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Case Report

Rivaroxaban Induced Acute Pancreatitis-A Case Report

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Abstract

Acute pancreatitis is a medical emergency that has been associated with considerable morbidity and mortality. Alcohol intake and gall stones are two of the major causes of acute pancreatitis. A number of medications are also known to cause acute pancreatitis. Angiotensin converting enzyme inhibitors (ACE-I), statins, hormone replacement therapy, oral contraceptives, diuretics, antiretroviral therapy (HAART), valproic acid and hypoglycemic agents are most commonly implicated drugs in this regard. Rivaroxaban an oral anticoagulant can also, exceptionally, cause acute pancreatitis. Here we describe a case of acute pancreatitis in a patient receiving Rivaroxaban.

Key words: Case report, Rivaroxaban, Acute Pancreatitis.

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Introduction

Acute pancreatitis is a potentially life-threatening clinical condition associated with significant morbidity and mortality. The estimated incidence of acute pancreatitis in England is approximately 56 cases per 100,000 per year.[1] In united States the incidence of acute pancreatitis is 13-45 per 100000 population and comprised over 275,000 hospital admissions in 2009.[2] Gall stones, alcohol intake, hypertriglyceridemia, trauma, hypercalcemia, endoscopic retrograde cholangiopancreatography (ERCP), scorpion venom, smoking, malignancy and infection are the common causes of acute pancreatitis.[3,4]

Various medications are also known to cause acute pancreatitis and are responsible for 0.1-2% cases of acute pancreatitis.[5-7] The majority of these cases are mild but some can progress to severe pancreatitis. Rivaroxaban, an oral direct Factor Xa inhibitor, can also cause acute pancreatitis. It is used for the management of venous thromboembolism and non-valvular atrial fibrillation. Its common adverse effects include bleeding diathesis and generalized body rash. It is also known to have drug interactions with CYP3A4 inducers and inhibitors.[8] Interestingly, acute pancreatitis is an extremely rare adverse effect of this relatively safe drug. Herein we describe a case report of Rivaroxaban induced pancreatitis. Our patient was extensively investigated for any other cause of acute pancreatitis and showed clinical and radiological improvement with cessation of the drug.

Case Presentation

A 46 years old, businessman, married, non-smoker and non-alcoholic presented with history of fever for past 4 days along with severe abdominal pain for 4-5 hours. Fever was low grade and undocumented. Abdominal pain was localized to upper abdomen. It was sudden in onset, severe in intensity, constant, dull aching in nature, radiated to the back and was accompanied by multiple episodes of non-bloody vomiting. He took antacids for relief of pain at home but the pain did not settle.

Patient was a diagnosed case of pulmonary hypertension leading to cor-pulmonale secondary to post tuberculosis lung damage. He was oxygen dependent with long-term oxygen therapy commenced a month before admission. He had deep venous thrombosis of left lower limb one month back for which he was taking Rivaroxaban 20 mg/day..

At presentation, he was distressed and irritable. His pulse was 110/minute, blood pressure 110/80 mmHg, respiratory rate of 26 per minute, and temperature 98.7 F°. He was pale, but not jaundiced. Abdomen was distended and tender in the epigastric area. No

mass or viscera was palpable. Bowel sounds were sluggish. Chest examination revealed fine crepitations in lower and middle part of chest on right side and in upper part on left side. The rest of the physical examination was normal.

He was admitted and managed initially with suspicion of peptic ulcer and acute pancreatitis and was given treatment for his primary medical issues as well. Acute coronary syndrome evaluation was also done that turned out to be negative. Mainstays of treatment included; nil per oral, cautious intravenous fluid administration, intravenous omeprazole, analgesics for pain, Oxygen administration, inhaled bronchodilators, and antibiotics (imipenem/cilastatin 500 mg TDS, injection metronidazole 500 mg TDS). Investigations performed are summarized in Table I and II.

Diagnosis of acute pancreatitis was made on basis of clinical, biochemical, and radiological findings. Standard multi-disciplinary management was continued. Magnetic resonance cholangiopancreatography (MRCP) was performed to rule out choledocholithiasis, biliary sludge and occult malignancy causing acute pancreatitis. This turned out to be unremarkable (Figure 2). Interestingly as there was no other obvious cause of acute pancreatitis like alcohol intake, smoking, dyslipidemia, and hypercalcemia, consideration was given to medications as the possible etiological factor. Rivaroxaban was suspected to be the culprit medication since the patient had been on other medications for a longer duration of time without any complication. Anticoagulation with heparin was instituted keeping in mind bilateral deep venous thrombosis of lower limb. Thrombophilia screening was also done. (Table I)

Patient condition improved both clinically and radiologically with our management, and was discharged on Capsule pancrelipase (enteric-coated) TDS, Injection Enoxaparin 40 mg subcutaneously daily, Capsule Omeprazole 40 mg daily, and Tablet Bosentan 62.5 mg BD along with long term oxygen therapy. Tablet Warfarin subsequently replaced Enoxaparin. Patient has re-commenced his business and is doing well. His final diagnosis was Rivaroxaban induced acute pancreatitis, Tuberculosis related lung damage, pulmonary hypertension, cor-pulmonale, bilateral lower limb deep venous thrombosis.

