



## Case report

## Ehlers-Danlos syndrome with infective endocarditis: A case report with literature review

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## ABSTRACT

We report a patient with Ehlers-Danlos syndrome and mitral valve infective endocarditis. The case was complicated due to multiorgan involvement and initially diagnosed as hand-foot-and-mouth disease. The patient was transferred to our hospital with cerebral septic emboli and bilateral lower extremity emboli requiring early surgery. Complications of this syndrome and surgical risks are discussed in this report.

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## Case report

A 28-year-old woman presented with a history of a headache, fever, chills, nausea, vomiting, abdominal pain, and generalized malaise. She had a past history of hepatitis C, IV drug abuse, and Ehlers-Danlos syndrome (EDS), which was diagnosed approximately 8 years ago following the birth of her son. She had first felt ill after injecting drugs several weeks ago and began to develop a rash on her lips, the inside of her mouth, and then on the palms and soles. She was evaluated an outside facility and diagnosed with hand-foot-and-mouth disease (HFMD) and sent home with symptomatic treatment. Her symptoms progressed over the following days with development of high fever, leukocytosis, thrombocytopenia, headaches, and confusion despite symptomatic treatment. She presented to a different outside facility where a CT scan of the brain revealed a probable cerebral hemorrhage, prompting her immediate transfer to our facility.

Upon arrival her blood pressure was 107/59 mmHg, with a sinus tachycardia (HR 113 bpm) and a grade 2/6 systolic murmur at the apex. Her respiratory rate was 20/min, SpO<sub>2</sub> 96% (RA), and BMI 22.47. Her platelet count on admission was 33,000 / μL and INR was 2.16. A dermatology consultant believed her symptoms were more suggestive of a bacterial process than HFMD. Blood cultures on admission were positive for methicillin susceptible

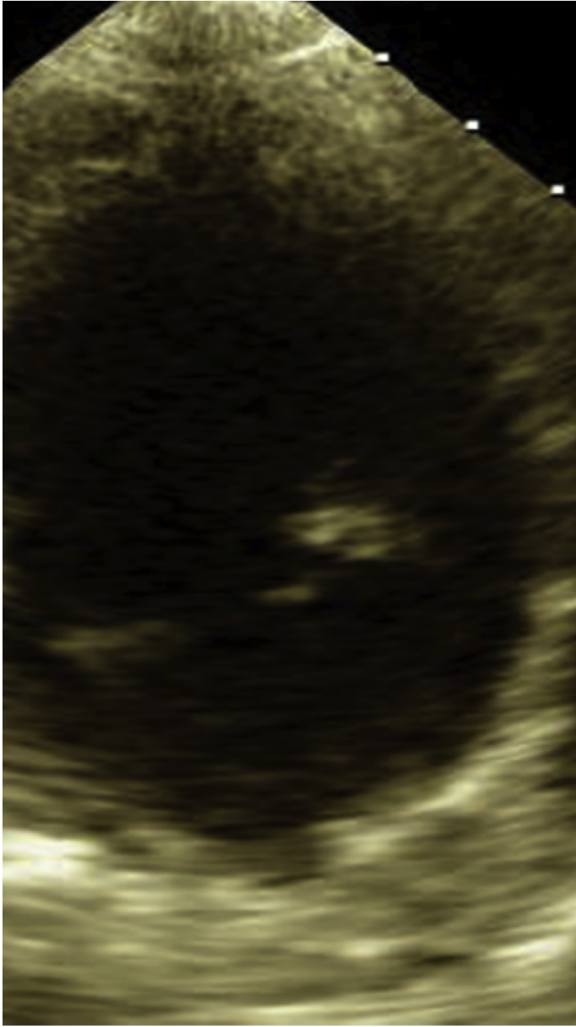
*Staphylococcus aureus* (MSSA). Subsequent examinations (transesophageal echocardiography (TEE), MRI, blood culture) delineated the diagnoses of acute mitral valve infective endocarditis, disseminated intravascular coagulopathy, and left cerebellar septic emboli (Figs. 1 and 2).

CT surgery evaluated the patient; however, given her thrombocytopenia and multiple brain lesions and suspected EDS, it was felt the patient was at a prohibitive operative risk. Initial broad-spectrum antimicrobials were deescalated with the patient continued on cefazolin through hospital day 10, when she developed a maculopapular rash felt to be related to beta lactams. She was switched to daptomycin dosed at 9 mg/kg. On that date her isolate was susceptible to daptomycin with an MIC of 0.25 μg/mL.

