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Acute ischaemic colitis after initiation of tirzepatide in an elderly patient with type 2 diabetes

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Abstract

Tirzepatide, a dual GLP-1/GIP receptor agonist, is increasingly used for the treatment of type 2 diabetes and obesity. While gastrointestinal side effects such as nausea and diarrhoea are common, reports of ischemic colitis potentially associated with tirzepatide are extremely rare. Understanding potential mechanisms is critical for early recognition and management. We report the case of a 77-year-old woman with type 2 diabetes, severe obesity, and cardiovascular comorbidities, who developed acute onset abdominal pain and rectal bleeding two days after her second dose of tirzepatide. On admission, laboratory evaluation showed leucocytosis and elevated C-reactive protein. Abdominal CT demonstrated segmental left-sided colitis with diverticulosis. Rectosigmoidoscopy revealed hyperaemic, oedematous, friable mucosa with superficial ulcerations in the sigmoid colon. Histology was consistent with erosive colitis with features suggestive of ischemic injury. Infectious workup was negative. The patient was promptly started on intravenous metronidazole, fluid resuscitation, and pantoprazole. Clinical symptoms resolved over the subsequent days, and laboratory markers improved. This case highlights a potential association between tirzepatide therapy and ischemic colitis. Mechanisms may include delayed gastrointestinal motility, increased intraluminal pressure, relative hypovolemia, and possible neuroenteric microvascular modulation. Clinicians should be aware of this rare but serious complication, particularly in patients with cardiovascular comorbidities.

Introduction

Tirzepatide is a novel dual Glucose-dependent Insulinotropic Polypeptide (GIP) and Glucagon-Like Peptide-1 (GLP-1) receptor agonist approved for the treatment of type 2 diabetes mellitus (T2DM) and obesity. Owing to its potent glycaemic and weight-reducing effects, its use has rapidly increased worldwide. Gastrointestinal adverse events, including nausea, vomiting, diarrhoea and constipation, are among the most frequently reported side effects, particularly during the early phases of treatment and dose escalation, as demonstrated in randomised controlled trials and meta-analyses.[1]

Ischaemic colitis represents the most common form of intestinal ischaemia and typically affects elderly patients with cardiovascular risk factors, often in the absence of major arterial occlusion. Drug-induced non-occlusive ischaemic colitis has been described with several medications capable of altering intestinal motility, intraluminal pressure or microvascular perfusion. In recent years, isolated case reports have suggested a potential association between GLP-1 receptor agonists and ischaemic colitis.

To date, only a very limited number of cases of tirzepatide-associated ischaemic colitis have been reported in the literature. A detailed case describing colonic ischaemia temporally related to tirzepatide therapy was published in 2024,[2] while additional cases have been presented as conference abstracts at major gastroenterology meetings.[3] Moreover, concerns regarding a possible under-recognised risk of ischaemic colitis with incretin-based therapies, including tirzepatide, have recently been raised in editorials and rapid responses.[4,5]

We report the case of an elderly woman who developed acute left-sided ischaemic colitis shortly after initiation of tirzepatide therapy. This case contributes additional clinicopathological evidence to the emerging literature and highlights the need for increased clinical awareness of severe gastrointestinal adverse events associated with incretin-based treatments, particularly in patients with multiple comorbidities.

Case Report

A 77-year-old woman with a history of T2DM, severe obesity, hypertension, hypothyroidism post-thyroidectomy, and right coxarthrosis presented to the emergency department with rectal bleeding and abdominal pain. She reported that her symptoms began on 11 November 2025, two days after

her second dose of tirzepatide, which had been initiated on 2 November 2025 and escalated to a second dose on 9 November 2025.

On presentation, she was alert and oriented, with a heart rate of 100 bpm, blood pressure 135/65 mmHg, respiratory rate 18/min, oxygen saturation 93% on ambient air, and temperature 36.1°C. Her weight was 91.6 kg and height 150 cm. Abdominal examination revealed mild tenderness in the left iliac fossa and flank without peritoneal signs, and bowel sounds were present. Laboratory investigations at emergency department admission and upon ward admission are summarised in table 1. Notable findings included leucocytosis, elevated C-reactive protein (CRP), acute kidney injury (creatinine 2.12–2.42 mg/dl), and mild hyperglycaemia.

