Young patients with aortic dissection – Two case reports with COL3A1 mutation

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Introduction

Aortic dissection is uncommon in young individuals. Patients who are less than 40 years old only account for 7% among all patients with aortic dissection [1]. Vascular Ehlers-Danlos syndrome (vEDS), a subtype of Ehlers-Danlos syndrome (EDS), is one of the connective tissue disorders that could predispose to arterial dissection, aneurysm or rupture. COL3A1, a gene related to synthesis of type III collagen, is associated with vEDS [2]. We report two cases of young patients who were found to have aortic dissection during autopsy. Mutation of COL3A1 gene were identified in both patients.

Patient 1

Clinical history

Patient 1 was a 34-year-old female presented with lower abdominal pain and shock. She was found to have retroperitoneal hemorrhage at right perinephric region on Computed Tomography (CT) scan (Figure 1). Nephrectomy was performed, showing dissecting aneurysm of the renal artery. Patient was in persistent lower abdominal pain after the operation. Repeated CT scan found dissecting abdominal aortic aneurysm with large retroperitoneal hematoma (Figure 2). Emergency operation was performed but failed to achieve hemostasis. Patient passed away shortly after.

Figure 1.

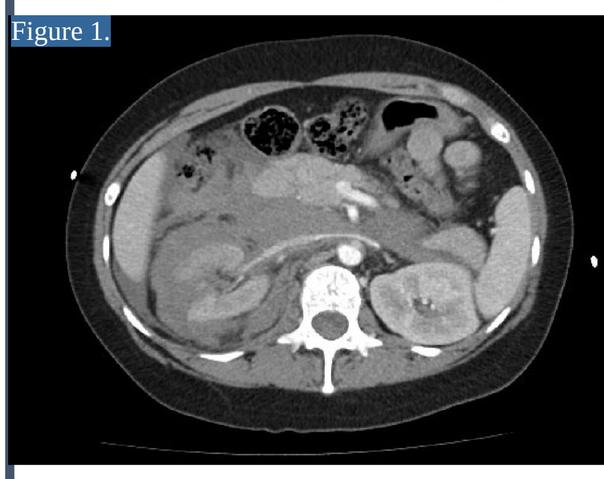
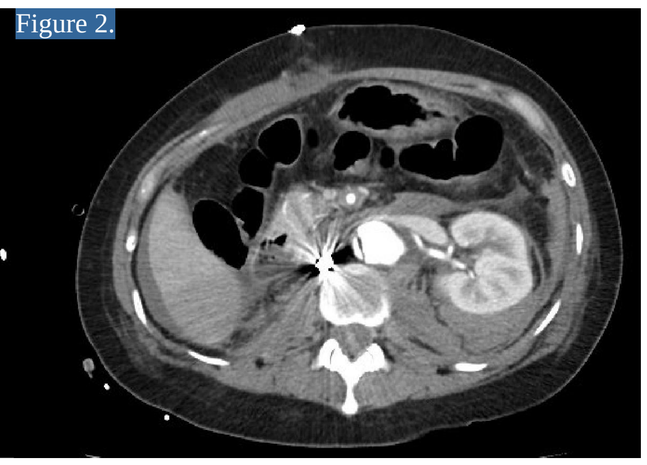


Figure 2.



Autopsy findings

Autopsy revealed aortic dissection with rupture of aorta into three segments. The break points were at the level above celiac branch and below the level of left renal branch. Dissection was detected from aortic arch down to bilateral iliac arteries with involvement of the celiac artery, left renal artery, superior mesenteric artery and inferior mesenteric artery. Dissection of the segmental branches of hepatic arteries was also seen. Hemoperitoneum of 800 ml was identified. Microscopic examination of the vessel wall confirmed arterial dissection with cystic medial degeneration (figure 3-6).

Figure 3.

