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Case Report

Management of aortic dilatation in Marfan syndrome associated with lung fibrosis

Volha V. Zenevich, Maria V. Rusu, Marina G. Myslivets, Naveen D. K. N. Direcksze*, Thilini K. Lamahewa, Mahima A. H. Isiwara

Department of Pediatrics, Grodno State Medical University, Grodno, Belarus

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***Correspondence:**
Dr. Naveen D. K. N. Direcksze,
E-mail: ndkndis@gmail.com

ABSTRACT

Marfan syndrome (MFS) is an autosomal dominant disorder caused by the mutation in the fibrillin-1 (FBN-1) on chromosome 15q21. The predominant clinical manifestations mainly in ocular, cardiovascular and skeletal system. MFS can also lead to deterioration of lungs progressively over time. In case of lung fibrosis or may be spontaneous in case of spontaneous pneumothorax. Physical examination of this patient revealed the following significant phenotypic manifestations of MFS like scoliosis and skin triae, wrist sign, displaced nasal septum, myopic astigmatism of both eyes pectus carinatum. Furthermore; the computed tomography (CT) scan depicted the fibrotic changes in the lung parenchyma and the echocardiogram depicted the dilation of the aortic root, mitral regurgitation, tricuspid regurgitation. Both X-ray and CT results revealed bilateral lung fibrosis. And the patient was monitored by performing spirometry tests series annually, to detect the evaluation of the prognosis of the patients' condition. According to the latest publications in MS with interstitial lung disease, this article further reveals the necessity of taking into account the diagnosis of pulmonary manifestations in MS patients with vascular complications. This case illustrates the importance of reviewing the timely management of aortic root dilatation in MFS with lung fibrosis.

Keywords: Marfan syndrome, Fibrillin-1 gene, Lung fibrosis, Interstitial lung disease, Aortic root dilatation, Paediatric

INTRODUCTION

Marfan syndrome (MFS) is one of the world's most frequent inherited autosomal dominant systemic connective tissue syndrome, with no specificity for gender or nationality.[1] MFS has a higher genetic potential, but a with significant association of interconnection between family members and relations. MFS has a recorded incidence rate of 1 in 3000 to 5000 people approximately 25% of cases arise from de novo mutations.[2] Each time a person with MFS has a child, they have a 50% probability of passing on the genetic mutation. 10% of patients have the typical Marfan phenotype, but no mutation in fibrillin-1 (FBN-1). Despite the availability of genetic testing, the Ghent criteria is still effective in making the diagnosis.[3] It is known that the probable cause of this syndrome is due to deletion or altered regulation of FBN-1 gene.[2] The mutation in the FBN-1 gene is the main cause of MFS, this gene causes the production of fibrillin, which is localized on the chromosome 15.[1,2] FBN-1 is a prominent connective tissue protein that is important in formation of structural integrity in microfibrils, which are elastic in nature.[4] The important functions of microfibrils are shown in maintenance of mechanical strength, regulation of growth factors, development of tissues and maintenance of a homeostatic environment through the integrity of many body features such as skin, blood vessels, lung parenchyma, cardiac valves, and ocular ligaments.[4] A mutation in this gene causes an increase in the protein transforming growth factor beta, or TGF-β. Increased TGF-β causes problems in connective tissues throughout the body, resulting in the characteristics and medical problems associated with MFS and some related conditions.[5]

