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CASE REPORT
Cardiac imaging

Prolapse and regurgitation of the four heart valves in a patient with Ehlers–Danlos Syndrome: a case report

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Background The Ehlers–Danlos Syndrome (EDS) is part of a group of connective tissue diseases that affect the synthesis and processing of collagen leading to alterations in the structure of many tissues and organs.

Case summary Herein, we reported a case of a patient with prolapse of the four cardiac valves. Non-significant regurgitation of the mitral, aortic, and tricuspid valves was observed. The pulmonary regurgitation (PR) was considered significant. Dilatation of the right ventricle with preserved systolic function was also noted. A cardiac magnetic resonance confirmed the findings of the echocardiogram and determined a severe PR (regurgitant fraction of 41%). The physical examination revealed hyperlaxity of the joints, skin hyperelasticity, defects in wound healing, and abdominal hernias suggesting EDS. The stress test did not develop any symptoms or complex arrhythmias. In this patient, the heart team initially decided medical treatment and evolutionary control. At the moment, he remains asymptomatic.

Discussion Valvular involvement in EDS is an infrequent event and the compromise of the four cardiac valves is exceptional. The existence of severe PR with a marked increase in ventricular volumes, even in the absence of symptoms, in most cases requires an intervention on the valve. However, in patients with EDS, there are a high rate of complications and interventions should be avoided as much as possible.

Keywords Valvular prolapse • Ehlers–Danlos Syndrome • Pulmonary regurgitation • Case report

Learning points

- Ehlers–Danlos Syndrome is a rare genetic disorder of the connective tissue with 13 subtypes, the Cardiac-Valvular subtype with a compromise of all the heart valves is a rare and exceptional finding.
- Severe pulmonary regurgitation may lead to heart failure and in some cases requires valvular replacement. However, EDS patients require a multidisciplinary risk–benefit approach for any interventional resolution.
- The timing to decide valve replacement when the patient is asymptomatic remains controversial and requires a strict clinical follow-up, stress testing, and cardiological imaging.

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Introduction

Ehlers–Danlos Syndrome (EDS) is the term used for a group of relatively rare genetic disorders of the connective tissue that are characterized by one or several features including hyperextensibility of the skin, joint hypermobility, and tissue fragility. The general frequency of the EDSs is 1 in 5000.[1]

Over the past two decades, the Villefranche Nosology, which delineated six subtypes, has been widely used as the standard for clinical diagnosis of EDS. However, the 2017 international classification of EDS recognizes 13 subtypes.[2] The genetic basis for most types of EDS has been defined, except for the hypermobility type (which is likely to be genetically heterogeneous), and genetic tests may be useful for the diagnosis of several of these alterations. Clinical diagnoses are based on a series of major and minor criteria, which differ according to the type of EDS. Additionally, patients may have superimposed characteristics from different types, and are not easily classified.[3]

The Cardiac-Valvular EDS (cvEDS) is a subtype of EDS with inheritance autosomal recessive with severe progressive cardiac-valvular problems (aortic valve, mitral valve), skin hyperextensibility, atrophic scars, thin skin, easy bruising and joint hypermobility (generalized or restricted to small joints) as the major criteria. While inguinal hernia, pectus deformity (especially excavatum), joint dislocations, foot deformities: pes planus, pes planovalgus, hallux valgus form part of the minor criteria. Molecular screening by Sanger sequencing of COL1A2 or targeted resequencing of a gene panel that includes COL1A2 is indicated for diagnosis verification.[2]

Timeline

Time	Events
A heart murmur was detected prior to echocardiography study	The study showed prolapse and regurgitation of the four cardiac valves. Pulmonary regurgitation was significant. Physical examination revealed hyperlaxity of the joints, skin hyperelasticity, defects in wound healing, abdominal hernias suggesting Ehlers–Danlos Syndrome
A month later was referred for a stress echocardiography	The test was well tolerated without symptoms or complex arrhythmias. The heart team decided medical treatment and evolutionary control
Six months later to the diagnosis	He remains asymptomatic and a new echocardiogram didn't reveal any changes about right ventricle function parameters, tricuspid annular plane systolic excursion (TAPSE), tissue Doppler imaging (TDI) analysis, and dimensions.

