Case Report

Ehlers-Danlos Syndrome Type IV in a Young Man

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ABSTRACT. We describe a 19-year-old male, with a family history of both systemic lupus erythematosus and Marfan syndrome, who had a history of bruising easily and skin lesions since childhood. He had a spontaneous colonic perforation at the age of 16 years, followed 3 years later by sudden development of bilateral renal infarctions and hypertension, which on angiography were found to be due to dissection of both renal arteries. Transient elevations of 3 types of antiphospholipid antibodies (aPL) were detected. Skin biopsy showed typical elastosis perforans serpiginosa. The history together with the generalized connective tissue phenotype, histology, and angiographic features combined to establish a diagnosis of vascular Ehlers-Danlos syndrome, type IV; the body habitus resembled the phenotypically–related condition of Marfan syndrome. The coincidental finding of transient aPL elevations combined to make this a difficult diagnostic and clinical management problem. (J Rheumatol 2006;33:2091–6)

Key Indexing Terms:
EHLERS-DANLOS TYPE IV
COLONIC PERFORATION
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The Ehlers-Danlos syndrome (EDS) is a family of heritable disorders comprising 9 types. The vascular type (EDS type IV) is a rare autosomal inherited disorder of connective tissue resulting from a mutation of the C0L3AI gene encoding type 111 collagen. We describe a young man with this condition, who presented with bilateral renal infarctions complicated by hypertension, and who posed considerable diagnostic problems because of a high C-reactive protein level and elevated von Willebrand factor antigen, which initially suggested a vasculitic pathology. This was further complicated with demonstration of positive antiphospholipid antibodies (aPL). The diagnosis of EDS of the vascular type (type IV) only became clear after extensive radiological investigations and skin biopsies had been performed.

CASE REPORT

The patient was a 19-year-old Caucasian male. His family history was significant in that his father had recently been diagnosed with systemic lupus erythematosus and a maternal uncle had the Marfan syndrome and had suffered a spontaneous pneumothorax.

Since the age of 10 years he had had skin fragility with easy bruising. There was a 10 year history of skin lesions, later identified as elastosis perforans serpiginosa affecting the upper arms, forearms, and thighs. He had minor discomfort of the feet on exercise. In November 2000 he spontaneously perforated his sigmoid colon and required a temporary defunctioning colostomy. No histology of the resected area or supplying vessels was performed at that time.

In May 2003 he suddenly developed bilateral loin pain. At that time, all pulses were palpable and equal and no bruits were audible. A computer tomography (CT) scan showed thrombosis of both renal arteries with well defined segmental infarctions of both kidneys. Serum creatinine was elevated at 135 mmol/l but urine flow was good. He was fully anticoagulated with heparin and subsequently with warfarin. General clinical examination showed long, thin fingers and bilateral pes cavus and quite abnormally long toes, reminiscent of Marfan syndrome. However, there was no high arch palate and ectopia lentis was not present. Additionally there were facial signs of EDS type IV, with large eyes, a slightly thin nose, and tubeless ears, together with widespread elastosis perforans lesions forming characteristic concentric circles over the forearms, elbows, popliteal fossae, shins, and upper thighs posteriorly (Figure 1A) confirmed by the histology (Figure 1B). There was nail dystrophy, affecting the thumbs particularly.

There was an audible midsystolic click and late systolic murmur of mitral valve prolapse, later confirmed by echocardiography. He was hypertensive (160/110 mm Hg).

