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CASE REPORT

Homozygous factor Ⅴ Leiden mutation in type Ⅳ Ehlers-Danlos patient

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Abstract

Ehlers-Danlos syndrome (EDS) is a group of inherited connective tissue disorders caused by collagen synthesis defects. Several hemostatic abnormalities have been described in EDS patients that increase the bleeding tendencies of these patients. This case report illustrates a patient with an unusual presentation of a patient with type Ⅳ EDS, platelet δ-storage pool disease and factor Ⅴ Leiden mutation. Young woman having previous bilateral deep vein thrombosis and pulmonary emboli coexisting with ruptured splenic aneurysm and multiple other aneurysms now presented with myocardial infarction. Presence of factor Ⅴ Leiden mutation raises the possibility that the infarct was due to acute coronary thrombosis, although coronary artery aneurysm and dissection with myocardial infarction is known to occur in vascular type EDS. This is the first report in the medical literature of factor Ⅴ Leiden mutation in an EDS patient which made the management of our patient challenging with propensity to both bleeding and clotting.

Key words: Ehlers-Danlos syndrome; Factor V Leiden; Platelets; Coagulopathy

Core tip: Hemostatic abnormalities that have already been described in Ehlers-Danlos syndrome patients include platelet abnormalities (release defects, δ-storage pool disease) as well as clotting factor deficiencies that increase the bleeding tendencies of patients. The coexistence of platelet δ-storage pool disease and factor Ⅴ Leiden mutation in our patient manifested as having aneurysms of the splenic, renal, hepatic, gastric, mesenteric arteries and diffuse aneurysms of the upper and lower extremities as well as bilateral lower extremity deep vein thromboses and pulmonary emboli. This propensity to both bleeding and clotting made the management of our patient challenging on this presentation with acute anterolateral myocardial infarction.

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INTRODUCTION

Ehlers-Danlos syndrome (EDS) is a group of heterogeneous heritable diseases that cause hyperextensibility of the skin, hypermobility of the large joints and easy bruising. It is classified in regard to main symptoms, the causative gene and the inheritance pattern. Among the eleven described types of EDS, type Ⅳ EDS known as vascular form, is a rare autosomal dominant inherited disorder with a 100% phenotypic penetrance caused by a mutation of the *COL3A1* gene encoding type Ⅲ collagen. EDS has an estimated prevalence of 1:5000 to 1:250000 births, and among all, vascular type accounts for 5%-10% of cases[1,2]. The vascular type is the most severe because

of vascular system complications as type Ⅲ collagen rich systemic arteries may undergo dissection, aneurysm, or rupture. Vascular rupture or other organ rupture are the presenting signs in 70% of patients with vascular EDS and the mean age for first major arterial or gastrointestinal complication is 23 years[1]. As for the hemostatic abnormalities previously reported in EDS, patients have more tendency to bleed due to platelet abnormalities (release defects, δ-storage pool disease) and clotting factors deficiencies. We report a case of a 40-year-old female with type Ⅳ EDS, platelet δ-storage pool disease and factor V Leiden mutation. Patient who had multiple previous complications including rupture splenic aneurysm and multiple other aneurysms in addition to coexisting bilateral deep vein thrombosis and pulmonary emboli, presented with acute myocardial infarction.

CASE REPORT

The patient is a 40-year-old woman previously diagnosed with Ehlers-Danlos syndrome type Ⅳ and aneurysms of the splenic, renal, hepatic, gastric, and mesenteric arteries as well as diffuse aneurysms of the upper and lower extremities. She was transferred emergently from an outside hospital with nausea, vomiting, chest pain, shortness of breath, productive cough, and fever of two days duration. Her history was significant for coagulopathy associated with platelet storage pool defect, factor V Leiden with large bilateral lower extremity deep vein thromboses and pulmonary emboli, and diet controlled diabetes mellitus. Further history obtained from the patient and medical record revealed a healthy childhood and generally good health in early adulthood. The patient noted that she had always been "double jointed" in her hands. She had excessive bleeding after cesearian section and deep vein thrombosis in her twenties that prompted hematologic evaluation. This revealed a prolonged bleeding time and platelet storage defect, and factor V Leiden homozygous mutation. The patient denied a tobacco smoking history.

