Hypercoagulability in a patient with Marfan syndrome

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Abstract

A 39 year old man with Marfan syndrome presented with multiple pulmonary emboli and renal, hepatic, and splenic infarcts of unknown aetiology. The combination of thromboemboli and physical features initially suggested homocystinuria; however, laboratory examination showed no evidence for this disorder. Laboratory evaluation identified no coagulation abnormalities. This patient represents the unusual occurrence of hypercoagulability in a patient with Marfan syndrome.

Marfan syndrome is an autosomal dominant disorder of connective tissue defined clinically by the presence of ectopia lentis, aortic root disease, long limbed body habitus, and a positive family history.¹ Homocystinuria, a disorder commonly associated with arterial and venous thromboembolic phenomena,² has a similar phenotype and can be confused with Marfan syndrome. Although cardiovascular disease is by far the leading cause of morbidity and mortality in Marfan syndrome,³ thromboembolism has rarely been reported.⁴ Many laboratory assays are now available to help determine specific aetiologies in young patients with unexplained thromboemboli; however, some patients defy thorough investigation.⁵ We present the unusual occurrence of both arterial

and venous thromboemboli in multiple organs with no identifiable source in a patient with Marfan syndrome.

Case report

A 39 year old man was evaluated in August 1989 for episodic, crampy epigastric pain. No laboratory evidence of liver, kidney, or pancreatic dysfunction was found. Abdominal x rays, abdominal ultrasound, barium enema, upper gastrointestinal series with small bowel follow through, oesophagogastroduodenoscopy, and intravenous pyelogram were all normal except for mild antral gastritis.

In December 1989, the patient was admitted to an outside hospital with complaints of abdominal pain, malaise, and a non-productive cough of one week's duration and one day of left sided pleuritic chest pain. Chest x ray and CT scan of the abdomen and chest were normal except for a delayed left nephrogram. Over the next few days the patient became dyspnoeic and febrile to 39.4°C with worsening abdominal pain. Hypoxaemia and diffuse bilateral infiltrates on chest x ray developed. The patient was intubated, mechanically ventilated, and started on antibiotics. Echocardiogram showed a left ventricular ejection fraction of 20%, normal cardiac valves without vegetations, absence of intracardiac masses or thrombi, and a dilated aortic root and ascending aorta. Right heart catheterisation showed raised pulmonary wedge pressure. CK levels were not raised, and the electrocardiogram was unchanged. Renal and hepatic dysfunction also developed. The creatinine rose from 105 µmol/l on admission to 725 µmol/l (normal 60 to 115 µmol/l) by the fifth day in hospital, at which time haemodialysis was begun. Multiple cultures of blood and sputum were negative. On day 9 the patient became asystolic, in the setting of digoxin toxicity and hyperkalaemia, but was resuscitated. Peak creatine kinase was 2860 U/l (normal 0 to 204 U/l) with 0.046 MB fraction (normal <0.03). The patient was transferred to the University of Virginia Hospital in January 1990.

Additional history obtained on transfer included a negative personal and family history of thromboembolic problems. The patient's half brother (common mother) had died several years earlier of chronic myelogenous leukaemia. No cytogenetic studies had been performed on the brother. Later examination of

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Received for publication 16 July 1990.

Revised version accepted for publication 4 October 1990.

the patient's mother showed no features of Marfan syndrome; his father and two other sibs were described as short and stocky with no history of ocular or cardiac disease. There was no history of cigarette smoking.

On admission the patient was a tall, thin, lethargic white male. His height was 1.93 m, weight 56.5 kg, and arm span 201 cm. He was normotensive and afebrile. Fundoscopic examination showed cataracts and bilateral ectopia lentis; both lenses were displaced superiorly and nasally. A grade 2/6 aortic regurgitation murmur was present on cardiac examination. No chest wall deformities were noted; however, the extremities were long and thin and the fingers showed arachnodactyly. No striae were noted on skin examination.

Laboratory studies on transfer are shown in the table. The combination of fulminant respiratory failure and acute renal failure suggested the possibility of Goodpasture's syndrome or a vasculitis, such as Wegener's granulomatosis. Open lung biopsies of the right upper, middle, and lower lobes showed multiple thromboemboli with haemorrhagic necrosis and no evidence of vasculitis. Immunofluorescent stains excluded Goodpasture's syndrome. A CT scan of the chest and abdomen with contrast showed a 5 cm dilated aortic root and evidence of multiple hepatic, splenic, and right renal infarcts. No evidence of aortic dissection was seen. Bilateral lower extremity venograms and an inferior venocavogram with visualisation of both renal veins showed no thrombosis. Doppler ultrasound examination of the abdomen showed normal blood flow to and from both kidneys.

