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Acute Ulceronecrotic Gastritis With Cytomegalovirus Reactivation: Uncommon Toxicity of Immune Checkpoint Inhibitors in Microsatellite Instability–High Metastatic Colorectal Cancer

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Title: Acute ulcero-necrotic gastritis with cytomegalovirus (CMV) reactivation: an uncommon toxicity of immune checkpoint inhibitors (ICI) in a patient with microsatellite instability-high metastatic colorectal cancer (MSI-H mCRC).

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Key-words: immunotherapy; toxicity; gastritis; CMV reactivation; colorectal cancer.

Introduction:

Ipilimumab (anti-cytotoxic T lymphocyte-associated antigen 4 or anti-CTLA4) and Nivolumab (anti-programmed cell death protein 1 or anti-PD1) combination have demonstrated a high anti-tumoral activity, mostly in melanoma¹ and metastatic renal cell carcinoma². Compared to anti-PD-1 monotherapy, the incidence and the severity of adverse events, especially immune-related adverse events (irAEs), are increased^{3,4,5}, sometimes leading to definitely stop ICI. In the CheckMate-142 study⁶ with nivolumab + ipilimumab in MSI-H mCRC, the most common adverse events were dominated by diarrhea (22%), fatigue (18%), pruritus (17%), and colitis (3 %).

Case report:

Herein, we describe the case of a 35 year-old woman treated by a combination of Ipilimumab and Nivolumab for a MSI-H mCRC. After 4 injections of Nivolumab + Ipilimumab, the treatment schedule planned to start a maintenance phase with Nivolumab alone. At that time, a CT scan evaluation confirmed the disease control but emphasized an edema of the gastric wall suggesting gastritis (figure 1). Among clinical symptoms, grade 2 epigastric pain and grade 2 vomiting were correlated with CT-scan images, and grade 3 fatigue, the predominant symptom, required hospitalization. A gastric endoscopy showed macroscopic signs of gastritis, such as erythema with large detached shreds of gastric mucosa (figure 2A). Biopsies allowed the diagnosis of ulcerative lymphocytic gastritis (figure 2B and C), without cytomegalovirus (CMV) – positive cells by immunohistochemistry. The symptomatic treatment included high dose of corticosteroids (2mg/kg/day for 4 days) with proton pump inhibitor and local anti-acid. After 4 days of treatment, even though upper digestive symptoms rapidly improved, a second endoscopy showed persistence of pangastritis, associated with duodenal ulceration (figure 3). New biopsies confirmed the persistence of ulcero-necrotic lymphocytic gastritis, without CMV-positive cells. Colonoscopy did not visualize any macroscopic abnormalities, and colonic biopsies were normal. Because of the clinical improvement, the patient

restarted oral intakes with a progressive reduction of oral corticosteroids (-10mg/week). After 3 weeks, while the patient was asymptomatic, a new gastroscopy revealed the coexistence of some healing lesions and micro-ulcerative pangastritis (figure 4A), which still microscopically corresponded to lymphocytic gastritis. However, at that time, some CMV-positive cells were identified (figure 4B and C), and blood CMV PCR was positive (2825 UI/mL; 3.5 log).

An anti viral treatment was started with IV Ganciclovir 5mg/kg/day, inducing a rapid negativation of blood CMV PCR within 72 hours. After that, an oral treatment with Valganciclovir 1800mg/day was prescribed for 7 days, followed with a dose of 900mg/day for 7 days. Abdominal CT scan was performed 1 month after, and showed complete regression of the gastritis (figure 5). Clinical evolution was favorable and maintenance with Nivolumab was restarted.

Discussion:

To our knowledge, we report herein the first case of severe lymphocytic gastritis induced by ICI and secondarily associated with CMV upon corticotherapy. Thus, this case highlights the role of immunosuppression induced by high dose corticosteroids favorizing CMV reactivation in this context. In 2015, Uslu U. et al first reported a case of a patient developing immune-related colitis (irColitis) with additional CMV-induced hepatitis and no CMV reactivation in colonic biopsies⁷.

Lankes K. et al described another case of irColitis persisting after high dose steroids and infliximab (anti-TNF), leading to the diagnosis of CMV reactivation in colonic biopsies. Clinical symptoms were controlled after antiviral therapy⁸.

In 2017, Franklin C. et al retrospectively analyzed data of 370 patients treated by ICI for metastatic melanoma. Authors identified 41 of them with irColitis. Among them, 5 were refractory to steroids and infliximab combination. All of them had detectable CMV in blood or biopsies. They underlined that presence of CMV DNA in both colonic biopsies and plasma was strongly associated with therapy-refractory irColitis⁹.

