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LETTER TO EDITOR

Spontaneous Gastrointestinal Perforations in STAT3-Deficient Hyper-IgE Syndrome

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To the Editor,

Dominant negative mutations in signal transducer and activator of transcription 3 (STAT3) cause a rare primary immune deficiency, STAT3-deficient hyper-IgE syndrome (STAT3 LOF), characterized by recurrent skin and pulmonary infections, eczematous rashes, and mucocutaneous candidiasis, as well as connective tissue, skeletal, and vascular abnormalities such as scoliosis and craniosynostosis [1]. Gastrointestinal (GI) symptoms are common, with 60% of patients reporting at least one GI symptom in our cohort, most commonly gastroesophageal reflux disease, dysphagia, dysmotility, constipation, and diarrhea [1, 2]. Bowel perforations have been reported infrequently [2, 3].

Recent data has emerged suggesting an increased frequency of gastrointestinal perforation due to tocilizumab, a monoclonal antibody to the interleukin-6 (IL-6) receptor that is approved for use in rheumatoid arthritis and other rheumatologic conditions [4]. Given that IL-6 signals through STAT3 and intestinal perforations have been reported in STAT3 LOF patients, we sought to characterize the incidence and clinical presentations of intestinal perforations in our STAT3 LOF cohort. This cohort consists of patients followed on a National Institute of Allergy and Infectious Diseases (NIAID) institutional review board (IRB)-approved natural history study to which all patients, or their guardians, had provided informed consent. We reviewed 158 STAT3 LOF charts and found 10 patients who suffered from a gastrointestinal perforation, for an overall rate of 6.3%. Here, we present one case in detail with each case summarized in Table 1.

Case Descriptions

A 32-year-old man with STAT3 LOF (STAT3 mutation R382W) complicated by recurrent pneumonia with bronchiectasis and pneumatoceles, severe tracheomalacia in infancy requiring a tracheostomy, gastroesophageal reflux disease status post Nissen fundoplication, and eosinophilic esophagitis presented with 3 days of fevers and upper respiratory symptoms (patient 2 in Table 1). His prophylactic medications at the time included trimethoprim sulfamethoxazole (TMP/SMX), azithromycin, posaconazole, and intravenous immunoglobulin (IVIG). He endorsed nausea and one episode of emesis, as well as malaise and fatigue. Coronavirus OC43 was diagnosed on respiratory viral panel, and *Pseudomonas aeruginosa* grew from respiratory sputum cultures. Intravenous cefepime was initiated with symptomatic improvement. However, on hospital day two, he developed acute-onset lower abdominal pain. An abdominal x-ray did not show any evidence of free air but showed stable marked dilation of several colonic loops. His abdominal pain improved, and he tolerated oral diet and activity. On hospital day four, due to mild lingering abdominal pain and an increasing C-reactive protein (CRP) of > 300 mg/L, a CT of the abdomen/pelvis was performed which revealed a small amount of free air and pelvic free fluid. He then developed fevers and tachycardia with worsening of his abdominal pain. He was taken for an exploratory laparotomy where surgeons

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Table 1 Characteristics of gastrointestinal perforations in our cohort of STAT3 LOF patients

Patient	Age at perforation (years)	Sex	Genetic mutation	Binding domain	HIES score	Unique clinical manifestations*	Peak serum IgE (IU/ml)	Acute comorbid conditions at time of perforation	Prophylaxis at time of perforation	Clinical symptoms at time of perforation	Location of perforation	Clinical course and surgical management
1	29	F	R382W (1144C > T)	DNA	58	Discoid lupus, lymphoma	3880	Diffuse large B cell lymphoma, sinusitis	Cephalexin, fluconazole	Abdominal pain and fatigue	Duodenum	Primary repair; subsequent imaging revealed a contained perforation; after completing chemotherapy for lymphoma, she underwent antrectomy and retrocolic Roux-en-Y gastrojejunostomy
2	32	M	R382W (1144C > T)	DNA	72	Severe tracheomalacia as infant requiring tracheostomy, gastroesophageal reflux disease (GERD) status post Nissen fundoplication, eosinophilic esophagitis	30,586	*Pseudomonas* pneumonia treated with cefepime	TMP/SMX, azithromycin, posaconazole, intravenous immunoglobulin (IVIG)	Abdominal pain, fever developed after 2 days	Ileum	Primary repair (case discussed within the text)
3	5	F	L706P (2117 T > C)	SH2	73	Orbital abscess with subdural empyema	26,268	Pneumonia	TMP/SMX, IVIG	Abdominal pain	Cecum	Outpatient imaging for abdominal pain demonstrated free air leading to emergent primary repair
4	15	F	K658E (1972A > G)	SH2	69	Constipation	5564	MRSA pneumonia treated with vancomycin followed by linezolid	Fluconazole	Fevers, nausea, abdominal pain, obstipation	Transverse colon	Imaging for abdominal pain and fever demonstrated evidence of a perforation leading to surgery with transverse colectomy with colostomy
5	7	M	R382W (1144C > T)	DNA	73	Severe lung disease with multiple surgeries early in life	7651	Pneumonia	None	Fevers, nausea, abdominal pain	Sigmoid colon	Initial exploratory laparotomy was unrevealing, but a second exploratory laparotomy was performed due to worsening clinical course which revealed the perforation, and he underwent primary repair
6	8	F	V637M (1909G > A)	SH2	60	Lower peak IgE	775	Diarrhea	None	Abdominal pain, diarrhea	Sigmoid colon	Evidence of perforation on imaging led to surgery with sigmoidectomy with diverting colostomy
7**	26	M	R382W (1144C > T)	DNA	73	Hepatic steatohepatitis	6237	Diverticulitis with abscess	Dicloxacillin, IVIG	Abdominal pain, diarrhea	Sigmoid colon	Initial imaging showed microperforation which was treated with antibiotics, but abscess formation and subsequent clinical deterioration lead to sigmoidectomy
8	37	F		SH2	64		13,539					

