

Ruptured thoracoabdominal aneurysm in a 27-year-old with hyper IgE syndrome

Orwa Falah, MRCS(Ed), FRCS(Ed), FRCS(Gen. Surg), Stephen E. Thwaites, MBBS, FRACS, and R. T. A. Chalmers, MD, FRCS *Edinburgh, United Kingdom*

Hyperimmunoglobulin E syndrome is a rare primary immunodeficiency disorder defined by high serum immunoglobulin E titers and associated with characteristic infectious, dermatologic, skeletal, and dental abnormalities. We present the case of a 27-year-old man presenting acutely with a ruptured type IV thoracoabdominal aortic aneurysm. He was successfully treated by open operative repair and discharged with long-term prophylactic antibiotics. To our knowledge, this is the first such case reported in the English literature. (*J Vasc Surg* 2011;■■:■■■.)

Hyperimmunoglobulin E syndrome (HIES) is an immunodeficiency disorder with well-described multisystem effects, including arterial aneurysm. Rupture of a thoracoabdominal aneurysm, no matter the underlying cause, carries a high risk of mortality. This report describes the case of a young man previously diagnosed with HIES, presenting acutely with a ruptured thoracoabdominal aneurysm, which was treated successfully with open surgical repair.

CASE REPORT

A 27-year-old man presented acutely with a history of sudden onset of left-sided abdominal pain, followed by an episode of dizziness and brief loss of consciousness. During assessment, he was noted to develop increasing left iliac fossa pain in addition to lower back pain. At the time of emergency presentation, we had no knowledge that the patient had HIES.

He had experienced recurrent pyogenic infections throughout childhood and adolescence. At age 3, a right nephrectomy was performed for chronic pyelonephritis, the nephrectomy itself being complicated by a renal bed abscess. His medical history also included chronic suppurative sinusitis, for which he had undergone multiple procedures, recurrent chest infections, and an empyema. He had suffered multiple bone fractures and, at presentation, had a chronic, intermittently discharging sinus associated with nonunion of a clavicular fracture.

On arrival, he appeared pale, with a heart rate of 112 and blood pressure of 127/90. Abdominal examination revealed a pulsatile epigastric mass with left abdominal guarding and percussion tenderness.

An urgent contrast-enhanced computed tomography (CT) scan demonstrated a 9-cm ruptured type IV thoracoabdominal aortic aneurysm. A single left kidney was present. A large left retroperitoneal hematoma confirmed rupture of the aneurysm (Figs 1 and 2).

An open Crawford type IV thoracoabdominal aneurysm repair was performed. Proximal control of the distal descending aorta was initially attempted through the pleural space, however, this was found to be obliterated, consistent with the patient's history of a previous empyema. The distal descending thoracic aorta was subsequently exposed by splitting the diaphragm radially. Medial visceral rotation was performed and the aneurysm sac was opened after clamping. A 24-mm woven Dacron graft was anastomosed with the heel incorporating the superior mesenteric artery. The left renal artery could not be incorporated within the neck and a preattached side arm was anastomosed in a lazy-C configuration to the ostium of the left renal artery. Visceral ischemic time was 57 minutes.

The patient made an excellent recovery with normal renal function on discharge. Operative specimens sent for microbiology did not reveal any evidence to support a mycotic etiology, however, in consultation with the microbiology department and because of the risk of bacterial infection in another part of the body, it seemed prudent to maintain this patient on long-term antibiotics, and the patient was discharged on oral ciprofloxacin to be reviewed on an ongoing basis. Follow-up CT angiogram was satisfactory (Fig 3). He has now been fully assessed by a geneticist and confirmed as having STAT3 autosomal-dominant HIES.

DISCUSSION

HIES was first reported in 1966 by Davis, Schaller, and Wedgwood, who described cases characterized by recurrent staphylococcal abscesses and pneumonia.¹ In 1972, Buckley et al,² further defined the clinical and immunologic phenotype of the condition.

In recent years, it has become evident that two distinct forms of HIES exist. The autosomal-dominant (AD) form which accounts for most cases of AD-HIES is distinguished by recurrent skin and pulmonary infections (predominantly pyogenic), eczema, and certain skeletal and soft tissue abnormalities. These include characteristic faces, cranial abnormalities, scoliosis, recurrent fractures, joint hyperextensibility, and arterial aneurysms.³ There is no predilection

From the Department of Vascular Surgery, Royal Infirmary of Edinburgh University Hospital.

Competition of interest: none.

