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Safety of Major Abdominal Surgical Procedures in Patients with Hyperimmunoglobulinemia E (Job's Syndrome): a Changing Paradigm?

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Abstract

Introduction—Autosomal dominant hyperimmunoglobulinemia E syndrome (HIES), also called Job's syndrome, is a primary immunodeficiency characterized by the triad of elevated immunoglobulin E levels, eczema, and infections. Its clinical course manifests as recurrent skin

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and pulmonary infections, and variable skeletal, connective tissue, and vascular abnormalities. There is evidence of abnormal tissue remodeling with pneumatocoels frequently complicating pyogenic pneumonias and leading to secondary infections that cause the majority of morbidity and mortality. Complications are known to occur after lung surgery with a high frequency of bronchopleural fistulae, but little has been reported concerning abdominal surgeries.

Discussion—Here, we report on the outcome and safety of two separate complex cases (hepatectomy and subtotal gastrectomy) and document our entire experience with abdominal surgical procedures performed on patients with HIES. Despite initial complications, all patients eventually made a full recovery.

Conclusion—As HIES patients now frequently live beyond the third and fourth decade, surgical issues similar to those in the general population may increase. Complex surgical procedures can be performed safely and benefit select patients with HIES, but benefit strongly from multidisciplinary teams and awareness of complications related to abnormal healing. We discuss current treatment and potential complications post-operatively in patients with HIES.

Keywords

Job's syndrome; Hyperimmunoglobulinemia E; Immunodeficiency; Liver resection; Gastrectomy; Colon resection

Introduction

Autosomal dominant hyperimmunoglobulin E syndrome (HIES), also known as Job's syndrome, is a primary immunodeficiency characterized by elevated immunoglobulin E (IgE), eczema, and infections.¹ HIES is caused by dominant-negative mutations in the signal transducer and activator of transcription 3 (STAT3) gene (Fig. 1).^{2,3} STAT3 is expressed widely and crucial to many cellular and biological functions, consistent with the diverse clinical manifestations seen with its mutations. Hotspot mutations in the SH2- and DNA-binding domains of STAT3 predominate, with no clear genotype–phenotype correlations.⁴ The majority of these mutations are missense or short in-frame deletions associated with normal protein expression but diminished function of STAT3.⁴

Clinical manifestations include recurrent skin abscesses, pneumonias, mucocutaneous candidiasis, as well as other skeletal and connective tissue abnormalities.⁵ Recently, the early development of aneurysms with paucity of atherosclerosis, and osteoporosis have been added as non-immunologic manifestations of the syndrome.⁶ Recurrent pyogenic pneumonias typically progress to bronchiectasis and pneumatocoels which subsequently become superinfected with *Pseudomonas aeruginosa*, molds such as *Aspergillus*, and nontuberculous mycobacteria.⁵ Due to these difficult-to-treat chronic infections, the diagnosis of HIES has historically portended a poor prognosis. In recent years, there have been strides in understanding the pathogenesis of HIES. The most consistent immunologic abnormalities is failure of differentiation of Th17 lymphocytes leading to impaired upregulation of antimicrobial peptides at epithelial surfaces leading to *Candida* and *Staphylococcus aureus* infections.⁷ Disorders of tissue remodeling likely explain the vascular aneurysms, poor lung healing after pneumonias, and characteristic facial

appearance with porous skin. Dysregulated matrix metalloproteinases (MMPs) may contribute to these findings.⁸

In the last decades, the outcome of patients with HIES has improved, with early diagnosis and aggressive treatment of infections, and more recently consideration of bone marrow transplant.^{3,9-11} Though infectious complications still comprise the vast majority of morbidities and mortalities associated with this syndrome, HIES patients are now living longer and may present with common surgical problems.¹² Major surgical procedures on this patient population may pose a management dilemma. Historically, the majority of surgical interventions have been dogmatically avoided and have been confined to incision and drainage of abscesses and resections of pneumatoceles and areas of progressive bronchiectasis. Lung surgeries have had an increased risk of bronchopleural fistulae, often leading to difficult to treat empyemas and further surgeries. Avoidance of surgery has stemmed from the concern of impaired healing as well as the anesthetic risks due to impaired lung function in the late stages of the disease. There is a paucity of data on the feasibility, safety, and outcome of major surgical procedures in patients with HIES. Given the increased survival of patients with HIES, it is wise to consider likely surgical interventions in these patients and how they might be managed.