MFS primarily affects the skeletal, ocular, and cardiovascular systems. MFS patients have skeleton deformities such as dolichostenomelia (long upper extremities compared to trunk), arachnodactyly (unusually long and thin digits), thoracolumbar scoliosis, and deformities in chest configuration (such as pectus excavatum and pectus carinatum). In the cardiovascular system, the most frequently manifested conditions are aortic regurgitation, dilatation, and aneurysms. Mitral valve prolapses and other valvular pathologies can be another possibility. Ocular manifestations such as lens dislocation, cataract, myopia, and retinal detachment can be characteristic of MFS. The diagnosis of MFS is usually made under clinically based abnormalities. The physical features which is of the highest diagnostic results were craniofacial characteristics, thumb and wrist signs, severe hindfoot valgus, and pectus carinatum.[2] Pulmonary symptoms are not generally regarded as a primary feature of MFS, and up to 10% of people have MFS-related respiratory disorders.[4,6-8] Many patients have underlying pulmonary pathology, but only a few pleuropulmonary abnormalities have been identified. Spontaneous pneumothorax is a common clinical manifestation, and little is known about connective tissue changes in the respiratory system.[4] MFS may also present as lung manifestations such as generalized or cystic reformation in a patchy context, emphysema, and spontaneous pneumothorax, in addition to, focal pneumonia, bronchiectasis, bullae, congenital pulmonary malformations (particularly middle lobe hypoplasia), and apical fibrosis is seen.[4] One of the studies have reported four cases of upper lobe lung fibrosis among 100 patients with MFS in 1985, hypothesizing that the fibrosis was caused by the healing process of the damage caused by stresses in the apical parts of the lung.[7,8] According to the 2010 Ghent revised criteria, the diagnosis of MFS is possible in the appearance of: aortic root dilatation/dissection with ectopia lentis; aortic root dilatation/dissection with FBN1 mutation; and ectopia lentis with FBN1 mutation (known to have been previously associated with aortic root dilatation in the literature, or present in the family).[9] Due to age-dependent manifestations and the difficulty of making a proper diagnosis in pediatric patients with a negative family history, the Kid Short Marfan score (Kid-SMS) was introduced.[10] It is an easily usable tool for the risk stratification of pediatric patients with suspicion of MFS. Children are classified into three groups based on risk: very-high risk, high risk, and moderate risk. When the diagnosis cannot be confirmed, Kid-SMS recommends a safe follow-up program. This technique requires the following manifestations: aortic root dilatation, ectopia lentis, mitral valve prolapse, tricuspid valve prolapse, pulmonary artery dilatation, and skeletal features.[10] A comparison with age-dependent benchmarks is necessary to determine if aortic measurements, especially in pediatric patients, fall within the normal range. However, it is generally accepted that aortic roots measuring ≥40 mm in diameter in adults to signify dilation. Studies show that in the MFS population, without preventive surgery, the most prevalent type of aortic dissection is type A, which involves the aortic root and frequently the descending aorta.[11] The risk of dissection depends on the aortic diameter (the bigger the diameter is, the more significant the risk becomes); few cases of dissections were observed in patients with mild aortic dilatation or even with no dilatation. In addition, the rate of aortic growth and family history are included among risk factors. MFS patients with surgical aortic root replacement commonly face the onset of aneurysms and/or dissections along the arterial tree.[12] The main management is surgical approach for MFS patients which is aortic root replacement surgery. Recently, new concept of "personalized surgery" introduces a viable option in aortic root surgery for MFS patients, referred to as the personalized external aortic root support (PEARS) technique, where; an external device that supports the ascending aorta, avoiding its replacement. The term "personalized" refers to the device being manufactured as a 3D reconstruction of an individual patient's aorta. The device, made of medical grade polymer fabric, wraps around the patient's aorta, and its placement does not usually require cardiopulmonary bypass. Thus, preserves the blood–endothelial interface. PEARS is not indicated in the presence of more than mild aortic regurgitation, and is usually performed in patients with a smaller aortic diameter than those who undergo valve-sparing surgery.[13] But there is a symptomatic therapy of application of anti-hypertensive medication such as beta-blockers, angiotensin-receptor blockers and angiotensin converting enzyme (ACE) inhibitors, which in turn effectively reduce the dilatation of aortic root.[14] If there is a causal relationship between lung fibrosis and MFS, it is tempting to speculate that fibrosis is caused by the healing of damage caused by stresses in these tall people's lungs. So, the goal of this article is to elaborate how MFS may contribute to the lung fibrosis and respiratory complications.

CASE REPORT

A 15-year-old female from Belarus with a confirmed diagnosis of MFS presented to the Emergency Department of the General Paediatric Hospital in Grodno, Belarus. MFS, a connective tissue disorder caused by mutations in the FBN1 gene, is associated with multisystemic manifestations affecting the cardiovascular, musculoskeletal, and ocular systems. This case underscores the significance of a multidisciplinary perspective in management of the complex clinical profile of MFS.

The patient arrived with complaints of severe tachycardia, palpitations, stabbing chest pain localized to the apex of the heart, generalized weakness, fatigue following physical exertion, sweating, and significant discomfort. Initial examination revealed a blood pressure of 85/60 mmHg in both upper extremities (right and left arm). Furthermore; pulse was symmetrical in both arms showing no signs of atherosclerosis or peripheral vessel damage.

