(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 7, Issue 1 , Page No: 375-382
January-February 2024

IJMSCR

A coexistent Ankylosing Spondylitis with Marfan Syndrome - A Case Report

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Type of Publication: Case Report
Conflicts of Interest: Nil

Abstract

A 31 year old male presented with a 4-5 yr history of pain in the thoracic and lumbar region which was associated with morning stiffness and aggravated by rest. On physical examination, patient presented with classical features of Marfan's Syndrome (MFS), along with restriction of both chest expansion and movement in all planes of lumbar spine. On MRI, T2 hyperintensity was noted involving the inferior sacral part of bilateral sacroiliac joints suggestive of bilateral sacroilitis. Radiographs shows scolosis of thoracic spine. Laboratory tests were consistent with an inflammatory state ie ESR and CRP were raised and HLA B27 was positive. Transthoracic echocardiography showed mild mitral insufficency and aortic insufficency with dilated aortic root diameter. We diagnosed the simultaneous existence of marfan syndrome with ankylosing spondylitis(AS). Association of these two diseases together makes it interesting case as MFS leads to hypermobility of peripheral joints due to ligamentous hyperlaxity whereas AS leads to restriction of chest expansion and limited axial skeleton movement. The major cause of mortality in both diseases is cardiovascular system, follow-up with echocardiography monitoring is indispensable.

Keywords: Ankylosing spondylitis, Echocardiography, HLA-B27, Marfan syndrome

Introduction

Marfan syndrome (MFS) is mostly caused by mutations in FBN1, the gene encoding fibrillin 1, located on chromosome 15, a structural component of the extracellular matrix (ECM) also involved in the regulation of transforming growth factor beta (TGF-beta)[1]. It is an connective tissue disorder (CTD) characterised by skeletal, cardiovascular, and ocular abnormalities[1]. MFS is an autosomal dominant inherited disorder but in at least one-quarter of MFS patients there is no family history, suggesting the disease is caused by new mutations[2].

Ankylosing spondylitis (AS) is an chronic inflammatory disease that mainly affects the sacroiliac joints and axial skeleton. AS may also include peripheral joint involvement and extraskeletal manifestations, such as acute anterior uveitis, aortic insufficiency, and cardiac conduction abnormality[3.] 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 enthesis, and later, ankylosis and loss of mobility of the affected joints[3].AS is associated with HLA-B27.

Case Report:

In October 2022, a 31 year old male presented with a 4.5 to 5 years history of pain in the lumbar region which is associated with morning stiffness which

lasted for more than an hour, aggravated by rest and improved with movement and having partial response to NSAIDS. On admission, his vitals were blood pressure 134/74mmhg, heart rate 80 per minute.

On examination, he was 186.9cm tall, weighed 65kg, upper segment 85.4cm, lower segment 100.5cm and arm span 196.3cm. He had pectus excavatum and spider likes finger and toes ie arachnodactyly. He had positive thumb (Steinberger) (figure -1a and 1b) and wrist (Walker-Murdoch) signs(figure -2a,2b).

