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A Rare Case of Recurrent Pancreatitis Secondary to Rifampicin in a Patient with Disseminated Tuberculosis

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Abstract: *Background*: Anti-tuberculous drug (ATD) induced pancreatitis is a rare complication of ATDs, but it has serious consequences if it is not managed promptly. Early recognition of ATD induced pancreatitis and identification of the culprit ATD are important approach with subsequent causative drug withdrawal, while at the same time, not impeding the ATD treatment of tuberculosis infection are unquestionably challenging. The objective of this clinical case report is to highlight an unusual case of Rifampicin induced pancreatitis to avoid future delayed diagnosis and management. *Case Report*: A 38 year-old male presented with acute dyspnea and cough. He was diagnosed to have smear positive disseminated tuberculosis infection with pulmonary and urinary system involvement. The intensive regime of ATDs (Rifampicin, Isoniazid, Pyrazinamide and Ethambutol) was started immediately. Nonetheless, he developed acute pancreatitis with severe abdominal pain after 1 week of ATDs therapy initiation. Usual etiologies of pancreatitis were eliminated. He demonstrated clinical improvement and his serum amylase reduced after his ATD regimen was withheld. Once his pancreatitis resolved, he was re-challenged with individual ATD one at a time in order to form an effective ATD regime. However, he developed another 3 episodes of pancreatitis in the following weeks with failed attempts to re-challenge with Rifampicin, which is an important core drug of ATD. Eventually, he succumbed to his severe tuberculosis illness. *Conclusion*: This clinical case is a rare case of Rifampicin induced pancreatitis with an unfavourable outcome. It is essential for clinicians to have a high index of suspicion for ATD induced acute pancreatitis in the patients with active tuberculosis infection and to identify the offending agent promptly without compromising the intensive phase of ATD treatment.

Keywords: Drug Induced Pancreatitis, Rifampicin, Tuberculosis, Withdrawal, Infectious Disease

1. Introduction

The incidence of drug-induced acute pancreatitis is rare, with the reported prevalence of less than 4% [1, 2]. Isoniazid and Rifampicin, which represent the mainstay of ATD treatment regime have been reported to cause drug induced pancreatitis in the past. Early recognition of the culprit agent followed by prompt withdrawal of the drug is paramount to avoid further complications [3-5]. Herein, we report a case of recurrent pancreatitis secondary to Rifampicin in a patient with disseminated tuberculosis.

2. Case Report

A 38 year old male with no prior medical illness, presented with 1 month history of productive cough and 1 week history of worsening shortness of breath. He denied recent consumption of alcohol and traditional medications. On assessment, he appeared cachexic. His vital signs were as follows: blood pressure (BP) 107/64; pulse rate 108/minute; respiratory rate 32; temperature 36.6°C. He required high flow oxygen mask on presentation due to worsening respiratory distress. Clinical and chest radiography imaging (figure 1) revealed he had right sided pneumothorax which

necessitated chest tube drainage. CT imaging revealed tree-in-bud appearance involving bilateral lung fields (figure 2) and incidental findings of pyelitis and urethritis. (figure 3) His sputum and urine samples were positive for acid fast bacilli. These constellation of findings confirmed a diagnosis of disseminated tuberculosis.

The patient was initiated on first line ATD regime upon diagnosis of TB, which consisted of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol (RIPE). One week after ATD introduction, he developed severe abdominal pain, requiring morphine for pain relief. A diagnosis of acute pancreatitis was made based on his elevated serum amylase levels (1498 U/L) and his CT imaging findings of peri-pancreatic fluid collection (figure 4). One of the components of the ATD regime was deduced to be the triggering factor and ATD treatment was therefore withheld, after which his abdominal pain gradually improved.

Throughout his admission, he was monitored daily using the numerical rating scale for assessment of pain recurrence. He had 3 similar episodes of pancreatitis in the ensuing 5 weeks, all which coincided with the reintroduction of Rifampicin. Each episode of pancreatitis was associated with characteristic epigastric pain with raised serum amylase of more than 3 times upper limit of normal values. During each episode of pancreatitis he was managed conservatively by immediately withholding the ATD regimen and thereafter keeping him nil by mouth (NBM) with intravenous hydration and adequate analgesia. Due to the frequency of the bouts of pancreatitis requiring fasting intermittently, total parenteral nutrition was initiated. Octreotide infusion was commenced in an attempt to alleviate clinical symptoms.

