Galore International Journal of Health Sciences and Research
Vol.3; Issue: 1; Jan.-March 2018
Website: www.gijhsr.com
Case Report *P-ISSN: 2456-9321*

Pregnancy-Related Death in a Woman with Vascular Ehlers-Danlos Syndrome; Dissection and Rupture of Internal Carotid Artery Aneurysm Accompanied by Preeclampsia

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ABSTRACT

Ehlers-Danlos syndrome is a rare inherited disorder of connective tissue, characterized by a collagen synthesis defect. Vascular type is the most serious type. Dissections of the vertebral and carotid arteries in their extra- and intra-cranial segments are typical. Pain is the initial symptom of a spontaneous internal carotid artery dissection presenting to a physician. Headache (including neck and facial pain) is usually described as constant and severe and is commonly ipsilateral to the dissected artery. Failure to consider the diagnosis in young patients presenting with neurologic symptoms is a potential medico-legal pitfall. We describe a 37 year old pregnant woman with undiagnosed Ehlers-Danlos syndrome type IV, presenting with dissection and rupture of extra-cranial segment of internal carotid aneurysm associated with preeclampsia in 33 weeks of gestation.

Key words: Ehlers-Danlos syndrome, Carotid artery, Dissection, Pregnancy.

INTRODUCTION

Ehlers-Danlos syndrome is a hereditary connective tissue disorder. The type most frequently encountered by surgeons is vascular type, also named type IV. The diagnosis is often made after vascular or gastrointestinal complications have occurred. Carotid aneurysm are rare, accounting for less than 4% of all aneurysms, and repair of this entity comprises only 0.9% of all carotid procedures at major referral centers. Dissection and rupture of a non-traumatic carotid aneurysm is an exceedingly rare event, with only a handful of cases documented in the world literature, most of which presented as an acute, life threatening emergency. Severe headache that begins suddenly is a characteristic sign of a ruptured aneurysm in the carotid artery, as well as other arteries in the brain. High clinical suspicion is needed for diagnosis. Definitive diagnosis is made by MR or CT angiography. We describe a young pregnant woman with EDS who presented with dissection and rupture of internal carotid aneurysm in late pregnancy. CT angiography showed dissected and ruptured right internal carotid artery with massive hemothorax and pressure effect on trachea, thyroid gland and right jugular vein. She unfortunately died during surgery due to massive hemorrhage.

CASE PRESENTATION

The patient is a 37 year old Iranian woman, with 33 weeks of gestation. She was a case of diabetes mellitus which diagnosed in early pregnancy and her blood sugar was controlled with insulin and also was case of hypothyroidism on medication. She had a history of alopecia since adolescence, easy bruising skin and delayed

