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Cronkhite Canada Syndrome: dramatic response to infliximab and a possible clue to pathogenesis

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Dear Editor

A previously healthy 40-year-old woman developed nausea, vomiting, diarrhea, and unintentional weight loss with alopecia and nail deformities. She had no family history of gastrointestinal disease. Upper endoscopy revealed enlarged gastric folds with diffuse edema and prominent duodenal folds with hamartomatous polyps, while colonoscopy showed enlarged folds in the terminal ileum and multiple polyps (consisting of hamartomas, sessile serrated adenomas, and tubular adenomas) throughout (Figures 1 and 2). After diagnosis with Cronkhite Canada syndrome (CCS), total parenteral nutrition and intravenous steroids were administered without improvement. Subsequent initiation of immunomodulator therapy with azathioprine (AZA) and infliximab (IFX) resulted in rapid clinical improvement with weight gain and normalization of albumin. Repeat upper endoscopy and colonoscopy after 4 months of infliximab showed near resolution of enlarged gastric, duodenal and terminal ileal folds, with corresponding near resolution of inflammation, which was persistent through 33 months of follow up (Figure 1).

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CCS pathogenesis is not well understood, but is unique in that it must include molecular events that simultaneously predispose to a phenotype that includes inflammation and the development of hamartomatous polyps and possibly pre-neoplastic lesions. In this case, we hypothesized that such events might be caused by one or more rare germline mutations, or one more key somatic mutations. To test this hypothesis, we performed whole exome sequencing on germline DNA (blood) as well as polyp tissue from a representative gastric and colonic polyp. The two polyps did not share common non-silent somatic mutations, suggesting distinct origin without a common molecular pathway (Supplementary Materials). On germline analysis, we identified a rare variant affecting *PRKDC*, protein kinase DNA-activated catalytic polypeptide (DNA-PKcs). While not predicted to be deleterious (PMID: 12824425), its specific functional consequences are unknown.

Interestingly, a review of the literature suggests that *PRKDC* dysfunction might account for some of the manifestations of CCS. *PRKDC* encodes a catalytic subunit (DNA-PKcs) involved in double-stranded DNA break repair and V(D)J recombination in developing T and B cells(1). *Prkdc*^{-/-}, but not *Prkdc*^{+/+} or *Prkdc*^{+/-}, mice have been noted to have gastrointestinal tract abnormalities, including dramatically reduced Peyer's patches in the small intestine, inflammatory infiltrates resulting in changes consistent with inflammatory polyps, and colonic mucosa changes consistent with a range of lesions linked to carcinogenesis(2). Thus, data from the murine model raises the possibility that DNA-PKcs dysfunction could account for the inflammation and diverse neoplastic lesions observed in our CCS patient. Accordingly, *PRKDC* may merit further investigation, including examination of whether other individuals with CCS have *PRKDC* variations.

Treatment for CCS is largely anecdotal, traditionally consisting of nutritional support, histamine receptor antagonists, steroids, or immune suppression associated with infrequent response and high mortality. In contrast, including our case, there are now three reports of successful treatment of CCS as an inflammatory process with a dramatic response to a tumor necrosis factor (TNF) inhibitor(3, 4). The high disease mortality associated with CCS and early success reported with TNF inhibitors in these cases demand that this approach should be investigated as a first-line therapy(5).

In summary, we present a prototypical case of CCS with a dramatic response to anti-TNF therapy not only supporting early use of TNF inhibitors as a possible first-line approach, but also suggesting that this syndrome is fundamentally inflammatory in nature. Whole exome analyses of our case suggest that *PRKDC* DNA variants might contribute to CCS pathogenesis though much genetic and epidemiologic work remains to be done to understand the pathogenesis of this rare but highly lethal disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Pre-infliximab endoscopic images of stomach (1A), duodenum (1B), ileum (1C), and colon (1D). Images of stomach (1E), duodenum (1F), ileum (1G), and colon (1H) 33 months post initiation of infliximab show resolution of mucosal fold hypertrophy and polyposis.

Figure 2.

Baseline histology. (2A) Gastric Hamartomatous Polyp: cystic dilatation of the epithelium, patchy inflammation, and mucosal edema (H&E,40X). (2B) Colonic Hamartomatous Polyp: subtle epithelial hyperplasia, patchy inflammation, and mucosal edema (H&E,40X).