ejpmr, 2023, 10(7), 512-515

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Case Study

ISSN 2394-3211

EJPMR

DRUG INDUCED ACUTE SEVERE NECROTISING PANCREATITIS

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Article Received on 19/05/2023 **Article Revised on 09/06/2023** **Article Accepted on 30/06/2023**

ABSTRACT

Acute necrotizing pancreatitis is a life threatening form of acute pancreatitis and is characterised by inflammation associated with pancreatic parenchymal necrosis or peripancreatic necrosis. After alcohol and gallstones are ruled out, drug-induced pancreatitis (DIP), which accounts for up to 5% of all acute pancreatitis cases, is the third most common cause of acute pancreatitis. Drug-induced pancreatitis affects around 5-80 persons worldwide per 100,000. In addition to youngsters, the elderly, and those with inflammatory bowel disease, DIP has been observed to be greater in people who are immunosuppressed. Didanosine, Azathioprine, Valproic acid, Mercaptopurine, Mesalamine, Tetracycline, Steroids, Furosemide, etc. are the medications most frequently documented to cause acute pancreatitis (those in which reaction reappeared after challenge dechallenge-rechallenge). However, other drugs like Rifampin, Erythromycin, Octreotide and several others have also been known to cause acute pancreatitis. In this case report we present the case of a 17 year old female patient who developed acute severe necrotizing pancreatitis following treatment with Azathioprine, Eltrombopag and Prednisolone for Immune thrombocytopenic purpura (ITP).

KEYWORDS: Eltrombopag, Azathioprine, Prednisolone, Acute Necrotizing Pancreatitis, Immune Thrombocytopenic Purpura.

INTRODUCTION

Acute necrotizing pancreatitis is a severe form of acute pancreatitis characterised by necrosis in and around the pancreas and is associated with high rates of morbidity and mortality.[1] While only 10–15% of patients with acute edematous pancreatitis develop the necrotizing variant of the disease, the mortality rates associated with necrosis range from 27% to 86%.[2, 3, 4] Among the various etiologic factors, drugs are often overlooked as a causative agent. Drugs are responsible for 0.1 to 2% cases of drug induced acute pancreatitis. The incidence of drug-induced pancreatitis is increasing globally.[5] Management of drug-induced acute pancreatitis requires withdrawal of the offending agent and supportive care, and the failure in identifying the offending drug can result in critical delays.[6]

Here we present the case of a 17-year-old female with ITP who was on treatment with Azathioprine, Elthrombopag, and Prednisolone, who later developed acute severe necrotising pancreatitis following the follow up period.

CASE REPORT

A 17 year old female who is a known case of ITP was presented to the Emergency Department with complaints of severe abdominal pain for 1 day. Her pain was acute and progressive in nature, which radiated posteriorly to her abdomen and caused significant distress on lying supine and was associated with recurrent vomiting. She had no history of fever or loose stools She was on treatment with the following drugs-Azathioprine, Eltrombopag and Prednisolone for a period of eight, six and four months respectively. The patient also had hypothyroidism for which she was on thyroxine supplementation.

Her blood investigation showed leukocytosis-(Total Count-16340), Haemoglobin (15.6 g/dL), Platelet count (3.43 lakh cell/ cu mm), Lipase (873), amylase (126.3). She was started on Fentanyl infusion due to her severe pain. Ultrasound (USG) Doppler showed no evidence of thrombosis in any of the abdominal vessels. Contrast Enhanced Computerised Tomography (CECT) abdomen showed features of acute interstitial edematous pancreatitis with mild to moderate ascites. Modified CT Severity Index (CTSI) score showed moderate severity pancreatitis (4/10) and Fatty liver. Patient was kept under

NPO (nil per os) and was started on IV Antibiotics and other supportive treatment. Her steroids and immunosuppressants were withheld in view of drug induced pancreatitis. Blood culture and urine culture were sterile. A repeat CECT Abdomen was taken again in view of the persisting symptoms which showed features of acute necrotising pancreatitis (Fig. 1). Modified CTSI score was severe (10/10). USG upper Abdomen suggested features of acute necrotizing pancreatitis. After the patient was discharged, the dose of Eltrombopag was tapered to 25 mg once weekly regimen and all other drugs including steroid and immunosuppressants were stopped. The patient was clinically and hemodynamically stable on follow up and her USG Abdomen showed features of resolving pancreatitis.

