Short reports

Minoxidil, hypercoagulability and thrombo-embolic disease of the lung

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Summary

Minoxidil is a potent antihypertensive agent used in the treatment of resistant hypertension. A case is presented which illustrates a probably fatal interaction between minoxidil and a coagulation disorder.

Keywords: minoxidil, hypertension, coagulation disorder

A 65-year-old man attended for a routine follow up at the hypertension clinic. He was first diagnosed in 1971. Satisfactory control was achieved in 1985 with propranolol 80 mg bid, minoxidil 40 mg once daily, nifedipine 20 mg bid and frusemide 80 mg once daily. In the past he had received hydralazine, prazosin and hydrochlorothiazide. He had not tolerated angiotensin-converting enzyme inhibitors. Chest X-ray was normal in 1987. Other than his hypertension, he had been fit and well in the past with no lung disease.

He commented that he had lost 10 kg in weight in the preceding three months. Examination revealed lymphadenopathy was present bilaterally in the posterior cervical chains and in the right supraclavicular node. A mild purpuric rash was observed on the extensor surfaces of the legs. Blood pressure was 120/96 mmHg. Right-sided heart failure was detected with jugular venous pressure elevated by 10 cm, clinical evidence of tricuspid regurgitation (prominent V waves, pansystolic murmur at the sternal edge and pulsatile hepatomegaly of 6 cm) and marked pitting oedema to mid-calf. The rest of the physical examination was unremarkable.

After bleeding excessively from a routine venepuncture, he was found to be in a state of disseminated intravascular coagulation (DIC): haemoglobin 16.3 g/dl, white blood cell count $13.3 \times 10^9/l$, platelets $100 \times 10^9/l$, INR 2.7, fibrinogen degradation products 1000 pg/l (normal < 500 pg/l), fibrinogen 4 $\mu g/l$, partial thromboplastin time 59 s (control 40 s). Urea and electrolytes were normal as was urinalysis. However, liver function tests were deranged: alkaline phosphatase 198 U/l, gamma glutamyl transferase 137 U/l and bilirubin 34 mg/l. Thyroid function tests were normal. Blood cultures and titres for bacterial, fungal and rickettsial causes of infectious endocarditis were negative. C-Reactive protein was elevated at 3.6 mg/l. Autoantibodies and

complement studies, including C3d, were normal. Chest X-ray showed cardiomegaly and a mass at the right apex. An electrocardiogram suggested left ventricular hypertrophy. Echocardiography showed paradoxical septal movement, concentric left ventricular hypertrophy, a grossly dilated right ventricle and echogenic structures on the tricuspid valve, the other cardiac valves were normal. Ultrasound of the abdomen confirmed the enlarged congested liver and demonstrated ascites with prominent hepatic veins and inferior vena cava.

Over the course of the next four days he remained asymptomatic and afebrile. Minoxidil and propranolol were stopped and captopril 6.25 mg bid was started. Nifedipine and frusemide were continued. His blood pressure remained under control. The DIC was treated with daily administration of six units of cryoprecipitate and two units of fresh frozen plasma. Despite these measures the DIC progressed. Two days after admission the indices were: fibrinogen 0.2 $\mu g/l$, fibrinogen degradation products 4000 pg/l, INR 4 and platelets $50 \times 10^9/l$. At this stage treatment of a culture-negative infectious endocarditis was started: benzyl penicillin 1.2 g bid, tetracycline 1 g bid and gentamicin 120 mg tid.

On the fourth day he became suddenly dyspnoeic and cyanosed during micturition. A diagnosis of probable pulmonary embolism was made. He recovered quickly on continuous oxygen. Four hours later he sustained a sudden asystolic arrest and was successfully resuscitated. However, shortly afterwards he sustained a fatal asystolic cardiac arrest.

Autopsy findings

Multiple pulmonary emboli of varying ages and a 3 cm well-circumscribed bronchial carcinoma at the apex of the right lung were present. There were severe pulmonary artery atheroma indicating established pulmonary hypertension. The heart was enlarged with biventricular hypertrophy and right ventricular dilatation free of thrombus. The tricuspid valve was dilated with a circumference of 14 cm (normal 11–13 cm) with numerous small, friable vegetations on the cusps. The right atrium was dilated with thrombus in the appendage. The coronary arteries were patent and there was no evidence of acute myocardial infarction. There was venous congestion of the spleen and liver indicative of right ventricular failure.

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Minoxidil: cardiovascular implications
<ul style="list-style-type: none">• contraindications: phaeochromocytoma• adverse cardiovascular effects (ECG changes: ST depression, T wave inversion)• reflex tachycardia (not controlled by β-blockade)• pericardial effusion• pulmonary hypertension• peripheral oedema and ascites• right atrial myocyte vacuolation• profound hypotension after overdose

Learning points
<ul style="list-style-type: none">• minoxidil causes right atrial dilation• minoxidil may cause pulmonary hypertension• thromboembolism may arise from the dilated right atrium which may exacerbate the minoxidil-induced pulmonary hypertension• these phenomena are potentiated in the presence of a paraneoplastic hypercoagulable state

Histology demonstrated vacuolation of the right atrial myocytes with an intact endocardium but no focal haemorrhagic lesions were present. The rest of the myocardium was normal. The tricuspid valve vegetations were composed of platelets and fibrin consistent with non-bacterial thrombotic endocarditis. There was no evidence of intravascular coagulation in any other organ. Adenocarcinoma of the bronchus was confirmed with metastases to the local lymph nodes. Examination of the bone marrow was unremarkable.

Discussion

The cause of death was multiple pulmonary emboli, originating from thrombus in the right atrial appendage, and associated severe pulmonary hypertension. The extensive recanalisation of occluded pulmonary vessels indicates longstanding pulmonary thromboembolism leading to pulmonary hypertension. However, it seems likely that the malignancy was responsible for the state of DIC.

Minoxidil is a potent antihypertensive agent which acts either on vascular smooth muscle transmembrane calcium flux or by inhibition of endothelial uridine kinase.¹ It has been shown to elicit a variety of adverse cardiovascular affects. Haemorrhagic necrosis of right atrial cardiac myocytes and papillary muscle necrosis

has been observed in dogs treated with minoxidil.^{2,3} However, the lesions have not been described in man.⁴ Vacuolation of myocytes in the right atrium of humans, as in this case, has been reported in humans treated with minoxidil.² The difference in the lesions seen at autopsy in man and those occurring experimentally in animals may be due to the 10-fold higher dose of drug/body weight ratio used in animal studies.

High right atrial and pulmonary arterial pressures have been reported during long-term treatment with minoxidil.⁵ Whether, in the present case, the pulmonary hypertension was a primary event or secondary to the thromboemboli originating from the right atrium is a matter of conjecture. However, the autopsy findings favour the latter explanation.

Our case seems to be unique in that thrombosis in the right atrium was associated with a hypercoagulable state induced by a bronchial adenocarcinoma. The importance of this case lies in the fact that demonstrable minoxidil-induced right atrial damage appears to have predisposed the patient to this complication and therefore indirectly caused his death through subsequent thromboembolic disease. Whether *in situ* right atrial thrombus is a general risk in minoxidil-treated patients who develop coincidentally a coagulation disorder is unknown. Since this problem has not been previously reported, clinicians who treat severely hypertensive patients with minoxidil should be aware of it.

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