Case presentation

A 46-year-old patient with a past medical history of hypertension, HIV positive on treatment with antiretrovirals was referred for an echocardiographic study of a heart murmur. Physical examination revealed moderate jugular venous distention and large C-V waves. No right or left ventricular heave was found, and cardiac auscultation confirmed a Grade 4/6 diastolic decrescendo murmur best heard in the left second intercostal space; Grade 3/6 holosystolic murmur best heard at the left lower sternal border that accentuates with inspiration; no S3 or S4. He was in NYHA Class I and denied any other cardiac symptoms. Electrocardiogram shown sinus rhythm, right bundle branch block with qRs of 160 ms, left anterior fascicular, and a first-degree auriculoventricular (AV) block (*Figure 1*). The transthoracic echocardiogram revealed the prolapse and regurgitation of the four cardiac valves as an impressive finding. The left ventricular function was estimated into the normality. Right ventricle noted marked dilatation with parameters of preserved systolic function. The pulmonary artery systolic pressure was estimated around 45 mmHg compatible with mild pulmonary hypertension (*Figure 2*). Analysis of valvular abnormalities required further evaluation by transoesophageal echocardiography. The mitral valve had mild thickening of its leaflets and prolapse of the middle segment of the posterior leaflet (P2) as well as the lateral segment (A1) of the anterior leaflet. Mild to moderate mitral regurgitation was estimated (*Figure 3*, Supplementary material online, *Video S1*). The aortic valve had three cusps, and prolapse of the non-coronary cusp with mild regurgitation (*Figure 4*). The tricuspid valve had clear prolapse, thickened valves, increased length, atrialization, and elongation of the tendon cords. These findings demonstrate the presence of a moderate degree of valvular failure with at least two regurgitant jets (*Figure 5*). The pulmonary valve was thickened and had evident prolapse of its valves. The pulmonary regurgitation (PR) impressed moderate to severe. (*Figure 6*, Supplementary material online, *Video S2*).

The study was completed by cardiac magnetic resonance. Dilatation of the right ventricle and the pulmonary artery was observed. Diastolic volume of RV was 148 mL/m^2 of the body surface and the indexed systolic volume was 74 mL/m^2. The systolic function was in range of mild deterioration with an ejection fraction of 49.6%. A regurgitant fraction of 41.7% allowed to confirm severe PR (Supplementary material online, *Video S3*). The other three valves presented with prolapse and non-significant regurgitation. Stress echocardiography was performed to denote the presence of effort symptoms or the presence of arrhythmias. He finished the test with adequate functional capacity. He walked for 9.5 min and 12 metabolic equivalents (METs). The test was well tolerated without any symptoms or complex arrhythmias.

The unusual finding of prolapse of the four cardiac valves with regurgitant involvement prompted the search for some connective tissue disease. Extra-cardiac findings of the physical examination were: (i) hypermobility of the joints of the extremities, (ii) hyperelastic and velvety skin, and (iii) The history of bilateral abdominal and inguinal hernia (*Figure 7*). This highlights suggest cvEDS. The other imaging studies ruled out the presence of an aortic aneurysm in its

