International Journal of Research in Medical Sciences
Oraijah AA et al. Int J Res Med Sci. 2026 Aug;14(8):3604-3607
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20262657

Case Report

Peripheral eosinophilia with eosinophilic gastroenteritis associated with semaglutide: a case report and literature review

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Received: 17 June 2026
Revised: 14 July 2026
Accepted: 20 July 2026

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ABSTRACT

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are widely used for the management of type 2 diabetes mellitus and obesity. Although generally well tolerated, gastrointestinal adverse effects are common, and rare immune-mediated complications have increasingly been reported. We describe the case of a 57-year-old woman with type 2 diabetes mellitus, treated with semaglutide, who presented with a four-month history of chronic epigastric pain, anorexia, and unintentional weight loss. Laboratory evaluation revealed marked peripheral eosinophilia, and endoscopic biopsies of the stomach and duodenum demonstrated extensive eosinophilic infiltration of the lamina propria, confirming a diagnosis of eosinophilic gastroenteritis. Secondary causes, including parasitic infection, allergic disease, and hematologic malignancy, were excluded. Given the temporal relationship between semaglutide initiation and symptom onset, the drug was discontinued. Over the following months, the patient's symptoms resolved and her eosinophil count normalized, with repeat biopsy confirming histological resolution. This case adds to a growing body of literature describing eosinophilic gastrointestinal and systemic reactions associated with GLP-1 RA therapy. Clinicians should maintain a high index of suspicion for drug-induced eosinophilic disorders in patients on GLP-1 RAs who present with persistent or atypical gastrointestinal symptoms, as early recognition and prompt drug discontinuation can prevent long-term morbidity and lead to complete clinical and histological recovery.

Keywords: Semaglutide, Eosinophilic gastroenteritis, GLP-1 receptor agonists, Peripheral eosinophilia, Drug-induced hypersensitivity

INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as a cornerstone in the management of type 2 diabetes mellitus and obesity.[1] These agents mimic the effects of the naturally occurring incretin hormone GLP-1, enhancing glucose-dependent insulin secretion, suppressing glucagon release, slowing gastric emptying, and promoting satiety. Over the last two decades, long-acting formulations and dual- or triple-agonist molecules have broadened the therapeutic landscape.[2] These advances have delivered efficacy in weight loss that can rival surgical interventions.[3]

Although GLP-1 RAs are generally well tolerated, gastrointestinal adverse events such as nausea, vomiting, diarrhea, and constipation are commonly reported, particularly in non-diabetic patients with overweight or obesity.[4,5] Rare immune-mediated complications, however, are increasingly recognized, including

eosinophilic infiltration of various tissues such as the gastrointestinal tract, kidneys, and fascia.[6] Here, we describe a case of peripheral eosinophilia with eosinophilic gastroenteritis temporally associated with semaglutide therapy, highlighting the importance of considering unusual immune-mediated adverse effects in patients with unexplained gastrointestinal symptoms.

CASE REPORT

A 57-year-old woman with type 2 diabetes mellitus and a history of total abdominal hysterectomy with bilateral oophorectomy presented with a four-month history of chronic epigastric pain, anorexia, and unintentional weight loss. Her medications included empagliflozin 25 mg daily, atorvastatin 40 mg daily, insulin glargine 30 units daily, and semaglutide 1 mg weekly, initiated one year prior to presentation. She denied fever, vomiting, diarrhea, gastrointestinal bleeding, food or drug allergies, or recent travel.

On examination, she was alert, oriented, and comfortable at rest. Vital signs were within normal limits. Cardiovascular, respiratory, and musculoskeletal examinations were unremarkable. Abdominal examination revealed a soft, non-tender abdomen with no organomegaly. There was no jaundice, pallor, cyanosis, rash, or lymphadenopathy.

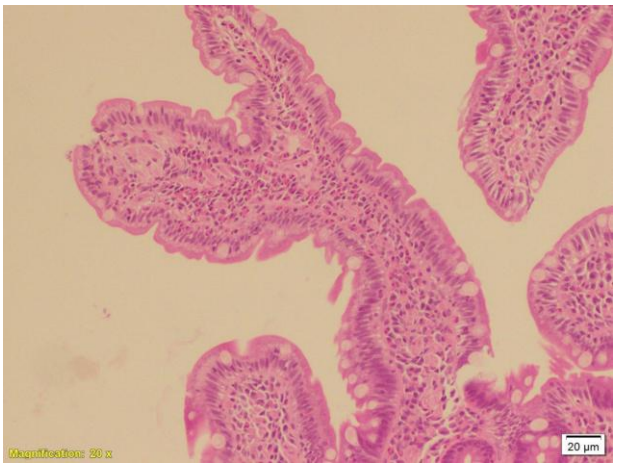

Figure 1: Duodenal biopsy shows abundant eosinophilic infiltration.

