ANCA-associated vasculitis presenting with tongue necrosis and severe gastrointestinal involvement

Sirs,

Granulomatosis with polyangiitis (GPA) is an anti-neutrophil cytoplasmic antibody (ANCA)-related, multisystemic, necrotising small-vessel vasculitis that usually affects the upper and lower respiratory tract and kidneys. Gastrointestinal involvement is rare in ANCA-associated vasculitis, reported in less than 10% of the cases (1). Tongue necrosis, as a manifestation of oral gastrointestinal involvement, is extremely rare in GPA and is occasionally observed in large-vessel vasculitides (2). Here, we present a fatal case of GPA presenting with tongue necrosis and multiorgan involvement, including the skin, lungs, kidneys, and gastrointestinal system.

A 38-year-old man with no history of chronic disease was admitted to the emergency room due to constitutional symptoms, arthralgia, palpable purpura on the lower extremities, and tongue necrosis that had developed gradually over the previous month. Physical examination revealed haemorrhagic bullae on both legs, bilateral ankle arthritis, and a large necrosis on the edge of the tongue (Fig. 1a-b). Laboratory evaluation showed neutrophilic leukocytosis, hypochromic microcytic anaemia, acute kidney injury (creatinine: 3.9 mg/dl), elevated acute phase reactants (C-reactive protein: 354 mg/L) and microscopic haematuria. Serological evaluation showed anti-proteinase-3 (PR3)-ANCA positivity [300 IU/ml (<18 IU/ml)]. Thorax computed tomography (CT) scan was compatible with diffuse alveolar haemorrhage (DAH). The patient was diagnosed with GPA and 1 gram of methylprednisolone for 3 days, followed by 60 mg/day, 1 gram of cyclophosphamide and rituximab 1 gr, and therapeutic plasma exchange therapy (PLEX) were initiated.

On the third day of his hospitalisation, he developed melena with a two-point drop in haemoglobin. Upper gastrointestinal enteroscopy revealed multiple mucosal ulcers on the third portion of the duodenum and proximal jejunum (Fig. 1c-d). Haemodialysis was initiated due to volume overload and uraemia. Endoscopic haemoclips were applied to the bleeding sites and vasopressin and proton pump inhibitor infusion were initiated. However, active upper gastrointestinal bleeding continued, and he needed 3–4 units of erythrocyte suspension transfusion, 4 units of fresh-frozen plasma, and 1 unit of platelet suspension on average per day over a week period. Abdomen CT angiography showed active bleeding from the distal duodenum and proximal jejunum. Interventional digital subtraction angiography was performed for transcatheter arterial embolisation, but active bleeding could not be detected. PLEX was stopped, and 2 g/kg of intravenous immunoglobulin (IVIG) was initiated. Over a period of 10 days, the frequency of melena and the transfusion need of the patient decreased day by day, and control thorax CT scan revealed resolution of DAH. His skin lesions, arthritis, and tongue necrosis were also alleviated with immunosuppressive therapy. After a 4-day stable period without any need for transfusion, the patient had massive haematochezia and was transferred to the intensive care unit (ICU) due to rapidly progressive haemorrhagic shock. He received massive transfusion and 1 gram of methylprednisolone and underwent urgent abdominal surgery. The part of the small intestine, starting from the third part of the duodenum and extending to 60 cm of the proximal jejunum, was resected. The abdomen was closed with primary end-to-end anastomosis. During the operation, the ulcers were macroscopically visible throughout the whole intestine in a skipped pattern (Fig. 1e-f). Histopathological examination of the resected material revealed macroscopically visible ulcers (Fig. 1g-h) and microscopic evidence of necrotising vasculitis affecting small- and medium-sized vessels (Fig. 1i-j). Treatment was continued with methylprednisolone 100mg/day, IVIG, and broad-spectrum antibiotics. Despite an initial improvement after surgery, the patient died due to pan-resistant Klebsiella septicaemia 10 days after the operation and 35 days after the initial diagnosis of GPA.