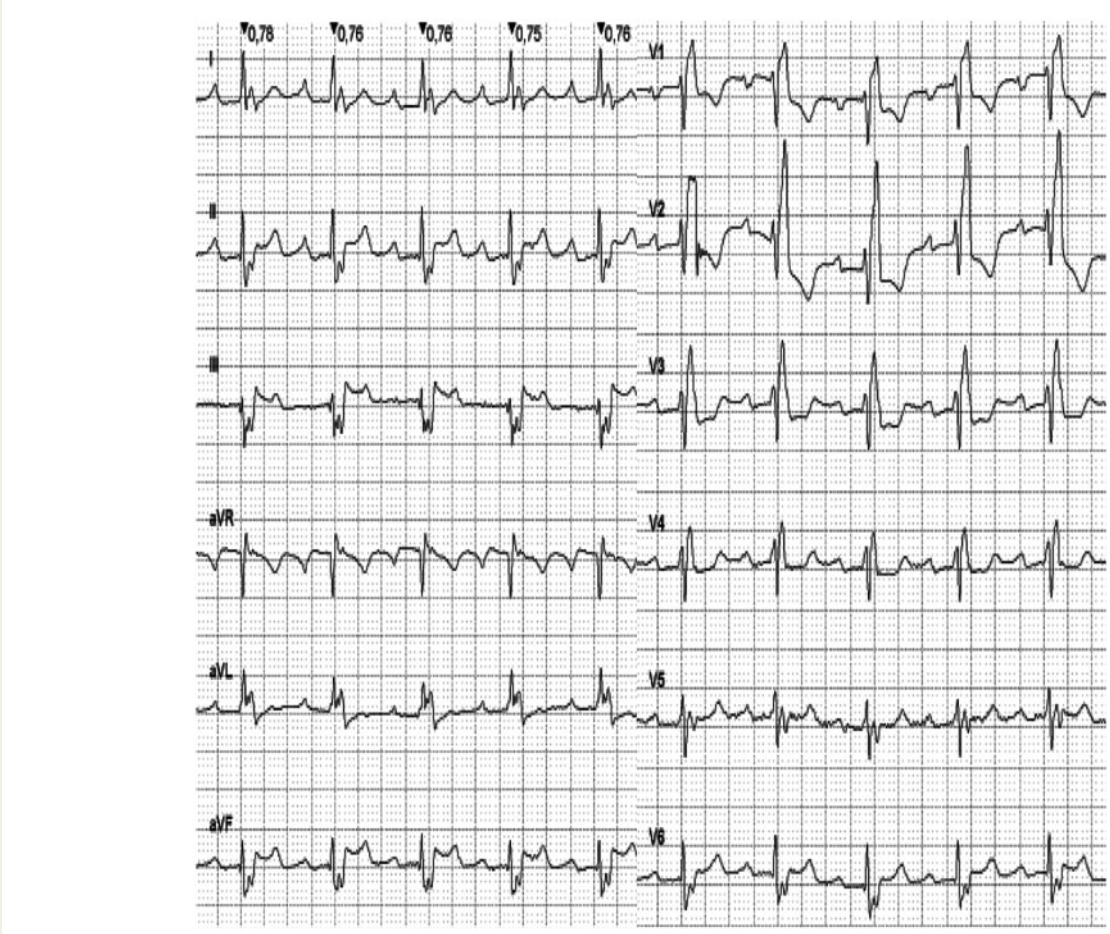

Figure 1 Twelve-lead electrocardiogram: sinus rhythm, right bundle branch block, left anterior fascicular, and a first-degree auriculoventricular (AV) block (trifascicular pattern).

trajectory in the thorax and abdomen as well as in the carotid and iliac arteries. Genetic confirmation of the disorder was not possible because of the high costs of the test and the lack of medical coverage. The evaluation of the first-degree relative was recommended. No history of premature valvular disease or arterial dissections was found.

Presence of severe PR with marked right ventricular dilatation, even in an asymptomatic patient, in most cases will require valvular intervention in order to avoid the development of heart failure. However, in patients with EDS, where the healing conditions are seriously affected, the valve replacement is much more controversial. In this patient, the heart team initially decided medical treatment and evolutionary control. Six months later he remains without any symptoms, imaging testing does not evidence changes in right ventricular dimensions and parameters of the systolic function.

Discussion

The cvEDS is an infrequent subtype of EDS with classical mitral or aortic valve involvement. In this occasion, we presented the case report of prolapse and regurgitation of all the heart valves. Monitoring and cardiological treatment will depend on the degree of valvular disease. Severe PR is the most significative finding of our patient and could determine progressive right ventricular dilatation will subsequently lead to right ventricular failure and the appearance of symptoms over the time.[4] The timing of intervention is a crucial factor for long-term patient morbidity and survival. Surgical pulmonary valve replacement is a well-established treatment strategy with <1% periprocedural mortality when performed by an experienced surgeon, and excellent long-term outcome with >60% freedom from reoperation at 10 years.[5] On the other hand, there are very little evidence of cardiac interventions in patients with EDS. Wiesmann *et al.*[6] described the recommendations on pre- and perioperative management of this patient based on the analysis of small cohorts, isolated clinical cases, and recommendation of experts. Making clear that any type of intervention presumes an important morbidity and mortality. Orotracheal intubation may cause dislocation of the temporomandibular joint. The fragility of the internal organs can promote spontaneous ruptures. Attempts should be made to avoid arterial punctures in order to prevent rupture of the vessel wall. The presence of nausea and vomiting can promote oesophageal rupture

