



CASE REPORT

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Life-threatening gastrointestinal tract complications in a patient of rheumatoid arthritis. Is it drug or disease-related?

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Introduction: Gastrointestinal (GI) complications are very frequent and sometimes fatal in patients with Rheumatoid Arthritis (RA). Gastrointestinal perforation is a rare but serious event, most frequently involving the lower GIT, which has been observed in patients with RA.

Case Presentation: We present here an Adverse Drug Reaction (ADR) which is small bowel ischemia with perforation in a 61-year-old RA patient, who was taking a tablet of Prednisolone and tablet Hydroxychloroquine.

Discussion: Several studies indicated that RA patients may be at a higher risk of GI perforation. This could be attributed to the disease pathophysiology or the use of drugs for treatment like Glucocorticoids and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Rheumatologists must be vigilant for GI complications while prescribing anti-rheumatoid drugs.

Conclusion: GI perforations are rare events in RA patients, but cause significant morbidity and mortality. Increasing age and other comorbid conditions also increase the risk of adverse GI events.

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Introduction

Gastrointestinal tract (GIT) emergencies can sometimes be attributed to drugs. It is known that drugs like Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Glucocorticoids, Hydroxychloroquine, Methotrexate, etc cause gastritis, ulcerations, in severe cases perforations. Gastrointestinal perforation is a rare but serious, sometimes fatal event, most frequently involving the lower GIT, which has been observed in patients with Rheumatoid Arthritis (RA) (Curtis *et al.*, 2011; Curtis *et al.*, 2012).

RA is a chronic systemic inflammatory process of autoimmune nature with a wide range of acute

complications. It primarily affects joint function but may also have many systemic effects. The disease can affect several vital organ systems, including the cardiovascular, pulmonary, gastrointestinal, musculoskeletal, hematological, renal, neurological, and dermatological systems. In addition, complications can arise from the specific therapies used to treat RA. Certain patient populations can have atypical presentations of the disease or may have an exaggerated response to the medications.^[2] Serious medication-related adverse events are an important issue when selecting appropriate therapies for individual patients who may be at higher risk than others (Curtis *et al.*, 2011).



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The most significant factors associated with an increased risk of GI perforation were a history of diverticulitis, use of glucocorticoids, exposure to NSAIDs, increasing age, and higher levels of comorbidity.

Here we present a case of RA, a 61-year-old female patient, who was taking tablet Prednisolone and tablet Hydroxychloroquine, admitted to tertiary care hospital with suspected ADR, small bowel ischemia with perforation.

Case Details

A 61-year-old female patient, a known case of RA was brought to a tertiary care hospital with a complaint of abdominal pain associated with nausea and vomiting, blood, and pus in urine for 4 to 5 days. The patient had been taking tablet Prednisolone and tablet Hydroxychloroquine irregularly for RA for 7 years. She was taking tablets of Hydroxychloroquine 10 to 15 days before the symptoms appeared.

The patient was relatively asymptomatic before 7 days. On the day of admission, the patient was brought to our hospital with a complaint of sudden onset of abdominal pain which was dull aching, non-radiating, generalized, and turned excruciating in the lower abdomen, along with the complaint of nausea and vomiting which was non-projectile and non-bilious. Blood and pus were also present in urine.

The patient had developed diarrhea and vomiting 7 days before the admission, and for that, she was admitted to a private hospital. The patient was treated with IV fluids, antacids, anti-emetics, and antibiotics. Condition improved and the patient was discharged.

The day before admission patient had a complaint of urinary retention, and for that patient went to a private hospital where urinary catheterization was done. Urine was passed and the patient was discharged.

The patient was a known case of Bronchial Asthma for 5 years and taking Levosalbutamol and Ipratropium inhalers at home. No history of diabetes, hypertension, tuberculosis, or jaundice. History of tubal ligation/hysterectomy 20 years ago. History of Acute Ischemic Stroke with hemorrhagic transformation in March 2020.

Drug history was suggestive of taking tablet Prednisolone 5 mg OD, tablet Hydroxychloroquine (HCQ) 300 mg OD, tablet Azithromycin 250 mg OD, tablet Doxycycline 200 mg half tablet BD, tablet Aspirin 75 mg OD and tablet Atorvastatin 40 mg OD. The patient had been on tablet Methotrexate (MTX), which was discontinued 2 months ago because of poor gastrointestinal intolerance by the patient. Then the patient was advised to continue tablet Hydroxychloroquine.

On admission, her vitals were: Temperature: normal, Pulse: 110/min, SBP: 80 mmHg, SpO₂: 99 % on Room Air. All the routine blood and radiological investigations were done.

Blood investigation suggested Hb: 10.4 g/dl, WBC: 19.88 kU/L, S. Procalcitonin: 6.32 ng/ml, S. Calcium: 7.9 mg/dl, S. Potassium: 3 mmol/L, S. Chloride: 92 mmol/L, S. Creatinine: 0.98 mg/dl, Blood Urea: 66.6 mg/dl, S. Triglycerides: 177 mg/dl, S. Amylase: 158 U/L, S. Alkaline phosphatase: 208 U/L, S. Protein: 4.76 g/dl, S. Albumin: 2.72 g/dl, PT: 18.8 second, INR: 1.39. Urine for routine examination findings suggested the presence of blood and urobilinogen in urine.