Herein, we report from a registry of patients with HIES on the outcome of those who underwent complex abdominal surgical procedures: We found that advanced surgical procedures may be complicated by impaired healing, but can be performed safely and benefit select patients. Relevant literature discussing current treatment methodology, potential pitfalls post-operatively, and improved clinical outcomes through the use of multimodality therapy are detailed.

Materials and Methods

All patient records with HIES followed at the National Institute of Allergy and Infectious Diseases from 1986 to 2011 were screened for those who underwent abdominal surgeries. Ten patients out of 47 were identified who underwent 12 abdominal surgical procedures (Table 1). The most common post-operative complication was wound dehiscence and delayed healing. We describe in detail two major abdominal surgeries in HIES patients which occurred without long-term sequelae.

Hepatectomy

A 36-year-old woman with STAT3 g.1144C→T, p.R382W in the DNA-binding domain was referred with a 12×12×8-cm symptomatic hemangioma in the right hepatic lobe (Fig. 2a). She was diagnosed with HIES 10 years after developing multiple subcutaneous abscesses. She had pneumonia complicated by empyema requiring thoracotomy at age 23, two episodes of *Escherichia coli* sepsis with multiorgan failure, tooth extractions for mandibular abscesses, maxillary sinusitis requiring debridement and tympanic membrane repair.

Due to the increasing size of the hepatic hemangioma and concern for high-output congestive heart failure, the patient was taken to the operating room for a partial right hepatectomy. She tolerated the procedure well and was discharged home. Eleven days post-

operatively, she was found to have a sub-diaphragmatic biliary collection requiring percutaneous catheter drainage, and placement of an indwelling drainage catheter. The patient was discharged home on post-operative day 15, on her standard prophylactic HIES antibiotics (posaconazole and trimethoprim/sulfamethoxazole DS).

One-month post-operative imaging revealed expected compensatory right hepatic hypertrophy. The indwelling biliary drain was in place, with a resolving peri-hepatic fluid collection. The biliary drain was draining approximately 200 mL of non-purulent bile per day. However, no healing of the biliocutaneous fistula had occurred by 2 months and the patient required upsizing of her biliary drain for an increasing peri-hepatic fluid collection. Following this procedure, purulent biliary drainage was noted. This was managed with a 4-weeks course of intravenous meropenem, at which time the purulent drainage had resolved. Over the subsequent 2 months, the drainage slowly resolved, and the drain was eventually removed 4 months post-operatively without evidence of a biliary fistula. Figure 2b shows the CT scan post-closure of the patient's fistula.

Subtotal Gastrectomy

A 29-year-old woman with STAT3 g.1144C→T, p.R382W in the DNA-binding domain was referred for surgical consultation. Past medical history was significant for pneumonia, recurrent otitis media, bilateral tympanic perforations, recurrent sinusitis, and skin abscesses. Nine years following her diagnosis of HIES she had an emergency exploratory laparotomy for free air. Upon entering the abdomen, a liver lesion was identified and biopsied, showing high grade large B cell lymphoma. A perforated duodenal ulcer was repaired with a Graham patch. The duodenal ulcer was not biopsied but presumed to be due to lymphoma. She was subsequently treated with five cycles of etoposide, doxorubicin, vincristine, cyclophosphamide, prednisone, and rituximab (EPOCH-R) chemotherapy for her lymphoma.

