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Case Report
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Granulomatous/Sarcoid-like Reaction to Nivolumab in a Patient with Cholangiocarcinoma

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Abstract

Immune Checkpoint Inhibitors (ICIs) are associated with many adverse side effects, including a number of dermal eruptions. Here we report a rare case of granulomatous/sarcoid-like lesions developing after use of ICI nivolumab, the first case to be reported in a primary tumor of the gastrointestinal tract. The patient is a 70-year-old female with treatment resistant stage IV cholangiocarcinoma, who was started on nivolumab, a monoclonal antibody which inhibits PD-1. During her second cycle, she developed three tender nodules on her upper thigh and lower back. On biopsy, the nodules revealed coalescing granulomas, most consistent with a sarcoid-like reaction to her ICI. The pathophysiology of sarcoid-like reactions involves an imbalance of a subset of T-helper cells, namely Th1 and Th17, which are activated by ICIs and drive fibrosis and inflammation. This reaction can be managed by discontinuing the offending ICI, administering steroids, or careful observation. With on-going clinical trials investigating ICIs in gastrointestinal cancers, it is likely their use will become more widespread in these diseases. Thus, it is essential for clinicians to be aware of their rare side effects, how they present, and how they can be managed.

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Introduction

In the realm of cancer, immunotherapy potentiates the host's ability to detect and destroy malignant cells. Immune Checkpoint Inhibitors (ICIs), a type of immunotherapy, block escape of tumor cells from antigenic detection by T-cells. ICIs are monoclonal antibodies which block one of two inhibitory T-cell signaling cascades, either at the Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4) (e.g. ipilimumab, tremelimumab) or Programmed Cell Death protein 1 (PD-1) (e.g. nivolumab, pembrolizumab). This prevents cancer cells which upregulate either CD80 or PD-L1 to avoid detection, resulting in antigenic activation of T-cells and subsequent destruction.

The advent of ICIs has improved survival for multiple types of cancers, but their use has also been associated with a number of immune-related side effects. Skin findings are particularly common and have a broad range including dermal hypersensitivity, mucocutaneous lichenoid eruptions, and immunobullous reactions. Granulomatous/sarcoid-like lesions have also been reported as an adverse effect of ICIs, usually presenting as tender skin nodules, but sometimes as painful lymphadenopathy, dyspnea, or arthralgias. This reaction is not well understood, but one hypothesis is that T-cell proliferation secondary to ICIs, particular the interplay of Th1, Th17, and T-regulatory cells, create an imbalance of cytokines which drive epithelioid cells to form granulomas [1,2]. The reports of granulomatous/sarcoid-like lesions on ICIs are overwhelmingly in people who have metastatic melanoma, perhaps due to the immunogenic nature of melanomas and widespread ICI use in the disease. Few other reports have been published in lung adenocarcinoma [3], prostate cancer [4], and ovarian cancer [5]. Here we report the first case of ICI associated granulomatous/sarcoid-like lesions with a primary tumor of the gastrointestinal tract.

Case Presentation

A 70-year old female with a past medical history of osteoarthritis presented to the emergency department with new onset of dark urine, jaundice, and unintentional 10 lb weight loss over one year. She is a non-smoker and has a non-contributory family history. She has no family history of autoimmune disorders.

On ultrasound she was found to have a gallbladder mass which extended from the neck of the gallbladder to the common bile duct contiguous with a 2.3 cm × 1.8 cm mass invading segment 5 of

Table 1: Results of whole exome sequencing on lymph node biopsy. 642 cancer genes were examined using an EXaCT-1 test, which has an analytical sensitivity of 10%. Development and validation of the test were done at The Englander Institute for Precision Medicine/New York Hospital Laboratories.

