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Treatment of Inflammatory Bowel Disease and Pediatric Onset Multiple Sclerosis With Ocrelizumab and Ustekinumab in a JC-virus Positive Adolescent

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Abstract: Inflammatory bowel disease (IBD) and multiple sclerosis (MS) are known to co-occur. Many disease modifying therapies for MS may exacerbate IBD and several carry risk of progressive multifocal leukoencephalopathy in JC-virus (JCV) positive patients. Some biologics used for IBD can exacerbate MS. These factors make comanagement of these diseases difficult. We report a 17-year-old female who presented with right leg weakness and paresthesia and was diagnosed with pediatric onset MS (POMS). She then had worsening abdominal pain and diarrhea, accompanied by weight loss, and was subsequently diagnosed with Crohn's disease. She was weakly JCV positive, so a short trial of natalizumab was initiated, which controlled her POMS well but not her IBD. Ustekinumab and ocrelizumab were initiated and achieved remission of both diseases. In the absence of established treatment guidelines, we recommend considering this combination of therapies for cases where standard treatment modalities are not viable options.

Key Words: inflammatory bowel disease, Crohn's disease, multiple sclerosis, ustekinumab

INTRODUCTION

Inflammatory bowel disease (IBD) and multiple sclerosis (MS) are known to be associated (1,2). Many disease modifying therapies (DMT) for MS, such as interferon beta-1a and 1b, and glatiramer acetate may exacerbate IBD (3,4). Rituximab, used off label to treat MS, has not been successful in treating IBD (5). Some MS DMTs carry high risk for development of progressive multifocal leukoencephalopathy (PML) in JC-Virus (JCV) positive patients (6). Biologic therapies such as tumor necrosis factor inhibitors used for IBD are reported to exacerbate MS (7). Currently, fingolimod is the only FDA approved DMT for treating pediatric onset MS (POMS), though clinical trials of several other DMTs in POMS are on-going (8,9). These factors can make comanagement of these diseases difficult. Successful comanagement of these disorders with ocrelizumab and ustekinumab has not been reported. Additionally, few studies report comanagement of IBD and MS in pediatric patients.

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CASE PRESENTATION

A 17-year-old G1P1 female initially presented four months postpartum with right leg weakness, right leg paresthesia, and blurry vision. She was admitted for evaluation. Magnetic resonance imaging (MRI) of the brain, cervical spine, and thoracic spine with and without contrast showed periventricular opacities and multiple lesions in the brain and cerebellum, and she was diagnosed with POMS (Fig. 1). Lumbar puncture showed albuminocytologic dissociation, consistent with her diagnosis. She was treated with high-dose intravenous corticosteroids with resolution of blurry vision and improvement of weakness. She was discharged home with an oral corticosteroid taper.

Follow-up appointment with ophthalmology did not demonstrate optic neuritis. At follow-up appointment with neurology, the patient noted chronic abdominal pain, diarrhea, and weight loss, which had improved during pregnancy but recurred postpartum. JC-virus testing was initiated at this appointment before initiation of DMT, and she was prescribed tizanidine for right-sided muscle spasm. Gastroenterology consult noted decline in BMI from 20% to 3% over a few months and a several month history of multiple loose watery stools daily. Laboratory evaluation documented anemia, with hemoglobin 10.7 g/dL and elevated C-reactive protein (6 mg/dL [ref range 0–1 mg/dL]). Albumin was normal, and serology for celiac disease was weakly positive and thought not to be clinically significant (TTG IgA 21.3 units [ref range 0–20 units]). Symptoms improved with corticosteroid administration and returned with tapering of corticosteroids. Upper endoscopy and colonoscopy demonstrated scalloping in duodenum, patchy aphthous ulceration of the ascending colon, and ulceration and erythema of the terminal ileum (TI) with inflammatory exudate (Fig. 2). Biopsies demonstrated diffuse chronic active inflammation in the TI and right colon with cryptitis, crypt abscesses, and plasma cell and lymphocytic infiltration. The patient was diagnosed with Crohn's disease 6 weeks after POMS diagnosis.

Natalizumab was considered as initial treatment. JCV testing returned positive with index <0.9, suggesting lower risk for PML in the first 2 treatment years. MR Enterography revealed TI and jejunal involvement (Fig. 3). Persistent muscle spasm was managed with high-dose 3-day pulse corticosteroid treatment of 1 g methylprednisolone IV per day along with prolonged oral prednisone taper for Crohn's disease. Following delay for 8 weeks awaiting insurance approval, natalizumab was started 4 months after diagnosis.

Soon after initiation of natalizumab, follow-up MRI brain revealed three new T2 hyperintense lesions without corresponding T1 gadolinium enhancement, suggesting they developed before starting DMT (Fig. 4). The patient's neurologic symptoms improved, and she did not have any clinical evidence of relapse. In contrast to MS, her Crohn's disease remained poorly controlled on natalizumab, with continued weight loss, loose watery stools, and abdominal pain despite multiple courses of oral steroids. She received a total of 1670 mg prednisone and 810 mg budesonide while on natalizumab. After 10 months of treatment with natalizumab, symptomatic improvement of Crohn's disease was minimal. Repeat upper endoscopy and colonoscopy showed no change in gross appearance of colon with no change noted on endoscopic pathology.

