Stavudine Induced Acute Pancreatitis in Paediatric Human Immunodeficiency Virus Infection

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Introduction

Acute pancreatitis (AP) is a rare but life threatening complication associated with paediatric human immunodeficiency virus (HIV) infection due to virus itself or side effects of antiretroviral therapy with nucleoside reverse transcriptase inhibitors (NRTI) particularly didanosine [1,2]. We report a case of acute severe pancreatitis due to stavudine.

Case Report

Ten years old female child, a follow up case of HIV infection on anti retroviral therapy (stavudine, lamivudine and nevirapine) for eight months, was brought with sudden onset of moderately severe non-colicky pain in upper abdomen associated with vomiting and diarrhoea. On examination, she weighed 24.5 kg, was anxious, restless, afebrile, dehydrated and had tachycardia with blood pressure (BP) of 100/70 mm of Hg. Per abdomen examination revealed tense abdomen with guarding and tenderness in epigastrium. Other systemic examination was unremarkable. An urgent ultrasonography (USG) of the abdomen revealed features of acute pancreatitis and mild hepatomegaly. Further investigations revealed haemoglobin (Hb) -10.5 gm/dl, total leucocyte count (TLC) of 18000/cumm with 86% polymorphs. Serum amylase was 510 IU/L (normal 30-100 IU/L) and urinary amylase 1500 IU/L (normal 2.6 - 12.2 IU/L). Serum lipase was 240 IU/L (normal 3-32 IU/L). Computed tomography (CT) scan of the abdomen showed evidence of acute severe pancreatitis (Fig. 1). Her CD4 count was 219 cells/cumm. She was put on intravenous fluids and antibiotics (Inj Imipenem). Anti retroviral therapy (ART) was withheld in view of suspected drug toxicity. On the third day, she developed severe respiratory distress, hypotension and left basal consolidation. Arterial blood gas analysis showed PaO₂ / FiO₂ as 216.7 mm Hg suggestive of acute lung injury and she was put on mechanical ventilation. A naso-jejunal tube was passed to relieve abdominal distention and to aid in nutrition. She showed a sustained improvement over next one week and was weaned off the ventilator. Repeat serum amylase was 43

IU/L. She was restarted on ART after one month with zidovudine, lamivudine and nevirapine. On follow up after six months, she was asymptomatic, gaining weight and tolerating ART well.

Discussion

AP is a rare complication seen in HIV positive patients. It may be due to the HIV infection of pancreas itself or due to the side effects of the antiretroviral agents. Patients infected with HIV are 35 to 800 times more likely to develop AP than the general population. In a recent multicentric study of 2575 HIV-infected children, among the incidence of non infectious conditions, pancreatitis constitutes approximately 0.30% [3]. Antiretroviral agents linked to AP include nucleoside reverse transcriptase inhibitors (NRTI) and protease inhibitors (PI). Didanosine is the most frequently reported agent with mean daily dose exceeding 360 mg/m² and another four fold higher incidence when used in combination with hydroxyurea [4]. Stavudine is a synthetic thymidine nucleoside analogue, active against HIV virus. Stavudine alone causing pancreatitis is rare, however if used in combination with other drugs, that have pancreatic toxic effects (other nucleoside analogs or drugs used for treatment/prevention of pneumocystis pneumonia), the incidence of pancreatitis is high. Other side effects of stavudine include lactic acidosis, peripheral neuropathy, headache, diarrhoea and allergic manifestations. Other drugs associated with AP are 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors, acetylcholine esterase (ACE) inhibitors, estrogens / hormone replacement therapy, diuretics and valproic acid [2]. Advanced HIV disease, preexisting liver disease, low CD4 cell count (< 200 / cumm), opportunistic infections, such as cytomegalovirus (CMV), mycobacterium avium intracellulare (MAI) and candida are other identified risk factors for pancreatitis

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Fig. 1 : CT scan of abdomen showing the features of acute severe pancreatitis

in an HIV patient [4,5]. The pancreatitis in our patient was due to stavudine as she was on HAART for last eight months with stavudine, lamivudine and nevirapine. All viral markers and other possible causes of pancreatitis were ruled out after detailed investigations and she showed a good recovery following cessation of the drug. After recovery, she was put on zidovudine, lamivudine and nevirapine therapy and is doing well ever since. Hence, stavudine seems to be the most likely agent.

In most cases there is an increase in serum amylase, but symptomatic pancreatitis is very rare. In severe AP, patients progress to systemic inflammatory response syndrome, sepsis, and multiple organ failure. In a retrospective cohort study, investigators utilized the Ohio Medicaid claims database to evaluate the risk of AP with various HAART drug regimens and noticed that out of 4972 patients who received ART, 3.2% developed AP mainly on NRTI. It is diagnosed on the basis of an elevated lipase measurement (elevated amylase may be caused by parotid gland inflammation associated with HIV or other causes) and imaging studies. The manifestations of pancreatitis in HIV patients are similar

to those in the general population with the following differences: a high frequency of medication-associated pancreatitis, a low frequency of gallstone pancreatitis, additional symptoms and signs due to underlying immunosuppression, and a more severe hospital course [6].

The medical management entails supportive measures including bed rest, intravenous fluids, analgesics, antispasmodics and drainage of gastric secretions by nasogastric tube. Indications for surgery are pancreatic necrosis and pseudocyst formation. It is advisable to stop all antiretroviral drugs simultaneously until the patient is stabilized. Prognosis is usually good, if diagnosed early and aggressive therapy instituted. About three to 13% of AP cases may progress to chronic pancreatitis. AP is a rare but life threatening complication in paediatric HIV, especially on HAART. A high index of suspicion, early diagnosis and treatment can be life saving. AP must be kept in mind while dealing with a case of unexplained severe abdominal pain in a setting of HIV infection on HAART.

Conflicts of Interest

None identified

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