Table 1 (continued)

Patient	Age at perforation (years)	Sex	Genetic mutation	Binding domain	HIES score	Unique clinical manifestations*	Peak serum IgE (IU/ml)	Acute comorbid conditions at time of perforation	Prophylaxis at time of perforation	Clinical symptoms at time of perforation	Location of perforation	Clinical course and surgical management
			V537M (1909G > A)			Severe bronchiectasis with chronic *Pseudomonas* and *Scedosporium* infection leading to recurrent and then fatal massive hemoptysis		Pneumonia, diverticulitis with abscess	Azithromycin, TMP/SMX, voriconazole, IVIG	Abdominal pain, shoulder pain	Sigmoid colon	Contained perforation managed conservatively with antibiotics initially; recurrent symptoms led to low anterior resection with end to end anastomosis
9	43	F	R382W (1144C > T)	DNA	83	No unusual features	24,282	Diverticulitis	TMP/SMX, posaconazole, IVIG	Fevers, abdominal pain	Sigmoid colon	Initial imaging without evidence of perforation and she was managed conservation, but repeat imaging due to worsening clinical status showed the perforation and she underwent sigmoidectomy with diverting colostomy
10	60	M	T622I (1865C > T)	SH2	92	Upper gastrointestinal bleeding secondary to Dieulafoy lesion; esophageal *Cryptococcus*; GERD status post Nissen fundoplication	2932	Diverticulitis with abscess	Dicloxacillin, azithromycin	Diarrhea followed by constipation, abdominal pain	Sigmoid colon	Diverticulitis treated initially with antibiotics, re-imaging after clinical worsening showed free air, leading to sigmoidectomy with diverting colostomy

*For clinical manifestations, all of the included patients had the typical symptoms of STAT3LOF with eczema, recurrent skin and sinopulmonary infections, and non-immunologic findings such as retained primary teeth. Unique or particularly severe complications were listed

**Patient 7 has been previously reported [3]

identified a 3-mm ulcer with fibrinous exudate approximately 10 cm proximal to the ileocecal valve, as well as free purulent fluid. This ulceration was thought to be the etiology of his perforation, and it was oversewn. He was treated with intravenous meropenem and recovered, with no further intestinal issues 1 year later.

Of the ten perforations in our cohort of 158 patients, six patients were female and four were male. Their ages at perforation ranged from five to 62 years old with a median age of 27.5 years old (IQR 30.75). Their genetic mutations were localized to the SH2 domain ($n = 5$) or the DNA-binding domain ($n = 5$) of STAT3. All ten patients presented clinically with some degree of abdominal pain. Other reported symptoms included fevers, diarrhea, and constipation. Six perforations occurred in the sigmoid colon whereas one each occurred in the duodenum, ileum, cecum, and transverse colon. The case involving the duodenum was associated with infiltration of the duodenum with diffuse large B cell lymphoma (DLBCL) and subsequent ulceration of the lymphoma.

Five patients were on treatment for pneumonia at the time of their perforation. Four perforations were associated with diverticulitis, including three with diverticular abscesses. One patient was being treated for sinusitis. Only one patient did not have a diagnosed infection at the time of perforation although she was experiencing diarrhea.

All ten patients required surgery for management of their perforations. Six patients required bowel resection. Three patients underwent primary closure of the defect. The patient whose perforation was due to duodenal DLBCL infiltration initially underwent a primary repair, but the perforation recurred after receiving chemotherapy leading to a subsequent Roux-en-Y repair. Four patients required ostomies, all of which were later reversed. All ten patients survived their perforations and have not had any further perforations (apart from the DLBCL case, as mentioned above), although one patient required a subsequent small bowel resection due to gastrointestinal bleeding. One patient has since died of pulmonary hemorrhage; however, the other nine patients are alive at the time of publication.

