The cause of the eosinophilia in our patient was considered to be idiopathic, since no parasitic infection or neoplastic disorder was detected, and there was no history of asthma or allergic rhinitis, which is suggestive of Churg-Strauss syndrome. Moreover, the absence of the characteristic histologic markers (i.e., granulomas, epithelioid cells, and giant cells) and the negative results of tests for antineutrophil cytoplasmic antibodies ruled out Churg-Strauss syndrome, which also has been described in nonasthmatic cases. The disease was still in the active necrotic phase, as documented by the intense endomyocarditis and vasculitis also involving the abnormal intramyocardial and intraventricular vessels. Due to the potential release of cationic proteins from degranulating eosinophils, the use of steroids along with surgical intervention was necessary in order to avert such major cardiovascular complications as malignant arrhythmias, or the recurrence of valvular dysfunction leading to untreatable heart failure.

CONCLUSION

Cardiac angiodysplasia involving epicardial, intramural, and intraventricular vessels is a rare abnormality that is susceptible to inflammatory complications, which, in turn, lead to multiple valvular dysfunction and heart failure. The patients may benefit from combined surgical and medical therapy.

REFERENCES


A rare, but frequently fatal, side effect of the anti-psychotic drug clozapine is myocarditis. We report a case of hypersensitivity myocarditis secondary to clozapine administration that was diagnosed in vitro for the first time through endomyocardial biopsy and was successfully treated with corticosteroids. Histologic diagnosis was based on the evidence of eosinophil infiltration of the endomyocardium and eosinophil degranulation. Endomyocardial biopsy was performed in order to establish or exclude a clear-cut relationship between cardiac dysfunction and clozapine, and was crucial to establish a correct diagnosis and appropriate treatment. Clozapine withdrawal and targeted 8-day, low-dose corticosteroid therapy resolved the symptoms and restored cardiac function.

(CHEST 2004; 126:1703–1705)

Key words: differential diagnosis; drug hypersensitivity; endomyocardial biopsy; myocarditis; schizophrenia

Abbreviations: LV = left ventricle, ventricular

Clozapine is the “gold standard” treatment for schizophrenic patients who are resistant to neuroleptics. Its use, limited by the well-known agranulocytosis risk, has also been associated with severe cardiovascular side effects and sudden death.1–3 Both dilated cardiomyopathy and myocarditis, as result of direct toxicity and drug hypersensitivity, respectively, have been described at autopsy.2,3 We report a case of hypersensitivity myocarditis secondary to clozapine administration diagnosed for the first time in vivo by endomyocardial biopsy and successfully treated with corticosteroids.

CASE REPORTS

A 27-year-old chronic schizophrenic man (according to criteria of the Diagnostic and Statistical Manual of Mental Disorders IV), who was resistant and intolerant to neuroleptic drugs was admitted for the first time to our psychiatric ward because of severe psychotic symptoms, including a delusion of gender transformation and self-defeat behavior. After stopping treatment with haloperidol, risperidone, and biperiden, which were ineffective and burdened the patient with severe akathisia, clozapine therapy was started. The dose was increased up to 250 mg/d for a period of 11 days, while concomitant therapy with lorazepam was tapered from 6 to 3 mg/d. A clozapine plasma concentration of 425 ng/mL was found on day 12, when a full antipsychotic response was appreciated. On the same day, a persistent fever (temperature, 38.5°C) associated with pharyngodynia and neutrophilic leukocytosis appeared. Within 72 h, the clinical picture worsened, despite antibiotic treatment for a suspected infections disease. The patient showed severe malaise and dyspnea, while the chest radiogram showed a slight enlargement of cardiac silhouette. Clozapine-related myocarditis or acute viral myo-

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carditis following a throat infection then was suspected, clozapine therapy was withdrawn, and the patient was transferred into the ICU.