Blood tests showed a highly elevated C-reactive protein (CRP) of 129.2 mg/l, a normal blood cell count and differential count, slightly elevated rheumatoid factor of 18.80 IU/ml (normal 0–15 IU/ml), and negative antinuclear antibodies and negative antineutrophil cytoplasmic antibodies (ANCA); but an aPL screen revealed positive antibodies to cardiolipin (IgG) of 16.34 GPL U/ml (normal 0–9), elevated anti-$ß_2$-glycoprotein antibodies (IgG) of 35.8 arbitrary ELISA units (AEU)/ml (normal 0–9), and elevated antibodies to prothrombin (IgM) of 22.8 AEU/ml (normal 0–12). Because of suspected polyarteritis nodosa when he presented with loin pain, he was given intravenous cyclophosphamide and parenteral steroids, followed by oral prednisone in reducing dosages. He was referred to us when the results of the phospholipid screen became available. By then the von Willebrand factor (vWF) antigen and CRP had returned to normal levels. In view of the findings

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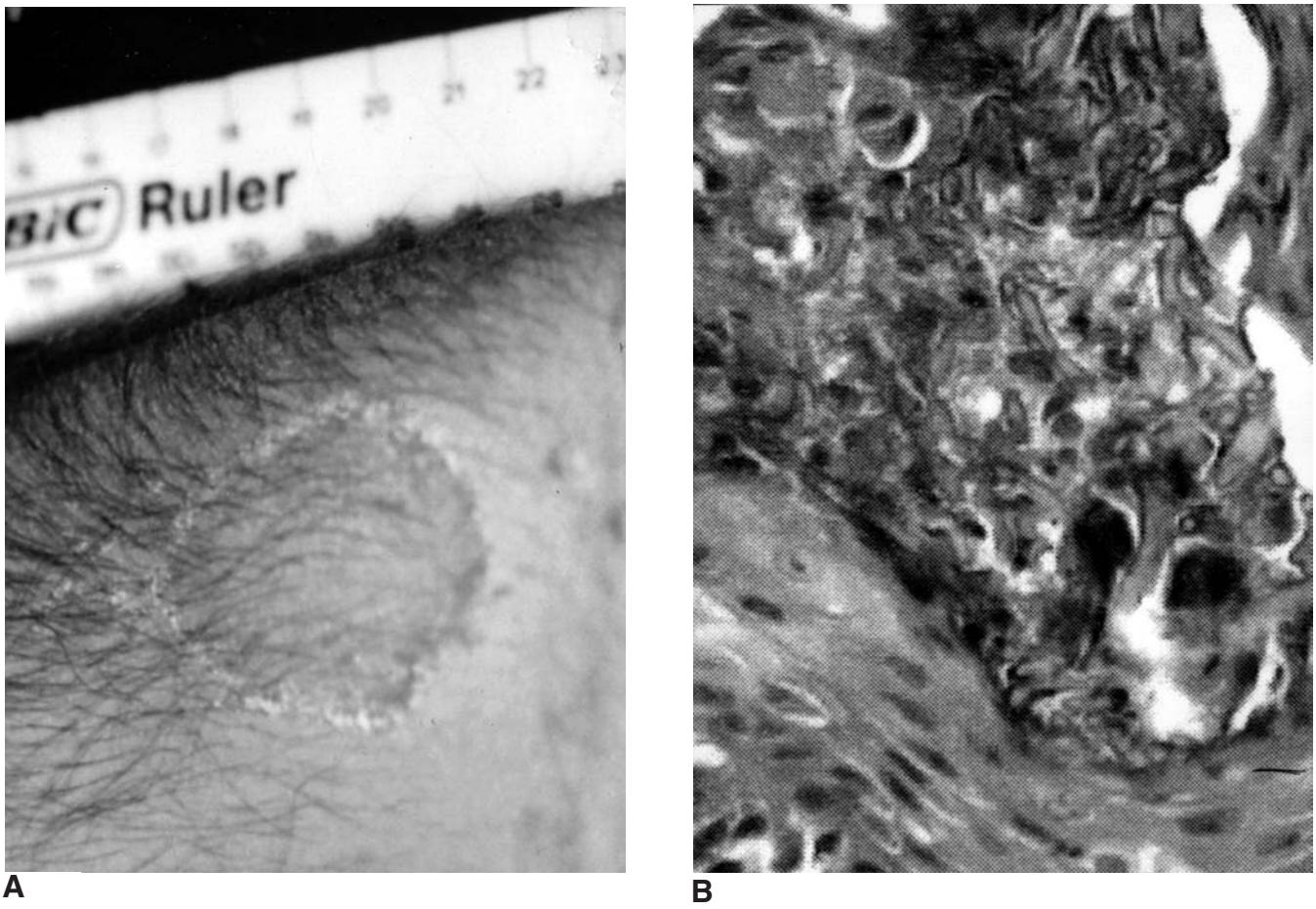

Figure 1. (A) Skin lesion of elastosis perforans serpiginosa of the upper thigh. (B) Histology of typical skin lesions.

of positive antibodies to phospholipid, oral steroids were gradually withdrawn.

