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A Rare Case of Cotrimoxazole Induced Acute Pancreatitis, Acute Kidney Injury and Crystalluria (APAKIC).

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ABSTRACT

Cotrimoxazole (TMP/SMX) is the drug of choice for treating Pneumocystis Jeroveci pneumonia (PJP) in retroviral infections. Incidence of Co-trimoxazole causing pancreatitis and kidney injury being extremely rare, adverse drug reaction (ADR) monitoring is warranted. A 50 year old female newly diagnosed patient with HIV1 positive was treated with TMP/SMX for pneumocystis pneumonia. A total of 3 tablets each containing 800mg sulfamethoxazole and 160 mg trimethoprim thrice daily for 24 days along with intravenous injection once daily for 6 days was given. Three adverse drug reports were reported. Rise in serum amylase/lipase suggesting acute pancreatitis and rise in urea, creatinine and electrolytes suggesting acute kidney injury was observed along with crystalluria. As a part of intervention the drug was stopped, 5% dextrose along with sodium bicarbonate were given. Kidney injury and crystalluria resolved, pancreatitis is still resolving. All ADRs were classified as probable according to Naranjo scale, moderately severe according to Hartwig's scale. The kidney injury is preventable and acute pancreatitis and crystalluria are not preventable according to Schumock and Thornton scale .This case demonstrates a causal relationship between TMP/SMX and above mentioned adverse events. Hence, it is prudent enough to exercise caution when using Cotrimoxazole.

Keywords: APAKIC, Cotrimoxazole, Pancreatitis, Crystalluria

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INTRODUCTION

Human immunodeficiency virus (HIV) infection is estimated to have a prevalence of 0.36%, with 2.5 million people living with HIV in India [1]. Pneumocystis Jeroveci pneumonia (PJP), a common opportunistic infection manifests in a HIV infected patient when the CD4 count is less than 200 cells/cumm. Cotrimoxazole is the drug of choice for prophylaxis and treatment of PCP.

Incidence of drug induced pancreatitis and nephrotoxicity is 0.1 to 2% and 20% respectively [2, 3] based on random case reports. Incidence of drug induced adverse reactions escalates to almost 40 % in patients receiving anti –retroviral therapy (ART) along with other drugs [4]. Cotrimoxazole, a usually well tolerated drug has many side effects, some of them are life threatening such as renal failure, hepatic failure and hypersensitivity. We report a unique case of cotrimoxazole induced acute pancreatitis and acute kidney injury along with crystalluria in a newly diagnosed HIV positive patient not on ART which differs from the above.

Case Report

Fifty year old Asian Indian came with the complaints of fever with, myalgia, fatigue and productive cough. She did not have any significant past history. She was admitted with signs of oral candidiasis and auscultation revealed bilateral crepitation. In view of acute respiratory distress syndrome (ARDS) a chest X-ray was taken which revealed consolidation (Figure 1). A CT scan was done to confirm it which showed ground glass appearance in peri-hilar region and both the lower lobes strongly suggesting PJP (Figure 2). Hence, evaluation for HIV was done and she was diagnosed as HIV positive with CD 4cell count -141 cells/cumm. She was started on cotrimoxazole orally, three tablets, three times a day, each tablet containing 800 mg of sulfamethoxazole and 160 mg of trimethoprim.

On 23rd day acute pancreatitis and renal failure were suspected when the patient complained of nausea vomiting and abdominal pain with epigastric tenderness. Baseline investigations revealed elevated serum amylase, serum lipase and CT abdomen (Figure 3) suggestive of acute pancreatitis and increased serum urea, serum creatinine and suggestive of acute kidney injury as depicted in Table 1. Urine analysis revealed crystals suggestive of crystalluria. Cotrimoxazole induced acute pancreatitis and acute kidney injury along with crystalluria was considered as the probable cause. As a part of medical management cotrimoxazole was stopped, 5% dextrose with sodium bicarbonate was given and patient was kept on nil per oral. Renal parameters returned to normal, serum amylase and serum lipase continued to remain elevated.

