

Coexistent Marfan's Syndrome and Ankylosing Spondylitis

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ABSTRACT. We describe a 22-year-old woman with coexisting Marfan's syndrome (MFS) and ankylosing spondylitis (AS). A change of fibrillin-1 due to mutation of the *FBNI* gene (MFS) or a cell-mediated autoimmune response in AS could account for a common pathology. (J Rheumatol 2006;33:1199–200)

Key Indexing Terms:

ANKYLOSING SPONDYLITIS

FIBRILLIN-1

MARFAN'S SYNDROME

Marfan's syndrome (MFS), one of the most common inherited connective tissue disorders, is characterized by skeletal, cardiovascular, and ocular abnormalities. It was first described by Bernard Antoine Marfan in 1896¹. MFS is inherited as an autosomal dominant trait, but in at least one-quarter of MFS patients there is no family history, suggesting the disease is caused by new mutations². In 1991 the *FBNI* gene, which encodes the fibrillin-1 protein, was found to be the locus for mutations that result in MFS. *FBNI* is located on the long arm of chromosome 15³. Fibrillin-1 is a major component of extracellular matrix structures known as microfibrils upon which elastin appears to be deposited⁴.

Ankylosing spondylitis (AS) is an HLA-B27-associated inflammatory disease that mainly affects the sacroiliac joints and axial skeleton. AS may also include peripheral joint involvement and extraskelletal manifestations, such as acute anterior uveitis, aortic insufficiency, and cardiac conduction disturbances⁵. The main histopathologic features of AS include juxtaarticular osteitis, synovitis of the apophyseal and sacroiliac joints, and enthesitis at joint capsules and intervertebral disc margins. These processes initially cause fibrosis and ossification of cartilage and entheses, and later, ankylosis and loss of mobility of the affected joints⁵. To our knowledge, the coexistence of MFS and AS has been reported only twice^{6,7}. We describe a young woman with both diseases.

CASE REPORT

In July 2004 a 21-year-old woman presented with a one year history of right hip, low back, and sternal pain with associated morning stiffness. She had a history of hip dysplasia, pectus carinatum, scoliosis, arachnodactyly, articu-

lar laxity, and pes planus. On examination she was 170 cm in height and weighed 58 kg. She had a high arched palate, crowding of the teeth, mild hyperelasticity of the skin, striae atrophicae, and sinus tachycardia (110 per min). She had limitation of chest expansion (3 cm), global restriction in lumbar spine movements, and painful restricted movements of the right hip. There was evidence of kyphoscoliosis, dolichostenomelia (upper to lower segment ratio of 1.7), finger arachnodactyly with positive thumb (Steinberger) and wrist (Walker-Murdoch) signs, and hyperextendible peripheral joints. On laboratory testing her erythrocyte sedimentation rate (ESR) was elevated at 57 mm/h (Westergren) and C-reactive protein (CRP) elevated at 48 (units). Rheumatoid factor and antinuclear antibody were negative. HLA-B27 was positive. Plain anteroposterior view of the pelvis showed bilateral sacroiliitis (ankylosis on the right side, grade II-III on the left). Chest radiograph findings were normal apart from showing evidence of the kyphoscoliosis and pectus carinatus. Echocardiography showed dilatation of the ascending aorta, mitral valve prolapse, and mild mitral insufficiency. Thoracic computed tomography (CT) and abdominal CT angiography showed dilatation of the ascending aorta. Hip ultrasound showed synovitis. CT of both hips showed signs of avascular necrosis on the right side. Bone mineral density measurement (LUNAR DPX-L) revealed T-score -3.0 at L2-4. A diagnosis of MFS was made based on the Ghent criteria and AS based on the New York criteria^{8,9}.

She initially started nonsteroidal antiinflammatory drugs and physiotherapy, followed by sulfasalazine. Neither clinical or laboratory variables improved and she was commenced on anti-tumor necrosis factor therapy, which seemed effective; after the first 2 infusions, her ESR decreased significantly and spinal movements improved. However, due to severe hip destruction, she was referred to orthopedic surgeons for consideration of hip surgery.

