CORRESPONDENCE

Nivolumab-associated active neutrophilic gastritis

In recent years, the increasing use of immune checkpoint inhibitors for the treatment of multiple metastatic malignancies has revealed a wide spectrum of immune-related adverse events (irAEs), many of which are managed by the gastroenterologist.[1–3]

Among all gastrointestinal (GI)-irAEs, while colitis has been extensively described, gastritis has only been sporadically reported.[3–5]

We here describe the endoscopic and histopathological features of an acute nivolumab-induced gastritis, before and after oral corticosteroid therapy.

A 57-year-old woman, affected by metastatic clear cell renal carcinoma treated with twelve cycles of nivolumab with complete response, had epigastric pain and loss of appetite. She underwent an upper gastrointestinal endoscopy (UGIE) which revealed diffuse, geographical ulcerations covered with whitish fibrin-like membranes, with surrounding erythematous friable mucosa (figure 1). Oesophagus and duodenum were macroscopically normal. In both antrum and corpus biopsies, histology showed a chronic active *Helicobacter pylori*-negative gastritis with full-thickness mixed (neutrophilic and lymphoplasmacytic) mucosal inflammation, neutrophilic infiltration into glandular epithelium, numerous glandular neutrophilic microabscesses, few apoptotic bodies and reactive (p53-negative) epithelial cell atypia (figure 2). No intraepithelial lymphocytosis or neuroendocrine cell hyperplasia was observed. Cytomegalovirus and Epstein-Barr viruses were not found. A checkpoint inhibitor-induced gastritis was diagnosed, nivolumab therapy was stopped and the patient was treated with 1 mg/kg of oral prednisone and pantoprazole 40 mg daily. After a 2-week treatment, the patient reported remarkable clinical improvement with regular food intake, therefore a gradual tapering of the steroid was started. Since no metastatic recurrence was documented at CT scan, immunotherapy was definitely discontinued. An 8-week follow-up UGIE showed complete mucosal healing (figure 3), also confirmed by histology (figure 4).

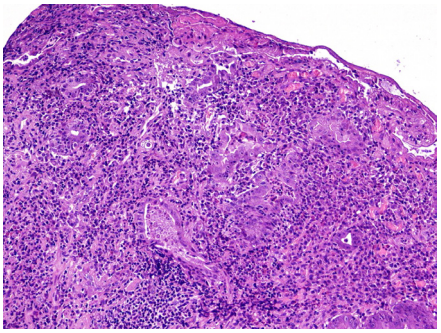

Figure 2 Histology of antral biopsies showing a severe chronic active gastritis with numerous glandular neutrophilic microabscesses and reactive epithelial cell atypia. H&E staining, original magnification x100.

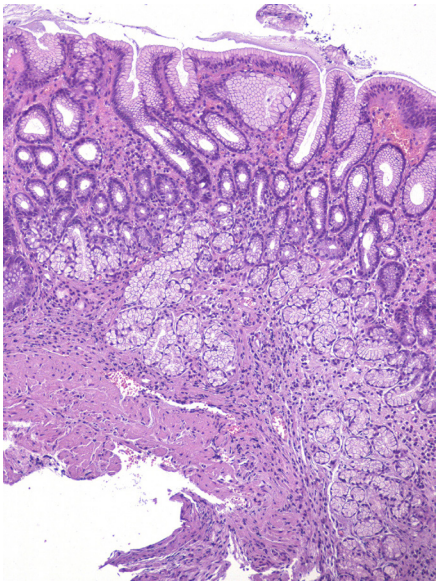

Figure 4 Histology of antral biopsies exhibiting mild chronic gastritis after 8 weeks of oral corticosteroids. No sign of activity was found. H&E staining, original magnification x100.

Immune checkpoint inhibitors GI toxicity is increasingly reported and its underlying mechanisms are object of current interest, but the prompt recognition of its clinical manifestations might be challenging, particularly in an outpatient setting. First, irAEs are characterised by a delayed onset and prolonged duration of symptoms, which should raise their suspicious even months after commencement or discontinuation of immunotherapy. Second, the histopathological assessment is crucial to differentiate them from other more common conditions. A recent study revealed that 22 out of 39 patients suspected for GI-irAEs presented mucosal injury, and that a periglandular inflammation positively correlated with GI-irAEs.[6] Johncilla *et al* characterised histological features of gastritis caused by different immune checkpoint inhibitors, identifying a pattern of injury which includes intraepithelial lymphocytosis and increased apoptotic activity, neutrophilic infiltration within glandular epithelium and 'corkscrew' shaped foveolar hyperplasia . However, in their case series, only one patient received nivolumab as monotherapy, which was responsible for whole GI tract involvement.[7] Therefore, as an immune-related gastritis can mimic different other conditions, such as infectious gastritis (*H. pylori*, herpes viruses, others), vasculitis, Crohn's disease and Behçet's syndrome, histological confirmation is needed and pathologist should be informed of the clinical suspect in order to specifically look for histopathological features which characterise GI-irAEs and help making an accurate diagnosis. Checkpoint inhibitors-associated gastritis, as well as other GI-irAEs, must be considered and promptly treated in this setting, as this might affect the course of their underlying oncological disease due to discontinuation of immunotherapy.

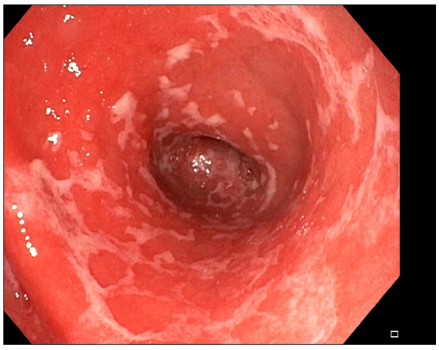

Figure 1 Endoscopic view of the antrum: erythematous mucosa with whitish fibrin-like exudate.

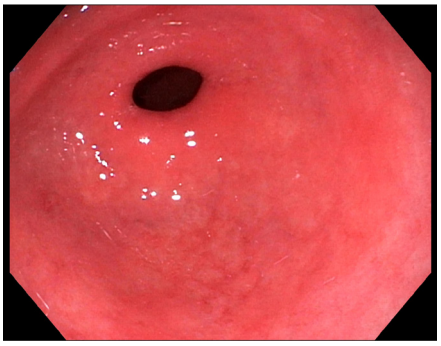

Figure 3 Endoscopic view of the antrum showing complete mucosal healing after 8 weeks of oral corticosteroids.

Laura Rovedatti, [1] **Marco Vincenzo Lenti**,[1] **Alessandro Vanoli**,[2] **Monica Feltri**,[2] **Federico De Grazia**,[1] **Antonio Di Sabatino**[1]

[1]First Department of Internal Medicine, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy
[2]Unit of Pathology, Department of Molecular Medicine, University of Pavia and Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Correspondence to Dr Laura Rovedatti, First Department of Internal Medicine, Fondazione IRCCS Policlinico San Matteo, Pavia 27100, Italy; l.rovedatti@smatteo.pv.it

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ORCID iD

Laura Rovedatti http://orcid.org/0000-0001-6333-7485

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