On ICU admission, physical examination revealed tachycardia (heart rate, 130 beats/min) with gallop rhythm, and BP was 100/60 mm Hg. An ECG showed sinus tachycardia with diffuse ST-segment and T-wave abnormalities. The erythrocyte sedimentation rate was 47 mm/h (normal range, 2 to 10 mm/h), the C-reactive protein level was 205.4 mg/L (normal range, 2.0 to 6.0 mg/L), and the blood cell count showed leukocytosis (14 × 10^9/L) with 7.0% eosinophils. The troponin I level was slightly increased (1.65 ng/mL; normal level, < 1.5 ng/mL). A two-dimensional echocardiogram showed a mild left ventricular (LV) dilatation (LV end-diastolic diameter, 57 mm) with a markedly reduced contractility (ejection fraction, 35%). Serology findings for the most common cardiotropic viruses, including hepatitis C virus and HIV, and the results of immunologic studies were negative. Four days later, after the patient gave informed consent, cardiac catheterization with ventriculography, coronary angiography, and an LV endomyocardial biopsy were performed in order to establish a clear-cut relationship between cardiac dysfunction and clozapine. This information was essential in deciding whether to resume the patient’s most successful antipsychotic treatment. The results of coronary angiography were normal, and the LV was diffusely hypokinetic. Six good-sized LV endomyocardial samples were drawn and processed for histology and polymerase chain reaction for the most common cardiotropic viruses.1 Histology in all samples showed the presence of extensive inflammatory infiltrates, mainly represented by degranulated eosinophils and lymphocytes, which often were adherent to injured myocytes (Fig 1), infiltrating the endocardium with the focal apposition of cytocites, which often were adherent to injured myocytes (Fig 1) and with the likely release of the cationic protein that ultimately mediates both myocyte damage and endocardial thrombus formation.

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On the basis of the histologic findings and molecular biology study results, myocarditis was treated with prednisone for a short period (1 mg/kg/d for 4 days tapered to 0.33 mg/kg/d for the following 4 days) in order to limit a possible worsening of psychosis. After 8 days of treatment, the patient had a visible improvement of symptoms, with a reduction of heart rate to 75 beats/min and the disappearance of a gallop rhythm. An ECG showed an increase of voltages with the disappearance of repolarization abnormalities. The echocardiogram showed a reduction of LV dimensions (LV end-diastolic diameter, 52 mm), with marked improvement of LV contractility (ejection fraction, 65%). The patient was discharged from the ICU without therapy with cardiac drugs, while the persisting psychotic remission allowed a prolongation of antipsychotic washout before starting a new treatment. Cardiac function improvement was maintained after corticosteroids withdrawal and after three months follow-up.

**Discussion**

We have reported the first endomyocardial biopsy detection of clozapine-induced hypersensitivity myocarditis. The histologic diagnosis was based on the evidence of eosinophilic infiltration of the endomyocardium, and on eosinophil degranulation with the likely release of the cationic protein that ultimately mediates both myocyte damage and endocardial thrombus formation.

Along with clozapine, several other drugs have been associated with hypersensitivity myocarditis, including sulfonamides, penicillin, tetracycline, streptomycin, diuretics, methyldopa, and amitriptyline. Unfortunately, drug hypersensitivity with a reaction confined to the heart is difficult to recognize, so that the majority of the reports are indeed postmortem observations.5

In our patient, clozapine therapy was clearly indicated, and had a rapid and impressive efficacy, therefore drug withdrawal required clear evidence of an iatrogenic cause of myocarditis. Time course, treatment schedule, and clinical presentation corresponded to the common presentation of this idiosyncratic reaction.2,5 Nevertheless, the clinical manifestation of fever associated with cardiac dysfunction and increase in troponin I level are nonspecific, and in our case could well have been due to a viral infection or a toxic mechanism. Corticosteroids would have been ineffective in treating a case of toxic damage, and deleterious in the presence of viral myocarditis, as they can promote viral replication and spreading in myocardial tissue.4 Conversely, corticosteroid efficacy in patients with hypersensitivity and autoimmune myocarditis has been established,3 with expected benefits clearly overcoming the known risk of psychotic relapse. Although we cannot completely exclude the idea that clozapine withdrawal alone would have provided cardiac recovery, the additional curative role of steroidal therapy is supported by the persistence of severe cardiac dysfunction in the week following drug withdrawal and preceding corticosteroid treatment.

In our case, endomyocardial biopsy was crucial to establish a correct diagnosis and appropriate treatment, allowing a prompt recovery of the patient’s cardiac compromise. Early recognition, instrumental diagnosis, and related specific treatment made this patient’s course favorable.

**Conclusion**

Clozapine-induced hypersensitivity myocarditis should be suspected by psychiatrists and physicians when cardiac dysfunction appears suddenly, and appropriate diagnostic and therapeutic strategies must be undertaken promptly.

