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Ustekinumab for corticodependent immune-mediated colitis by pembrolizumab, an alternative for patients with concomitant liver injury

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Pembrolizumab, a programmed cell death receptor (PD-1) inhibitor, have improved the prognosis in several types of cancer. Despite the important clinical benefits, checkpoint inhibition have been associated with inflammatory and immune-related side effects (irAE) [(1)].

We report the case of a 56-year-old woman with stage IV large cell lung cancer who was treated with pembrolizumab. The patient developed diarrhea, more than six stools per day, requiring hospital admission. Laboratory tests showed high fecal calprotectin (2355 μg/g), negative coproculture, proctosigmoiditis in the colonoscopy and the biopsy was consistent with immune-mediated colitis (figure 1). The patient evolved unfavourably, so we prescribed intravenous methylprednisolone with clinical improvement.

On the other hand, elevated gamma-glutamyltransferase (GGT) and alkaline phosphatase (ALP) were detected. A complete study was performed, including serology, ANA, SMA and antiKLM negatives, with the rest of metabolic study normal.

No intrahepatic and extrahepatic bile duct pathology was found in the magnetic resonance cholangiopancreatography. The liver biopsy was determinant for the diagnosis of liver noninmmune-mediated injury. Thus, our patient was diagnosed with cholestatic liver injury induced by pembrolizumab. Kurokawa et al [(2)] reported the only case of nonimmune-mediated toxicity secondary to Pembrolizumab in the literature. This adverse effect has consequently conditioned the treatment of immune-mediated colitis.

In order to reduce the high doses of prednisone required, we decided to start maintenance immunosuppressive therapy. Treatment with Infliximab, Mycophenolate or Vedolizumab are indicated in patients with steroid refractory or corticodependent colitis. Nevertheless, hepatotoxicity has been described with all these drugs. Queiroz N. et al. [(3)] have described hepatobiliary alterations in patients treated with Vedolizumab, 5 of the 23 hepatic events were categorised as serious. In others studies, Ustekinumab was an effective alternative in patients treated with Vedolizumab and incomplete response. [(4.5)]

Hence, we decided to start treatment with Ustekinumab (390 mg intravenous and 8 weeks later 90 mg subcutaneous) as a first-line biological avoiding anti-TNF alpha and vedolizumab to avoid worsening the liver lesion. In relation to the cholestasic liver injury we add ursodexicolic acid (15 mg/kg daily).

The clinical evolution was favourable with normalisation of hepatic function, clear improvement of colitis with clinical, radiological and histological remission.
In conclusion, we report a patient with immune-mediated colitis and nonimmune-mediated cholestasic injury induced by pembrolizumab. We consider Ustekinumab as a good therapeutic option in these patients in order to prevent a worsening in liver injury.

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Figure 1. A. Active colitis with only mild architectural changes. Frequent microabcesses wihout granulomas. HE, 40x. B. High power view of inflammatory colonic changes. Frequent neutrophilic microabceses and isolated apoptosis suggested toxicity. Without architectural changes. HE, 400x. C. Portal tracts showed a moderate mixed inflammatory infiltrate with mild periportal hepatocyte lesions. HE, 400x. D. Duct epithelium showed injury with “dysmorphic changes”and lymphocytes. HE, 400x.

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