present in previous aspirates. No organisms were cultured from the fluid. In particular, there was no evidence of tubercle bacilli which had also been looked for on several previous occasions. The predominant cell type was lymphocytic and no malignant cells were found. A pleural biopsy was obtained at the time of aspiration with normal findings.

In view of the fact that the yellow discoloured nails and the longstanding oedema of the legs, suggested an abnormality of the lymphatic system, a lymphangiogram of the left arm was performed. This X-ray confirmed a defect by showing a marked hypoplasia of the lymphatic drainage. A similar hypoplasia of the lung's lymphatic system would account for the effusions following episodes of lung infection.

Discussion

Discolouration of the nails associated with lymphatic deficiency and lymphoedema was termed the 'yellow nail' syndrome by Samman & Whyte (1964). They described thirteen cases, the oldest of whom was 65 at the time of presentation, and pointed out the characteristic features of the nails as exhibited in this case. The predominant involvement of the nails of the index finger on both hands is similar to that of the case reported by Dilley *et al.* (1968). This distribution is unexplained.

The further association of pleural effusions complicating the lymphoedema and yellow nails was described by Emerson (1966) and since then reported in such cases as that of D'Souza (1970). The theory of the development of the effusions is that respiratory infections may damage a previously adequate but hypoplastic lymphatic drainage system of the lung, so that it is no longer able to deal with the increased

load following further incidents. In the limbs, it is known that persistent lymphoedema may develop following an infection or other episode which overloads a hypoplastic system which hitherto had been able to function adequately.

In a recent review of pulmonary manifestations of the yellow nail syndrome by Hiller, Rosenow & Olsen (1972), the oldest case reported was a patient of 71 who had had chronic oedema of his lower extremities for 4-5 years, and yellow nails for 2 years before presenting with respiratory symptoms associated with a pleural effusion. The interest in this present case is in the even later age that the yellow nails developed, and the fact that it was not until the ninth decade that pleural effusions developed despite evidence to suggest lifelong lymphatic hypoplasia in the persistence of chronic oedema of the legs since childhood.

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The use of intra-arterial Urokinase in a case of recurrent arterial occlusion

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Summary

The present case report describes the use of intra-arterial Urokinase in an occlusive episode involving the right radial and ulnar arteries. Details of the case history are given and the choice of thrombolytic therapy, plus its route of administration are discussed.

Introduction

The use of intravenous lytic therapeutic agents

has been well defined in the treatment of occlusive venous thrombosis (Kakkar *et al.*, 1969; Robertson, Nilsson & Nylander, 1969), although there is no ideal regime for their use (Study Group, 1970). Streptokinase has been widely used in episodes of acute arterial thrombo-occlusive disease (Polidwoda *et al.*, 1969; Martin, Schoop & Zeitler, 1970; Amery *et al.*, 1970) and occasionally it has been given intra-arterially by local perfusion (McNicol *et al.*, 1963;

Bose, Brose & Hartley, 1969). The human fibrinolytic activator, Urokinase, has also been used intra-arterially, but only infrequently (Tsapogas, 1964) and not in the upper limb, although successful lysis of arterial thrombi in the left arm has been achieved with streptokinase (Bose *et al.*, 1969).

Case report

J.M., aged 47 at death.

Aged 43 and 46 transient tingling of fingers and toes was noted.

Aged 46 and 47—two transient episodes of unsteadiness with diplopia, following the second of which he was admitted to hospital and reduced pulse and blood pressure were noted in the left arm (BP 120/80 left and 140/90 right) with a left subclavian bruit. Acute ischaemia developed in the fingers of the left hand and angiography showed left subclavian narrowing proximal to the origin of the left vertebral artery. Left subclavian endarterectomy and left cervical sympathectomy were performed, followed 8 hr later by left subclavian thrombectomy. Despite initial recovery and adequate anticoagulation with heparin and then Warfarin, acute ischaemic episodes led, during the next 3 months, to successive amputations of the fingers of the left hand followed by total amputation of the left hand above the wrist. When ischaemic lesions led to amputation of the toes of the left foot the diagnosis was reviewed. No vasculitis had been found, and an atrial myxoma was excluded by ultrasonic and angiocardiographic examinations. There was also no positive evidence of bacterial endocarditis. Clotting and fibrinolytic mechanisms were not examined in detail. During the next 4 months whilst on adequate doses of Warfarin and despite right cervical sympathectomy and a course of α adrenergic blocking agents, the fingers and distal phalanx of the thumb on the right hand and all the toes of the right foot were amputated successively because of episodes of further acute arterial occlusion. Although he was a heavy smoker there was no evidence of Buerger's disease.

