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DOI: <https://doi.org/10.1016/j.pathol.2021.11.010>

A case of steroid responsive nivolumab induced cholangitis

To the Editor,

Immune checkpoint inhibitors (ICIs) are increasingly being used for the treatment of a range of advanced malignancies after demonstrating sustained clinical responses and improved long term survival in phase III clinical trials for a subset of treated patients.¹ The current ICIs in clinical use are monoclonal antibodies that bind specific immune checkpoint proteins: cytotoxic T-lymphocyte-associated protein 4 (CTLA-4); programmed cell death protein 1 (PD-1) or its ligand (PD-L1). Upon binding, these antibodies inhibit the action of these checkpoints and enhance the T-cell mediated anti-tumour response.² This increased immune response is also associated with a distinct set of immunologically mediated toxicities referred to as immune related adverse events

(irAEs). Hepatotoxicity is a common irAE which typically manifests as an asymptomatic rise in the transaminases.³ Small and large duct cholangitis have been very rarely reported and currently lack established diagnostic criteria or specific treatment guidelines.⁴ Nivolumab is a PD-1 inhibitor currently approved in Australia for the treatment of non-small cell lung cancer (NSCLC) and other advanced cancers.⁵ Here we present the clinicopathological aspects of what is to our knowledge the first Australian case of nivolumab induced small duct cholangitis in a patient with NSCLC.

A 75-year-old female with locally advanced NSCLC was commenced on palliative nivolumab (480 mg, 4-weekly) after she presented with clinical and radiological disease progression despite initial treatment with chemoradiation. Her liver function tests (LFTs) were all within the normal range prior to starting nivolumab. Other past medical history included chronic obstructive pulmonary disease, previous embolic cerebrovascular accident secondary to chronic atrial fibrillation, and colonic adenocarcinoma currently in remission after resection and adjuvant chemotherapy. Her only medications at the time were apixaban (2.5 mg twice daily) and sotalolol (40 mg twice daily). Routine blood tests 45 days after commencing nivolumab (2 cycles) demonstrated a cholestatic predominant LFT derangement with no synthetic dysfunction (Fig. 1). Tests for viral and autoimmune hepatitis were negative. Abdominal ultrasonography showed no biliary obstruction or liver metastases. Due to the temporal relationship with nivolumab administration the patient was treated for a presumptive immune related liver injury. Nivolumab was ceased and she was started on intravenous methylprednisolone followed by oral prednisone weaned over the subsequent two months leading to complete resolution of LFT derangement. She remained asymptomatic throughout this period. However, 15 days after her cessation of oral prednisone, the patient re-presented with nausea, jaundice and a rebound of her cholestatic LFT derangement. Further investigations with computed tomography of the abdomen and pelvis and magnetic resonance cholangiopancreatography were unremarkable. Additionally, a percutaneous liver biopsy was performed. The patient was again treated with 3 days of methylprednisolone followed by oral prednisone which was weaned and ceased 2 months later after resolution of her LFT derangement.

In view of the strong temporal correlation between drug administration and rise in LFTs, the normal radiological findings, the absence of other possible aetiologies and the histological findings outlined below, a diagnosis of small duct nivolumab induced cholangitis was made. It was subsequently decided to permanently discontinue her nivolumab. At time of writing, 15 months after the last administration of nivolumab, the patient has normal LFTs and stable disease despite having no further anti-cancer therapy.