ICI are now an integral part of the cancer therapeutic armamentarium. Medical oncologists face new secondary effects called irAEs, which are managed according to expert recommendations¹⁰. For grade 3 or 4 gastro-intestinal toxicities, the use of high dose steroids is recommended. Immunosuppressive drugs, such as infliximab, can be prescribed after failure of corticosteroid. In our case, clearly, immunosuppression due to corticosteroids is the cause of the CMV reactivation. It points out that before introduction of immunosuppressive therapy, when digestive symptoms persist after high dose of steroids, CMV reactivation should be systematically ruled out. On a larger scale, our case underlines the importance of excluding differential diagnosis when immune related adverse events are suspected. In this case endoscopy and histological analysis played a key role.

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Figures:

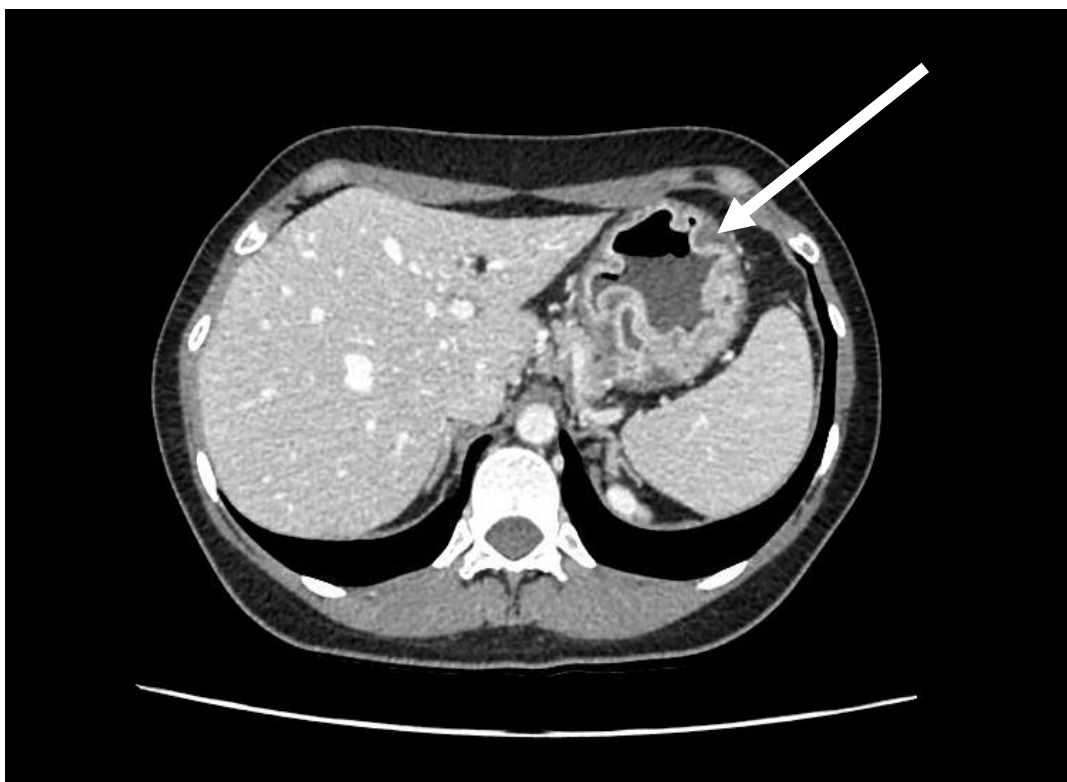


Figure 1: First CT scan performed, showing radiologic sign of gastritis: edema of the gastric wall.

