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Coronary Artery Aneurysms in Patients with Hyper IgE Recurrent Infection Syndrome

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Abstract

Hyper IgE recurrent infection syndrome (HIES, or Job's syndrome), is a primary immunodeficiency characterized by recurrent skin and lung infections, eczema, elevated serum immunoglobulin E (IgE) levels, and various connective tissue and skeletal system abnormalities including characteristic facies, scoliosis, joint hyperextensibility, retained primary dentition, craniosynostosis, osteopenia, and pathologic fractures. We have identified two patients with aneurysmal coronary artery disease. One was a forty-three year old man with HIES and coronary artery aneurysms and ectasia identified on cardiac catheterization following myocardial infarction. The other was a 48 year old man with coronary artery ectasia-aneurysm identified after cardiac catheterization for evaluation of chest pain. Although connective tissue abnormalities are common in HIES, this is the first report of coronary artery aneurysms in HIES. Further studies are necessary to determine the incidence, pathogenesis, and optimal therapy of these arterial abnormalities in HIES.

Introduction

Hyper IgE recurrent infection syndrome (HIES, or Job's syndrome) is a primary immunodeficiency characterized by the classic triad of recurrent skin and lung infections, eczema, and elevated serum immunoglobulin E (IgE). In addition to the immunologic abnormalities, HIES is a multisystem disorder involving the connective tissue and skeletal systems, including characteristic facies, scoliosis, joint hyperextensibility, retained primary dentition, craniosynostosis, osteopenia, and pathologic fractures¹. The exact immunologic defects and genetic etiology are unknown. Most cases follow either an autosomal dominant pattern, or are sporadic. A distinct recessive form of HIES has been recently described, in

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which the patients have autoimmunity, vasculitis, central nervous system complications, and increased susceptibility to viral infections².

We have identified two men with dominant or sporadic HIES and aneurysmal coronary artery disease. One had coronary artery aneurysms (CAAs) identified during evaluation following myocardial infarction; the other had coronary artery ectasia identified during evaluation of chest pain. This is the first report of myocardial infarction (MI) and CAAs in HIES.

Case Reports

Case 1

A 43 year old Caucasian man with sporadic HIES diagnosed in early childhood had eczema, boils, recurrent pneumonias with pneumatocele formation, lobectomy for aspergillus pneumonia, scoliosis, pathologic fractures, and characteristic facies. Based on an HIES scoring system including immunologic and non-immunologic features, his score was 79 (a score of greater than 40 is considered likely to be affected)³. He has been previously reported^{1,4} (patient #24 for reference 1). He also had mild hypercholesteremia controlled with pravastatin (recent values: total cholesterol 192 mg/dL, triglycerides 379 mg/dL, high density lipoprotein 53 mg/dL, and low density lipoprotein 87 mg/dL), and hypertension controlled with calcium channel blockers. He had a history of Wernicke encephalopathy and a left thalamic lacunar infarct several years prior. He had used tobacco for over 20 pack-years and had previously abused alcohol.

The patient was found slumped over in a car in ventricular fibrillation. He was resuscitated and taken to a local emergency room, where an acute antero-septal myocardial infarction was confirmed by electrocardiogram (EKG) and cardiac enzymes. He was managed conservatively. He was then transferred to the National Institutes of Health (NIH).

Echocardiogram (post MI day #3) demonstrated mid-anterior and septal akinesia and apical septal hypokinesia, consistent with infarction in the left anterior descending (LAD) territory. There was mildly decreased left ventricular systolic function (ejection fraction of 45%). Coronary angiography demonstrated a 9mm fusiform aneurysm involving the LAD and its first diagonal branch (Figure 1). Within the mid-LAD aneurysmal segment, there appeared to be a filling defect thought to represent a dissection flap or thrombus. The right coronary artery (RCA) was diffusely enlarged (ectatic). Intravascular ultrasound revealed only minimal intimal thickening and no arterial calcification, both of which are more characteristic of atherosclerosis.

Contrast enhanced cardiac MRI showed a transmural myocardial infarction in the LAD distribution. Computerized tomography (CT) coronary angiograms corroborated these findings (Figure 1).

He was felt ineligible for long-term warfarin anticoagulation and was instead treated with aspirin and clopidogrel.

Case 2

A 48 year old Caucasian man was diagnosed with autosomal dominant HIES at 38 years of age based on a history of recurrent pneumonias with lobectomy, boils, recurrent sinusitis, disseminated histoplasmosis, cryptococcal meningitis, mucocutaneous candidiasis, and characteristic facies (previously reported⁵). His HIES score was 79. His medical history was also significant for two hernia repairs and esophageal reflux and diverticula for which he took omeprazole. He denied tobacco or alcohol use.

He presented to an outside hospital with chest pain and tightness associated with shortness of breath that occurred while driving. Cardiac enzymes were normal and EKG demonstrated nonspecific T-wave abnormalities. Echocardiogram showed normal left ventricular systolic function and left ventricular hypertrophy. Exercise scintigraphy was equivocal. Coronary arteriography showed no obstruction but proximal LAD and RCA ectasia. CT coronary angiogram two years later confirmed LAD ectasia-aneurysm with a maximum diameter of 6.5 mm, and long RCA ectasia with a maximum diameter of 6.5 mm. These were relatively unchanged from prior catheterization. Coronary MR angiography corroborated these findings (Figure 2). Serum lipids were: total cholesterol 176 mg/dL, triglycerides 237 mg/dL, high density lipoprotein 50 mg/dL, and low density lipoprotein 81 mg/dL. He was treated with aspirin.

