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Marfan Syndrome: A Case Report

Marfan Sendromu: Olgu Sunumu

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Abstract

Marfan syndrome (MFS) is a connective tissue disorder inherited by autosomal dominant pattern that affects primarily cardiovascular, ocular, musculoskeletal and nervous systems. Even though, mutation in the fibrillin-1 gene (FBN1) located on Chromosome 15 was detected in 66-91% in the case with MFS, 27% of the cases were caused by novel mutations. The clinical diagnosis in adults is established according to Ghent Criteria. Early diagnosis, aortic valve-sparing medical and surgical treatments, and regular patient follow-up are helpful in preventing and delaying serious complications. In this case report, we have presented a 30-year-old case who admitted to the hospital due to the complaints of purulent bloody sputum, fever and sweating, and was diagnosed with Marfan syndrome.

Key words: *Marfan's Syndrome, lung, diagnosis.*

Özet

Marfan sendromu (MFS), otozomal dominant geçişli başlıca kardiyovasküler, oküler, kas-iskelet ve sinir sistemlerini etkileyen bir bağ dokusu bozukluğudur. MFS'lu olguların %66-91'inde 15. kromozomdaki fibrillin -1 (FBN1) gen mutasyonu saptanmış olmakla beraber, olguların %27'si yeni mutasyonlardan kaynaklanır. Yetişkinlerde klinik tanı Ghent kriterlerine göre yapılmalıdır. Erken tanı, aortu koruyucu medikal ve cerrahi tedaviler ve düzenli takip ciddi komplikasyonların önlenmesine veya geciktirilmesine yardım eder. Otuz yaşında pürülan kanlı balgam, ateş ve terleme şikayetleri olan Marfan sendromu tanısı koyduğumuz olgumuzu sunduk.

Anahtar Sözcükler: *Marfan Sendromu, akciğer, tanı.*

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Marfan Syndrome (MFS) is a rarely seen connective tissue disorder inherited by autosomal dominant pattern. It primarily affects skeletal, pulmonary, central nervous, oro-oculo-facial and cardiovascular systems. MFS has an incidence of 1:10,000 (probably 1/3000-1/5000) in the population. These rates make MFS one of the most commonly seen single-gene malformation syndromes (1,2). Although, the mutation of the fibrillin-1 (FBN1) gene located on Chromosome 15 was detected in 66-91% of the cases with MFS, it has been shown that 27% of the cases were caused by novel mutations. The mutations of the transforming growth factor b-receptor 2 (TGFBR2) and TGFBR1 genes were identified in 5-10% cases (3,4).

MFS is characterized by many clinical manifestations. These entities include annuloaortic ectasia, aortic aneurysm, aortic dissection, pulmonary artery dilatation and mitral valvular prolapse as well as cardiovascular involvement and aortic valvular regurgitation. Scoliosis, pectus excavatum and carinatum, arachnodactyly and acetabular protrusion are the examples of musculoskeletal involvement. Myopia and lens dislocation may be detected in the eyes (5). Since its clinical appearance is quite changeable, thin and tall body structure, long extremities, arachnodactyly, pectus deformities and occasionally scoliosis primarily in a young person suggest the diagnosis of Marfan syndrome (6).

Berlin 1986 Diagnostic Criteria were revised to diagnose MFS accurately and elevate the prognostic value of these criteria, and defined as 'Ghent Criteria' in 1996 (7). We aimed to review the diagnostic criteria of MFS in our case and to present its complications experienced during monitoring and management of these patients in the light of current literature.

CASE

A 30-year-old male patient was hospitalized due to the complaints of expectorating abundantly purulent and occasionally bloody sputum, fever and sweating. His medical history included diagnosed bronchiectasis 11 years ago, previous operation for scoliosis 6 years ago and previous implementation of bronchial artery embolization for hemoptysis 3 years ago. The patient had no smoking or drug abuse.

