Spontaneous Multiple Arterial Dissections Presenting With Renal Infarction and Subarachnoid Hemorrhage in a Patient Under Treatment for Infertility

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A 36-year-old woman developed multiple spontaneous arterial dissections in both renal arteries, the carotid artery, superior mesenteric artery, and vertebral artery, but not the aorta, and she suffered a renal infarction and subarachnoid hemorrhage within a short period of time. She had been undergoing frequent injections of human chorionic gonadotropin and human menopausal gonadotropin, together with oral estrogen therapy, during a 5-year infertility treatment regimen. As she had no other history of any disorder affecting the arterial walls, this therapy is suspected to have caused the multiple arterial deformities. Although cases of isolated arterial dissection are occasionally reported, it is rare for multiple dissections and serious symptoms to occur simultaneously. (Circ J 2005; 69: 368–372)

Key Words: Arterial dissection; Human chorionic gonadotropin (hCG); Human menopausal gonadotropin (hMG); Renal infarction; Subarachnoid hemorrhage

A rterial dissection is defined as a dissection of the sub-intimal–medial or medial–adventitial area of the vessel, accompanied by an intimal tear. The etiology of arterial dissection includes atherosclerosis, trauma, iatrogenic causes, pregnancy, fibromuscular dysplasia, inflammatory diseases, connective tissue diseases, and other congenital disorders of the vascular wall. It mostly occurs in the carotid and renal arteries, rarely in the coronary and visceral arteries, and may or may not include aortic dissection.1–3 Arterial dissection usually results in an infarction and bleeding, but is occasionally asymptomatic. We report a case of multiple spontaneous arterial dissections in various arteries without aortic dissection in a female patient undergoing treatment for infertility.

Case Report

A 36-year-old woman was referred to hospital in October 2001 with an acute onset of left flank pain. She had nausea and was vomiting by the time she arrived at the emergency room and had never before experienced these symptoms nor had she eaten any raw food during the past few weeks. There was no history of abdominal trauma, connective tissue disease, vasculitis, or infection. However, she had been undergoing frequent injections of human chorionic gonadotropin (hCG) and human menopausal gonadotropin (hMG) during the past 5 years, in addition to oral estrogen therapy. Her family history did not include Ehlers-Danlos syndrome or hereditary abnormalities of connective tissue.

Upon examination, her temperature was 38.5°C and her blood pressure was 134/82 mmHg. She had a moderate tenderness in the left costovertebral angle. Abdominal bruits were not heard. Although a skin biopsy was not performed,

Fig 1. CT scan after intravenous infusion of contrast material shows low-density areas in the upper (a, arrows) and lower (b, arrows) poles of the left kidney. The scan was performed on the same day as the onset of left flank pain. The right kidney appears to be intact.
her skin appeared normal without any hyperelasticity or abnormal lesion. None of her joints was hypermobile. Urinalysis revealed more than 100 red blood cells and 4–5 red cell casts per high-power field. Laboratory tests revealed that the white-cell count was 11,000/mm³ with a normal differential count, the eosinophil count was 110/mm³, lactate dehydrogenase (LDH) concentration was 1,331IU/L, aspartate aminotransferase (GOT) was 57IU/L, and C-reactive protein was 12.6mg/dl. The serum creatinine concentration was normal and plasma renin activity was slightly elevated to 4.9ng/ml per h in the supine position. The coagulation time was also normal. The anti-nuclear antibody and lupus anti-coagulant were negative. A body computed tomography with a contrast media infusion was performed, which revealed low-density areas in the upper and middle poles of the left kidney (Fig 1). The patient was diagnosed with renal infarction and admitted to hospital. A daily injection of 10,000IU of heparin sulfate was immediately begun.