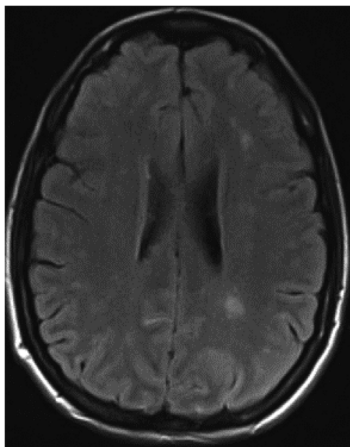
Her persistent bacteremia led us to arrange for transfer to a higher level valve surgery center, but on hospital day (HD) 13 before the transfer could occur she became more tachycardic with worsening congestive heart failure. She developed a pericardial effusion and septic emboli to her bilateral lower extremities. Repeat echocardiograms showed further enlargement of known mitral vegetation and perforation of the posterior leaflet of the mitral valve. The endocarditis team evaluated possible benefits and risks for emergent surgery with the patient undergoing mitral valve replacement with a 29 St. Jude mechanical valve and bilateral femoral artery cutdown with thrombectomy on HD 14. Cultures of resected valve tissue recovered MSSA, as did postoperative blood cultures on HD 15. Intravenous gentamicin and oral rifampin were added. Blood cultures remained positive for MSSA, with rising daptomycin MICs to 2 μg/mL by HD 19 and to 4 μg/mL by HD 20. Gentamicin was discontinued, and ceftaroline dosed at 600 mg IV every 8 h was added on HD 19. She did not develop a recurrence of

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**Fig. 1.** Vegetation on posterior mitral valve leaflet at a size of around 3.3 cm × 2.1 cm as seen on TEE.



**Fig. 2.** Numerous foci of restricted diffusion in both cerebral hemispheres and in the left cerebellum representing either embolic infarcts or septic emboli as seen on MRI.

her rash after this addition. Her blood cultures drawn on HD 22 ultimately resulted as no growth.

She recovered well after the addition of ceftaroline but developed myalgias and elevated CPK levels on HD 32

necessitating discontinuation of daptomycin. On HD 34 she was transferred to a hospital near her hometown out of state to continue antimicrobials therapy with recommendations to continue ceftaroline and rifampin for a total of six weeks from her date of negative blood cultures.

## Discussion

Ehlers-Danlos syndrome (EDS) refers to the three primary symptoms of a group of genetic diseases: fragile skin and blood vessels, skin hyperelasticity, and joint hypermobility [1]. The cause of EDS is not yet clear, but it is thought to have mostly an autosomal dominant inheritance and results in hypoplasia in the mesoderm owing to alterations in the formation of collagen. Modern biochemical studies have shown that EDS patients display metabolic abnormalities and lack necessary enzymes and mucopolysaccharides, which cause obvious flaws in the collagen molecules of the connective tissue [2]. There are 11 subtypes of EDS. Type IV, vascular EDS (vEDS), is the most severe of these. Patients with vEDS often die from arterial rupture or perforation of the digestive tract and rarely live to be 20 years old. In other subtypes, most patients live normal lives if they do not display other complications before age 20.

Infective endocarditis (IE) is rare, with a yearly incidence of about 3–10 per 100,000 people, but has a high mortality rate in developed countries (10%–40%) [3]. Although new diagnostic and therapeutic strategies have emerged, the 1-year mortality has not improved. Based on previous research, degenerative valve disease, diabetes, cancer, intravenous drug use, and congenital heart disease are major risk factors for IE. *S. aureus* is the most frequently isolated microorganism associated with IE in high-income countries and is reported up to 30% of cases [4].

The case we reported here has several unique aspects worth noting. First, both IE and EDS are uncommon. As far as we know, only 3 cases of endocarditis with EDS have been reported (Table 1), only one of which occurred on a native valve [5–7]. As reticular endothelial cells of the immune system also form in mesoderm groups, EDS patients display different degrees of immune incompetence [2]. Some types of EDS affect the cardiac valves, causing structural abnormalities that increase risk for endocarditis.

