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Letter to the Editor

Three cases of immune cholangitis related to anti–programmed cell death and programmed cell death ligand agents for the treatment of non-small cell lung cancer

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Dear editors,

Anti-programmed cell death (anti-PD1) and anti-programmed cell death ligand (anti-PDL1) agents are immunotherapy with a growing number of indications. The safety profile is different from chemotherapy resulting of the abnormal activation of the immune system. Most of immune-related adverse events become common, but some, infrequent, are not very well-known. Here, we report the observation of three patients followed in our oncology department for lung cancer, presenting similar features of immune-related cholangitis without any other immune-related adverse events.

A 52-year-old man, treated since 2015 for an advanced lung adenocarcinoma, started nivolumab on July 2017 because of new liver and brain metastasis. In November 2017, after 8 injections, he presented abdominal pain with no fever. Laboratory tests showed hyperleukocytosis, grade I cytolysis and grade III cholestasis (Fig. 1). Autoantibodies and viral infections were negative. He had no history of liver disease and hepatotoxic medication.

Ultrasonography and computed tomography (CT) scan showed a medium-sized biliary duct without obstruction. The small and unique liver metastasis

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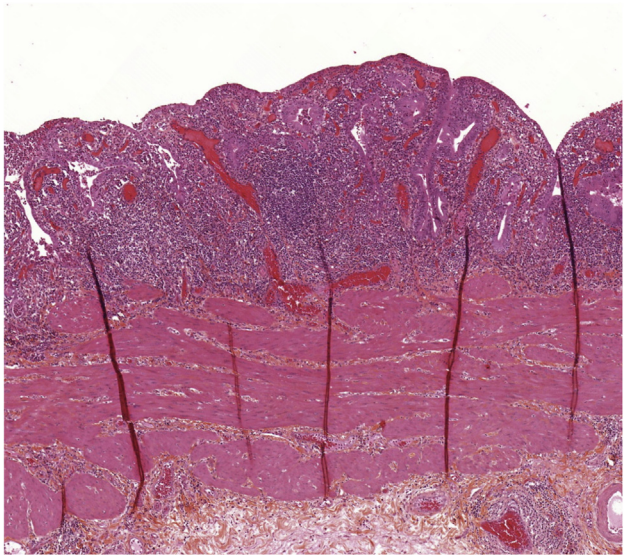

Fig. 1. Hematoxylin Eosin (Hematoxylin Eosin staining) (HEx5) inflammatory infiltrate of the gall bladder.

remained stable, and no thrombosis was found. His treatment was the same as for an infectious cholangitis treatment with cholecystectomy and antibiotherapy. Histology (Fig. 1) was in favor of an acute cholecystitis. As no improvement occurred, a corticosteroid therapy at 0.5 mg/kg was started (Fig. 2.) and immunotherapy was discontinued allowing for clinico-biological improvement. Ursodeoxycholic acid was started at standard dosage three months after the end of the corticosteroid therapy because of the slow decrease of biological abnormalities. It was pursued until laboratory tests returned to normal. Diagnosis of immune-related cholangitis was retained. At this day, despite the discontinuation of immunotherapy, the tumor response keeps persisting.

The second patient had a squamous cell lung cancer metastatic to the liver and bones. In March 2016, he was included in a clinical trial evaluating the combination of durvalumab and tremelimumab in first line. Complete response was achieved, but after the 4th injection, he presented fever, abdominal pain and biological inflammation (Fig. 3). Immunologic and viral explorations were negative. He had no past of liver disease and hepatotoxic medication. CT scan permitted to find a bile duct dilatation. Treatment was the same as for an infectious cholangitis with antibiotic and surgery. Histology (Fig. 4) was in favor of an acute cholecystitis with CD8+ lymphocyte infiltration. The serum IgG4 marking was negative. The bacterial sampling returned negative. Despite treatment, abdominal pain remained unchanged. Further tests showed grade III cholestasis and grade I cytolysis. Considering it as a sign of immune-related cholangitis, a daily treatment of 120 mg of prednisolone was initiated for five days, then reduced to a daily dose of 60 mg. The patient was removed from the trial. As pain decreased and blood tests improved, daily dosage of prednisolone was reduced to 40 mg. Symptoms reappeared. A slow tapering of the prednisolone dosage and introduction of ursodeoxycholic acid helped reducing both abdominal pain and improving blood anomalies. The cancer remained stable for two years after the immunotherapy discontinuation before recurrence.

The third patient, a 61-year-old man, underwent surgery for a localized pT3N0R0 lung adenocarcinoma. After adjuvant chemotherapy, he was included in a clinical trial evaluating pembrolizumab. After the 17th injection, biological hepatic abnormalities appeared with grade II cytolysis and grade III cholangitis. He had no past of hepatic disease and hepatotoxic medication. Endoscopic sonography of the bile ducts found an inflammatory cholangitis. Immune-related cholangitis was mentioned at first. We started corticosteroid therapy at a daily dosage of 1 mg/kg. Blood tests improved immediately. We then stopped immunotherapy. Cholestasis reappeared due to fast tapering of corticosteroids. Daily dosage of corticosteroids was increased to manage it. (Fig. 5) At this day, there is no evidence of cancer progression.