A repeat CT abdomen performed 2 weeks after the index episode of pancreatitis, revealed a more organised peri-pancreatic fluid collection which had increased in size measuring 3.3cm X 3.7cm X 2.8cm (AP X W X CC) with concomitant ascites (figure 5). We performed an abdominal paracentesis followed by pigtail drain insertion. The ascitic fluid analysis subsequently revealed an elevated amylase levels (8296 U/L), which was consistent with pancreatic ascites.

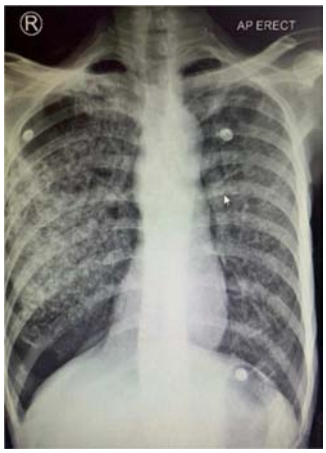

Figure 1. *Chest X-ray shows Bilateral diffuse miliary opacities with right pneumothorax.*

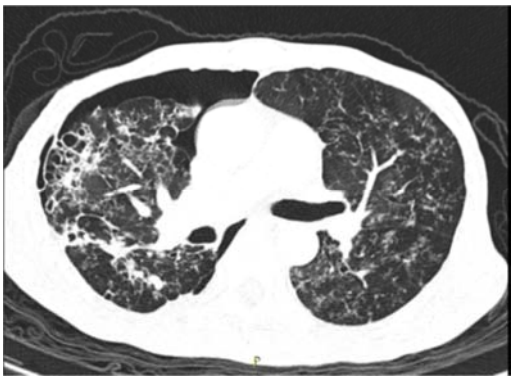

Figure 2. *CT thorax imaging shows tree-in-bud appearance over bilateral lung field with right pneumothorax.*

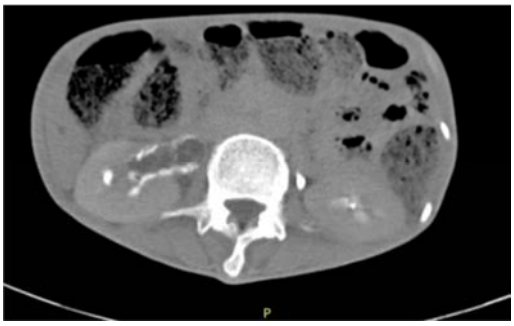

Figure 3. *CT abdomen imaging shows right ureteric calculi causing hydroureter. Enhancement of renal pelvis and ureteric wall suggestive of pyelitis and urethritis.*

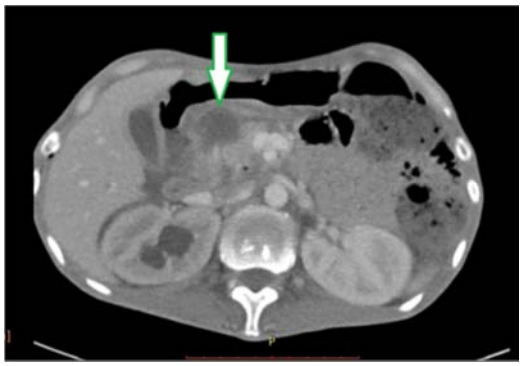

Figure 4. *CT abdomen imaging shows peripancreatic fluid collection.*

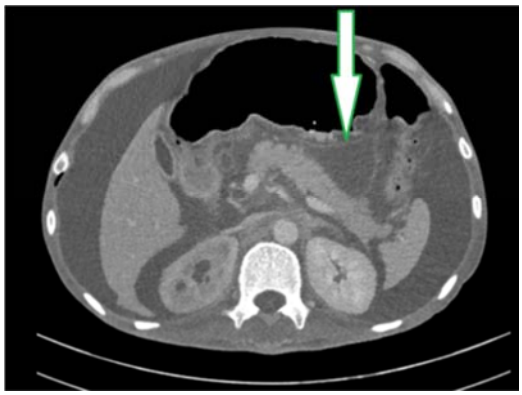

Figure 5. *Repeated CT abdomen imaging shows larger peripancreatic fluid collection measuring 3.3cm X 3.7cm X 2.8cm (AP X W X CC) with concomitant ascites.*

Due to the complex nature of the case, he was planned for transfer to a centre with access to pulmonology and gastroenterology services, however his clinical condition did not permit the transfer. This was further compounded with a deterioration in GCS (Glasgow Coma Scale) 1 month after presentation. It was attributed to TB meningoencephalitis based upon a positive cerebrospinal fluid (CSF) MTB Gene Xpert result. He unfortunately succumbed to his extensive tuberculosis illness shortly after that.