The inspection during physical examination revealed asymmetrical chest and less movement in the left hemithorax, reduced anteroposterior chest diameter, left-sided scoliosis, pectus excavatum appearance in the sternum and scar along the vertebra. The fingers and toes of the patient were remarkably long and digital clubbing was prominent. Auscultation indicated diffuse rhonchi and rales, predominantly in the bilateral lung bases. The baseline values of the patient were as following: Fever: 38.5°C, respiratory rate 24/min, Pulse: 110/min, O_2 saturation: 74%, WBC: $10.18x10^3$/uL, Hb: 15.5 g/dl, Creatinine: 0.62mg/dl, ALT: 9 U/L, AST: 44 U/L, pH: 7.40, pCO_2: 57 mmHg, pO_2: 42 mmHg.

Chest x-ray showed blockage of left sinus, nearly homogeneous increase of density in the lateral part of left lower lung zone and infiltration in the infrahilar region of right lower lung zone. The platinization used in scoliosis operation was patent (Figure 1).

A homogeneous increase of density with an appearance of "finger in glove" (bronchocele) on the right, diffuse bronchiectasis areas in the right lung middle lobe and right lung lower lobe superior segment. The appearance of consolidation and ground-glass in the left lung was encountered on Thoracic CT (Figure 2). The growth of Pseudomonas aeruginosa was detected in the sputum culture of the patient and appropriate antibiotic treatment, bronchodilator treatment and oxygen therapy were initiated.

The presence of scoliosis, pectus excavatum and arachnodactyly (long-thin spider-like digits) suggested the probability of MFS. The sum of the lengths of the bilateral arms and chest higher than height of the patient supported the diagnosis (Figure 3 and 4). Steinberg "thumb" sign (At apposition, thumb extending beyond the ulnar edge of the fisted hand) and Walker "wrist sign" (overlapping distal phalanxes in the first and fourth fingers of the hand curled around the wrist of the other hand) were positive (Figure 5, 6 and 7). The presence of the uncles with similar body morpholgies were reported in the family history.

EF 60%, thickened mitral valve and prolapse were encountered by echocardiography in the cardiological examination. No pathology was encountered in the ophthalmological examination. The antibiotic therapy was completed and control sputum culture indicated no growth, the patient was discharged by planning long-term oxygen therapy, and pneumococcal and influenza immunization, he was followed-up by pulmonary rehabilitation polyclinic.

DISCUSSION

MFS is a connective tissue disorder inherited by an autosomal dominant pattern that has been first identified in a five-year-old female patient in 1896 by Antonie Marfan, a French pediatrician (7). It has been discovered that the

mutations of the fibrillin-1 (FBN1) gene located on Chromosome 15q21.1 causes MFS approximately 100 years after its first identification. As a consequence, absence or deficiency of fibrillin leads to impairment of structural integrity in all the tissues and organs, primarily three cardinal systems (skeletal, ocular and cardiovascular systems). Although, autosomal dominant inheritance is well-known, spontaneous mutations cause MFS rather than inheritance from the parents in 25% of the patients. For instance, the mutations on the TGFβR1–2 gene and beside fibrillin 2 gene located on Chromosome 5 may cause classical MFS (7). MFS may be diagnosed in any age such as prenatal, neonatal, childhood or late adulthood periods. Its neonatal form manifests a more severe clinical course in the follow-up period than all others (8).

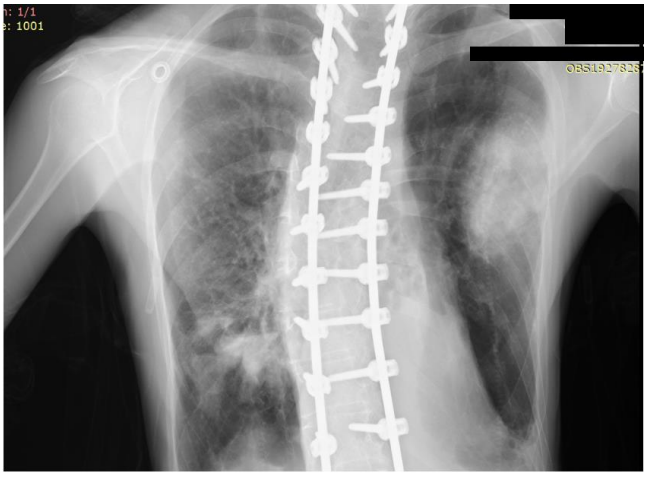

Figure 1: *PA chest x-ray revealed nearly homogeneous increase of density in the lateral part of left lower lung zone and infiltration in the infrahilar region of right lower lung zone. The platinization used in scoliosis operation was patent*

