Case in Point

Suspected Clozapine-Induced Cardiomyopathy and Heart Failure With Reduced Ejection Fraction

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An increased awareness of the adverse effects associated with clozapine can help physicians quickly diagnose this rare and potentially fatal condition.

Clozapine is an atypical antipsychotic that is usually reserved for use in patients with treatment-resistant schizophrenia or schizoaffective disorder with suicidality. Due to the risk of severe neutropenia, clozapine is available only through a restricted Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program, which requires provider certification, patient enrollment and adherence with absolute neutrophil count (ANC) testing and monitoring, and dispensing pharmacy certification. In addition, clozapine (Clozaril) prescribing information contains a boxed warning for potentially fatal cardiomyopathy. One recently published study from Australia demonstrated a 4.65% incidence of cardiomyopathy in patients started on clozapine, which is much higher than the incidence provided by national drug surveillance programs. An increased awareness is needed among health care professionals, including physicians, pharmacists, and nurses, about this serious fatal condition.

Clozapine-induced cardiomyopathy is a diagnosis of exclusion that requires the absence of other etiologies of cardiac dysfunction (ie, coronary artery disease, hypertension, valvular disease, congenital heart disease, etc). Diagnosing a clozapine-related cardiomyopathy may be a long and laborious task. Patients with cardiomyopathy may present with many nonspecific signs and symptoms, such as fatigue, dyspnea, edema, and/or nausea and vomiting, which are present in other diseases; therefore, multiple encounters and lab tests may be needed until a cardiac source is implicated. The exact mechanism is unknown; however, Chow and colleagues believe that clozapine is a direct toxin of the myocardium.

CASE PRESENTATION

A 30-year-old woman with a history of asthma, hypothyroidism (euthyroid with supplementation), posttraumatic stress disorder, and schizoaffective disorder was started on clozapine due to major depression and increased suicidal ideation despite previous treatment with several other antipsychotic agents. Clozapine was gradually titrated to a dose of 150 mg twice a day during an inpatient psychiatric admission. Prior to starting clozapine, this patient had been admitted to the psychiatry unit 11 times within the prior 2 years. After initiating and titrating clozapine over 4 months, her psychiatric symptoms markedly improved.

More than 4 years after the initiation of clozapine and after various treatments for multiple symptoms (Sidebar), the patient was diagnosed with heart failure (HF) with a reduced ejection fraction (EF) of 10% to 15%. She was referred to the cardiology HF clinic. Her dose of clozapine 150 mg at bedtime was discontinued after a discussion with psychiatry. She had a negative workup for other HF etiologies and was started on HF medications that included carvedilol, losartan, and spironolactone. After discontinuation of clozapine, her psychiatric symptoms worsened, and she was admitted to the psychiatry unit twice within a year. Two months after clozapine was

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discontinued, a repeat echocardiogram (ECHO) was obtained and was essentially unchanged. A chest X-ray (CXR) obtained 4 months after clozapine discontinuation demonstrated a normalized cardio-mediastinal silhouette. A third ECHO was ordered during her second psychiatric admission, which was 11 months after clozapine discontinuation; this revealed an improved left ventricular EF (LVEF) of 30% to 35% and resolution of left ventricular (LV) dilation.

This patient’s clinical course led to an extensive chart review that investigated whether there may have been earlier signs and symptoms of HF or cardiomyopathy. It was discovered that the initial HF signs and symptoms were likely present for about 1 year before the diagnosis was made and after having been on clozapine for about 40 months (Videos of the patient’s ECHO before and after clozapine discontinuation available at www.fedprac.com).

**DISCUSSION**

In retrospect, this patient likely had HF for many months prior to the official diagnosis; however, given this patient’s young age, prior history of asthma, respiratory disorders, underlyng severe psychiatric disease, and confounding symptoms, it is easy to understand why the diagnosis was initially overlooked and delayed.

This patient did not have significant lower extremity edema, but she reported nausea, vomiting, and weight loss. Typical patients with HF exhibit edema and weight gain unless they experience cardiac cachexia. It is not clear whether this patient had a coexisting gastrointestinal (GI) disorder or whether the GI symptoms were secondary to cardiac cachexia. Additionally, weight gain and metabolic syndrome have been documented with clozapine therapy.

It is interesting that a repeat ECHO within 2 months of clozapine discontinuation did not show an improvement, whereas a CXR at 4 months showed a normal cardiac silhouette, and an ECHO at 11 months showed an improvement in EF and normalization of LV size while on appropriate HF medications. It would have been interesting if an ECHO had been completed at 4 months to correspond with the time when the CXR normalized.

There does not seem to be a high level of awareness regarding this potentially fatal diagnosis of cardiomyopathy related to the use of clozapine. A recent review of clozapine-induced cardiomyopathy by Alawami and colleagues revealed characteristics, including median age of diagnosis of 33.5 years, a mean daily dose of 360 mg (range 125-700 mg/d), average time of therapy until the development of symptoms 14.4 months (range between 3 weeks and 4 years), and the presence of ventricular dilation in 39%. The most common symptoms on clinical presentation were shortness of breath (60%), palpitations (36%), cough (16%), fatigue (16%), and chest pain (8%).

It is interesting that edema was not present in the patients studied in their review; this difference from the usual presentation of severe HF may lower clinical suspicion and makes diagnosing this type of cardiomyopathy more difficult. Alawami also noted that patients with an LVEF < 25% at the time of diagnosis tended to have a poorer prognosis with the highest risk of mortality and limited recovery. Fortunately, in this case, the patient’s LVEF improved significantly, and it will be interesting to continue to monitor the patient for further improvement.

As a result of this case, the
authors have performed a chart review on all patients prescribed clozapine at VA Loma Linda Healthcare System. Additionally, this case supports the implementation of better cardiomyopathy monitoring of all clozapine patients. It may be recommended to obtain a baseline CXR in all patients starting clozapine, conduct monthly cardiomyopathy symptom screening that coincides with ANC monitoring, and perform an ECHO immediately on any clinical suspicion of cardiomyopathy.

**CONCLUSION**
Better awareness and regular screening for signs and symptoms of HF may help prevent a delay in diagnosing a rare but serious and potentially fatal condition associated with clozapine. Chest X-rays demonstrating cardiomegaly can be helpful when the early diagnosis of HF is suspected and may be the first diagnostic imaging test to normalize after clozapine discontinuation.

Since clozapine is a REMS medication and all patients are scheduled for regular ANC follow-up, it would seem prudent that patients also should be screened for signs and symptoms of HF, including the new onset or worsening of baseline shortness of breath, palpitations, cough, fatigue, chest pain, edema, gastroparesis, and perhaps extreme weight loss. Once a physician suspects HF, an ECHO should be obtained immediately.

In addition to the clozapine boxed warning for cardiomyopathy, it would be helpful if the clozapine patient counseling information section had a specific warning that advises patients to contact their clinician if they develop the signs and symptoms of HF. 

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**REFERENCES**