Figure No:1a-Steinberger Sign or Thumb Sign

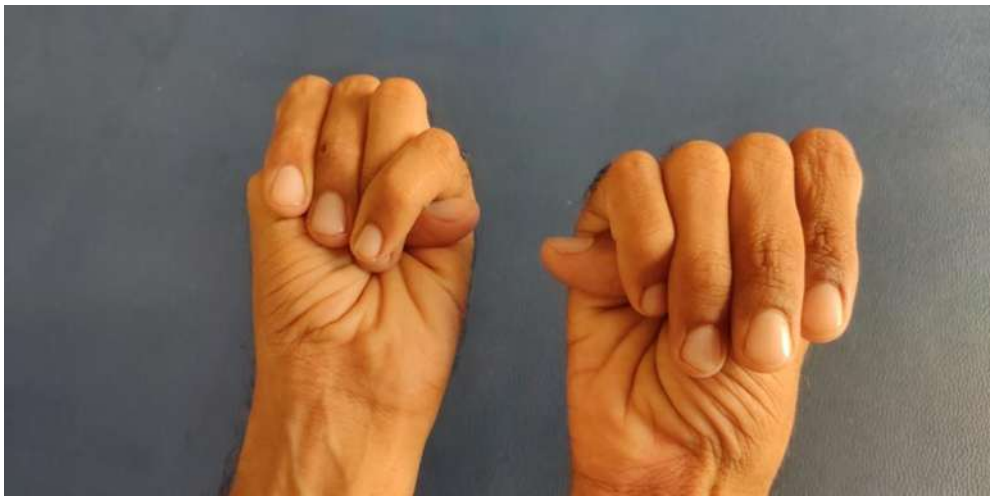

Figure No:1b-Steinberger Sign or Thumb Sign

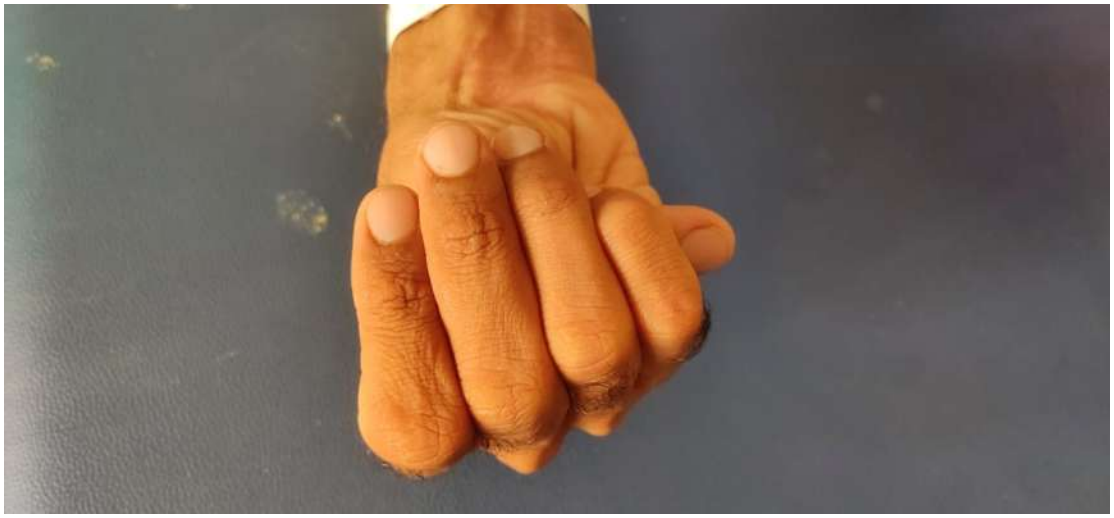

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Figure No: 2a: Walker-Murdoch Sign. or Wrist Sign

He had highly arched palate, overcrowding of teeth, dental caries, dolicocephalic face and malar hypoplasia (figure -3). The Patrick test was positive. He had both restricted chest expansion of less than 2cm and lumbar spine movement in all planes.On fundus examination, myopic disc was present with incresed length of globe. Laboratory investigations showed erythrocyte sedimentation rate (ESR) 60mm at 1hr (Westergren), C-reactive protein (CRP) 11mg/dl. Rheumatoid factor and antinuclear antibody were negative. HLA typing for B27 antigen was positive.

Figure No:03 :- Highly arched palate, Overcrowding of teeth, Dental caries

Plain radiographs of thoracolumbar spine on lateral view showed scoliosis with convexity towards right side. Plain radiograph of lumbosacral spine on AP/lateral view showed minimal scoliosis is noted at the level of L4-L5 vertebral body. Plain radiograph of pelvis with both hips AP view showed sclerosis was noted involving endplates of the bilateral sacroiliac joints suggestive of Grade III sacroilitis (New York Classification) (Figure No:4). PFT showed FEV1 /FVC >0.70 (0.98) ie restrictive pattern. Echocardiography showed mitral regurgitation with aortic regurgitation and aortic root diameter 43mm. MRI whole spine with pelvis showed T2 hyperintensity involving the inferior sacral part of bilateral sacroiliac joint suggestive of bilateral sacroilitis and dural ectasia (Figure No:05).Early degenerative changes in form of IV disc dessication, facet joint arthropathy and Schmorl's nodes were also seen. Diffuse disc bulge was present at the level of L4-L5 and L5-S1.