During the physical examination of this patient, the following classical phenotypic features of MFS were demonstrated, including skeletal manifestations such as positive thumb signs (Figures 1a and b), scoliosis (Figure 2), arachnodactyly (Figure 3a) and dolichostenomelia (long, slender limbs and fingers (Figure 3b), positive wrist signs (Figures 1c), high-arched palate (Figure 5a), and pectus excavatum (Figures 4a and b), cutaneous finding like skin striae (Figure 2), particularly on the thoracic and abdominal regions, ocular features were bilateral myopic astigmatism. Craniofacial abnormalities were displaced nasal septum and hypertrophy of the palatine tonsils (Figure 5b).

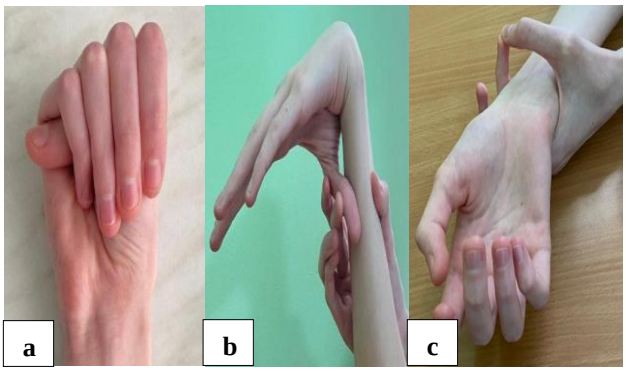

Figure 1 (a-c): Positive thumb and wrist signs.

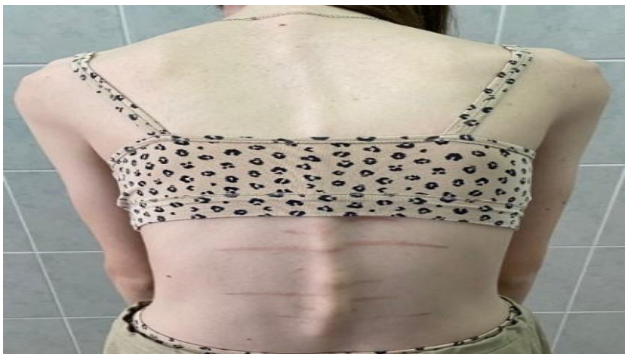

Figure 2: Scoliosis and skin striae.

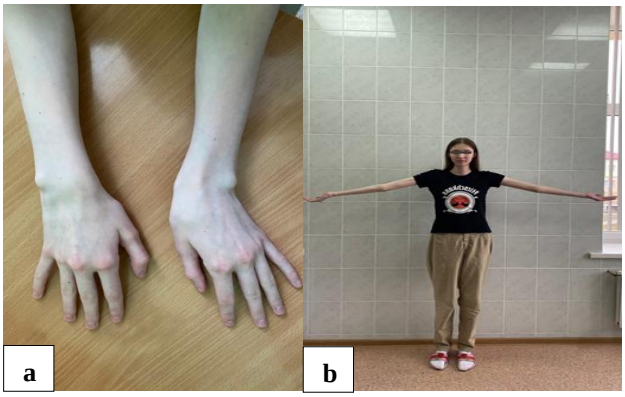

Figure 3 (a and b): Arachnodactyly and dolichostenomelia.

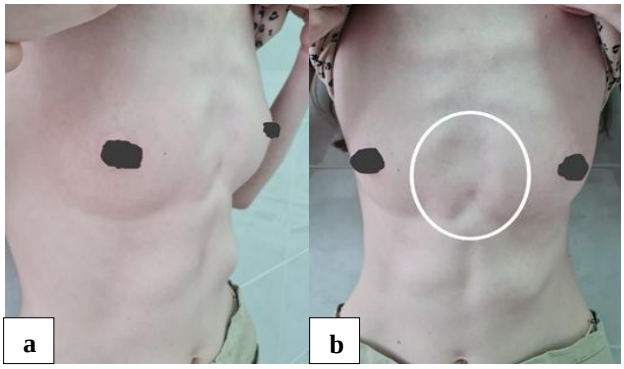

Figure 4 (a and b): Petuc excavatum.