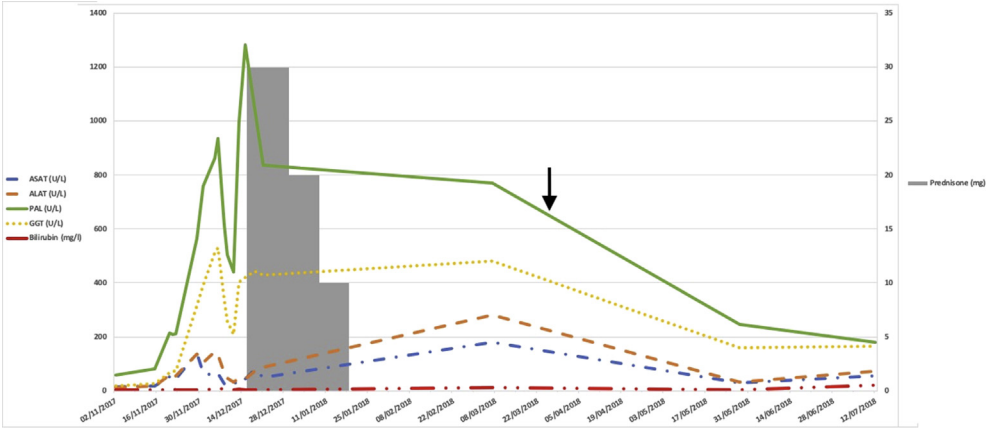

Fig. 2. Biological abnormalities and corticosteroid therapy of the first patient. Arrow for the beginning of ursodeoxycholic acid.

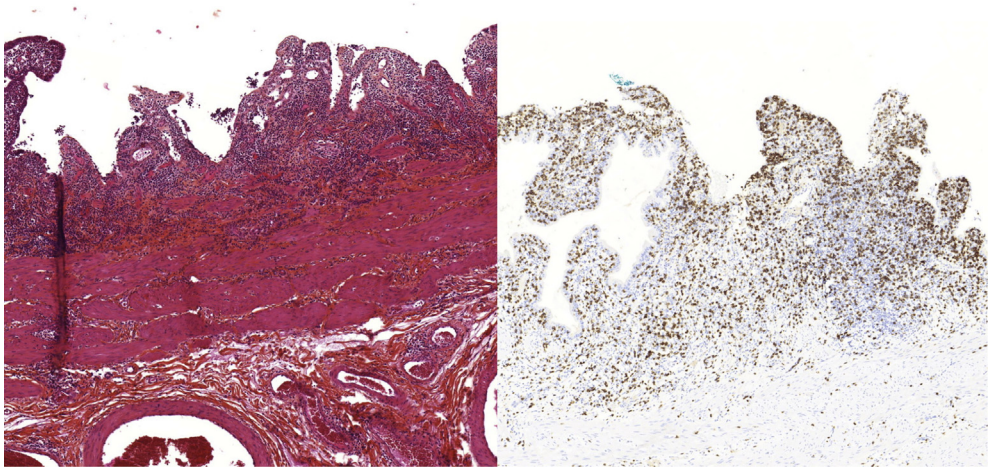

Fig. 3. (left) HEx10: lesion of acute cholecystitis with a dystrophic aspect of some glandular recess in connection with inflammatory changes. (right) CD8: marking of many elements with labeling of intraepithelial lymphocytes.