Second, this case was initially thought to be a presentation of HFMD, but actually the rash on the patient's hands and feet were likely Janeway lesions in the setting of left-sided disease and probable embolic phenomena. The clinical presentation of IE is particularly diverse and non-specific. Fever and cardiac murmur are the most common signs, and cutaneous manifestations such as petechial or splinter hemorrhages also support the diagnosis [4]. Fukuchi et al demonstrated that even though half the patients had underlying risk factors associated with IE, only 12% of patients were suspected of possible IE on the first visit [8]. Although new diagnostic methods have developed since that research, the accuracy of early diagnosis still needs improvement.

Third, early surgery has always been a challenge, considering the associated complications and unpredictable response to antimicrobials therapy. Delaying surgery may allow a longer duration of antibiotic therapy and hemodynamic stabilization, but can also increase the risk of disease progression to acute heart failure, embolic complications, and even death. A recent meta-analysis of 21 studies indicated that patients who had surgical intervention at 7 days or less, OR of all-cause mortality was 0.61 (95% CI 0.39 to 0.96,  $p=0.034$ ) and in those who had surgical intervention within 8–20 days, the OR of mortality was 0.64 (95% CI 0.48 to 0.86,  $p=0.003$ ) compared with conservative management. This study suggest patients received early surgery at 7 days or less from diagnosis carries mortality benefits on a long-term because the lower mortality in patients with surgical intervention within

**Table 1**

The summary of 3 cases of EDS with IE.

Reference	Sex	Age	EDS Type	Main syndrome	Duration from onset to hospital	Examination	High risk for endocarditis	Pathogen	Valve involved	Surgery	Prognosis
5	M	23	II	Muscle and joint pains, fever, vomiting	1 week	Rash, murmur	Not mentioned	Staphylococci	Mitral Valve	Yes	Discharge, follow-up.
6	M	58	Unknown	Fever, weight loss	6 weeks	Petechial hemorrhages, Splenomegaly	Aortic graft, Mechanical aortic valve 10 years ago	B. henselae	Aortic Valve	No	Discharge, follow-up.
7	M	24	IV	Weight loss, night sweat	5 weeks	Not mentioned	Aortic root replacement 1 year ago, dental procedure 5 weeks ago	P. lilacinum	Aortic Valve	Yes	Admitted to hospital for endocarditis 2 times in the next 4 years. Died age 28.

the first week as observed could partially be secondary to the decreased embolic events following surgical intervention [9]. Our patient was received early surgery (less than 20 days from admission) because of positive blood culture, acute heart failure, and new signs of arterial emboli in the extremities. The patient said her brother and mother had also been diagnosed with EDS, and her brother's diaphragm ruptured at age 10, which is possible with vEDS. This type of patient can form an aortic dissected aneurysm which is prone to spontaneous rupture, or aortic root dilatation resulting in aortic regurgitation. During her hospital stay, genetic analysis of the COL3A1 gene (numerous mutations of which are associated with vEDS) was performed (Esoteric Genetic Laboratories, Westborough, MA), which resulted as heterozygous for c1972G > A, a variant of uncertain clinical significance.

Her antimicrobial therapy was complicated by adverse drug reactions to cefazolin (rash) and daptomycin (myotoxicity), and her MSSA isolate rapidly developed resistance to daptomycin while on therapy, with a rise in MIC from 0.25 µg/mL to 4 µg/mL over a period of ten days. Her MSSA isolates maintained susceptibility to first generation cephalosporin throughout her hospital course.

## Conclusion

The case of EDS with IE is rare, but as with this case, it remains critically important to identify associated medical syndromes and risk factors for the occurrence of IE in such a population as regards diagnosis and treatment options. More research and recognition of IE in patients with inherited disease.

## Conflict of interest

No potential conflicts of interest to disclose.

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request

## Author statement

The article I have submitted to the journal for case-report is original, has been written by the stated authors and has not been

previously published. The article do not infringe any copyright, violate any other intellectual property, privacy or other rights of any person or entity, or contain any libelous or other unlawful matter.

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## CRedit authorship contribution statement

**Yang Jiao:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing, Validation. **Mark S. Rasnake:** Data curation, Writing - review & editing. **Michael T. McCormack:** Visualization, Investigation. **J. Francis Turner:** Data curation, Methodology, Writing - review & editing.

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