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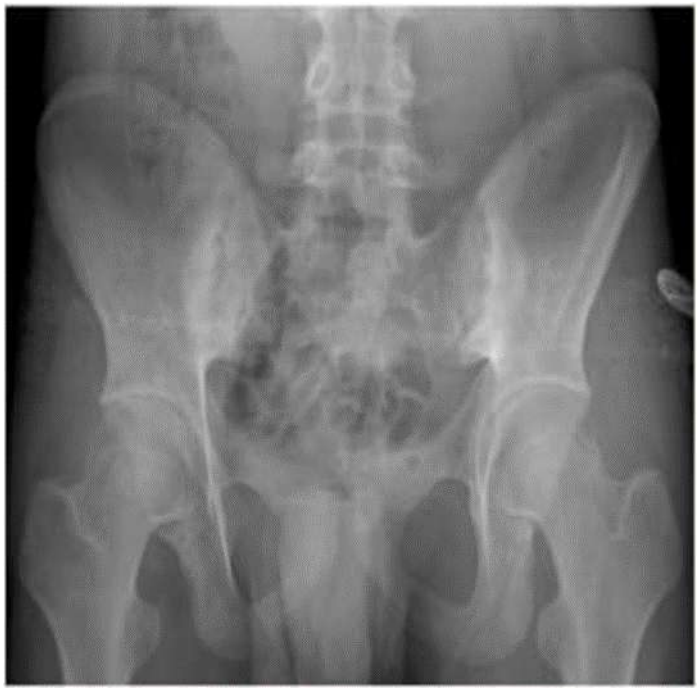
Figure No:04 :- Plain radiograph of pelvis with both hips AP view showed sclerosis was noted involving endplates of the bilateral sacroiliac joints. Grade III sacroilitis (New York Classification).



We diagnosed this as a case of ankylosing spondylitis with Marfan syndrome based on The Modified New York criteria for Diagnosis of Ankylosing Spondylitis and Revised Ghent criteria for the diagnosis of Marfan syndrome (MFS) and related conditions respectively. Patient was started on Pharmacotherapy (NSAID) and physical therapy which provided almost insignificant pain relief with the NRS (Numeric Reating Scale) pain score consistant at 8/10. The patient was posted for sacroiliac intra-articular joint injection which was performed fluroscopic guided by an interventional pain physician. The patient had significant improvement in his NRS pain score,from 8/10 to 1/10 immediately post procedure. The patient was discharged healthy and completely pain free in 2 days with an advise to continue physiotherapy and mobility exercises on a daily basis. The patient was evaluated at regular follow-ups at 1, 3 , 6 , and 12 months period and there was no evidence of ectopia lentis, the aortic root diameter was unchanged, the inflammatory markers (ESR and CRP) dropped down to normal and the patient was completey pain free.

