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Reversible Dysgeusia Attributed to Azathioprine

TO THE EDITOR: We report the case of a patient in whom oral azathioprine induced reversible taste disturbance on two occasions.

Azathioprine is an imidazole derivative of 6-mercaptopurine and is classified as an antiproliferative immunosuppressant.

A 67-yr-old gentleman with steroid-dependent ulcerative colitis was commenced on azathioprine. The dose was gradually increased to 100 mg daily. Clinical remission had been previously obtained by means of intravenous cyclosporine.

A few days after his azathioprine was prescribed, the patient started complaining of a persistent salty taste. The patient had been given palliative measures (use of mints, sugarless gums, and mouthwashes) to ameliorate his dysgeusia.

The patient was losing weight rapidly. He lost 4 kilograms over a 4-wk period. The azathioprine dosage was progressively decreased and eventually stopped. The patient's symptoms resolved completely when the drug was stopped. He was extensively investigated for other causes of dysgeusia. All were negative. More importantly, there was no evidence of Crohn's disease (1). After about 2 months the patient was rechallenged with azathioprine, but the symptoms recurred and the treatment was stopped again. Once again the dysgeusia resolved.

An extensive literature review uncovered only one review (2), which claimed that azathioprine could cause dysgeusia.

The temporal association suggests a causal relation between dysgeusia and the use of azathioprine. This case was reported to the Maltese Medicines Authority as well as the manufacturer who had never encountered this side effect.

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Successful Treatment of a Crohn's Disease Patient Infected With Bacteremic *Mycobacterium paratuberculosis*

TO THE EDITOR: Antibiotic therapy in the treatment of Crohn's disease is controversial (1, 2). The profound clinical and colonoscopic response to atypical mycobacterial antibiotic therapy documented in this case establishes that properly chosen antibiotics may be beneficial for some Crohn's disease patients. The presence and subsequent disappearance of *Mycobacterium paratuberculosis* DNA in the blood from a Crohn's disease patient associated with complete clinical remission is intriguing.

At the age of 43, this male patient was hospitalized with severe colitis and mouth ulcers. At age 48, the patient was diagnosed with granulomatous colitis; however, the symptoms

subsided without specific therapy until age 58, when he re-experienced the same symptoms including the detection of granulomatous colitis and was finally diagnosed with Crohn's disease for which he received increasing doses of mesalamine, prednisone 60 mg daily, and 6-MP 100 mg daily. At age 61, he developed severe chronic ulcers on his feet and legs that were diagnosed as pyoderma gangrenosum. His symptoms of abdominal cramps, diarrhea, rectal bleeding, fatigue, and weight loss worsened. He had recurrent mouth ulcers for the past 4 yr. His surgical history was positive for bilateral inguinal hernias. He had no other medical problems, and did not smoke nor drink alcohol. He grew up in the Seattle countryside, ate a normal diet including dairy products, and has no family history of IBD.

At age 63, this Crohn's disease patient refused treatment with infliximab because of concern of possible side effects. The result of his colonoscopy was consistent with severe Crohn's disease, in which the cecum and right colon were severely involved, but skip lesions were found in the transverse, descending, and sigmoid. The rectum appeared normal. Lesions consisted of edema, exudates, cobblestoning, and ulcers (Fig. 1A). The patient consented to give two 4-mL tubes of blood for analyses of the presence of *M. paratuberculosis*, the causative agent of Johne's disease in cattle and a debated sus-

pect in Crohn's disease pathogenesis. Circulating leukocytes were analyzed for the presence of *M. paratuberculosis* DNA using nested PCR and nucleotide sequencing (3). As shown in Figure 1C, *M. paratuberculosis* DNA is present in the patient's blood. Consequently, the patient started treatment consisting of split doses of clarithromycin 1,000 mg daily, rifabutin 300–450 mg daily, and levofloxacin 500 mg daily. His treatment with prednisone and 6-MP were slowly discontinued. He experienced fevers and "flu-like" symptoms. Three weeks later, his Crohn's disease symptoms of abdominal pains, diarrhea, and fatigue disappeared. His appetite returned and he gained 12 lbs over the ensuing months.

He returned for a follow-up visit 6 months later, at which time he was judged to be in total clinical remission from his Crohn's disease. A colonoscopy was performed that showed no evidence of any active inflammation. There were residual mucosal pseudopolyps in the areas of previous involvement. Importantly, the areas of previous severe involvement in the cecum and ascending colon were normal (Fig. 1B). Blood analysis for the presence of *M. paratuberculosis* DNA was negative in the patients' blood following treatment (Fig. 1C).

