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Lesson of the week

Clarithromycin and pulmonary infiltration with eosinophilia

Claudio Terzano, Angelo Petroianni

Pulmonary diseases induced by drugs include bronchial asthma, pulmonary infiltration with eosinophilia, diffuse fibrosing alveolitis, vasculitis, and pleural diseases. Most such diseases recede when the drug is withdrawn, although on rare occasions the pulmonary damage is irreversible and progressive. We describe a patient with asthma referred to our respiratory diseases clinic who twice developed fever and pulmonary infiltration with eosinophilia after taking antibiotics.

Case report

A 17 year old white man who has had bronchial asthma since childhood was referred to our clinic in January 2002. The patient also reported sinusitis and allergic rhinitis. Results of earlier prick tests and radioallergosorbent tests were positive for wall pellitory (Parietaria judaica) and grasses, and the tests resulted in a mild increase in peripheral blood eosinophil counts (0.6–0.7 × 10^9/l (6–7%).) His general practitioner had prescribed salbutamol as a rescue treatment. The patient did not report any allergy to drugs.

In December 2001 he had reported fever (38°C), accompanied by mucopurulent nasal secretion and pain in his forehead. X-ray pictures of the paranasal sinuses showed maxillary sinusitis on the right side and hypertrophy of the turbinates. The general practitioner prescribed combined amoxicillin (875 mg) and clavulanic acid (125 mg) twice daily for seven days, followed by clarithromycin (500 mg) twice daily for a further seven days. Figure 1 shows the patient’s course of treatment. At the end of this treatment period the patient reported dry cough and mild dyspnoea. Chest x-ray pictures showed pulmonary consolidations localised at the right apex.

A few days later he had a new episode of fever (38.5°C) and was admitted to the infectious diseases department of a hospital. His blood eosinophil count was 1.43 × 10^9/l (14%) and his erythrocyte sedimentation rate was 52 mm in one hour. Results of faecal examination (parasites), throat culture (swab specimen), haemoculture, and the purified protein derivative tuberculosis test were negative. He was treated with cefotaxime (1 g as intravenous injection) three times a day and clarithromycin (500 mg) twice daily. After a week of treatment he no longer had fever, his asthmatic symptoms improved mildly, and his peripheral eosinophil count was 3.74 × 10^9/l (29%). Twelve days later, while he still was taking antibiotics, fever (39°C) returned, accompanied by dyspnoea and wheezing. His eosinophil count worsened, to 5.17 × 10^9/l (35%). Computed tomography of his chest showed bilateral peripheral pulmonary infiltrates. A sputum test indicated eosinophilia, and serum IgE levels for parasites and aspergillus were negative. Bone marrow biopsy confirmed eosinophilia. The patient was referred to our lung unit, where antibiotic treatment was immediately withdrawn. Prednisone 25 mg twice daily, fluticasone propionate 250 µg from a metered dose inhaler (two puffs twice daily), formoterol 12 µg from a metered dose inhaler (one puff twice daily), and ranitidine 150 mg taken orally once daily were prescribed instead. A few days later his eosinophil count reduced dramatically to 0.27 × 10^9/l (1%).

Two weeks later his eosinophil count was 0.92 × 10^9/l (8%). Lung function tests showed a moderate obstructive ventilatory defect, accompanied by a reduction in carbon monoxide diffusing capacity; forced expiratory volume in 1 second (FEV1) 59.9% of predicted value, ratio of FEV1 to forced vital capacity 69.3%, carbon monoxide diffusing capacity (DLCO) 76.3%, and ratio of DLCO to alveolar volume 68.5%. Diffuse wheezing was detected in both lungs.

After a month his general condition improved. The dosage of prednisone was reduced to a maintenance dosage of 5 mg twice a day. His eosinophil count fell to 0.53 × 10^9/l (7%). Computed tomography of his chest showed a complete recovery of the pulmonary consolidations (figure 2). Lung function tests showed an improvement of the obstructive defect, accompanied by a normal carbon monoxide transfer factor (FEV1 89.1%, ratio of FEV1 to forced vital capacity 89.5%, DLCO 78.1%, and ratio of DLCO to alveolar volume 80.8% of predicted values). A bronchodilator (salbutamol) response test showed an increase in FEV1 of 770 ml, a 22% increase from the baseline value.

In April 2002 his general practitioner prescribed clarithromycin 500 mg twice daily for the onset of rhinorrhoea accompanied by headache. Three days after the start of treatment he developed fever (37.2°C) and mild dyspnoea with eosinophilia (eosinophil count 1.84 × 10^9/l (17%)). He was again referred to our lung unit. Computed tomography of the chest showed apical infiltrates in both lungs (figure 2).

Antibiotic treatment was immediately withdrawn, and the patient quickly recovered. Corticosteroid treat-
Clinical review

Differential diagnoses include helminthic infesta-
tions, aspergillosis, tuberculosis, sarcoidosis, Hodgkin's
disease, and other lymphoproliferative disturbances
such as pulmonary eosinophilic granuloma, interstitial
pneumonia, and vascular collagen disturbances. 1, 2, 3, 5

Appropriate laboratory tests include a blood cell count
to determine the eosinophil count. 6 Other important
tests include plasma IgE, erythrocyte sedimentation
rate, eosinophilia in sputum, faecal test for helminths,
skin allergy tests, and plasma parasite evaluation. 2, 3, 5

Radiographic characteristics of drug induced pulmo-
nary infiltration with eosinophilia include focal
alveolar opacity, diffuse alveolar opacity, diffuse
interstitial opacity, and pulmonary nodules. 7 Generally,
lung function tests in the acute phase of pulmonary
infiltration with eosinophilia show a restrictive ventila-
tory defect, which is accompanied by a reduction in
carbon monoxide transfer factor. However, when
asthma is present an obstructive ventilatory defect can
appear during recovery, as in our patient. 17, 18

Often a diagnosis of drug induced pulmonary infiltr-
ating with eosinophilia is made on the basis of a tem-
poral relation between drug treatment and the onset of
symptoms. 1, 8 Rarely, when the clinical picture is not
specific for the condition, diagnosis can be confirmed
by a rechallenge test (which would be unethical) or a
lymphocyte stimulation test with the suspected drug
(which has low sensitivity). 19

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