wound healing, who was not evaluated because of these. She did not have any other problems during pregnancy and her blood pressure was normal during prenatal care. She had a history of Down's syndrome in her two brothers and cousins and also sudden death in her mother in early adult. She was presented with neck pain and headache in 33 weeks of gestation and referred to our center with high blood pressure. She did not have nausea, vomiting, epigastric pain and blurred vision. On arrival, in physical examination, she had: Glasgow Coma Scale:15, blood pressure: systolic 170 mmHg and diastolic 110 mmHg (measured by left upper extremity), pulse rate: 96 beats per minute, temperature: 37C. Neurological examination was normal. In general physical examination, she had short stature, buffalo hump, alopecia, and central obesity. She also had large eyes and small earlobes. She had a tender soft mass on right side of neck (6*6 cm) and radial artery pulse was weaker in right upper extremity than left upper extremity and systolic blood pressure differed about 50 mmHg between two upper extremities. Lung and heart examination was normal. She had pitting edema in lower extremities. Her blood pressure was controlled with intravenous hydralazine. Mg-SO4 started intravenously for seizure prophylaxis. Lab tests showed: Hgb: 13, Platlet: 260,000, Urine protein: 4+, Creatinin:0.8, LFT: normal, Electrolytes: normal, coagulation tests: normal. Because of high suspicion to dissection of carotid artery, consultation with internist and general surgeon was done. Before evaluation of neck mass by ultrasound and visiting of patient by internist and general surgeon, cesarean section was planned due to fetal distress (prolonged deceleration) one hour after admission. She was transferred to operation room with blood pressure: systolic 150 mmHg and diastolic 90 mmHg (measured by left upper extremity) and pulse rate: 106 beats per minute. The patient visited by anesthesiologist and because of suspicion to vessel dissection, cesarean section was done under spinal anesthesia. During operation, blood pressure was controlled and a male baby weighing 2100 gram, with good APGAR score was born. Her connective tissue was very loose during operation. After cesarean section, the patient visited by internist and general surgeon and with diagnosis of vessel dissection (carotid artery) chest x-ray and imaging with ultrasound, Doppler of vessels, and CT angiography were recommended. Chest x-ray was normal and did not showed mediastinal widening. Ultrasound showed swelling in the neck area and Doppler was normal.ECG showed sinus tachycardia and Echocardiography was normal. One hour after cesarean section, she had chest pain in right side and dyspnea. In physical examination, she had tachycardia and tachypnea (Blood pressure: 130/80, pulse rate: 130 beats per minute and respiratory rates: 28 per minute) and her O2 saturation was 99%. On that time, her Hgb was 10.7.Due to high clinical suspicion to dissection of vessels, the patient transferred to another center for CT angiography and visiting by vascular surgeon. In the second center, brain CT scan was normal but CT angiography and spiral chest CT scan showed dissection and rupture of right internal carotid artery aneurysm with massive hemothorax (Image 1) and pressure effect on trachea, thyroid gland and right internal jugular vein. (Image 2) She was intubated and transferred to operation room. She had dissection of extra-cranial segment of internal carotid artery aneurysm and massive hemothorax, and she unfortunately died during operation. Electron microscopic examination of the skin confirmed diagnosis of EDS due to massive hemorrhage.

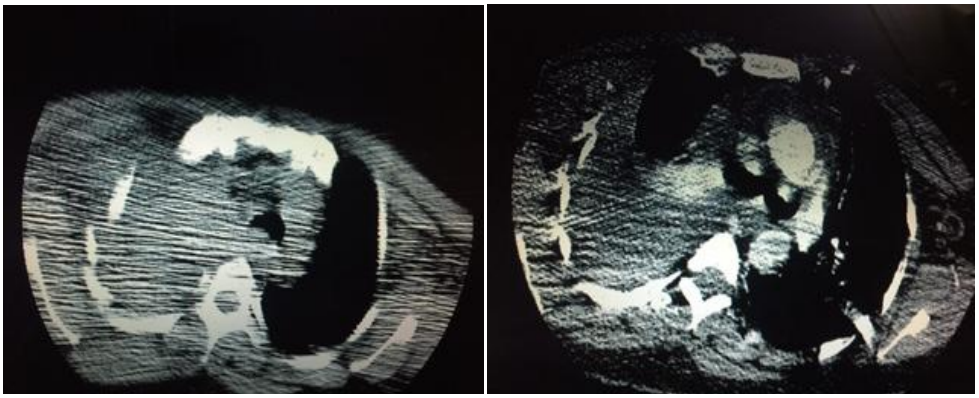

Image 1. Massive hemothorax in spiral chest CT scan.

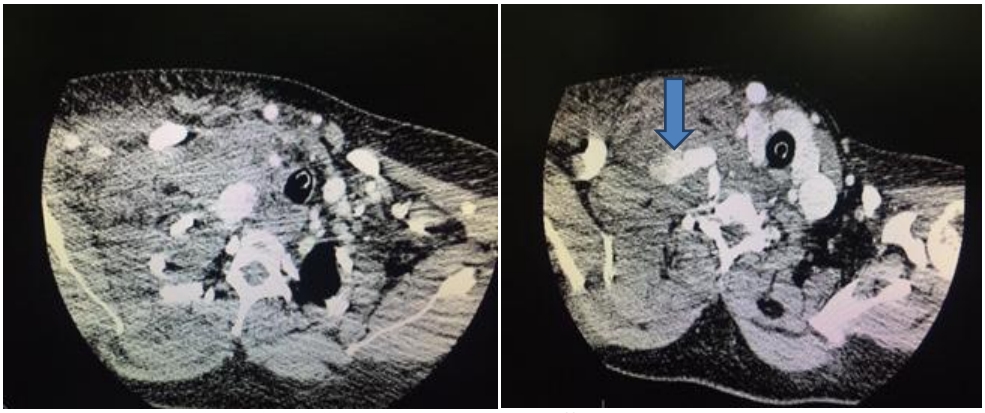

Image 2. Ruptured right internal carotid artery aneurysm with pressure effect on trachea, thyroid gland and right internal jugular vein.