Reprint requests: Orwa Falah, MRCS(Ed), FRCS(Ed), FRCS(Gen. Surg), Edinburgh Vascular Surgical Service, Clinical & Surgical Sciences (Surgery), The Royal Infirmary Of Edinburgh, University of Edinburgh, 51 Little France Crescent, Old Dalkeith Road, Edinburgh EH16 4SA, United Kingdom (e-mail: orwafalah@hotmail.com)

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a competition of interest.

0741-5214/\$36.00

Copyright © 2011 by the Society for Vascular Surgery.

doi:10.1016/j.jvs.2011.08.011



Fig 1. Contrast-enhanced computed tomography (CT) scan (sagittal section) shows a 9-cm ruptured type IV thoracoabdominal aortic aneurysm.

for race or gender. Autosomal-recessive HIES is marked by viral infections and neurologic complications but lacks the connective tissue or skeletal manifestations of the AD form.⁴

Elevated serum IgE is the hallmark of the syndrome, with titers usually more than 10 times normal. In AD-HIES, eosinophilia may be present in blood, sputum, and abscesses, while abnormalities within lymphocyte populations are known to occur.⁵ In vitro, production of TH1 cytokines such as interferon-gamma and tumor necrosis factor-alpha is greater in AD-HIES leukocytes than controls. Impaired responses to interleukin-6 and interleukin-10 are also found in AD-HIES.^{3,6}

It is now recognized that most cases of sporadic and inherited AD-HIES arise from dominant negative mutations of the signal transducer and activator of transcription 3 (STAT3) gene.^{6,7} STAT3 is involved in many signal transduction pathways, including those of several proinflammatory and anti-inflammatory cytokines. This may explain the immunologic dichotomy of AD-HIES, where manifestations of excessive inflammation and an inadequate immune response coexist. Consequences of immunologic dysfunction include eczema, boils, recurrent bacterial pneumonia with fungal superinfection, and pneumatocele formation. Mortality is high at a young age in autosomal-recessive HIES with sepsis more frequently than in AD-HIES.

One of the manifestations of AD-HIES, apparently unrelated to the immune system, is the development of arterial aneurysms. The most commonly reported cases of

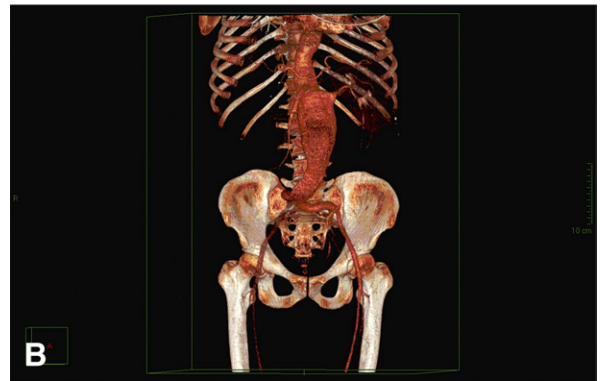


Fig 2. A, Contrast-enhanced computed tomography (CT) scan (coronal section) shows a 9-cm ruptured type IV thoracoabdominal aortic aneurysm. B, Colored three-dimensional (3D) CT angiography scan (front view) shows a 9-cm ruptured type IV thoracoabdominal aortic aneurysm.

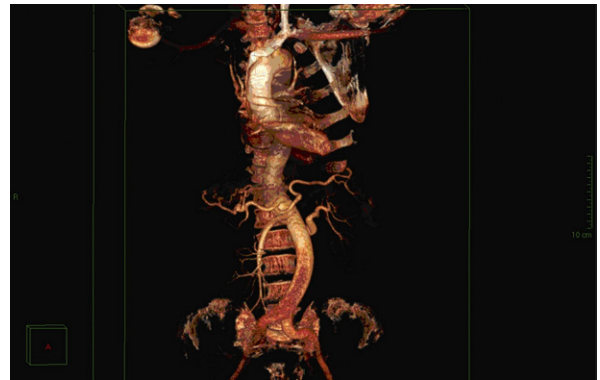


Fig 3. Colored three-dimensional (3D) computed tomography (CT) angiography scan (front view) of the abdomen showing the woven Dacron graft and side arm to left renal artery.

vascular abnormalities and aneurysm formation relate to the coronary and intracranial arteries.⁸ While vascular tortuosity and dilatation seem to predominate over aneurysm formation in the coronary circulation, bilateral berry aneurysms of the internal carotid arteries and a mycotic aneu-

rysm of the middle cerebral artery have been reported.⁹ Follow-up CT angiogram is recommended every 5 years to exclude aneurysmal dilatation.

van der Meer et al¹⁰ described aneurysmal dilatation of the ascending and descending thoracic aorta in a case report of two patients with clinical features consistent with autosomal-recessive HIES. Both subjects died from respiratory infections at the ages of 19 and 32, respectively.

