Systemic angioendotheliomatosis with metastases

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SYNOPSIS The clinical and pathological findings of a case of systemic angioendotheliomatosis are presented. The previously published cases of this disease are analysed. The present case is only the third to show clear evidence of metastasis.

Systemic angioendotheliomatosis is an uncommon condition first described by Pfleger and Tappeiner in 1959. Since then a further 12 cases have been reported. It presents either as purplish, indurated patches in the skin, which on histological examination consist of proliferating capillaries with hypertrophic atypical endothelium tending to fill the lumen or as a thrombotic process in a major organ without skin involvement (eg, Strouth *et al*, 1965). While the disease is confined to the skin the prognosis is relatively good but where systemic veins are involved the progression is much more rapid. Even in the latter type of case extravascular involvement is unusual. The present case shows both extravascular spread and distant metastasis.

Case Report

A 60-year-old man with 20 years' history of backache and slowly progressive rheumatoid arthritis had been under active treatment with cortisone since 1966. In 1971 he first attended the Rheumatology Centre at Droitwich. He was found to have diabetes mellitus, probably steroid induced, steroid myopathy, and rheumatoid arthritis of the left wrist and right ankle. He was treated both as an inpatient and as an outpatient over the next three years. A few days after his last admission on 15 November 1974 he developed marked pyrexia with nausea and vomiting. On 21 November 1974 he was transferred to the medical wards of the Worcester Royal Infirmary and found to have staphylococcal septicaemia. This was presumed to have started in the right mid-tarsal joint which had become painful. In spite of adequate therapy with fusidic acid and clindamycin his clinical course was prolonged and stormy. He developed swelling of the left ankle and calf, diagnosed as phlebothrombosis, and appeared to

suffer a single small pulmonary infarct. He slowly improved and returned to Droitwich on 13 January 1975. Because the severe swelling of the left foot and leg persisted he was transferred to the orthopaedic ward of the Worcester Royal Infirmary on 27 January 1975. Several attempts to locate a septic focus by aspiration produced only normal synovial fluid. A venogram was carried out on 10 February 1975. This showed that only the medial saphenous vein was patent in spite of controlled anticoagulant therapy from 1 to 14 January 1975. While in the Worcester Royal Infirmary his temperature rose on several occasions. On 21 February 1975 a biopsy was taken from the swollen subcutaneous tissue of the lateral aspect of the left leg. This was reported as intravascular angioendothelioma. Consequently a mid-thigh amputation of the left leg was carried out on 25 February 1975. After an initial rally he deteriorated rapidly with the appearance of a large swelling in the left groin and massive oedema of the right leg. He died on 19 March 1975.

PATHOLOGY

The findings from the surgical specimens and from the necropsy are presented in sequence to stress the rapid, relentless spread of the condition. The subcutaneous biopsy (figs 1-3) showed atypical proliferation of endothelium with partly fresh and partly organizing thrombus. There was ischaemic muscle damage but no extravascular spread of tumour.

The amputated left leg showed some brownish discolouration of the skin over the ankle and lower leg but no indurated plaques. There was massive oedema. Dissection showed occlusion and distension of virtually all venous channels by tumour and/or thrombus, thus confirming the findings of the venogram. Several enlarged lymph nodes were present in the popliteal fossa. The block in the main femoral vein stopped just short of the level of amputation. All arteries were markedly arteriosclerotic with

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Fig 1 Capillary in connective tissue showing atypical endothelium. Haematoxylin and eosin $\times 330$

Fig 2 Small vein showing atypical endothelium. H and E $\times 195$. Paraffin block.

Fig 3 Venule showing proliferating tumour. H and E $\times 195$. Paraffin block.

calcification but did not contain tumour or thrombus. The cut surfaces of the bones revealed widespread greyish-white deposits (fig 4) occupying much of the bone marrow, but the joint spaces were normal.

At necropsy tumour was found in the left femoral and iliac veins (fig 5), the left inguinal glands, both testes, and in a mass attached to the right side of the prostate and bladder. The liver was enlarged, weight 2600 g, and greyish-brown with a mottled cut surface pattern containing several large tumour nodules (fig 6). No other tumour was found at necropsy. The right femoral vein contained a simple thrombus.