DISCUSSION

An artery aneurysm is a bulging or balloting in the wall of the artery. True arterial aneurysms involve all three layers of the artery wall (intima, media and adventitia). The artery wall can balloon out symmetrically to form a fusiform aneurysm or there can be a local blow out to form a saccular aneurysm. Common sites are: abdominal aorta, iliac artery, popliteal artery, femoral artery. Risk factors are: anomalous vessels, coarctation of the aorta, polycystic kidney disease, fibro-muscular dysplasia, connective tissue disorders, vascular malformations and fistulae. Aneurysm of the extra-cranial carotid artery is rare, with a reported incidence of 0.2 to 5% of all carotid artery surgeries. [(1-3)] The location of the aneurysms was equally distributed between the internal and common carotid arteries. [(4)] Carotid artery aneurysms and pseudo aneurysms are uncommon and usually asymptomatic. [(4)] Symptoms for carotid artery aneurysms may include transient ischemic attacks (TIAs) or stroke. In addition, carotid artery aneurysms may form clots that block blood flow to the brain. Other symptoms can occur secondary to pressure of the aneurysm on surrounding structures such as veins and nerves. These symptoms can vary, depending upon what is compressed, but may include facial swelling, hoarseness or difficulty swallowing. Rarely, carotid artery aneurysms can rupture, or burst, which is a life threatening problem. In order to prevent this from occurring, treatment maybe warranted. Our patient did not have any symptom before the dissection and rupture of aneurysm. An aneurysm in the carotid artery can progressively stretch and weaken an area of the wall, leading to a rupture of the artery. Aneurysms cause much more obvious and life-threatening symptoms when they rupture, and emergency medical treatment is then required.

Dissecting aneurysm of the intracranial carotid artery and its major intracranial branches is a relatively rare occurrence. The lesion may develop

spontaneously or may be related to trauma or may extend from a more proximal dissection. Our patient had a spontaneous dissecting aneurysm arising in the internal carotid artery in the neck. Severe headache that begins suddenly is a characteristic sign of a ruptured aneurysm in the carotid artery, as well as other arteries in the brain. This pain is so severe that most individuals describe it as "worst pain ever felt". The extreme headache is usually accompanied by nausea and vomiting, a stiff neck and in some cases, temporary loss of consciousness. Our case had headache.

Ehlers-Danlos syndrome (EDS) is a risk factor for artery aneurysms and dissections. In our case, risk factors of dissection were hypertension and EDS. Ehlers-Danlos syndromes are a group of rare inherited conditions that affect connective tissue. The different types of EDS are caused by faults in certain genes that make connective tissue weaker. Depending on the type of EDS, the faulty gene may have been inherited from one parent, or both parents. Sometimes the faulty gene is not inherited, but occurs in the person for the first time. In our patient, the gene possibly inherited from her mother, duo to history of sudden death in early adulthood.EDS can affect people in different ways. For some, the condition is relatively mild, while for others their symptoms can be disabling. Some of the rare severe types can be life-threatening. Hyper mobile EDS is the most common type of EDS. Rare types include classical EDS, vascular EDS and kyphoscoliotic EDS. All forms of EDS share common features to varying degrees including joint hyper mobility, skin hyper extensibility, tissue fragility, poor wound healing, and easy bruising. Vascular EDS, also known as EDS type IV, is a rare type of EDS and is often considered to be the most serious. The estimated prevalence of EDS type IV is about 1:100,000 to 1:250,000 in the general population, and there is no ethnic or sex predilections. [(5,6)] It affects the blood vessels and internal organs, which cause them to split open and lead to life-threatening bleeding. Vascular complications may affect all anatomical areas, with a preference for large- and medium-sized arteries. Dissections of the vertebral and carotid arteries in their extra- and intra-cranial segments are typical. People with vascular EDS may have:

1. Skin that bruises very easily, like our case.
2. Thin skin with visible small blood vessels, particularly on the upper chest and legs.
3. Fragile blood vessels that can bulge or tear, resulting in serious internal bleeding, like our case.
4. A risk of organ problems, such as the bowel tearing, the womb tearing (in late pregnancy) and partial collapse of the lung.
5. Hypermobile fingers and toes, unusual facial features, (such as a thin nose and lips, large eyes and small earlobes) (like our case), varicose veins and delayed wound healing.

