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Brief Report

Noncompaction of the myocardium associated with Roifman syndrome

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Abstract Noncompaction of the ventricular myocardium, sometimes referred to as "spongy myocardium", appears as excessive and prominent trabeculations and deep intratrabecular recesses within the ventricular wall, usually involving the left ventricle, although the right ventricle and interventricular septum can also be affected. It may occur with or without additional heart malformations. Roifman syndrome is a constellation of antibody deficiency, spondyloepiphyseal dysplasia, facial dysmorphism, growth retardation, and retinal dystrophy. We report a patient with Roifman syndrome who presented with noncompaction of the left ventricular myocardium. Our findings expand the spectrum of diseases associated with noncompaction. The recognition of noncompaction among patients with Roifman syndrome is important, as the immune deficiencies may be subtle and undiagnosed until adulthood. Thus, some patients may first present with cardiac failure.

Keywords: non-compaction, dilated cardiomyopathy, heart failure, immunodeficiency

ROIFMAN SYNDROME IS A CONSTELLATION OF antibody deficiency, spondyloepiphyseal dysplasia, facial dysmorphism, growth retardation, and retinal dystrophy.[1] The combination of humoral immunodeficiency with skeletal dysplasia is rare, as most immunodeficiencies associated with bone dysplasias are T-cell defects or severe combined immunodeficiencies. These include cartilage hair hypoplasia, short limbed dwarfism, adenosine deaminase deficiency, and Schimke immuno-osseous dysplasia. There have been five patients with Roifman syndrome reported to date. All have been males, suggesting an X-linked pattern of inheritance.[1] We now report a patient with Roifman syndrome who presented with noncompaction of the left ventricular myocardium, an entity sometimes referred to as "spongy myocardium". Such noncompaction appears as excessive and prominent trabeculations and deep intratrabecular recesses within the ventricular wall, usually involving the left ventricle, although the right ventricle and ventricular septum can also be affected. It is believed to represent an arrest in endomyocardial morphogenesis and may occur with or without additional cardiac malformations. When seen in isolation, it occurs in a sporadic or a familial pattern compatible with autosomal recessive, autosomal dominant, or X-linked recessive inheritance.[2] Barth syndrome, an X-linked recessive disorder associated with dilated cardiomyopathy, skeletal myopathy, neutropenia and short stature, links cardiomyopathy with an immune defect, but is different from the humoral deficiency seen in Roifman syndrome. Linkage studies in Barth syndrome have localized isolated noncompaction of the ventricular myocardium to the locus Xp28. Mutations of a gene in this area, G4.5, which encodes protein products called taffazins, have been found to cause Barth syndrome, although their function is unknown.[3] This area has also been associated with congenital myopathies, as well as several types of bone dysplasias.[3]

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Case report

Our patient is a 14-year-old male, one of two brothers who have been previously reported with Roifman syndrome. The perinatal history was notable for prematurity and intrauterine growth retardation. Growth remains delayed with his height being less than the third centile. Motor development was also delayed and hypotonia noted, most markedly during the first few years of life. Electromyography and muscle biopsies were normal, while intelligence testing revealed borderline retardation. A skeletal survey demonstrated epiphyseal changes in multiple joints. Retinal findings consist of granular changes in the peripheral fundus. Karyotype and Fragile X analysis were normal, as were metabolic studies.

The patient experienced multiple episodes of upper and lower respiratory infections, dermal infections, and recurrent episodes of herpes simplex. While quantitative immunoglobulins were normal, the ability to produce specific antibodies was impaired and monthly infusions of intravenous immune globulin were required.

On this occasion, the patient presented with several days of vomiting and fatigue. He had complained of decreased energy over three months with repeated episodes of vomiting and several weeks of decreased exercise tolerance. Physical examination revealed tachycardia and tachypnea, although no respiratory distress was noted. Auscultation revealed a gallop rhythm and air entry was significantly decreased on the right side of the chest. The liver was enlarged, with a soft edge being palpated 6 cm below the right costal margin. There was no peripheral edema or limb swelling and peripheral perfusion was normal. A chest radiograph demonstrated cardiomegaly, pulmonary edema, and a right pleural effusion. Scalar electrocardiography revealed sinus rhythm with left ventricular hypertropy and generalized nonspecific abnormalities of repolarization. A cross-sectional echocardiogram revealed severe global left ventricular dysfunction with a left atrial thrombus and hypokinetic mural motion. The left ventricular cavity was dilated with an ejection fraction of only 17%. The wall demonstrated the appearance of marked noncompaction (Fig. 1). A computerized tomography scan of the chest revealed a large right pleural effusion, enlargment of the heart, but no other abnormalities (Fig. 2).

