Author's response to reviews

Title: Case Report: Acute pancreatitis related to therapeutic dosing with colchicine

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Author's response to reviews: see over
Dear Dr Kidd,

I would like to thank Basilios Papaziogas (Reviewer 1) and Ioannis Koutroubakis (Reviewer 2) for their feedback on “Acute pancreatitis related to therapeutic dosing with colchicine,” being considered for publication as a Case Report in Journal of Medical Case Reports.

I have tried to respond to their comments, starting from page 2 of this Cover Letter.

Acute gout is a frequent condition that is treated with colchicine. Due to its widespread cytotoxicity, colchicine has a narrow therapeutic window, and its dose limiting side effects include diarrhoea and vomiting. In overdose, it is frequently lethal.

Although acute pancreatitis related to colchicine overdose has rarely been reported, pancreatitis has not been known to occur with therapeutic colchicine dosing. Toxicity, including acute pancreatitis, is more of a risk with impaired drug clearance, especially in the elderly. The confluence of frequent gout in an increasingly aging population being treated with colchicine may result in greater burden of toxicity including pancreatitis.

This manuscript has not been submitted to any other journal in any medium.

I look forward to hearing again from Journal of Medical Case Reports.

Yours sincerely

Dr Joseph Ting
Response to Reviewer 1 Comments:

1. The relation between acute pancreatitis and colchicine appears to be correlative.

I agree with this; as such, paragraph 3 p 5 and paragraphs 1-3 p 6 have been added to emphasize that although there is a temporal sequence of acute pancreatitis following the initiation of colchicine therapy, this association is NOT causative as a re-challenge was not carried out and the patient’s chronic renal failure, microlithiasis and frusemide treatment may be implicated as well. However, the patient improved with cessation of colchicine therapy alone and with no change in these other potential aetiological factors.

Paragraph 3 p 5 Identifying the underlying cause of acute pancreatitis allows avoidance or treatment of the precipitant and improves chances of recovery [10]. This patient sustained mild and self-limited acute pancreatitis associated with recent commencement of colchicine for gout, which has not previously been reported. However, comorbidities implicated in acute pancreatitis make a trigger or co-factor role for colchicine more likely [9], rather than colchicine being the sole aetiological agent. In this case, microlithiasis [8], chronic renal failure [10, 11, 14] and frusemide [10] may have set the scene for acute pancreatitis precipitated by colchicine. With a normal bilirubin level however, the patient had liver function tests which were more consistent with a hepatitic rather than an obstructive enzymosis. Furthermore, he did not have hypercalcaemia or hypertriglyceridaemia, metabolic factors well known to contribute to pancreatic inflammation [8, 14].
There was no evidence of acute seroconversion to hepatitis A, B, C viruses; Epstein - Barr virus, Cytomegalovirus and herpes simplex 1 and 2 viruses. As such, acute viral hepatitis or pancreatitis was unlikely. Non-drug aetiologies for pancreatitis in this patient (renal failure, microlithiasis, ongoing use of frusemide) remained; despite this, rapid clinical recovery occurred with withdrawal of colchicine. This renders colchicine the most eminent association to pancreatitis in this case.

Sole attribution for acute pancreatitis to a single drug remains difficult due to high rates of concurrent contributory diseases in acute pancreatitis [9]. Aside from frusemide, of which there had been no recent dose escalation, none of this patient’s other prescribed medications have been reported to increase risk of acute pancreatitis [10, 14]. Nitrates have been known to reduce pancreatitis pain and relapse [13], with diltiazem improving survival in rat models of acute pancreatitis [12].

The Conclusion within the Abstract has also been altered to reflect this causal ambiguity (paragraph 3, p 2): Aside from myelosuppression, myoneuropathy and multiple organ failure, colchicine may now be associated with acute pancreatitis even with therapeutic dosing; this has not previously being reported.
2. The presence of calculi within the gall-bladder cannot exclude the development of pancreatitis on the grounds of ductal calculi.

I agree with the reviewer’s comments here. Transabdominal ultrasonography is more sensitive than either CT or MRI for identifying gallstones and detecting bile duct dilatation, but it is insensitive for detecting stones in the distal bile duct [8]. However, USS is often the first choice investigation for hepatobiliary problems in most hospitals [10]. MRCP and endoscopic USS were not performed as the patient improved clinically with withdrawal of colchicine. A normal bilirubin and hepatic rather than obstructive enzymosis would argue against an obstructing distal ductal stone.

3. Exclusion of other known causes of pancreatitis: The patient was a life long non-drinker, had a normal serum calcium and triglyceride level. Except for frusemide, of which there was no recent dose escalation, none of his other regular medications have been associated with pancreatitis.

4. The Discussion is now more fully developed, focusing on difficulties in sole attribution of pancreatitis to colchicine and other aetiological factors at play.

5. Liver function tests are now fully reported in the latter half of paragraph 2, p 4.

6. The Case Report has now been reported in the past tense.
Response to Reviewer 2 Comments:

1. CRF is now acknowledged as a potential contributor to pancreatitis in this Case Report (paragraph 3, p 5).

Identifying the underlying cause of acute pancreatitis allows avoidance or treatment of the precipitant and improves chances of recovery [10]. This patient sustained mild and self-limited acute pancreatitis associated with recent commencement of colchicine for gout, which has not previously been reported. However, comorbidities implicated in acute pancreatitis make a trigger or co-factor role for colchicine more likely [9], rather than colchicine being the sole aetiological agent. In this case, microlithiasis [8], chronic renal failure [10, 11, 14] and frusemide [10] may have set the scene for acute pancreatitis precipitated by colchicine.

2. Absence of re-challenge was not carried out. This was indeed the case, but cessation of colchicine with no alteration in other potential aetiological factors was associated with rapid recovery, implicating colchicine pre-eminently.

3. MRI and MRCP was not done: Transabdominal ultrasonography is more sensitive than either CT or MRI for identifying gallstones and detecting bile duct dilatation, but it is insensitive for detecting stones in the distal bile duct [8]. However, USS is often the first choice investigation for hepatobiliary problems in most hospitals [10]. MRCP and endoscopic USS were not performed as the patient improved clinically with withdrawal of colchicine.

Ultrasound is the preferred investigation for biliary disease [10]. Magnetic Resonance Cholangio-Pancreatography and endoscopic ultrasound may offer
diagnostic advantages over upper abdominal ultrasound and CT upper abdomen, but the latter two imaging modalities are the first recommended tests in most hospitals [10]

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