Persistent pulmonary lesion in a patient with rheumatoid arthritis

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Case report
In June 1993 a 63 year old man attended hospital complaining of acute dizziness. He also reported a three week history of left-sided chest pain.

In 1987 the patient had been diagnosed as having seropositive rheumatoid arthritis. He had initially been treated with non-steroidal anti-inflammatory drugs and gold salts, and since 1991 with prednisolone up to 10 mg daily. In June 1988 a melanoma had been totally excised from the right anterolateral chest wall. Subsequent regular follow up visits had not revealed evidence of recurrence or metastases. In March 1989 the patient was found to be suffering from refractory anaemia and a myelodysplastic syndrome was subsequently confirmed by iliac crest bone marrow biopsy. The patient was treated with regular transfusions of red cell concentrates and administration of desferrioxamine mesylate. In January 1992 the patient was diagnosed as having non-insulin-dependent diabetes.

On initial examination the patient was clinically anaemic. Arthritic changes were present in the hands. Chest percussion elicited dullness at the left base, and fine to medium crackles were audible on auscultation. The patient's temperature was normal. Abdominal examination revealed marked hepatosplenomegaly. The erythrocyte sedimentation rate was 98 mm/h and the C reactive protein concentration clearly increased, at 103 mg/l. On serum electrophoresis, the α₂ and γ globulin fractions were relatively increased with respect to albumin. The following abnormalities were seen in whole blood: haemoglobin 6.7 g/dl, packed cell volume 21%, red cells 2.4 x 10¹²/l, white cells 2.0 x 10⁹/l, platelets 113 x 10⁹/l.

The differential count showed a moderate left shift with no eosinophilia. In the chest x ray, a small effusion was seen at the left base, accompanied by infiltrate changes with no air rim in the left lower zone (fig 1). Abdominal ultrasound permitted quantification of the hepatosplenomegaly, but showed no evidence of lymphoma or metastases.

After admission of the patient to hospital, the anaemia was rapidly corrected with transfusions. On the suspicion of bacterial pneumonia, antibiotic therapy was instituted with ciprofloxacin. Cultures and serological testing elicited no evidence of infection with Mycoplasma, Legionella, Chlamydia, Mycobacterium tuberculosis or other bacterial pathogens. Mycological serology was likewise negative for Candida and Aspergillus. The left-sided chest pain improved markedly in response to antibiotic treatment, and the patient felt well and remained without fever. However, the repeat chest x ray film showed an unaltered pathological appearance, and there was only a slight regression of inflammatory indices. The patient's medication was therefore changed to a combined antibacterial-antifungal regimen of piperacillin, fluoxacillin and fluconazole. Subsequently, repeated bronchoscopies showed a macroscopically unremarkable bronchial system. On thoracic computed tomography, the pulmonary infiltrate was confirmed in the 9th and 10th left segments. Samples were obtained on several occasions by bronchoalveolar lavage and CT assisted aspiration. However, apart from isolated findings of Candida albicans and Candida glabrata in small concentrations, no pathogenic organisms were demonstrated by culture or serology. No tumour cells were detected. Fontana staining for melanin, performed because of the suspicion of melanoma metastases, was consistently negative. At the last bronchoscopy, clear signs of active cytomegalovirus infection were detected in the lavage fluid. In view of this constellation of findings, with only slight radiographic improvement, the treatment was again changed, this time to itraconazole (in view of the presence of Candida glabrata and possible aspergillosis') and imipenem (because of the possibility of nocardiosis). Cytomegalovirus specific immunoglobulin was also given. Pharmacological alternatives, such as ganciclovir or amphotericin B, were withheld in view of the existing myelodysplastic syndrome.

Figure 1 Patient with Aspergillus infection. Chest x ray before treatment shows a soft shadow in left lower zone.
Persistent pulmonary lesion in a patient with rheumatoid arthritis

Despite treatment, the roughly circular mass remained unchanged in size on computed tomography, though it was now free of a surrounding infiltrate (fig 2). Because of these circumstances, resection of the left lower lobe was performed, together with partial decortication of the parietal pleura, and lymph node dissection. Histological examination of the resected tissue showed chronic mycotic bronchopneumonia consistent with aspergillus infection (aspergilloma), accompanied by local fibrinous and fibrous pleuritic changes (figs 3, 4).

The patient’s postoperative recovery was uneventful. After discharge, treatment was continued on an ambulatory basis with itraconazole 100 mg daily for 2 months. Clinical and laboratory findings have remained normal throughout this period, therefore we assume that the aspergilloma has been cured.

Discussion
As a rule, invasive aspergillosis is rare in immunocompetent individuals. However, as seen in the present patient, it would be a grave error to assume that such infections occur only in high risk categories, such as the severely immunodeficient, patients undergoing polychemotherapy or long term intensive care, and transplant recipients.

In this patient, the initial suspicion was of primary bacterial pneumonia and treatment was performed accordingly. However, it became increasingly evident that an alternative cause would have to be considered for the pathological lung findings. In this patient the probable causes, in addition to late metastatic melanoma, other neoplasm and rheumatoid nodule, included a fungal infection such as...
aspergilloma. However, throughout the course of the illness, neither imaging procedures nor serological monitoring (aspergillus antigen latex agglutination test—Pastorex®, Sanofi Diagnostics Pasteur, France) provided any evidence of pulmonary aspergillosis, and the diagnosis was confirmed only after histological examination of the material obtained at curative resection. Figures 3 and 4 impressively demonstrate that the lesion exhibited only limited tissue invasiveness, but was about to penetrate the vascular system. Had this occurred, aspergillus antigens would certainly have been detected on serological monitoring. However, the resultant systemic fungal spread would also have led to an incomparably worse prognosis. The difficulty of diagnosing aspergillosis is apparently related less to an inefficacy of laboratory methods—in other cases very good results have already been achieved with the Pastorex® test we used¹—than to the fact that certain patients are not considered to be at risk and are therefore omitted from mycological surveillance. It is important to remember in this context that representatives of the aspergillus genus are classic opportunists. Because of their minimal virulence, they infect only in the presence of certain predisposing factors, and these are evidently not restricted to so-called high risk patients. The predisposition for aspergillosis in the present patient was apparently attributable to a combination of factors. First, it is reasonable to speculate that immunological resistance to fungal infection in this multimorbid patient was decreased by long term use of up to 10 mg of prednisolone daily for rheumatoid arthritis and by the neutropenia of myelodysplastic syndrome.⁴⁻⁷ Also, it is likely that establishment of the infection was further encouraged by the patient’s diabetic metabolic state.⁵—¹⁰

The favourable outcome in this case is attributable to several factors. Although the early antibacterial-antifungal treatment was unable to effect a cure, it may well have improved the conditions for surgery. The curative operation was then evidently performed just in time to pre-empt haematogenous dissemination of the fungal infection. Postoperative antifungal therapy was with itraconazole, and both the patient’s satisfactory recovery and subsequent aspergillus antigen negativity clearly demonstrate the success of the treatment.

The lesson

• The possibility of opportunistic aspergillus infection should always be considered in patients with rheumatic diseases when corticosteroid therapy is combined with other predisposing factors.
• Serological monitoring with negative results does not definitely exclude aspergilloma, because the process may still be of limited invasiveness.