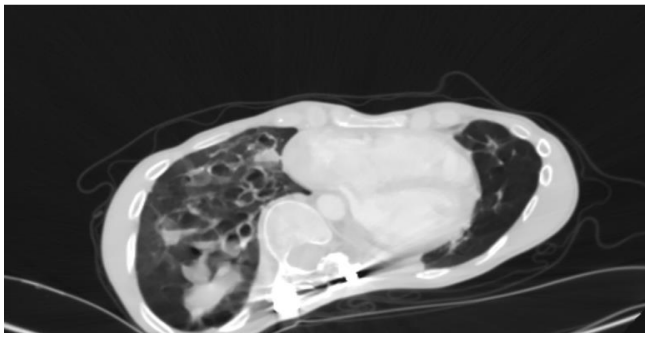

Figure 2: *A homogeneous increase of density with an appearance of "finger in glove" (bronchocele) on the right, diffuse bronchiectasis areas in the right lung middle lobe and right lung lower lobe superior segment. The appearance of consolidation and ground-glass in the left lung on Thoracic CT*

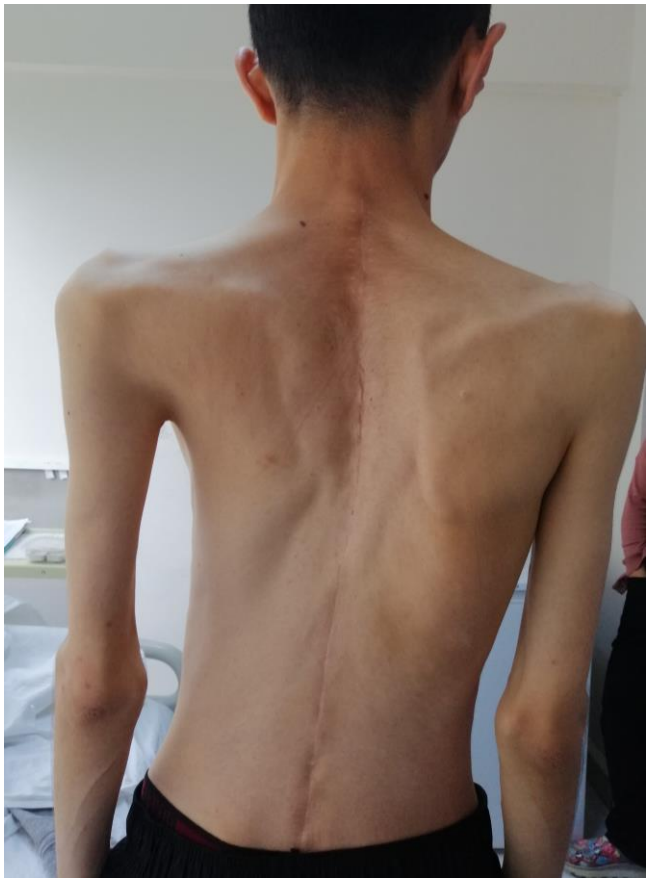

Figure 3: *Scoliosis and asymmetric thorax*

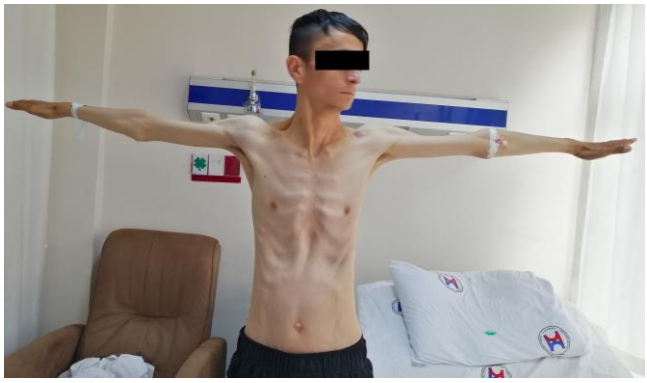

Figure 4: *Arm length disproportionately with chest length and pectus excavatum*

Berlin 1986 Diagnostic Criteria previously used in the diagnosis of MFS were revised and Ghent Criteria involving additionally family history and molecular data have been established. Ghent Criteria comprises three essential components as following:

1- The clinical symptoms from six distinct organ systems (Cardiovascular system, ocular, skeletal, pulmonary, skin and central nervous system),

2- Family history and

3- Molecular evidence.

