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Letter to the Editor

Focal immune-related pancreatitis occurring after treatment with programmed cell death 1 inhibitors: a distinct form of autoimmune pancreatitis?

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Dear Editor,

A 76-year-old female was diagnosed with urothelial carcinoma and treated with R0 nephroureterectomy (pT3, N0, M0, G3) plus adjuvant M-VAC (methotrexate, vinblastine, Adriamycin, cisplatin). She received intravenous pembrolizumab (200 mg/3 weeks), a humanised antibody against programmed cell death 1 (PD-1) receptor, for local nodal recurrence with complete response. Her personal and family history was unremarkable, and she was not a smoker or alcohol drinker.

She came to our attention at the end of treatment, for recent onset of grade 2 diarrhoea and weight loss. A follow-up computed tomography (CT) showed mild dilation of the main pancreatic duct (MPD), and a magnetic resonance imaging (MRI) with cholangiopancreatography was performed, confirming MPD dilation secondary to a tapered stricture in the pancreatic head (Fig. 1A). On conventional T1- and T2-weighted images, no clear focal lesions were detected in the pancreatic neck (Fig. 1B), which, however, showed a diffuse signal restriction on diffusion-weighted imaging (DWI) (Fig. 1C).

An endoscopic ultrasound (EUS) performed to rule out a pancreatic neoplasia showed a 2-cm hypoechoic solid lesion of the pancreatic neck, stiff at elastography, with low vascularity after the administration of contrast agent (SonoVue) (Fig. 2A and B), causing stenosis of the MPD with upstream dilation. EUS findings and behaviour at elastography and after contrast media suggested a diagnosis of pancreatic adenocarcinoma. Fine-needle aspiration was performed with cytology negative for neoplasia, revealing, however, a dense granulocytic inflammation. Amylase, lipase, IgG4 and CA 19-9 levels were normal, while faecal elastase reduced (41 mcg/g; normal>200), suggesting exocrine pancreatic insufficiency (EPI). Therefore, she started

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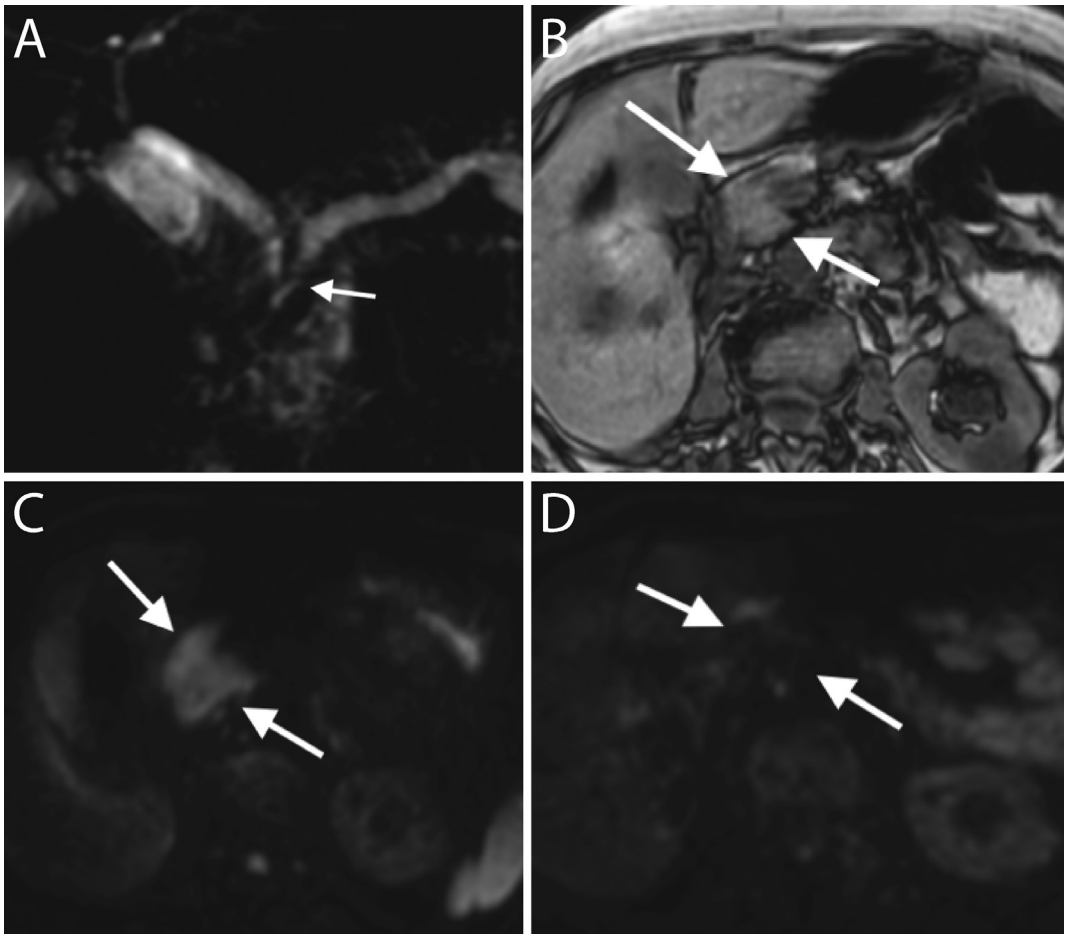