Upon admission, the patient was promptly started on intravenous therapy, including metronidazole 500 mg three times daily, 0.9% sodium chloride 500 mL three times daily for hydration, and pantoprazole 40 mg daily.

The patient was admitted to the Internal Medicine ward on 13 November 2025. Initial imaging with abdominal CT scan revealed segmental left-sided colitis associated with sigmoid diverticulosis. Gastroenterology consultation recommended diagnostic endoscopy. Rectosigmoidoscopy performed on 18 November 2025 demonstrated segmental colonic mucosal erythema, oedema, friability, and multiple superficial ulcerations covered with fibrin in the sigmoid colon (Figure 1). The rectal mucosa appeared normal. Multiple biopsies were obtained. Histopathology revealed focal mucosal erosion, glandular distortion with severe mucin depletion, lamina propria congestion, marked hyalinisation, chronic active inflammation, focal crypt abscesses, and regenerative glandular hyperplasia, consistent with a diagnosis of colitis compatible with ischemic injury (Figure 2). Stool cultures, parasitology, and Clostridium difficile testing performed on 20 November 2025 were negative.

During hospitalisation, the patient experienced gradual clinical improvement, with resolution of abdominal pain and cessation of rectal bleeding. Laboratory markers of inflammation decreased (CRP 25.11 mg/dl at presentation to 4.69 mg/dl at discharge), and renal function partially recovered (creatinine 1.81 mg/dl at discharge). The patient was discharged in stable condition on 25 November 2025 with outpatient follow-up recommendations, including repeat colonoscopy in eight weeks. Tirzepatide therapy was stopped.

Temporal association between symptom onset and tirzepatide administration, absence of other identifiable infectious causes, and supportive histopathological findings suggest a possible link between tirzepatide therapy and segmental ischemic colitis in this patient (Figure 3).

Discussion

Ischaemic Colitis (IC) is the most common form of colonic ischaemia and generally arises from transient reduction in blood flow to vulnerable segments of the colon, particularly “watershed” areas such as the splenic flexure and rectosigmoid junction. These regions have relatively tenuous collateral circulation and are predisposed to injury when perfusion decreases even modestly (e.g., hypovolaemia, vasoconstriction, or increased intraluminal pressure).[6,7] Advanced age, cardiovascular comorbidities, T2DM, and chronic kidney disease further increase susceptibility by compromising microvascular integrity and systemic perfusion.[6,8]

Unlike classic mesenteric arterial occlusion, most cases of IC are non-occlusive and result from microvascular hypoperfusion, segmental vasoconstriction, or local intraluminal factors rather than large-vessel thrombosis.[7] In this context, drugs that alter gut motility, intraluminal pressure, or systemic haemodynamics have been implicated as rare but clinically relevant precipitants.

GLP-1 receptor agonists (GLP-1 RAs), including tirzepatide, are associated with gastrointestinal side effects such as nausea, vomiting, diarrhoea and constipation across clinical use, reflecting their effects on gastric emptying and intestinal transit.[1,9] These effects can theoretically contribute to local perfusion perturbations in the colon through several plausible mechanisms.

GLP-1 receptor agonists delay gastrointestinal motility at multiple levels, leading to prolonged transit times and increased intraluminal pressure, which may compromise mucosal blood flow in vulnerable watershed regions of the colon (delayed gastric emptying and whole-gut transit time documented with GLP-1Ras; Figure 4).[10,11]

Persistent constipation or diarrhoea, often accompanied by reduced oral intake, may predispose to relative hypovolaemia and diminished splanchnic perfusion, a key mechanism in non-occlusive colonic ischaemia.[11] In our patient, the urea/creatinine ratio (≈41) was midly elevated, which may support the presence of relative hypovolemia and reduced effective circulating volume, a recognized contributor to non-occlusive colonic ischemia. In addition, diabetic microvascular disease may impair intestinal microcirculation, further increasing the susceptibility of the colonic mucosa to ischaemic injury in patients with long standing diabetes (Figure 4).[12]

Neural and enteric reflex modulation by incretin agonism may alter mesenteric microvascular tone, although direct evidence for this mechanism remains speculative (Figure 4).[13,14]

A limited number of reports have linked tirzepatide to IC. A detailed case report described colonic ischemia in a 62-year-old woman shortly after initiating tirzepatide, with resolution after drug discontinuation.[12] Similar clinical patterns have been presented in conference abstracts, documenting left-sided IC in patients on tirzepatide with negative infectious workups and patent mesenteric vessels, which improved after withdrawal of therapy.[3,8] These reports, together with the

present case, share several features: absence of identifiable occlusive vascular disease, typical endoscopic distribution, and a temporal association with tirzepatide administration.