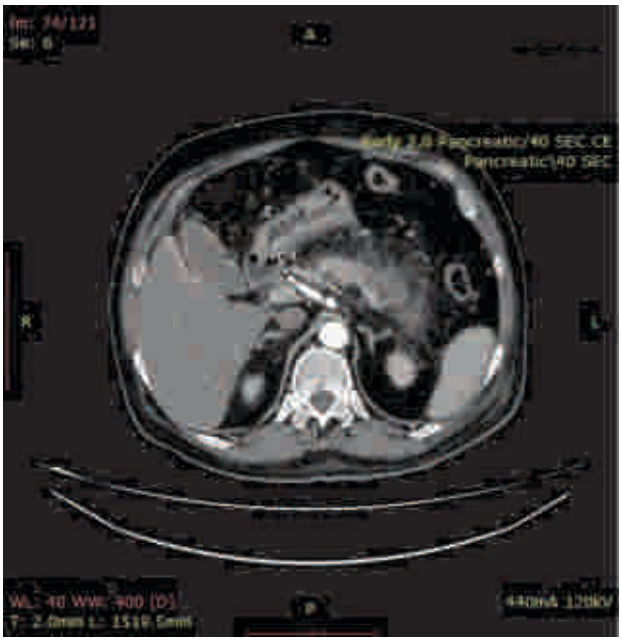

Figure 1: *Contrast Enhanced CT Abdomen Showing Necrosis in Head and Body*

Table 1: *Summary of the Imaging Studies Performed on Admission*

Test	Timing	Report
Ultrasound abdomen	At admission in emergency room	Liver span 15 cm, mildly raised echogenicity, portal vein diameter 11 mm, common bile duct diameter 3 mm, contracted gall bladder, bilateral grade I-II echogenic kidneys
Ultrasound Abdomen	Four days post admission	Portal vein diameter 7 mm and common bile duct diameter 3 mm, normal liver echogenicity and a streak of fluid in Morrison's pouch.
Contrast enhanced CT abdomen/pelvis	04/02/2019	Acute necrotizing pancreatitis with modified CT Scoring Index of 10, fibrocalcific scarring with dilated ectatic vessel in posterior basal segment of right lower lobe: sequelae of previous pulmonary tuberculosis
Venous Doppler Lower Limbs. Technique: Duplex imaging with color flow scanning for venous system of both lower limbs along with gray scale imaging using high resolution linear probe	During admission	Partial echogenic thrombus in common femoral veins extending into great saphenous veins bilaterally, the veins were non compressible and showed partial flow on Doppler, popliteal veins appeared normal.

Table 2: *Summary of the various laboratory investigations*

Test	Normal range	30/3/2019	01/04/2019	03/04/2019
CBC				
Leukocyte count	4-10 × 10^9	8.1	7.8	
Hemoglobin	13-18 mg/dl	10.0	9.8	
Hct	41-45 l/l	37.5	32.3	
MCV	78-96 fl	73	98	
MCHC	31.5-355 g/dl	26.6	30.3	
Platelets	150-400 x 10^3	166	370	
ESR			07	
Cardiac Enzymes				
CPK	190 u/l	29.1		
CK-MB	Up to 25 u/l	22.6		
Serum Electrolytes				
Sodium	135-150 mmol/l	132		140
Potassium	3.5-5.0 mmol/l	4.84		5.0
Chloride	98-108 mmol/l	96		99
Liver Function Tests				
Serum Bilirubin	0.2-1.2 mg/dl			0.9
ALT	20-60 IU/L		34	14
ALP	44-147 IU/L		165	126
Renal Function Tests				
Serum Urea	10-52 mg/dl	46	57	51
Serum Creatinine	Up to 1.2mg/dl	1.3	1.2	1.3
Clotting profile				
PT	Control- 13 s	20 s		
Aptt	Control- 36 s	44 s		
D Dimer Test	Less than 200 ng/ml			400
Serum Lipase	Up to 38 U/L	218		29
Serum Amylase	Up to 90 U/L		59	
Lipid Profile				
S. Cholesterol	Up to 200mg/dl			128
S. Triglyceride	35-165 mg/dl			92
S. HDL	35-62 mg/dl			28
S. VLDL	29-92 mg/dl			18
S. LDL	Up to 190 mg/dl			82
Total Lipids	400-1000 mg/dl			550
Cholesterol/HDL Ratio	Less than 5.0			4.5

