Idiopathic pancreatitis in a patient with a *STAT3* mutation

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ABSTRACT

Background: *Hyperimmunoglobulin E syndrome (HIES) is a rare primary immunodeficiency characterized by recurrent skin infections with abscesses, recurrent pneumonias with pneumatoceles, and immunoglobulin E levels of >10 times the upper limit of normal.*

Case: *The patient described herein had a classic case of signal transducer and activator of transcription 3 (STAT3) deficiency associated with HIES diagnosed several years before this particular presentation. He demonstrated extraimmune manifestations of the disease as well, including characteristic facies and a history of skeletal fractures. In addition, the patient had several distinct episodes of idiopathic pancreatitis for which a full gastrointestinal workup had been performed. STAT3 mutation was confirmed by genotyping at the time of diagnosis of HIES.*

Conclusions: *STAT3, a mammalian protein that regulates cell growth, survival, and differentiation, has been linked to human pancreatic carcinogenesis as well as the above-mentioned immune deficiency. Mouse studies demonstrated that genetic ablation of STAT3 exacerbates the course of acute pancreatitis, whereas normal pancreatic STAT3 seems to have a protective effect against necrotizing pancreatitis. An association between STAT3 mutations and pancreatitis has not yet been revealed in humans. Here we describe a case of acute pancreatitis that presented in a patient with STAT3 mutation.*

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Signal transducer and activator of transcription 3 (STAT3) is one of several mammalian proteins within the STAT family capable of transcriptional activation within the cell, which regulates critical components of cell growth, survival, and differentiation.[1] It is known for its clinical correlation with hyperimmunoglobulin E syndrome (HIES), a rare primary immunodeficiency and multisystem disorder first described by Davis *et al.*[2] as Job syndrome and later expanded on by Buckley *et al.*[3] and Grimbacher *et al.*[4] The STAT3 molecule is also known for its association with cancer, and, specifically, the importance of STAT3 in human pancreatic carcinogenesis has been documented. Its role in the pancreas extends beyond cancer and into the realm of pancreatitis, as seen in mouse models; however, in humans, an association between *STAT3* mutations and pancreatitis has not yet been revealed. Here, we describe a case of recurrent bouts of otherwise unexplained acute pancreatitis in a patient with a *STAT3* mutation and HIES.

CASE

We present a 39-year-old black male with a history of HIES associated with *STAT3* mutation that involved exon 12, Thr389Ile.[5] He was initially diagnosed at age 35 years old with a total serum immunoglobulin E level of 2728 kU/L and HIES National Institutes of Health score of 53 points (≥15 points is "likely" to carry an HIES genotype, 10–14 points is "indeterminate," and <10 points is "unlikely" to carry an HIES genotype).[4] The patient had a history of multiple infections, including an empyema at age 2 years, which required thoracotomy with surgical lobectomy; left knee abscess and right arm abscess, each required incision and drainage; skeletal fractures; eczema; recurrent oral candidiasis; multiple upper respiratory tract infections; and four distinct pneumonias, each required hospitalization. This history, in addition to his characteristic facies, increased nasal bridge, and hyperextensibility, was what contributed to his elevated HIES National Institutes of Health score and eventually prompted genotyping for *STAT3* mutation. He had no family history of similar syndromes and, therefore, this was thought to be a sporadic form of *STAT3* mutation. Since his initial HIES workup, he was diagnosed with eosinophilic esophagitis and had experienced multiple recurrent bouts of idiopathic pancreatitis, although he did not have any known preexisting hepatobiliary disease.

During his most recent episode, he presented with a 2-day history of severe abdominal pain associated with nausea and vomiting. The pain was sharp, located in the epigastrium, with radiation to the left upper quadrant and made worse with food intake. Symptoms were consistent with his previous episodes of pancreatitis for which an etiology had never been identified, despite a complete gastrointestinal workup, including

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Table 1 **Laboratory values**