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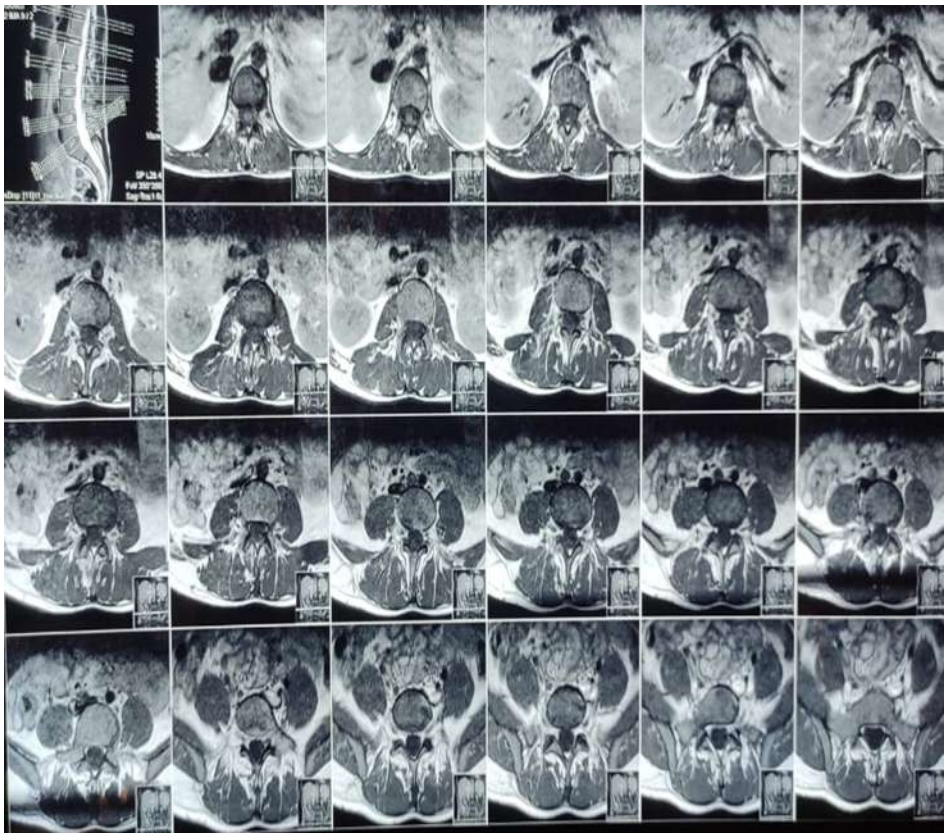
Figure No:-05 -MRI whole spine with pelvis showed T2 hyperintensity - Bilateral Sacroilitis and Dural Ectasia



For the diagnosis of MFS we follow the **Revised Ghent criteria for the diagnosis of Marfan syndrome (MFS) and related conditions**[13].

	In the absence of a family history
(1)	Ao (Z ≥ 2) AND EL = MFS
(2)	Ao (Z ≥ 2) AND FBN1 = MFS
(3)	Ao (Z ≥ 2) AND Syst (≥7 points) = MFSa
(4)	EL AND FBN1 with known Ao = MFS

	In the absence of a family history
(1)	Ao (Z ≥ 2) AND EL = MFS
(2)	Ao (Z ≥ 2) AND FBN1 = MFS
(3)	Ao (Z ≥ 2) AND Syst (≥7 points) = MFSa
(4)	EL AND FBN1 with known Ao = MFS

EL with or without Syst AND with an FBN1 not known with Ao or no FBN1 = ELS

Ao (Z < 2) AND Syst (≥5) with at least one skeletal feature without EL = MASS

MVP AND Ao (Z < 2) AND Syst (>5) without EL = MVPS

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	Systemic score	
1)	Wrist AND thumb sign Wrist OR thumb sign	3 1
2)	Pectus carinatum deformity pectus excavatum or chest asymmetry	2 1
3)	Hindfoot deformity plain pes planus	2 1
4)	Pneumothorax	2
5)	Dural ectasia	2
6)	Protrusio acetabuli	2
7)	Reduced US/LS AND increased arm/height AND no severe scoliosis	1
8)	Scoliosis or thoracolumbar kyphosis	1
9)	Reduced elbow extension	1
10)	Facial features (3/5) (dolichocephaly, enophtalmos, downslanting palpebral fissures, malar hyoplasia, retrognathia)	1
11)	Skin striae	1
12)	Myopia >3 diopters	1
13)	Mitral valve prolapse (all types)	1

Ao = aortic root diameter at the sinuses of valsalva above indicated Z score or aortic root dissection; EL = ectopia lentis; ELS = ectopia lentis syndrome; FBN1 = fibrillin-1 mutation; FH = family history; MASS = mitral valve prolapse, borderline (Z <2) aortic root dilatation, striae, skeletal findings phenotype; MFS = Marfan syndrome; MVPS = mitral valve prolapse syndrome; Syst = systemic score; Z = Z-score

Maximum total: 20 points; score ≥ 7 indicates systemic involvement.

