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Letter to the Editor

Acute pancreatitis after vismodegib for basal cell carcinoma: a causal relation?

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Dear Editor,

Vismodegib, a hedgehog pathway inhibitor, is indicated for treatment of adults with locally advanced or metastatic basal cell carcinoma (BCC) [1]. The most commonly reported adverse reactions associated with vismodegib are muscle cramps/spasms, alopecia, dysgeusia, weight loss, nausea, decreased appetite, fatigue and diarrhoea [1].

Acute pancreatitis is an acute inflammation of the pancreas that varies in severity from mild to life threatening. The major causes of acute pancreatitis are gallstones (30–60%) and heavy alcohol use (15–30%). Drug-induced pancreatitis is rare (1–2%) [2].

Here, we present a case of vismodegib-induced pancreatitis in a woman treated for BCC.

1. Case report

A 79-year-old white woman presented in 2018 with a locally advanced recurrent BCC of the right ear. The tumour was considered non-resectable, and a targeted therapy with the sonic hedgehog inhibitor vismodegib was initiated at 150 mg/d. The patient's medical history included diabetes mellitus, chronic obstructive pulmonary disease, depression, glaucoma and hypertension.

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She was treated for more than 5 years with insulin glargine, liraglutide, repaglinide, metformin, pravastatin, irbesartan/hydrochlorothiazide, amlodipine, aspirin, bisoprolol, sertraline, salmeterol plus fluticasone propionate and latanoprost.

At day 26 after vismodegib initiation, she complained of epigastric pain, minor muscle cramps and hypogeusia. At day 28, the epigastric pain was more intense with post-prandial reinforcement. At physical examination, she had lost 4 kg, abdominal palpation was normal, she was haemodynamically stable and had no fever, chills, jaundice or scleral icterus. She did not report any history of liver disease, hepatitis, or alcohol use. The patient also denied concurrent use of any other medications including steroids.

Laboratory tests revealed increased levels of serum lipase 276 U/L (N < 60), normal white cell count and CRP: 2 mg/dL. Liver tests revealed normal aspartate aminotransferase 28 UI/L, alanine aminotransferase 38 UI/L, alkaline phosphatase 93 UI/L and total bilirubin 2.5 mg/L but elevated gamma glutamyl transpeptidase 115 UI/L (N < 36).

Vismodegib was discontinued at day 28, and abdominal computed tomography revealed an interstitial edematous acute pancreatitis with focal enlargement of the pancreatic tail, loss of its lobulation, mild surrounding fat stranding and no parenchymal or peripancreatic necrosis (Fig. 1). She was referred to the gastroenterology department where abdominal ultrasonography ruled out the presence of gallstones, biliary sludge, biliary ductal dilatation or choledocholithiasis. No biological severity biomarker was found: mild hypertriglyceridemia (2.08 mmol/L, N < 1,7) and no hypercalcaemia (corrected calcium: 2.25 mmol/L). Her symptoms resolved, and the lipase level went back to normal after 35 days. Magnetic resonance cholangiopancreatography (MRCP) was completed few weeks after and revealed side-branch intraductal papillary mucinous neoplasms (IPMNs) located to the head of the pancreas.

Vismodegib was not reintroduced, and the patient had a surgical resection of her BCC. After a follow-up of 12 months, she did not present any clinical or biological sign of pancreatitis.

2. Discussion

Here, we report a case of acute pancreatitis appearing less than one month after introduction of vismodegib and resuming after stopping the drug. This chronology strongly suggests a link between vismodegib and the pancreatitis. Drug-induced acute pancreatitis is now well characterised and classified [2,3]. Several potential mechanisms have been proposed from duct constriction due to localised angioedema and arteriolar thrombosis to cytotoxic and metabolic effects or hypersensitivity reactions [2]. The diagnosis of drug-induced acute pancreatitis requires elimination of all other possible etiologies. In our case, many usual pancreatitis causes have been ruled out: gallstones, biliary sludge and microlithiasis, alcohol, severe hypertriglyceridemia, hypercalcaemia, post-endoscopic retrograde cholangiopancreatography, steroids intake, infection, trauma and vascular disease [2].

IPMNs that were fortuitously discovered in our patient with MRCP is a possible aetiology, but they were very limited in size and located on a side branch at the pancreatic head, while the pancreatitis was located on the tail on computed tomography scan. For those reasons, we think, as suggested by the timing of events, that MRCP could have been rather a predisposing pancreatitis factor while the patient was on vismodegib. The responsibility of vismodegib is reinforced by experimental data showing that hedgehog pathway is critical in pancreas development and physiology [4].

Moreover, interrogating the EudraVigilance database and the FDA Adverse Events Reporting System, we found that 5 cases of pancreatitis have been reported in association with vismodegib therapy. In the Canadian monography of vismodegib, one case of fatal

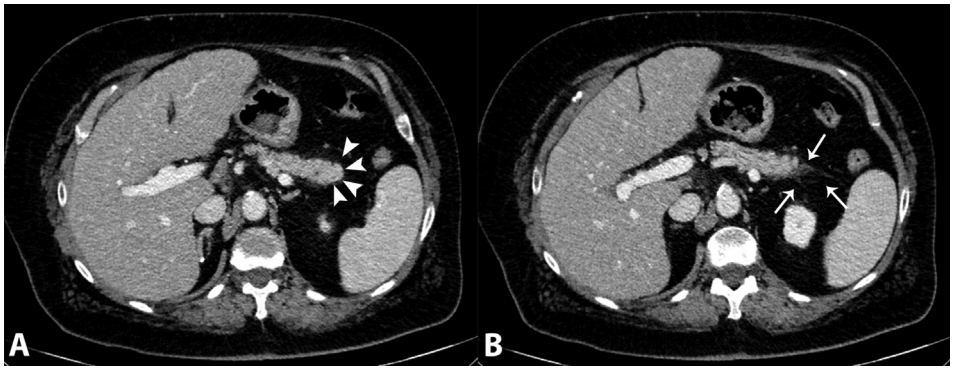

Fig. 1. CT scan of our patient showing (A) a loss of the lobulations of the pancreatic tail (arrowheads) and (B) a mild surrounding fat stranding (arrows), characteristics of interstitial oedematous pancreatitis. CT, computed tomography.

pancreatitis is also mentioned. In one phase II trial, increased lipase concentration elevations grade III–IV were reported in 5% of patients treated with sonidegib for advanced BCC [5].

Overall, drug-induced pancreatitis represent approximately 0.1–2% of acute pancreatitis incidents, and this information is mostly collected via clinical case reports or small series of patients presenting with this rare adverse event. This suggests that true incidence of drug-induced pancreatitis could be even higher [2,6]. It is thus critical to report these cases to the community. Management of drug-induced acute pancreatitis requires withdrawal of the offending agent and supportive care. Failure or delay in identifying the responsible drug might have serious consequences since, although the majority of drug-induced pancreatitis is mild to moderate in severity; severe and even fatal cases can occur [2].

3. Conclusion

Pancreatitis is a rare and potentially severe adverse event during vismodegib treatment that could be facilitated by an underlying silent anatomical pancreatic condition like in our patient. Physicians should be aware of this possible relationship because an early diagnosis and prompt cessation of the offending agent are critical. Further investigations are needed to learn more about the relationship between pancreatic and sonic hedgehog pathway inhibitors.

Conflict of interest statement

C.R. has acted as a consultant of BMS, Pierre Fabre, Merck, Novartis and Roche.C.V. and J.B. declare no competing interests.

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Additional contributions

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