A CASE REPORT OF AN END-STAGE RENAL FAILURE PATIENT WITH PEPTIC ULCER DISEASE

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ABSTRACT

A 64-year-old man with a background of chronic kidney disease (CKD) was admitted to hospital for symptoms of uraemia and was subsequently initiated on haemodialysis (HD). On day 13 of HD, he developed per rectal bleeding with a significant drop in his haemoglobin (Hb) level. Oesophagoduodenoscopy (OGD) was performed and showed several antral and duodenal ulcers. Colonoscopy was unremarkable. He was started on high-dose PPI and his Hb level remained stable with no recurrence of symptoms. This case report highlights the association between HD and the increased risk of developing peptic ulcer disease (PUD) in patients with end-stage renal failure. Abdominal symptoms are common in the primary care setting and it is crucial for family physicians to be able to recognise the red flags of PUD in this group of high-risk patients as timely referral and intervention reduces morbidity and mortality.

Chronic Kidney Disease; End-stage Renal Failure; Haemodialysis; Peptic Ulcer Disease;

INTRODUCTION

Peptic ulcer disease (PUD) is a common condition among patients who are elderly and those with multiple comorbidities. *Helicobacter pylori* infection and the use of non-steroidal anti-inflammatory drugs (NSAIDs) are the primary causes of PUD in the general population.[1] However, patients with chronic kidney disease (CKD) have distinct causative factors and studies have also demonstrated that CKD patients have a higher risk of peptic ulcer bleeding and bleeding-related morbidity and mortality.[2-4] We report a case of PUD in a patient with end-stage renal failure (ESRF) who was newly initiated on dialysis.

PATIENT'S REVELATION: WHAT HAPPENED?

Mr T was a 64-year-old single gentleman, who stayed alone in a one-room rental flat and was premorbid ADL independent and community ambulant without aid. He had a background medical history of type 2 diabetes mellitus, hypertension, hyperlipidaemia, ischaemic heart disease (for which he

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underwent coronary artery bypass grafting in 2005), and chronic kidney disease. His medications comprised insulin Mixtard 20U pre-breakfast and 10U pre-dinner, aspirin 100mg OM, bisoprolol 5mg OM, losartan 50mg OM, atorvastatin 40mg ON, and omeprazole 20mg OM. Apart from the listed medications, he denied use of non-prescribed medications such as traditional Chinese medicine, steroid or NSAID. On further questioning, he volunteered a history of recent hospital admission six months earlier for acute gastroenteritis complicated by oliguric acute on chronic kidney disease and rhabdomyolysis which improved after treatment. He was a non-smoker and non-drinker.

Mr T was admitted this time for two weeks' history of lethargy and vomiting. He did not seek medical attention until he was noticed by his cousin to be slightly drowsy and unable to tolerate orally. On arrival at the emergency department, he was lethargic but haemodynamically stable. Systemic examinations revealed a mildly tender abdomen with otherwise normal bowel sound, and no guarding or rebound tenderness. Per rectal examination was unremarkable. There was no sign of fluid overload.

Blood tests done on admission showed a significantly raised serum creatinine of 929umol/L (up from 400umol/L 6 months earlier). Other significant blood results were raised serum amylase and lipase. His haemoglobin level on admission was 12.1mmol/L.

Mr T was immediately initiated on sustained low-efficiency dialysis (SLED) in the Renal High-dependency Ward on the day of admission. He was also found to have acute on chronic pancreatitis secondary to gallstone disease as confirmed by CT abdomen and pelvis, and magnetic resonance cholangiopancreatography (MRCP) which were ordered to investigate the raised serum amylase and lipase although he denied having previous history of pancreatitis or symptoms suggestive of that. He was planned for interval cholecystectomy at a later date after review by the surgical team.

After a few days of hospitalisation, Mr T showed significant improvement both clinically and biochemically. He was more alert, had increased appetite and had improvements in his mobility and function. He was continued on regular haemodialysis three times a week in the ward via a vascular catheter and tolerated it well.