3. Discussion

The incidence of drug-induced acute pancreatitis is rare [1, 2], and should be considered after excluding other causes, such as cholelithiasis, alcohol consumption, infection, tumour, post Endoscopic Retrograde Cholangiopancreatography (ERCP) and abdominal trauma [6, 7].

Since their discovery, Isoniazid and Rifampicin have remained being the first-line drugs of choice in the treatment of tuberculosis [8]. Isoniazid and Rifampicin are the backbone of the ATD regime, and have been rarely implicated as the causes of acute pancreatitis [9, 10]. We present a case of acute pancreatitis secondary to Rifampicin in a patient with disseminated tuberculosis infection.

The state of Sabah bears a disproportionately higher burden of tuberculosis rates in comparison to the rest of Malaysia. 33193 tuberculosis cases were reported in Sabah (128 cases per 100000 population) between 2012 and 2018. In 2018, the tuberculosis case notification rate in the state of Sabah was 47% higher than that of the average national tuberculosis case notification rate of Malaysia [11].

A total of 25 case reports of acute pancreatitis attributed to Rifampicin, and 11 case reports of acute pancreatitis secondary to Isoniazid have been published [9]. Nitsche et al. had summarized 26 cases in which the association of Rifampicin with pancreatitis were definite or probable [1]. Nevertheless, in none of these cases was rechallenge of culprit ATD attempted. In a subsequent review, the same authors, Nitsche et al. incorporated case reports of drug induced acute pancreatitis published between 2003 and 2011, but had found no new cases. As such, the authors had concluded that the association of Rifampicin with pancreatitis as no more than probable. [12]

Following our patient's initial episode of pancreatitis, we suspected that the offending agent was Isoniazid due to its previously reported frequency as a causative agent as opposed to other ATD regimen components. Badalov et al. assigned Isoniazid as class IA in the classification of drug induced pancreatitis, which was implicated in more than 20 reported cases of acute pancreatitis with at least one documented case after re-exposure. Meanwhile, Rifampicin was assigned in class IV, in which neither a re-challenge nor a consistent latency period was established, and only one case report had been published. [13] This case report is unique, because as illustrated, the patient developed pancreatitis following the reintroduction of Rifampicin.

It is conceivable that the development of pancreatic ascites in our patient was a result of pancreatic duct injury owing to the recurrent bouts of pancreatitis. In light of that, this patient should have been managed in a tertiary centre with access to a secretin-enhanced magnetic resonance cholangiopancreatography (s-MRCP) which has a much higher sensitivity and specificity, i.e. 66 and 85%, respectively, than conventional MRCP in the evaluation of pancreatic duct integrity [14-16]. This modality serves as an important road-map prior to consideration of therapeutic intervention such as Pancreatic Duct (PD) stenting. However, as patient's clinical condition did not permit for a transfer to a facility with these modalities, he was managed with a conservative approach of withholding oral feedings, initiation of total parenteral nutrition, insertion of a pigtail drain and administration of octreotide.

Management of ATD induced pancreatitis comprises of early recognition and withdrawal of offending agent in the appropriate clinical setting. [9] In this case, a more appropriate approach would have been to use alternative drugs such as fluoroquinolones or bedaquiline, especially after the first rechallenge resulted in recurrence of symptoms. More studies are needed to help guide the management of ATD induced pancreatitis, especially in patients are suffering from active tuberculosis infection.

4. Conclusion

This is a reported case of acute pancreatitis secondary to Rifampicin in a patient with disseminated tuberculosis infection. It is essential for clinicians to have a high index of suspicion for drug induced acute pancreatitis and to discontinue the offending agent in a timely manner to avoid further complications.

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