At the age of 33 she was hospitalized for abdominal pain and underwent appendectomy for presumed appendicitis. Approximately one month later she presented again with further abdominal pain and was found to have a ruptured splenic artery aneurysm and multiple aneurysms of the hepatic, renal, gastric, and mesenteric arteries. She underwent emergent splenectomy. Extensive vascular adhesions were found on laparotomy at that time. Four days later she developed a left arm compartment syndrome due to an automated sphygmomanometer and underwent emergent vascular reconstruction of her brachial artery. That hospitalization was further complicated by post-op intrabdominal bleeding requiring repeat laparotomy and Jackson-Pratt drainage placement, and hematochezia due to anal fissures. During recovery from these acute events she developed thigh pain and pleuritic chest pain and was found with large bilateral deep vein thromboses and small pulmonary emboli. Surgical pathological examination of the splenic artery aneurysm with molecular and biochemical analysis were diagnostic of Ehlers-Danlos syndrome type Ⅳ.

Initial examination was significant for a woman in moderate distress, pulse of 115 bpm, blood pressure of 80/40 mmHg, respiratory rate of 24 per minute with 96% oxygen saturation on 15 L/min non-rebreather, and temperature of 101.7 F. She had elevated jugular venous pressure to 6 cm above the angle of Louis, and diminished breath sounds in the right lung with right basilar rales. Her cardiac exam revealed no visible heave, a diminished point of maximum intensity, a rapid regular rhythm, and a normal first and second heart sound with no audible S3. She had a holosystolic Ⅱ/Ⅵ murmur loudest at the left sternal border that did not vary with respiration, and she had no pericardial rub. Her extremities were warm, and distal pulses were normal except for a diminished left radial pulse. She had a large surgical scar running the medial length of her left arm from axilla to distal forearm. She had no peripheral edema. Further physical examination was notable for prominent veins of the extremities with a transparent appearance of the skin. Her finger, hand, and wrist joints were hypermobile with passive range of motion.

Electrocardiogram revealed sinus tachycardia with 2 mm ST elevations and Q waves in the antero-lateral leads consistent with acute antero-lateral myocardial infarction. Initial laboratory evaluation was significant for troponin I of 189 ng/mL. Chest X-ray was significant for bilateral hazy infiltrates. The patient was offered emergent cardiac catheterization but declined. She also declined all antiplatelet and anticoagulant medications. Echocardiogram was performed revealing severely decreased systolic function with severe hypokinesis of the anterior wall, septum, apex and inferior wall. The remaining segments were hypokinetic. Right ventricular size and function and estimated pulmonary artery pressures were normal, and mild to moderate mitral regurgitation was present. Her mental status, blood pressure, and chest pain improved with supportive measures including empiric antibiotics for community acquired pneumonia. The patient's recovery from anterolateral myocardial infarction and pneumonia was complicated by parapneumonic effusion. She tolerated percutaneous pleural drainage well and was discharged home.

DISCUSSION

Among the eleven described types of EDS, type Ⅳ EDS, also known as vascular form, is a rare autosomal inherited disorder of connective tissue due to a mutation of the *COL3A1* gene encoding type Ⅲ collagen. It presents a decreased amount of type Ⅲ collagen and therefore an increased vascular friability and fragility. The vascular morbidity this patient has experienced is typical of patients with vascular EDS type Ⅳ who do not express the typical hyperextensible skin and joints[3]. In fact, it is the most severe form and leads to premature death due to hemorrhage from the rupture of the major and visceral arteries. Besides the connective pathology responsible for the bleeding tendency, several hemostatic abnormalities have been described in EDS patients. These include platelet abnormalities (release defects, δ-storage pool