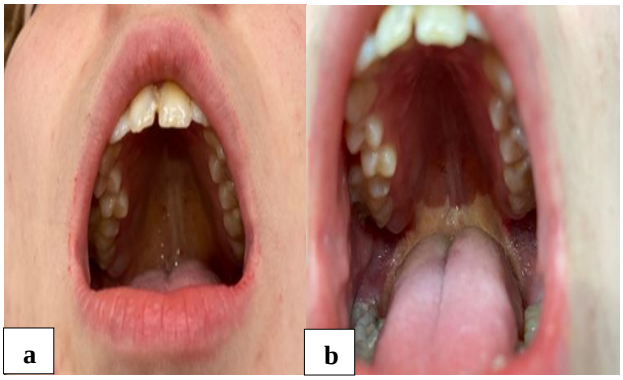

Figure 5 (a and b): High-arched palate and hypertrophy of the palatine tonsils.

Lab findings

The complete blood count and biochemical parameters, shown in Table 1 did not reveal any significant deviations from normal values, thus imaging and instrumental diagnostics was followed up for further evaluation of this case.

Table 1: Complete blood count and biochemical parameters.

CBC and biochemical parameters	Values
Red blood cells/l	4.31×10/12
Haemoglobin (g/l)	137
Haematocrit (%)	39.7
MCV (average volume of red blood cells) (Fl)	92.1
MCH (haemoglobin content in erythrocytes) (pg)	31.8
C-reactive protein (mg/l)	0.1
Total bilirubin (mmol/l)	14.3
Direct bilirubin (mmol/l)	3.3
Indirect bilirubin (mmol/l)	11.0
Calcium (mmol/l)	2.3
Phosphorus (mmol/l)	1.3
Vitamin D (ng/ml)	35.9

Imaging and instrumental findings

Since the patients' condition was not satisfactory and given her clinical instability, a series of diagnostic evaluations were performed to investigate the underlying cause and assess systemic involvement, where the following cardiovascular evaluation were implemented such as echocardiography revealing dilation of the aortic root, mitral valve regurgitation, tricuspid valve regurgitation and electrocardiogram (ECG) showing consistent with severe tachycardia and evidence of left atrial dilation.

Thoracic imaging such as computed tomography (CT) scan was useful in revealing an Incidental finding of fibrotic changes in the lung parenchyma, suggesting pulmonary fibrosis (Figure 6), Structural cardiac abnormalities were confirmed; correlating with echocardiographic findings and chest X-ray revealed thoracic spine curvature consistent with scoliosis (Figure 7), signs of lung fibrosis (Figure 8).

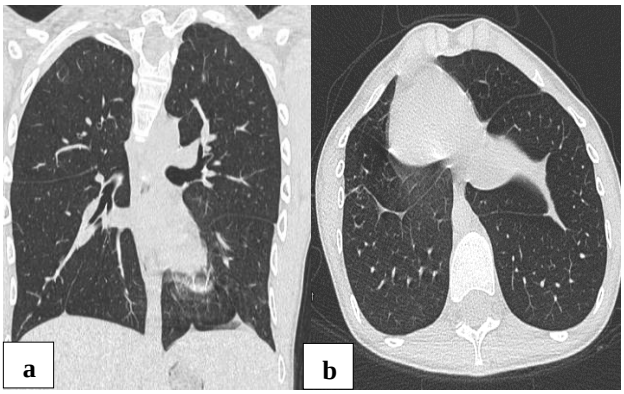

Figure 6 (a and b): CT images showing lung fibrosis.

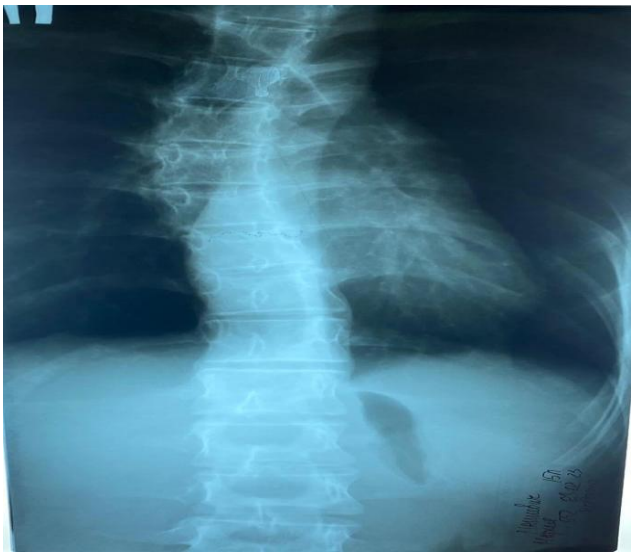

Figure 7: X-ray showing scoliosis.

