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CASE REPORT

Marfan Syndrome
Correct diagnosis can save lives

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متلازمة مارفان – تقرير لأول حالة من عُمان
التشخيص الصحيح يمكن أن ينقذ حياة

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الملخص: متلازمة مارفان اضطراب وراثي يصيب الأنسجة الضامّة ويؤثر على العديد من أجهزة الجسم. ومع ذلك، فإن أكثر المضاعفات الخطيرة لدى المرضى الذين يعانون من متلازمة مارفان هو التوسيع التدريجي لجذر الشريان الأبهر، مما قد يؤدي إلى تَسَلُّخ الأَبْهَر وتمزقه، أو حصول القَلَسُ الأَبْهَرِيّ. إنّ الوقاية من هذه المضاعفات التي تهدد الحياة مهم جدا في علاج هذه الحالة. نُدرج هنا حالة رجل عُماني يبلغ من العُمُر 39 عاما مصابا بمتلازمة مارفان، وكان بحاجة إلى العناية الطبية نظرا لإصابته بضيق تدريجي في التنفس، وقد أجريت له عملية جراحية كُبرى ناجحة في القلب. من المهم جدا تشخيص متلازمة مارفان مبكرا من أجل اتخاذ إجراءات وقائية ممكنة قبل حدوث المضاعفات.

مفتاح الكلمات: متلازمة مارفان، تَسَلُّخُ الأَبْهَر، أم الدم الأبهري، ملامح متلازمة مارفان، علم جنت لتصنيف الأمراض، تقرير حالة، عُمان.

ABSTRACT: Marfan syndrome is a heritable disorder of the connective tissue that affects many systems of the body. However, the most serious complication in patients with Marfan syndrome is progressive enlargement of the aortic root, which may lead to aortic dissection, rupture, or aortic regurgitation. Prevention of these life threatening complications is very important in the management of this condition. A 39-year-old Omani man presented with progressive shortness of breath and eventually underwent major but successful cardiac surgery. It is very important to recognise Marfan syndrome early as preventive actions are possible if the condition is diagnosed before complications occur.

Keywords: Marfan syndrome; Aortic dissection; Aortic aneurysm; Marfanoid habitus; Case report; Oman.

Marfan syndrome is one of the most common inherited autosomal genetic disorders of the connective tissue. The syndrome is inherited as a dominant trait, carried by the gene FBN1, which encodes the connective protein fibrillin-1. Marfan has a reported incidence of 1 in 3,000 to 5,000 individuals.[1–2] Sufferers tend to be unusually tall, with long limbs and fingers. Marfan affects many different organ systems; however, cardiovascular disease, particularly aortic root disease—leading to aneurysmal dilatation, aortic regurgitation, and dissection—is the main cause of morbidity and mortality associated with this disorder. The progressive and potentially fatal complications of Marfan syndrome warrant an early diagnosis. It demonstrates the role of the family physician in making a correct diagnosis of the disease, despite late presentation, and the importance of proper follow-up, referral, and counselling.

Case Report

A 39-year-old Omani man presented to the Family Medicine Clinic of Sultan Qaboos University Hospital complaining of a dry cough and progressive shortness of breath for 5 days. His shortness of breath was manifesting as orthopnoea and paroxysmal nocturnal dyspnoea. He reported that this was the first time he had experienced these problems. The patient denied having any chest pain and was not known to have any cardiac or respiratory disease, nor had he any history of prior hospitalisation. His four brothers had all died of

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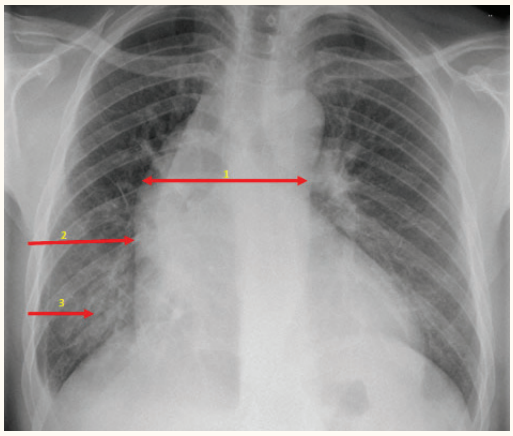

Figure 1: Frontal chest X-ray showing mediastinal widening (top arrow) and dilatation of the ascending aorta (middle arrow) with signs of heart failure (bottom arrow).

unknown causes before reaching their first year of life and his mother had died suddenly at the age of 64. His maternal uncle had died suddenly at age 25. The patient is the father of three children. He had no family history of hypertension, diabetes, heart disease, or any known inherited disorder.

On examination, the patient's respiratory rate was 24 breaths per minute with a collapsing pulse and a rate of 80 beats per minute. His blood pressure was 115/60 mmHg and oxygen saturation was 97%. He had a height of 182 cm and an arm span of 194 cm, giving him an arm span to height ratio of 1.06. He had hypermobile joints, a positive thumb sign, and a high arched palate with some element of teeth crowding. The patient had a pectus carinatum deformity and auscultation of the lungs revealed bilateral basal crepitations. A cardiovascular examination revealed a displaced heaving apex, dual heart sounds with palpable pulsation at the right parasternal area, a mid-systolic murmur and a Grade 3–4/6 early diastolic murmur which was best heard at the right sternal area radiating to the carotid. He had no pedal oedema.