Discussion

We report ten cases of gastrointestinal perforation in patients with STAT3 LOF. Five cases were associated with known risk factors for bowel perforation, such as diverticulitis and malignant duodenal infiltration. Similar to other cases of gastrointestinal perforations in STAT3 LOF in which infections such as pneumonia and abscesses were reported [5, 6], nine of the 10 cases occurred during treatment or recovery from infectious conditions such as pneumonia, diverticulitis, and sinusitis; although the tenth case did not carry any specific diagnosis, she was experiencing diarrhea at the time which could have been infectious. Diverticulitis is associated with a risk of free perforation as high as 25.3% in first-time episodes, with the risk decreasing with each subsequent episode [7]. Although infections are common in this population and largely not associated with intestinal perforation, it is possible that the concomitant infections lead to some increased risk and lowered the threshold for perforation, possibly from decreased mobility leading to decreased gut motility on top of preexisting gut dysmotility, or alternately antibiotic exposure, leading to alterations in glut flora and subsequent inflammation.

STAT3 LOF has a connective tissue phenotype with hyperextensible joints, scoliosis, and vascular aneurysms, as well as diverticular disease, that overlaps with other connective tissue disorders associated with increased risk of gastrointestinal perforations, for example, Ehlers-Danlos syndrome [1, 2]. We note that the ages of the patients presented here who developed diverticulitis are lower than patients in the general population who develop diverticulitis [7]. In our cohort, we have had occasional patients with diverticulitis noted as incidental findings on abdominal imaging, but the only episodes of diverticulitis we noted were the few included in this report with perforation. In part, the connective tissue phenotype of STAT3 LOF, including the intestinal perforation, may be due to TGF-β dysregulation, similar to that of Marfan syndrome and Loeys-Dietz syndrome; furthermore, TGF-β has been shown to play a role in intestinal healing [8, 9].

The role of IL-6 signaling in maintaining intestinal health is suggested by the increased risk of gastrointestinal perforation in patients taking tocilizumab for rheumatologic conditions [4]. Similar to our cohort, patients on tocilizumab with perforations may present atypically, with mild symptoms and even lack of abdominal pain, reminiscent of patients on prednisone [4]. Given that IL-6 signaling is diminished in STAT3 LOF, it appears that impaired IL-6 signaling also plays a key role in increasing perforation risk in this cohort as well. Furthermore, a case of a fatal gastrointestinal perforation in a 3-year-old child suspected to have IL-6 signal transducer (IL6ST) deficiency (due to confirmed diagnosis in the sibling and consistent phenotype) provides additional evidence that impaired IL-6 signaling may lead to gastrointestinal perforations [10].

Mouse data supports a role for IL-6 in intestinal wound healing in response to inflammatory processes such as colitis [11–13]. Mice with an antibiotic-treated induced colitis model given an anti-IL-6 monoclonal antibody had higher levels of mucosal damage than mice injected with a control IgG monoclonal antibody [11]. In another study, IL-6-knockout mice given dextran sodium sulfate to induce colitis had higher levels of colitis, colonic ulceration, inflammatory cell infiltration, and weight loss than did wild-type mice given the same chemical [12]. The anti-IL-6 monoclonal antibody-treated mice displayed higher levels of crypt loss compared with controls which the authors posited was related to decreased epithelial proliferation from IL-6 blockade [11], similar to the IL-

6-knockout mice which also demonstrated lower levels of intraepithelial cell proliferation within crypts compared with controls [12]. Colonic response to bacterial infection also appears to depend on IL-6 signaling in mice, as mice deficient in IL-6 with *Citrobacter rodentium* colitis displayed increased colonic epithelium apoptosis and ulceration than did wild-type mice [13]. Evidence for the role of IL-6 in intestinal repair in humans is seen in intestines resected due to perforation which demonstrate elevated levels of IL-6 at perforation sites compared to other areas of the bowel [11].

The pathogenesis of the gastrointestinal perforations seen in our cohort of patients with STAT3 LOF is unclear; however, we posit that the perforations resulted as a combination of abnormal physiologic changes due to concomitant infections, underlying connective tissue disease, and abnormal IL-6 signaling. Together, these factors result in decreased intestinal motility, altered gut flora, abnormal underlying connective tissue, and impaired epithelial wound healing and may contribute to gastrointestinal perforations in STAT3 LOF. Due to the increased risk as well as atypical presentations of gastrointestinal perforations in STAT3 LOF patients, it is important to maintain a high suspicion of this complication in these patients. As noted above, one patient with presumed biallelic IL6ST deficiency had intestinal perforation, but it will need to be determined whether perforations will be a finding in other syndromes with a hyper-IgE phenotype (such as ZNF341 deficiency) as more patients are diagnosed.

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Compliance with Ethical Standards

Conflict of Interest The authors declared that they have no conflict of interest.

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