Her chemotherapeutic course was complicated by numerous episodes of neutropenic fever, treated with broad-spectrum antibiotics. Restaging scans identified a new intra-abdominal mass adjacent to the duodenum and abutting the left liver (Fig. 2c). Endoscopy did not show lymphoma and computed tomography (CT) scan was consistent with a large inflammatory response in this area. This mass was classified as a contained proximal duodenal perforation and the patient was maintained on intravenous antibiotics and bowel rest for 4 weeks.

Interval imaging demonstrated no resolution (Fig. 2d), and the patient was then taken to the operating room. Subtotal gastrectomy, partial duodenectomy, vagotomy, and Roux-en-Y reconstruction was performed. Patient tolerated the procedure well. Post-operatively she developed a persistent gastric outlet obstruction at the gastrojejunostomy site, which was treated with endoscopic dilatation. Patient also had an abdominal wound dehiscence, which was allowed to heal by secondary intention over several months. Overall, the patient did well following these interventions, and was eventually discharged on a regular diet 2 months following surgery.

Review of Other Abdominal Surgeries

The National Institute of Allergy and Infectious Disease, National Institutes of Health database identified ten patients who underwent 12 abdominal surgeries (Table 1). Four of the surgeries had complications. The complicated surgeries included: the two cases discussed above, partial small bowel resections for Dieulafoy's lesions in a 53-year-old patient complicated by dehiscence of the wound and internal herniation, and a partial sigmoid colectomy for perforated diverticulitis in a 25-year-old complicated by prolonged seroma. The remainder of surgical procedures were uncomplicated and included three cholecystectomies, two appendectomies (one with simultaneous cholecystectomy), open umbilical hernia repair, open gastrostomy, open small bowel resection for intussusception, and an open repair of an isolated cecal perforation.

Discussion

Hyperimmunoglobulin E syndrome (Job's syndrome) is a multisystem immunodeficiency disorder characterized by eczema, abscesses, recurrent staphylococcal infections of the skin and lungs, pneumatocele formation, candidiasis, eosinophilia, and elevated IgE levels.^{3,13} Non-immunologic features of the syndrome include a characteristic facial appearance, skeletal abnormalities including pathologic fractures and scoliosis, retained primary teeth, craniosynostosis, and vascular aneurysm and tortuosity.³ STAT3 is crucial to many cellular and biological functions, consistent with the diverse clinical manifestations seen with its mutation. Hotspot mutations in the SH2- and DNA-binding domains of STAT3 have been identified, with few significant phenotypic differences between the different genotypes.⁴ Earlier diagnosis of HIES through greater recognition of clinical phenotype and genetic testing will allow earlier implementation of preventative antimicrobial treatment and will likely allow for greater longevity. Hence, an increasing number of patients with HIES will be facing surgical issues seen often in the unaffected population.

HIES has long been recognized as a multisystem disorder. Several clinical features suggest abnormal tissue remodeling, and a particular propensity of delayed and abnormal healing. Recurrent pneumonias lead to pneumatoceles and bronchiectasis, and abnormal pulmonary healing is also evident by the high rate of bronchopleural fistulae following lung surgeries (Freeman et al., submitted). The vascular aneurysms and coarse facial features likely also stem from disordered tissue remodeling. Dysregulation of metalloproteinases (MMPs), have been identified that may underlie some of the disordered wound healing.⁸ In addition, animal model data suggest that STAT3 is involved in pulmonary and intestinal repair. Kida et al. analyzed the role of STAT3 in the repair of bronchiolar epithelium. In vitro, they found that wild-type STAT3 activated migration of airway epithelial cells during repair whereas dominant-negative STAT3 inhibited this migration.¹⁴ In vivo, bronchiolar repair following injury with naphthalene demonstrated that STAT3 transgenic mice had impaired healing of the pulmonary epithelium compared to wild-type controls.¹⁴ The authors concluded that STAT3 signaling functions to restore cell shape and cell count required for the repair of the bronchiolar epithelium following injury.¹⁴ Pickert et al. recently found that intestinal epithelial STAT3 activation regulates immune homeostasis in the intestine through the promotion of IL-22-dependant mucosal wound healing.¹⁵ In vitro, gene chip arrays indicated

that STAT3 regulates cellular stress responses, cell death and pathways associated with wound healing in intestinal epithelial cells.¹⁵ In vivo studies demonstrated that STAT3 knockout mice were highly susceptible to experimental colitis.¹⁵ Therefore, extrapolating these preclinical data to HIES patients undergoing surgery, it is evident that surgeons need to be cognizant of intestinal wound healing complications.