Laboratory investigations revealed marked eosinophilic leukocytosis, with a total leukocyte count of $29\times10^3/\mu l$ and an absolute eosinophil count of $14.5\times10^3/\mu l$. Hemoglobin and platelet counts were within normal ranges. Peripheral blood smear confirmed eosinophilia without abnormal cells. Renal and liver function tests were normal, and flow cytometry showed no evidence of hematologic malignancy. Allergen-specific IgE testing was unremarkable, and stool studies were negative for ova and parasites.

Contrast-enhanced CT of the abdomen and pelvis demonstrated mild duodenal wall thickening. Upper and lower gastrointestinal endoscopy revealed mild antral gastritis but otherwise normal mucosa. Histopathological examination of gastric and duodenal biopsies showed extensive eosinophilic infiltration of the lamina propria, with counts exceeding 30 eosinophils per high-power field (Figures 1 and 2), confirming eosinophilic gastroenteritis. Helicobacter pylori testing was negative at that time.

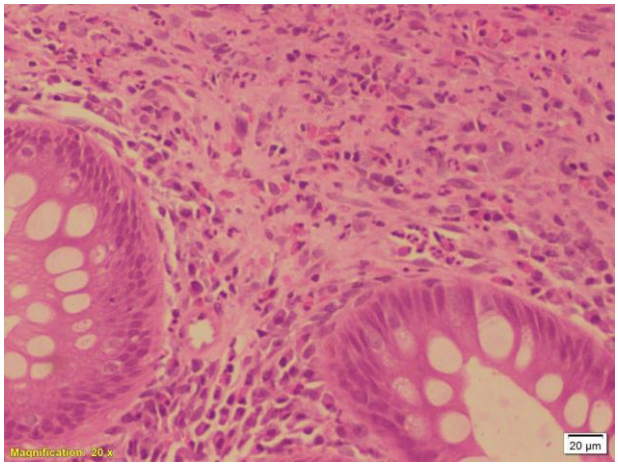

Figure 2: Gastric biopsy shows abundant eosinophilic infiltration.

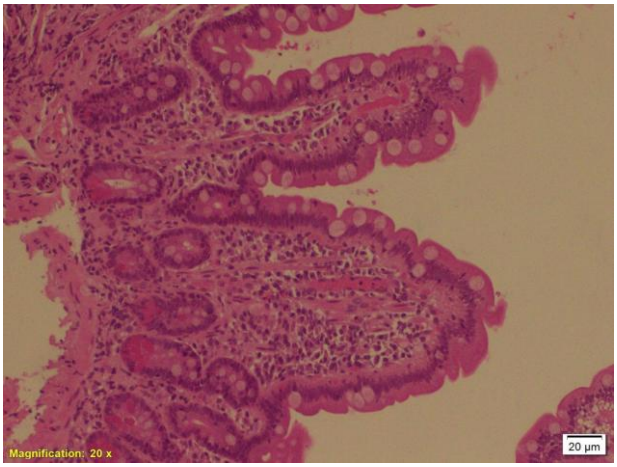

Figure 3: Duodenal biopsy shows reactive lymphocytes and scattered eosinophils.

The patient initially underwent conservative management with dietary modifications. Systemic corticosteroid therapy was offered but declined. Despite these measures, her symptoms persisted, and peripheral eosinophilia remained elevated. Given the temporal relationship between semaglutide initiation and symptom onset, the medication was suspected as the likely trigger. Semaglutide was discontinued, and the patient was closely followed in the outpatient setting.

Over the next three months, she experienced significant clinical improvement, with resolution of abdominal pain

and normalization of eosinophil counts. One year later, repeat upper gastrointestinal endoscopy and duodenal biopsy demonstrated resolution of eosinophilic infiltration (Figure 3), although nodular gastritis associated with Helicobacter pylori was noted. The patient remains asymptomatic and continues regular follow-up in the gastroenterology clinic.

DISCUSSION

GLP-1 receptor agonists have revolutionized the management of type 2 diabetes and obesity, offering substantial metabolic and weight-loss benefits. Their gastrointestinal effects nausea, vomiting, diarrhea, and constipation, are well recognized, particularly in patients with overweight or obesity.[4,5] However, beyond these common side effects, rare immune-mediated complications have emerged, affecting multiple organ systems and challenging clinicians to recognize unusual presentations.