Evidence from other incretin-based agents suggests that altered motility and secondary dehydration may also predispose to IC with drugs such as semaglutide. A case of semaglutide-associated ischaemic colitis in a patient without traditional vascular risk factors was reported, with symptom resolution following drug cessation.[4] Respectable authors have highlighted emerging but under-recognised instances of IC associated with GLP-1 RAs, underscoring the need for heightened clinical awareness.[5]

In the present case, the precise temporal relationship — onset of gastrointestinal bleeding 2 days after the second weekly dose of tirzepatide — and exclusion of infectious, occlusive vascular, and other common causes of colonic injury strengthen the argument for a drug-related event. Moreover, causality assessment using the Naranjo Adverse Drug Reaction Probability Scale[15] yielded a score of 6, consistent with a probable adverse drug reaction (Table 2). Although the evidence remains insufficient to establish definitive causality, the convergence of clinical, endoscopic, and histological findings across several reports suggests a reproducible pattern that warrants further systematic investigation. Importantly, early recognition and discontinuation of the suspected agent, along with supportive care, appear to be associated with favourable outcomes in most reported instances.

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Table 1. Laboratory results at emergency department presentation and hospital admission.

Parameter	Reference Range	11/11/2025 (ED)	13/11/2025 (Admission)
Glucose (mg/dL)	70–110	187 ↑	139 ↑
Urea (mg/dL)	15–50	88 ↑	94 ↑
Creatinine (mg/dL)	0.51–0.95	2.12 ↑	2.42 ↑
eGFR (mL/min/1.73 m²)	>90	24	20
Sodium (mEq/L)	136–145	137	140
Potassium (mEq/L)	3.5–5.1	4.2	3.9
CRP (mg/dL)	0–0.5	25.11 ↑	21.14 ↑
WBC (×10³/µL)	4–11	16.9 ↑	12.7 ↑
Hemoglobin (g/dL)	12–15.5	12.8	11.5 ↓
Platelets (×10³/µL)	150–450	256	229
AST (U/L)	0–32	16	12
ALT (U/L)	0–33	11	8
LDH (U/L)	135–214	–	208
Albumin (g/dL)	3.5–5.2	–	3.4 ↓
Ferritin (ng/mL)	15–150	–	320 ↑
HbA1c (%)	4.8–5.9	–	7.1 ↑

Abbreviations: CRP, C-reactive protein; ED, emergency department; eGFR, estimated glomerular filtration rate; WBC, white blood cells; ↑, above normal; ↓, below normal.

Figure 1. Endoscopic findings in the sigmoid colon of a patient with suspected tirzepatide-associated ischemic colitis

