



Cyclophosphamide Doxorubicin-Induced Acute Pancreatitis; Internist Should Be Aware Of

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Abstract

The incidence of Drug-induced pancreatitis ranges from between 0.1% and 2%. Chemotherapy-induced pancreatitis should remain as a differential diagnosis in patients receiving chemotherapy regimens and presenting with acute pancreatitis. We present a case of cyclophosphamide induced acute pancreatitis in a 53 year old female with no other risk factor for pancreatitis, symptoms resolved in a few days after discontinuation of the drugs.

Keywords: Acute pancreatitis; Chemotherapy side effects; Cyclophosphamide; Drug-induced pancreatitis

Introduction

Acute pancreatitis is an inflammatory condition of the pancreas characterized by abdominal pain and elevated levels of pancreatic enzymes in the blood. Acute pancreatitis is a leading gastrointestinal cause of hospitalization in the United States [1]. Several conditions have been associated with acute pancreatitis. Of these, gallstones and chronic alcohol abuse accounting for approximately two-thirds of cases [2]. The estimated overall incidence of drug-induced pancreatitis ranges from between 0.1% and 2% based on individual case reports and case control studies [3,4]. This report describes a 53 year old female patient with recent diagnosis of stage 2 breast cancer who developed acute pancreatitis on day 4 after combination chemotherapy of cyclophosphamide and doxorubicin.

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Case Presentation

This is a 53 year old female patient recently diagnosis of right sided breast cancer which was found to be triple positive, PR, ER and HER2/neu positive. She underwent multiple lumpectomies with inadequate clearing of margins. Patient received her first dose of adjuvant chemotherapy with IV cyclophosphamide and doxorubicin 4 days prior to admission along with pegfilgrastim. The patient reports later that evening, she started to experience severe mid epigastric pain, radiating to her back that was partially relieved by leaning forward but not much with Non-Steroidal Anti-Inflammatory Drugs (NSAID). Her symptoms were associated with nausea, loss of appetite, and one episode of vomiting. She denied any fevers, change in bowel movements, dysuria, vaginal bleeding or recent trauma. Her past medical history includes ovarian cysts. She has no previous history of pancreatitis. She is a nonsmoker and drinks alcohol occasionally and denies any history of illicit drug use. Family history was noncontributory. Patient was not on any medications except for lorazepam, reglan and zofran that were prescribed to her on the day of chemotherapy.

On physical examination, stable vital signs, anicteric sclera and moist mucous membranes. Heart and lung examination were unremarkable. Abdomen examination was positive for significant epigastric tenderness, normoactive bowel sound, no palpable organomegaly and negative Murphy's sign.

Initial laboratory investigation showed white blood count of 30.8 with 80% neutrophils. Basic metabolic panel was within normal range except for mild hyponatremia 131 mmol/L (normal 136 to 145 mmol/L). Serum amylase and lipase were markedly elevated 914 U/L (Normal 23 to 85 U/L) and 710 U/L (0 to 160 U/L) respectively. Liver function tests and coagulation profile were within normal range. Lipid profile was also within normal range. Imaging of the abdomen including an abdominal ultrasound showed no evidence of biliary ductal dilation and no cholelithiasis, wall thickening or pericholecystic fluid. CT scan with IV and oral contrast showed no peripancreatic inflammatory changes or focal lesions. Patient was admitted to medical floors with the diagnosis of acute pancreatitis presumed to be secondary to cyclophosphamide and doxorubicin as other

causes were excluded and based on clinical presentation and elevated enzymes. Upon admission patient was managed conservatively with intravenous fluid, pain medication and NPO initially. During her stay, routine labs including and serum amylase and lipase were monitored closely. Her symptoms resolved completely with improvement of biochemical parameters. Discussed with patient regarding possible drug induced pancreatitis and communicated with her oncologist. Patient was counseled not to have any more Cyclophosphamide and doxorubicin chemo regimen. White blood counts along with amylase and lipase were trending down. Her abdominal pain, and nausea improved and her diet was advanced gradually as tolerated.

Discussion

Cyclophosphamide is an alkylating agent that acts by preventing cell division by cross-linking DNA strands and decreasing DNA synthesis [5]. Cyclophosphamide also possesses potent immunosuppressive activity and it's considered as a pro-drug that must be metabolized to active metabolites in the liver. Some of the adverse reaction well described in literature includes endocrine side effects such as altered hormone level (increased gonadotropin secretion), amenorrhea and gastrointestinal side effects such as abdominal pain, anorexia, diarrhea, mucositis, nausea, vomiting (dose-related), and stomatitis [3].

Drug induced acute pancreatitis account for 1.4% to 2% and chemotherapy-induced pancreatitis is rarer [6-8]. The physiologic mechanism of chemotherapy-induced pancreatitis may be by direct damage by antibody formation and interaction with pancreatic cells. This response can activate T cells in vitro and results in tissue damage that is probably T lymphocyte Mediated [3]. Another potential mechanism includes direct tissue injury by the medication.

Cyclophosphamide and doxorubicin either alone or in combination, is quite rare that even the drug labels registered with the FDA, do not indicate acute pancreatitis as one of the possible complications and there are very few cases reported this side effect [5]. In our patient, acute pancreatitis developed on the 4th day of the administration of chemotherapy, and resolved within a few days after discontinuation of the drugs. She didn't have any other risk factors for pancreatitis as she doesn't drink alcohol and laboratory finding including serum triglyceride, calcium levels, bilirubin, sedimentation rate and C-reactive protein were all within normal levels. Liver ultrasound was negative for gallstones or biliary sludge, Also the patient didn't receive dexamethasone during her first chemotherapy cycle.

Review of other case reports such as Ben Kridis et al. [8] presented a 20 year old patient that developed acute pancreatitis the second day after administration of doxorubicin and ifosfamide. She developed two episodes one was with metoclopramide and methylprednisolone and the second chemotherapy course was received without and both were complicated by pancreatitis. Ben Kridis et al. [8] mentioned 4

pediatric cases of acute pancreatitis after administration of ifosfamide. He also described Doxorubicin as a rarely blamed medication for acute pancreatitis as per available data.

Another case report by Vincent et al. [9] described the development of acute pancreatitis in a patient with breast cancer three days after receiving the chemotherapy regimen consisting of cyclophosphamide and doxorubicin. Another episode after re-challenging the patient with cyclophosphamide, and again a few weeks later with a derivative of doxorubicin, epirubicin, acute pancreatitis recurred on each occasion. Reflecting that cyclophosphamide was probably the inflecting agent in both episodes.

Conclusion

Due to the increasing number of case reports, chemotherapy-induced pancreatitis should remain as a differential diagnosis in patients receiving chemotherapy regimens and presenting with symptoms and signs typical of acute pancreatitis. Physicians can report new suspected adverse drug reactions directly to the FDA via its Med Watch program, by contacting the manufacturer of the drug, and by publishing case reports. Also post-marketing surveillance and adverse drug reporting should be done get a wide angle vision on the true incidence of chemotherapy induced pancreatitis.

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