The patient was treated with furosemide, digoxin, enalapril, heparin, and subsequently warfarin. His symptoms improved with normalization of the cardiac and respiratory rates and resolution of the right pleural effusion and hepatomegaly. A radionuclide cardiac angiogram done one week after anticongestive therapy was begun revealed an improved but still low left ventricular ejection fraction of 29%. The symptoms then resolved, except for a mild residual

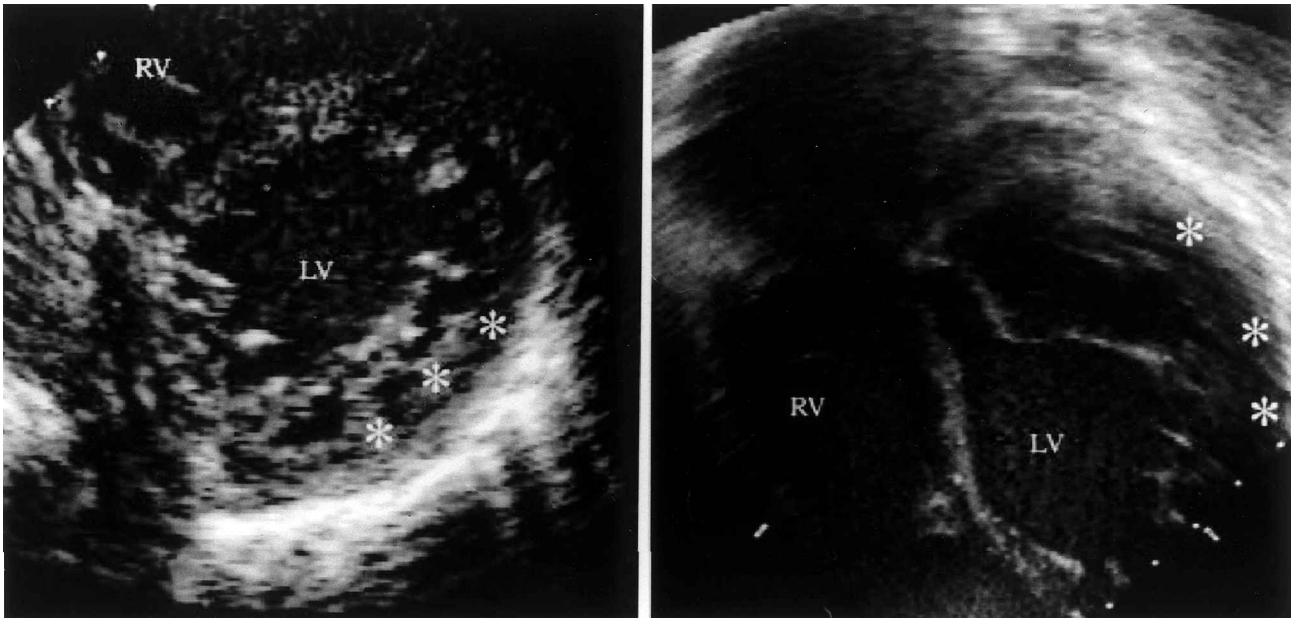

Figure 1:
Echocardiogram demonstrating the appearance of noncompaction of the left myocardium, the left ventricular wall being thick and "spongy" as seen in both the short and long axis.

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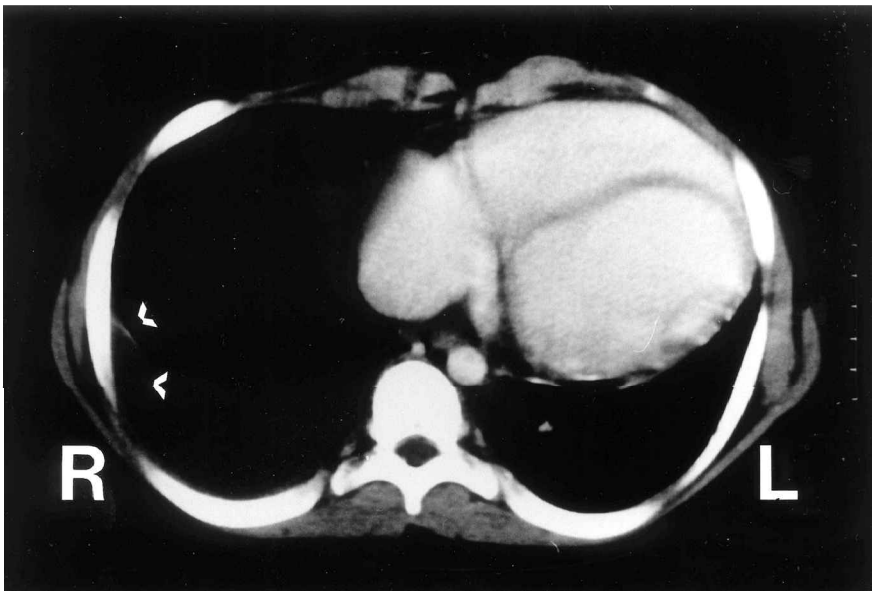