Histopathology demonstrated expanded, mildly oedematous portal tract regions in which there was a mixed inflammatory cell infiltrate including neutrophils with smaller numbers of lymphocytes, eosinophils and histiocytes noted. Plasma cells were inconspicuous, and no interface hepatitis was seen. Interlobular bile ducts were damaged and focally disrupted with intraepithelial lymphocytes noted and cytokeratin 7 immunohistochemistry highlighted a mild ductular reaction. No periductal fibrosis was seen. Routine liver special stains were unremarkable and there was no significant fibrosis identified. As large duct obstruction and sepsis had

Fig. 1 Summary of timeline between nivolumab therapy, liver biochemistry, imaging, liver biopsy and corticosteroid therapy. The coloured regions depict periods of steroid therapy (purple, methylprednisone; yellow, oral prednisone). Black arrows represent the timing of investigations performed as follows: (A) liver ultrasonography; (B) computed tomography of the abdomen and pelvis; (C) magnetic resonance cholangiopancreatography; (D) liver biopsy. ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase.

been excluded in this patient, this pattern of injury was consistent with a diagnosis of nivolumab induced cholangitis. Representative images are presented in Fig. 2.

ICI induced cholangitis is a rare but important potential irAE due to the increasing use and number of indications for ICIs. Since it was first described in 2017⁶ there have been 20 cases of biopsy-proven nivolumab associated cholangitis reported in the literature to date^{4,7–10} (Table 1). The collective experience of these clinicopathological reports are important due to the current lack of diagnostic criteria or evidence based therapeutic guidelines.⁶ Typically, cholestatic pattern ICI-related irAEs are more common with the use of PD-1 and PD-L1 inhibitors (such as nivolumab) rather than anti-CTLA-4 inhibitors, an effect which has been conjectured to be due to the differential expression of these molecules by biliary epithelial cells.¹¹

Histological findings of ICI-cholangitis include lymphocytic bile duct infiltration with variable degrees of periductal fibrosis with intraepithelial lymphocytes and a CD8+ T cell predominance, a general feature of all ICI-irAEs.⁴ Overall, the response rate of ICI-cholangitis to steroid therapy has been reported to be poor in contrast to other types of immune related hepatobiliary disease.^{9,12} In their review, Onoyama and colleagues⁴ made a distinction between intra-hepatic, extra-hepatic and diffuse phenotypes of PD-1 inhibitor cholangitis noting that the two reported cases of purely intra-hepatic disease both responded well to steroid therapy as was

seen in our case. This raises the possibility that intrahepatic ICI-cholangitis may be more steroid responsive; however, there are currently limited data available to support this.

Another interesting feature of our case was that despite receiving an adequate steroid weaning duration as suggested by international guidelines for ICI hepatotoxicity,³ the patient still developed a rebound of disease following cessation of oral prednisone. The second disease flare which was more severe with hyperbilirubinaemia also responded well to corticosteroids. Currently there is no evidence to guide the optimal duration of therapy in such situations and thus it is unclear whether a longer oral prednisone wean would have been helpful. However, it does highlight the need for ongoing LFTs monitoring after apparent resolution of derangements and cessation of therapy for ICI-hepatotoxicity.

In conclusion, we present to our knowledge the first Australian case of biopsy demonstrated nivolumab related small duct cholangitis showing an excellent response to corticosteroid therapy for both the initial flare and subsequent rebound. Given previous reports of poor corticosteroid response, more clinicopathological data is needed to characterise the heterogeneous nature of ICI-cholangitis. Though rare, the increasingly common use of these agents makes this an important reaction pattern which pathologists and clinicians should be aware of.

Fig. 2 Liver biopsy. (A) H&E showing an oedematous portal tract region with duct damage visible. Note is made of adjacent hepatocytes showing two toned change. (B) Higher power H&E showing duct damage with intra epithelial lymphocytes. (C) CD8 IHC shows predominance of CD8 positive T lymphocytes.

