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CALCINEURIN CRISIS: A RARE CASE SERIES OF PANCREATITIS AND AKI INDUCED BY CALCINEURIN INHIBITORS.

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ABSTRACT Drug-induced pancreatitis is an uncommon and under-reported cause of acute pancreatitis, with limited evidence supporting the association of many suspected medications. This case series presents two rare instances of acute pancreatitis: one induced by Tacrolimus and the other by Cyclosporine, highlighting these medications as infrequent and poorly documented contributors to this condition. We report two cases of acute pancreatitis linked to immunosuppressive therapy. A 57-year-old female developed pancreatitis one month after starting Tacrolimus for steroid-resistant FSGS, and a 41-year-old male on Cyclosporine for 15 days for aplastic anemia presented with similar features. Clinical, laboratory, and imaging findings confirmed the diagnosis in both cases, with Tacrolimus and Cyclosporine identified as the likely causes after excluding other etiologies. These cases highlight the need for clinicians to consider Tacrolimus and Cyclosporine as potential triggers of acute pancreatitis in patients receiving these treatments and in managing patients with acute pancreatitis.

KEYWORDS : Acute pancreatitis, Calcineurin Inhibitors, Tacrolimus, Cyclosporin, Bulky pancreas, Drug induced acute pancreatitis

INTRODUCTION

Acute pancreatitis is one of the most common causes of patients presenting with abdominal pain with studies suggesting an incidence of 33.7 per 100,000. Approximately, 20% of the patients develop moderate to severe pancreatitis with a mortality rate of 20-40% [1]. Therefore, identifying the cause of pancreatitis becomes paramount for proper management and reduced recurrence rates. Various etiological agents include alcohol, gallstones, hypertriglyceridemia, idiopathic and drug-induced pancreatitis, etc. According to data available, 0.1-2% of total cases of acute pancreatitis are drug-induced with the most frequently reported drugs being mesalazine, azathioprine, tetracyclines, isoniazid, macrolides, and simvastatin [2]. Tacrolimus is an infrequent cause of pancreatitis and is mostly associated with side effects like neurotoxicity, nephrotoxicity, hepatotoxicity, infections, etc. Similarly, Cyclosporine, commonly used as an immunosuppressant, is associated with nephrotoxicity, hypertension, dyslipidemia, and increased infection risk [3]. However, cyclosporine-induced pancreatitis is a rare and infrequently reported complication in these patients. Here, we present two cases, a case of Tacrolimus-related pancreatitis and another of Cyclosporin-induced pancreatitis.

Case Presentation 1

The patient is a 57-year-old female who presented with a 4-day history of severe, stabbing epigastric pain radiating to the back associated with vomiting. Fever, jaundice, loose stools, obstipation, or constipation did not accompany the pain. She has a known history of Focal Segmental Glomerular Sclerosis (FSGS) for 1 year, previously treated with T. Methylprednisolone. One month ago, she was diagnosed with steroid-resistant FSGS and was started on T. Tacrolimus. At presentation, she was on T. Tacrolimus 3 mg twice daily. On examination, the patient had tenderness in the epigastric region. The remaining systemic examination was unremarkable.

Laboratory tests revealed elevated levels of amylase (405 IU/L) and lipase (3077 IU/L), consistent with a diagnosis of pancreatitis. A computed tomography (CT) scan of the abdomen confirmed this, showing marked peripancreatic fat stranding (Figure 1). Common causes of pancreatitis, such as alcohol use, hypercalcemia, hypertriglyceridemia, and gallstones, were excluded. Anti-nuclear antibody (ANA) was negative. The patient was a non-smoker and non-alcoholic, and a non-contrast computed tomography (NCCT) abdomen revealed a normal biliary tract with no extra-hepatic biliary obstruction or gallbladder issues. Tacrolimus was identified as the likely cause of pancreatitis, though its levels couldn't be measured due to the unavailability of this facility in our hospital. The drug was discontinued, and the patient showed clinical and biochemical improvement.

The patient's urea and creatinine levels were elevated at presentation and urinary spot sodium was 54 mEq which indicated renal cause of acute kidney injury (AKI). Urine routine microscopy was normal ruling out urinary tract infection (UTI). However, urea and creatinine gradually normalized during the hospital stay (Table 1) after discontinuing the offending drug T. Tacrolimus.

