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CASE STUDY

Granulomatous *Pneumocystis carinii* pneumonia in Wegener's granulomatosis

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Granulomatous Pneumocystis carinii *pneumonia in Wegener's granulomatosis. E. Ullmer, M. Mayr, I. Binet, C. Ebnother-Staub, P. Dalquen, M. Solèr, M. Tamm. ©ERS Journals Ltd 2000.*

ABSTRACT: This study reports on a first case of granulomatous *Pneumocystis carinii* pneumonia (PCP) in a human immunodeficiency virus-negative patient with antineutrophil cytoplasmic antibody-positive Wegener's granulomatosis whilst receiving immunosuppressive treatment. The patient presented with diffuse alveolar haemorrhage, pauci-immune rapid progressive glomerulonephritis and leukocytoclastic vasculitis of the skin. Granulomatous *Pneumocystis carinii* pneumonia developed under immunosuppressive treatment with cyclophosphamide and prednisone. At the time *Pneumocystis carinii* pneumonia developed, there was a marked lymphopenia with a very low CD8+ cell count in the blood. Grocott staining in bronchoalveolar lavage fluid revealed no *Pneumocystis carinii*. The diagnosis was made *via* a video-assisted thoracoscopic lung biopsy which showed granulomas containing high numbers of *Pneumocystis carinii* cysts.

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Wegener's granulomatosis (WG) is a small-vessel vasculitis characterized by the triad of granulomatous inflammation of the upper and/or lower airways, disseminated vasculitis and glomerulonephritis [1]. Pulmonary nodules on chest radiography, which show cavitation in ~50% of patients, are typical manifestations [2–4]. This report describes a patient with nodular lung infiltrates not caused by WG itself but by an atypical form of *Pneumocystis carinii* pneumonia (PCP).

PCP is a well recognized complication in patients with WG treated with immunosuppressive agents [5]. Up to 5% of acquired immune deficiency syndrome (AIDS) patients with PCP show an atypical granulomatous tissue-response [6–12]. In contrast, only a few cases of granulomatous PCP have been described in human immunodeficiency virus (HIV)-negative patients with haematological diseases and in patients under immunosuppression following solid organ transplantation [13–15]. To the authors knowledge, no case of a granulomatous PCP in a patient with WG has been reported up to now.

Case report

A 62-yr-old male was admitted to hospital in November 1996 with a 2-week history of arthralgia, fever up to 39°C and dry cough. Symptoms became complicated by severe haemoptysis and dyspnoea. In the past, the patient had only complained of bloody nasal discharge over a period of 6 months.

Physical examination presented diffuse crackles and cutaneous purpura. Laboratory findings showed leukocytosis, anaemia and mild hypoxaemia. The C-reactive protein (CRP) (173 $mg \cdot L^{-1}$), sedimentation rate (50 $mm \cdot h^{-1}$) and creatinine (128 μM) were elevated and there was a nephritic urine sediment. The chest radiography revealed rapidly progressive bilateral infiltrates, interpreted as diffuse alveolar

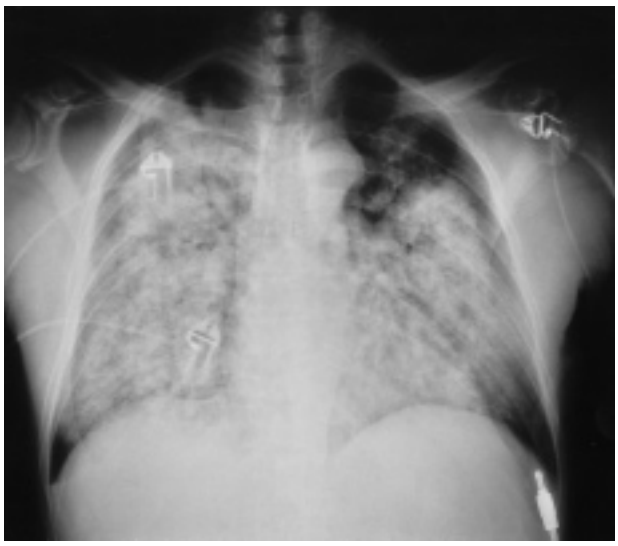

Fig. 1. – Chest radiography from November 1996 revealing bilateral alveolar infiltrates with apical sparing corresponding to alveolar haemorrhage.

haemorrhage (fig. 1). Haemodialysis had to be started because of renal failure due to rapid progressive glomerulonephritis and the patient required mechanical ventilation. Skin biopsy showed leukocytoclastic vasculitis. Antineutrophil cytoplasmic antibodies (c-ANCA) were positive (1:400). Perinuclear-ANCA and anti-deoxyribonucleic acid (DNA) antibodies were negative. A diagnosis of WG was established and immunosuppressive therapy with *i.v.* steroids (methylprednisolone 500 mg three times daily for 3 days) and cyclophosphamide 200 mg·day^{-1} was initiated. The patient could be extubated after 12 days and renal function recovered. Under immunosuppressive therapy consisting of 100 mg cyclophosphamide and 15 mg prednisone, agranulocytosis developed 3 months later complicated by lobar pneumonia. The cyclophosphamide dose had to be adjusted to 50 mg daily and steroids were reduced to 10 mg of prednosone daily.