Ghent Criteria revised for the diagnosis of MFS were summarized in Table 1 (2-9).

Tablo 1: Revised Ghent Criteria for diagnosis of Marfan syndrome (1996)

System	Major criteria	Minor criteria (Involvement)
Family history and genetic	• Parent, child or sibling meeting these diagnostic • FBN1 mutation known to be causing • The presence of a FBN1-linking haploid known to be associated with MFS in the family	N/A
Cardiovascular system	• Aortic root dilatation • The dissection of ascending aorta	• MVP, • (<40 years of age); mitral annular calcification or dilatation of pulmonary artery • Dilatation/dissection of the other aorta
Ocular	• Lens dislocation (ectopia lentis)	Two of following are required: • Flat cornea • Myopia • Increased axial length of eye globe, 'Elongated globe' • Hypoplastic iris or ciliary muscle (reduced miosis) • Glaucoma or cataract below 50 years of age (nuclear sclerotic)
Skeletal (*)	At least 4 of those: • Pectus excavatum • Pectus carinatum • Pes planus • Arachnodactyly • Scoliosis (>20 degree) or spondylolisthesis • Arm span-height ratio >1.05 or upper/lower segment ratio < 0.86, • Protrusio acetabuli • Reduced elbow extension (< 170 degrees)	Two of major criteria or 1 major criterium accompanied by two of the followings: • Moderate pectus excavatum • Dental crowding • Highly arched palate • Typical face features (dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, downslanting palpebral fissures) • Joint hypermobility
Lung	N/A	• Spontaneous pneumothorax • Apical bullae
Skin	N/A	• Atrophic striae (striae distensae) • Recurrence of incisional hernia
Central nervous system	•Lumbosacral dural ectasia (**)	N/A

(*) The diagnosis of involvement in the skeletal system requires the presence of 2 major criteria or 1 major criterium accompanied by 2 minor findings.

(**) Lumbosacral dural ectasia and protrusio acetabuli can be diagnosed using magnetic resonance imaging or computed tomography scanning

According to Ghent Criteria; clinical diagnosis of MFS requires the presence of major criteria at least in two distinct organ systems and involvement in a third different system in the absence of family genetic history. If a genetic mutation known to cause MFS is detected; the presence of a major criteria in any organ and a minor involvement in a second system are adequate for diagnosis of MFS (7). The presence of scoliosis higher than 20 degrees from major criteria, arm span-height ratio >1.05, the presence of moderate degree pectus excavatum from minor criteria, the presence of mitral valve prolapse in the cardiovascular system from the minor criteria and family genetic history met the required diagnostic criteria for MFS in our case.

It has been reported that dentists face with these cases in the early ages because of orthodontic problems associated with highly-arched palate and mandibular retrognathia as well as dental crowding (10).