The patient was treated with intravenous fluids and analgesics, and T. Tacrolimus was discontinued. Her abdominal pain resolved, and she was discharged with instructions to follow up on an outpatient basis.

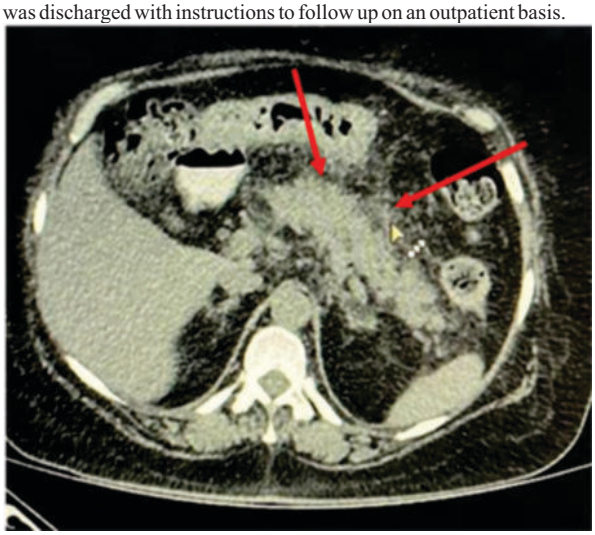

Figure 1- Marked Peripancreatic Fat Stranding.

Table 1- Lab Investigations Of The Patient

Laboratory Investigations	DAY 1	DAY 3	DAY 5	DAY 7
Cholesterol	96			
HDL cholesterol	29			
LDL Cholesterol	40			
Triglycerides	61			
Urea (15-45 mg/dl)	200	226	145	14
Creatinine (0.8-1.8 mg/dl)	5.1	3.8	2.2	0.8
Calcium (8-10.4 mg/dl)	9.0	9.5	9.6	7.4
Phosphorus (2.5-4.5 mg/dl)	6.0	4.9	3.4	3.7
Amylase (20-125 IU/L)	405			
Lipase (20-60 IU/L)	3077			
Urine spot sodium (mEq)	54			

Case Presentation 2

A 41-year-old male patient who is a known case of aplastic anaemia and has been taking T. Cyclosporine 100 mg twice daily for the last 15 days. He presented to emergency department with severe epigastric pain radiating to his back for the past 2 days associated with multiple

episodes of vomiting. There was no history of fever, alcohol intake, trauma to abdomen or jaundice.

On physical examination, vital signs showed a body temperature of 37°C, a blood pressure of 110/60 mmHg, and tachycardia (heart rate of 120 beats per minute). In addition, he had epigastric tenderness.

Initial laboratory tests revealed an elevation of serum amylase level (203 IU/L) and lipase levels (256 IU/L). Complete blood count showed pancytopenia and his serum electrolytes, and liver functions were normal. However, his renal functions were dearranged with raised urea and creatinine indicating AKI as shown in Table 2. Urine spot sodium was sent which was 68 mEq/L suggesting renal cause of AKI. Ultrasonography of the abdomen suggested a bulky heterogenous pancreatic head. So, a diagnosis of acute pancreatitis was made. Thorough workup for causes of pancreatitis, such as hypercalcemia, hypertriglyceridemia, gallstones, and autoimmune causes were excluded. The ANA was negative. The patient was a non-smoker and a non-alcoholic (ruled out alcohol as a cause), with no history of trauma to the abdomen and fever ruling out traumatic and infectious causes respectively. A CECT abdomen revealed a bulky pancreatic body and tail with peri pancreatic fat stranding with a normal biliary tract with no extra-hepatic biliary obstruction or gallbladder issues as shown in (Figure 2).

Cyclosporine was identified as the likely cause of pancreatitis, though its levels couldn't be measured due to the unavailability of this facility in our hospital. The drug was discontinued, and the patient showed clinical and biochemical improvement.

