

childhood to adulthood is similar to that observed in atopic patients. Although aeroallergen sensitization is common, exacerbation of EE during the pollen season is rare.¹⁰

Our findings that allergic airway diseases precede EE suggest that the initial sensitization might take place in the airways. Therefore it appears that EE is just an additional involvement of another organ, the esophagus, in a preexisting IgE-mediated allergic syndrome. Because the relevant allergens do not change in this process, it is possible that factors unrelated to atopy determine the susceptibility for the development of EE in patients with allergic rhinitis with or without bronchial asthma. Our study provides further information that EE should be considered an additional manifestation of atopy. Therefore the concept of the united airways⁴ can be extended to the upper gastrointestinal tract because the allergic inflammation can obviously also reach the esophagus.

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Use of GM-CSF in the treatment of colitis associated with chronic granulomatous disease

To the Editor:

Chronic granulomatous disease (CGD) is a primary immunodeficiency characterized by the inability of phagocytes to kill ingested catalase-positive organisms.¹ In addition to increased susceptibility to bacterial and fungal infections, patients have a higher incidence of mucosal inflammatory disorders¹ such as colitis, enteritis, and gastric outlet obstruction. Antibiotics and steroids have been the main treatment options for the management of colitis associated with CGD. Immunomodulatory agents, found to be effective in inflammatory bowel disease, have also been used; however, recent reports of infectious complications associated with these medications preclude their broader use. Some success has been reported with the use of granulocyte colony-stimulating factor (G-CSF) and GM-CSF in the treatment of mucosal inflammation in glycogen storage disease Ib and Crohn's disease.^{2,3} Here we report a case of severe colitis and anal fissure associated with CGD that improved with GM-CSF treatment.

MG is a 19-year-old male with CGD diagnosed by nitroblue tetrazolium assay at 5 months of age after evaluation for cellulitis and frequent upper respiratory tract infections. He did well until 15 years of age, when he developed left cervical adenitis, which failed to improve on oral antibiotics, forming an abscess that required incision and drainage and intravenous antibiotics. He was subsequently started on IFN- γ 100 μ g subcutaneously 3 times a week.

He did well until 18 years of age, when he developed a rectal abscess that required incision and drainage. Subsequently, an enterocutaneous fistula developed, associated with abdominal and rectal pain with bloody stools. He was diagnosed with Crohn's-like colitis. Mesalamine, cortisone enemas, and 5-aminosalicylic acid suppository therapy were initiated. After debridement of the fistula, he experienced worsening of bloody stools, abdominal pain, and severe rectal pain. Surgical closure of the fistula was attempted twice without success.

Because of worsening colitis, he was treated with 1 dose of infliximab (5 mg/kg/dose). Initially, his gastrointestinal symptoms improved; however, he concurrently developed tooth pain, swelling, and fever. His right upper wisdom tooth abscessed and was removed. Post-operatively, he continued to have fevers (40°C) and worsening severe rectal pain, and he was admitted to his

local hospital. Chest computed tomography was consistent with septic emboli. He underwent bronchoscopy and, later, video-assisted thoracic surgery with biopsy of his left upper and lower lobes. Fungal stains revealed hyphae, but cultures remained negative. He was treated with caspofungin 50 mg IV every day. Linezolid 600 mg every 12 hours was added for concurrent staphylococcal bacteremia, and metronidazole 250 mg every 8 hours for perirectal disease.

The fevers recurred within 1 week, accompanied by nausea. Caspofungin was changed to voriconazole 200 mg twice a day. However, he continued to have fevers, nausea, vomiting, a 10-pound weight loss, severe abdominal and rectal pain, and frequent blood-streaked stools. He was admitted to Mount Sinai Hospital for an examination under anesthesia, which revealed a large posterior midline fissure, and abdominal CT demonstrated colitis. Daily subcutaneous GM-CSF 0.6 μ g/kg/dose was started and IV antibiotics (increased voriconazole to 250 mg twice a day, metronidazole 250 mg three times a day, and linezolid 600 mg every 12 hours) and total parenteral nutrition continued. After 4 days on GM-CSF, the rectal pain and spasm decreased, and hydrocortisone enemas could be started. Rectal and abdominal pain significantly improved, and he no longer had blood-streaked stools. He tolerated a regular diet and was discharged home 10 days after starting the GM-CSF. He has been doing well since starting GM-CSF, with no rectal or abdominal pain and with no blood in the stool.

