Drug-induced pulmonary toxicity in a patient treated with mesalazine and azathioprine for ulcerative colitis

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Abstract

We report a case of an 18-yr-old male with high-grade persistent fever, productive cough, malaise, diarrhea and associated abnormal findings on chest radiography. The patient suffered from ulcerative colitis receiving mesalazine and azathioprine.

After a further and scrutinized work-up the diagnosis of drug-induced pulmonary toxicity was made. His condition was improved after discontinuing both drugs and the administration of corticosteroids.

This is a rarely reported case of eosinophilic pneumonia. Although it has not been reported previously, the possibility of mesalazine and azathioprine synergism cannot be excluded. The clinical, aetiological, diagnostic and therapeutic aspects of the disease are discussed demonstrating the paramount importance of bronchoalveolar lavage in the diagnosis of this disorder. One should be aware of this entity in patients with inflammatory bowel disease. (Acta gastroenterol. belg., **2007**, 70, **290-292**).

Introduction

Inflammatory bowel disease (IBD) has been associated with a variety of extraintestinal manifestations, including pulmonary complications. Most of the reported patients with pulmonary involvement associated with IBD had ulcerative colitis (88%) (1).

Sulfasalazine and 5-aminosalicylic acid (mesalazine) as well as corticosteroids comprise frequent treatment options for this disease. Nevertheless, sulfasalazine and mesalazine have been implicated as causative agents in interstitial lung diseases (ILD) (bronchiolitis obliterans organizing pneumonia (BOOP), syndrome of pulmonary infiltrates and eosinophilia) (2,3,4), along a long list of side effects (5,6).

Azathioprine is also useful for the treatment of ulcerative colitis, as it demonstrates a steroid-sparing effect (7,8). There have been a few reports of azathioprine pneumonitis, in spite of the widespread use of this drug (9).

This study deals with a case of drug-induced pulmonary toxicity in a patient with ulcerative colitis, treated with both mesalazine and azathioprine.

Case report

An 18-yr-old male was referred to our department because of fever, productive cough with mucopurulent expectoration, diarrhea (4-5 episodes /day) and lassitude for a week before his admission. He was a student and suffered from ulcerative colitis that had been diagnosed one year previously. He was under a combination regimen of mesalazine and azathioprine for one year and the disease remained quiescent.

On admission, the patient had high-grade fever (39°C). The rest of the clinical findings were unremarkable. Blood tests demonstrated peripheral eosinophilia (700 cells/μL), mild thrombocytosis (513.000/μL), increased erythrocyte sedimentation rate (ESR = 65 mm/h) and C-reactive protein (CRP = 243 mg/L). Serum biochemistry tests were within normal limits. Arterial blood gases were normal.

The chest radiograph disclosed patchy shadows with ill-defined margins located bilaterally in the apical segments of the upper lobes. The infiltrates were more intense in the left upper lobe.

Further work-up of the patient, including serum complement analysis, rheumatoid factor, antinuclear antibodies, antineutrophilic cytoplasmic antibodies, immunoglobulin levels, serologic tests for hepatitis A, B and C, human immunodeficiency virus as well as for common viruses and atypical infectious agents, did not revealed any abnormal findings. Skin tests for both *M. tuberculosis* and atypical mycobacteria were negative. Computed tomography (CT) of the chest with high resolution scans (HRCT) demonstrated patchy small shadows in the upper lobes with a tendency to coalesce mostly in the left one (Fig. 1).