Discussion

In order to make diagnoses of acute pancreatitis following should be present; 1) severe persistent acute onset epigastric pain often radiating to the back (2) serum lipase (or amylase activity) at least three times greater than upper limit of normal, and 3) characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT) and less commonly on magnetic resonance imaging (MRI) or trans abdominal ultrasonography.[1,3] Our patient had both clinical and CT findings suggestive of acute pancreatitis. His serum amylase and lipase were however not raised up to three-fold. It is to be noted that in many of acute pancreatitis cases serum amylase and lipase may not be raised more than three times the normal. This generally occurs when there is delay between onset and presentation of acute pancreatitis.[4]

Figure 2: *MRCP Image showing normal common hepatic, cystic, common bile ducts as well as pancreatic duct and peri-ampullary region*

For establishing a drug as a possible etiological factor for acute pancreatitis following conditions should be fulfilled; 1) diagnosis of acute pancreatitis, 2) association between start of drug therapy and development of pancreatitis, 3) improvement when the drug is discontinued, and 4) re introducing the drug provokes a second pancreatitis episode.[5]

Commonest causes of acute pancreatitis as mentioned earlier were absent in our patient. So what could be the possible the cause of pancreatitis in our case? Drug induced or idiopathic pancreatitis were two worth considering causes.

Around five hundred and twenty-five medications are known to cause acute pancreatitis. Of these thirty have been confirmed to cause acute pancreatitis. Highest risk of pancreatitis has been associated with mesalazine, azathioprine, and simvastatin use.[6,9] Interestingly Rivaroxaban in not included in this list.

Bleeding is the commonest adverse effect of Rivaro-

xaban.[5] Acute pancreatitis complicating Rivaroxaban therapy is uncommon but is being increasingly recognized as a possible adverse effect. According to the Food and Drug Authority (FDA) USA, out of 81, 217 Rivaroxaban associated adverse effects 81 (0.09%) were acute pancreatitis. Majority (60.87%) cases of acute pancreatitis are reported within first month of start of Rivaroxaban, and 21.74% in next 1- 6 months. During 2018, thirty cases of Rivaroxaban associated acute pancreatitis were reported.[10]

Pathogenesis of drug induce pancreatitis is unclear and is different for different drugs. As far as Rivaroxaban induced pancreatitis is concerned, it is postulated that it is due to drug interactions with cytochrome P450 inducers or activators.[4,7]

It is worthy to mention that if there is need for ongoing anti coagulation, as was in our patient, other novel oral anticoagulants (NOACs) like apixaban or dabigatran may be started with precaution as they may cause pancreatitis as well. However, in our case apixaban and dabigatran were not available. Hence, the patient was started long acting heparin and subsequently was shifted to warfarin.

Conclusion

Although advent of novel oral anticoagulant (NOAC) has been the harbinger of better and effective anticoagulation therapy, Rivaroxaban induced pancreatitis is a rare but important adverse effect that should be considered in relevant clinical scenario.

Conflict of Interest: None

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References

1. Shah AP, Mourad MM, Bramhall SR. Acute pancreatitis: current perspectives on diagnosis and manangement. J Inflam Res. 2018;11(1):77-85.
2. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterol. 2013; 144(6): 1252-61.
3. Whitecomb DC. Acute Pancreatitis. N Engl J Med. 2006;354(20):2142-50.
4. Mathur AK, Whitaker A, Kolli H, Nguyen T. Acute Pancreatitis with normal serum lipase and amylase:A rare presentation. J Pancr. 2016;17(1):98–101.
5. Jones MR, Hall OM, Kaye AM, Kaye AD. Drug-induced Acute Pancreatitis: A review. Ochsner J. 2015; 15(1): 45–51.
6. Nitsche CJ, Jamieson NM, Lerch MV, Mayerle Jundefined. Drug induced Pancreatitis. Best Pract Res Clin Gastroenterol. 2010;24(2):143–55.
7. Kaurich T. Drug-induced Acute Pancreatitis. Baylor Univ Med Center Proc. 2008;21(1):77–81.
8. Christopoulou EC, Filippatos TD, Elisaf Ms. Non-hemorrhage-related adverse effects of Rivroxaban. Arch Med Sci Atheroscl Dis. 2017;2 (2):e108–e112.
9. Badalov N, Baradarian R, Iswara K, Li J, Steinberg W. Drug-Induced Acute Pancreatitis:An Evidence-Based Review. Clin Gastroentrol Hepatol. 2007;5 (4): 648–61.
10. Sirkeci Ö, Sirkeci EE, Taşel B. Rivaroxaban-induced acute pancreatitis. Europ Res J. 2019;5(3):569-71.