While waiting for community dialysis placement, he developed per rectal bleeding on day 13 of HD. The medical team noted stale blood stains on his trousers, however he did not notice passing blood in the stools or malaena since admission. Apart from that, he was asymptomatic with no symptoms of abdominal pain, recent changes in bowel habit,

loss of appetite, or loss of weight. There was no previous history of peptic ulcer disease and gastrointestinal bleeding nor family history of gastrointestinal malignancy. No recent steroid, traditional Chinese medication or NSAID use was identified. Digital rectal examination revealed minimal dried blood with external piles. Initial impression was per rectal bleeding, likely secondary to haemorrhoids. After a review by the colorectal team, he was scheduled for an elective colonoscopy in a week's time. Aspirin was held off.

However, a full blood count done on the next day showed significant haemoglobin drop from 10.5mmol/L a week earlier to 4.8mmol/L. A repeat FBC reconfirmed this. Mr T also started to notice stale blood in his stools but was otherwise haemodynamically stable. He was transfused with 3 units of packed red blood cells.

An urgent OGD performed the next day revealed several clean-based antral and duodenal ulcers. CLO test for H. pylori was negative. Colonoscopy showed a few benign polyps in the sigmoid colon and hepatic flexure. He was started on high-dose oral omeprazole and his haemoglobin level remained stable over the next few days with no more symptoms of per rectal bleed. He was subsequently discharged well with long-term outpatient haemodialysis and oral omeprazole 40mg BD. Aspirin was held off and to be reviewed again in a colorectal outpatient appointment after a repeat scope.

GAINING INSIGHT: WHAT ARE THE ISSUES?

This case highlights several issues for discussion:
1. Are patients with CKD at higher risk of developing PUD?
2. Does HD increase the risk of PUD in patients with ESRF? If so, do patients on peritoneal dialysis (PD) have similar risk?
3. How should we manage PUD in a patient undergoing HD, and when should antiplatelet agents be restarted?

DISCUSSION

The global incidence of PUD is between 0.10 – 0.19 percent per year and prevalence 0.12 – 1.50 percent per year.[5] It is a common condition worldwide, contributing to 28-59 percent (duodenal ulcer 17-37% and gastric ulcer 11-24%) of acute non-variceal upper gastrointestinal bleeding.[6-7] The two main causative factors for PUD are *H. pylori* infection and NSAIDs consumption. Other risk factors include smoking, severe physiological stress, systemic corticosteroid use, and hypersecretory states such as Zollinger-Ellison syndrome.

A 10-year retrospective cohort study in Taiwan compared the incidence of PUD among non-CKD, non-dialysis CKD and ESRF patients receiving different modalities of dialysis. Compared with non-CKD matched controls, non-dialysis CKD patients and those on PD were at higher risk of developing PUD, (hazard ratio [HR] 3.99, 95% CI 2.24 – 7.13 and 3.71, 95% CI 2.00 – 6.87 respectively). But patients who received HD carried the highest risk (HR 11.96, 95% CI 7.04 – 20.31).[8] Another similar study also yielded similar conclusions.[9]

One of the reasons for the above trend could be due to the fact that compared to non-CKD patients, non-dialysis CKD and ESRF patients have increased risk of bleeding from uraemia-related platelet dysfunction, impaired platelet-vessel wall interaction, and abnormalities in blood coagulation.[10-11] Delayed gastric emptying associated with CKD may also contribute to the development of PUD.[12] As for patients on HD, the anticoagulant use during HD is postulated to be one of the contributing factors for the increased risk of PUD in ESRF patients after the commencement of HD. Other possible reasons include intra-dialysis hypotension during HD which induces splanchnic hypoperfusion and subsequent gastrointestinal mucosal ischaemia with impaired healing.[9] This is often worsened by concurrent acute illnesses such as sepsis and acute coronary syndrome.