Tongue necrosis is an uncommon manifestation of systemic vasculitis. In large-vessel vasculitis, it results from arterial occlusion of lingual or external carotid artery, whereas in AAV, it reflects small-vessel necrotising inflammation. Patients with

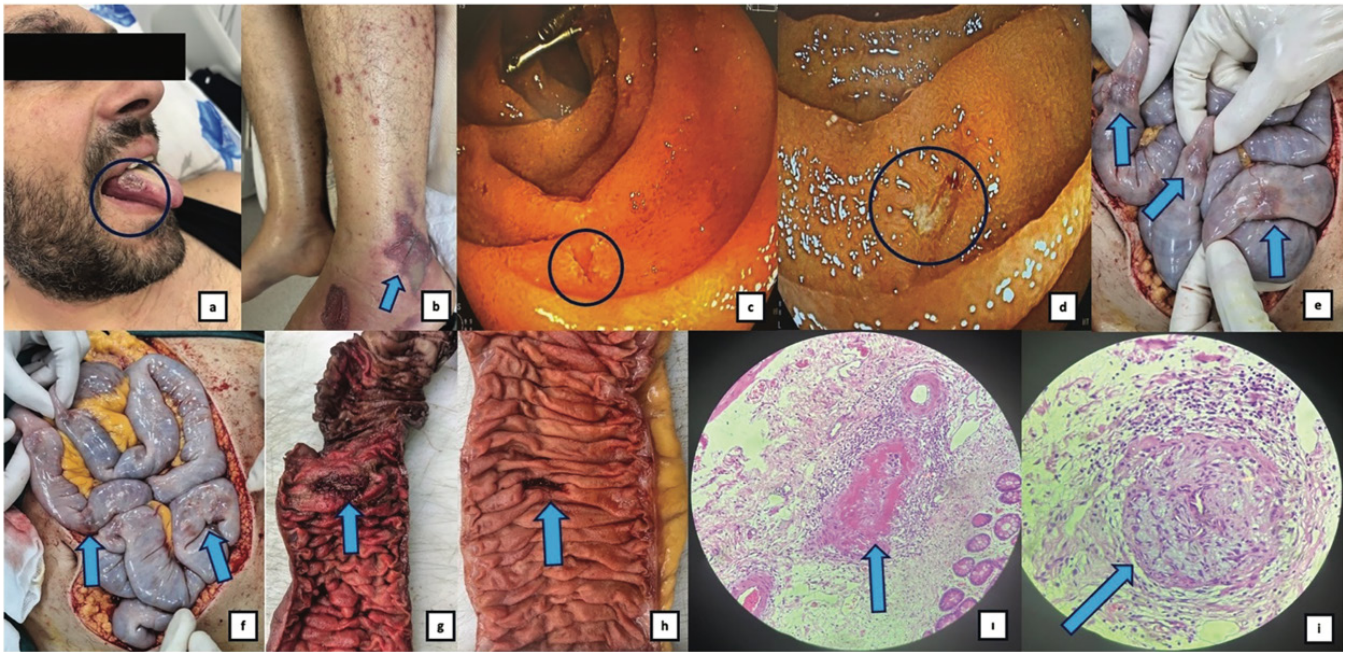

Fig. 1. a) Tongue necrosis (blue circle); **b)** Haemorrhagic bullae (blue arrow); **c-d)** Endoscopic appearance of intestinal vasculitic ulcers (blue circles); **e-f)** Macroscopic appearance of intestinal vasculitic ulcers (blue arrows); **g-h)** Intestinal ulcers on resected intestinal material (blue arrows); **i)** Histopathological findings of ulcers; necrotising vasculitis of small and medium-sized vessels (fibrinoid necrosis), haematoxylin-eosin (blue arrows); **j)** Mesenchymal proliferation in the vessel wall, myxoid degeneration, obliterative changes in the lumen, mixed inflammatory cell infiltration predominantly composed of mononuclear cells, and increased connective tissue in the periphery, haematoxylin-eosin (blue arrows).