Table 1 Summary of the clinical features of all previous cases of liver biopsy nivolumab associated cholangitis to our knowledge reported in the literature as of August 2021

Original article ^a	Age and gender	Indication for nivolumab therapy	Presentation	Imaging modalities and findings	Treatment	Outcome of hepatotoxicity
Gelsomino (2017)	79M	NSCLC	Itching, jaundice	No abnormality on imaging (not specified which types performed)	Methylprednisolone, ursodeoxycholic acid	Partially resolved
Kawakami (2017)	64M	NSCLC (adenocarcinoma)	Fever, abdominal discomfort	CT: extrahepatic bile duct dilation, hypertrophy of the gallbladder EUS: diffuse hypertrophy of the gallbladder and extrahepatic bile duct, normal intrahepatic bile duct findings	Prednisone	Not resolved
Kawakami (2017)	82F	NSCLC (squamous cell carcinoma)	Fever, fatigue	CT: extrahepatic bile duct dilation EUS: diffuse hypertrophy of the extrahepatic bile duct	Biliary drainage	Unknown
Kashima (2017)	63M	NSCLC (adenocarcinoma)	Epigastric pain, soft stools	CT: wall thickening at the lower part of the bile duct and cholecystitis	Prednisone and biliary drainage, moderate response	Partially resolved
Doherty (2017)	59F	Melanoma (BRAF wild-type)	Abnormal LFTs	No imaging reported	Prednisone and ursodeoxycholic acid	Completely resolved
Hamoir (2018)	71M	NSCLC	Abnormal LFTs	CT: normal MRCP: intrahepatic cholangitis	Methylprednisolone and ursodeoxycholic acid	Completely resolved
Kuraoka (2018)	69M	NSCLC (adenocarcinoma)	Pruritic rash, abnormal LFTs	CT: diffuse hypertrophy of extrahepatic bile ducts EUS: slight dilation of the extrahepatic bile ducts	Prednisone and methylprednisolone	No resolution, patient death
Sawada (2019)	76M	Gastric cancer (tubular adenocarcinoma)	Abnormal LFTs	CT: mild dilation of the extrahepatic bile duct	Prednisone and ursodeoxycholic acid	Completely resolved
Oda (2019)	43M	Gastric cancer (adenocarcinoma)	Fever, tachycardia, appetite loss, malaise	CT: no abnormality detected	Prednisone and mycophenolate mofetil	No resolution, patient death
Calugreanu (2019)	43F	Melanoma	Epigastric pain, anorexia	CT: multiple strictures and dilation	Prednisone	Partially resolved
Anderson (2019)	67M	NSCLC (mixed squamous and adenocarcinoma)	RUQ pain	CT: slight thickening of the common bile duct MRCP: beaded appearance of the biliary ducts indistinguishable from PSC, with predominant intrahepatic ductal dilation	Methylprednisolone, mycophenolate mofetil and tacrolimus	No resolution/ patient death
Onoyama (2020)	82F	NSCLC	Abnormal LFTs	Biliary dilation, diffuse hypertrophy of the tract	Methylprednisolone	Partially resolved
McClure (2020)	79M	NSCLC (adenocarcinoma)	LFT derangement, abdominal pain	MRCP: intrahepatic beading of bile ducts No biliary hypertrophy or dilation	Prednisone	Partially resolved
Yosikawa (2021)	75M	NSCLC (squamous cell carcinoma)	Abnormal LFTs	MRCP: diffuse dilatation of the common bile duct and multifocal stenosis pre-stenotic dilatation from the perihilar to intrahepatic bile duct	Prednisone	No resolution, patient death
Talbot (2021)	69M	NSCLC (squamous cell carcinoma)	Abnormal LFTs	MRCP: irregular intrahepatic biliary tree with focal areas of beading and structuring	Prednisone and mycophenolate mofetil then ursodeoxycholic acid	Partially resolved
Hirasawa (2021)	64M	NSCLC (squamous cell carcinoma)	Abdominal pain and deranged LFTs	MRCP: beaded constriction and dilatation of the peripheral intrahepatic bile duct; thickening of extrahepatic bile duct	Prednisone, mycophenolate mofetil, tacrolimus	No resolution, patient death
Present case	75F	NSCLC	Abnormal LFTs, jaundice	CT and MRCP: no abnormalities detected	Methylprednisolone and prednisone	Completely resolved

Adapted in part from Onoyama *et al.*⁴

CT, computed tomography; EUS, endoscopic ultrasound; LFTs, liver function tests; MRCP, magnetic resonance cholangiopancreatography; NSCLC, non-small cell carcinoma.