On the third hospital day, the patient underwent abdominal aorta arteriography, which revealed that both renal arteries had been dissected and dilated, but there were not any abnormal findings of the aorta, such as aneurysm, aortitis, or atherosclerosis (Fig 2). Selective renal arteriography confirmed the dissections of the bilateral renal arteries and the diagnosis was left renal infarction with hypoperfusion of the upper pole of the left kidney. A thrombus appeared to be present at the beginning of the
distal end of the dissection of the left renal artery, and flap formation was discovered in the same area (Fig 3). Therefore, the occlusion of the renal artery by the thrombus and the acute hemodynamic deterioration caused by dissection had resulted in renal infarction. Thrombus and flap formation were also evident in the distal area of the right renal artery (Fig 4). Typical findings of fibromuscular dysplasia, such as strings and beads, were not detected. The radiological diagnosis was bilateral dissection of the renal arteries. In order to rule out the possibility of ischemic colitis, arteriography of both the celiac and superior mesenteric arteries was conducted, which revealed dissection of the superior mesenteric artery with evidence of an intimal flap (Fig 5). After the examination, the patient’s blood pressure gradually elevated to 160/80 mmHg.

On her fourth day in the hospital, the patient felt severe nausea with a headache and she abruptly lost consciousness. Cardiovascular monitoring showed cardiopulmonary arrest, and she was immediately intubated and placed on mechanically controlled ventilation. Intravenous dopamine was administered to support her cardiac function even though she was in a coma. A brain CT revealed a subarachnoid hemorrhage and cerebral angiography showed dissection of the right vertebral artery with an intimal flap and thrombus formation in the false lumen (Fig 6). The extravasation of contrast media from the false lumen and the presence of no other abnormalities, such as an aneurysm, in any other part of the cerebral arteries lead to the conclusion that a dissection of the vertebral artery was the origin of the subarachnoid hemorrhage. The patient then underwent intravascular embolization to prevent additional bleeding, but as of December 2002, the patient has remained in a coma in the intensive care unit.

Discussion

Several reports regarding isolated instances of renal arterial dissection have documented the existence of additional vessel complications at the time of the necropsy. Edwards et al reported 2 cases of additional dissection of the hepatic and splenic arteries and the superior and inferior mesenteric arteries complicating renal arterial dissection; however, the final diagnoses were made during the autopsy. It is noteworthy that one of those 2 patients died of a subarachnoid hemorrhage. Multivessel complications and dissections have been reported in fibromuscular dysplasia, but the present case did not show the typical angiographic signs of it. There also reports connecting multiple arterial

Fig 4. Selective right renal arteriogram shows dissection of the main branch artery to the upper pole with the intimal flap and thrombus formation in the false lumen. Renal perfusion appears to be intact.

Fig 5. Selective arteriogram of the superior mesenteric artery shows dissection with an intimal flap formation (a). (b) Magnified image of the dissection.
dissections with pregnancy and some connective tissue diseases. Hartman et al have reported cases of the discovery at the time of necropsy of aortic, coronary, and renal artery dissection associated with pregnancy. Witz et al reported multiple aneurysmal lesions and dissections of the right femoral artery in a young male with type IV Ehlers-Danlos syndrome, which was complicated by aneurysmal dilatation of the left renal artery. The present case is rare because the multiple spontaneous arterial dissections presented with various symptoms during a short period of time, and all were diagnosed almost simultaneously by angiography before the necropsy. However, we could not determine when the dissections had occurred these vessels and therefore we cannot rule out the possibility that these dissections had been previously asymptomatic.

