Abstract. Background: Acute eosinophilic pneumonia (AEP) is a severe syndrome which can be induced for many reasons, including drugs. AEP has rarely been associated with first-generation antipsychotics and never been reported after use of second–generation antipsychotics, such as risperidone. Case Report: We report a case of a 64-year-old man with a medical history of alcoholism and paranoid symptoms, treated with risperidone at low doses. Following risperidone medication, he presented with respiratory distress. Bronchoalveolar lavage (BAL) specimen was indicated of AEP. All evidence indicated risperidone as the most probable causal factor. The syndrome rapidly resolved after discontinuation of the drug. Discussion: Pathophysiological mechanisms implicated in the development of AEP in our patient seem to be associated with eotaxin and serotonin eosinophilic-specific chemoattracting action, through the serotoninergic action of risperidone. Conclusion: To our knowledge, this is the first case report of a clinical adverse reaction of AEP from an atypical antipsychotic agent (risperidone).

Eosinophilic lung diseases are a heterogeneous group of disorders that share the feature of abnormally increased numbers of eosinophils within the lungs (1). The defining characteristics needed for the diagnosis of pulmonary eosinophilia include either peripheral blood eosinophilia with radiographically or tomographically identified pulmonary abnormalities, lung tissue eosinophilia demonstrated in transbronchial or open lung biopsies or increased eosinophils in BAL fluid (2).

Peripheral blood eosinophilia is not uniformly increased in many types of eosinophilic lung diseases, and routine chest radiographs may fail to detect infiltrates in some cases (3). The clinical presentation ranges from asymptomatic pulmonary infiltration with eosinophilia to chronic cough with or without dyspnea and fever to AEP.

Many causes such as collagen diseases, infections, irradiation, toxins, neoplasia and a long list of drugs can be implicated in the development of AEP (4). Antibiotics and non-steroid anti-inflammatory drugs (NSAIDs), are the most commonly reported drugs associated with AEP. Toxins suspected of causing eosinophilic pneumonia include cigarette smoke and illicit drugs (cocaine, heroine). Drug- or toxin-induced eosinophilic pneumonia is indistinguishable from idiopathic acute or chronic eosinophilic pneumonia by clinical, radiographic, and histopathologic criteria. Diagnosis is supported by a temporal relationship to a drug or toxin. The condition usually resolves with removal of the agent and recurs with rechallenge (5).

AEP is a rarely reported side-effect of first-generation antipsychotic drugs (such as chlorpromazine) (6). There is no evidence in the literature of AEP induced by second-generation antipsychotic drugs, as far as we are aware of. However, AEP has been reported after treatment with antidepressant agents (sertraline, venlafaxine) (7-10).

We present a case of AEP, induced by the second-generation antipsychotic agent, risperidone.

Case Report

A 64-year-old Caucasian man, highly educated (20 years of education), with no history of cigarette smoking, was admitted with fever of 38˚C and pleuretic chest pain in his lower left pulmonary field.

Regarding his medical history, he had no known allergies and did not mention any recent travels. He had a history of arterial hypertension and hyperlipidemia.

The patient also had a past medical history of alcoholism according to Diagnostic statistical manual (DSM-IV) criteria from the age of 53 years, when he first presented delusional ideas of persecution [Positive and negative syndrome scale (PANSS), positive subscale score=20]. He visited a...
psychiatrist and received detoxification treatment for 10 days, with gabapentin, diazepam and vitamin B complex for the prevention of a withdrawal syndrome. Diazepam was gradually reduced. The patient stopped drinking alcohol. He was then treated with risperidone (3 mg/day) for the psychotic symptomatology. He responded well to the treatment, with improvement of his mental state (PANSS positive subscale score=8). After a 6-month period and while he was still under this treatment, he presented to the Emergency Department of the General Hospital with fever, pleuritic chest pain in his lower left pulmonary field and evidence of mild respiratory distress. He was admitted to the pulmonary clinic.

On admission, the patient was febrile, with blood pressure of 120/80 mmHg, heart rate 68/min and with mild respiratory distress and was placed on 2 l of O2. His oxygen saturation was 92% on ambient air. The remaining physical examination revealed reduced breath sounds of both lung bases. Labaratory studies revealed a leucocyte count of 9660/μl (neutrophils 73%, lymphocytes 13% and eosinophils 2.3%), hemocrit 39%, platelet count 290,000/μl, C-reactive protein (CRP) 47.3 mg/l and erythrocyte sedimentation rate (ESR) 83. Chest X-ray revealed bilateral peripheral infiltrates and right-side blunting of the costophrenic angle due to pleural effusion. Therefore initially, he was considered as having pneumonia with parapneumonic effusion and was treated with ceftriaxone and clindamycin. Risperidone was discontinued, due to the fever. The fever did not respond to the administered antimicrobial treatment. Therefore, an additional empirical antimicrobial regimen was initiated (intravenous ceftazidime and metranidazole, doxycycline per os). Meanwhile, three sets of blood cultures for common bacterial pathogens were found to be negative. Tuberculin skin reaction was also negative.