^a First author and year published.

Conflicts of interest and sources of funding: The authors state that there are no conflicts of interest to disclose.

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DOI: <https://doi.org/10.1016/j.pathol.2021.11.009>

Primary high grade serous carcinoma of the appendix: a diagnostic dilemma

To the Editor,

High grade serous carcinoma (HGSC) constitutes the major subtype of surface epithelial gynaecological cancer. The ovaries/fallopian tubes are the usual likely primary organs; however, the uterus, cervix, and peritoneum have also been reported as other primary sites. Rarely, it has been reported in extraperitoneal locations such as retroperitoneum, broad

ligament, endocervix, and pelvic and retroperitoneal lymph nodes. The 2019 World Health Organization (WHO) classification of digestive system tumours does not list Müllerian type serous carcinoma as an entity in the digestive system. It does discuss a malignant transformation in a pancreatic cystadenoma (serous cystadenocarcinoma),¹ which has morphology and immunophenotype quite unlike the Müllerian type serous carcinoma, which is one of the most common tumours of the female genital tract.^{2,3}

Exhaustive literature search by various keyword combinations via Google Scholar and PubMed failed to produce a single case report of any primary gastrointestinal serous carcinoma of the Müllerian type. Even case reports of non-gastrointestinal serous carcinoma mimicking a gastrointestinal primary are a rarity. One report described a peritoneal primary⁴ and another was a metastasis from a microscopic primary in the fimbria.⁵

We report a patient presenting with HGSC involving solely the lower gastrointestinal tract without a trace of a primary elsewhere and with no history of chemotherapy before her debulking surgery.

A middle-aged female presented at an outside medical centre with pain in the abdomen which was clinically diagnosed as appendicitis. Laparoscopic appendectomy was done which was reported as a Grade 3 neuroendocrine tumour in a peripheral laboratory without immunohistochemistry. The histopathology report of the appendix was reviewed at our centre and it was reported as a HGSC. The tumour appeared as a whitish irregular growth involving the wall of the appendix with base involved; the proper anatomy of the specimen was not ascertained as per the outside report. Lymphovascular invasion was seen. Immunohistochemistry (IHC) was strongly positive for PAX-8 and WT1; p16 showed block-like positivity; synaptophysin was negative; and p53 was strongly and diffusely positive (mutated phenotype) (Fig. 1). The immunophenotype suggested an ovarian/tubal/peritoneal primary, therefore gynaecological consultation was recommended.

Her serum CA-125 was subsequently found to be elevated at 191.0 U/mL while CEA was normal (3.62 ng/mL). Positron emission tomography-computed tomography scan, done outside and reviewed in-house, showed that there was no peritoneal disease but there was significant nodal disease along the retro peritoneum and pelvis. The disease appeared to be resectable and the patient was taken up for primary debulking surgery.

Intraoperatively, there was a large tumour of size 10 cm at the mesentery near the ileo-caecal junction, which was suspicious for an enlarged lymph nodal mass. The base of the appendix was also indurated. The rest of the small bowel and mesentery were free from disease. The porta hepatis and root of mesentery were palpated and were found to be free from infiltrative disease. The large bowel was free from gross disease. All quadrants of the abdomen (as per Sugarbaker's PCI score) were assessed and the disease was deemed resectable to less than 1 cm residual disease. Incision was extended and cytoreductive procedures started. The patient underwent total omentectomy, hysterectomy with bilateral salpingo-oophorectomy, right hemicolectomy and ileo-colic anastomosis, removal of parietal peritoneum deposit, and peritoneal lavage.

Surgical specimens were processed and examined in house. The uterus, cervix, and bilateral adnexal were free of