The diagnosis of this case merits comments. A multi-vessel complication implies the existence of some systemic disorder or predisposing hemodynamic factors, but the present patient did not have any etiological diseases such as connective tissue disease or congenital disorders of the vascular wall. One of the plausible diagnoses for this case is segmental mediolytic arteriopathy (SMA), which is a rare, non-inflammatory, non-atherosclerotic arteriopathy that involves the splanchnic and renal arteries. Other similar cases concerning multiple, simultaneous dissecting aneurysms have been reported in recent years. In one case, the vessels involved were the vertebral, internal carotid, superior mesenteric, renal, and external iliac arteries and the patient died from a subarachnoid hemorrhage. Although we had no histopathological evidence of SMA, the rapid progressive clinical course and multi-vessel complication implies its possibility. Several recent studies have pointed out that abnormalities of α1-anti-trypsin (A1-AT), a type I collagen, may be the underlying cause of arterial dissection. A1-AT is a circulating serine proteinase inhibitor of the proteolytic enzymes that contribute to the maintenance of connective tissues and its deficiency is a genetic disorder that may result in degradation of the arterial wall. It ranges from the severe form with low circulating concentrations at 10% of normal in homozygous patients to moderately low concentrations at 60–70% normal in heterozygous patients. Vila et al recently showed that A1-AT plasma concentrations less than 90 mg/dl were associated with spontaneous cervical artery dissections regardless of age, sex, or vascular risk factors. The family history of the present patient does not support this diagnosis, but measurement of her serum concentration of A1-AT and genetic diagnosis may have been helpful. The differential diagnosis includes any abnormalities in the type I collagen molecules, such as the defect of fibrillin in Marfan syndrome, the COL3A1 gene in Ehlers-Danlos syndrome type IV, and lysyl hydroxylase in Ehlers-Danlos syndrome type VI. However, all have typical findings of the skin and the body structure and could be ruled out in the present case because of the patient’s history and physical examination. Mayer et al reported one case of spontaneous multi-vessel cervical artery dissection in a patient who had a mutation in the type I collagen gene and no family history of arterial dissection, and that case can be considered as a mild phenotypic variant of osteogenesis imperfecta, which should be also included in the differential diagnosis of the present case. Another possible diagnosis is eosinophilic arteritis, which is also complicated by multiple arterial dissections but is unlikely in the present case because the signs and symptoms of chronic systemic inflammatory disease were absent before the onset of renal infarction, and because eosinophilia did not occur during the clinical course.

The present patient had been undergoing treatment with hCG and hMG to induce ovulation and this therapy is often accompanied by side effects because of the increased estrogen concentration. We assume that the therapy played a role in pathogenesis of the arterial dissections because it has been reported that coronary artery dissections occur in pregnant women are caused partly by the high estrogen concentration, which can induce morphologic changes of the vessel wall or alterations of connective tissue. Another possible explanation for pregnancy-associated arterial dissection is degradation of the vessel wall by proteases released from eosinophils. Because similar humoral changes might have existed in the present patient, and other definite factors involving vascular complication could not be identified, the etiology of the multiple dissections is ascribed to the high estrogen concentrations induced by ovulation therapy. We also hypothesize that the dissections might have resulted from decidualization by some cell type within the vascular tissues; that is, the aggressive therapy may have induced some estrogen-receptor rich cells within the vascular tissues that promoted formation of decidua that fell off after the estrogen drop during the course of the infertility therapy. We do not have definite...
evidence, such as pathological findings or measurement of the systemic estrogen concentrations, to support these 2 hypotheses, but they deserve some further investigation.

In the current case, the initial symptom of the dissection was a renal infarction. The usual clinical manifestation of renal artery dissection is the sudden onset of severe, persistent, and poorly controlled hypertension. The patient presented with the usual symptom, as well as sudden onset of flank pain, nausea, vomiting, peripheral leukocytosis, and increased levels of LDH, GOT, and alanine aminotransferase, although she was only hypertensive after the onset of renal infarction and in fact had been hypotensive rather than hypertensive. This implies that the renal perfusion had been sufficient and did not raise the plasma renin concentration. The selective renal arteriogram of both renal arteries showed thrombus formation, which in part caused the infarction in the left kidney. Although the laboratory findings did not indicate a prolonged coagulation time, the extended therapy with hCG and hMG for infertility may have led to a state of hypercoagulation that may also have lead to the renal infarction by thrombosis despite a normal coagulation time at the time of hospitalization.

In conclusion, we report a case of multiple spontaneous arterial dissections without aortic complication, presenting as simultaneous renal infarction and subarachnoid hemorrhage. Therapy with hCG and hMG for infertility is suspected to be the cause of the patient’s multiple arterial deformities. Although cases of isolated arterial dissection are occasionally reported, this case is rare because the multiple dissections presented concurrently with serious symptoms.

References