The patient had to be readmitted to hospital in October 1997 because of weakness, dyspnoea and nonproductive cough. Laboratory data showed severe Coombs-positive autoimmune-haemolytic anaemia and lymphopenia (total lymphocytes 150 cells·μL^{-1}; CD4 71 cells·μL^{-1}; CD8 15 cells·μL^{-1}). CRP was 45 mg·L^{-1} and the c-ANCA titer 1:75. The computed tomography of the lung revealed multiple nodular infiltrates (fig. 2). Stains and cultures for bacteria, mycobacteria and fungi were negative in bronchoalveolar lavage (BAL) fluid. Cytomegalovirus (CMV) could be cultured from BAL fluid but immunostaining with monoclonal antibodies against CMV was negative. Due to a lack of diagnosis, videoassisted thoracoscopic biopsy was performed. Histology showed granulomas with small necrotic centres and pallisades of histiocytes and epithelioid cells (fig. 3a). Grocott silver stain revealed *P. carinii* cysts inside the granulomas. No *Pneumocystis* organisms were present in the surrounding lung parenchyma (fig. 3b). Therapy with trimethoprim-sulphamethoxazole had to be stopped because of exanthema; atovaquon was given. The patient recovered and current immunosuppression consists of 20 mg prednisone and of 25 mg cyclophosphamide daily (April 1999) without evidence of active Wegener′s disease.

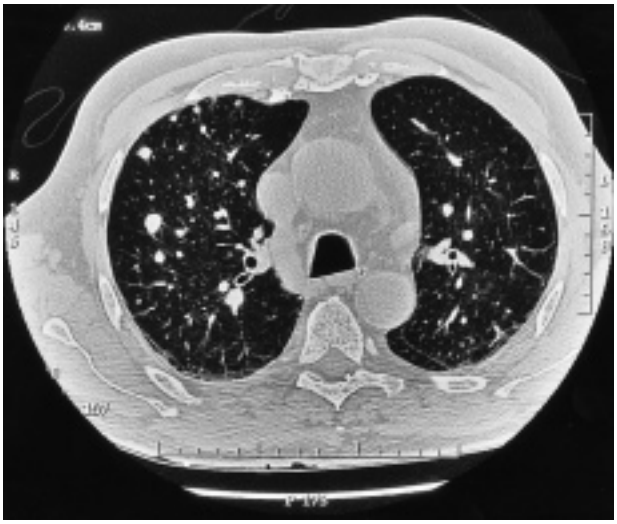

Fig. 2. – Computed tomography of the chest (October 1997) revealing multiple nodules in both lungs.

Discussion

The diagnosis of WG in this patient was based on the presence of alveolar haemorrhage, pauci-immune rapidly progressive glomerulonephritis and leukocytoclastic vasculitis of the skin [1, 2]. The initial presentation of diffuse alveolar haemorrhage is typical for small-vessel vasculitis [3, 16–18]. Furthermore, c-ANCA could be found, which in active disease has a sensitivity of 91% and a specificity of 99% for the diagnosis of WG [19]. Oral cyclophosphamide combined with glucocorticosteroids are considered the standard therapy for WG. In 1973, FAUCI and WOLFF [20] treated 18 patients with a combination of steroids and cyclophosphamide achieving sustained remissions and prolonged survival. Steroids alone are able to improve skin or upper airway lesions but do not influence generalized forms with life-threatening complications such as rapidly progressive glomerulonephritis or pulmonary haemorrhage. The improved survival with cyclophosphamide is burdened by adverse effects such as leukopenia, haemorrhagic cystitis and in the long-term by bladder cancer, lymphoma and infertility. Leukopenia, as in the present case, increases the risk of opportunistic infections.

In the current patient, immunosuppressive treatment was successful with regard to renal and respiratory failure. However, this treatment was complicated by granulomatous *P. carinii* infection. The diagnostic dilemma was to

