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CASE REPORT

Resolution of Metastatic Colon Cancer upon Withdrawal of Anti-TNF Therapy for Crohn's Disease

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Introduction

Patients with Crohn's disease have an increased risk of developing colon cancer, with an estimated incidence of 2–5% after 10 years [1, 2]. Higher risks of cancer development have been observed in patients with longer duration of Crohn's disease or with severe colonic involvement [1, 2]. Anti-tumor necrosis factor (TNF) agents are commonly used in the treatment of moderate to severe Crohn's disease [3]. Whether anti-TNF therapy is associated with a higher risk of developing malignancy is controversial. Most meta-analyses and randomized controlled trials with patients treated with anti-TNF therapy have not shown increased risks of malignancy [4, 5], but other reports have suggested increased risk of lymphoma and a potential dose-dependent increase in malignancy risk [6, 7]. We present the first reported case of a patient with colon cancer who developed biopsy proven recurrence 6 months after the initiation of infliximab therapy for Crohn's disease. In the absence of any cancer treatment, the metastatic disease completely resolved after discontinuation of infliximab.

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Case Description

This now 84-year-old female patient initially presented in 2001 with a 6-month history of diarrhea, fatigue, and anemia. Colonoscopy on March 27, 2001 demonstrated a near obstructing mass above the cecum, biopsy confirming adenocarcinoma. The distal ileum was thickened consistent with Crohn's disease. The pathology after right hemicolectomy on April 6, 2001 found pT2pN0 poorly differentiated medullary carcinoma with a heavy lymphocyte reaction, no perineural or lymphovascular invasion, and clear resection margins. Five lymph nodes were recovered without malignancy. Ileitis was present consistent with Crohn's disease. No adjuvant cancer therapy was administered.

The Crohn's disease was relatively quiescent until 2006 when the patient presented with bowel obstruction and had methylamine initiated. In April 2008, she presented with rectal bleeding and anemia with a hemoglobin of 63 g/L. Gastroscopy was normal, and colonoscopy on April 27, 2008 could not visualize beyond the previous ileo-colic anastomosis. Computerized tomography (CT) of the abdomen on April 28, 2008 demonstrated inflammation in the terminal ileum, with no evidence of cancer recurrence and no retroperitoneal lymphadenopathy (Fig. 1a).

The patient was discharged on May 1, 2008 with a plan to start outpatient infliximab but required readmission on May 6, 2008 with another flare of Crohn's disease with abdominal pain, vomiting, and diarrhea. She received the first infusion of intravenous infliximab on May 8, 2008 and had subsequent treatments as an outpatient, 300 mg every 8 weeks. After 6 months, follow-up CT on November 4, 2008 surprisingly demonstrated new development of two large necrotic nodal masses in the upper abdomen (Fig. 1b). The first mass was above the portal confluence measuring 4.8 × 2.5 × 2.7 cm. The second was in the portacaval region measuring 3.8 × 2.0 × 4.0 cm. Fine needle aspiration biopsy of a node November 7, 2008 demonstrated poor-

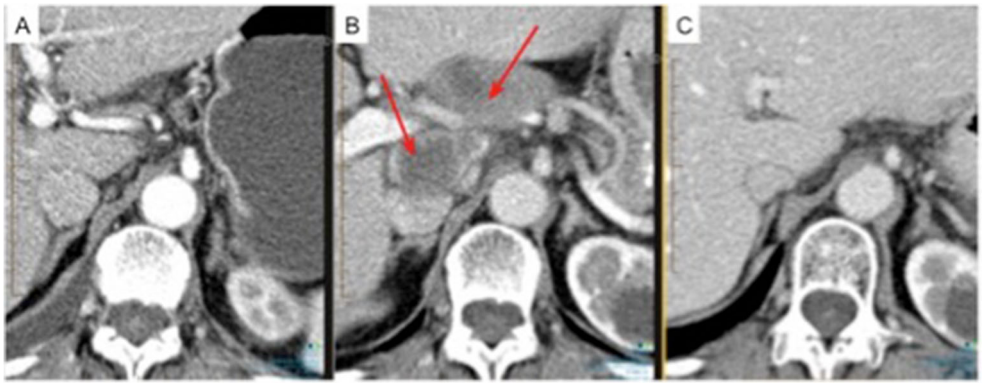

Fig. 1 Serial abdominal CT scans showing: **a** no evidence of disease in April 2008, **b** metastatic retroperitoneal lymph nodes in November 2008 indicated by red arrows, and (**c**) complete resolution of disease in October 2009

ly differentiated carcinoma with large pleomorphic nuclei, scanty cytoplasm, and cellular cohesion (Fig. 2). There was no evidence of lymphoma.

The patient's gastroenterologist was concerned that the infliximab may have contributed to cancer recurrence, and hence discontinued it in November 2008. The patient did not receive radiation therapy or systemic therapy for the recurrence as it was felt to be incurable and she was asymptomatic. On follow-up CT imaging, the metastatic adenopathy was noted to decrease in January 2009, with further improvement in May 2009, and complete resolution in October 2009 (Fig. 1c).