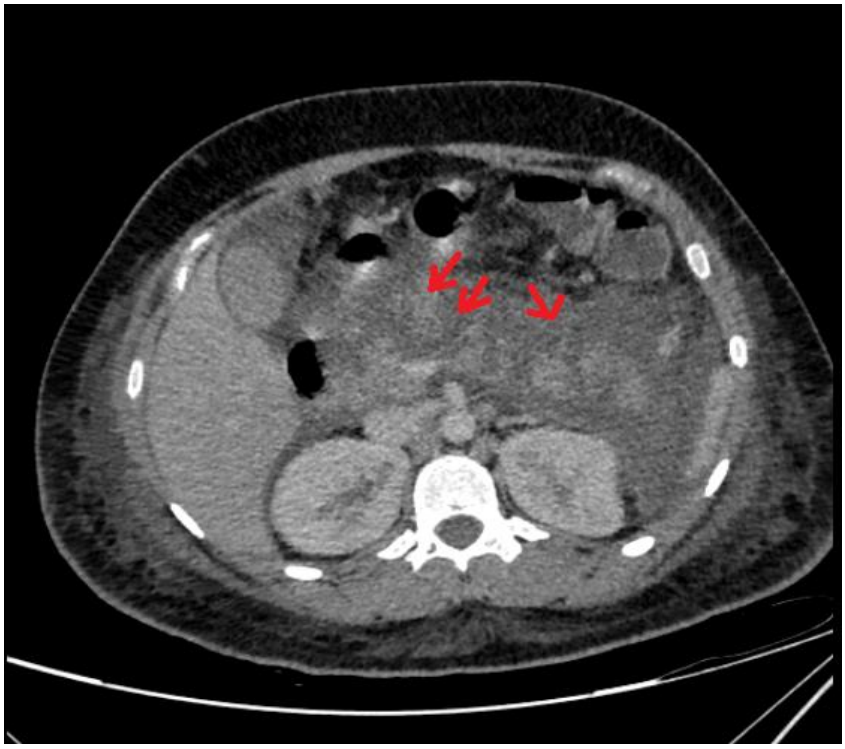

Fig. 1: **CECT Abdomen showing acute necrotising pancreatitis**.

DISCUSSION

This case report illustrates the development of Acute severe necrotising pancreatitis in a patient with ITP while on treatment with the following drugs- Azathioprine, Prednisolone and Eltrombopag. During her initial clinical diagnosis of ITP, she was initiated on Prednisolone and Thrombopoietin analogue (Eltrombopag). Two weeks later she was initiated on Azathioprine 50mg OD. The steroids were tapered and Stopped over 8 weeks and the dose of Eltrombopag was titrated to 75mg OD. One week later, the dose of Azathioprine was titrated to 75mg and all other medications were continued in the same dose. For the next 8 months, Azathioprine was continuously administered by the patient at a dose of 75mg OD along. Danazol was added to enhance the response. Also in view of increased platelet counts, Elthrombopag was stopped after 6 months of initiating it. The drug was again reinitiated as 25 mg alternative days in view of declining platelets 1 month before the development of acute pancreatitis. There was no history of alcohol intake or gallstones. The imaging and Biochemical investigations confirmed Acute severe necrotising pancreatitis following 8 months of administration of these drugs. These medications are previously reported in literature to carry the risk of acute pancreatitis.[7, 8, 9] In the present case, there is a possible likelihood of either one of these drugs or a combined effect of all of them might have contributed to the development of acute necrotizing pancreatitis.

The pathogenesis of drug-induced pancreatitis is generally not known. Acute pancreatitis occurring as a result of drug overdose is uncommon.[10, 11] The signs and symptoms of drug-induced pancreatitis are not well defined. Consequently, hypothesised causes include direct intrinsic toxicity, pancreatic duct constriction, cytotoxic, osmotic, pressure, or metabolic effects of medicines. When there is damage to the acinar cells or injury to the pancreatic duct it can lead to inappropriate accumulation and activation of proenzymes within the pancreas. The activated pancreatic enzymes digest the cell membranes of the pancreas and activate an inflammatory response, which increases the vascular permeability of the pancreas. This can further lead to haemorrhage, edema, ischemia, and necrosis.[10, 12] Drug-induced pancreatitis has azathioprine as one of its known causes. Rarely occurring acute necrotizing pancreatitis caused by azathioprine is thought to have an idiosyncratic aetiology. The possible pathophysiological

hypothesis include destruction of acinar cell by either activation of circulating vasoactive mediators or by formation of microthrombi or by direct injury of capillary endothelium.[13] Most indications and symptoms of this adverse reaction disappear quickly within a time frame of 1 to 11 days following the drug's withdrawal. It often begins after a latent period of 3 to 6 weeks following drug exposure.[14,15] Prednisolone is a synthetic glucocorticoid and a form of the cortisol steroid hormone. Compared to other steroids, prednisolone users had a 41% higher risk of developing acute pancreatitis. It has been suggested that steroids may impact the pancreas by making pancreatic secretions more viscous and delaying emptying. Reports that successfully identify steroids as the initiating factor are extremely rare, and a delay in the condition's definitive diagnosis might result in complications and an extended hospital stay.[5] In order to treat primary ITP, thrombopoietin receptor agonists such as romiplostim and eltrombopag represent a novel strategy. Eltrombopag is a non-peptide, oral thrombopoietin receptor antagonist that promotes platelet production by binding to a transmembrane location on the receptor. When Eltrombopag was used to treat chronic secondary ITP, pancreatitis occurred in 1% of all subjects.[6]

Table 1: Amylase values deranged during exposure.

Exposure status	Amylase values
During exposure to suspected drugs	126.3 U/L
After drugs are withdrawn (non-exposure)	51.1 U/L

CONCLUSION

This case report elucidates the potentiality of either any one among Azathioprine, Elthrombopag, Prednisolone or a combination of these three drugs to cause acute, severe necrotizing pancreatitis because of the probable association between the administration of the drugs, the onset of symptoms, the improvement of clinical symptoms, and the resolution of abnormal laboratory parameters when the drugs were stopped.

ACKNOWLEDGEMENT

The authors would like to express our sincere gratitude to the Department of Clinical Haematology, Department of Gastroenterology, Department of Radiology, Believers Church Medical College Hospital, Thiruvalla and Department of Pharmacy Practice, Nazareth College of Pharmacy, Thiruvalla for their immense support and guidance in reporting this case.

CONFLICTS OF INTEREST

There are no conflicts of interest.

ABBREVIATIONS

DIP- Drug induced pancreatitis
ITP- Immune thrombocytopenic purpura
USG- Ultra sonogram
CECT - Contrast Enhanced Computerised Tomography
CTSI - CT Severity Index
NPO - Non Per Oral

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