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Infliximab: A treatment option for multisystem inflammatory syndrome in children with ulcerative colitis?

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We read with great interest the review of Haslak et al. (1) about the diagnosis and management of multisystem inflammatory syndrome in children (MIS-C). MIS-C, temporally related to coronavirus disease 2019 (COVID-19), is a serious clinical condition in which different parts of the body can become inflamed, including the heart, lungs, kidneys, brain, skin, eyes, or gastrointestinal organs, by the cytokine storm. Diagnosis of MIS-C can be confused with other gastrointestinal infections and inflammatory bowel disease (IBD) (2). Optimal treatment for a patient with MIS-C is not known. Further studies are needed to determine the best therapeutic approach to MIS-C (2). We report a case of MIS-C with ulcerative colitis (UC).

A 15-year-old girl with UC was admitted with fever, bloody diarrhea, abdominal pain, anosmia, and dysgeusia. In her medical history, she was diagnosed with steroid-refractory severe UC. Infliximab (IFX) was started 5 months ago in chronically active and steroid-dependent UC for both induction and maintenance of remission. Clinical condition was uncontrolled by 5-aminosalicylic acid and thiopurine. Complete response was observed after administrations of 2 doses of IFX (5 mg/kg dose, 0 and 2 weeks) for initial therapy. During this time, physical examination revealed blood pressure of 110/65 mmHg, fever (39.5°C), and tachycardia (heart rate 130 beats/minute). The patient had no hypotension, abdominal tenderness, or distension and significant pain. Laboratory examinations revealed neutrophilic leukocytosis (15.6×10^3 cells/mL, neutrophils 60%); anemia (hemoglobin 7.6 g/dL); an increase in erythrocyte sedimentation rate (97 mm/hour); an elevation in C-reactive protein level (103 mg/L); and an increase in D-dimer level (1150 ng/mL), international normalized ratio (INR) (1.5 seconds). and interleukin (IL)-6 (81 pg/mL). There was no electrolyte disturbance, and albumin was normal at 3.7 g/dL. There was no radiographic evidence of colonic distention in abdominal X-ray for diagnosis of toxic megaco-

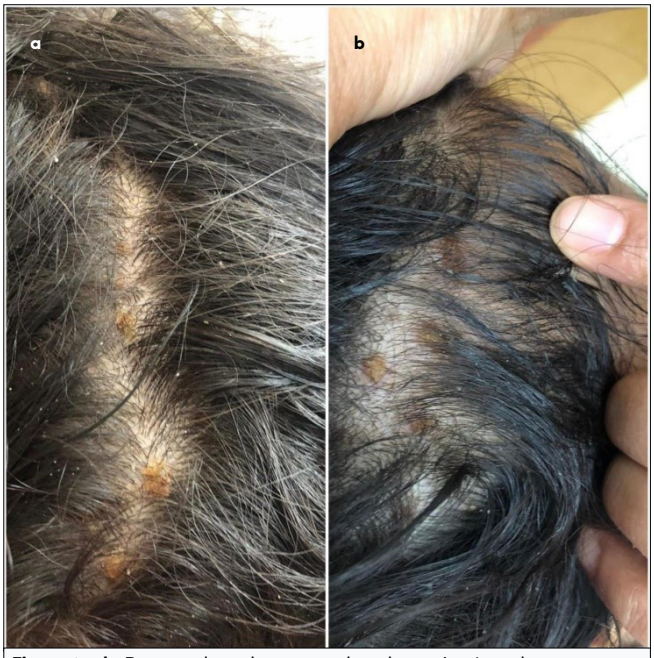

Figure 1 a-b. Dry papule rash appeared on the patient's scalp

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Table 1. Acute phase reactants results profile of patient during follow-up on hospitalization

	Day 0	Day 3	Day 6	Day 7	Day 9
Added therapy		IVIG	Anti-TNFa		
WBC (3.5-10.5) X10^3/mm^3)	15.6	22	17	14	9.8
Neutrophils (%)	61%	80%	76%	60%	39%
Hemoglobin (12-14.5 g/dl)	7.6	6.4	9.3	8	8.3
Platelets (150-450/mm^3)	550	454	278	499	710
erythrocyte sedimentation rate (0-20 mm/hr)	97	110	72	50	40
C-reactive protein (0-8 mg/L)	103	147	91	42	7
Procalcitonin (0-0.5 ng/L)	0.15	8	40	14	0.8
Ferritin (11-306 ng/mL)	11.7	44.3	60	91	12
Fibrinogen(200-400 mg/dL)	360	415	508	353	311
D-dimer (0-500 ng/mL)	1150	1420	1270	965	575

lon (transverse colon diameter <56 mm). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction from nasopharyngeal swab was negative. SARS-CoV-2 immunoglobulin M from on-capillary whole blood samples was positive. Initially, the clinical condition was unclear, because both the UC flare-ups and the MIS-C were possible. At follow-up, a dry papule rash appeared on the patient's scalp (Figure 1a and 1b). Gastrointestinal, cutaneous involvement, and SARS-CoV-2 serology positivity supported MIS-C. However, studies of active IBD exacerbations have shown normal D-dimer level and INR; normal albumin level is unusual in IBD (3).

These clinical and laboratory findings also supported MIS-C. Clinical improvement was refractory to intravenous immunoglobulin (IVIG) (2 g/kg) on day 3. Tocilizumab treatment was planned, but we hesitated because of a possible complication of intestinal perforation. A few studies indicate that tocilizumab treatment can increase the risk of intestinal perforation in patients with a history of UC and concomitant use of glucocorticoids (4). The patient was treated with IFX (5 mg/kg) for management of UC and MIS-C associated cytokine storm on day 6. Within hours, fever and tachycardia resolved and inflammation markers improved to normal levels (Table 1). The patient was discharged with clinical recovery on day 30 of hospitalization.

Early initiation of immunomodulatory treatment (IVIG) and/or glucocorticoids can be lifesaving in MIS-C. Anakinra (recombinant human IL-1 receptor antagonist) and IL-6 neutralization with tocilizumab has been the recommended for patients with MIS-C who are refractory to treatment, but in a small number of patients reported in the literature (5).

IFX is an anti–tumor necrosis factor (TNF) agent for management of moderate to severe UC. Extrapolating from adults with IBD, glucocorticoid use may be associated with worse outcomes in patients with COVID-19, whereas treatment with TNF inhibitors may actually be protective against severe COVID-19 (6,7).

There are a small number of case reports on the usage of anti-TNF therapy in the acute setting in patients with COVID-19 and MIS-C. Anti-TNF therapy differs from anti–IL-6 therapy. TNF blockade leads to downregulation of other proinflammatory mediators, including IL-1, IL-6, and granulocyte-macrophage colony-stimulating factor, within 24 hours. Unlike anti–IL-6 or anti–IL-1 therapies, significant reductions in D-dimer were observed within 1 hour of anti-TNF therapy (8).

There is limited information about MIS-C management in patients with underlying diseases. Our case supports that IFX can be an alternative and safe therapy in patients with MIS-C who have underlying IBD. As clinicians share their experiences, treatment approaches for MIS-C will become clearer.

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