A newly diagnosed HIV positive, female patient, not started on ART, developed acute pancreatitis along with acute kidney injury and crystalluria as a consequence of receiving cotrimoxazole for 24 days, ultimately requiring the discontinuation of cotrimoxazole.

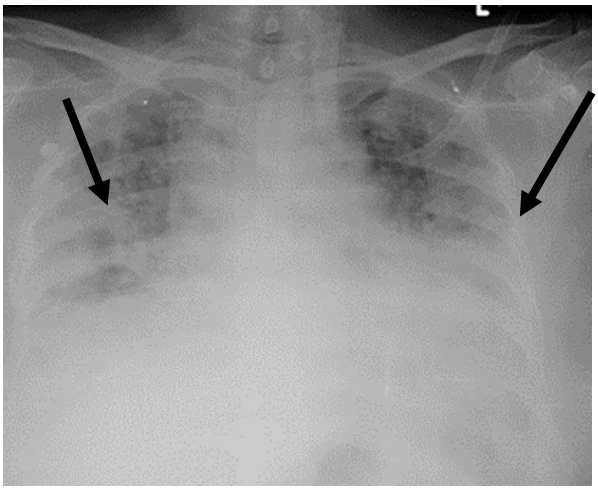

Figure 1: CHEST X-RAY- Bilateral consolidation of lungs.

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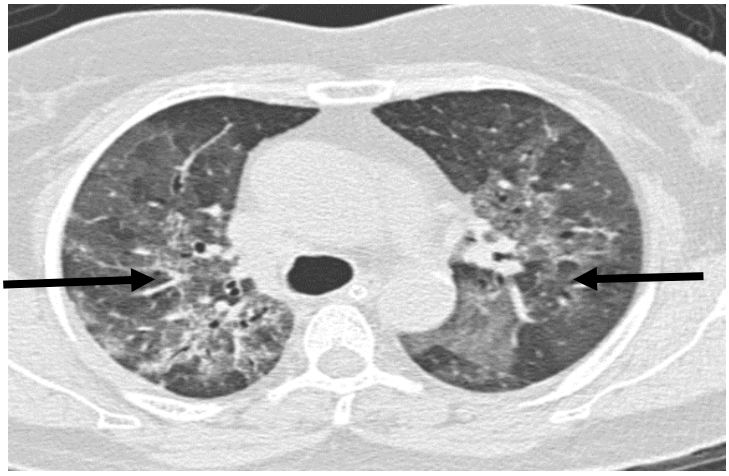

Figure 2: CT- CHEST – Bilateral ground glass opacity

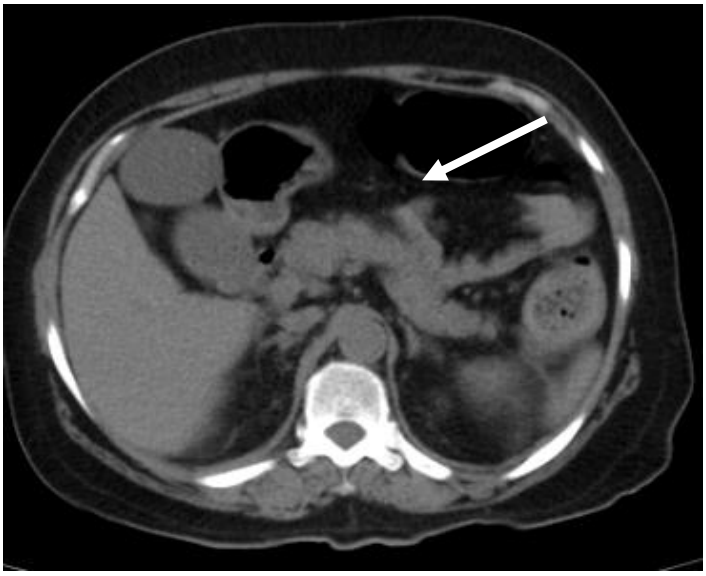

Figure 3: CT –ABDOMEN shows focal necrosis of pancreas

Table 1: Laboratory values

Dates	Sodium	Potassium	Urea	Creatinine	Amylase	Lipase
19/08/2015	129meq/L	4.8meq/L	31mg/dl	1.0 mg/dl	264IU/L	508IU/L
22/09/2015	120meq/L	6meq/L	54mg/dl	2.7 mg/dl	340IU/L	259IU/L
28/09/2015	130meq/L	3.4meq/L	29mg/dl	1 mg/dl	389IU/L	533IU/L