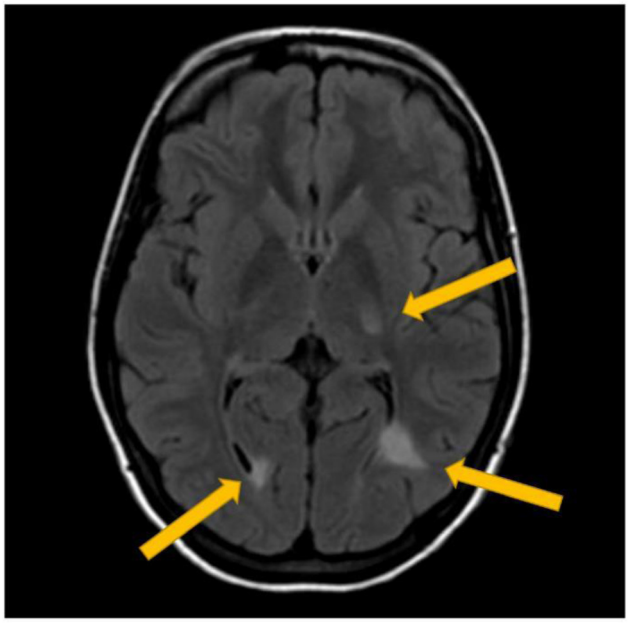

FIGURE 1. Axial T2 flair image of MRI brain with and without contrast demonstrating T2-weighted lesions in the occipital lobes and left globus pallidus of the internal capsule, diagnostic of MS. MRI = magnetic resonance imaging; MS = multiple sclerosis.

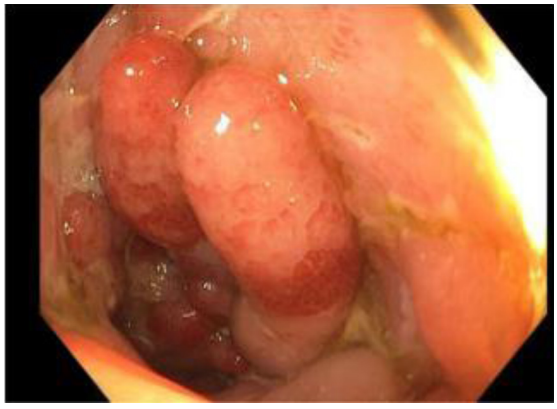

FIGURE 2. Image of terminal ileum on colonoscopy, demonstrating erythema and ulceration concerning for Crohn's disease.

After discussion between the Neurology and Gastroenterology teams around which therapies were least likely to adversely affect either disease process, natalizumab was discontinued, and the patient was initiated on ocrelizumab and ustekinumab 14 months after initiation of natalizumab. MRI brain at the time of DMT change was stable from previous studies, and she remained clinically at her neurologic baseline. Crohn's disease symptoms dramatically improved with ustekinumab, with improved weight gain, resolution of abdominal pain, and normalization of laboratory inflammatory markers.

After 18 months on ocrelizumab and ustekinumab, the patient's Crohn's disease remains in clinical remission, without need for further corticosteroid courses, with no known clinical or laboratory side effects. The patient's most recent MRI brain, 18 months after initiation of this regimen, showed only stable MS plaques from before initiation of DMT, and she continues to do well clinically without any neurological symptoms.

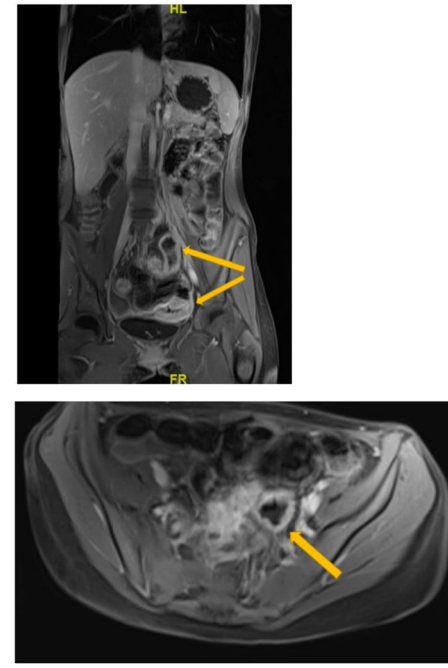

FIGURE 3. Coronal and axial images of MRI enterography with and without contrast demonstrating active Crohn's disease in 20–25 cm of distal ileum in pelvis and an adjacent area of phlegmonous change. MRI = magnetic resonance imaging.

