

# A case of nivolumab-related cholangitis and literature review: how to look for the right tools for a correct diagnosis of this rare immune-related adverse event

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**Summary** Anti-programmed cell death-1 (PD-1) monoclonal antibodies, such as nivolumab, used for the treatment of several tumors, can trigger effector T-cells against tumor- and self-antigens, leading to the occurrence of different immune-related adverse events. Among them, liver injuries are rare and usually transient. To date, only four cases of immune-related cholangitis in non-small cell lung cancer (NSCLC) patients have been described during nivolumab treatment. Here, we describe laboratory tests, imaging and liver biopsy features that confirm this diagnosis as opposed to other forms of autoimmune liver disease; nevertheless, we also provide evidence of the presence of different clinical-pathological patterns of immune-related cholangitis.

**Keywords** Nivolumab · Cholangitis · Non-small cell lung cancer · Immunotherapy

Recent advances in the field of cancer have led to a paradigm shift in the management of several solid tumors, including melanoma and non-small cell lung cancer (NSCLC). Different immune-oncology (I-O) agents have been developed and already approved. Among them, nivolumab, a fully human IgG4 monoclonal antibody, blocks the interaction between programmed cell death-1 (PD-1) receptor and its

ligands (PD-L1 and PD-L2). The inhibition of PD-1/PD-L1 axis restores immune competence, overcoming the mechanisms of escape of tumor cells [1, 2].

In early phase I and II trials, nivolumab showed promising antitumor activity and a good safety profile [3–5]. Two phase III trials demonstrated that nivolumab is more effective and safe than standard docetaxel second-line therapy in advanced NSCLC [6, 7]. These data led to its approval for the treatment of both squamous and non-squamous NSCLC histologies.

However, the inhibition of PD-1/PD-L1 pathway can lead to an abnormal activation of the immune system, reducing its competence to recognize the normal cells as “self”. This process can promote the emergence of autoimmune disorders, known as immune-related adverse events (ir-AEs). Among these toxicities, liver injuries are rare and usually transient, reaching 1–3% and <1% for grade 1–2 and 3–4 hepatitis, respectively [8]. Conversely, only one case of nivolumab-related cholangitis was previously described [9]. More recently, Kawakami and colleagues reported other three cases from a single Institution database including 91 advanced NSCLC patients treated with nivolumab [10].

None of these Japanese patients had a previous history of autoimmune cholangitis. They presented with fever, abdominal discomfort and fatigue. Viral hepatitis markers, as well as autoantibodies associated with liver disease, were negative; however, antinuclear antibodies (ANA) were positive in one case.

The absence of serum IgG4 elevation made unlikely a diagnosis of IgG4-related cholangitis. No information was reported about perinuclear antineutrophil cytoplasmic antibodies (pANCA), usually associated with primitive sclerosing cholangitis.

A predominant elevation of alkaline phosphatase (ALP) and gamma-glutamyl-transpeptidase (GGT) enzymes was reported in all patients, while transaminases (AST/ALT) and

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total bilirubin values were only moderately increased. Ultrasonography showed a diffuse hypertrophy of the extrahepatic bile duct, whereas computed tomography (CT) scan demonstrated the presence of bile duct dilation without obstruction. In two cases, liver function tests (LFT) abnormalities appeared 3 and 4 months after the beginning of nivolumab; in one case LFT became abnormal 2 months after the last administration. The time course of LFT evolution was different for each patient. Two patients, treated with moderate doses of prednisolone, had a modest response and showed a biliary enzymes flare after steroid tapering and nivolumab resumption. Liver biopsy showed a predominant CD8-positive T cell infiltrate, without spotting or bridging necrosis.

We also differentiated our case [9] from autoimmune hepatitis (AIH) and principle forms of cholangitis by performing laboratory tests, autoantibodies, imaging techniques and liver biopsy.