What about the use of anti-platelet drugs? Studies showed that the use of ulcerogenic medications such as NSAIDs and clopidogrel further increases the risk of PUD in CKD patients although CKD patients receiving aspirin were not at significantly higher risk.[9] Nevertheless, aspirin is still known to be one of the important causes of PUD in the general population of developed countries.[13] The risk of bleeding is further increased by combining other anti-platelet drugs with aspirin.[14]

Clinical Presentations

CKD patients with PUD may have more adverse outcomes and carry higher morbidity and mortality. It is thus important for doctors, including primary care physicians, to be able to identify the alarming features or "red flag" signs of PUD. Epigastric pain, dyspepsia, and heartburn are some of the commonest presenting complaints. Typical symptoms include episodic gnawing or burning epigastric pain; pain occurring two to five hours after meals or on an empty stomach; and nocturnal pain relieved by food intake, antacids, or antisecretory agents. However, some patients may be asymptomatic and in uncomplicated PUD the clinical findings are few and nonspecific.

Some of the alarming signs that warrant prompt referral include acute bleeding, anaemia, early satiety, unexplained weight loss, progressive dysphagia, recurrent vomiting, and family history of gastrointestinal cancer. Ulcer perforation should be suspected in those who develop a sudden onset of severe sharp abdominal pain, and abdominal examination usually discloses generalised tenderness, rebound tenderness, guarding, or rigidity.

Lessons from Mr T's Case

In this case, Mr T's age, background medical comorbidities such as CKD, the use of aspirin for secondary prophylaxis for ischaemic heart disease, and the initiation of HD put him at higher risk for developing PUD. Accurate and early identification of high-risk patients is important as it allows for early intervention and management which may improve their outcomes. Although per rectal bleeding often represents

bleeding from the lower gastrointestinal tract, bear in mind that massive upper gastrointestinal haemorrhage can also present with per rectal bleeding.

MANAGEMENT

Screening for risk factors such as NSAID use or a history of *H. pylori* infection is important when diagnosis of PUD is suspected. OGD is the preferred and most accurate diagnostic test in the evaluation of patients with suspected PUD as it allows for biopsies of suspicious lesions and detection of *H. pylori* infection with a rapid urease test. Other options for *H. pylori* detection include the urea breath test and stool antigen test. However, patients who are on proton pump inhibitors (PPIs) can have false negative breath and stool tests. Serologic tests may only be useful in mass population surveys and in patients who cannot stop taking PPIs (e.g. those with gastrointestinal bleeding or continuous NSAIDs use) because these tests are not affected by PPI or antibiotic use.[15]

Eradication of *H. pylori* Infection

All patients with PUD should be tested for infection with *H. pylori* and treated. First-line therapy should have an eradication rate of more than 80 percent.[16] In patients with uncomplicated *H. pylori*-positive ulcers, recommended first-line treatment is triple therapy with a PPI, amoxicillin and clarithromycin for 7 to 14 days. Because amoxicillin and clarithromycin are primarily eliminated in the kidneys, their doses should be reduced in CKD patients based on their creatinine clearance. If patients are on HD, the dose should be taken after dialysis. The efficacy of a low-dose triple therapy (omeprazole 40mg once daily, amoxicillin 500mg once daily and clarithromycin 500mg once daily) achieved 83.4 percent eradication of *H. pylori* in HD patients and was concluded to be safe and effective.[17] Metronidazole can be substituted for amoxicillin in penicillin-allergic patients and renal adjustment is not necessary.

Quadruple therapy is suggested for re-treatment in non-CKD patients who fail triple therapy, or as initial treatment in areas where clarithromycin resistance is high, or in patients with recent or repeated exposure to clarithromycin or metronidazole.[16] It consists of a PPI combined with bismuth subsalicylate and two antibiotics (metronidazole and tetracycline) for 14 days. However, in patients with renal impairment, bismuth subsalicylate should not be used as the accumulation of their cations due to reduced renal clearance can cause neurotoxicity, neuromuscular spasm and weakness, gastrointestinal complications, and hearing loss.[18] The dose of tetracycline in CKD and dialysis has to be renal adjusted as well. In the event of toxicity, bismuth and tetracycline are non-dialysable. The authors suggest working with a gastroenterologist to manage CKD patients with or without dialysis who fail first-line *H. pylori* eradication therapy.