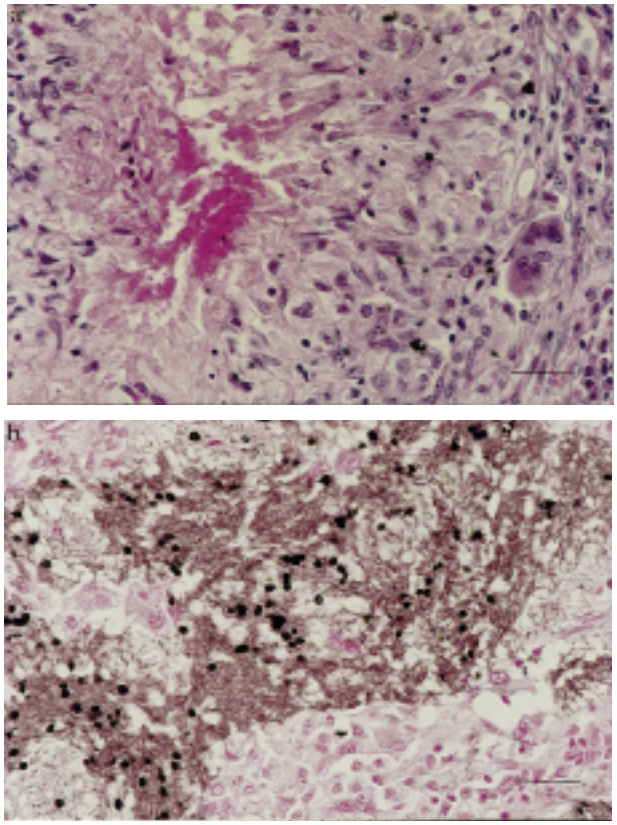

Fig. 3. – a) Lung specimen obtained by videoassisted thoracoscopic biopsy showing epithelioid cells forming granulomas with central areas of necrosis and a giant cell. (Internal scale bar=500 mm haematoxylin and eosin stain.) b) Cysts of *Pneumocystis carinii* were found within the granulomas. No *Pneumocystis* organisms were seen in the surrounding lung parenchyma. (Internal scale bar=500 μm Grocott silver stain.)

determine the underlying cause of the pulmonary nodules developing after 1 yr of immunosuppressive therapy and to establish the appropriate therapy. Manifestations of WG itself, granuloma forming opportunistic infections such as mycobacterial or fungal infections, metastases and malignant nodular pulmonary lymphoma, were considered in the differential diagnosis of these nodules. Thoracoscopic lung biopsy revealed granulomatous PCP. The pallisades of histiocytes, walling off the *Pneumocystis* organisms, possibly rendered them inaccessible to the diagnosis by BAL. Amplification of DNA in BAL samples might improve the diagnostic yield of BAL in these cases [21]. Other diagnostic approaches in case of nodular infiltrates include percutaneous needle biopsy (ultrasonically or computed tomography-guided) and open lung biopsy [22, 23].

The first reported case of an atypical granulomatous histological appearance of PCP occurred in a patient receiving immunosuppressive therapy after renal transplantation [15]. Meanwhile, granulomatous PCP has appeared as a well known variant of PCP in patients with AIDS but it has rarely been described in patients with haematological diseases, mainly lymphoma. Common radiographic findings in patients with WG are nodules, which may cavitate, alveolar infiltrates or pleural opacities [4]. In the present case, the granulomatous lesions might have been mistaken for typical WG nodules, which made the differential diagnosis particularly difficult [3, 4]. C-ANCA and CRP known to correlate with disease activity in patients with WG, were only slightly elevated and therefore not conclusive in favour of a relapse of WG. In WG under immunosuppressive therapy, PCP is a major complication [5], but granulomatous PCP has not been described until now. Atypical granulomatous PCP was described in AIDS patients in association with inhaled pentamidine prophylaxis [7, 8, 11]. It was hypothesized that pentamidine crystals may precipitate in the lung, inducing a foreign body reaction. A subtherapeutic aerosol deposition in peripheral lung areas may allow pneumocystis organisms to survive, resulting in a smouldering localized infection. The current patient had inhaled pentamidine only once after immunosuppressive therapy was started in December 1996. Other authors have suggested that the intake of zidovudine increases helper T-lymphcytes and thereby may restore delayed hypersensitivity in previously anergic patients [24]. In the present case, a speculative explanation for the granulomatous reaction to PCP infection might be an imbalance of helper and suppressor T-lymphocytes. Despite a low total lymphocyte count, the CD4: CD8 ratio was elevated in the blood of this patient.

The diagnosis of a granulomatous PCP requires the presence of *Pneumocystis* organisms inside a granuloma and the absence of other pathogens such as bacteria, mycobacteria or fungi. Sometimes, as in the current patient, simultaneous CMV infection can be found. This reflects the severely immunocompromised status and a likelihood for opportunistic infections and might have favoured an atypical response to PCP. However the pathogenetic role of coinfection with CMV in granulomatous PCP is still unclear.

In conclusion, in patients with Wegener′s granulomatosis under immunosuppressive treatment, nodular lung infiltrates need further investigation. They may be manifestation of uncontrolled Wegener′s granulomatosis itself, but opportunistic infections including granulomatous *Pneumocystis carinii* pneumonia or malignancy have to be ruled out. In cases of equivocal bronchoalveolar lavage or transbronchial biopsy, video-assisted lung biopsy should be performed to obtain a correct diagnosis and to avoid missing a curable complication of immunosuppression.

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