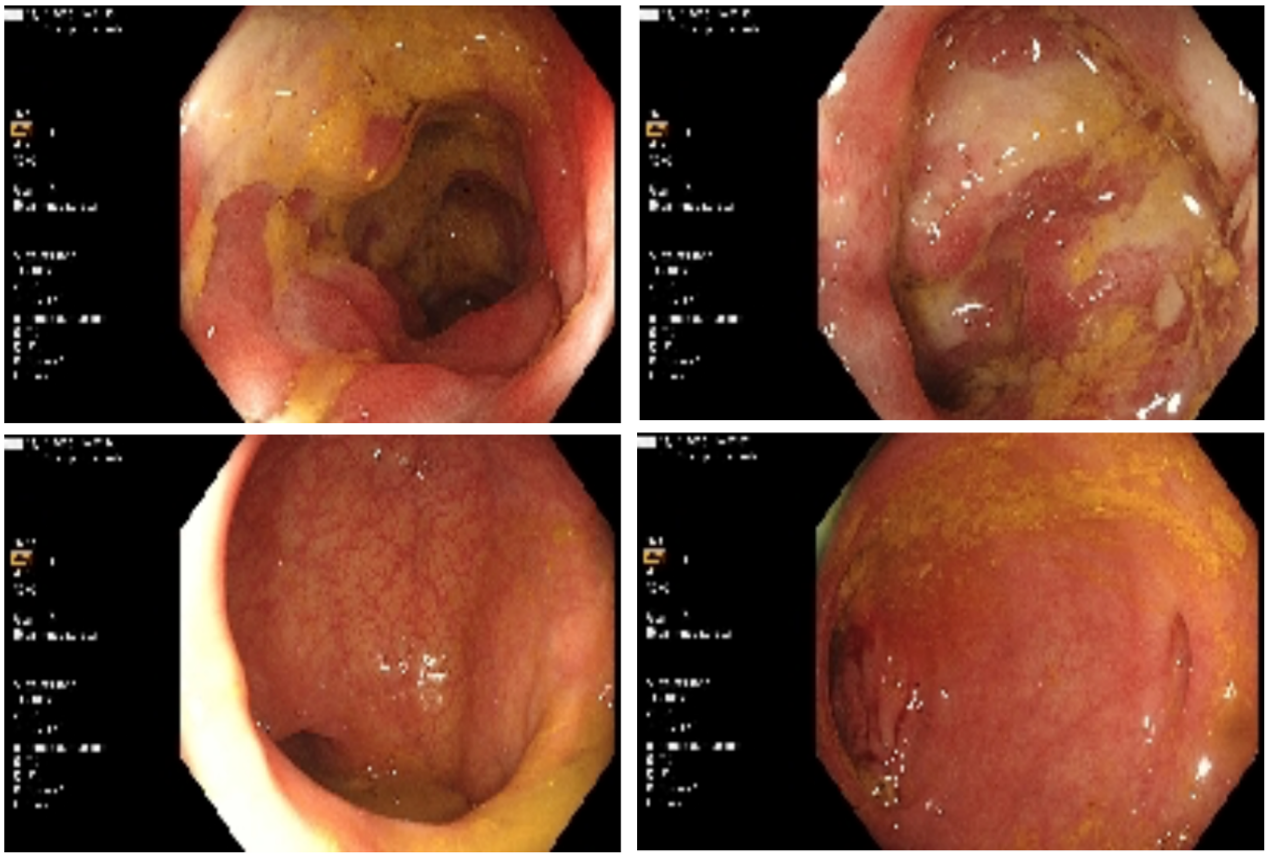
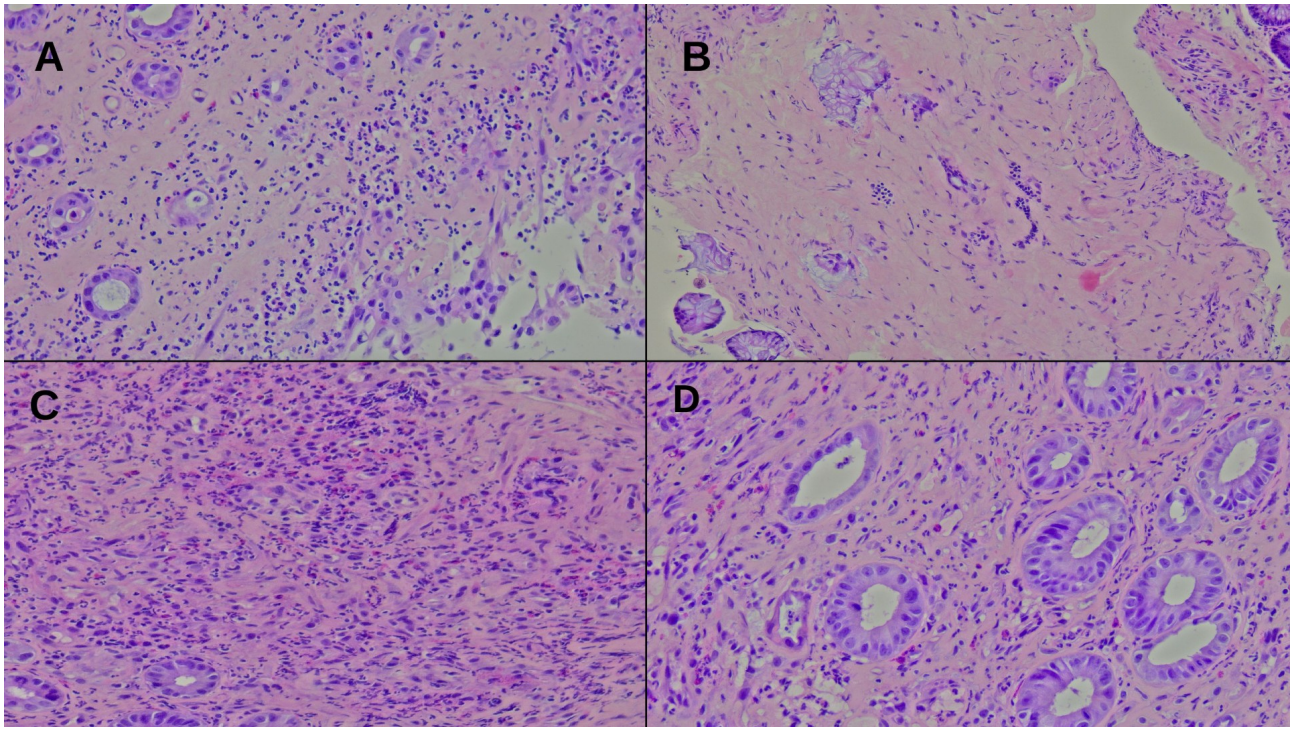
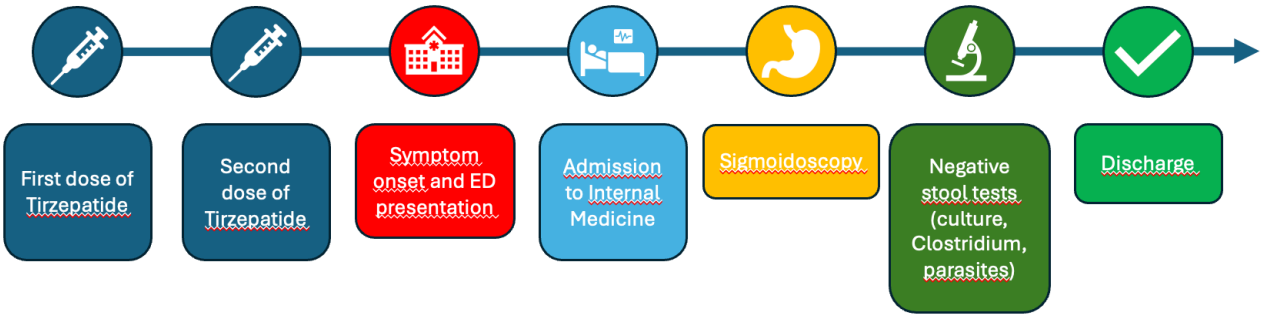