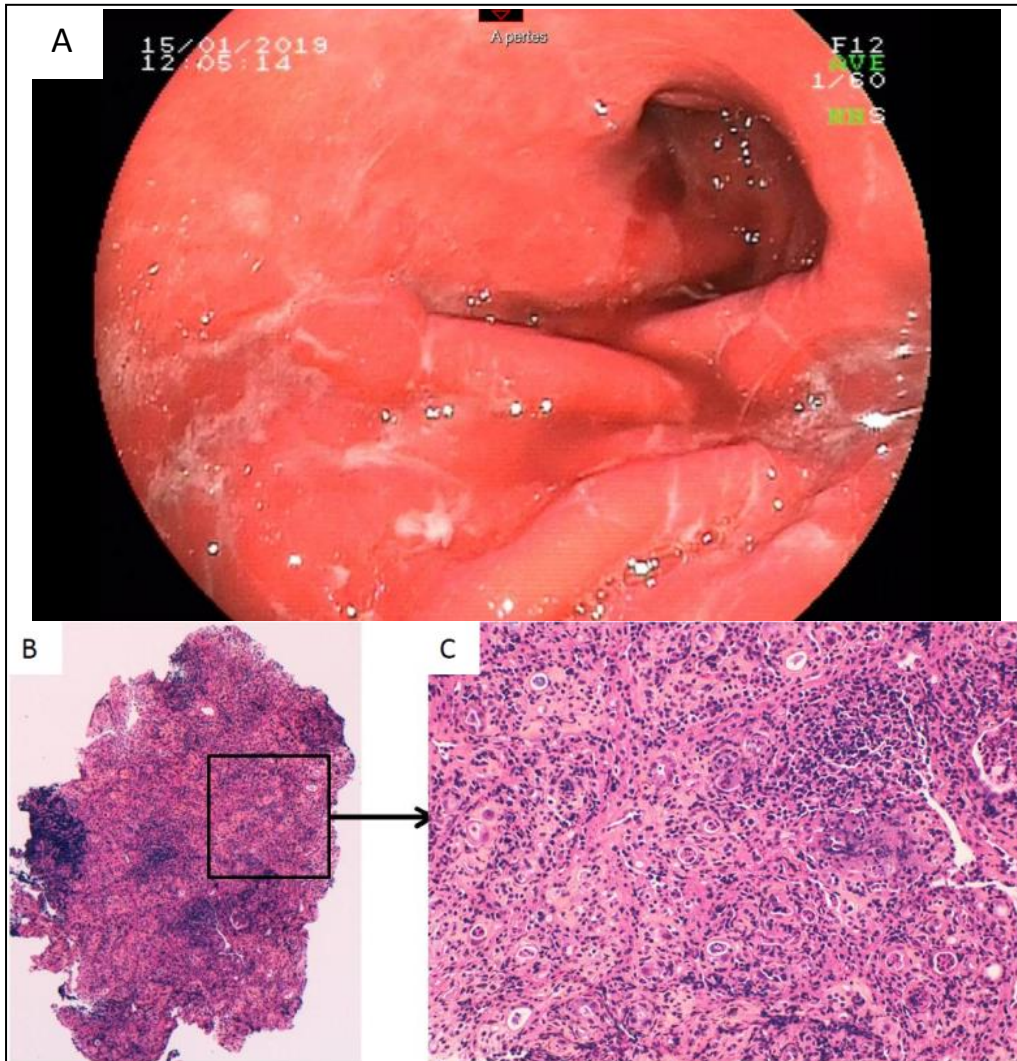


Figure 2A: Photography of the first gastroscopy, after 7 days of symptomatic treatment, showing macroscopic signs of gastritis, such as erythema with large detached shreds of gastric mucosa.

Figure 2B and C: First biopsies, allowing diagnosis of an ulcerative lymphocytic gastritis. (B) HES x40. (C) HES x200.

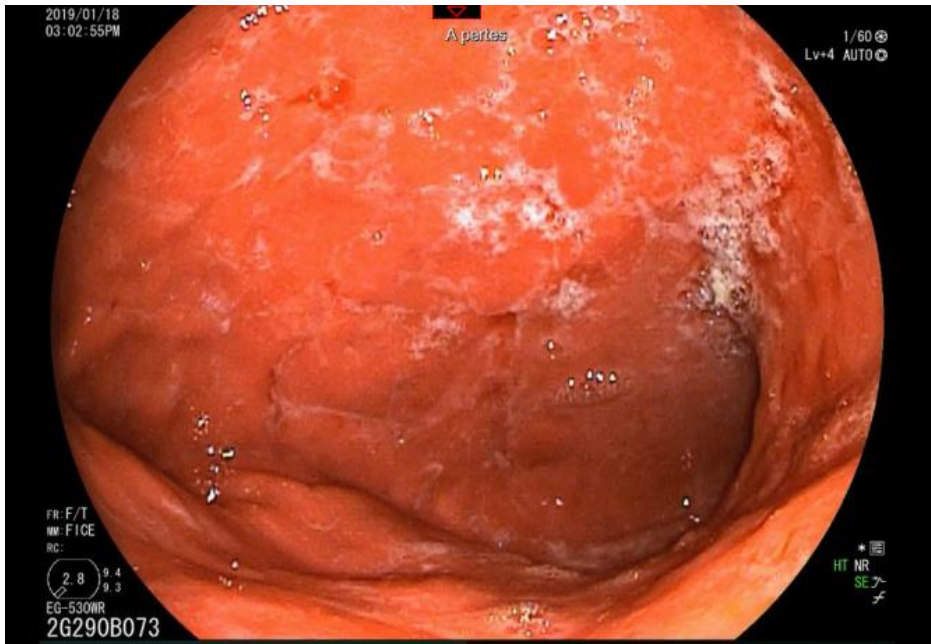


Figure 3: Photography of the second gastroscopy, after 4 days of steroid therapy. Upper digestive symptoms had improved, but pangastritis persisted.