Gene	Mutation Type	Location	Significance
Cancer Genes			
PTPRC	Nonsense	p.Tyr982* (c.2946delT)	CD45; key regulator of T- and B-cell antigen receptor signaling
TP53	Missense	p.Tyr234Cys (c.701A>G)	Encodes tumor suppressor p53, associated with worse prognosis in BTCs
NF1	Frame shift	p.His1494Glnfs*7 (c.4482_4483delTA)	Encodes tumor suppressor neurofibromin
RANBP17	Focal loss	5:170, 345, 788-170, 610, 378	Encodes member of importin-beta family of nuclear receptors. Repetitively mutated in ALL
Unknown Significance			
SGK223	Missense	p.Pro354Ala (c.1060C>G)	
KRTAP5-5	Missense	p. Tyr182Ser (c. 545A>C)	
TNRC6A	Missense	p.Pro115Gln (c.344C>A)	
ANGPTL6	Missense	p.Leu96Pro (c.287T>C)	

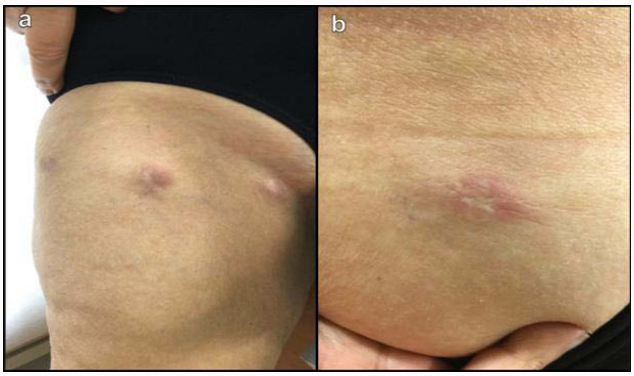

Figure 1: Three tender nodular skin lesions on the right thigh **(a)** and one lesion on the lower back (b).Informed written consent was obtained to use these pictures.

the liver, with a few malignant appearing nodes in the porta hepatis and aortocaval regions. She underwent fine needle aspiration of the periportal lymph nodes that revealed adenocarcinoma consistent with a gastrointestinal or pancreaticobiliary origin (CK20, CDX2, CA19.9 and CK 7 positive). An endoscopic ultra sound-guided stent was placed that extended from the duodenum to the gallbladder to relieve the biliary obstruction. Upon review of the imaging, she was diagnosed with American Joint Committee on Cancer (AJCC) stage IV cholangiocarcinoma.

The patient was started on neoadjuvant gemcitabine and cisplatin and finished 5 three-week cycles before developing cholecystitis requiring hospitalization and internal drainage. After recovery from the hospitalization, she underwent a resection composed of a right trisegmentectomy, duodenectomy, partial gastrectomy, Roux En Y hepaticojejunostomy and hilar lymphadenectomy. Surgical pathology confirmed invasive adenocarcinoma of the gallbladder, with invasion of liver, duodenum, and lymph nodes. Tumor was staged pT3N1, with one of four lymph nodes biopsied positive for metastasis. Whole exome sequencing of the tumor revealed point mutations in TP53 and NF1, among others (Table 1).

After surgical recovery, she was started on a combination of nab-paclitaxel and gemcitabine, for which she completed three cycles. A follow up MRCP showed a left juxtadiaphragmatic lymph node which was increased in size and subsequent fine needle aspiration was positive for adenocarcinoma.