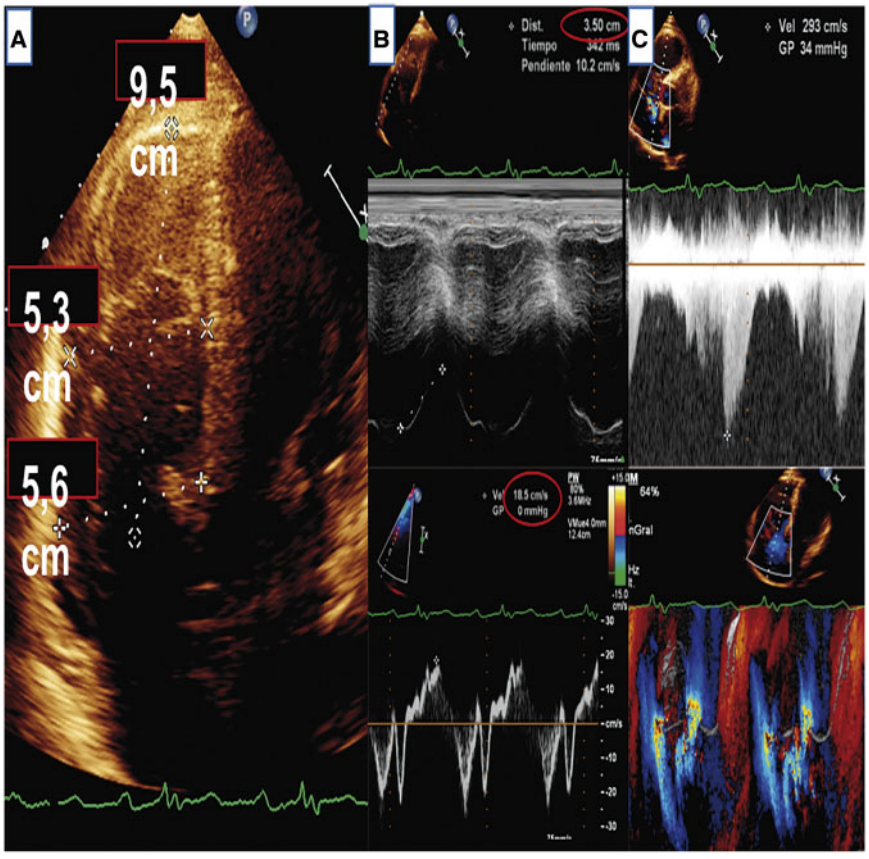

Figure 2 Right ventricular (RV) dilatation in apical four chambers view of the transthoracic echocardiography (*A*). Right ventricular systolic function was found in normal values with a tricuspid annular plane systolic excursion (TAPSE), of 35 mm, and a systolic velocity 'S wave' of tissue Doppler imaging (TDI) analysis was estimated in 18.5 cm/s (*B*). Continuous Doppler analysis of the tricuspid regurgitation allowed to calculate a systolic pulmonary artery pressure of 40 mmHg (*C*).

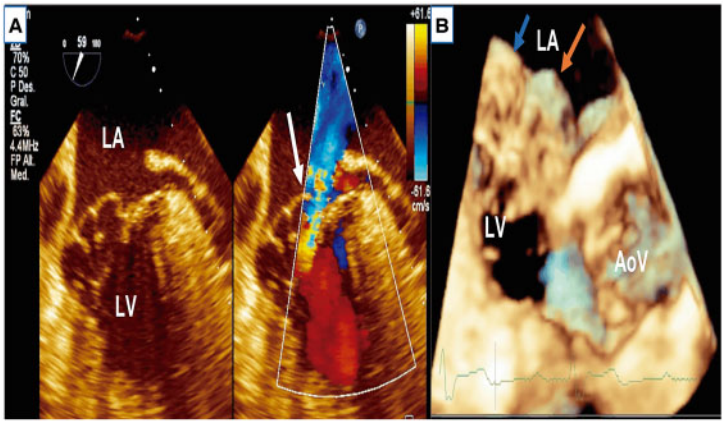

Figure 3 Transoesophageal mid-oesophageal view observed the prolapse and regurgitation of the mitral valve (*A*) 3D echocardiography volume rendering identified the prolapsing leaflets segments P2 and A1 of the mitral valve (*B*). AoV, aortic valve; LA, left atrium; LV, left ventricle. blue and orange narrows allow to identify the prolapse segments of the leaflets.

