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Case Report

Remote Vascular Catastrophes after Neurovascular Interventional Therapy for Type 4 Ehlers-Danlos Syndrome

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Summary: Type 4 Ehlers-Danlos Syndrome (EDS 4) is the most malignant form of Ehlers-Danlos Syndrome, often accompanied by neurovasacular complications secondary to vessel dissection or aneurysms. The fragile nature of connective tissue in these patients makes exovascular and endovascular treatment hazardous. We have treated four patients with EDS 4 over the last 8 years by using neuroendovascular procedures. Two of these individuals suffered remote vascular injuries around the time of their procedures and ultimately died. The circumstances surrounding their deaths will make up the body of this report.

Ehlers-Danlos Syndrome type 4 (EDS 4) is a malignant connective tissue disorder characterized by spontaneous visceral and vascular injuries. Because of the fragile nature of the EDS 4 patient's tissues, such injuries can be difficult to repair. Herein we elucidate the potential morbidity and mortality of attempted therapies and the malignant nature of this disease process. Any plan for treating patients suffering from EDS 4 must take into consideration these potential hazards.

Case Reports

Case 1

An 18 year-old-woman with EDS 4 presented with left orbital proptosis and chemosis. MR imaging revealed a dilated left superior ophthalmic vein (SOV). A cerebral arteriogram confirmed the presence of a left direct carotid cavernous fistula (DCCF). Although the patient was under systemic heparinization and general anesthesia, the fistula was occluded by advancing a 0.018-in microcatheter across the hole in the internal carotid artery (ICA) and into the SOV. Guglielmi detatachable coils (GDCs) (Target Therapeutics, Natick, MA) were used to pack the vein and occlude the fistula. A diagnostic arteriogram at the conclusion of the procedure showed left ICA occlusion at the level of the anterior clinoid process. A right ICA arteriogram opacified the left middle cerebral artery via the anterior communicating artery. An unsuccessful attempt was made to dilate the left supraclinoid carotid artery by using an angioplasty balloon. After awakening from anesthesia, the patient remained on heparin, and the results of her neurologic examination were normal.

Forty-five minutes after her transfer to the intensive care unit (ICU), the patient vomited violently and complained of sudden, severe neck pain. The left side of her neck appeared swollen. An emergent arteriogram was performed, which revealed a new, left, cervical ICA dissection without pseudoaneurysmal formation or contrast extravasation. The left supraclinoid ICA was now patent. The patient returned to the ICU and heparinization was continued.

Three days later, a follow-up arteriography was performed to view the ICA dissection. At the conclusion of the procedure, the patient vomited violently and became hypotensive and tachycardic. After volume resuscitation and intubation, an abdominal CT scan was performed to confirm a retroperitoneal hemorrhage or hollow organ rupture. CT showed diffuse retroperitoneal and abdominal bleeding. The patient was brought immediately to the operating room where a laparotomy revealed a ruptured splenic artery. The vessel was ligated, and hemostasis ultimately was achieved.

During the next 18 days, the patient began to make a gradual but slow recovery, despite numerous postoperative complications. The day she expired, she was awake and alert, conversing with her parents. She suddenly screamed and became unresponsive, with hypotension and tachycardia that progressed to electrical activity with no pulse. Despite attempts at resuscitation, she died. Postmortem examination revealed a ruptured cardiac posteromedial papillary muscle.

Case 2

A 40-year-old woman with EDS 4 presented with a left DCCF. Embolization of the DCCF was performed successfully via a venous route. After embolization, the patient became tachycardic, with a hematocrit of 21%. Pelvic CT revealed retroperitoneal blood likely secondary to pelvic vein rupture. Conservative management with transfusions and bed rest led to complete recovery.

Seven years later, the patient returned, complaining of headache. Examination revealed a loud, left, cervical bruit. Repeat arteriography revealed cervical vertebral artery arteriovenous fistula (AVF), with the fistula site at approximately the C5 level. The patient was asymptomatic, yet returned 1 month later with the new complaint of a right-sided rushing sound. Repeat arteriography now showed a new right DCCF. Minimal anterior drainage left the patient's eye normal and intraocular pressure was less than 20. Venous drainage to the basal vein of Rosenthal, however, put the patient at increased risk for subarachnoid hemorrhage, and treatment was planned for the near future. Four days later, the patient arrived at the hospital with complaints of nausea, emesis, vertigo, and diplopia. Ce-

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rebral MR imaging, including diffusion studies, revealed no posterior fossa parenchymal infarcts. Repeat arteriography, however, revealed a new right vertebral artery AVF. Of note, catheterization of this vessel had not been performed at the time of the previous arteriogram. It was assumed that the patient was now symptomatic from posterior fossa ischemia on the basis of bilateral vertebral artery steal secondary to the bilateral vertebral artery AVFs and the right DCCF, which limited posterior communicating artery perfusion. Working under this assumption, a therapeutic interventional procedure was planned.

Two days later, the patient underwent stenting of the left vertebral artery performed using a Wallstent (Schneider USA, Minneapolis, MN) placed across the fistula site. Catheterization of the fistula was then performed through the stent interstices by using a 0.018-in microcatheter. The venous side was subsequently filled with GDC coils. At the conclusion of the embolization, flow through the left vertebral artery and basilar artery appeared increased, and flow at the fistula site appeared much reduced. We then placed a stent across the numerous small fistula sites involving the right vertebral artery.