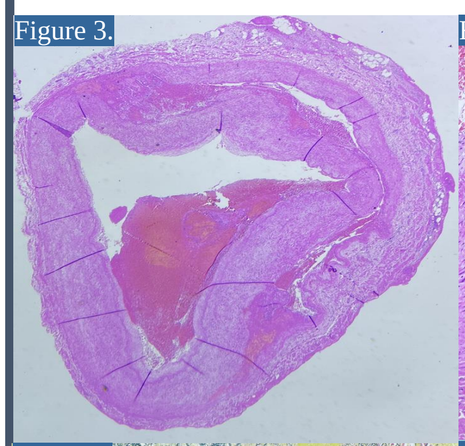


Figure 4.

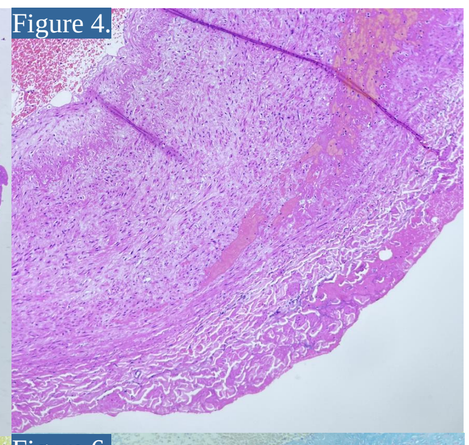


Figure 5.

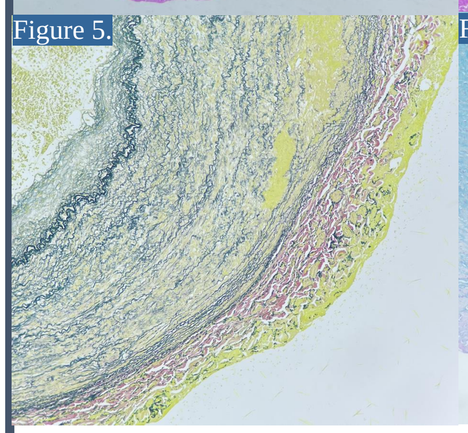
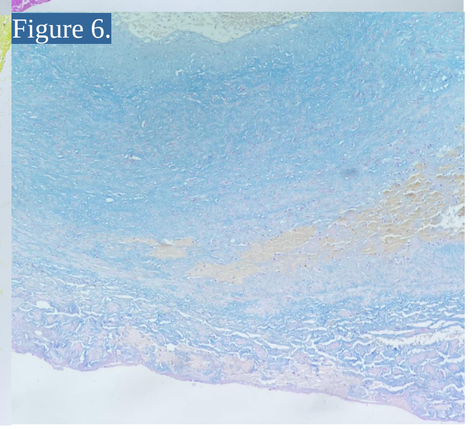


Figure 6.



Genetic testing

Genetic tests showed heterozygous COL3A1 c.655G>A p.(Gly218Ser) mutation, which was classified as likely pathogenic for vascular Ehlers-Danlos syndrome.

Patient 2

Clinical history

Patient 2 was a 31-year-old female with good past heath. She presented with anemia (Hemoglobin: 9.9 g/dL) and right thigh bruises. She subsequently developed generalized numbness after admission and was found to have sudden cardiac arrest shortly after.

Autopsy findings

Autopsy revealed aortic dissection with intimal tear at 2 cm proximal to the bifurcation of abdominal aorta. It extended proximally to aortic root and distally to bilateral iliac arteries. The left renal artery was also involved. An adventitial tear (figure 7), which is 0.8 cm in size and 1 cm above the aortic root, was identified with 300 ml of hemopericardium (figure 8). Soft tissue hematoma (12 x 9 x 5 cm) was also noted in the right groin surrounding the dissected iliac arteries. Microscopic examination of the vessel wall confirmed arterial dissection with cystic medial degeneration (figure 9).

Figure 7.

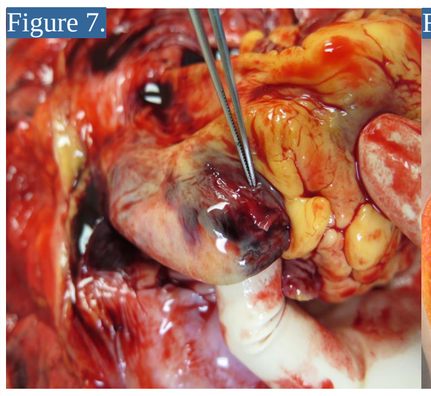


Figure 8.