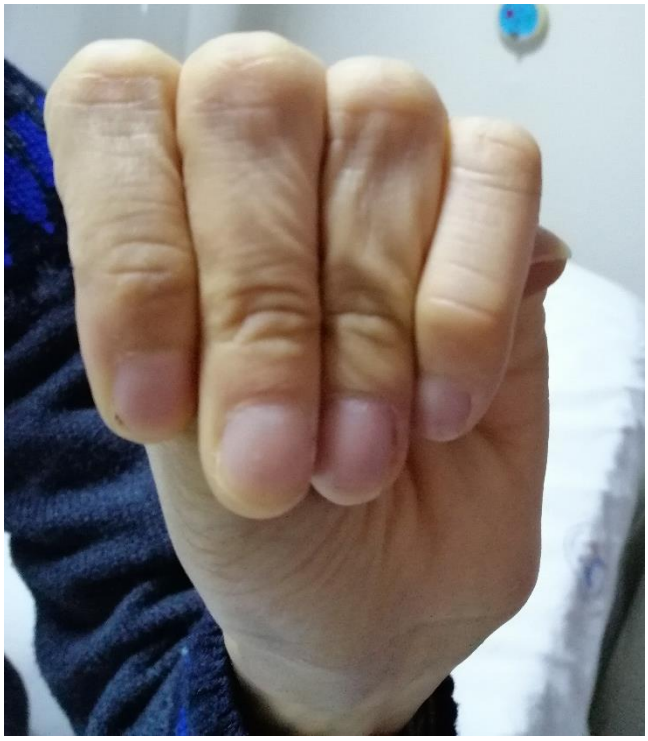

Figure 5: *Positive thumb (Steinberg) sign*

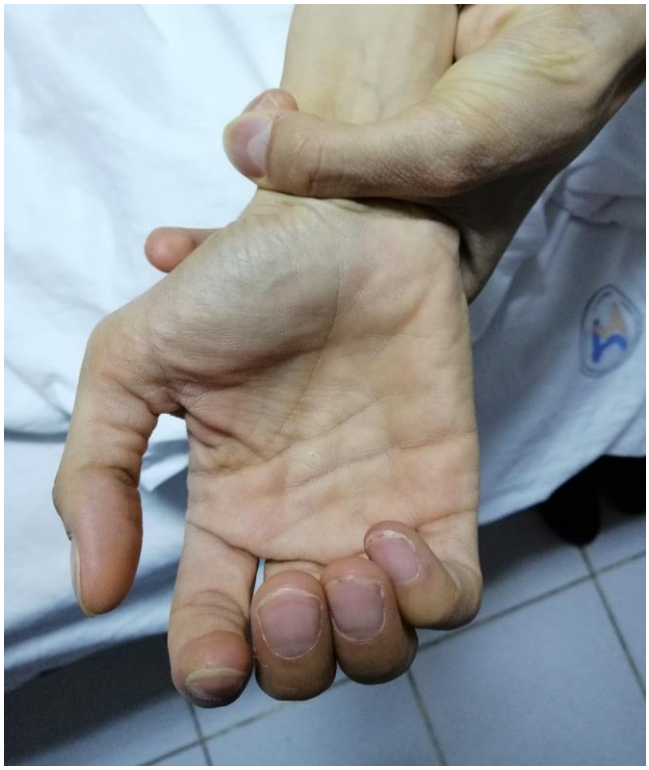

Figure 6: *Positive wrist (Walker) sign*

The differential diagnosis of MFS involves the genetic circumstances that caused by the mutations in FBN1, however, do not meet the diagnostic criteria of MFS such as MASS phenotype (myopia, mitral valve prolapse, mild aortic dilatation), familial mitral valve prolapse syndrome, familial ectopia lentis, familial Marfan-like appearance, and genetic entities such as Loeys-Dietz syndrome, congenital contractural arachnodactyly, familial thoracic aortic aneurysm and dissection, Homocystinuria, Stickler syndrome, Shprintzen-Goldberg syndrome (2).

No definite treatment has been identified for MFS; however, a well-regulated clinical follow-up process and also appropriate approaches for the emerging morbidities increase quality of life and lifetime duration in these patients (1).

The most common morbidity and mortality cause in MFS is cardiovascular involvement. That involvement comprises aortic-mitral valve prolapse and mitral regurgitation, left ventricular dilation, heart failure, pulmonary artery dilatation, aortic root dilatation and aortic dissection. Severe mitral regurgitation is the most common mortality factor in children while rupture of dissected aorta is the most common death cause in adults. Aortic root dissection may lead to myocardial infarction since it occludes coronary ostium. Compared with 70s; reduced mortality rates and prolonged lifetime durations have been reported thanks to successful treatment of aortic complications by performing medical and surgical interventions in the MFS patients (5). The patient can be followed-up under beta-blocker medication if aorta is dilated, however, lower than 4 cm in diameter. Aortic diameter over 5 cm, the presence of a dilatation of 1.5 mm per year, the presence of a dilatation beyond sinus valsalva or aortic dissection in the family history are interpreted in favor of risk factor for aortic dissection. Prophylactic aortic root surgery should be considered if aortic diameter reaches over 4 cm in the sinus valsalva. The risk for aortic dissection increases in pregnancy, close cardiovascular monitoring is needed in the pregnancy and postpartum period (11).