Pulmonary assessment was analysed with the initiation of spirometry to monitor pulmonary function, showing decreased lung compliance attributable to fibrotic changes. The results of bronchodilator test revealed no changes, suggesting a restrictive nature of lung fibrosis. The following pharmacological management initiated in the patient was Bisoprolol 5 mg once daily, a beta-blocker targeting cardiovascular stability by reducing heart rate and myocardial oxygen demand, thereby delaying the dilatation of aortic root in the sinus of valsalva. Other cardio-metabolic therapy was given such as Levocarnitine 500 mg once daily, for 30 days; coenzyme Q10 30 mg once daily, for 30 days; and finally, Magne B6 (preparation of magnesium sulphate with vitamin B6) bid for 30 days. Annual monitoring of echocardiography and spirometry was recommended to assess cardiovascular and pulmonary progression of this disease. In addition, prophylactic dose of vitamin D3 of 500 IU was given daily as a lifelong therapy, but during the period of autumn to winter this dose was increased up to 1000 IU to maintain a normal level of vitamin D3 in the patient. Moreover, no disturbances in bowel and bladder function were reported during the hospitalization period.

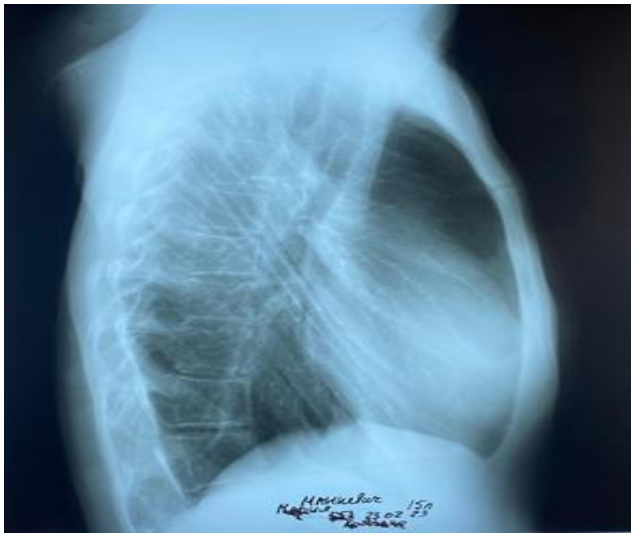

Figure 8: X-ray showing lung fibrosis.

DISCUSSION

MFS is a multisystem connective tissue disorder which can be inherited autosomal dominant in nature for 75% of the cases due to a mutation in FBN1 gene and 25% of the cases due to de novo mutations.[1] The gene FBN1 is mutated and leads to anomalies in the development of fibrillin-1 protein, which in turn leads to abnormal development of extracellular matrix. Furthermore, mutations in the gene encoding the transforming growth factor beta receptor (TGFBR) leads cardiovascular manifestations like aortic aneurysms, aortic root dilation, aortic root dissection, tricuspid valve regurgitation, mitral valve regurgitation and mitral valve prolapse.[2] However, this FBN1 mutation can also lead to musculoskeletal manifestations like spine deformities (scoliosis and kyphosis), chest deformities (pectus excavatum and pectus carinatum), foot deformities (long, thin feet, flat feet (very low arch or extra-high arch),

long toes, hammer and claw toes, calluses, bunions and turned ankles (medial displacement)), ocular manifestations like ectopia lentis, retinal detachment, severe myopia, astigmatism, amblyopia, strabismus and pre-senile cataracts, pulmonary manifestation like spontaneous pneumothorax, cystic changes, emphysema, focal pneumonia, congenital pulmonary manifestations (particularly middle lobe hypoplasia) and apical blebs.[4,15-17]

Our patient has a family history of MFS, in which grandfather, father and eldest daughter were diagnosed with MFS and genetic testing was done. The diagnosis of MFS in this patient was fulfilled by the modified Ghent criteria. This patient revealed cardiac features such as aortic root dilation with other manifestations like pectus carinatum, scoliosis, skin striae, positive thumb and wrist sign and with a systemic score of 11. A major contributor to mortality and morbidity in MFS is aortic root dilation, which led to a significant cardiovascular complication like aortic dissection. Thus, leading to the primary cause of mortality in MFS.