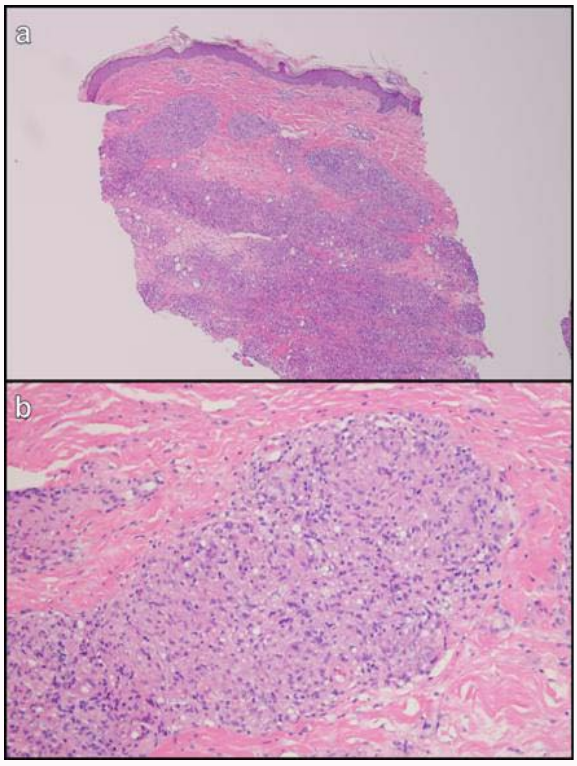

Figure 2: (a) This scanning magnification shows a striking coalescing granulomatous reaction involving the superficial and deep dermis. A grenz zone separates this granulomatous process from the overlying epidermis (hematoxylin and eosin, 100x). **(b)** This higher magnification image demonstrates the cohesive non-necrotizing epithelioid quality of the granuloma. It is predominated by activated epithelioid monocytes. While a number of the cells exhibit vacuolated cytoplasm, there is no history of lipid injection such as with silica. The overall morphology is one reminiscent of an immunogenic granulomatous response reflective of a classic TH1 dominant type IV hypersensitivity reaction. As there is no clear cut defined antigenic stimulus, the process defines a morphology and pathobiology reminiscent of sarcoidosis. Expectedly special stains to evaluate for microbial pathogens are negative (hematoxylin and eosin, 400x).

Immunohistochemistry for PD-L1 was performed on the biopsied lymph node, which was overwhelmingly positive, with a Combined Positive Score (CPS) of 150 (normal range 1 to 10). A decision was made to use immunotherapy in conjunction with radiation to the metastatic node to induce an abscopal effect. The patient received nivolumab 240 mg every two weeks in combination with stereotactic

beam radiation. During her second cycle of nivolumab, the patient reported the development of three nodular lesions on her right upper thigh, which were tender but non-pruritic (Figure 1). She later developed lesions on her lower back, left knee, and waist. Punch biopsies from the upper thigh and lower back revealed coalescing epithelioid granulomas and modest lymphocytic infiltration in both biopsies, most consistent with sarcoid-like granulomatous reaction secondary to ICIs (Figure 2).

After dermatologic evaluation and review of the literature about management of this skin toxicity from ICIs, the decision was made to monitor the nodules and continue treatment. She completed 5 cycles of nivolumab, with a couple more nodules arising on her knees and hip. After the 5th cycle, FDG-PET scan showed progression of disease with two new liver lesions and hypermetabolic thoracic lymph nodes, but improved disease at the sites of SBRT to the lymph nodes. Given this progression and the start of the COVID-19 pandemic, nivolumab was discontinued and she was started on chemotherapy with capecitabine and oxaliplatin. She completed four cycles with significant reduction in tumor markers and imaging was consistent with a complete response to therapy. The patient subsequently pursued experimental neoantigen-directed tumor vaccine but unfortunately experienced recurrence which led to her death in June of 2021. She provided written informed consent for the publication of this case report.

Discussion

Here we report the first case of a granulomatous sarcoid-like reaction to ICIs in a primary tumor of the gastrointestinal tract. Nivolumab, the ICI used here, is a monoclonal, fully human and highly specific IgG4 antibody that binds PD-1 and prevents its interaction with its ligands, PD-L1 and PD-L2, which are often expressed on cancer cells. Nivolumab has been shown to greatly improve survival in patients with metastatic melanoma [6], and there are ongoing investigations adopting its use in gastrointestinal malignancies, with some success. Nivolumab is approved by the FDA for use in the subset of colorectal cancers that have high microsatellite instability, hepatocellular carcinoma, and for third-line therapy of metastatic gastroesophageal cancers.

With the advent of checkpoint inhibitors, granulomatous/sarcoid-like reactions have been reported to be associated with ICIs, particularly with ipilimumab in melanoma patients. In response to this reaction, most reports either discontinue CPI therapy or administer systemic steroids concurrently with treatment. Regardless of management, 96% of cases reported improvement or resolution of symptoms [7]. In patients who continue therapy with ICI, and who tolerate the subsequent toxicities, we think that careful monitoring for progression of symptoms is a reasonable approach.