Abdominal aortography and bilateral selective renal arteriography were carried out September 9, 2003, and showed 2 arteries supplying each kidney. The main trunks of the larger vessels on each side demonstrated dissection. On the right side (Figure 2) the proximal half of the "false" lumen had thrombosed and a jet of contrast medium was seen between the true lumen and the distal segment of the false lumen. The intrarenal vessels distal to the dissected artery appeared normal at that time. On the left side (Figure 3), the dissection flap was easily identified and a false lumen was seen as a grossly dilated, blind-ended vessel.

A CT scan (Figure 4) October 7, 2003, showed extensive bilateral renal infarcts.

In view of these findings and prior to the diagnosis of EDS, a decision was made to occlude the dissection by means of a covered stent (Figure 5). This was carried out using a J0 coronary stent on November 7, 2003. The covered stent successfully isolated the false lumen. This was confirmed by the disappearance of the jet and non-filling of the distal half of the false lumen due to thrombus. A further CT scan January 25, 2004, showed the rapid development of neo-intimal hyperplasia within the stent, narrowing the vessel by about 50% (Figure 6). It was noted that there was also a fairly marked fusiform dilatation of the inferior branch of the main renal artery, which was not present on the original angiogram. For these reasons, the intention of introducing a stent across the dissection on the left side was abandoned.

The patient was maintained taking only anticoagulants thereafter, as it was felt that the initial phospholipid positivity might have contributed to the thrombosis in the false lumen. Once a diagnosis of EDS was made, however, he was advised to discontinue his anticoagulation. Blood pressure control was good with a combination of amlodipine (Norvasc; 2.5 mg bid) and a beta-blocker, bisoprolol (Concor; 2.5 mg bid). The patient traveled to London, UK, and was examined by Dr. Pope, who confirmed the diagnosis. Unfortunately, collagen type-111 protein analysis from cultured fibroblasts and studies of the COL3A1 gene could not be performed because of financial constraints. However, because of the clinical history and clinical phenotype, which included the facial and cutaneous features, arterial dissection, the history of spontaneous colonic perforation, in addition to the distinctive skin histopathology and angiographic findings, a diagnosis of vascular EDS type IV was made and confirmed by several clinicians.

DISCUSSION

This patient had an unusual combination of pathologies that gave rise to considerable diagnostic and therapeutic problems during the first months after presentation. The high CRP was suggestive of vasculitis, and the elevation of vWF antigen seemed to confirm this. The family history of SLE and positive aPL initially then suggested an antiphospholipid syndrome, possibly reinforced by the thrombosis in the "false" lumen, which had developed on the right side. He had a history of spontaneous perforation of sigmoid colon at the age of 18 years. The etiology of this event, unusual in a young

