CASE STUDY

Eosinophilic pneumonia and respiratory failure associated with venlafaxine treatment

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Eosinophilic pneumonia and respiratory failure associated with venlafaxine treatment. M.C. Fleisch, F. Blauer, J.G.H. Gubler, M. Kuhn, T.A. Scherer. ©ERS Journals Ltd 2000.

ABSTRACT: Drugs are well known causes of eosinophilic lung disease. In many patients, symptoms increase slowly, pulmonary infiltrates and eosinophilia progress over weeks, and resolve upon withdrawal of the offending agent.

Rarely, the disease presents like acute eosinophilic pneumonia with acute onset of symptoms and rapidly progressing infiltrates which may be associated with respiratory failure.

This report describes a case of venlafaxine-induced acute eosinophilic pneumonia causing respiratory insufficiency that rapidly resolved upon institution of corticosteroid treatment.

This 5-hydroxytryptamine and noradrenaline reuptake inhibitor was previously not known to cause lung or peripheral blood eosinophilia. Considering the increasing use of this class of medication physicians have to be aware of this life-threatening and fully reversible complication.

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Drug reactions rank highly among the causes of pulmonary infiltrates with blood and/or alveolar eosinophilia [1]. In many cases, drug-induced eosinophilic lung disease presents with transient eosinophilic infiltrates that disappear after discontinuation of the drug. Some patients, however, experience a fulminant, acute eosinophilic pneumonia-like disease, and require corticosteroid treatment. Acute eosinophilic pneumonia (AEP) differs from chronic eosinophilic pneumonia (CEP) in several important aspects. The onset is within a few days, may lead to respiratory failure, and it usually does not recur after discontinuing corticosteroid treatment [1, 2]. CEP has an insidious onset, responds promptly to corticosteroids, but the relapse rate after discontinuing treatment is quite high, although most patients are eventually able to come off corticosteroids [3]. This report describes a case with acute eosinophilic lung disease, resembling AEP, associated with venlafaxine treatment, a new antidepressant with 5-hydroxytryptamine and noradrenaline reuptake inhibiting actions [4].

Case report

A 41-yr-old Caucasian male was transferred from another hospital because of fever up to 38.9°C, increasing shortness of breath, dry cough, chest pain, and myalgias, which had occurred over the previous 2 days.

Because of major depression he had been admitted to the psychiatry department 3 weeks prior to transfer to the authors' hospital. Five days after admission to psychiatric treatment, venlafaxine was started at a dose of 37.5 mg

daily for 9 days and 75 mg daily for the following 8 days. He was put on no other medication.

He had stopped smoking 8 yrs previously but restarted 2 weeks prior to admission (total of 8 pack-years) and took 3–4 glasses of beer per day. He had never consumed illicit drugs, had no allergies, and had not visited a foreign country during the previous 5 yrs. He worked as a dentist in private practice.

On admission, the patient was in moderate respiratory distress, with a blood pressure of 170/100 mmHg, a heart rate of 112 beats per minute, and a respiratory rate of 30 breaths per minute. On examination he had bibasilar crackles and rales and dullness to percussion with otherwise normal findings. An arterial blood gas analysis on room air revealed a oxygen tension in arterial blood (P_{a,O_2}) of 7.0 kPa, a carbon dioxide tension in arterial blood (P_{a,CO_2}) of 4.77 kPa, a pH of 7.48, and an oxygen saturation of 89.4%. Except for a white blood cell count of $19.7 \times 10^3 \cdot \text{mm}^{-3}$ with 32.5% bands and 1% eosinophils and a C-reactive protein of $239 \text{ mg} \cdot \text{L}^{-1}$ (normal: $<3 \text{ mg} \cdot \text{L}^{-1}$) laboratory results including human immunodeficiency virus (HIV) testing, serological screening for vasculitis (autoantibodies to deoxyribonucleic acid (DNA), double stranded DNA, proteinase 3, myeloperoxidase, rheumatoid factor, and circulating immune complexes) and various pulmonary pathogens (*Strongyloides stercoralis*, *Toxocara canis*, *Schinococcus species*, and *Trichinella spiralis*), urinalysis, and stool tests for ova and parasites were normal. Total serum immunoglobulin (Ig)E was $5 \text{ kU} \cdot \text{L}^{-1}$ (within normal limits).

A chest radiograph revealed bilateral interstitial infiltrates with prominent Kerley B lines and airspace opacities in the right lower lung field (fig. 1).

Fig. 1. – Chest radiography on admission with bilateral interstitial and right lower lobe airspace opacities. The heart and pulmonary circulation are normal.

The patient was admitted to the intensive care unit and underwent bronchoscopy. The bronchi appeared inflamed and contained increased secretions. Gram stain and cultures of the bronchial washings did not reveal any infectious organism and cytological examination showed 30% eosinophils. Treatment with high dose corticosteroids (*i.v.* methylprednisolone 1000 mg per day for 3 days) and clarithromycin 500 mg *p.o. b.i.d* was instituted.