In addition to recurrent infections, CGD is associated with inflammatory and/or rheumatic diseases, including obstructive lesions of the gastrointestinal or urinary tracts, inflammatory bowel disease–like colitis, chorioretinitis, immune thrombocytopenic purpura, and systemic lupus erythematosus.¹ Gastrointestinal manifestations, seen in approximately 50% of patients,⁴ are complicated by anemia and failure to thrive. Colitis/enteritis has been found in approximately 17% of patients in a series of 368 CGD patients.¹ The etiology of CGD colitis is unclear. Hypotheses include recurrent infections causing a chronic inflammatory state secondary to low-grade encounters with microbes in the gastrointestinal tract, or the colitis may be a manifestation of defects in innate immunity promoting mucosal dysregulation.⁴

Symptoms of CGD colitis may be similar to inflammatory bowel disease (IBD), but there are distinguishing histologic features. Large pigmented macrophages are often present, and there may be an apparent paucity of neutrophils in CGD colitis. Granulomas are seen in some cases, with greater numbers of macrophages than in Crohn's granulomas.⁴

Until now, treatment for CGD colitis has been primarily the use of antibiotics, because the excess inflammation is generally attributed to infection. However, when stool is cultured, there are typically no clear pathogens.⁴ With the clinical and pathological similarities to IBD, trials using therapies known to be effective in IBD have been attempted. Infliximab has been found to be effective for moderate to severe Crohn's disease in clinical trials and

was used in our patient for worsening colitis. However, he developed a fungal pulmonary infection shortly thereafter. Despite the reported safety of infliximab (and etanercept), fungal infections associated with these medications have been reported.⁵

Recently, GM-CSF and G-CSF have been used with some success in the treatment of colitis associated with glycogen storage disease and Crohn's disease. Roe et al² described the use of GM-CSF in the treatment of 2 patients with enteritis associated with glycogen storage disease type Ib. The oral lesions and perianal abscesses improved, and patients remained symptom-free for 10 to 12 months after treatment. There have been subsequent reports of improvement in symptoms of Crohn's disease with G-CSF^{3,6} and GM-CSF treatment.⁷ Because colitis associated with CGD has similarities with these diseases and the colitis may be a manifestation of the underlying neutrophil disorder, use of G-CSF or GM-CSF may be beneficial in treating the gastrointestinal symptoms in this complicated population. Myrup et al⁸ reported 2 brothers diagnosed with CGD-associated colitis who improved on G-CSF within the first month of treatment. With these encouraging reports, we tried GM-CSF for our patient who had a large anal fissure and complications of fungal pulmonary infection after receiving infliximab. He experienced decreased abdominal and rectal pain and diarrhea 2 weeks after starting GM-CSF and has maintained a remitted state. He has not reported bone pain, and he has maintained normal white blood cell counts.

The mechanism of GM-CSF in the treatment of colitis is unclear. GM-CSF induces proliferation and survival of neutrophils, monocytes/macrophages, and eosinophils. Although GM-CSF enhances neutrophil function, including oxidative metabolism, degranulation, cytokine secretion, phagocytosis, and cytotoxicity,⁹ it is possible that augmentation of macrophage proliferation and function may help overcome some of the neutrophil defect seen in patients with CGD. Macrophages participate both in the clearance of infection as well as wound healing. In addition to phagocytosis, macrophages produce nitric oxide, which has antimicrobial properties, is immunomodulatory, and has been found to have a role in re-epithelialization and wound closure in murine models.¹⁰ In this case, the defect in innate immunity may have predisposed this patient to mucosal inflammation and infection. GM-CSF may be beneficial by clearing any infection that may hinder wound closure as well as restoring or compensating for an innate immune defect.

Colitis/enteritis has been found to be associated with CGD in 17% of cases.¹ Although clinically similar to Crohn's disease, there are some histological differences. Treatment options, including immunosuppressives, are based on established IBD therapies; however, caution needs to be taken in the CGD population, because they are susceptible to infection as a result of their neutrophil dysfunction. Because fungal infections associated with TNF inhibitors have been reported, fungal prophylaxis is necessary for patients with CGD who are considered for this treatment. GM-CSF may be a preferable alternative

for the management of colitis in this population because there is no increased risk of infection and it has been well-tolerated by the general population.

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