Eosinophilic gastroenteritis is classically categorized according to the depth of eosinophilic infiltration into mucosal, muscular, and serosal patterns, each producing a distinct clinical picture.[7] Our patient developed persistent upper abdominal pain, anorexia, and unintentional weight loss, accompanied by marked peripheral eosinophilia. Histopathological examination confirmed eosinophilic gastroenteritis, and symptoms resolved only after semaglutide discontinuation. The temporal relationship and clinical course strongly suggest a drug-induced hypersensitivity reaction. While eosinophilic gastroenteritis is rare, this case mirrors other reports of GLP-1 RA–associated eosinophilic disorders, suggesting that such reactions, though uncommon, may be part of a broader spectrum of immune-mediated effects.

For instance, Khalid et al. described a patient who developed eosinophilic colitis shortly after initiating semaglutide, presenting with severe abdominal pain and watery diarrhea. Diffuse colonic eosinophilic infiltration and elevated serum IgE supported a hypersensitivity mechanism, with rapid improvement following drug discontinuation.[8] Similarly, acute interstitial nephritis has been reported in GLP-1 RA users without prior kidney disease, characterized by interstitial lymphoplasmacytic infiltrates with eosinophils and acute tubular injury, with renal function recovering fully after drug withdrawal and corticosteroid therapy.[6] Beyond the kidneys, eosinophilic fasciitis has also been observed, manifesting as limb swelling, skin thickening, and peripheral eosinophilia, which resolved after cessation of therapy.[6] More recently, GLP-1 RA–associated eosinophilic duodenitis presenting as bowel obstruction and drug-induced eosinophilic esophagitis have also been described, further widening the recognized spectrum of gastrointestinal eosinophilic disease associated with this drug class.[9,10]

Beyond drug-induced disease, eosinophilic gastroenteritis in the general population is a heterogeneous disorder that can present with malabsorption, ascites, or intestinal obstruction, and its diagnosis and management remain largely guided by case series and expert opinion rather than controlled trials.[11,12] Refractory cases unresponsive to corticosteroids have increasingly been managed with biologic agents such as the anti-interleukin-5 antibody mepolizumab, with favorable clinical response.[13] These observations reinforce the value of keeping eosinophilic gastroenteritis, whether idiopathic or drug-induced, within the differential diagnosis of unexplained gastrointestinal symptoms accompanied by peripheral eosinophilia.

Taken together, these cases illustrate a pattern: GLP-1 receptor agonists, while generally safe, can rarely trigger systemic eosinophilic reactions affecting diverse organs. The unifying feature appears to be an immune-mediated hypersensitivity response, manifesting variably depending on the target tissue. Gastrointestinal involvement may present with nonspecific symptoms such as abdominal pain, anorexia, or diarrhea, while renal or musculoskeletal involvement can produce organ-specific dysfunction.

Recognition requires a high index of suspicion, particularly when symptoms persist beyond typical early gastrointestinal effects or occur with peripheral eosinophilia.

Importantly, these reactions appear largely reversible. Across reported cases, withdrawal of the GLP-1 RA, with or without corticosteroids, led to symptom resolution and normalization of laboratory abnormalities. This underscores the critical role of early identification and prompt intervention in preventing long-term morbidity. Awareness of these potential complications is particularly relevant as GLP-1 RA use expands to non-diabetic populations with overweight or obesity, where subtle gastrointestinal complaints may otherwise be attributed to common adverse effects.[4]

Ultimately, our case, together with reports of eosinophilic colitis, nephritis, and fasciitis, highlights a rare but clinically significant spectrum of immune-mediated complications associated with GLP-1 receptor agonists. Vigilance is essential for safe prescribing, timely diagnosis, and appropriate management, ensuring patients benefit from these therapies while minimizing risk.

CONCLUSION

GLP-1 receptor agonists are highly effective in managing diabetes and obesity; however, clinicians should remain aware of rare immune-mediated complications, including eosinophilic gastroenteritis, colitis, nephritis, and fasciitis. Our case illustrates a severe but reversible manifestation of semaglutide therapy. Early recognition, withdrawal of the causative agent, and close follow-up are key to ensuring patient safety. As GLP-1 RA use expands to broader populations, careful monitoring for atypical presentations is warranted.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Oraijah AA, Abdullahi HMM, Alidrisi GA, Alghamdi M. Peripheral eosinophilia with eosinophilic gastroenteritis associated with semaglutide: a case report and literature review. Int J Res Med Sci 2026;14:3604-7.