Figure 2.
Computerized tomographic scan of chest demonstrating enlarged heart and right pleural effusion (arrows).

decrease in exercise tolerance. He continues to receive monthly infusions of intravenous immunoglobulins.

The presumed X-linked inheritance of Roifman syndrome, and the description of recurrent infections and sepsis in Barth X-linked syndrome, led to investigation of a possible mutation in the G4.5 gene. Sequencing of the G4.5 gene using the Thermosequenase kit from Amersham did not reveal any mutations. The prominent finding of spondyloepiphyseal dysplasia in our patient, together with presumed X-linked inheritance, also led us thoroughly to investigate mutations in the gene responsible for X-linked spondyloepiphyseal dysplasia. We were not able to show any clinically significant mutation in that gene, or in the pseudogene located on chromosome 19.

Discussion

Isolated noncompaction of the ventricular myocardium is a rare cause of cardiac failure, ventricular arrhythmias, and embolization. It can be an incidental discovery during transthoracic echocardiography. The abnormally prominent trabeculations and deep intratrabecular recesses of the ventricular muscle may predispose to the formation of thrombus. The abnormal myocardial development leads to a spongy muscular configuration that results in decreased cardiac output, ventricular hypertrophy, and dilation. This, in turn, leads to cardiac failure and the potential for arrhythmias.

Many of the patients described with isolated noncompaction, either familial or isolated cases, were diagnosed at an early age.[4] Our patient did not have clinical evidence of previous cardiac dysfunction or enlargement on multiple examinations, chest radiographs, or computerized tomographic scans performed during evaluation of his immunologic abnormalities. This delayed presentation can extend to adulthood.[2]

Noncompaction is amongst those endomyocardial abnormalities that can be recognized clinically.[5] The designation, however, is probably inadequate in its application, as it does not represent histopathological alterations.[5] O'Connor et al.[6] categorized at least one form of this myocardial disorder as a defect in regional myocardial development and vascularization. Mori and colleagues,[7] in contrast, suggested the abnormality to be a form of myocardial dysplasia. The myocardium is spongy in consistency, especially the often enlarged septum. Such defective myocardial development and vascularization can occur in isolation,[8] or it may be associated with other congenital cardiac malformations.[9] The characterization of described cases in the literature suggest a spectrum of myocardial architectural disorders.

The finding of noncompaction in our patient led us to assess the G4.5 gene. This gene codes for at least 10 different mRNA isoforms.[3] In our patient, the various mRNA species were identified and no mutation in the genetic sequence could be found.

The presence of isolated noncompaction of the ventricular myocardium in a patient with Roifman syndrome may be a coincidence. The low prevalence of both diseases, nonetheless, makes the possibility unlikely. The association of noncompaction and non-X chromosome mutations has been described.[10] The absence of a mutation in our

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patient could indicate that the abnormality is not due to a mutation in the X chromosome, although all five described cases with Roifman syndrome are males, strongly suggesting an X-linked disease. In addition, most of the features described among patients with Roifman syndrome have been found to be associated with mutations in X-chromosome genes. These include abnormal production of immunoglobulins, spondyloepiphyseal dysplasia, retinal dystrophy, and hypogonadotropic hypogonadism. Interestingly, screening such patients with for mutations in the Bruton's tyrosine kinase gene for X-linked agammaglobulinemia, or the sedlin gene for spondyloepiphyseal dysplasia, did not reveal any abnormalities in either genomic sequence.[1]

Our patient broadens further the spectrum of diseases associated with isolated noncompaction of the ventricular myocardium, which has obvious implications for genetic counseling. The recognition of isolated noncompaction among patients with Roifman syndrome is important, as the immune deficiencies may be subtle and undiagnosed until adulthood. Some patients, therefore, may first present with cardiac failure. The association of isolated noncompaction of the ventricular myocardium and Roifman syndrome is also relevant for those studying the genetic aspects of these diseases, as both seem to be related to abnormalities of the X chromosome.

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