In the context of further investigation, the patient underwent fiberoptic bronchoscopy. Bronchoalveolar lavage (BAL) was performed and transbronchial lung biopsies (TBLB) were taken from the left upper lobe and the lingula. The differential cell count of the BAL fluid was : 60% eosinophils, 20% lymphocytes, macrophages 15% and neutrophils 5%. CD4:CD8 ratio was normal. Microbiologic examination of the BAL samples for common pathogens as well as mycobacteria was negative. Cytologic examination was also negative and

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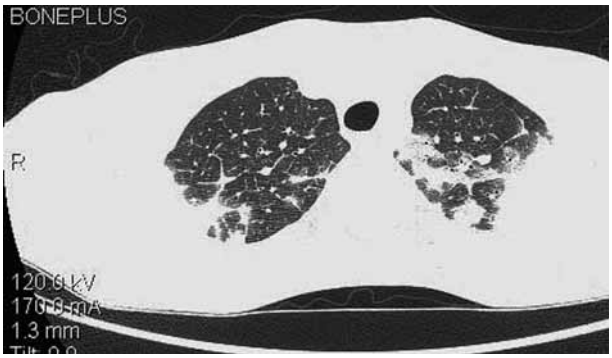

Fig. 1. — A CT scan of the chest on admission reveals patchy infiltrates in both apexes.

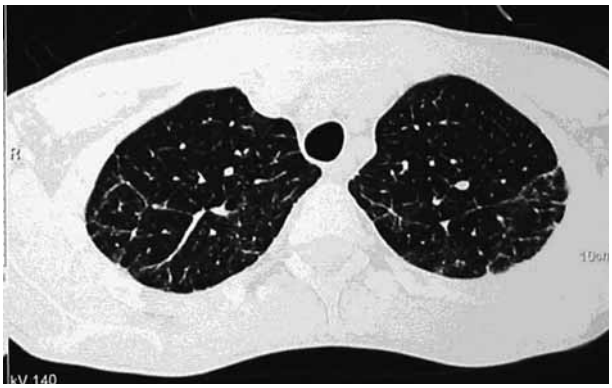

Fig. 2. — A CT scan of the chest, one month after the initiation of corticosteroid treatment, reveals a marked improvement of the pulmonary lesions.

histologic specimens from the TBLBs were non-diagnostic.

The diagnosis of drug-induced eosinophilic pneumonia was made and the patient's medication was discontinued. Although a slight improvement in patient's condition was noted after the withdrawal of culprit drugs, it was decided to initiate corticosteroid therapy to hasten recovery. Prednisolone 40 mg /day was administered with gradual tapering over the next three months. The patient responded satisfactorily in this regimen in terms of his clinical and radiological picture (Fig. 2). At this time the patient is in the best of health and receives an alternative regimen for ulcerative colitis.

Discussion

In the present case, BAL technique was proved to be a valuable adjunct to diagnosis. It mainly excluded the possibility of an infection (particularly tuberculosis), which was an important consideration since the patient had been treated for a long time with azathioprine (a well known immunosuppressant). The cellular pattern from the BAL fluid analysis was predominantly eosinophilic with a concomitant increase of lymphocytes, and was compatible with eosinophilic lung disease (10). After careful deliberation, the diagnostic approach was focused on the primary disease (ulcerative colitis) and its associated pulmonary manifestations. Excluding most of the possible IBD-related pulmonary diseases by virtue of clinical, imaging and BAL features, we concluded that our patient suffered from drug-induced eosinophilic pneumonia.

Pulmonary eosinophilia is generally considered as an increased percentage of eosinophils in BAL fluid (> 25%) or a predominance of eosinophils in lung biopsies. A slight increase of lymphocytes with a decreased CD4:CD8 ratio may be an accompanying feature (11). Drug-induced eosinophilic pneumonia is a diagnosis of exclusion. Nevertheless, five diagnostic criteria for this disorder have been suggested : (i) exclusion of other lung diseases, (ii) history of drug exposure, (iii) clinical, imaging, BAL fluid or tissue findings compatible with drug-induced eosinophilic lung disease, (iv) time course consistent with drug-induced lung disease and (v) improvement following withdrawal of the suspect drug. The definitive way to determine if a patient has a drug-induced eosinophilic pneumonia is the recurrence of symptoms on drug rechallenge. This is considered risky and unethical and should be avoided in most cases. Patients, who fulfill all criteria, are considered as having "definitive" disease ; those who meet 4 criteria are deemed as having "possible" disease, and patients with 3 criteria have the "suspicion" of disease (12).