	Reference Range	Admission	24 Hours after Admission	Discharge
White blood cells, $\times 10^9$/L	4.4–11.3	5.5	8.7	5.9
Hematocrit, g/dL	41.0–52.0	43.4	38.6	40.3
Blood urea nitrogen, mg/dL	7–18	9	9	7
Creatinine, mg/dL	0.8–1.3	1.08	0.90	0.87
Lipase, U/L	73–393	1325	5919	380
Alanine transaminase, U/L	10–65	179	148	53
Aspartate transaminase, U/L	10–37	97	60	36
Triglycerides, mg/dL	0–149	121	—	—
Ethanol, mg/dL	<10	<10	—	—

testing for autoimmune causes. He had no history of alcohol abuse or gallstones. As with previous episodes, the patient was not on any medications that are known to be associated with precipitation of pancreatitis. Results of his physical examination revealed a man who was stable and who appeared uncomfortable but in no acute distress. He was tachycardic, with a resting heart rate of 125 beats per minute, normotensive, and afebrile. Results of an abdominal examination revealed tenderness to palpation in the epigastrium but no rebound or guarding. Results of the rest of his examination was normal. His lipase level was 1325 U/L on admission (see Table 1 for a complete reference of his laboratory values).

A computed tomography of the abdomen revealed findings suspicious for mild acute pancreatitis in the midbody of the pancreas without associated mass, pseudocyst, abscess, hemorrhage, or pancreatic ductal dilatation. An abdominal ultrasound was unremarkable aside from fatty infiltration of the liver with otherwise normal anatomy of the hepatic and biliary system. He was treated with standard medical care, received aggressive intravenous fluid resuscitation, and bowel rest. The patient did not demonstrate any signs of alcohol withdrawal. His hospital stay was complicated by ileus; however, his symptoms resolved over the course of an 8-day admission, and he was eventually discharged to home on a regular diet.

DISCUSSION

STAT3 mutations are associated with Job syndrome, also known as HIES. These are rare primary immunodeficiencies characterized by recurrent staphylococcal skin infections with abscesses, recurrent pneumonias with pneumatoceles, eosinophilia, eczema, and immunoglobulin E levels that are >10 times the upper limit of normal.[4] Extraimmune manifestations are prominent in this disease as well, which makes HIES a significant multisystem disorder important across several disciplines. Such manifestations include abnormalities of the dentition, bone, and connective tissue. Specifically, the propensity of patients with HIES for developing craniosynostosis, having retained primary teeth, poor wound healing, and developing scoliosis have been recognized.[6] This particular patient demonstrated a number of extraimmune manifestations as discussed in the case above.

Aside from HIES, STAT3 has been associated with pancreatic carcinogenesis. Activation of STAT3 has been reported in pancreatic ductal adenocarcinoma, and the association of STAT3 with acinar-to-ductal metaplasia has been noted.[7,8] Its role in the pancreas has been further delineated through *in vivo* murine studies with targeted gene deletions. These studies demonstrated that genetic ablation of *STAT3* in the pancreas exacerbates the course of acute pancreatitis, whereas comparatively normal pancreatic *STAT3* has a protective effect against necrotizing pancreatitis.[9] Interestingly, phosphorylated STAT3 has been shown to be expressed in high quantities in mice with induced chronic pancreatitis,[8,10,11] thereby bringing into question that *STAT3* expression may be upregulated in a normal subject during times of pancreatic inflammation to buffer the pancreatic damage sustained. In humans, however, the role of STAT3 in pancreatitis has not been well elucidated. Conceptually, one could draw the conclusion that *STAT3* deficiency may predispose an individual to recurrent, otherwise unexplained pancreatitis. This case highlights the possibility that *STAT3* mutations in patients with HIES may be at risk for what would otherwise be categorized as idiopathic acute pancreatitis and supports previously reported mouse data that STAT3 may protect against pancreatitis in normal healthy subjects.

CONCLUSION

The patient described herein has *STAT3*-deficient HIES and a history of multiple bouts of otherwise unexplained pancreatitis. He was evaluated for other potential precipitating factors that could have triggered his pancreatitis, which included gallstones, anatomic anomalies, hypertriglyceridemia, autoimmune

pancreatitis, and infection; he had had no exposure to alcohol, toxins, or known associated medications that trigger pancreatitis. Although it is possible that this patient may have truly had "idiopathic" pancreatitis, especially given the fatty infiltration of his liver seen on abdominal ultrasound, which may indicate preexisting hepatobiliary disease, analysis of the mouse data indicated that an alternative explanation may be at play. Similar cases would be needed to help support the hypothesis that *STAT3* deficiency may be associated with clinically relevant pancreatitis. To the best of our knowledge, this is the first known case of acute pancreatitis that presented in a patient with a *STAT3* mutation.

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