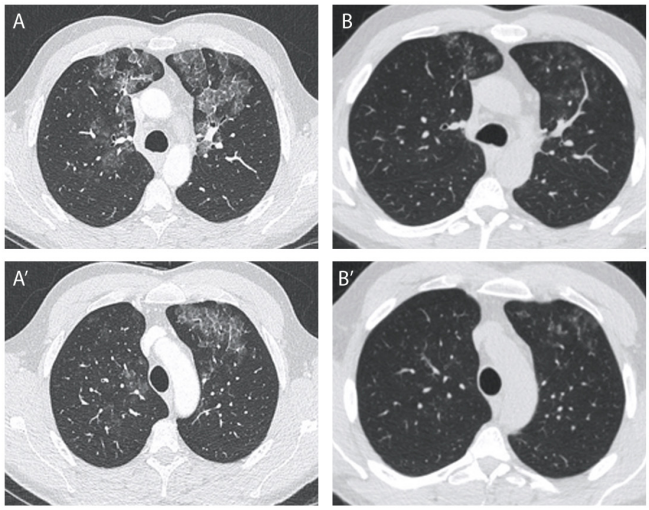

Figure 1 Evolution of radiological lesions on chest CT showing spontaneous resolution (B, B′) of ground glass opacities and crazy paving pattern (A, A′).

major cellular components of innate immunity against *Cryptococcus*. In experimental mice with *Cryptococcus* lung infection, GM-CSF promotes the differentiation, activation and localisation of pulmonary dendritic cells and macrophages in alveoli.[6] In vitro, anti-GM-CSF antibodies prevent the phosphorylation of STAT5 (signal transducer and activator of transcription 5) and the production of MIP-1α (macrophage inflammatory protein 1-alpha), two proteins implicated in phagocytosis and inflammatory reaction.[7] Anti-GM-CSF antibodies may therefore lead to susceptibility to opportunistic infections in otherwise immunocompetent patients. Anti-GM-CSF antibodies have been identified in four formerly immunocompetent patients with CM, two of whom later developed PAP.[7] Screening of archived serum found anti-GM-CSF autoantibodies in 3/67 (4.4%) immunocompetent patients with a history of CM, compared with none of 36 immunocompromised patients with CM and 64 healthy individuals.[7] In vitro anti-GM-CSF autoantibodies were identified in patients with central nervous nocardiosis (n=5/7) and in no healthy controls (n=14).[8] However, there is no evidence to recommend systematic testing for anti-GM-CSF antibodies in patients with cryptococcal infection, as their prognostic role is not well established in the absence of PAP.

Although anti-GM-CSF antibodies likely contributed to infection, the alternative hypothesis that infection with *Cryptococcus* might have triggered autoimmunity cannot be ruled out. In our patient, PAP developed several years after the occurrence of CM and the anti-GM-CSF titre decreased following antifungal treatment. Because the level of anti-GM-CSF antibodies was not measured before the development of PAP, the temporal relationship of autoimmunity and infection is unknown.

In summary, the presence of anti-GM-CSF antibodies may be the common ground for the development of PAP and of opportunistic infections. Our case suggests that anti-GM-CSF antibodies be measured in patients who present with *C. gattii* meningitis.

Learning points

- Autoimmune pulmonary alveolar proteinosis is a rare lung disease due to granulocyte macrophage colony-stimulating factor (GM-CSF) autoantibodies.
- Anti-GM-CSF antibodies may lead to opportunistic infections because they alter the phagocytic properties of monocytes, macrophages and neutrophils.
- Anti-GM-CSF antibodies should be measured in patients who present with *Cryptococcus* meningitis or *Nocardia* infection.

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