disease) as well as clotting factor Ⅷ, Ⅸ, XI and XIII deficiencies[4-6]. However, cause of the acute anterolateral myocardial infarction remains unclear in this unfortunate young woman with the combination of platelet storage pool defect with coagulopathy and factor Ⅴ Leiden mutation with history of deep vein thromboses and pulmonary emboli. Coronary artery aneurysm and dissection with myocardial infarction is known to occur in vascular type EDS[7-14]. The coexistence of factor Ⅴ Leiden mutation further raises the possibility that the infarct was due to acute coronary thrombosis, although a clear association between MI and factor Ⅴ Leiden in non-smokers has not been established[15]. Coronary artery aneurysm with or without dissection as an anatomic substrate for acute coronary thrombosis in this individual with factor Ⅴ Leiden is one possibility that could tie together her vascular and hematologic abnormalities that resulted in acute anterolateral myocardial infarction. This patient had an unusual combination of pathologies. This rare association of EDS type Ⅳ, platelet δ-storage pool disease and factor Ⅴ mutation is not previously described. As our patient illustrates, this association predisposes to bleeding and clotting tendencies. While there is no therapy for EDS, desmopressin acetate reduces the bleeding time in patients with EDS type Ⅳ and platelet δ-storage pool disease[16].

COMMENTS

Case characteristics

A 40-years-old female diagnosed with Ehlers-Danlos syndrome (EDS) type Ⅳ presented with chest pain, shortness of breath and productive cough.

Clinical diagnosis

Diminished breath sounds in the right lung, holosystolic Ⅱ/Ⅵ murmer loudest at left sternal border and elevated jugular venous pressure to 6 cm above the angle of Louis.

Differential diagnosis

Myocardial infarction, pulmonary embolism, pneumonia.

Laboratory diagnosis

Troponin I 189 ng/mL.

Imaging diagnosis

Electrocardiogram (ECG): 2 mm ST elevations and Q waves in anterolateral leads; chest X-ray: Bilateral hazy infiltrates; echocardiogram: Decreased systolic function with severe hypokinesis of anterior wall, septum, apex and inferior wall.

Pathological diagnosis

ECG and troponin suggestive of anterolateral myocardial infarction.

Treatment

Patient declined both emergent cardiac catheterization and antiplatelet/anticoagulation medications.

Related reports

Patients with type Ⅳ Ehler-Danlos are reported to have increased tendency to bleed rather than having hypercoagulability state.

Experiences and lessons

This case report shows unusual coexistence of platelet storage disease and factor Ⅴ Leiden mutation in EDS, predisposing our patient to bleeding and clotting tendencies.

Peer review

This article reports an interesting factor Ⅴ Leiden mutation in an Ehlers-Danlos patient.

REFERENCES

1 **Beridze N**, Frishman WH. Vascular Ehlers-Danlos syndrome: pathophysiology, diagnosis, and prevention and treatment of its complications. *Cardiol Rev* 2012; **20**: 4-7 [PMID: 22143279 DOI: 10.1097/CRD.0b013e3182342316]

2 **Nakamura M**, Yajima J, Oikawa Y, Ogasawara K, Uejima T, Abe K, Aizawa T. Vascular Ehlers-Danlos syndrome--all three coronary artery spontaneous dissections. *J Cardiol* 2009; **53**: 458-462 [PMID: 19477391 DOI: 10.1016/j.jjcc.2008.09.007]

3 **Oderich GS**, Panneton JM, Bower TC, Lindor NM, Cherry KJ, Noel AA, Kalra M, Sullivan T, Gloviczki P. The spectrum, management and clinical outcome of Ehlers-Danlos syndrome type IV: a 30-year experience. *J Vasc Surg* 2005; **42**: 98-106 [PMID: 16012458 DOI: 10.1016/j.jvs.2005.03.053]