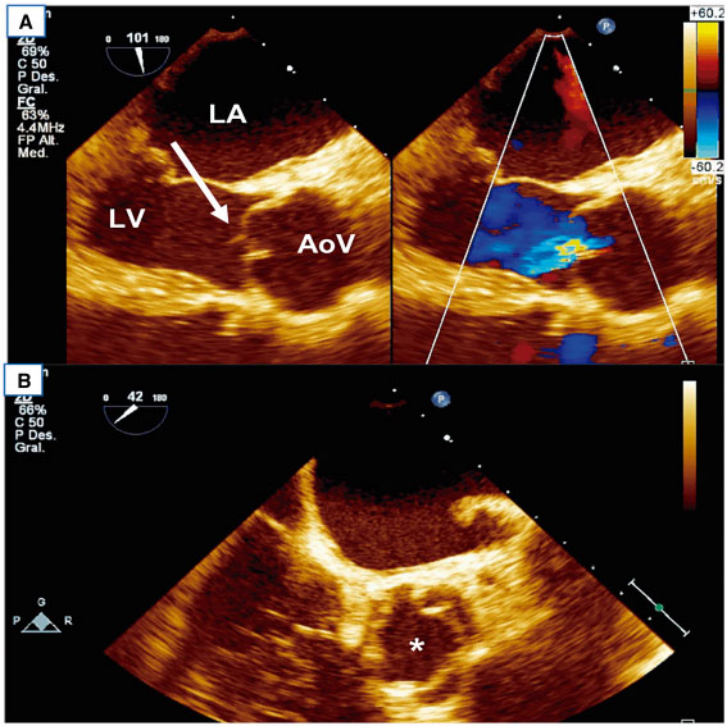

Figure 4 Transoesophageal echocardiogram long-axis view of the aortic valve noted the prolapse and regurgitation of the prolapse of the non-coronary cusp (*A*) short axis denoted three aortic cusps (*B*). AoV, aortic valve; LA, left atrium; LV, left ventricle; * mirror in the three cusps aortic valve opening.

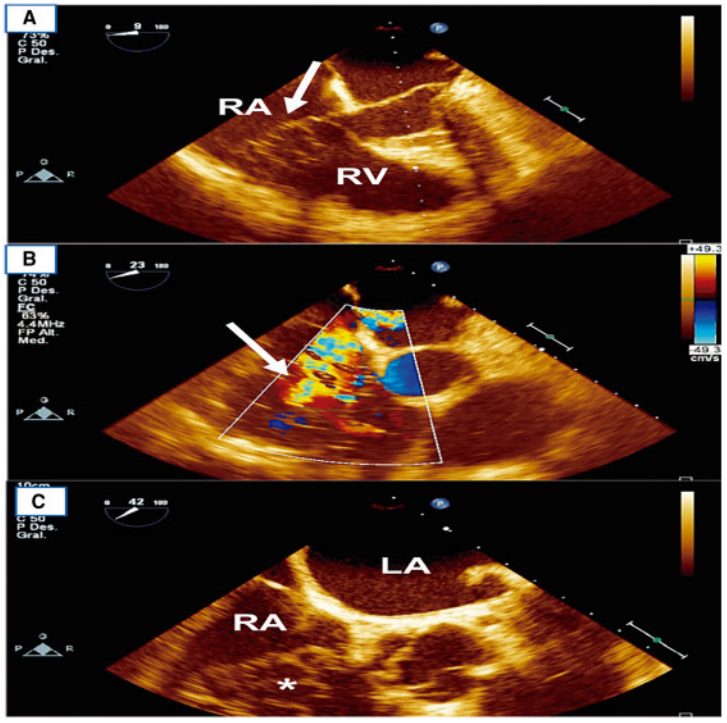

Figure 5 Transoesophageal echocardiography four-chamber view of the tricuspid valve (*A*) thickened valves, increased length, (*B*) no significant tricuspid regurgitation and elongation of the tendon cords was also recognized (*C*). LA, left atrium; RA, right atrium; RV, right ventricle.

