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Case Report

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Isoniazid Induced Pancreatitis — A Case Report

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Abstract

Isoniazid is one of the very important drugs used in antitubercular therapy. Pancreatitis is an uncommon adverse effect of isoniazid. Our case highlights the need for treating physicians to maintain a high level of vigilance while following up patients who are on antitubercular therapy in order to recognize symptoms related to this rare adverse event at an early stage. Immediate drug withdrawal and ensuring isoniazid free course of treatment in future is warranted when a patient develops this adverse event.

Keywords: Isoniazid, Pancreatitis, antitubercular therapy.

Introduction

Drug induced pancreatitis is a rare, but a serious entity, which necessitates withdrawal of the culprit drug. Therefore it goes without saying that early reorganization of symptoms is extremely important in these cases. Most of the times, it leads to rapid improvement of patients' symptoms.(1) Isoniazid is one of the first line drugs used for the treatment of tuberculosis.(2) It is a bactericidal drug and it exerts its action by inhibition of mycolic acid synthesis. Liver plays an important role in its metabolism, by the action of hepatic N-acetyltransferase.(3) Its most commonly recognised side effects are hepatitis and peripheral neuropathy.(2) Although Isoniazid has been known to cause pancreatitis since 1973, its occurrence is rare; .(4) Herein, we are reporting an occurrence of acute pancreatitis in a patient caused by isoniazid.

Case Report

A 28 year old male weighing 60 kg reported to medicine emergency department with complaint of four episodes of generalized tonic- clonic seizures (GTCS). The first episode occurred seven days back for which he took no treatment and the three episodes of GTCS occurred on the day of presentation. On further questioning he also reported to have headache for the last 3 weeks. He had low grade fever for the last 4 weeks, he also reported that his appetite was reduced for the last 4 weeks and he had also lost 4 kgs of weight during the same time. He shared his accommodation with his father, mother and 3 siblings. His brother was diagnosed as a case of pulmonary tuberculosis 5 months back, for which he was taking treatment from a local hospital. The recent episodes of seizures were witnessed by his mother. At that time he had violent shaking of the body with jerky movements, upward rolling of eyeballs, frothing from

mouth and loss of consciousness for about 5 minutes. He did not lose bowel or bladder control during these episodes.

On presentation his temperature was 37⁰ C, blood pressure was 126/ 80 mm of Hg and pulse was 78 per minute, regular in rhythm. His random blood sugar, renal function, liver functions, complete blood count, erythrocyte sedimentation rate (ESR), electrolytes and ECG were within normal limits. His montoux test was negative, but chest X ray revealed mediastinal lymphadenopathy. He did not agree for electroencephalography (EEG) test. Magnetic resonance imaging (MRI) of brain showed multiple ring enhancing lesions of both cerebral hemispheres with central necrosis, irregular outlines and perilesional oedema. Based on these findings, a diagnosis of tuberculoma was made and he was started on daily antitubercular treatment (ATT) with four drugs isoniazid (5mg/Kg), rifampin (10mg/Kg), pyrazinamide (25mg/Kg) and ethambutol (15mg/Kg). He was also started on 0.4 mg/kg dose of intravenous dexamethasone for the first week with instructions of decreasing this dose by 0.1 mg/kg every week, and then to start on oral tapering dose. His course of stay during one week of hospitalization was uneventful, and was discharged from the hospital in stable condition with instructions of continuing ATT. During his first follow up visit after 10 days, he did not report any fresh episodes of seizure, his headache frequency and severity was reduced, and he gained 2.5 kgs of weight since the time of his first day of hospitalization.

Within 3 weeks of his discharge from the hospital, he reported to Emergency department with complaints of severe abdominal pain and vomiting. He denied any urinary complaints, and was passing stools normally. On examination he was afebrile, did not have any icterus and his vitals were within normal limits. On palpation of abdomen, epigastric tenderness was noted and there was guarding of abdominal muscles. Systemic exam of the patient did not reveal any other abnormality. Lab investigations and imaging tests were performed on the patient. His serum amylase levels were found to be 2548 IU/ L (normal value 40-140), his serum lipase levels were 1430 (normal value 0-50). (5, 6) His liver functions, white blood cell counts, triglyceride levels and calcium levels were within normal range. Computerized tomography (CT) of abdomen was ordered which showed signs of acute pancreatitis in body and tail of pancreas with surrounding oedema. All his oral medications including ATT were stopped and he was given

parenteral antitubercular medications including intravenously administered rifampin, amikacin and moxifloxacin, and intramuscular injections of streptomycin for a period of seven days. He was also put on "Bowel rest" and all his oral feeds and fluids were stopped and was placed on total parenteral nutrition. His blood urea nitrogen (BUN) and hematocrit were measured every 12 hourly for the first two days of admission and every day thereafter for one week. His symptoms normalized within a week. His steroid regimen was changed from intravenous to oral route at this time. It was also decided to restart oral ATT regimen this time, but before doing that, it was decided to find out the cause of pancreatitis so as to avoid relapse.