Polyarteritis nodosa was reported on histological examination at this time and prednisone therapy (10 mg t.d.s.) was commenced. The patient was transferred from surgical care for an attempt at rehabilitation. A month later, whilst prednisone was being reduced (since further histological review had failed to confirm polyarteritis nodosa), the right radial and ulnar arteries thrombosed from the wrist to above the elbow over a period of 12 hr. The extent of the occlusion was confirmed by Doppler ultrasonic detectors. A Seldinger arterial catheter was inserted into the right subclavian artery, and 300,000 units of Urokinase was given in 50 ml of normal saline over 2 hr using a constant infusion pump (Anderson *et al.*, 1961). The brachial and right radial pulses returned

clinically within 12 hr and normal flow was confirmed using ultrasound. Twelve hours later serum plasminogen was measured and found to be within normal limits. This allowed anticoagulation to be continued with Arvin, which was given initially at a dosage of 2 units/kg in 200 ml of normal saline over 6 hr by constant intravenous infusion, followed by 2 units/kg in 20 ml of normal saline given intravenously twice daily for 5 days. Estimations were taken daily of plasma fibrinogen and clot formation, and a state of circulating fibrinogen depletion was maintained. On the same day that Arvin therapy began, oral administration of fibrinolytic therapy was started with phenformin (50 mg b.d.) and ethyl-oestrenol (2 mg q.d.s.). Three weeks later the patient became confused and following a small melaena he died suddenly, despite adequate blood transfusion.

Necropsy revealed widespread embolization from aseptic thrombotic vegetations on the mitral valve. The valve itself was normal with no underlying rheumatic heart disease. There were scattered foci of fibrous replacement of the myocardium. The aorta showed marked atheroma. All the main arteries were normal with the exception of the left subclavian, which 1 cm from its origin narrowed for a distance of 4 cm to a solid cord 2 mm in diameter. The brachial, radial, femoral and dorsalis pedis arteries on each side appeared normal. Histological examination revealed atheromatous plaques in both brachial and right radial arteries. The right dorsalis pedis artery was occluded by organized thrombus.

There was an aseptic splenic infarct and evidence of fibrin occlusion of scattered interlobular arteries in the kidney. There were organizing thrombi in the meningeal vessels with an area of softening in the right frontal lobe.

Other organs were normal with the exception of an haemorrhagic purulent pneumonia of both lower lobes. There was no evidence of gastro-intestinal haemorrhage.

Sections from various amputation specimens and extensive necropsy study failed to show any arteritis. The constant abnormality was small arteries occluded by thrombus.

Discussion

The reason for this man's peripheral arterial occlusions was never adequately clarified in life although the clinical course and necropsy findings suggest that he suffered repeated embolization to small and large arteries from aseptic thrombotic vegetations on the mitral valve with some local arterial thrombosis.

The continued episodes of arterial occlusion over a period of 9 months despite adequate anticoagulation suggests that he may have had a defect in fibrinolysis. When the final arterial block in the right

arm developed it was felt that fibrinolytic therapy might be effective whether the occlusion was thrombotic or embolic.

In view of the reports of successful use of Urokinase in local arterial occlusion (Tsapogas, 1964) and the low incidence of reactions (Hansen *et al.*, 1961) when compared with streptokinase (Amery *et al.*, 1970; Hume, 1970; Verstraete, 1971) Urokinase was chosen. It was, however, in short supply and in order to achieve maximum local effect it was infused intra-arterially. Intra-arterial catheterization may be associated with an increased risk of arterial spasm but it was thought that the patient's previous cervical sympathectomy would help minimize this risk. Nevertheless, the patient's digitless state, his absolute refusal to contemplate further amputation and the threatened loss of his only remaining grip mechanism reinforced the decision to use Urokinase locally. It is significant that this episode, treated with Urokinase, was the only overt episode of arterial occlusion to be followed by recovery without further amputation, and indeed it was followed by stump healing in the 2–3 weeks before he died. We consider that local Urokinase was effective in restoring the local circulation. The decision to maintain anticoagulation by defibrination with Arvin (Ashford, Ross & Southgate, 1968; Bell, Pitney & Goodwin, 1968; Sharp *et al.*, 1968; Kakker *et al.*, 1969) was made because previous arterial occlusion had developed whilst on heparin and on Warfarin and because controlled Arvin therapy carries a lower risk of serious bleeding from normal tissues than do other anticoagulation regimens. However, both the defibrination and the steroid therapy may well have contributed to the subsequent gut bleeding although the likely cause of death was from widespread peripheral emboli—with involvement of meningeal vessels. There was a terminal broncho-pneumonia.

Efforts to improve fibrinolytic mechanisms with phenformin and ethyloestrenol were made too late to have contributed either to his gut bleeding or to the maintenance of patency of his remaining arterial circulation (Fearnley, Chakrabarti & Hocking, 1967; Chakrabarti *et al.*, 1968; Brown *et al.*, 1971).

In conclusion, this patient's case history demonstrates that intra-arterial Urokinase can be a useful adjunct to therapy in the difficult problem of recurrent arterial occlusion.

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