Chest computed tomography revealed bilateral pleural effusion and pulmonary infiltrates in middle lobe and lingula. Complementary laboratory exams for collagen diseases were negative (antinuclear antibodies, anti-double strand DNA antibodies, antineutrophil cytoplasmic, anti smooth muscle and anti-mitochondrial antibodies). Screening tests for tropical disease were also negative (Wright, Widal, mono test, Epstein-Barr, urine for Legionella and Pneumonococcus, cultures for parasites). Urine cultures for common bacteria and cultures of sputum for B-Koch were negative. Urine test for toxic agents showed no use of illicit drugs.

Doppler echocardiogram of the heart was normal. Although the patient remained with fever (37.6-37.9˚C), bronchoscopy was performed to obtain a BAL specimen which contained 3.4% lymphocytes and 42.6% eosinophils, indicative of AEP.

All evidence indicated risperidone as the most probable causative factor. Amisulpride at 400 mg was initiated instead, when fever resolved. Amisulpride was chosen due to the lack of serotoninergic activity of this agent.

One month after his discharge a second BAL was found to have no eosinophils. On a psychiatry follow-up, the patient showed no clinical recurrence of his psychotic symptoms (PANSS positive subscale score=8) under medication with 400 mg of amisulpride.

Discussion

To our knowledge, no case of risperidone-induced AEP has been reported before. First-generation antipsychotics, such as chlorpromazine have been implicated in the psychopathology of pulmonary eosinophilic syndrome (6). However, as new drugs are developed, many will result in eosinophilic lung disease in susceptible patients (11).

In our case, the patient’s clinical course, radiographic and bronchoscopic findings, strongly support risperidone-induced AEP, in the absence of any other positive historical and laboratory evidence.

Risperidone is widely known as an atypical antipsychotic, with a pharmacological profile of serotonin-dopamine antagonist (SDA). Risperidone at low doses has serotoninergic action due mainly to its affinity for 5HT2a receptors, although at high doses, it has dopaminergic activity through its binding to post-synaptic D2 receptors (12).

While the triggering factor of AEP is unknown, it is currently believed to be secondary to the action of eosinophilic-specific chemoattractants, including eotaxin, T-cell-expressed chemokines and Interleukin-5 released from T2 lymphocytes. The role of serotonin in the pathophysiology of asthma is well-established, as 5HT2A stimulates different signaling pathways and regulates cytokine release in airway epithelial cells (13). It is also known that elevated levels of serotonin are observed in the serum of asthmatics. The role of 5HT2a in the immune response outside of the central nervous system has also been reported, as a mediator of the inflammation (14). Recently it has been demonstrated that serotonin has an eosinophil chemoattractant profile as well as eotaxin (15). Furthermore, it is well-known that serotonin acts as a smooth muscle constrictor in lungs and elsewhere. It has been also showed that an early event in the evolution of acute respiratory failure is the activation of platelets, their pulmonary entrapment and subsequent release of serotonin (16). Therefore, inhibition of serotonin would improve lung function. For example, the selective 5HT7 receptor antagonist ketanserin is mentioned as being capable of partially decreasing airway hyper-responsiveness and eosinophilic infiltration (17).

It is of great interest that AEP in our patient occurred at low doses of risperidone, which is probably related to the serotoninergic activity of risperidone at low doses.

Anti-depressant agents have been reported to cause AEP (7-10). It has been hypothesized that the serotoninergic effect of some drugs may be implicated in the pathophysiology of AEP (9).
In conclusion, to our knowledge, this is the first case of AEP possibly induced by an atypical antipsychotic drug (risperidone) with a serotoninergic mechanism of action, due to its antagonistic action to 5HT
2a receptors. In regard to the pathophysiology of AEP, a possible specific pattern of serotoninergic action that could result in such a reaction alone or synergically with idiosyncratic features, remains a challenge of in vitro and in vivo confirmation. Drug-induced AEP seems to be a rare, dangerous, but totally reversible side-effect that physicians should be aware of.

References