Figure 2. Histopathologic findings of sigma biopsy



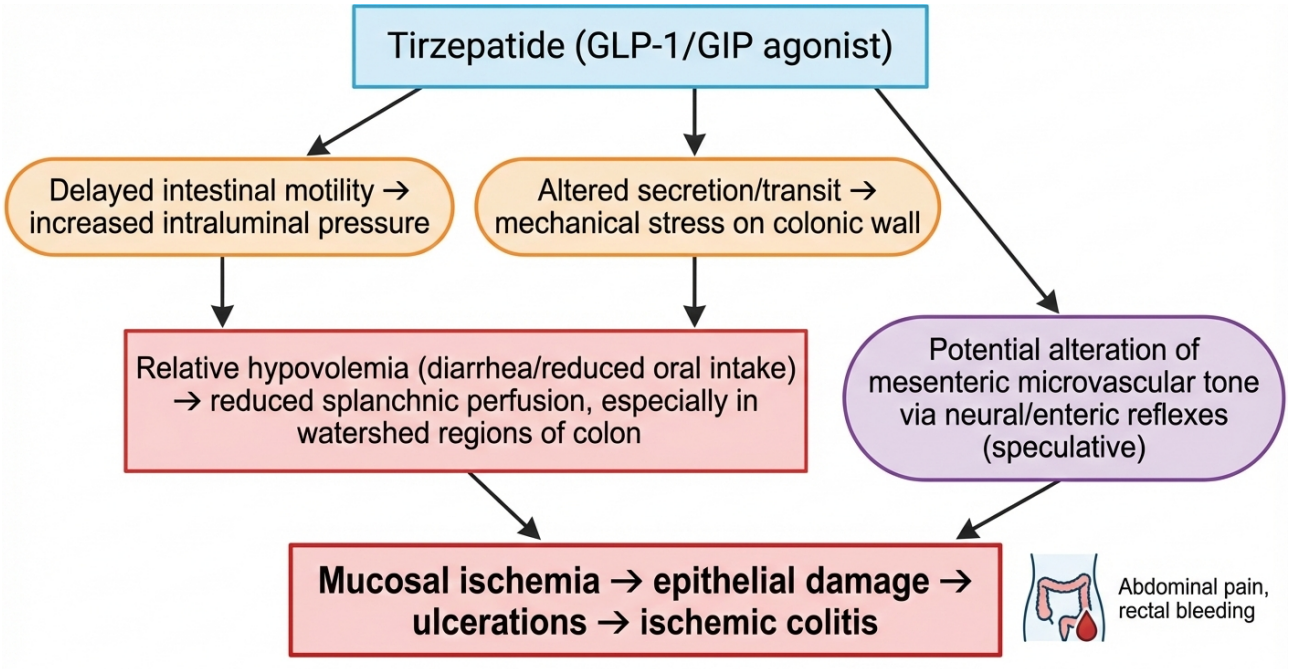
(A) Colonic mucosa showing ischemic-type injury with superficial epithelial damage, “microcrypts” formation and a predominantly neutrophilic inflammatory infiltrate. (Hematoxylin–Eosin, 100X). (B) Severe lamina propria hyalinization with reduced crypt density and architectural distortion. (200X). (C) Mixed inflammatory infiltrate of the lamina propria, composed of eosinophils, lymphocytes, and granulocytes (100X). (D) Colonic mucosa showing marked nuclear atypia and crypt abscesses (200X).