Our patient satisfied the criteria aortic root dilation without the family history and systemic score more than 7 (total score =14; Positive wrist AND thumb sing=3 , pectus excavatum=1, Hindfoot defority=2 Dural ectasia=2 , Reduced US/LS AND increased arm/height AND no severe scoliosis =1, Scoliosis=1, Facial feature dolichocephaly, downslanting palpebral fissures, malar hyoplasia, =3/5, Myopia > 3 diopters =1)[13].

For Anakylosing Spondylitis we follow; The Modified New York criteria for Diagnosis of Ankylosing Spondylitis

Clinical Criteria	**Radiographic Criteria**
Low back pain and stiffness, more than 3 months, which improves with exercise	Bilateral sacroiliitis grade 2 or higher

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but is not relieved by rest	
Limitation of lumbar spine motion in sagittal and frontal planes	Unilateral sacroiliitis grade 3 or higher
Limitation of chest expansion relative to normal values for age and sex	

Grading of Radiographic Sacroiliitis

Grade 0	Normal
Grade 1	Suspicious changes
Grade 2	Minimal abnormality - small localised areas with erosion or sclerosis, without changes in joint width
Grade 3	Unequivocal abnormality - moderate or advanced sacroiliitis with one or more of: erosions, evidence of sclerosis, widening, narrowing or partial ankylosis
Grade 4	Severe abnormality - total ankylosis

Chronic Inflammatory back pain, limitation of both chest expansion and lumbar spine movements, sacroiliitis on radiogaph, and a positive HLA-B27 antigen all supported the diagnosis of AS[3].

Discussion:

Marfan syndrome is connective tissue disorder with autosimal dominant inheritance pattern. Most common mutaion in FBN1 gene; which is located on long arm chromosome 15q21.1[4] results in an alteration in the structure of fibrillin-1, which contributes to articular and nonarticular features of the disease [2,4]. Involvement of the cardiovascular system i.e mitral valve prolapse, mitral insufficiency, left ventricular dilatation and cardiac failure, pulonary artery dilatation, but aortic root dilataion, aortic dissection major cuse of mortality.

Aortic valve incompetence usually arises in the context of a dilated aortic root, and the risk of aortic dissection increases when the diameter at the sinus of Valsalva exceeds 5 cm[11,12]. In ocular features of MFS i.e bilateral ectopia lentis, myopia and retinal detachment also increase the mortality rate in MFS. The eye and aorta are also sites of nonarticular morbidity in patients with AS. Musculoskeletal system involvement Joint hypermobility is common in children and adults lower backache arthralgia, myalgia or ligamentous injury common in MFS[5] .

A further similarity between AS and MFS is the significant risk of protrusio acetabula in patients with MFS[6].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 fibrocartilage in connective tissue exposed to repetitive biomechanical stressing[7,8]. *Simkin, et al* suggested a role for fibrillin-1, a 350 kDa glycoprotein found throughout the extracellular matrix, in the pathogenesis of AS[7]. In AS fibrocartilage is important because it can be found at most disease sites, such as the iliac side of

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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. The 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[2,4]. Fibrillin-1 is the main component of microfibrils and it is 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-assemblage of fibrillin-1 into a microfibrillar structure reduces the tensile strength of these supporting tissues, causing a wide spectrum of clinical manifestations[4].

Byers proposes that loss of fibrillin-1 protein by any of several mechanisms and the subsequent effect on the pool of transforming growth factor-ß (TGF-ß) may be more relevant in the development of MFS[9]. In addition to the proposed pathomechanism driven by TGF-ß in MFS, TGF-ß might also be involved in new bone formation in AS[10].

A coexistance of these two diseases together makes it interesting case as MFS leads to hypermobility of peripheral joints due to ligamentous hyperlaxity whereas AS leads to restriction of chest expansion and limited axial skeleton movement.

Conclusion:

In conclusion we think that this case, where one disorder with two 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 only few 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 hypothesis[7], both a genetically determined and an inflammation derived fibrillin-1 defect might coexist.

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