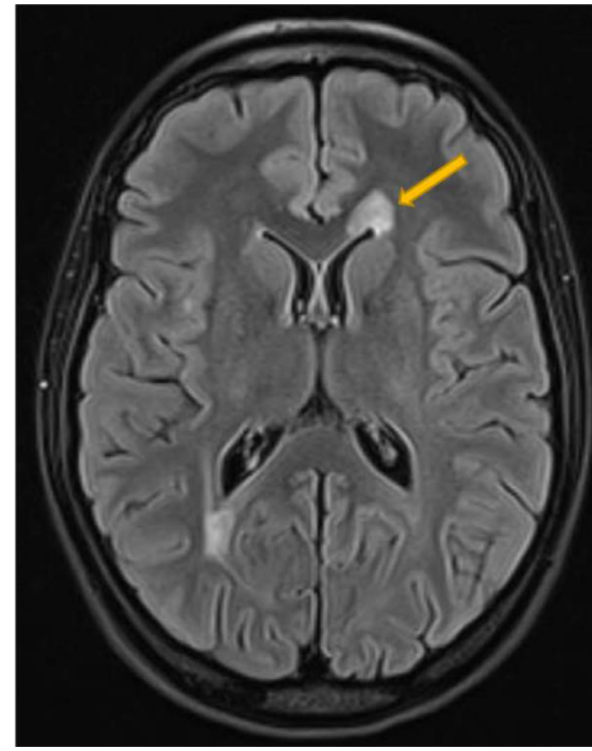

FIGURE 4. Axial T2 flair image of follow-up MRI brain with and without contrast demonstrating new MS plaque in left frontal lobe and redemonstrating plaque in occipital lobe. Postcontrast images had no enhancement, indicating plaques inactive. MRI = magnetic resonance imaging; MS = multiple sclerosis.

DISCUSSION

This case illustrates successful management of a patient with POMS and IBD with ocrelizumab and ustekinumab after an initially difficult course. Monotherapy with natalizumab, while successful in treating the patient's POMS, did not effectively manage the patient's IBD, and furthermore would not have been a viable long-term option in this patient due to her JC-Virus positive status. Clinical trials directly comparing natalizumab with ustekinumab are lacking, and it remains unclear why natalizumab was not effective at inducing remission in this patient. Ocrelizumab has been successful in treating the patient's POMS, as evidenced by her stable clinical status and unchanged neuroimaging, which did not worsen or exacerbate her IBD. Ustekinumab therapy has successfully managed this patient's IBD, and she has gained weight appropriately with well-controlled symptoms for the first 18 months of therapy. Ustekinumab was studied in Phase II RCTs for MS in adults, and did not show efficacy in treating MS, but was found to be well tolerated (10). Ustekinumab is reported to successfully treat psoriasis in patients with MS (11). In the absence of established treatment guidelines, we recommend considering the combination of ustekinumab and ocrelizumab for cases, where standard treatment modalities are not viable options.

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Informed consent was obtained from the patient (over 18 years) for publication of the details of this case.

REFERENCES

1. Kosmidou M, Katsanos AH, Katsanos KH, et al. Multiple sclerosis and inflammatory bowel diseases: a systematic review and meta-analysis. *J Neurol.* 2017;264:254–259.
2. Pokorny CS, Beran RG, Pokorny MJ. Association between ulcerative colitis and multiple sclerosis. *Intern Med J.* 2007;37:721–724.
3. Samson M, Audia S, Duchêne C, et al. Crohn's disease during the course of multiple sclerosis: role of interferon-beta therapy. *Rev Med Interne.* 2009;30:816–819.
4. Charach G, Grosskopf I, Weintraub M. Development of Crohn's disease in a patient with multiple sclerosis treated with copaxone. *Digestion.* 2008;77:198–200.
5. Leiper K, Martin K, Ellis A, et al. Randomised placebo-controlled trial of rituximab (anti-CD20) in active ulcerative colitis. *Gut.* 2011;60:1520–1526.
6. Mills EA, Mao-Draayer Y. Understanding progressive multifocal leukoencephalopathy risk in multiple sclerosis patients treated with immunomodulatory therapies: a bird's eye view. *Front Immunol.* 2018;9:138.
7. Kemanetzoglou E, Andreadou E. CNS Demyelination with TNF-α Blockers. *Curr Neurol Neurosci Rep.* 2017;17:36.
8. Chitnis T, Arnold DL, Banwell B, et al; PARADIGMS Study Group. Trial of fingolimod versus interferon beta-1a in pediatric multiple sclerosis. *N Engl J Med.* 2018;379:1017–1027.
9. Wassmer E, Chitnis T, Pohl D, et al. International pediatric MS study group global members symposium report. *Neurology.* 2016;87(9 Suppl 2):S110–S116.
10. Segal BM, Constantinescu CS, Raychaudhuri A, et al; Ustekinumab MS Investigators. Repeated subcutaneous injections of IL12/23 p40 neutralising antibody, ustekinumab, in patients with relapsing-remitting multiple sclerosis: a phase II, double-blind, placebo-controlled, randomised, dose-ranging study. *Lancet Neurol.* 2008;7:796–804.
11. Chang S, Chambers CJ, Liu FT, et al. Successful treatment of psoriasis with ustekinumab in patients with multiple sclerosis. *Dermatol Online J.* 2015;21:13030/qt3bs971cr.