The relationship between the genetic fingerprint of AD-HIES and the physical and immunologic sequelae remains the subject of ongoing investigation. In a model of targeted STAT3 disruption in murine hematopoietic cells, increased osteoclastogenesis and osteopenia were present,¹¹ reflecting the propensity for fractures. Cardiac myocyte STAT3 deficiency has been shown to lead to cardiac inflammation and early cardiac failure,¹² while STAT3 deficiency in pulmonary epithelium has been shown to lead to exacerbated immune responses and impaired bronchiolar epithelial repair.^{13,14} The role of STAT3 deficiency in vascular ectasia, inflammation, and aneurysm formation is, as yet, undefined and a subject for future research.

Our subject had a history, physical findings, and DNA genetic testing, which was done after surgery consistent with the AD form of HIES, including recurrent pyogenic infections, multiple bone fractures, and characteristic faces.

This report is the first case in the published literature of a thoracoabdominal aneurysm associated with HIES.

REFERENCES

1. Davis SD, Schaller J, Wedgwood RJ. Job's Syndrome. Recurrent, "cold", staphylococcal abscesses. *Lancet* 1966;1:1013-5.
2. Buckley RH, Wray BB, Belmaker EZ. Extreme hyperimmunoglobulinemia E and undue susceptibility to infection. *Pediatrics* 1972;49:59-70.
3. Grimbacher B, Holland SM, Gallin JI, Greenberg F, Hill SC, Malech HL, et al. Hyper-IgE syndrome with recurrent infections—an autosomal dominant multisystem disorder. *N Eng J Med* 1999;340:692-702.
4. Renner ED, Puck JM, Holland SM, Schmitt M, Weiss M, Frosch M, et al. Autosomal recessive hyperimmunoglobulin E syndrome: a distinct disease entity. *J Pediatr* 2004;144:93-9.
5. de Beaucoudrey L, Puel A, Filipe-Santos O, Cobat A, Ghandil P, Chrabieh M, et al. Mutations in STAT3 and IL12RB1 impair the development of human IL-17-producing T cells. *J Exp Med* 2008;205:1543-50.
6. Minegishi Y, Saito M, Tsuchiya S, Tsuge I, Takada H, Hara T, et al. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. *Nature* 2007;448:1058-62.
7. Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, et al. STAT3 mutations in the hyper-IgE syndrome. *N Engl J Med* 2007;18:1608-19.
8. Ling JC, Freeman AF, Gharib AM, Arai AE, Lederman RJ, Rosing DR, et al. Coronary artery aneurysms in patients with hyper IgE recurrent infection syndrome. *Clin Immunol* 2007;122:255-8.
9. Freeman AF, Kleiner DE, Nadiminti H, Davis J, Quezado M, Anderson V, et al. Causes of death in hyper-IgE syndrome. *J Allergy Clin Immunol* 2007;119:1234-40.
10. van der Meer JW, Weemaes CM, van Krieken JH, Blomjous CE, van Die CE, Netea MG, et al. Critical aneurysmal dilatation of the thoracic aorta in young adolescents with variant hyperimmunoglobulin E syndrome. *J Intern Med* 2006;259:615-8.
11. Zhang Z, Welte T, Troiano N, Maher SE, Fu XY, Bothwell AL. Osteoporosis with increased osteoclastogenesis in hematopoietic cell-specific STAT3-deficient mice. *Biochem Biophys Res Commun* 2005;328:800-7.
12. Jacoby JJ, Kalinowski A, Liu MG, Zhang SS, Gao Q, Chai GX, et al. Cardiomyocyte-restricted knockout of STAT3 results in higher sensitivity to inflammation, cardiac fibrosis, and heart failure with advanced age. *Proc Natl Acad Sci U S A* 2003;100:12929-34.
13. Hokuto I, Ikegami M, Yoshida M, Takeda K, Akira S, Perl AK, et al. Stat-3 is required for pulmonary homeostasis during hyperoxia. *J Clin Invest* 2004;113:28-37.
14. Kida H, Mucenski ML, Thitoff AR, Le Cras TD, Park KS, Ikegami M, et al. GP130-STAT3 regulates epithelial cell migration and is required for repair of the bronchiolar epithelium. *Am J Pathol* 2008;172:1542-54.

Submitted May 31, 2011; accepted Aug 11, 2011.