In addition, the echocardiogram revealed mitral valve prolapse of 1st degree, this is usually found in 42-56% of cases patients in MFS.[3] About quarter of these cases of patients with MFS and MVP have progressive development from controlled to uncontrolled mitral valve regurgitation.[3] This juvenile patient (15 years of age) and the clinical intensity of her manifestations, emphasizes the early importance of cardiovascular association (e.g., dilation of aortic root, regurgitation of mitral valve and tricuspid valve) in MFS. It is necessary to note the importance of early diagnosis and management of mitral and tricuspid regurgitation to prevent long-term complications like heart failure.

The musculoskeletal manifestations like hypermobile joints (demonstrated in thumb signs) (Figures 1a-c), scoliosis, pectus carinatum and arachnodactyly made the patient to be refrained from strenuous exercises and contact sports, but moderate cardiovascular exercises were encouraged. Other systemic manifestations including ocular features like bilateral astigmatism and craniofacial abnormalities such as displaced nasal septum and hypertrophy of the palatine tonsils were noted furthering the diagnostic profile of MFS in patient.

Both X-ray and CT results revealed bilateral lung fibrosis, which is a rare and atypical clinical presentation in this disease. This pulmonary manifestation (lung fibrosis) together with MFS, which is not a hallmark feature for MFS adds complexity to the management. Furthermore; this clinical feature also limits the physical activity of the patient to greater extent, leading to less favourable quality of life.

Since the patient was presented with intermittent tachycardia, the main cardiovascular management was beta-blocker therapy (first-line therapy in MFS) of Bisoprolol, which has been shown to decrease myocardial contractility and strengthen the elastic properties of aorta.[18] Furthermore; progression to cardiovascular complications was averted by administration of preparations of magnesium and vitamin B6.[19] Echocardiograms were done annually to eliminate the progression of aortic root dilation to aortic dissection, which was a significant preventive care to reduce the risk of development of aortic dissection, thus leading to better prognosis for the patient. There is a planned mitral valve and aortic root replacement surgery in the future to improve the prognosis of the patient. The main pulmonary assessment was spirometry tests series done annually to detect the evaluation of this condition. Musculoskeletal and ocular manifestations were monitored carefully to improve the quality of life.

This case emphasizes the importance of multidisciplinary approach to management of MFS, effectively addressing complex clinical presentations. And it is necessary for a lifelong follow-up regime with multidisciplinary team for better prophylaxis of complications due to the multisystemic nature of this disease. This case also represents classical MFS signs with an atypical clinical presentation of LF when compared to typical case presentations of MFS, which adds significance to early pulmonary assessment of MFS patients potentially improvising clinical practice and personalised care towards to clinically complex MFS cases.

Limitations

The following limitations were found in this case such as incomplete long term follow-up regime and missing genetic testing data.

Recent studies suggested a new type of treatment for lung fibrosis (LF) with the help of pharmacological therapy by using CMR316; a first-class drug, which stimulates the lung stem cells to regenerate lung tissue. Further studies are needed to evaluate the efficacy of this drug and in the future, prognosis of patients with LF due to MFS could improve.[20]

If there is a novel relationship between lung fibrosis and MFS, it is intriguing to believe that fibrosis is caused by the healing of damage caused by stressful situations in these tall people's lungs. So, the aim of this article is to elaborate how MFS with lung fibrosis may contribute to early diagnosis and management.

CONCLUSION

The management of patients with MFS with lung fibrosis requires a comprehensive interdisciplinary approach. Our patient presented classical signs of MFS such as positive wrist and thumb signs, pectus deformities, scoliosis, displaced nasal septum, hypertrophy of palatine tonsils, skin striae, accompanied by complications such as aortic root dilatation, mitral and tricuspid regurgitation. Hence,

timely management of vascular complications mainly aortic root dilatation, plays a crucial role in determining the prognosis of the patient's outcome. This case illustrates the importance of reviewing the timely management of aortic root dilatation in MFS with lung fibrosis into consideration for better prognosis of the patient.

Recommendations

Further genetic and clinical studies are warranted to explore the correlation between phenotypic variability and pulmonary manifestations in MFS.