An electrocardiogram (ECG) displayed a sinus rhythm with a heart rate of 80 beats per minute, but no other significant abnormality. A chest X-ray [Figure 1] showed mediastinal widening and cardiomegaly with interstitial pulmonary oedema. A troponin I assay was negative. He was assessed by the cardiologist on call. Left ventricular failure was suspected at that stage and intravenous furosemide was administered to the patient which led to significant improvement; therefore, he was discharged home on furosemide and carvedilol. Four weeks later, a transthoracic echocardiogram (TTE) was performed which showed a severely dilated left ventricle, severe aortic regurgitation, a dilated aortic root, and an ascending aorta (82 mm) with aortic dissection extending from the root to the ascending aorta. The patient was immediately sent for a contrast enhanced computed tomography (CT) of the chest. It demonstrated a large aneurysm of the ascending aorta measuring 9.9 x 9 cm with dissection and minimal pericardial effusion [Figures 2 and 3]. The aortic arch and descending aorta were both normal. As a result, the patient was urgently

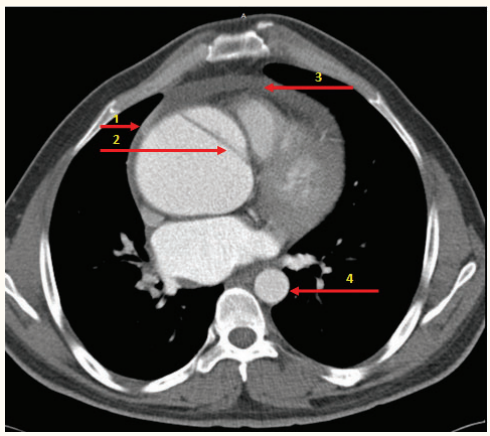

Figure 2: Axial computed tomography (CT) image through ascending (AA) and descending (DA) thoracic aorta showing the aneurysmal dilatation of the ascending aorta (top-right arrow) with intimal flap (type A dissection, top-left arrow) and pericardial effusion (middle arrow). Compare the diameter of ascending aorta with descending aorta (bottom arrow).

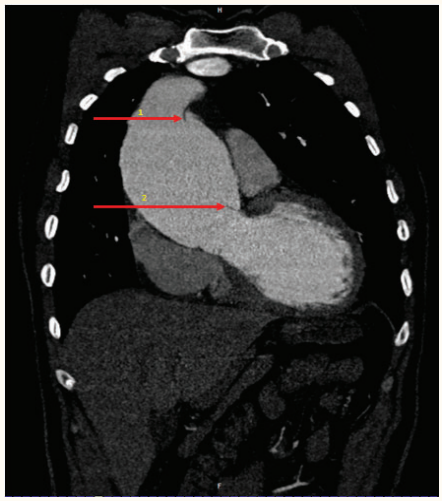

Figure 3: Coronal reformat of the same computed tomography (CT) chest scan showing the extent of the aneurysmal dilatation of the ascending aorta as well as the dissection (both arrows).

Table 1: Major and minor Ghent criteria for the diagnosis of Marfan syndrome

Criteria	Major	Minor
Skeletal	Four of the following eight skeletal system features: • Upper to lower body segment ratio <0.85 or arm span-height ratio >1.05 • Scoliosis >20° or spondylolisthesis • Arachnodactyly of fingers and toes, with positive thumb* and wrist signs • Pes planus due to medial malleolus displacement • Reduced extension at the elbows (<170°) • Pectus excavatum requiring surgical intervention • Pectus carinatum •Protrusio acetabuli	2 of the major features, or 1 major feature and 2 of the following: • Moderate pectus excavatu • Joint hypermobility •High arched palate with crowding of teeth •Facial features like dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, or down-slanting palpebral fissures
Cardiovascular	•Dilatation of the aorta with or without aortic regurgitation •Ascending aortic dissection	• Mitral valve prolapse • Mitral regurgitation • Calcification of the mitral valve before age 40 • Dilatation of pulmonary artery before age 40 • Dilatation/dissection of descending aorta before age 50
Ocular	Ectopia lentis	•Flat cornea •Increased axial length of globe • Hypoplastic iris or ciliary muscle •Myopia •Retinal detachment.
Pulmonary	None	•Spontaneous pneumothorax •Apical blebs
Skin/Integument	None	•Cutaneous striae distensae •Recurrent or incisional hernia
Dura	•Lumbosacral dural ectasia	None

Source: Ades L. CSANZ Cardiovascular Genetics Working Group. Guidelines for the diagnosis and management of Marfan syndrome.[3]

** = Positive thumb sign: entire thumbnail protrudes beyond ulnar border of clenched fist; ¶ = Positive wrist sign: thumb and fifth digit overlap when encircling the wrist.*

referred for surgical intervention. He underwent a Bentall procedure that involved a composite graft replacement of the aortic valve, aortic root, and ascending aorta, with re-implantation of the coronary arteries into the graft. The patient recovered well from this major surgery with significant improvement of his symptoms. A post-operative chest X-ray also showed a remarkable improvement [Figure 4]. The patient was discharged on the seventh postoperative day.