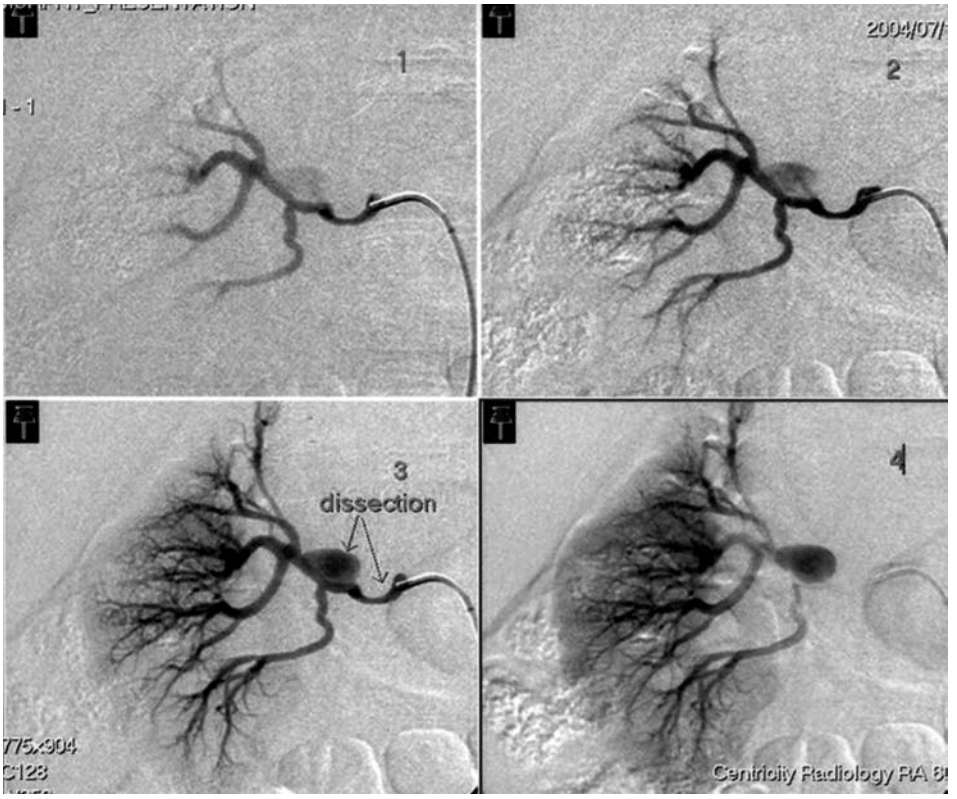

Figure 2. Right renal angiogram shows dissection of the main renal artery. The proximal half of the false lumen is thrombosed, and the distal half remains patent. Note the jet of contrast medium between the true and false lumens.

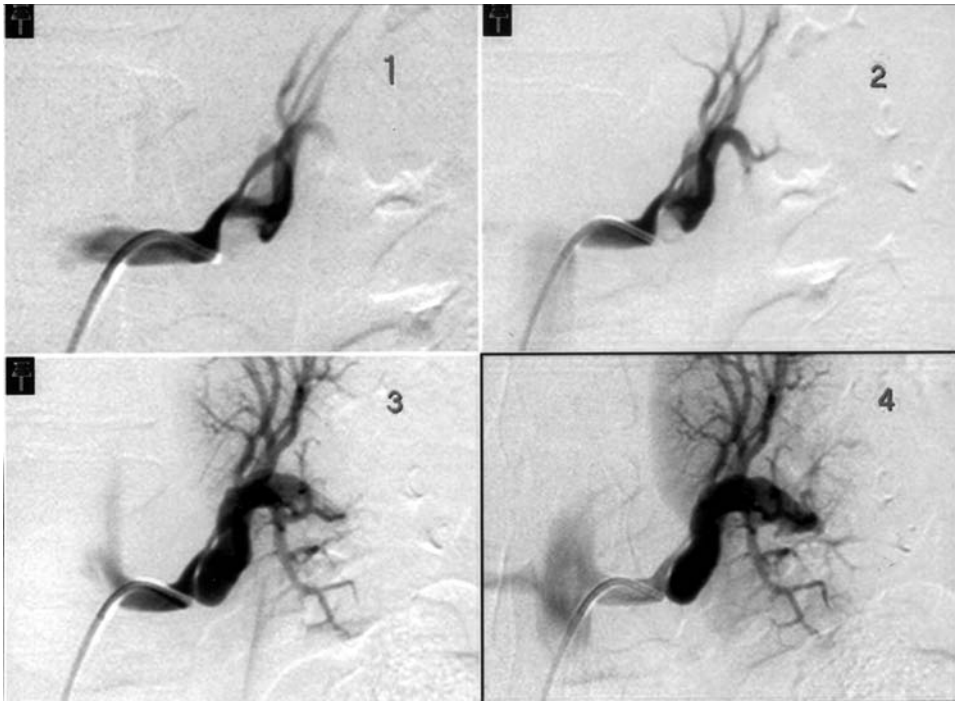

Figure 3. Left renal angiogram shows dissection of the left renal artery. The wide, blind-ending vessel is the false lumen.