Eradication of infection should be confirmed 4 or more weeks after the completion of therapy with urea breath test or stool antigen test.[19]

Medical Management of NSAID Ulcers

Contributing factors should be also addressed and treated. Patients with NSAID-associated ulcers should be advised to avoid NSAIDs and should be treated with a PPI for a duration of at least 8 weeks. According to the American College of Gastroenterology (ACG) guideline, all patients who are beginning long-term NSAIDs therapy should first be tested for *H. pylori*, and NSAIDs should be immediately discontinued in those with positive *H. pylori* test results if clinically feasible.[20]

In those who need to remain on NSAIDs or aspirin, maintenance PPI should be considered to reduce the risk of ulcer complications or recurrence.[21] Changing to a COX-2 selective inhibitor is also an option.

Endoscopy after Initial Therapy

In patients with complicated duodenal ulcers and in those with gastric ulcers, antisecretory therapy with a PPI is suggested for 4 to 8 weeks and 8 to 12 weeks, respectively. In patients with gastric ulcers, antisecretory therapy should only be discontinued after ulcer healing has been confirmed by upper endoscopy. A surveillance endoscopy (with biopsies of the ulcer if still present) is recommended to be performed after 12 weeks of antisecretory therapy in the following patients with gastric ulcers: persistent symptoms despite medical therapy; giant ulcer of greater than 2 cm; biopsies not performed or inadequate sampling; ulcers suspicious for malignancy or in those with risk factors for gastric cancer. Meanwhile in patients with duodenal ulcers, a repeat endoscopy is not routinely performed given the low risk of malignancy unless symptoms persist or recur.

Surgery

The need for elective surgery has been greatly reduced over the recent decades with the development of potent antisecretory agents (H2 blockers and PPIs) and the recognition that *H. pylori* eradication can eliminate most ulcer recurrences.[22] Indications of surgical management of PUD include suspected malignancy and management of complications from PUD such as bleeding, obstruction, and perforation.

Restarting Antiplatelet Agents

When should antiplatelet agents be restarted after a gastrointestinal bleed due to PUD? The decision to restart antiplatelet agents or anticoagulants should involve a patient-specific approach regarding potential risks and benefits. In low-risk patients on antiplatelets (i.e. for primary cardiovascular prevention), reinitiation can be reasonably delayed as the risk of rebleeding likely outweighs the potential benefit of restarting therapy.[23]

Whereas for patients who are at intermediate and/or high risk (i.e. for secondary prevention of cardiovascular disease), studies found that aspirin non-adherence or withdrawal after a gastrointestinal bleed was associated with a three-fold higher

risk of major adverse cardiac event.[24] Cardiac event rates were highest in the group of patients with a history of prior percutaneous coronary stenting. Thus reinstitution of aspirin as soon as possible (preferably within 5 days) is recommended following a gastrointestinal haemorrhage after endoscopically obtained haemostasis of PUD with PPI co-therapy as a mainstay for secondary prevention.[23]

Long Term Management

Maintenance or prophylactic antisecretory therapy with a proton pump inhibitor is also recommended in high-risk patients with PUD such as those with multiple comorbidities, older than 50 years, refractory ulcer, *H. pylori*-negative or NSAID-negative ulcer, giant ulcer, recurrent ulcer, continued NSAIDs use, or those with history of *H. pylori* eradication.

Although the general evaluation and treatment of upper gastrointestinal bleeding is similar in patients with and without CKD, extreme caution should be exercised when managing CKD patients as they are more prone to rebleeding due to underlying platelet dysfunction and anaemia and should receive more aggressive care to reduce this risk. Medications used should also be renal adjusted according to their creatinine clearance.

CONCLUSION

PUD is a major cause of morbidity and mortality and should be managed with care especially in elderly patients with multiple comorbidities. It is thus essential for family physicians to know the increased risk of PUD in ESRF and HD patients, and be able to properly evaluate and recognise "red flag" features of PUD as gastrointestinal symptoms are among the commonest and most frequent complaints in the general population. A high index of suspicion is necessary when dealing with high-risk patients so that early referrals can be made to rule out the more serious pathologies when patients present with per rectal bleeding.

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