For Biliary Tract Cancers (BTCs) like the case presented here, there are solid priori reasons that they are promising candidates for ICIs; however the progress in clinical evidence has been slower than other GI cancers due to the rarity of this disease. In a molecular analysis of 260 BTCs, 45% showed mutations in targetable immune checkpoint molecules and in a distinct molecular subset of BTCs with the worst prognosis, immune checkpoint mutations were further enriched [8]. Interim results of clinical trial KEYNOTE-028 suggest that among a cohort of 21 PD-L1 positive cholangiocarcinoma patients, 17% had an objective response with CPI monotherapy [9].

Mirroring colorectal carcinoma, more promise is emerging for ICIs in the subset of microsatellite unstable (MSI-High) cholangiocarcinoma. There are case reports of pembrolizumab being successfully used in MSI-High cholangiocarcinomas, and recent data from phase II clinical trial KEYNOTE-158 suggests that, of the 22 patients with MSI-High cholangiocarcinoma who were then treated with pembrolizumab, 41% had an objective response [10]. The patient presented here did not have a response to nivolumab with a PD-L1 positive tumor; however her microsatellite status is unknown. Additionally, response to ICIs may occur many weeks into the treatment regimen, and even after discontinuation of therapy, so this patient may have benefitted from ICI therapy.

As data continues to coalesce, it is likely that we will see more use of ICIs in specific, biomarker-positive gastrointestinal cancers. With a rise in frequency of use, gastrointestinal oncologists must be aware of potential adverse reactions to ICIs, how they present, and possible management strategies.

References

1. Wolchok JD, Neyns B, Linette G, Negrier S, Lutzky J, Thomas L, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: A randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol. 2010;11(2):155-64.
2. Mortaz E, Rezayat F, Amani D, Kiani A, Garssen J, Adcock IM, et al. The roles of T Helper 1, T Helper 17 and regulatory T cells in the pathogenesis of sarcoidosis. Iran J Allergy Asthma Immunol. 2016;15(4):334-9.
3. Birnbaum MR, Ma MW, Fleisig S, Packer S, Amin BD, Jacobson M, et al. Nivolumab-related cutaneous sarcoidosis in a patient with lung adenocarcinoma. JAAD Case Rep. 2017;3(3):208-11.
4. van den Eertwegh AJ, Versluis J, van den Berg HP, Santegoets SJ, van Moorselaar RJ, van der Sluis TM, et al. Combined immunotherapy with granulocyte-macrophage colony-stimulating factor-transduced allogeneic prostate cancer cells and ipilimumab in patients with metastatic castration-resistant prostate cancer: A phase 1 dose-escalation trial. Lancet Oncol. 2012;13(5):509-17.
5. Tetzlaff MT, Jazaeri AA, Torres-Cabala CA, Korivi BR, Landon GA, Nagarajan P, et al. Erythema nodosum-like panniculitis mimicking disease recurrence: A novel toxicity from immune checkpoint blockade therapy-report of 2 patients. J Cutan Pathol. 2017;44(12):1080-6.
6. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372(4):320-30.
7. Tetzlaff MT, Nelson KC, Diab A, Staerkel GA, Nagarajan P, Torres-Cabala CA, et al. Granulomatous/sarcoid-like lesions associated with checkpoint inhibitors: A marker of therapy response in a subset of melanoma patients. J Immunother Cancer. 2018;6(1):14.
8. Nakamura H, Arai Y, Totoki Y, Shirota T, Elzawahry A, Kato M, et al. Genomic spectra of biliary tract cancer. Nat Genet. 2015;47(9):1003-10.
9. Bang YJ, Doi T, Braud FD, Piha-Paul S, Hollebecque A, Razak ARA, et al. 525 safety and efficacy of pembrolizumab (MK-3475) in patients (pts) with advanced biliary tract cancer: Interim results of KEYNOTE-028. Eur J Cancer. 2015;51(3):S112.
10. Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord JP, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. J Clin Oncol. 2020;38(1):1-10.