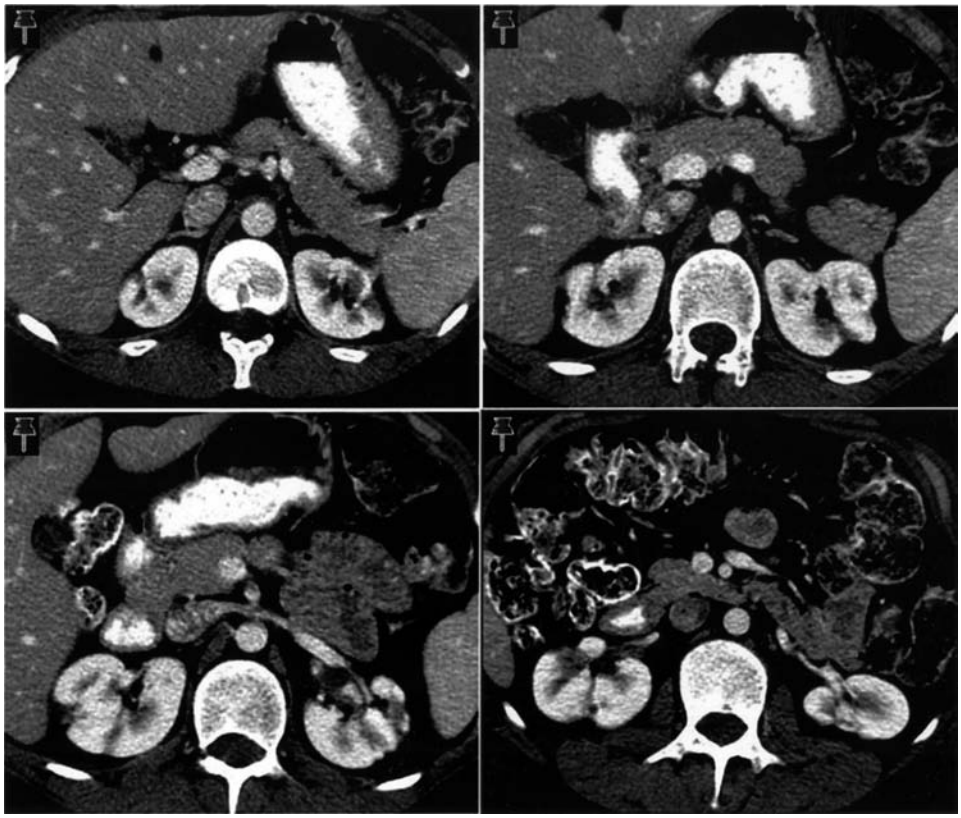

Figure 4. CT scan shows bilateral renal infarction.