Additional laboratory studies included normal antinuclear antibody and rheumatoid factor antibody titres; negative HIV and hepatitis B surface antibody titres; normal plasma catecholamines; negative Ham's and sucrose haemolysis tests for paroxysmal nocturnal haemoglobinuria; and negative urine porphyrin screen. Serology for tularaemia, leptospirosis, legionella, and mycoplasma were negative. Plasma amino acid levels were normal, and a urine homocystine assay by the cyanide-nitroprusside reaction showed no evidence of homocystinuria. No evidence of an inherited or acquired thrombophilia was detected.

Laboratory evaluations.

Assay	Patient	Normal range
Haematocrit	0.25	0.40-0.52
Leucocyte count ($\times 10^9/l$)	13.8	4-11
Platelet count ($\times 10^9/l$)	113	150-450
Prothrombin time (seconds)	14	10-13.5
Partial thromboplastin time (seconds)	43.6	24-38
Blood urea nitrogen (mmol/l)	35.5	3.5-7.0
Creatinine ($\mu\text{mol/l}$)	610	60-115
Alanine aminotransferase (U/l)	96	6-65
Aspartate aminotransferase (U/l)	76	7-40

Antithrombin III heparin cofactor activity, protein C, and protein S (total and free) antigens were within the normal ranges and titres of fibrinogen/fibrin split products and anticardiolipin antibodies were not raised. The reptilase time was normal at 10.4 seconds (normal 10 to 13.3 seconds). Karyotypic analysis of peripheral blood was normal (46,XY) in all 20 cells examined.

Initial management included parenteral nutrition, mechanical ventilation, intermittent haemodialysis, and antibiotics for the possibility of sepsis. Intravenous heparin infusion was begun after pulmonary emboli were found on open lung biopsy. Hepatic, renal, and pulmonary function gradually improved. The patient was extubated and haemodialysis was discontinued. Warfarin was substituted for heparin and the patient was discharged. A repeat urine homocystine assay performed one month after the last haemodialysis treatment was again negative.

Discussion

The patient reported here presented with life threatening thromboemboli involving both the pulmonary and systemic arterial circulations, documented on open lung biopsy and by CT scanning. Thorough evaluation of the venous system and heart identified no source of the emboli. It is possible that a septal defect, such as an incompetent foramen ovale, allowed the occurrence of both pulmonary and systemic arterial emboli in this patient. The echocardiograms showed no interatrial defect, but were not performed with a contrast agent, which greatly improves the detection of these defects.

Venous thrombosis in patients with Marfan syndrome has been reported only once before. In 1968 Alarcón-Segovia *et al.*⁴ reported on a 19 year old man with bilateral renal vein thrombosis. Assays for the endogenous anticoagulants, protein C, protein S, and antithrombin III, were not available. However, the patient also had nephrotic syndrome, a disorder associated with thrombosis possibly secondary to an acquired antithrombin III deficiency. Emboli of cardiac origin may be seen in Marfan patients with endocarditis⁶; however, no valvular lesions were seen on multiple echocardiograms performed on the patient reported here.

This patient clearly fulfils the major diagnostic criteria for Marfan syndrome¹; delay of the diagnosis of Marfan syndrome in a patient of this age is not unusual.⁷ However, the initial concern in view of this patient's body habitus, ectopia lentis, and thromboemboli was the possibility of homocystinuria. Assays of plasma amino acids and urine homocystine failed to support this diagnosis.

The urine homocystine assay could potentially be affected by oliguric renal failure and produce a false negative result. Moreover, plasma amino acids are

removed by haemodialysis⁸ and raised levels of methionine and homocystine could potentially be reduced into the normal range by haemodialysis. A repeat urine assay performed when the patient's renal function had returned to normal and the patient was off haemodialysis was again negative. This repeat negative study is strongly against, but does not absolutely exclude, the diagnosis of homocystinuria in this patient.

The occurrence of thromboemboli in a relatively young patient without apparent risk factors prompted an evaluation for hypercoagulability. No evidence for deficiencies of proteins C or S or of antithrombin III was found.⁵ No dysfibrinogen, antiphospholipid antibody, or evidence of low grade disseminated intravascular coagulation was detected. Although myeloproliferative disorders can predispose to thromboembolic phenomena, no persistent rise in the leucocyte, erythrocyte, or platelet counts was noted, and all counts were normal on discharge. Less frequent disorders, including deficiency or dysfunction of plasminogen or tissue plasminogen activator, were not excluded.

The precise genetic and metabolic abnormalities in patients with Marfan syndrome are yet to be determined. The extreme rarity of reports of thromboembolic problems in these patients suggests that they

may not be at an increased risk of thromboembolism and may even be relatively protected. Further investigations into the pathogenesis and genetic origins of Marfan syndrome and hypercoagulable states, including the study of unusual patients such as the patient presented here, may lead to an increased understanding of both disorders.

Dr Humphries is supported by NIH Training Grant No 1T32AM07509.

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