Although showing that one Crohn's disease patient responds so dramatically to properly chosen antibiotics establishes the concept that antibiotics can be beneficial for some Crohn's patients, it does not establish that antimycobacterial

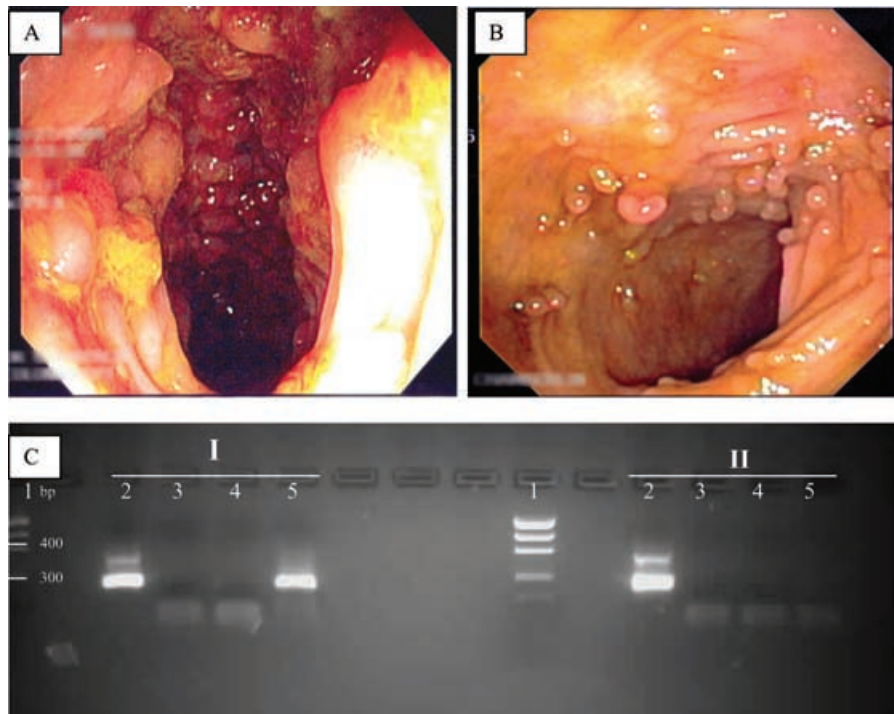


Figure 1. Colonoscopy healing in a Crohn's disease patient using antibiotic therapy. (A) represents a colonoscopy image before antibiotic treatment, whereas (B) represents colonoscopy image following 6 months of treatment with split doses of clarithromycin 1,000 mg daily, rifabutin 300–450 mg daily, and levofloxacin 500 mg. (C) represents PCR detection of *M. paratuberculosis* DNA in the blood from a Crohn's disease patient, whereas *M. paratuberculosis* DNA was detected in the blood before the treatment (lane I-5) and absent in the patient's blood after 6 months of treatment (lane II-5). The amplified PCR product on agarose gel in image C is 298 bp from the IS900 gene of *M. paratuberculosis*. Lane 1 contains molecular weight marker in base pair (bp). Lane 2 contains DNA template from a laboratory strain of *M. paratuberculosis* (positive control). Lanes 3 and 4 represent negative controls (no *M. paratuberculosis* DNA).

antibiotics are effective for all patients, nor does it prove that *Mycobacterium* is necessarily one of the causes of the Crohn's syndrome. Detection of *M. paratuberculosis* fingerprints in the blood of this Crohn's patient confirms our earlier report (3) and may suggest that a wide spread of this bacterium in our food chain may be alarming. Disappearance of *M. paratuberculosis* in this case study is due to the effective choice of the antibiotics and not because of the anti-inflammatory property of these agents, because the patients did not respond to years of treatment with prednisone.

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IgG4-Related Sclerosing Cholangitis Should Be Included as an Exclusion Criterion for the Diagnosis of Primary Sclerosing Cholangitis

TO THE EDITOR: This year's study by Mendes *et al.* presented invaluable results regarding the frequency of high serum IgG4 concentrations in patients with primary sclerosing cholangitis (PSC) (1, 2). PSC is a chronic cholestatic liver disease characterized by progressive destruction of the bile ducts and the eventual development of biliary cirrhosis. However, some PSC patients seem to respond to corticosteroid therapy while others do not. This suggests that PSC may be a heterogeneous condition. To diagnosis PSC, the Mayo Clinic's criteria are now widely used (3). However, researchers at the Mayo Clinic have shown that nearly 10% of PSC patients have elevated IgG4 and that as many as half of this select group of patients may need to undergo a liver transplantation.

The role of IgG4 in patients with PSC has been used to differentiate clinical syndromes of atypical PSC cases. In 1991, Kawaguchi *et al.* first described clinical and pathological features of variant cases of PSC, which was later known as sclerosing cholangitis complicated with autoimmune pancreatitis (AIP) (4). In 1995, Takikawa *et al.* analyzed 192 cases of Japanese PSC and found two peaks in the age distribution. Some cases in elderly patients were complicated with chronic pancreatitis, which was regarded as sclerosing cholangitis complicated with autoimmune pancreatitis (AIP-related sclerosing cholangitis) (5). Later, Nakazawa *et al.* reported atypical PSC, which corresponded to AIP-related sclerosing cholangitis (6). In 2004, Takikawa *et al.* analyzed 269 additional cases of Japanese PSC and showed that 7% of these cases had AIP (7).

In the present study by Mendes *et al.*, 9% of PSC patients had an elevated serum IgG4. This study reveals that AIP-related sclerosing cholangitis may have been included among PSC cases in the United States. In addition, the study shows that patients who are suspected of having PSC may respond to corticosteroids and could also meet the Mayo Clinic's criteria for PSC. To exclude such patients from the diagnosis of PSC, we propose adding IgG4-related sclerosing cholangitis with a high serum IgG4 concentration or abundant IgG4+ cell infiltrates as an exclusion criterion to the Mayo Clinic's diagnostic criteria (8). In Japan, this was the consensus of an expert panel following a workshop at Digestive Disease Week, Japan, 2003 (7).

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