Although rarely, pancreatitis is a known adverse event linked to two antitubercular drugs- isoniazid and rifampin. Therefore in order to pin point the adverse event to the possible offending medication, we decided to stop these two medications from patient's treatment regimen alternatively and to observe for symptom progression closely. As isoniazid induced pancreatitis is known to reverse with drug withdrawal, we first stopped isoniazid from the treatment regimen for some time while all other ATT medications including rifampin were restarted. Careful monitoring of symptoms for redevelopment of pancreatitis was done. Twice a week his lab investigations were repeated which showed decreasing serum amylase and serum lipase levels which gradually normalised after 2 weeks of hospitalization. His ultrasound of abdomen showed that inflammation of the pancreas was decreasing. Subsequent laboratory investigation in the following week did not show any abnormalities or increase in pancreatic enzyme levels. Thus it was clinically confirmed that the episode of pancreatitis was caused by antitubercular drug isoniazid, and the patient recovered from it after stoppage of this medication. Therefore there was no need to exclude rifampicin from patient's treatment chart. The patient was discharged from the hospital after starting on revised tubercular regimen which included four drugs, namely rifampin, pyrazinamide, ethambutol and streptomycin for two months and three medications rifampin, pyrazinamide and ethambutol for the next ten months. No further derangement of pancreatic enzymes or symptoms development suggestive of pancreatitis was seen in next follow up visits.

Discussion

Drug induced pancreatitis is a rare occurrence. It is estimated that about 0.1 to 2% of all cases of pancreatitis are drug related. (7) As the clinical findings and investigations of this subset of pancreatitis is no different than other type of pancreatitis, this sometimes leads to difficulty in diagnosis. Luckily most of the cases of drug induced pancreatitis are mild, but sometimes severe cases are reported. One of the most important management of drug induced pancreatitis is immediate discontinuation of the offending drug. Therefore awareness of physician about drug action and their adverse effects is extremely important for prevention and for diagnosing this condition at an early stage. (8)

With about 2.5 million cases in 2015, India has the highest prevalence of tuberculosis in the world. (9) Because of such a large disease burden, it is understandable that the number of patients using isoniazid and rifampin, two important first line drugs against tuberculosis, is quite high in India. Literature review reveals that pancreatitis is a rare side effect attributed to these two antitubercular drugs. Although it is difficult to find out the offending drug with 100 per cent certainty in all cases (10-14), largely because of the fact that most of the times these two drugs are given together as a combination therapy along with other antitubercular drugs in order to decrease the chances of developing resistance to these medications, but in this particular case we can say with reasonable amount of certainty that the pancreatitis in our patient was caused by isoniazid. This is because the patient presented with symptoms of pancreatitis within 3 weeks of starting isoniazid, which is consistent with previous study which has reported the time of development of pancreatitis with isoniazid to be between 0.5 to 35 days period. (15) This is further supported by the fact that pancreatitis in our patient did not reoccur after starting modified oral antitubercular regime which included rifampin but did not include isoniazid.

Literature search also shows that most of the cases of isoniazid induced pancreatitis are mild to moderate in severity if diagnosed early (15), and after withdrawal of this drug, the patient improves symptomatically and biochemically within 2 days to 2 weeks. (9) This is also concordant with our findings in this case, where the patient improved within 2 weeks of stoppage of the drug. But as reported by Dickson, if these symptoms of pancreatitis are ignored and timely action is not taken by promptly discontinuing isoniazid, there is a

possibility of these symptoms to become fatal. (16) After establishing the diagnosis, it is important to have this adverse drug record available for treating physician's reference for all future healthcare visits by the patients. This is especially because of the fact that in past pancreatitis has been reported to have reoccurred in a patient after re-exposure of this drug as long as 12 years after the initial episode. (10) This presents a unique challenge, especially because isoniazid is extensively used in developing countries where computerized healthcare record facilities may not be readily available. In the given scenario, educating patients about this health condition and maintaining good manual health records become extremely important.

Conclusion

Although Isoniazid is one of the uncommon drugs causing pancreatitis, but considering extremely large number of patients taking this medication, and severity of symptoms related to this adverse effect makes it important to study this condition in detail. This is particularly so considering the reversibility of this condition which is often seen upon stoppage of this drug. After making the diagnosis, it is important to avoid this drug in future because recurrent pancreatitis can occur with re-challenge of isoniazid.

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