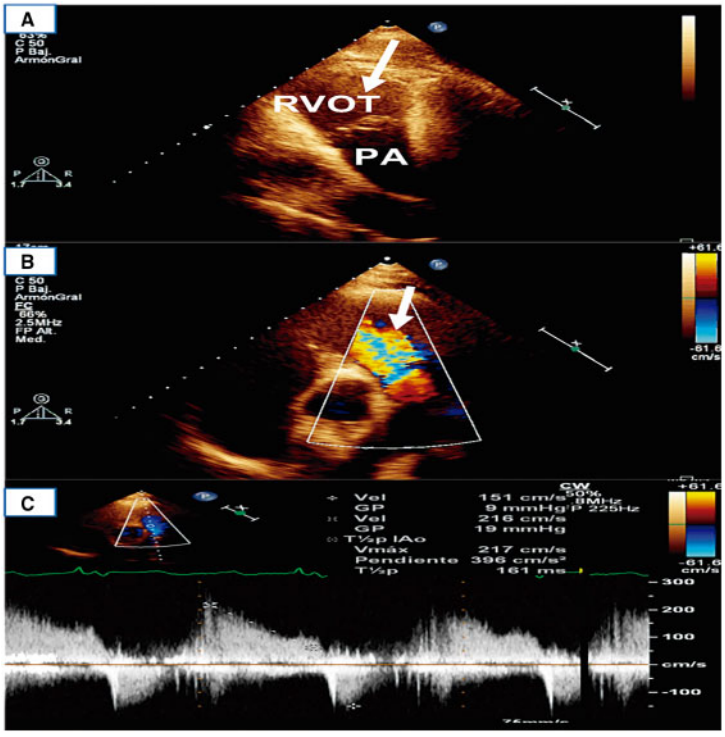

Figure 6 Continuous Doppler analysis of pulmonary regurgitation, a jet was registered that occupies all the diastole, with a pressure halftime of 161 ms (*A*). Transthoracic echocardiography of the pulmonary valve, thickened valves, and prolapse of its leaflets was observed (*B*). Pulmonary regurgitation jet was estimated into moderate to severe degree (*C*). PA, pulmonary artery; RVOT, right ventricle outflow tract.

for which a correct antiemetic prophylaxis will have to be carried out. These are individuals with a high risk of bleeding and even a normal laboratory does not exclude the risk of serious bleeding, thus the administration of blood products should be taken into account. Choosing the prosthetic valve to prefer is another relevant point. Permanent anticoagulation of mechanical valves is not desired since it would add an additional risk of bleeding. Bioprosthetic valves could require temporary oral anticoagulation for 3–6 months after pulmonary valve replacement due to bioprosthetic valve thrombosis.[7] Percutaneous replacement is an option for patients with prosthetic pulmonary valve regurgitation. However, native PR is rarely candidate for percutaneous replacement. The configuration of the native right ventricular outflow tract is highly variable and depends on the type of initial intervention; thus, there is an increased risk of perivalvular regurgitation and device embolization. Although percutaneous pulmonary valve implantation has been performed in some cases of native PR, limited data are available to support this approach.[8] The freedom from reintervention after percutaneous pulmonary valve replacement is >90% at 1 year, but long-term data are lacking.[9]

Patients with moderate or greater PR should also undergo evaluation by cardiovascular magnetic resonance (CMR) if available, which enables quantitative assessment of PR and of right ventricular size and function, which may impact the timing of intervention. Cardiovascular magnetic resonance imaging is the preferred modality for the assessment of right ventricular enlargement and dysfunction, important sequelae of long-standing severe PR.[10] Surgical pulmonary valve replacement is recommended for symptomatic, severe PR.[11] In addition, pulmonary valve replacement for asymptomatic severe PR in the setting of severe right ventricular dilation and/or dysfunction (CMR-derived right ventricular end-diastolic volume >150 mL/m^2, end-systolic volume >80 mL/m^2, ejection fraction <47%,[7] or symptomatic atrial and/or ventricular arrhythmias) is also recommended.[12]

Cardiopulmonary exercise testing provides prognostic information and may also be useful in deciding the timing of pulmonary valve replacement in patients with exertional symptoms out of proportion to disease severity and the degree of right ventricular dysfunction.[13] It is helpful in screening for exercise-induced arrhythmias as well as in the risk stratification for sudden death.