The vascular form of the disease is an inherited dominant autosomal disorder caused by mutations in gene COL3A1, located in 2Q32.2, which encodes the pro-alpha 1 chain (III) of the fibrillar collagen type III. [(5-7)]

The incidence of all types of EDS in pregnancy is estimated at 1 in 15,000. [(8)] The vascular type accounts for 10% of all cases. [(8)] Complications relating to EDS are infrequently seen in obstetric practice. [(9)] It presents with a range of considerations, which are specific to the classification of type. Some types are associated with severe maternal complications, whereas others are associated with more favorable outcomes. [(10)] Due to the hormonal changes taking place in pregnancy, many with EDS experience an increase in the number and severity of symptoms (varicose veins, oedema, nausea and vomiting, musculo-skeletal problems and etc.) Ehlers-Danlos syndrome increases risk of cervical insufficiency, PPROM, preterm birth, fetal growth restriction, perineal trauma and

wound healing after delivery and postpartum hemorrhage. In pregnant women with EDS, vessels are at risk due to hormonally induced relaxation and increased cardiac output increases the risk of vessel rupture. In assessing potential complications that may occur in the antenatal, intrapartum and postnatal periods in patients with EDS, the type and severity of EDS should be identified. [(8)] Classical and vascular types of EDS can have serious implications in pregnancy, and so prenatal counseling is vital for these patients. [(11,12)] In patients with EDS, maternal evaluation with electrocardiogram, screening carotid and abdominal aorta Doppler analysis and genetic assessment is needed. Genetic consult and maternal testing best done prior to pregnancy since work up may take too much time to offer prenatal diagnosis. The diagnosis of EDS type IV was confirmed by electron microscopic examination of a skin biopsy. Vascular EDS carries a high risk of maternal morbidity and mortality [(13)] which is estimated to be as high as 25%, predominantly due to arterial rupture. [(12)] The risk of pregnancy-related complications is increased in women with vascular EDS compared with the general population; however, survival data indicate that pregnancy does not appear to affect overall mortality compared with nulliparous women with vascular EDS. [(14)] Currently, there are no guidelines for pregnancy management in women with vascular EDS, and development of standards for care is challenged by the rarity of the condition and the lack of evidence-based risk information. [(14)] There is no agreed consensus on the mode or timing of delivery but a literature is supportive of delivery by cesarean section at 32 weeks. [(15)]

Patients with internal carotid artery dissection may present to the emergency department with various non-specific complaints and high index of suspicion is needed for diagnosis. If internal carotid artery dissection is included in the differential diagnosis, the possibility should be pursued until it is clinically ruled out. Initial CT of head is usually warranted, depending on the patient's presentation. If the scan yields negative results or the findings do not correlate with the patient's symptoms and signs, it should be followed up by a more definitive imaging modality, such as magnetic resonance angiography (MRA), CT angiography (CTA), or conventional angiography (depending on institutional preferences).

The mainstay of treatment of extra-cranial carotid artery aneurysm is surgical repair. The surgical repair entails the resection of that portion of the carotid artery that is involved with the aneurysm, followed by a bypass. There is no general consensus regarding optimal management of internal carotid artery dissection, but the choice among medical, endovascular, and surgical options may depend on the type of injury, the anatomic location, the mechanism of injury, coexisting injuries, and comorbid conditions. [(16)]

CONCLUSION

The risk of pregnancy-related complications is increased in women with EDS. Close monitoring of mother and child in a specialist unit with involvement of a multi-disciplinary team is necessary. Obstetric management plans should be made on a case-by-case basis, taking into account the diagnosis of type and severity of EDS, to optimize maternal and neonatal outcomes.

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How to cite this article: Saleh M, Mirzamoradi M, Gargari SS et al. Organic matter reduction by adsorption: Pregnancy-related death in a woman with vascular Ehlers-Danlos syndrome; dissection and rupture of internal carotid artery aneurysm accompanied by preeclampsia. Galore International Journal of Health Sciences & Research. 2018; 3(1): 5-10.

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