The patient subsequently developed two additional primary colon adenocarcinomas in 2010 and 2014. Both were treated with surgical resection with no adjuvant therapy. Interestingly, both colon cancers had MutL homolog 1 (MLH1) deficiency. Retrospective pathology review of the original colon cancer also confirmed MLH1 deficiency, and all three tumors expressed BRAF V600E on immunostaining indicating acquired MLH1 deficiency, not Lynch syndrome. Since 2014, follow-up CT scans, including the most recent in December 2017, showed no evidence of disease. At last follow-up in December 2017, the patient remained well on no active treatment for either colon cancer or Crohn's disease. The Crohn's disease was stable with mild abdominal cramping a few times per month, no rectal bleeding, and no extra-intestinal manifestations.

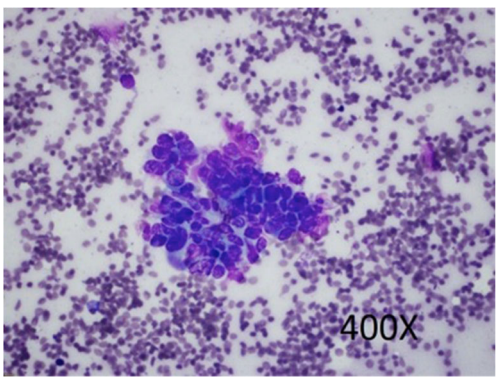

Fig. 2 Hematoxylin and eosin stained cytology of fine needle aspiration biopsy of a retroperitoneal lymph node. Magnification × 400

Discussion

This case is the first report of progression of colon cancer on anti-TNF therapy for Crohn's disease with subsequent resolution of biopsy-proven nodal metastasis upon anti-TNF discontinuation. This patient had a period of 7 years after initial cancer surgery with no evidence of recurrence until the initiation of infliximab therapy. With the development of retroperitoneal nodal metastasis on infliximab and its resolution upon withdrawal of therapy, we hypothesize that this case represents the reactivation of quiescent micro-metastatic disease upon initiation of anti-TNF therapy and that the cancer recurrence subsequently regressed upon withdrawal of anti-TNF therapy after host immunocompetence was restored.

There is suggestive evidence that metastatic disease may remain in an occult state for protracted periods of time, and a model of dormancy and reactivation in malignancy has been proposed [8, 9]. Adaptive immunity may play a crucial role in maintaining a state of equilibrium between cancer proliferation and elimination by the immune repose in occult disease [10]. TNF acts to modulate cell proliferation, apoptosis, and immune responses through its receptors, tumor necrosis factor receptors 1 and 2 (TNFR1 and TNFR2) [11]. A study on murine models suggests that TNF could maintain malignancy in a dormant state through TNFR1-mediated activation of CD4+ T cells [12]. It is hence possible that in our patient's case, the blockade of TNF by infliximab allowed reactivation and proliferation of occult malignancy previously dormant within the retroperitoneal lymph nodes. After withdrawal of this therapy, adaptive immunity was able to suppress clinically apparent disease. This suggests that TNF-mediated cell signaling may be crucial in controlling a subset of malignancies.

Similar to our current case of colon cancer, one other report has described a non-small cell lung cancer that developed after initiation of infliximab and completely resolved after withdrawal of anti-TNF therapy and no cancer treatment. This lung cancer case exhibited overexpression of TNFR1 and TNFR2, leading the authors to hypothesize that TNF blockade contributed to carcinogenesis [13]. Three other reports have described the regression of hepatocellular carcinoma and lymphoma upon

discontinuation of anti-TNF therapy [14–16]. These reports, in addition to our own, suggest that in rare cases, anti-TNF therapy may lead to the development and progression of cancer.

In the current case, it should be noted that the right-sided colonic tumor in April 2001 was a poorly differentiated medullary carcicoma. As the retroperitoneal adenopathy may represent recurrence or another disease entity, biopsy was obtained for tissue diagnosis confirming poorly differentiated carcinoma and not reactive adenopathy or lymphoma. It is also interesting to note that the patient developed three primary colon cancers, all which were mismatch repair defective and displayed heavy infiltration of tumor infiltrating lymphocytes (TILs) suggestive of a strong host immune response. MLH1 is a crucial gene in regulating DNA mismatch repair (MMR) which may be associated with Lynch syndrome [17], a familial cancer syndrome caused by mutations in the DNA-mismatch-repair genes [18]. Sporadic MMR defective colorectal carcinomas are much more common than Lynch syndrome and affect older patients, and this patient had three such tumors. Colorectal cancers with MMR defects can accumulate many mutations and display microsatellite instability. Recent studies have shown that neoantigens expressed by these MMR deficient colorectal cancers due to their high mutation rate are strongly immunogenic and may be responsible for the immunogenicity of MMR colorectal cancers [19, 20]. The dramatic response of our patient's retroperitoneal metastases to the initiation and withdrawal of anti-TNF therapy suggests that patients with MMR deficient colorectal cancers may be particularly at risk of cancer progression while on anti-TNF therapy.

In summary, this case implicates TNF as a mediator of immune responses to cancer. Further study of the role of TNF signaling in this immune response may reveal novel treatment strategies or identify those at risk for development or progression of malignancy on anti-TNF therapy. In patients with colon cancer, particularly those with MMR-deficient disease who develop cancer recurrence on anti-TNF agents, it may be reasonable to withdraw these drugs as this may effect cancer regression in some cases.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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