Following surgery, the patient was examined by an ophthalmologist. He was found to have myopia of -2.5 diopters but had no signs of ectopia lentis or any other ocular features of Marfan syndrome. Screening of other family members was arranged and two of his children, aged 4 and 5 years, were found to have Marfanoid features along with aortic root dilatation on echo; they are currently being treated by a paediatric cardiologist.

Discussion

Marfan syndrome deserves particular attention by primary care physicians for two reasons. First, primary care is considered a patient's first portal of entry into the health care system. Second, there are helpful clinical clues that make it a screenable condition for primary care physicians.

The Ghent criteria [Table 1] represent the standard for diagnosing Marfan syndrome in accordance with clinical signs and family history.[3–4] They employs a set of major and minor manifestations in numerous tissues, including the skeletal, ocular, cardiovascular, and pulmonary systems, and the dura, skin and integument. Diagnosis is made if major criteria are identified in at least two different organ systems, and if there is involvement of a third organ system with either a major or minor manifestation. If a family history of Marfan syndrome is positive then involvement

of only two organ systems, including one major criterion, is necessary for diagnosis.[3–4] Any doubt in the clinician's assessment warrants further diagnostic evaluation.

Over the past 30 years, advances in medical and surgical management of the cardiovascular problems, especially mitral valve prolapse, aortic dilatation, and aortic dissection, together with a reduction of physical and haemodynamic stresses have resulted in remarkable improvement in life expectancy of Marfan syndrome sufferers.[5–6]

It is incumbent on the physicians who encounter these patients to emphasise preventive measures. These include periodic imaging of the aorta in order to evaluate its size and the progression of aortic enlargement; early administration of beta blockers mainly to delay aortic root enlargement, and prophylactic surgical repair when there is a high risk of dissection, rupture, or serious aortic regurgitation due to aortic dilatation.[7] Other pharmacological agents, such as angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and calcium-channel blockers (CCB) have all been used in patients who have unacceptable adverse events or no response to beta-blockers.[7–11] Initially, a biannual TTE is recommended to determine the rate of aortic dilation; thereafter, an annual TTE is recommended if aortic size remains stable. In instances of aortic dilatation of more than 45 mm, more frequent imaging of the aorta should be considered as rapid increase in size portends an increased risk of dissection.[10] Owing to these preventive measures, life expectancy has improved considerably.[6,12]

Patients diagnosed with Marfan syndrome should have appropriate counselling before choosing a career. Physically demanding jobs should be avoided. These patients should also be cautioned against participating in high intensity exercise, particularly isometric exercises. Instead, they should be encouraged to participate in lower intensity dynamic exercise.[13] It is important for primary health care providers to be aware of the current recommendations related to physical activity in these patients.[14]

Our case illustrates the importance of making a correct diagnosis of Marfan syndrome. The initial assessment should include a comprehensive medical history that includes a personal and family history of cardiovascular disease. Clinical assessment should include recognition of the physical stigmata of Marfan syndrome, an eye examination, and a TTE.

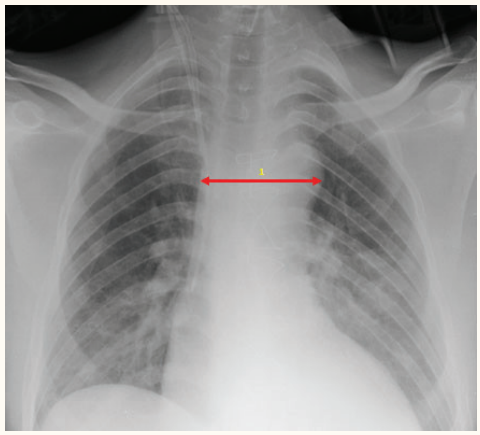

Figure 4: Postoperative chest X-ray showing reduction in mediastinal widening (arrow).

The primary care physician can play a crucial role in the early detection of this syndrome and is also important in facilitating a multi-disciplinary approach through coordination of care with other health care professionals. In addition, the primary health care provider should be aware of the availability of pharmacological means to prevent or delay aortic dilatation.

Conclusion

It is very important to recognise Marfan syndrome early. Despite the morbidity and mortality associated with Marfan syndrome, early medical and surgical management can improve the life expectancy of many patients. Advancing research holds the promise of further improvements. This case illustrates the importance of obtaining a complete family history, and the value of clinical correlation while assessing patients with unusual physical findings. Early diagnosis of this disease by physicians will help in initiating treatment and appropriate management, including patient education and genetic counselling, and will provide an opportunity for family screening.

INFORMED CONSENT

Informed consent was obtained from the patient to publish this case report.

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