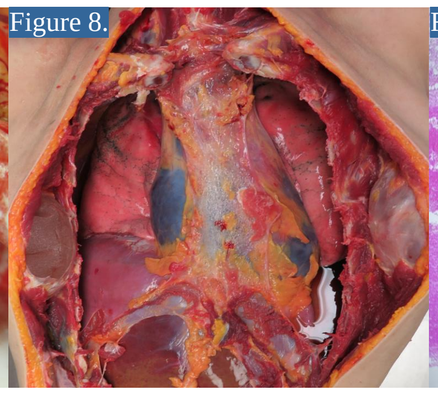
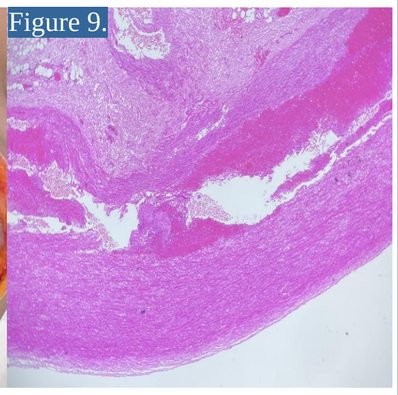


Figure 9.



Genetic testing

Genetic tests showed heterozygous COL3A1 c.1295G>T p.(Gly432Val) mutation and heterozygous COL5A2 c.2273C>T p.(Pro758Leu) mutation, which were both classified as variant of undetermined significance of vascular Ehlers-Danlos syndrome.

Discussion

Both patients presented with aortic dissection at a young age with no other usual risk factors including hypertension or atherosclerosis. Other predisposition factors need to be considered and genetic testing for an aortopathy panel should be performed. COL3A1 mutation was identified in both cases, which is strongly associated with Vascular Ehlers-Danlos syndrome.

Vascular Ehlers Danlos syndrome is a rare autosomal dominant connective tissue disorder, which differs from the classic and hypermobility forms in the increased risk for these patients of spontaneous vascular or visceral rupture and the absence of large-joint hyperextensibility. The prevalence is estimated to be 1/150 000 [2]. Vascular rupture or dissection and gastrointestinal perforation or organ rupture are the presenting signs in 70% of the affected individuals [3] *COL3A1* is a gene that closely associated with vEDS. It encodes the proα1(III) chain of type III procollagen, an extracellular fibrillar collagen with important roles in stabilizing the extracellular matrix that surrounds blood vessels and hollow viscera [4,5] . About 50% of affected individuals have inherited the *COL3A1* pathogenic variant from an affected parent, and about 50% of affected individuals have a de novo pathogenic variant [2]. Approximately 1000 heterozygous pathogenic variants in *COL3A1* have been identified in individuals with vEDS[2]. Most of the variants are heterozygous missense substitutions affecting one of the glycine residues [6].

Diagnosis of vEDS can be established by identification of a heterozygous pathogenic variant in *COL3A1* on molecular genetic testing or biochemical analysis of type III procollagen from cultured fibroblasts showing abnormalities in synthesis and mobility of type III collagen chains. They are performed when vEDS is suspected but molecular genetic testing does not identify a *COL3A1* pathogenic variant [3].

In patient 1, the change in amino acid (Glycine to Serine at 218th codon) resulted from the missense mutation identified in COL3A1 gene was reported in previous literature, which is associated with vEDS. This type of mutation is also not found in the general population. It is then classified as likely pathogenic.

In patient 2, the change in amino acid (Glycine to Valine at 432nd codon) resulted from the missense mutation identified in COL3A1 gene was not reported in previous literature or in major database. However, a different change in amino acid at same location was reported to be associated with vEDS. In additional, the type of mutation identified in our patient is also not found in the general population. Computational program also predicted deleterious effect on the gene product. It is therefore classified as a variant of uncertain significance.

With the above findings, the family members of both patients were subsequently referred to clinical genetic service for genetic counselling.

Conclusion

Recognition of underlying connective tissue disorders in young patients with aortic dissection is important. It could benefit their family members by early detection and intervention to prevent fatal complication.

Reference

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