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REFERENCES

1. Salik I, Rawla P. Marfan Syndrome. Treasure Island (FL): StatPearls Publishing. 2023.
2. Feather A, Randall D, Waterhouse M. Kumar and Clark's Clinical Medicine. 10th Edition. Elsevier Science Health Science. 2020.
3. Tun MH, Borg B, Godfrey M, Hadley-Miller N, Chan ED. Respiratory manifestations of Marfan syndrome: a narrative review. J Thorac Dis. 2021;13(10):6012-25.
4. Dyhdalo K, Farver C. Pulmonary histologic changes in Marfan syndrome: a case series and literature review. Am J Clin Pathol. 2011;136(6):857-63.
5. The Marfan Foundation. Marfan Syndrome - Marfan Foundation. 2022. Available at: https://marfan.org/conditions/marfan-syndrome/. Accessed on 12 January 2024.
6. Ramirez F, Dietz HC. Marfan syndrome: from molecular pathogenesis to clinical treatment. Curr Opin Genet Dev. 2007;17(3):252-8.
7. Wood JR, Bellamy D, Child AH, Citron KM. Pulmonary disease in patients with Marfan syndrome. Thorax. 1984;39(10):780-4.
8. Mizuguchi T, Collod-Beroud G, Akiyama T, Abifadel M, Harada N, Morisaki T, et al. Heterozygous TGFBR2 mutations in Marfan syndrome. Nat Genet. 2004;36(8):855-60.
9. Loeys BL, Dietz HC, Braverman AC, Callewaert BL, De Backer J, Devereux RB, et al. The revised Ghent nosology for the Marfan syndrome. J Med Genet. 2010;47(7):476-85.
10. Stark VC, Arndt F, Harring G, von Kodolitsch Y, Kozlik-Feldmann R, Mueller GC, et al. Kid-Short Marfan Score (Kid-SMS) Is a Useful Diagnostic Tool for Stratifying the Pre-Test Probability of Marfan Syndrome in Childhood. Diseases. 2015;3(1):24-33.
11. Isselbacher EM, Bonaca MP, Di Eusanio M, Froehlich J, Bossone E, Sechtem U, et al; International Registry of Aortic Dissection (IRAD) Investigators. Recurrent Aortic Dissection: Observations From the International Registry of Aortic Dissection. Circulation. 2016;134(14):1013-24.
12. Erbel R, Eggebrecht H. Aortic dimensions and the risk of dissection. Heart. 2006;92:137-42.
13. Treasure T, Austin C, Kenny LA, Pepper J. Personalised external aortic root support in aneurysm disease. Curr Opin Cardiol. 2022;37:454-8.
14. Singh MN, Lacro RV. Recent Clinical Drug Trials Evidence in Marfan Syndrome and Clinical Implications. Can J Cardiol. 2016;32(1):66-77.
15. The Marfan Foundation. Bones and joints in Marfan Syndrome - Marfan Foundation. 2021. Available at: https://marfan.org/resource-library/bones-and-joints-in-marfan-syndrome/. Accessed on 12 January 2024.
16. The Marfan Foundation. The Eyes in Marfan Syndrome - Marfan Foundation. 2021. Available at: https://marfan.org/resource-library/the-eyes-in-marfan-syndrome/. Accessed on 12 January 2024.
17. Loeys B, Nuytinck L, Delvaux I, De Bie S, De Paepe A. Genotype and phenotype analysis of 171 patients referred for molecular study of the fibrillin-1 gene FBN1 because of suspected Marfan syndrome. Arch Intern Med. 2001;161(20):2447-54.
18. Koo HK, Lawrence KA, Musini VM. Beta-blockers for preventing aortic dissection in Marfan syndrome. Cochrane Database Syst Rev. 2017;11(11):CD011103.
19. Igondjo-Tchen S, Pagès N, Bac P, Godeau G, Durlach J. Marfan syndrome, magnesium status and medical prevention of cardiovascular complications by hemodynamic treatments and antisense gene therapy. Magnes Res. 2003;16(1):59-64.
20. Scripps Research. How a new drug prototype regenerates lung tissue. Available at: https://www.scripps.edu/news-and-events/press-room/2024/20240410-schultz-bollong-lung-regeneration.html. Accessed on 12 January 2024.

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