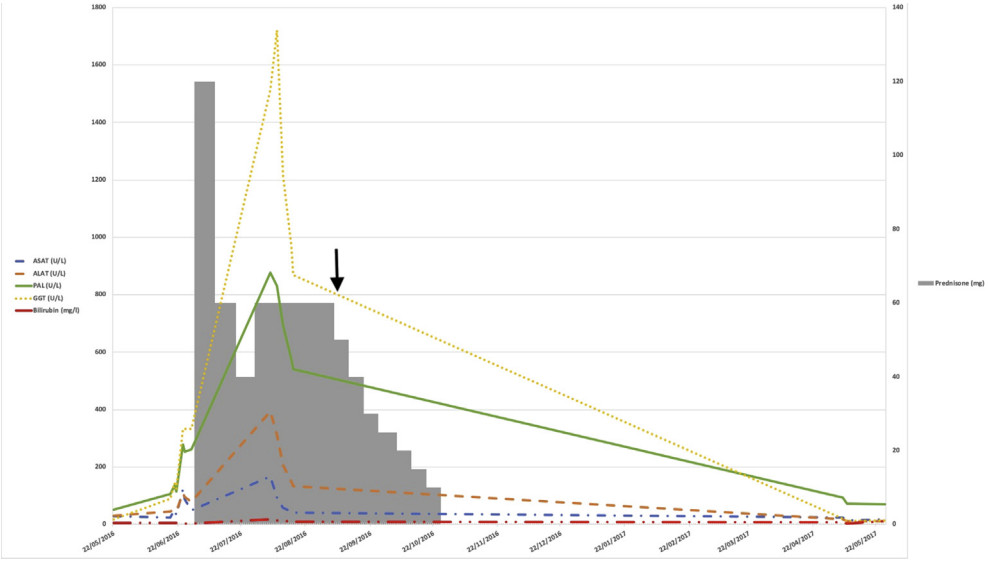

Fig. 4. Biological abnormalities and corticosteroid therapy of the second patient. Arrow for the beginning of ursodeoxycholic acid.

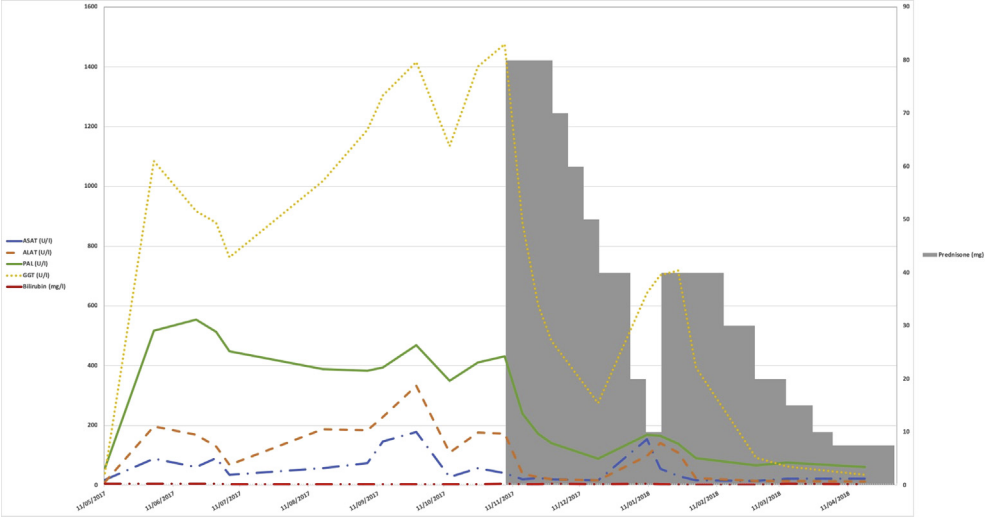

Fig. 5. Biological abnormalities and corticosteroid therapy of the third patient.

Immune cholangitis related to anti-PD1 is a very rare complication and newly described. Since the first observation in 2017 [1], to date, only 9 cases have been published [2,3]; 10 cases of immune cholangitis related to nivolumab and 4 to pembrolizumab have been reported to the French pharmacovigilance. Abnormalities started after a long exposition to the drug for the two cases with anti-PD1 and very earlier for the bitherapy anti-PDL1 and anti-CTLA4. In accordance with previously published cases, clinical symptoms were abdominal pain, fever and asthenia. Biochemical abnormalities were anicteric cholestasis, with a secondary moderate cytolysis. Gelsomino *et al.* [3] suggested to distinguish immune-related cholangitis from other autoimmune liver disease by detection of autoantibodies, serum IgG4 and histological features. Liver biopsies showed a CD8 positive T lymphocyte infiltration. We did not perform liver biopsy but had gall bladder histology for 2 patients which also showed CD8-positive lymphocyte infiltration and inflammation for the second. Autoimmune cholangitis management induced by immunotherapy is not codified, based on discontinuation of immunotherapy and initiating corticosteroid therapy [4,5]. Previously published cases reported disappointing response to steroids. The response was similar for our patients with gradual improvement of liver disorders. In all cases, clinical benefit appeared rapidly after the beginning of corticosteroid therapy. In 2 cases, reascension of biological abnormalities was reported during the decline of the corticosteroid treatment illustrating a corticodependence rather than a corticosteroid resistance. Cholecystectomy was performed for two of our patients because of the suspicion of infectious cholecystitis. It had no effect on the evolution of the autoimmune pathology.

Here, we report a series of 3 cases of immune-related cholangitis attributed to anti-PD1 and anti-PDL1 immunotherapy, including a first reported case of cholangitis with anti-PDL1 and anti-CTLA4. The diagnosis is based on several arguments. Histology should be performed to consolidate diagnosis. The stop of immunotherapy is needed, and corticotherapy leads to a clinical improvement but slow and inconstant normalization of biochemical abnormalities. The place of ursodeoxycholic acid remains to be defined. It is the clinical improvement at the end of the immunotherapy and the corticotherapy that will make it possible to establish or consolidate the diagnosis hypothesis.

Conflict of interest statement

None declared.

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