Figure 3. Timeline of clinical events in a 77-year-old woman with suspected tirzepatide-associated ischemic colitis



Horizontal timeline illustrating the sequence of key clinical events from initial tirzepatide administration to hospital discharge. Each icon is labeled with the corresponding date and event. *Abbreviations: ED, emergency department.*

Figure 4. Hypothetical pathophysiological mechanism of ischemic colitis associated with tirzepatide



Schematic diagram illustrating the proposed pathophysiological cascade linking tirzepatide therapy to ischemic colitis. Tirzepatide (GLP-1/GIP agonist) may induce delayed gastrointestinal motility and altered intestinal transit, leading to increased intraluminal pressure and mechanical stress on the colonic wall. Concomitant hypovolemia due to diarrhea or reduced oral intake may further reduce splanchnic perfusion, particularly in colonic watershed regions. Additionally, neural and enteric reflex modulation by incretin agonism could alter mesenteric microvascular tone, although this mechanism remains speculative. These combined effects may result in mucosal ischemia, epithelial damage, and ulceration, clinically manifesting as abdominal pain and rectal bleeding. This diagram represents a hypothetical mechanism based on physiological reasoning.

Table 2. Causality assessment using the Naranjo Adverse Drug Reaction Probability Scale for the association between tirzepatide and ischemic colitis

Question	Answer	Score
Are there previous conclusive reports on this reaction?	Yes	+1
Did the adverse event appear after the suspected drug was administered?	Yes	+2
Did the adverse reaction improve when the drug was discontinued?	Yes	+1
Did the adverse reaction reappear upon re-administration?	Not performed	0
Are there alternative causes that could have caused the reaction?	No (infectious and vascular causes excluded)	+2
Did the reaction reappear with placebo?	Not performed	0
Was the drug detected in toxic concentrations?	Not performed	0
Was the reaction more severe with increased dose or less severe with decreased dose?	Not performed	0
Did the patient have a similar reaction to the same or similar drugs previously?	No	0
Was the adverse event confirmed by objective evidence?	Yes	+1
Total score:	**6**	

Application of the Naranjo Adverse Drug Reaction Probability Scale to evaluate the likelihood of a causal relationship between tirzepatide therapy and the development of ischemic colitis in the present case. The total score of 6 indicates a probable adverse drug reaction according to the standard Naranjo classification.

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Conflicts of interest: the authors declare no conflicts of interest.

Ethics approval and consent to participate: no ethical committee approval was required for this case report by the Department, because this article does not contain any studies with human participants or animals.

Informed consent and consent for publication: informed consent for the use of anonymized clinical data was obtained from the patient at the time of hospital admission in accordance with local regulations.

Data availability statement: the data presented in this study are available on request from the corresponding author due to privacy and ethical restrictions.