DISCUSSION

Acute pancreatitis is an inflammatory disorder, common aetiology being alcohol consumption, gall stones and obesity, with a characteristic clinical presentation of radiating epigastric abdominal pain. Mortality of acute pancreatitis ranges from 1 to 30 percent based on its severity. Drug induced pancreatitis is a diagnosis of exclusion. Incidence of drug induced acute pancreatitis is low, reason being unawareness of this condition by the clinicians and under reporting of the cases5. Kidneys are the major route for drug excretion, therefore drug induced kidney injury is not uncommon, incidence being 20 -60 percent which depends on various factors such as age and co-morbid medical conditions. Aki due to Bactrim is seen in 10% of patients and crystaluria in 10.8 % of people with AKI [9].

Cotrimoxazole is a drug containing fixed dose combination of sulfamethoxazole and trimethoprim in the ratio of 1:5, used in the treatment of Methicillin - resistant Staphylococcus aureus (MRSA), respiratory and urinary tract infections. Its use in HIV patients is well established, both for the prophylaxis and treatment of PCP. This patient, a newly diagnosed HIV positive not started on ART developed cotrimoxazole induced acute pancreatitis, acute kidney injury along with crystalluria after 26 days of receiving it. The incidence of drug induced pancreatitis increases among HIV patients on ART6. This is an uncommon case because the patient was not on ART or other antibiotics, with no history of alcohol abuse, gall stones, hyperlipidaemia, autoimmune disorders, vasculitis, sepsis, crush injury, surgery and use of contrast agents, therefore making cotrimoxazole the culprit in causing acute pancreatitis and acute kidney injury along with crystalluria.

The probable mechanisms for drug induced pancreatitis are ductal obstruction, accumulation of toxic metabolites and hypersensitivity whereas for acute kidney injury they are impairment of glomerular, tubular function and crystal nephropathy. Crystalluria was confirmed with crystals in urine, sulfamethoxazole component of trimethoprim is responsible for causing crystal nephropathy [7].

As depicted in Table: 2 , all three adverse reactions namely acute pancreatitis , acute kidney injury and crystalluria were classified as probable and moderately severe according to Naranjo's scale and Hartwig's scale respectively. According to Schumock and Thornton scale acute pancreatitis and crystalluria are not preventable and acute kidney injury is a preventable adverse reaction. [8]

Table 2: Causality, severity and preventability assessment

Scale	Acute pancreatitis	Acute kidney injury	Crystalluria
Causality assessment *	5-probable	5-probable	5-probable
Severity assessment #	Level 5 (moderate)	Level 5(moderate)	Level 5 (moderate)
Preventability assessment ^	Not preventable	Probably preventable	Not preventable
* Naranjo's scale- >9: Definite, 5-8: Probable, 1-4: Possible # Hartwig's scale- Mild (level 1, 2), moderate (level 3, 4, 5) and severe (level 6, 7) ^ Schumock and Thornton scale- Definitely, probably or not preventable			

CONCLUSION

Apart from opportunistic infections and immunosuppression, drug related adverse reactions are of grave concern among HIV patients. According to literature severity of organ damage increases when other drugs are given along with anti - retroviral therapy. In this patient anti-retroviral therapy was not started and cotrimoxazole resulted in pancreatic and renal damage, therefore monitoring of renal and pancreatic function using routine parameters is essential in HIV patients with PCP not receiving ART. In near future these life threatening adverse reactions could become common hence clinician's awareness and knowledge is a critical need in order to prevent them.

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