When the patient awoke from anesthesia, the results of her neurologic examination were normal. Approximately 20 minutes later, while in the ICU, she became tachycardic and hypotensive. She was immediately returned to the angiography suite where a diagnostic arteriogram showed a right iliac artery perforation with active retroperitoneal bleeding. A wire was advanced beyond the perforation and an Olbert balloon (Meditech, Watertown, MA) was advanced across the bleeding site and inflated. The bleeding was now arrested. Our vascular surgery consultant felt that the patient required iliac artery ligation, which would likely result in amputation. We decided to place a Wallstent across the bleeding site in the hope that the stent would add strength to the vessel wall and allow for some type of direct surgical repair. After stent placement and balloon reinflation, the patient was transferred to the operating room.

Surgical exposure of the iliac artery was accompanied by significant venous bleeding because of the fragility of the patient's tissues. The iliac artery ultimately was identified and ligated. During the exposure, it was clear that in addition to the initial vessel blowout, the proximal stent had also perforated the vessel. The patient ultimately suffered excessive blood loss in the ICU shortly after surgery and died.

Discussion

The description by van Meckeren in the late 1860s of individuals with extraordinary skin elasticity may represent the first description of Ehlers-Danlos syndrome (1). In 1936, Weber formally described the Ehlers-Danlos syndrome (2). In the 1960s, the vascular component of this disease was recognized, and Andras Barbaras identified EDS 4 in 1967 (3). This subcategory remains the most malignant form of EDS because of the high likelihood of developing spontaneous blood vessel rupture from aneurysms, dissections, and transmural tears. Other fatal complications of EDS 4 include hollow viscera rupture, mitral valve prolapse, and spontaneous pneumothorax (4, 5).

There are currently nine types of EDS. EDS 4 comprises 4% of all EDS cases. Its biochemical cause rests upon an abnormality in the gene that codes for the pro L1(III) chain in type 3 collagen, which is a major component of distensible tissues such as skin, blood vessels, and hollow viscera. The responsible allele, COL3A1, is located on chromosome 2. Although EDS 4 may be passed on in an autosomal dominant fashion, 50% of cases are secondary to spontaneous mutations (4, 5).

From a structural standpoint, vessels in EDS 4 have reduced total collagen content, thin walls with irregular elastic fibrils, and reduced cross-sectional area. Each of these abnormalities predisposes patients to aneurysms, dissections, spontaneous ruptures, and fistula formation (4).

A number of authors have described neurovascular complications of EDS 4 (4, 6–15). North et al (4) reviewed 202 patients with EDS 4, 19 of whom (9.4%) had cerebrovascular complications that included fistulas, aneurysms, and dissections. Debrun et al (6) and Graf (9) reported three and two cases of spontaneous DCCF, respectively. Halbach et al (11) reported on four patients with EDS 4 in their series of 212 patients with DCCF.

Almost all reports of patients with symptomatic EDS 4 refer to the danger inherent in performing angiographic procedures through fragile vessels. In Freeman et al's series (16), 18 patients underwent angiography with a 22% major complication rate and 5.6% death rate. Schievink and colleagues (14) reported a 35% morbidity rate and 12% mortality rate with diagnostic angiography, and a 17% death rate as a result of interventional therapy. Halbach et al's series of four EDS 4 patients with DCCF had a 50% major morbidity rate and 25% mortality rate (11). In 1967, Schoolman and Kepes (15) reported the first case of bilateral DCCF and EDS 4. Immediately after angiography, the patient developed chest pain and died secondary to an intimal tear of the ascending aorta. One of two patients reported by Graf in 1965 died secondary to cardiac rupture (9). The other suffered significant postoperative puncture-site hemorrhage. Because of the dangers inherent to vessel manipulation and puncture in these patients, it is best to use noninvasive imaging methods whenever possible, such as CT and MR angiography, and to decide upon the need for treatment based upon the severity of a patient's symptoms.

Our two cases of remote vascular catastrophes occurring after what appeared to be successful neuroendovascular therapies, elucidate the fragile nature of EDS 4 patients. In the first case, the splenic artery and cardiac papillary muscle ruptures were unrelated to the procedure itself, although Valsalva maneuvers during postanesthesia retching may have contributed to rupture of a splenic artery aneurysm. In the second case, the iliac artery was likely weakened by repeated passing of wires and catheters through the femoral artery sheath en route to the vertebral arteries. It is clear from the vascular surgery literature that, once a peripheral vessel ruptures, repair is difficult, if not impossible. In 1987, Cikrit and Miles (17) reviewed the available cases in the English-language medical literature and found that aortic rupture or rupture of major vessels was uniformly fatal. Bergqvist (18) seconded this finding and made recommendations regarding appropriate vascular surgical techniques to be used in

the event of the need for surgical repair or ligation of involved vessels. The author emphasized the frequent futility in trying to salvage EDS 4 patients once major vessel injuries occur and recommended that diagnostic procedures requiring arterial puncture be avoided except in extreme circumstances. When injuries do occur, he suggested nonsurgical therapy, if possible. In both of our cases, we tried to follow the admonitions of Bergqvist's and others. Symptomatic fistulas, however, made treatment necessary. Perhaps, with the development of improved stents, endovascular management of iatrogenic or spontaneous vessel ruptures will be possible when conservative measures fail.

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