DISCUSSION

MFS is a heritable connective tissue disease that affects about one in 5,000 individuals. The disease is caused by a mutation of the gene encoding for fibrillin-1 on the long arm of chromosome 15³. This results in an alteration in the structure of fibrillin-1, which contributes to articular and nonarticular features of the disease. Involvement of the eye and ascending aorta in MFS results in significant morbidity. The eye and aorta are also sites of nonarticular morbidity in patients with AS. A further similarity between AS and MFS is the significant risk of protrusio acetabula in patients with MFS¹⁰. Thus the defective structure of microfibrils in MFS and the inflammation-targeted fibrillin-1 in AS may each lead to comparable structural phenotypes of failure, both involving sites of fibro-

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cartilage in connective tissue exposed to repetitive biomechanical stressing^{11,12}. Simkin, *et al* suggested a role for fibrillin-1, a 350 kDa glycoprotein found throughout the extracellular matrix, in the pathogenesis of AS¹¹. In AS fibrocartilage is important because it can be found at most disease sites, such as the iliac side of the sacroiliac joints, the acetabulum in the hip, and periarticular entheses. Since fibrillin-1 is a major component of microfibrils in fibrocartilage, it may be involved in the pathogenesis of spondylitic inflammation, likely as a target of a cell mediated autoimmune response.

Pleiotropic clinical manifestations of MFS are caused by the widespread distribution of fibrillin-1 in the extracellular matrix of the ligaments, tendons, periosteum, skin, heart valves, aorta, and ocular lenses^{2,3}. Fibrillin-1 is the main component of microfibrils. Microfibrils are components of all elastic fibers and are found in some elastin free fibers such as basal membrane, papillar dermis, condral hyalin, and fibrae zonulares of the lenses. The defective self-assembly of fibrillin-1 into a microfibrillar structure reduces the tensile strength of these supporting tissues, causing a wide spectrum of clinical manifestations³. The great quantity of mutations, more than 600, involving the *FBN1* gene accounts for the presence of such a wide spectrum of phenotypic expressions as well as the clinical severity of disease. Byers proposes that loss of fibrillin-1 protein by any of several mechanisms and the subsequent effect on the pool of transforming growth factor- β (TGF- β) may be more relevant in the development of MFS¹³. In addition to the proposed pathomechanism driven by TGF- β in MFS, TGF- β might also be involved in new bone formation in AS¹⁴.

Our patient satisfied the Ghent criteria for diagnosis of MFS⁸. To fulfil clinical diagnosis, a patient should satisfy 2 major criteria in different organ systems and one minor criterion in a third. Our patient satisfied 2 major criteria: skeletal (pectus carinatus, scoliosis, pes planus, dolichostenomelia, positive thumb and wrist sign) and vascular (dilatation of the ascending aorta); and 3 minor criteria: skeletal (hypermobility of the peripheral joints), cardiovascular (mitral valve prolapse with mitral insufficiency), and skin (striae atrophicae). Inflammatory back pain, limitation of both chest expansion and lumbar spine movements, sacroiliitis, and a positive HLA-B27 antigen all supported the diagnosis of AS⁵.

Predominantly nocturnal lumbar pain with morning stiffness that improves with exercise is a diagnostic criterion of AS⁵. However, patients with MFS may also complain of back pain probably owing to spinal deformity, paraspinal ligamentous laxity, skeletal muscular underdevelopment, or a combination of these⁶. Patients with AS may present with extraskeletal manifestations, such as ocular and cardiac abnormalities. In our patient the mitral prolapse may be related to MFS, while mitral insufficiency is a feature of both diseases.

In MFS cardiovascular abnormalities are the major source of morbidity and mortality¹⁵. In the last few years echocar-

diographic monitoring and improvements in therapy (beta-blockers, angiotensin-converting enzyme inhibitors) have contributed to improved outcomes for patients with MFS¹⁵.

In conclusion we think that this case, where 2 completely different and contrasting diseases such as MFS and AS were found to coexist, should be reported owing to the discrepancy between the hypermobility of peripheral joints and the significant reduction of both chest expansion and motion of the lumbar spine in axial skeleton. To our knowledge this patient is the third reported case of such an association. Because of the rarity of such coexistence, one might at first think these symptoms were coincidental, but according to Simkin's hypothesis¹¹, both a genetically determined and an inflammation derived fibrillin-1 defect might coexist.

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