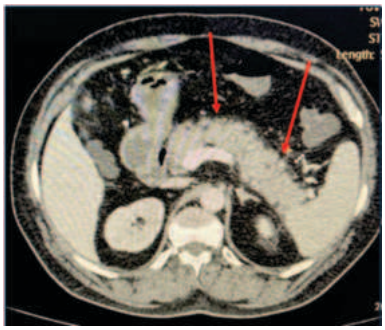

Figure 2- Bulky Pancreatic Body And Tail With Peripancreatic Fat Stranding

Table 2- Lab Investigations Of The Patient

Laboratory Investigations	DAY 1	DAY 3	DAY 4	DAY 5	DAY 6
Haemoglobin [Hb] (12-16 mg/dl)	6.5	6.7	7.0		
Total Leucocyte Count [TLC] (4-11 x 103/dl)	1.5	1.8	2.5		
Platelets count (150-450 x103/dl)	32	37	38		
Triglycerides	81				
Urea (15-45 mg/dl)	99	75	65	45	28
Creatinine (0.8-1.8 mg/dl)	6.4	4.6	2.4	2.0	1.5
Calcium (8-10.4 mg/dl)	8.8	8.3	8.2	8.4	8.3
Phosphorus (2.5-4.5 mg/dl)	4.7	3.6	2.8	3.2	3.1
Amylase (20-125 IU/L)	203				
Lipase (20-60 IU/L)	256				

The patient was treated with intravenous fluids and analgesics, and T. Cyclosporine was discontinued. His abdominal pain resolved. Urea and creatinine gradually decreased after discontinuation of the drug during the hospital stay.

DISCUSSION

A common cause of acute onset abdominal pain, acute pancreatitis can be caused due to multiple etiologies. Most common being alcohol and gallstones-related. Our patients were non-smokers and non-alcoholics with CT abdomen showing normal biliary tract, no extra-hepatic biliary obstruction and gall bladder. Other causes of acute pancreatitis were also similarly excluded, with no laboratory findings suggestive of hypertriglyceridemia, or hypercalcemia.

Drug-induced acute pancreatitis (DIAP) is typically diagnosed by excluding other potential causes.

The old classification system proposed by Mallory and Kern categorized drugs as having either a definite, probable, or possible association with acute pancreatitis depending on the following criteria: 1. The onset of pancreatitis during treatment with the drug, 2. The disappearance of symptoms upon withdrawal of the drug, 3. Exclusion of other causes and 4. Relapse of symptoms upon rechallenge. [4]

Both cases met with 3 out of 4 of the above criteria.

World Health Organization (WHO) has identified over 500 drugs linked to acute pancreatitis as an adverse drug reaction. While most cases of DIAP follow a mild to moderate course, severe and life-threatening instances have also been documented [5].

Tacrolimus-induced acute pancreatitis, sparsely reported, has been seen in males more than females with average age being 43 years [6]. So, case 1 is a unique presentation of DIAP due to Tacrolimus, with the patient being a 57-year-old female, who showed improvement after the drug was with-held. Additionally, only a limited number of case reports have identified cyclosporine as a cause of acute pancreatitis [7]. According to recent literature, cases have steadily increased over time, with a notable rise in recent years, particularly in Tacrolimus-related acute pancreatitis. In comparison, reports of Cyclosporine-induced acute pancreatitis have remained relatively consistent [6].

In addition to their primary presentation, both patients developed acute kidney injury, further highlighting the nephrotoxic potential of calcineurin inhibitors and adding to the growing evidence of their adverse renal effects [8] [9] [10].

The mechanisms of tacrolimus-induced acute pancreatitis may involve immunologic reactions, altered cell metabolism, or infections [6]. Calcineurin inhibitors, including tacrolimus, can cause hyperlipidemia by reducing lipoprotein lipase activity, potentially leading to hypertriglyceridemia, a known risk factor for acute pancreatitis. However, in our cases, both patients lacked hypertriglyceridemia. [11]

The management of Tacrolimus- and Cyclosporine-induced acute pancreatitis began with the immediate discontinuation of the offending drug [12]. Supportive care, including aggressive intravenous fluid resuscitation, pain management with analgesics, and nutritional support. In cases of severe pancreatitis, complications such as necrosis, infection, or organ failure should be closely monitored and managed with targeted interventions, including antibiotics for infections or drainage of fluid collections. Regular follow-up is crucial to assess recovery and prevent recurrence[13].

CONCLUSION

This case series highlights the rare yet severe adverse effects of calcineurin inhibitors, particularly Tacrolimus and Cyclosporine, in inducing pancreatitis along with acute kidney injury (AKI). Both cases underscore the importance of maintaining a high index of suspicion for such toxicities in patients on these medications, especially when common causes are excluded. Early recognition and prompt withdrawal of the offending agent are crucial for reversing these complications and preventing permanent organ damage. Further studies are warranted to understand the underlying mechanisms and risk factors predisposing patients to such dual organ injuries.

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