IBD, mostly ulcerative colitis, has been associated with a variety of pulmonary manifestations (1). Particularly, the patterns of respiratory involvement that have been described are classified into four categories : (i) airway disease (subglottic stenosis, chronic bronchitis, chronic bronchial suppuration, bronchiectasis, chronic bronchiolitis), (ii) ILD (BOOP, granulomatous lung disease, pulmonary eosinophilia), (iii) necrobiotic nodules and (iv) pleural disease **(**1,13). In the majority of patients respiratory symptoms may occur after the diagnosis of IBD has been made. Only in exceptional cases respiratory symptoms are either antecedent or concurrent to those of IBD.

Because drugs used to treat ulcerative colitis may also induce ILD, it would be difficult to clarify if the pulmonary involvement proceeds from the treatment or the disease itself. Nonetheless, ILD has been reported in untreated patients, indicating that such an association may exist without exposure to drugs (1,14). In corroboration of this statement, our patient had been treated for ulcerative colitis with azathioprine and mesalazine at least for a year, directly after its diagnosis. During this period of time, ulcerative colitis remained in remission, which makes very unlikely the patient's pulmonary manifestations to have been attributed to the underlying disease. *In extenso,* both agents tailored for ulcerative colitis treatment may cause pulmonary toxicity.

In particular, mesalazine has been associated with (i) pulmonary infiltrates with eosinophilia, (ii) BOOP, (iii) granulomatous ILD, (iv) eosinophilic pleural effusions, (v) bronchospasm (15). A few data exist about the pattern of cell count in BAL fluid analysis. Mesalazine-induced pulmonary eosinophilia as well as lymphocytic alveolitis have been both described, depending on the underlying pathological process (2,4,16). Overall, no more than 20 cases of mesalazine-induced pulmonary toxicity have been described in the literature (17). The mechanism of mesalazine-induced ILD remains vague to date, but it could be due to the molecular structure of the drug (2). It can be speculated that mesalazine toxicity is mediated by specific immunological reactions : alveolar macrophages may consume the drug and present it as antigen to T-lymphocytes with the consequent production of inflammatory cytokines (12). Direct toxicity of mesalazine to the lung parenchyma might be an alternative mechanism (3,17).

Azathioprine has been associated with (i) subacute cellular ILD, (ii) alveolar hemorrhage, (iii) bronchospasm and anaphylactic shock, (iv) vasculitis, and (v) upper airway obstruction (15). Little is known about the pattern of BAL fluid cell count in cases of azathioprine toxicity. Lymphocytosis with a normal CD4:CD8 ratio has been described in two patients (18,19). Overall, about 10 cases of azathioprine-induced pulmonary toxicity have been published in the literature (15). The net incidence of this condition must be very low given the widespread use of this agent in malignant and non-malignant diseases. However, the possibility of azathioprine-induced pulmonary toxicity should be considered in any individual who receives this drug. Azathioprine is metabolized to 6-mercaptopurine which has been implicated in lung toxicity as well. Although it remains unknown how azathioprine affects the lungs, direct cytotoxicity is probably the main mechanism. Induction of oxidative stress may be an additional factor (20,21).

In the present case pulmonary eosinophilia was the main finding. This is compatible with an adverse action of mesalazine, since eosinophilic pneumonia has never been previously associated with azathioprine. However, lymphocytosis with a normal CD4:CD8 ratio in BAL fluid, which was the case in the present patient, has been associated with azathioprine toxicity (22). Moreover, the same pattern of BAL lymphocytosis has been also found in cases of mesalazine-induced eosinophilic pneumonias (2). Although the pattern of BAL fluid cell count is not specific and the available data are inconclusive, the possibility of an additional toxic effect of azathioprine in the presented patient could not be excluded. This is the reason that both mesalazine and azathioprine were stopped when a drug-induced pulmonary toxicity was suspected.

In conclusion, the possibility of a drug-induced lung disease should always be considered in the differential diagnosis of ILDs. BAL fluid analysis is non-specific but it remains an important diagnostic tool. Its main indication is the exclusion of an infection, which may be of paramount importance in some clinical settings.

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