Hypersensitivity pneumonitis probably caused by cyclosporine. A case report

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Introduction

A case of hypersensitivity pneumonitis developing in a patient treated with cyclosporine for an exacerbation of Crohn’s colitis is reported. Cyclosporine is thought to be the causative agent, an observation that might have serious implications for those patients on cyclosporine therapy who develop diffuse bilateral infiltrates.

Case History

A 35-year-old white female was admitted to our hospital with fever, abdominal cramps, diarrhoea and weight loss. She had known Crohn’s colitis for 6 yrs which was treated with mesalazine. On admission, physical examination, laboratory tests of blood and stool, and coloscopy were all consistent with the diagnosis of an exacerbation of Crohn’s colitis. Systemic therapy with intravenous corticosteroids was initiated. After 4 weeks of treatment there was no improvement and cyclosporine, 4 mg kg⁻¹ of body weight day⁻¹, was added to the intravenous medication, under close monitoring of blood levels of cyclosporine. With this regimen, her condition improved and after 3 weeks, intravenous medication was replaced by oral administration of both prednisolone, 30 mg day⁻¹, and cyclosporine, 200 mg t.i.d., upon which patient’s condition continued to improve.

However, 3 weeks after the start of oral therapy, the patient developed arthralgia of the knees and petechiae, with a mild thrombocytopenia of 85 000 ml⁻¹, whereupon administration of cyclosporine was discontinued. The blood-cyclosporine level at this time was 244 µg l⁻¹.

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Blood cultures were taken, which remained negative. A bronchoalveolar lavage (BAL) was performed. Toluidine blue, Giemsa, Gram and Ziehl-Neelsen stains were all negative. BAL fluid cell-differentiation showed 52% neutrophils, 1% plasma cells and 37% lymphocytes with a CD4+/CD8+-ratio of 34. An open lung biopsy was performed through a limited incision left-sided thoracotomy. Material both for histology and cultures was taken. Cultures, specific cultures for Legionella, Mycoplasma and viruses included, both from lavage and open lung biopsy-specimens, remained negative, as did serological tests. Histological examination of the biopsies showed a diffuse thickening of the alveolar septa by oedema and an obvious infiltrate of neutrophilic granulocytes, lymphocytes and some plasma cells, with a local more strongly broadened interstitium with a proliferation of epithelial cells in vaguely circumscribed granuloma with sporadic multinucleated giant cells, an observation suggestive of an acute hypersensitivity pneumonitis.

After surgery, the patient was transferred to the Intensive Care Unit and treatment with prednisolone, intensified to 60 mg day⁻¹, was continued. No specific therapy was started other than supplemental oxygen therapy, and no medication given prior to the febrile episode, i.e. mesalazine, glibenclamide and prednisolone, was stopped. Within days the radiological abnormalities subsided and blood gases improved, and the patient was transferred to the ward where supplemental oxygen was soon stopped and prednisolone tapered. Within a week chest X-rays normalized as did blood gases at rest breathing room air.

Lung function tests at this time showed a TLC of 85% of predicted, a FEV₁/VC of 81% and a TLCO/VA of 76% of predicted.

The colitis, for which, after resolution of the pneumonitis, azathioprine was started in combination with prednisolone, remained in remission. The patient was released from hospital 2 weeks after the thoracotomy, after a total hospital stay of 13 weeks.

Discussion

The case presented was diagnosed as an acute hypersensitivity pneumonitis, based upon the histological findings and the demonstration of plasma cells in the BAL fluid in
comprehensive with both the absence of a demonstrable infectious cause and the spontaneous recovery without any specific antimicrobial therapy. In the case of a hypersensitivity pneumonitis one might have expected a different BAL fluid composition, i.e., a lymphocytic preponderance with a decreased CD4+/CD8+ ratio. However, neutrophilic preponderance is known to occur early in acute hypersensitivity pneumonitis as described by Fournier et al. (1), and an elevated CD4+/CD8+ ratio has been observed by White et al. (2) in methotrexate-induced pneumonitis. Furthermore, it may be that the withdrawal of cyclosporine in our case might have caused a rise in the CD4+/CD8+ ratio, resulting in the slightly elevated ratio of 3:0 in our patient.

Of course, alternative diagnoses were considered. In case of sarcoidosis, we would have expected more sharply circumscribed granuloma in the biopsies and a more pronounced rise in the CD4+/CD8+ ratio: Drent et al. (3) found a mean ratio of 8.0 (±1-2) in non-smoking patients with histologically verified sarcoidosis with respiratory symptoms. Besides, in 401 cases of sarcoidosis Drent discovered plasma cells in BAL fluid in only five patients, of whom all were known to be frequently exposed to birds. In contrast, in patients with extrinsic allergic alveolitis and drug-induced pneumonitis, Drent found plasma cells in BAL fluid in 42.5% and 35.7% of cases, respectively (4), an observation that further strengthens our diagnosis of hypersensitivity pneumonitis.