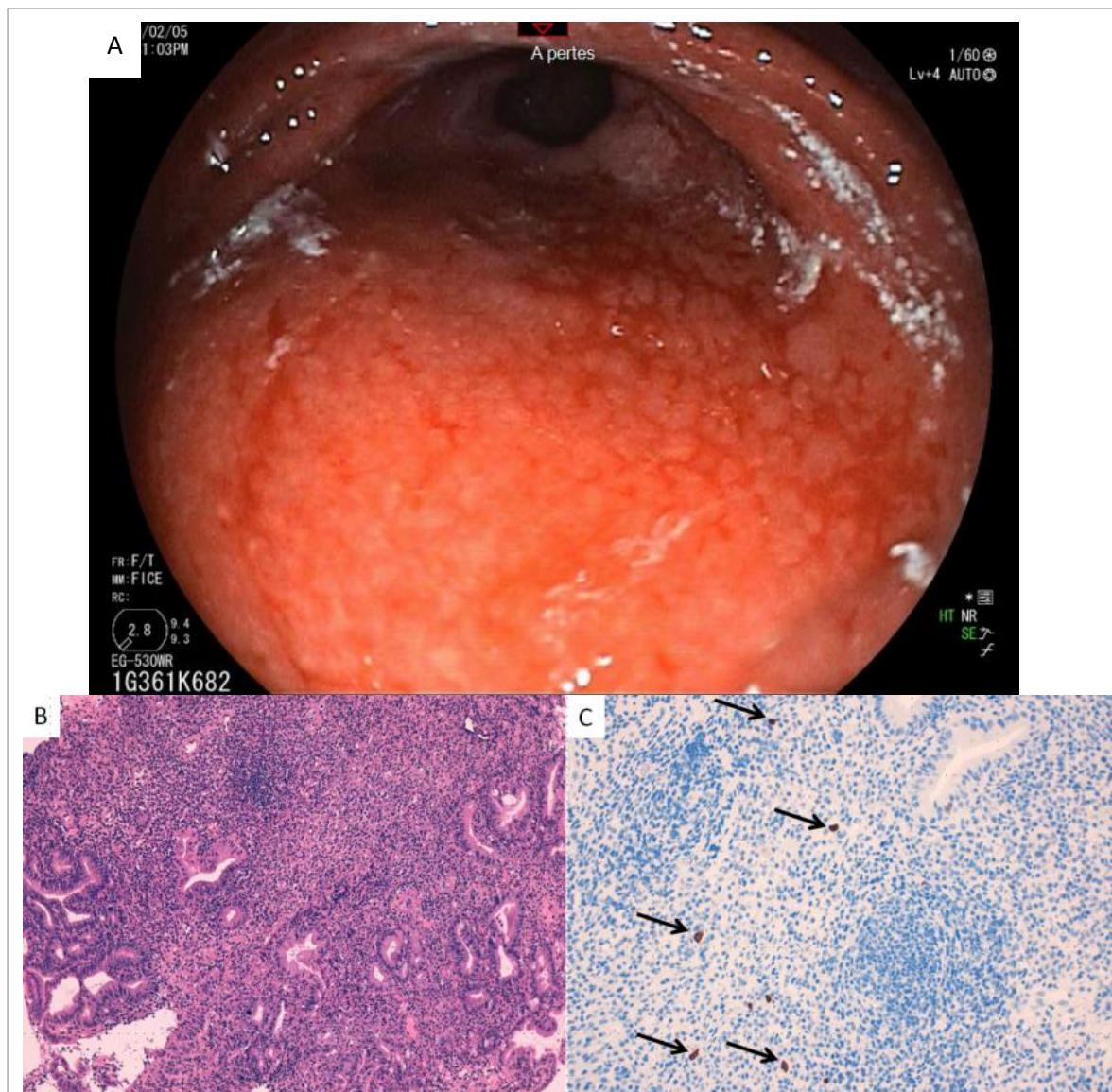


Figure 4A: Photography of the third gastroscopy, performed 3 weeks after the first one. Patient was asymptomatic, but it remained signs of micro-ulcerative gastritis.

Figure 4B and C: Biopsies showing persistence of ulcerative and lymphocytic gastritis, with CMV reactivation. (B) HES X200. (C) Immunohistochemistry anti-CMV showing nuclear labelling of endothelial cells into the gastric mucosa.



Figure 5: Abdominal CT scan showing complete regression of the gastritis, after anti viral treatment.