It would be considerable to avoid activities that may induce stress in the joints to prevent joint injuries in the patients with MFS. Heart beat rate, systolic blood pressure and cardiac output increases during both dynamic exercise (e.g. running) and static exercise (e.g. weightlifting). Peripheral vascular resistance and diastolic blood pressure tend to decrease during dynamic exercise; however, they increase during static exercise. Therefore, the patients with Marfan syndrome should avoid intense static exercises; however, they should be encouraged to participate in low intensity dynamic exercises. It is recommended to avoid contact sports to protect aorta and eye-lens and also scuba-diving increasing risk for pneumothorax (5).

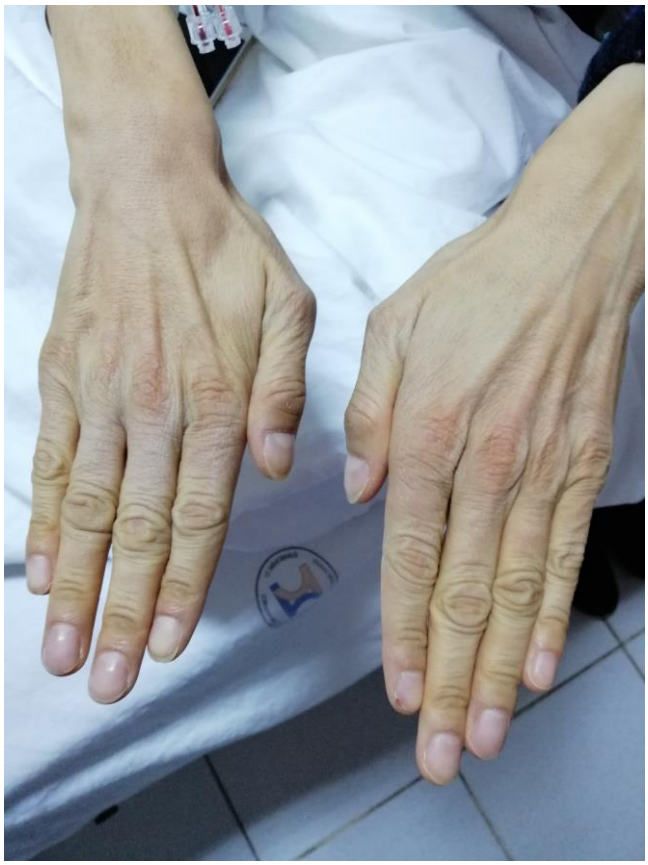

Figure 7: *Long-thin spider digits (arachnodactyly)*

Pectus excavatum is encountered in approximately two third of the patients with MFS, that entity may lead to serious restrictive respiratory insufficiency and also nay complicate the implementation of the cardiac surgical procedures (12). Spontaneous pneumothorax is found in 4-11% of the patients, it is associated with apical bullae and its recurrence is frequent (13). Upper airway tends to collapse during sleep in the adult patients with MFS and that condition leads to development of obstructive sleep apnea syndrome (OSAS). The anomalies of craniofacial structures also contribute to this entity.

A small number of cases have been reported in our country as associated with this syndrome with a general incidence of approximately 1:9,800 births (14,15). It is noticeable that diagnosis of MFS was not considered although our case was hospitalized in the department of Chest Diseases for several times and undergone surgery for scoliosis. This fact suggests that diagnosis of MFS is not considered in such cases. Although it is untreatable, diagnosis of MFS has a critical importance since early diagnosis; regular follow-up and appropriate life style involving the required precautions provide a good prognosis.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - M.G.O., T.Ö., B.A.B., E.S.A.K.; Planning and Design - M.G.O., T.Ö., B.A.B., E.S.A.K.; Supervision - M.G.O., T.Ö., B.A.B., E.S.A.K.; Funding -; Materials -; Data Collection and/or Processing - T.Ö.; Analysis and/or Interpretation - E.S.A.K., B.A.B.; Literature Review - E.S.A.K., B.A.B.; Writing - M.G.O.; Critical Review - M.G.O., E.S.A.K., B.A.B.

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