USG abdomen showed the signs of mild fluid in the inter-bowel region. Multidetector computed tomography (MDCT) scan findings were suggestive of small bowel ischemia of the mid ileal loop with possible perforation, pneumoperitoneum, and small bowel obstruction. Surgery was advised for the patient.

Till the last seen patient was shifted to a low-cost hospital for exploratory laparotomy and resection of the bowel.

This ADR, small bowel ischemia with perforation with Glucocorticoids has been reported to the Indian Pharmacopoeia Commission with the unique ID number IN-IPC-300638847. Causality assessment of this ADR is "Possible" since the underlying GIT manifestations could be explained by concurrent drugs or the disease also.

Discussion

Gastrointestinal (GI) hemorrhage is the most common GI manifestation of patients with RA. The mechanism typically follows a pattern of a perforating vasculitis of the viscera leading to hemorrhage. Bowel ischemia, ulcerations, and medication therapy side effects are also known to cause GI hemorrhage. Rarer complications of systemic chronic inflammation are cholecystitis, diverticulitis, pancreatitis, and bowel edema, which leads to strictures, stenosis, and finally bowel obstruction. Necrotizing vasculitis should be considered in any rheumatoid patient with an acute abdomen ([Curtis et al., 2011](#)).

GI perforation is a non-traumatic penetration of the wall of the GI tract. In the general population, lower GI perforations are most commonly associated with diverticular disease, a common condition in the Western world. As a result of the obstruction of a diverticulum, inflammation, infection, and subsequently, perforation may occur. This is often termed a 'micro-perforation'. A free perforation is the one that leads to the spillage of bowel contents into the intra-abdominal cavity and results in peritonitis. Free perforation is a life-threatening condition, with a high mortality rate of up to 30 % or higher, and usually necessitates urgent surgical intervention. In contrast, micro perforations are usually managed medically ([Jagpal et al., 2018](#)).

The risk of GI perforation is low in patients with RA and that perforation occurs more frequently in the lower GI tract than in the upper GI tract ([Curtis et al., 2012](#)). GI

perforations have been reported in RA, either in association with the disease itself or in association with NSAIDs, Glucocorticoids, or other RA therapies. Some studies have shown that patients who are immunocompromised, a common circumstance in RA, are more likely to have free perforation from acute diverticulitis and have a higher rate of emergent surgery. Furthermore, these patients have higher postoperative morbidity and mortality (Jagpal et al., 2018).

Pathogenic factors related to the underlying RA disease process may also increase the risk of perforation. The ability to disentangle perforations due to the disease process and its associated inflammation versus therapies used for RA treatment is often confounded, given that the standard of care in RA for almost all patients is to be treated with immunomodulatory or immunosuppressive therapies to reduce inflammation (Jagpal et al., 2018). In the above-mentioned case, the patient was suffering from RA for 7 years.

The majority of patients who had GI perforations were taking NSAIDs and/or Glucocorticoids. These drugs should be kept to a minimum in the RA population, with special attention to patients with advanced age and other comorbidities that render them at a higher risk of perforation (Curtis et al., 2012; Jagpal et al., 2018). In the case mentioned above, the patient was 61-year-old, belonging to the elderly age group which was one of the significant factors associated with an increased risk of GI perforation.

Glucocorticoid treatment has been associated with a broad array of adverse systemic events. Even at low doses, as commonly used in RA patients, long-term Glucocorticoid therapy is associated with gastritis, pancreatitis, gastric ulcers, edema, and GI bleeding when concomitantly used with NSAIDs. Additionally, oral Glucocorticoid use is associated with a 3-fold increase in the risk of diverticular perforation (Curtis et al., 2012).

Neither current treatment with biologic agents nor current treatment with MTX conferred increased risk. In contrast, current treatment with Glucocorticoids, with or without NSAIDs, was a significant risk factor for GI perforation.^[1] In the case mentioned above, the patient was taking tablet Prednisolone 5 mg, which was again a significant factor associated with increased risk of GI perforation.

Profound GI upset is the major side effect associated with MTX (Berman et al., 2018). Around 20 % to 70 % of RA patients experienced gastrointestinal (GI) side effects during the first 1 to 2 years of therapy. Common GI side effects include nausea, vomiting, diarrhea, abdominal upset, and anorexia which are dose-dependent. It was also suggested that swapping from oral to parenteral therapy could avoid certain GI toxicity because it was observed that the frequency of diarrhea was often higher in RA patients treated with oral MTX (Wang et al., 2018). In this case,

there was a history of taking MTX by the patient which was discontinued because of poor GI intolerance. It was reported that nearly 20 % to 30 % of RA patients stopped using MTX within the first year of therapy because they could not tolerate the side effects induced by MTX (Wang et al., 2018).

The patient was on HCQ and Glucocorticoids at the time of the event. HCQ can be associated with gastritis but life-threatening GIT complications are not known in the literature to happen with this drug. The patient was on MTX therapy, but that was discontinued 2 months before the event as the patient could not tolerate it. So, we conclude that the ADR reported above is likely to be due to Glucocorticoids. There is a temporal relationship between the use of Glucocorticoids and the occurrence of this ADR which has also been documented previously in the scientific literature.

Conclusion

GI perforation is rare in patients with RA and that perforation occurs more frequently in the lower GI tract than in the upper GI tract. The most significant factors associated with an increased risk of GI perforation were a history of diverticulitis, use of glucocorticoids, exposure to NSAIDs, increasing age, and higher levels of comorbidity or pathogenic factor itself.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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