4 **Kashiwagi H**, Riddle JM, Abraham JP, Frame B. Functional and ultrastructural abnormalities of platelets in ehlers-danlos syndrome. *Ann Intern Med* 1965; **63**: 249-254 [PMID: 14322851 DOI: 10.7326/0003-4819-63-2-249]

5 **Bertin P**, Treves R, Julia A, Gaillard S, Desproges-Gotteron R. Ehlers-Danlos syndrome, clotting disorders and muscular dystrophy. *Ann Rheum Dis* 1989; **48**: 953-956 [PMID: 2512864 DOI: 10.1136/ard.48.11.953]

6 **Anstey A**, Mayne K, Winter M, Van de Pette J, Pope FM. Platelet and coagulation studies in Ehlers-Danlos syndrome. *Br J Dermatol* 1991; **125**: 155-163 [PMID: 1911298 DOI: 10.1111/j.1365-2133.1991.tb06063.x]

7 **Di Mario C**, Zanchetta M, Maiolino P. Coronary aneurysms in a case of Ehlers-Danlos syndrome. *Jpn Heart J* 1988; **29**: 491-496 [PMID: 3184455 DOI: 10.1536/ihj.29.491]

8 **Eriksen UH**, Aunsholt NA, Nielsen TT. Enormous right coronary arterial aneurysm in a patient with type IV Ehlers-Danlos syndrome. *Int J Cardiol* 1992; **35**: 259-261 [PMID: 1572746 DOI: 10.1016/0167-5273(92)90185-6]

9 **Eltchaninoff H**, Cribier A, Letac B. Multiple spontaneous coronary artery dissections in young woman. *Lancet* 1995; **346**: 310-311 [PMID: 7630265 DOI: 10.1016/S0140-6736(95)92196-6]

10 **Catanese V**, Venot P, Lemesle F, Delille F, Runge I, Kuchly B. Myocardial infarction by spontaneous dissection of coronary arteries in a subject with type IV Ehlers-Danlos syndrome. *Presse Med* 1995; **24**: 1345-1347 [PMID: 7494846]

11 **Athanassiou AM**, Turrentine MA. Myocardial infarction and coronary artery dissection during pregnancy associated with type IV Ehlers-Danlos syndrome. *Am J Perinatol* 1996; **13**: 181-183 [PMID: 8688112 DOI: 10.1055/s-2007-994321]

12 **Zied ME**, Khalil MN, Wilson MF. Assessment of myocardial perfusion by cardiolite stress testing in a young woman with Ehler-Danlos syndrome and coronary dissection. *Am J Med* 1999; **107**: 295-296 [PMID: 10492330 DOI: 10.1016/S0002-9343(99)00180-1]

13 **Trichon BH**, Zidar JP, Bashore TM, Donahue M, Sketch MH. Acute myocardial infarction in a young female. *J Invasive Cardiol* 2001; **13**: 597-59, discussion 597-59, [PMID: 11481510]

14 **Dieter RS**, Murtaugh T, Black J, Russell DC. Coronary arteriomegaly in a patient with Ehlers-Danlos syndrome and multiple aneurysms--a case report. *Angiology* 2003; **54**: 733-736 [PMID: 14666965 DOI: 10.1177/000331970305400616]

15 **Rosendaal FR**, Siscovick DS, Schwartz SM, Beverly RK, Psaty BM, Longstreth WT, Raghunathan TE, Koepsell TD, Reitsma PH. Factor V Leiden (resistance to activated protein C) increases the risk of myocardial infarction in young women. *Blood* 1997; **89**: 2817-2821 [PMID: 9108400]

16 **Español I**, Hernández A, Pujol RM, Urrutia T, Pujol-Moix N. Type IV Ehlers-Danlos syndrome with platelet delta-storage pool disease. *Ann Hematol* 1998; **77**: 47-50 [PMID: 9760152]

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