Conclusion

The EDS is part of a group of connective tissue diseases that affect the synthesis and processing of collagen leading to alterations in the structure of many tissues and organs. The progressive and severe involvement of the heart valves forms part of the cvEDS. The compromise of the four cardiac valves is a rare and exceptional fact. In the present case, the treatment of the severe PR is very challenging. The occurrence of symptoms or the presence of right ventricular dysfunction with increased volumes evaluated by CMR in asymptomatic patients determine indications of valvular replacement to avoid

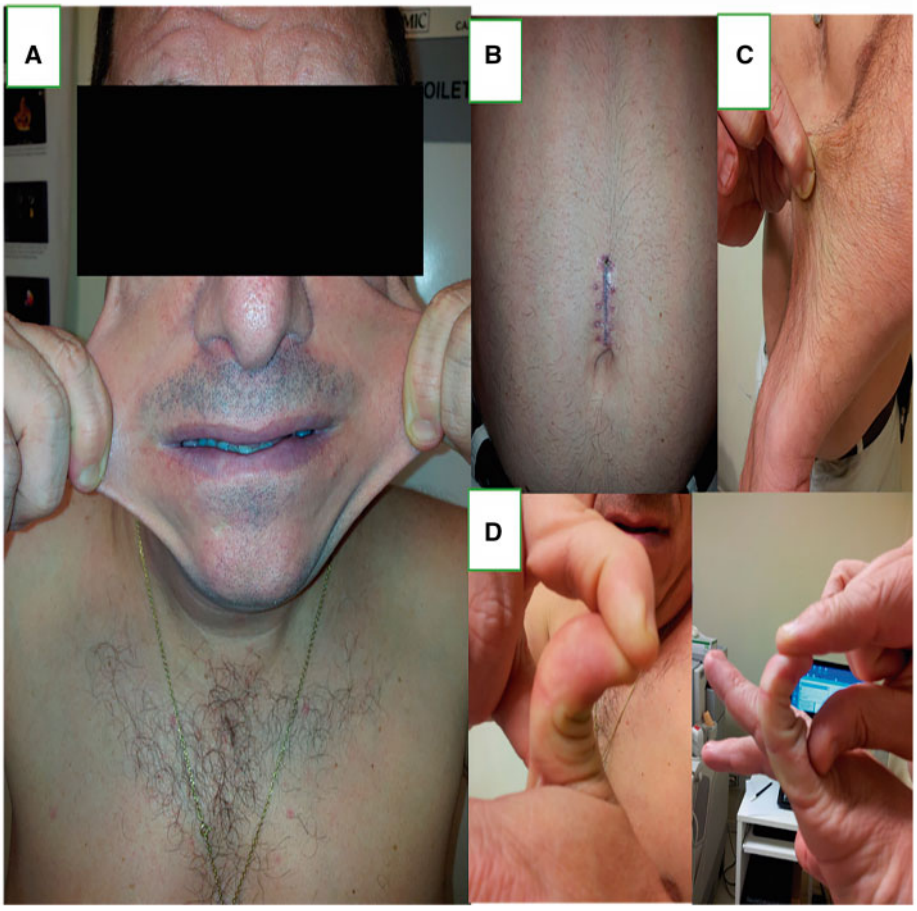

Figure 7 Extra-cardiac physical examination findings. (*A*, *C*) Hyperelastic and velvety skin. (*B*) History of bilateral abdominal and inguinal hernias. (*D*) Hypermobility of the joints of the extremities.

the appearance of heart failure. Strict clinical, cardiac imaging, and stress testing follow-up can help to determine the optimal time of intervention in patients with a high rate of intra- and post-operative complications.

Lead author biography

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Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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