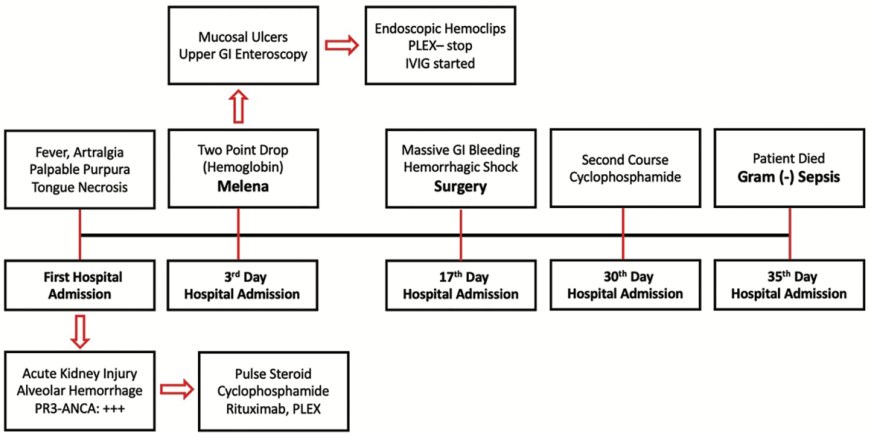

Fig. 2. Chronological summary of the patient's clinical course from diagnosis to outcome.

large-vessel vasculitis often present with jaw claudication, scalp tenderness, and elevated inflammatory markers (3), whereas AAV-associated cases more commonly exhibit concurrent renal, pulmonary, or ear-nose-throat involvement (4). Distinguishing these entities is crucial, as the prognosis and treatment options differ substantially.

Gastrointestinal involvement is an infrequent manifestation of systemic vasculitis and is associated with poor prognosis (5). It is more commonly observed in polyarteritis nodosa and IgA vasculitis (6) and is seen in only 7% of the patients with AAV (7). Gastrointestinal involvement most commonly occurs at the time of AAV diagnosis, usually together with active disease in other organs (1). Currently, no standardised treatment algorithm exists specifically addressing gastrointestinal involvement in AAV and the immunosuppressive agents used for pulmonary and renal involvement are also employed (8). In severe clinical scenarios, such as massive gastrointestinal haemorrhage or multiple bowel perforations, surgical intervention is often unsuccessful and associated with additional mortality. The prognosis is poor, with ICU admission, surgery, and/or death within 6 months of gastrointestinal involvement reported in 48% of cases (9). Our patient had gastrointestinal involvement that was refractory despite treatment with rituximab, cyclophosphamide, PLEX, and IVIG, and died due to infection. This case highlights that, even when other organ manifestations respond to therapy, gastrointestinal disease activity may persist and remain refractory to intensive immunosuppressive treatment. Although long-term mortality in AAV is commonly attributable to infections, cardiovascular disease, malignancy, and vasculitis itself, infections account for nearly half of early deaths (10). Our case, which overcame surgery with successful bleeding control, also underscores the challenge of balancing the need for aggressive immunosuppression with the prevention of infectious complications in refractory AAV.

A. Karakoc[1], *MD*
S. Kopac[1], *MD*
I. Atas[2], *MD*
Y. Z. Erzin[3], *MD*
T. Eskazan[3], *MD*
E. Hatipoglu[4], *MD*
S.N. Esatoglu[1], *MD*
N. Kepil[5], *MD*
A.F. Celik[3], *MD*
G. Hatemi[1], *MD*

[1]Division of Rheumatology, Department of Internal Medicine, Cerrahpaşa Medical School, Istanbul University-Cerrahpaşa, Istanbul;
[2]Department of Internal Medicine, Cerrahpaşa Medical School, Istanbul University-Cerrahpaşa, Istanbul;
[3]Division of Gastroenterology, Department of Internal Medicine, Cerrahpaşa Medical School, Istanbul University-Cerrahpaşa, Istanbul;
[4]Department of General Surgery, Cerrahpaşa Medical School, Istanbul University-Cerrahpaşa, Istanbul;
[5]Department of Medical Pathology, Cerrahpaşa Medical School, Istanbul University-Cerrahpaşa, Istanbul, Turkey.

Please address correspondence to:
Sinem Nihal Esatoglu
Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Kocamustafapaşa Street no: 53, Cerrahpaşa, 34098 Fatih, Istanbul, Turkey.
E-mail: nihalesatoglu@gmail.com

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