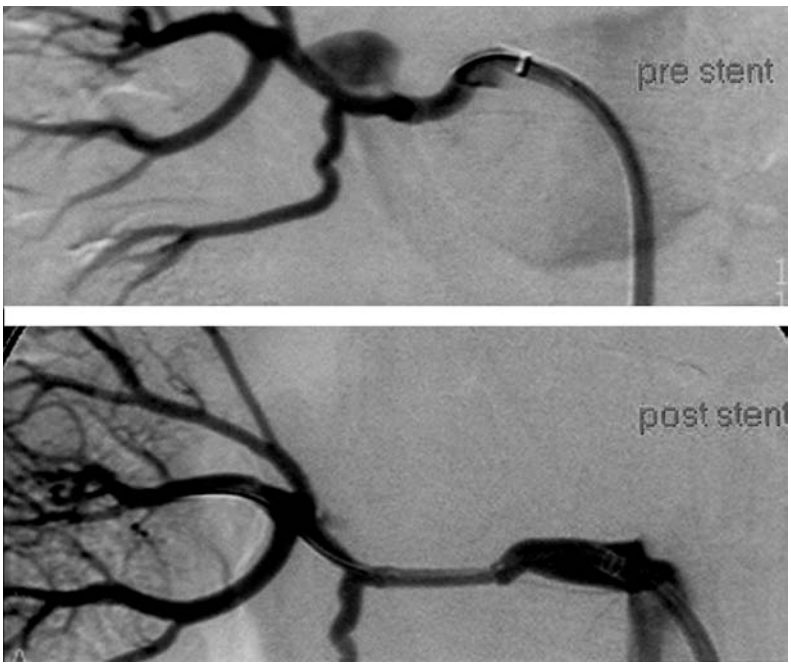

Figure 5. Right renal angiogram shows a covered stent placed in the true lumen and occluding the communication with the false lumen.

man, was unknown at the time, as histology was not performed. It was presumed to be vascular in view of the subsequent events caused by vascular occlusion affecting the renal vessels bilaterally and in keeping with the diagnosis of EDS type IV.

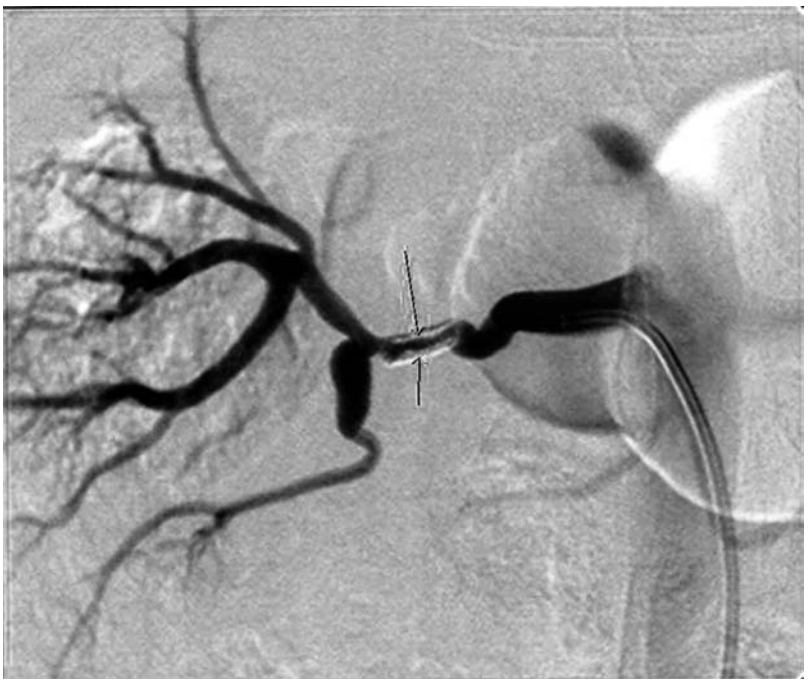

Figure 6. Three months later, angiogram reveals neo-intimal hyperplasia (arrows), narrowing the artery within the stent. Note aneurysmal dilatation of the inferior division of the main artery.

He presented 2 years later with sudden abdominal and flank pain, found to be due to multiple bilateral renal infarctions. He then developed hypertension. Radiographic investigations showed abnormalities of both renal arteries, dissection, and the appearance of a false lumen in the left main renal artery, with thrombus formation in an aneurysmal dilatation of the main renal artery. Renal artery aneurysms are not uncommon in EDS and may thrombose.

A presumed diagnosis of systemic vasculitis was made because of the combination of renal infarctions and hypertension in a young man. ANCA testing was negative, however. The first determination of the vWF antigen was negative, but subsequently became positive, and then returned to normal again. The initial negative test might have been due to the effect of high-dose steroids administered on admission.