HISTOLOGY

In small veins and capillaries the change from normal to abnormal endothelium was easily traced: it consisted of an enlargement and rounding off of the lining cells with proliferation into the lumen. The proliferated cell mass then grew within the lumen while the endothelial lining was normal. Thrombosis occurred readily where tumour occu-

Fig 4 Transverse slice of leg to show blocked vessels and tumour deposits in bones.

Fig 5 Femoral vein containing tumour and clot.

Fig 6 Slice of liver showing nodular deposit of tumour and diffuse infiltration.

ried the lumen. In some of the larger veins the tumour could be followed through the wall into the perivascular connective tissue (fig 7). In these the cells tended to be larger with rather variably shaped nuclei and some mitosis.

In the lymph nodes the tumour was fairly uniform with large numbers of mitoses (fig 8). The liver showed diffuse sinusoidal, periportal, and nodular involvement by tumour (figs 9 and 10). The bone marrow was replaced by uniform tumour tissue with occasional vessels showing intraluminal growth. There was no obvious bone destruction (fig 11). Extensive venous permeation was present in both spermatic cords, both atrophic testes (fig 12), and the prostate. There was invasive growth in the periurethral portion of the prostate (fig 13) and in the paraprostatic mass (fig 14). Small invasive, embolic lesions were seen in the kidneys (fig 15).

Discussion

The reported cases are analysed in the table to show the various presentations: (a) purely intravascular, (b) intravascular with invasion, (c) a and b plus metastasis. The analysis may not be quite accurate as in some of the reports it is not clear whether the term 'involved organ' means intravascular or invasive involvement. It does demonstrate the various combinations of presentation as (a) skin lesion only, (b) skin lesion with systemic spread, and (c) no skin lesion but systemic spread and metastases. Histologically the only significant difference between the various types is the appearance of mitotic figures in the invasive and metastatic lesions. One must conclude, therefore, that here is a disease with a wide spectrum of malignant potential. A

Fig 7

Fig 7 Small artery and its associated vein filled with organized thrombus and tumour. There is also spread of tumour into the perivascular tissue. *H and E* $\times 30$. Paraffin block.

Fig 8

Fig 8 Tumour in lymph node. Celestin blue, *H and E* $\times 325$. Glycol methacrylate block.

Fig 9 Liver: edge of nodular deposit. Celestin blue, *H and E* $\times 80$. Glycol methacrylate block.

Fig 10

Fig 10 *Liver: portal tract. Celestin blue, H and E $\times 80$. Glycol methacrylate block.*

Fig 11

Fig 11 *Bone. H and E $\times 80$. Paraffin block.*

Fig 12 *Testis. H and E $\times 80$. Paraffin block.*

Fig 13 Prostate. *H and E* $\times 30$. Paraffin block.

Fig 14 Prostate. *H and E* $\times 30$. Paraffin block.

Fig 15 Kidney. *Dominici stain* $\times 195$. Glycol methacrylate block.

Reference	Site
Pfleger and Tappeiner (1959)	Skin only
Braverman and Lerner (1961)	Skin, uveal tract (I, V), bone marrow, heart (I, V), thyroid (M), skull bones (M), brain (V), spleen (M)
Shtern and Likhachev (1963)	Brain
Haber <i>et al</i> (1964)	Skin, ? abdomen (clinical signs only)
Midana and Ormea (1965)	Skin
Strouth <i>et al</i> (1965)	Brain (V), adrenal (V)
Abulafia <i>et al</i> (1969)	Skin (V arteries and veins)
Fievez <i>et al</i> (1971)	Skin; capillaries in most of body
Okagaki and Richart (1971)	Genital tract (V)
Madara <i>et al</i> (1975)	Skin; capillaries of abdominal organs
Scott <i>et al</i> (1975)	Skin

Table Analysis of previously reported cases

V – intravascular; I – invasive; M – metastatic

puzzling feature of the present case is the failure to find the tumour cells in the peripheral blood. A series of buffy coat films collected between the time of amputation and death were examined without success. Yet the tumour was obviously progressing rapidly at this time.

Diagnosis is relatively straightforward when biopsy is taken from skin or from subcutaneous tissue in the early stages while the intravascular origin is still clear. It is doubtful whether a lymph node biopsy by itself could allow anything other than 'reticulo-sarcoma' as the diagnosis. The in-between stage of extension through the vessel wall is typical; the absence of vasoformation away from organizing thrombus should allow differentiation from the usual angiosarcoma. Special stains including silver methods for reticulin are not helpful.

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