On the contrary, our case presented with jaundice and itching; viral infections (HBV, HCV, HAV, HEV, CMV, EBV and Parvovirus B19) and storage diseases were excluded. Gamma-globulins and IgG4 levels were within the normal range. Further information included the absence of ANCA, LKM, SLA/LP, LC1, anti-MPO, anti-PR-3 antibodies and of liver injury induced by previous treatment. Human leukocyte antigen (HLA)-DR11 was found, but not HLA-DR3 or DR4, usually associated with AIH.

A liver ultrasonography did not demonstrate the presence of liver metastases, portal thrombosis or distension/alteration of the biliary tree.

Finally, histological examination of the liver biopsy showed the presence of a T lymphoid infiltrate (CD3+) with a prevalence of CD8-positive cells, as part of bile ducts aggression and intraductal microabscesses, and mild sinusoidal expansion without fibrosis.

Overall, our case presents some similarities and some differences respect to the cases reported by Kawakami and colleagues.

Histological findings were similar, providing the evidence of a significant T-cell infiltrate with predominant CD8-positive cluster in all cases; in our patient, additional immunohistochemistry showed a strong PD-L1 protein expression in hepatocytes and Kupffer cells and immunoreactivity for cytokeratin-19 and -7, consistent with ductular proliferation.

Time to resolution was in general very long, particularly for biliary enzymes, and response to steroid administration was disappointing. In Japanese patients, the low dose of steroid, along with a too rapid tapering, and the lack of ursodeoxycholic acid use could explain the biliary enzymes flare when nivolumab was resumed.

On the other hand, several features, as the time to onset, clinical presentation, LFT abnormalities and imaging patterns, varied from case to case. In our case, there was a predominant elevation of total bilirubin, GGT and ALT and, 2 months since

nivolumab was suspended, a CT scan continued to exclude biliary tract dilation. Conversely, it is noteworthy that mild extrahepatic bile duct distension was present in all three Japanese patients before the start of nivolumab, as a possible expression of a latent large-ducts cholangitis.

This comparison allowed us to hypothesize that this pattern of cholangitis differs from other autoimmune liver disease. The differential diagnosis between immune-related cholangitis and other forms is based on laboratory assays, imaging and histological features [11]. The detection of both circulating anti-mitochondrial antibodies (AMA) and elevated IgM levels associated with distinctive histological features, such as focal duct obliteration with granuloma formation, is consistent with a diagnosis of primary biliary cholangitis. Conversely, the identification of both circulating pANCA and elevated IgG levels, associated with periductal fibrosis, is suggestive of primary sclerosing cholangitis. Finally, the detection of both high serum IgG4 values and typical histological aspects, such as fibrous obliterative cholangitis associated with infiltration of IgG4-positive plasma cells, is suggestive of IgG4-related cholangitis. At the same time, a diagnosis of primary sclerosing cholangitis or IgG4-related cholangitis is also unlikely in absence of morphological alterations of the biliary tract by imaging.

Notably, in our opinion, the histological pictures should be considered a fundamental prerequisite for a correct diagnosis of immune-related cholangitis; therefore, we strongly suggest to perform a liver biopsy whenever possible. In fact, the detection in the liver tissue of a T lymphoid infiltrate (CD3+) with a prevalence of CD8-positive cells, along with mild sinusoidal expansion without fibrosis and ductular proliferation, allow us to obtain a more accurate diagnosis.

Finally, comparing these first reports, we think that there are different forms of immune-mediated cholangitis, such as “large-ducts cholangitis” reported by Kawakami and “small-ducts cholangitis”, as described by our group. These cholangitic patterns have different clinical presentation and biochemical evolution and are associated with various outcome. Furthermore, they seem to respond poorly to steroid treatment and, in presence of severe toxicity, it is our opinion that nivolumab should be permanently discontinued at least as long as more effective therapies for this liver injury are identified.

#### Compliance with ethical standards

**Conflict of interest** All authors declare that they have no conflict of interest.

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**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed consent** For this type of study, formal consent is not required.

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