Furthermore, a direct correlation between the underlying inflammatory bowel disease in our patient and the interstitial lung disease was considered. The occurrence of interstitial lung disease in patients with inflammatory bowel disease however, is usually insidious, with biopsies showing changes similar to those found in interstitial pulmonary fibrosis. There is only one report of two patients with ulcerative colitis in whom widespread alveolitis developed rapidly and responded promptly and completely to administration of prednisolone (5). Biopsies, however, showed interstitial infiltration and extensive cellular desquamatory in one and interstitial fibrosis with chronic inflammatory cells in the other, findings very distinct from the observations in our patient.

Diagnosing our patient as an acute case of hypersensitivity pneumonitis, the one question that remained to be answered was the identification of the causative agent. Our patient used mesalamine (5-ASA), which is the active compound of sulfasalazine and lacks the component sulfapyridine which is held responsible for most of the side-effects known for sulfasalazine, including interstitial lung disease. In regard to mesalamine, however, there is one report in the literature (6) concerning a case of bilateral interstitial infiltrates developing gradually in a patient on 5-ASA over a period of 2 years, with definite improvement within months after the discontinuation of the drug, a clinical course, very unlike our case. In our patient, mesalamine was continued during the entire course of events, practically excluding it as a possible cause of hypersensitivity in our patient, a statement that also applies to the other medication used by our patient, glibenclamide.

Since only the administration of cyclosporine was ceased, this drug was thought to be the probable causative agent, an observation neither mentioned before in major reports on drug-induced pulmonary disease (7–11) nor in the literature referring to cyclosporine-associated toxicity. Proof for this diagnosis could have been obtained by rechallenging the patient to cyclosporine, but this was considered unacceptable in view of the possible hazardous effect and the small benefit that could be expected of renewed cyclosporine administration, as the colitis was already in remission and the indication for cyclosporine was not uncontroversial, as stated in recent literature (12–15).

In conclusion, cyclosporine was identified as the probable cause of an acute hypersensitivity pneumonitis in our patient, on observation that might have serious implications for those patients treated with cyclosporine, e.g., after organ transplantation, in whom diffuse pulmonary infiltrates may develop without an infectious cause.

Withholding further cyclosporine therapy could then be considered as a possible treatment, preferably after obtaining histology.

We believe that cyclosporine should be added to the extensive list of pharmacological substances responsible for drug-induced lung disease.

References

Alglucerase treatment of type 1 Gaucher disease with pulmonary involvement

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Introduction

Gaucher disease (GD) is a rare condition caused by an inherited, autosomal recessive deficiency of the enzyme β-glucocerebrosidase, resulting in an accumulation of glucocerebroside in the lysosomes of macrophages and monocytes. Three distinct clinical forms are recognized. Type 1 (chronic non-neuropathic or ‘adult form’) is the most common, and its onset can occur at any age. This form is most frequent among Ashkenazy Jews, although any race can be affected. It is characterized by hepatosplenomegaly, thrombocytopenia and bone lesions, and lung involvement is rare (1). Type 2 (acute neuropathic) is characterized by severe visceral involvement and an intense and early neurological affection, with spasticity, bulbar signs and oculomotor palsy, and a fatal outcome within the first 2 years of life. Type 3 (subacute neuropathic) has a clinical pattern intermediate between types 1 and 2. We report our results of enzyme replacement therapy (ERT) with alglucerase in a patient suffering from type 1 GD with pulmonary interstitial involvement and severe pulmonary hypertension (PHT).

Case Report

A 29-year-old Caucasian, not Jewish, woman was first diagnosed with Gaucher disease at the age of 9 years, with a clinical picture consisting of a 7-cm hepatomegaly and a 12-cm splenomegaly, pancytopenia and bone lesions, and after observation of characteristic Gaucher disease cells in a bone marrow biopsy and detection of enzyme deficiency in peripheral leukocytes (6% of control value). DNA analysis showed a N370S/D55 genotype. Thrombocytopenia (platelet counts: 21 000 μl⁻¹), anaemia (haemoglobin: 8.1 g dl⁻¹) and haemorrhagic manifestations increased subsequently, and a splenectomy was performed at age 19 years, with a subsequent correction in blood counts.

From 1993 (at the age of 24 years), she began to suffer from progressive exertional dyspnoea and impaired pulmonary function tests, with a reduction of carbon monoxide diffusing capacity (DLCO) (Table 1). Chest