The high CRP levels also returned to normal 7–10 days after admission and there was no sustained neutrophilic leukocytosis indicative of an active vasculitic process. He was marfanoid in appearance, with unusual skin lesions in keeping with abnormalities of his elastic tissue. He clearly did not have Marfan syndrome as such, but rather a phenotypically related condition. A diagnosis of vascular EDS type IV explained all his cutaneous, colonic, arterial, and phenotypical features.

In the arterial ecchymotic type (which our patient had), the defect affects collagen, which is most abundant in the skin, blood vessels, and gastrointestinal tract. People with this disorder develop serious vascular, intestinal, and obstetric complications[1-6]. Some 80% of patients experience one or more complications prior to the age of 40 years, spontaneous arterial, intestinal, or uterine rupture accounting for most deaths. About 25% of patients have their first complication by the age of 20 years. This risk is increased in pregnancy, labor, and in the postpartum period. Intestinal perforation, as in our patient, is less often fatal[7,8]. Affected patients who undergo surgery are at risk of postoperative arterial rupture because surgical trauma increases collagenase activity. There is extreme tissue fragility and a very high risk of massive bleeding and anastomotic disruption with attempted surgical repair[9]. There are several distinctive features: (1) Facial dysmorphism with slenderness, prominent bones, sunken cheeks with protruding eyes, often periorbital pigmentation, and fine telangiectasia of the eyelids. The nose may be thin or pinched, the lips (particularly the upper) thin or puckered. It is stated in descriptions of the condition, however, that these features of acrogeria may be absent. (2) Dermatological manifestations, with thin, translucent, and easily bruised skin, which is fragile. (3) Bruising and hematomas with papyraceous scars over the bony prominences (knees and shins). Our patient had widespread elastosis perforans serpiginosa (Figure 1), which is more common in EDS type IV than in other inherited defects of connective tissue. (4) Visceral vascular involvement of vessels in the thorax and abdomen is seen in 50% of patients, middle-size arteries being most frequently involved. Arterial rupture occurs because of the congenitally thin and fragile tissues, as well as the occurrence of hematomas at puncture sites. Young patients may suffer strokes or hemorrhage. Carotid-cavernous fistula has also been reported[10]. Dissection of arteries may be seen, and this occurred in the renal arteries in our case.

The most frequent site of intestinal perforation is the sigmoid colon, also reported in our case.

Although joint hypermobility is less impressive in this type of EDS than in EDS types I, II, VI, and VII, there may be an overlap with the benign hypermobility syndrome.

A recent comprehensive review of this condition comprising 30 years' experience with 31 patients was published in 2005[11].

The initial elevation of aPL is of great interest and may have several explanations. Antiphospholipid antibodies have been reported in roughly 8% of healthy populations, but more frequently in older people and in patients with chronic diseases[12]. Our patient's father was reported to have had SLE and therefore there could have been a hereditary predisposition for the formation of antibodies such as those directed toward phospholipid. The initial trauma of a major vascular event such as dissection of the renal arteries might have triggered the production of these antibodies because of endothelial damage in a genetically predisposed individual. Adler, *et al*[13] reported that 6.9% of younger male patients (< 50 yrs) with myocardial infarctions were found to have elevated levels of aPL, which disappeared 3 months after the acute event. They ascribed this disappearance to either absorption of the antibodies or perhaps a cyclic phenomenon known to occur with other antibody production. The disappearance of the aPL in our patient and their absence on repeated investigation following the initial traumatic event raises the question whether certain aPL may be induced by endothelial cell trauma in genetically predisposed individuals.

The initial transient elevation of vWF antigen supports the diagnosis of endothelial cell damage. The extreme elevation of the CRP may have been caused by the multiple renal infarctions. Both these elevations were originally presumed to be due to a vasculitic process by the attending nephrologist.

EDS has been reported in only a single patient with SLE and myasthenia gravis and this appears to be the only documented case of the coexistence of EDS and SLE[14].

It should be stated that had the diagnosis of EDS been made initially when the patient presented, no invasive intravascular procedures including catheterization (with or without introduction of a stent) would have been performed, as these procedures are contraindicated in EDS type IV because of the extreme vascular fragility in these patients.

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