A computed tomographic (CT) scan of the chest 3 days after admission disclosed patchy areas of ground-glass attenuation accentuated in both upper lung fields, thickened interlobular septae, and bilateral pleural effusions (fig. 2). The following day bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy was performed. Total cell count on BAL was $177 \text{ cells} \cdot \mu\text{L}^{-1}$ with 25% eosinophils, 7% neutrophils, 57% macrophages, and 10% lymphocytes. Transbronchial biopsies revealed an accumulation of eosinophils and neutrophils within alveolar vessels and intra-alveolar accumulation of eosinophils, macrophages, and neutrophils (fig. 3). No bronchiolitis, intra-alveolar fibrous tissue plugs, granulomas, vasculitis, virus-associated changes, or fibrosis were detected. Special stains and cultures for mycobacteria, *Pneumocystis carinii*, fungi, *Legionella pneumophila*, *chlamydia*, and mycoplasma were negative. On tapering doses of corticosteroids the patient improved and remained afebrile after the third hospital day. The chest radiograph cleared markedly within 5 days of steroid treatment. Clarithromycin was stopped after 7 days of treatment. Pulmonary function tests (PFT) 9 days after admission showed a moderate restrictive ventilatory de-

Fig. 2. – Computed tomography scan at the level of the upper lobes 3 days after admission, showing bilateral patchy areas of ground-glass attenuation and prominent interstitial markings.

fect with a vital capacity (VC) of 3.47 L (71% predicted), an FEV₁ of 2.76 L (72% predicted), a total lung capacity (TLC) of 4.81 L (70% predicted), and a residual volume (RV) of 1.34 L (68% predicted).

The patient was discharged 10 days after admission. Follow-up examinations 1 and 3 weeks after discharge revealed normal laboratory results and a normal chest radiograph. The prednisone was discontinued after 4 weeks. PFT 1 week after discharge showed some residual restriction with a VC of 4.08 L (84% predicted), an FEV₁ of 3.2 L (83% predicted), a TLC of 5.58 L (81% predicted), and an RV of 1.5 L (77% predicted).

Five months after discharge the patient was examined in the authors' emergency room for signs of upper respiratory tract infection with cough and increased sputum production. The chest radiograph had remained normal and his symptoms disappeared within 6 days of symptomatic treatment. Eleven months after discharge the patient was contacted by phone. He had resumed his work as a dentist 2 months after discharge, was free of respiratory symptoms, continued to smoke, and was later put on trazodone without adverse effects.

Discussion

Acute eosinophilic pneumonia is a recently described disease entity [2] and involves acute onset of symptoms within ≤ 5 –7 days, fever $\geq 37.2^\circ\text{C}$, hypoxaemia, bilateral alveolar or mixed alveolar and interstitial infiltrates, and lung eosinophilia (BAL cell differential $\geq 25\%$ eosinophils and/or predominance of eosinophils in open lung biopsy), without any history of hypersensitivity to drugs, no evidence of infection, and no other known cause of eosinophilic lung disease [1, 5]. The histopathological features are characterized by diffuse alveolar damage with interstitial and alveolar eosinophils [6]. Radiological examination reveals diffuse interstitial and acinar opacities, ground-glass attenuation, and pleural effusion.

Fig. 3. – Transbronchial lung biopsy showing accumulation of eosinophils and neutrophils within alveolar vessels, and of eosinophils,

With BAL, a diagnosis can easily be established and should be performed in cases with respiratory failure, even if the peripheral blood eosinophil count is normal. In the largest published series only 5/15 patients had an increased peripheral blood eosinophil count [5]. Although many patients with respiratory failure due to AEP receive corticosteroids with prompt improvement of symptoms, spontaneous resolution even of severe symptoms after withdrawal of the offending agent is possible [7, 8].

Eosinophilic lung disease can have many causes [9–12] and drug reactions are among the most frequent ones. The clinical presentation is variable, ranging from almost asymptomatic transient eosinophilic infiltrates to acute respiratory failure requiring mechanical ventilation. The disease onset of the presented case closely resembles AEP. Acute onset of symptoms within 5–7 days has previously only been described for trazodone, a 5-hydroxytryptamine-reuptake inhibitor [13], minocycline [7, 8], ampicillin [14], acetaminophen [15], nitrofurantoin [16], pyrimethamine-sulphadoxine [17], inhalation of 1, 1, 1-trichloroethane [18], and freebase cocaine [19]. With some precaution isotretinoin P_{a,O_2} (10.3 kPa) [20], iohexol (no fever) [21], and tosylloxacin tosylate [22] have to be added to this list.

TAZELAAR *et al.* [6] suggest less stringent criteria for the diagnosis of AEP. Cases with a duration of symptoms of ≤ 5 days and those between 5–21 days demonstrated identical lung pathology. Using the criteria of TAZELAAR *et al.* [6], sulphasalazine [23], tenidap [24], diclofenac [25], carbamazepine [26], and chloroquine [27] have to be included. Methotrexate [11], granulocyte-macrophage colony-stimulating factor (GM-CSF) [28], piroxicam [29], and heroin can also cause acute eosinophilic lung disease, but the reported disease presentations do not completely fulfil the criteria of ALLEN *et al.* [2] or TAZELAAR *et al.* [6] criteria (lack of information about fever and unilateral infiltrate in GM-CSF).

Pulmonary complications related to 5-hydroxytryptamine reuptake inhibitors are uncommon. Except for trazodone, no reports are available in the literature. Interestingly, the patient was later put on trazodone and tolerated it without adverse effects, which means that his lung disease was not a class effect of the 5-hydroxytryptamine reuptake inhibitors.

This is the first report about venlafaxine induced eosinophilic lung disease. Considering the increasing use of

antidepressants, it is important that physicians are aware of this rare, potentially life-threatening, fully reversible complication.

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