Discussion

HIES is a multisystem disorder with abnormalities of the immunologic, skeletal, and connective tissue systems. Connective tissue and skeletal abnormalities include characteristic facies, hyperextensibility, scoliosis, failure of primary tooth deciduation, decreased bone mineral density, and minimal trauma fractures¹. Although not considered a feature of HIES, we have observed arterial abnormalities in autosomal dominant or sporadic HIES patients, including bilateral aneurysms at the carotid bifurcation in one patient, and a mycotic aneurysm in the left middle cerebral artery in another patient (unpublished data). Vascular abnormalities (e.g. aneurysms, stenoses, vasculitis) leading to neurologic complications have also been observed in the autosomal recessive form of HIES^{2,6}. These two cases represent the first reported patients with HIES and CAA; in one the CAA was complicated by myocardial infarction. CAA may lead to stasis, mural thrombosis, and thromboembolism leading to acute myocardial infarction.

CAAs are characterized by abnormal dilation of localized or diffuse segments of the coronary arterial tree⁷. The incidence of CAA found during coronary angiography varies from 1–5% and is usually attributed to severe atherosclerosis^{7–10}. Significant atherosclerotic disease was not observed in either of our patients.

In children, CAAs are most commonly associated with Kawasaki disease (KD), a vasculitis characterized by fever, rash, conjunctival injection, oral mucosa erythema, lymphadenopathy and hand and/or foot swelling and erythema¹¹. Although KD is suspected to have an infectious etiology, the incidence is not known to be increased in children with immune deficiencies. Two patients with HIES treated for KD have been reported; both responded promptly to their initial course of intravenous gammaglobulin and coronary artery sequelae

were not reported¹². Neither our patients nor their parents recalled symptoms or a history compatible with KD as a child, although this diagnosis can be missed and both patients had frequent fevers and rashes as children as part of their HIES.

Vascular aneurysms occur with heritable connective tissue disorders, such as Marfan and Ehlers-Danlos syndromes. HIES shares some connective tissue abnormalities with these syndromes, such as scoliosis, joint hypermobility, and high arched palate. In Ehlers-Danlos syndrome Type IV (vascular type), patients have an abnormality in Type III collagen, causing vascular complications, such as arterial dissection and rupture¹³. In Marfan syndrome, cardiac valvular disease as well as aortic root dilation, dissection, and rupture are common, but CAAs are rare^{14–16}. Loeys-Dietz syndrome, which has many phenotypic similarities to Marfan syndrome, also shares phenotypic features of HIES such as craniosynostosis and Chiari I malformations, and includes aneurysms and arterial tortuosity of the aorta and other arteries, including medium-sized arteries^{17–18}. TGF-beta dysregulation is found in both Marfan and Loeys-Dietz syndromes, secondary to the deficient fibrillin-1 protein in the Marfan syndrome and mutations in TGFBR1 or TGFBR2 in the Loeys-Dietz syndrome^{17–19}. Whether TGFbeta, which is involved in both connective tissue matrix homeostasis as well as inflammatory responses, plays a role in the pathogenesis of the many abnormalities of HIES remains to be determined.

Other etiologies of acquired CAAs include infection (mycotic, syphilitic, Epstein-Barr Virus induced), autoimmune (scleroderma and systemic lupus erythematosus), and those following coronary interventions^{8,20–24}. In addition, a small percentage of CAAs are congenital in origin²⁵. There was no evidence for any of these etiologies in our patients, although congenital CAA could not be excluded.

There have been recent advances in the medical therapy of arterial aneurysms. Matrix metalloproteinases (MMPs) are known to be critical in the degradation of the aortic wall leading to abdominal aortic aneurysms (AAA)²⁶, and blockage of the Jun Nterminal kinase (JNK) signalling pathway led to decreased MMP activity and blockage and regression of aneurysms in a mouse model²⁷. In a mouse model of the Marfan syndrome, the angiotensin II type 1 receptor antagonist losartan prevented aortic aneurysm formation, likely through inhibition of TGF-beta²⁸. If arterial aneurysms are increasingly recognized in HIES and their pathogenesis elucidated, then these and other therapeutic approaches will need investigation.

We have described the first cases of CAA in HIES, a multisystem disorder involving connective tissue and immunologic abnormalities. Together with other cases of arterial aneurysms in HIES, these suggest that vasculopathy may be part of the connective tissue aspect of HIES. Further examination of the incidence of these arterial abnormalities, their pathogenesis, and optimal therapy is necessary. Identifying the genetic etiology and immunologic defect of HIES is essential and will assist in uncovering the link between the immunologic and connective tissue abnormalities of HIES.

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Figure 1.

Patient 1. Contrast enhanced CT coronary angiogram and corresponding selective coronary arteriograms. The right coronary artery (RCA) has diffuse ectasia. The left anterior descending coronary artery (LAD) and its large diagonal branch have aneurysms. Reformatted slices from the CT show a filling defect in the LAD aneurysm in long (bottom left) and short (bottom right) axis views.

Figure 2.
Patient 2. Coronary MR angiography showing an ectatic segment of the proximal RCA (arrow heads) and aneurysmal segment of the LAD (arrow).