Although there remains a paucity of surgical literature, major surgical procedures in the HIES population have been described. In addition to the two described cardiothoracic procedures for intrathoracic vascular emergencies, our experience demonstrates that major abdominal surgical procedures can be safe, including proactive management of intestinal perforation and should not be delayed. However, poor healing must be anticipated as a possible complication and surgeons need be cognizant of this in the early post-operative period. Anastomotic leaks, fistula formation, and wound dehiscence should be diagnoses entertained early in the HIES post-operative population. It is interesting to note, however, that the reports of impaired healing appear to be limited to epithelial surfaces. Several HIES patients have undergone orthopedic surgeries, such as placement of Harrington rods for scoliosis, without significant complications noted.

Conclusion

Patients with HIES usually live into adulthood. Surgeons might encounter them and find a paucity of data to drive clinical decision making. Historically, surgical interventions have been confined to incision and drainage of abscesses and debridements for skin infections whereas more advanced procedures have been avoided. We describe our experience with major surgical procedures. The cases presented had favorable outcomes, albeit with impaired wound healing that required a multimodality approach for successful treatment. We believe this to be the first series reporting on major gastrointestinal surgical procedures in HIES. Based on our favorable outcomes following complex surgical procedures, including major abdominal procedures, we believe that major surgery need not be avoided in HIES patients if a multidisciplinary approach is undertaken.

Acknowledgments

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Fig. 2.

a Pre-operative portal venous phase CT depicting giant hemangioma in a 36-year female with HIES. **b** Post-operative CT following partial right hepatectomy denoting right liver hypertrophy and resolving peri-hepatic fluid collection. **c** Restaging CT scan of a 29-year Job syndrome female with extranodal lymphoma treated with EPOCH-R chemotherapy. CT identified a new intra-abdominal mass adjacent to the duodenum and abutting the right liver (*black arrow*). **d** Preoperative CT following 4 weeks of antibiotics and total parenteral nutrition depicting a decrease inflammation at the first portion of the duodenum (*black arrow*)

Table 1

Characteristics of NIAID, NIH abdominal surgical procedures on HIES patients

Complications after GI surgery in patients with HIES						
Patient ID	Sex	Mutation	Age at time of surgery	Year	Surgery	Time before resolution
1	M	1865 C-T	53	2004	Two small bowel resections and creation of ileostomy for Dieulafoy's lesion	2 years
2	F	1144 C-T	36	2010	Partial right hepatectomy for giant hemangioma	4 months
3	M	1144 C-T	25	2008	Sigmoid colectomy for perforated diverticulitis	1 month
4	F	1144 C-T	29	1998	Partial gastrectomy with Roux-en-Y reconstruction for perforated duodenal mass	3 Months
GI surgery in patients with HIES without complications						
Patient ID	Sex	Mutation	Age at Time of Surgery	Year	Surgery	
1	F	2117 T-C	5	2005	Repair of cecal perforation	
2	M	1909 G-A	3	1999	Unbilical hernia repair	
			5	2001	Appendectomy	
3	F	1865 C-T	18	2001	Cholesystectomy	
4	M	1144 C-T	5 month	1986	Gastrostomy	
5	F	2003 C-T	14	1988	Small bowel resection for intussusception	
			19	1993	Cholesystectomy and appendectomy	
6	F	1853 G-A	23	2010	Cholesystectomy	

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Database of abdominal surgical procedures on HIES patients