**Figure 1.** Hypersensitivity myocarditis by clozapine: massive myocardial infiltrates mainly represented by degranulated eosinophils are associated with fraying of the adjacent myocytes (arrows) [hematoxylin-eosin, original ×400].
Severe Obstructive Sleep Apnea in a Patient With Spinal Muscle Atrophy*

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Patients with spinal muscle atrophy (SMA) who survive to adulthood experience a slow, continuous loss of motor function but typically have a normal life expectancy. These patients, however, require vigilance on the part of their health-care providers to reverse treatable disorders to maintain a satisfactory quality of life. We report on a patient with obstructive sleep apnea and type 3 SMA. The treatment of his sleep-disordered breathing resulted in the resolution of symptoms that were initially attributed to his neuromuscular disease.

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Key words: continuous positive airway pressure; Kugelberg-Welander syndrome; neuromuscular disease; obstructive sleep apnea; spinal muscle atrophy

Abbreviations: CPAP = continuous positive airway pressure; OSA = obstructive sleep apnea; SMA = spinal muscle atrophy

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Pinal muscle atrophies (SMAs) represent a heterogeneous group of hereditary progressive motor neuron disorders. The inheritance pattern is typically autosomal-recessive, but autosomal-dominant variants also have been described, especially for type 3 and 4 SMAs. Each form of SMA is characterized by the selective destruction of α-motor neurons in the anterior horns of the spinal cord without pyramidal tract involvement. The different forms of SMA are classified according to clinical criteria, especially age of onset and motor disabilities.1,2

Type 3 SMA, also known as the Kugelberg-Welander syndrome, manifests itself after the age of 18 months. The initial clinical presentation is proximal, symmetrical leg weakness. These patients may have a delay in learning to stand and walk, but eventually they manage independent ambulation. Their ability to walk, however, is usually slowly lost during the course of the disease. Although patients with SMA type 3 experience a slow, continuous loss of muscle function that impinges on their activities of daily living, the individual’s life span is often not significantly reduced.1–3

Obstructive sleep apnea (OSA) affects 2% of adult women and 4% of adult men in the United States.4 However, the prevalence of sleep-disordered breathing in patients with neuromuscular diseases is > 40%. OSA occurs in 24% of adults with neuromuscular diseases.5 Despite these observations, the progressive symptoms of sleep-disordered breathing are often attributed to the untreatable progression of the underlying neuromuscular disease, rather than to the more easily treated sleep-disordered breathing.6 Our patient underscores the concept that close attention to the patient’s complaints and vigilance toward their treatment can improve their quality of life.

CASE REPORT

A 46-year-old white man with type 3 SMA was referred for the evaluation of progressive fatigue that was interfering with his usual activities of daily living. He also admitted to increasing somnolence during the day, morning headaches, and snoring with episodes of apnea while asleep. The patient reported no dyspnea, cough, or sputum production.

At 8 years of age, the patient had received a diagnosis of type 3 SMA. The patient stated that he initially was able to sit and walk independently, even though these occurred later than usual in comparison to other children in his age group. At the age of 5 years, he developed proximal muscle weakness, first in his legs, then later in his upper extremities. By the time of his diagnosis, he was confined to a wheelchair.

The patient was slightly below ideal body weight (body mass index, 17.4 kg/m²), and his weight had been stable for years. The patient was wheelchair-bound and had severe scoliosis. The only residual active muscular movements that were preserved were in his left forearm and neck.

All laboratory parameters, including a CBC count, serum electrolyte measurements, a biochemical survey, a coagulation profile, and a measurement of serum creatinine phosphokinase levels, were normal. His arterial blood gas analysis results were normal (pH, 7.47; PaO₂, 85.6 mm Hg; PaCO₂, 33.8 mm Hg). Pulmonary function tests were consistent with a restrictive ventilatory defect (FVC, 2.36 L/min and 59.1% predicted; FEV₁, 1.77 L/min and 55.2% predicted). His maximal inspiratory and expiratory pressures were decreased at 35.0 mm Hg (73% predicted) and 45.8 mm Hg (69% predicted), respectively. Electromyography demonstrated the following typical characteristics of type 3 SMA: spontaneous muscle activity with fibrillations and fasciculations, but normal transmission velocity of peripheral sensory nerves.