Fig. 1. (A) Magnetic resonance cholangiopancreatography showing main pancreatic duct dilatation (calibre, 5 mm), secondary to a tapered stricture (white arrow) in the pancreatic head. (B) On T1-weighted morphologic image, pancreatic head (arrows) has normal signal intensity with no evidence of solid focal lesions. (C) On diffusion-weighted image, a marked increase in signal intensity of the same region of the pancreatic head (arrows), indicating restricted diffusion, is evident. (D) At imaging follow-up, using diffusion-weighted images, complete normalisation of signal intensity of the pancreatic head is observed.

pancreatic enzyme replacement therapy (PERT), with pancrelipase (20.000 units at breakfast, 40.000 units at lunch and dinner), with prompt diarrhoea remission and weight gain.

A follow-up EUS after 2 months showed disappearance of the above-mentioned lesion and only finding of hypoechoic and inhomogeneous parenchyma, diffuse hyperechoic foci and strands, with pancreatic head atrophy; MPD was thin and irregular. These findings were consistent with an undetermined diagnosis of chronic pancreatitis according to the Rosemont classification. Notably, distal common bile duct (CBD) and superior mesenteric artery (SMA) showed thickening of walls (1 and 1.6 mm, respectively), as in cases of cholangitis and vasculitis (Fig. 2C and D).

After 2 other months, an MRI scan using DWI confirmed the absence of any solid pancreatic lesion (Fig. 1D). The patient remained asymptomatic and in good clinical conditions, although faecal elastase levels remained low and PERT was maintained.

Discussion

Treatment with PD-1 inhibitors, programmed cell death 1-ligand (PD-L1) inhibitors and cytotoxic T-lymphocyte antigen 4 (CTLA-4) blockers enhances anti-tumour immune response by directly blocking 'immune checkpoints' and has been proved effective against several tumours, including melanoma, Hodgkin lymphoma, non-small cell lung cancer, bladder and renal cancer and head and neck squamous-cell carcinoma [1]. These drugs are generally well tolerated, but occurrence of peculiar side-effects resembling immune-mediated disorders occurs [1].

Among them, 'immune-related pancreatitis' is uncommon, but of particular interest, given its potential significant morbidity and long-term consequences.

In a retrospective study evaluating side-effects in 496 patients with metastatic melanoma, 1.8% developed pancreatitis [2]. In all cases, steroids or interruption of treatment led to recovery, except for one case developing EPI.

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