

# Alveolar soft-part sarcoma

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**ABSTRACT** Alveolar soft-part sarcoma is a slow-growing but nevertheless malignant soft tissue tumour arising in muscle. It occurs most frequently in young women and often presents as a painless swelling in an upper or lower limb. The swelling, which may have been present for a considerable time, is firm and appears to be well circumscribed but it may recur locally after excision. Blood-borne metastases to the lung are common and this is frequently the mode of presentation. Lymphatic metastases are unusual. The tumour is composed of nests of large cells and the histological appearances may resemble those of a renal adenocarcinoma (hypernephroma). Six new cases of this very rare tumour are presented and the published reports are reviewed.

Alveolar soft-part sarcoma has been recognised as a clinical entity only since 1952.<sup>1,2</sup> It is a slow-growing but nevertheless malignant soft tissue tumour arising in muscle, usually in young adults. The primary growth may be inconspicuous but blood-borne metastases to the lung are common and this is frequently the mode of presentation. The tumour is usually radioresistant<sup>3</sup> and is unaffected by any known combination of cytotoxic drugs at present available, so that most cases pursue a slow but relentless course irrespective of treatment.

So far as can be ascertained, 171 cases have been reported worldwide but only two British cases have previously been described.<sup>4,5</sup> Six new cases are presented in this paper and the published reports are reviewed.

## Case reports

### CASE 1

A routine chest radiograph in 1967 of a 31-year-old man showed a well-defined, rounded, uncalcified lesion in the right mid zone (fig 1). The lesion had been seen 10 years previously but no action had been taken. It had not changed in size during this time. At thoracotomy the tumour was in the middle lobe just under the pleura; it was soft, looked like a raspberry, and shelled out easily. On histological examination it was thought to be a papillary adenoma. Six months later a swelling in the thenar eminence of the left hand

was excised and this was reported to be an alveolar soft-part sarcoma.

Nine months later a new shadow appeared in the right lung at the same site as before and at operation the tumour was removed by wedge resection. The histology of the two lung tumours and the hand tumour was then reviewed and all were found to be identical and to be alveolar soft-part sarcomas.

Three years later a further chest radiograph showed multiple well-defined opacities 0.5-1 cm in size throughout both lungs. The patient was given radiotherapy to the whole chest to a total of 2120 rad (21.2 Gy), followed by quadruple chemotherapy with cyclophosphamide, vincristine, fluorouracil, and methotrexate. There was little response to this treatment, or to subsequent monthly five-day courses of ICRF-159 250 mg daily and weekly courses of bleomycin, cyclophosphamide, and procarbazine. He developed cerebral and abdominal metastases and died nine years after the first operation, 19 years after the lung lesion had first been noticed.

### CASE 2

A 35-year-old man, whose chest radiograph (fig 2) in 1969 after a respiratory infection had showed multiple opacities in both lungs, underwent a small diagnostic thoracotomy. The lesion was reported to be a deposit of hypernephroma, though no primary kidney tumour could be shown by intravenous pyelogram or by renal arteriography.

At follow-up examination a year later the patient mentioned that he had had a swelling in his left thigh for the previous 10 years. This lesion, about 10 × 15

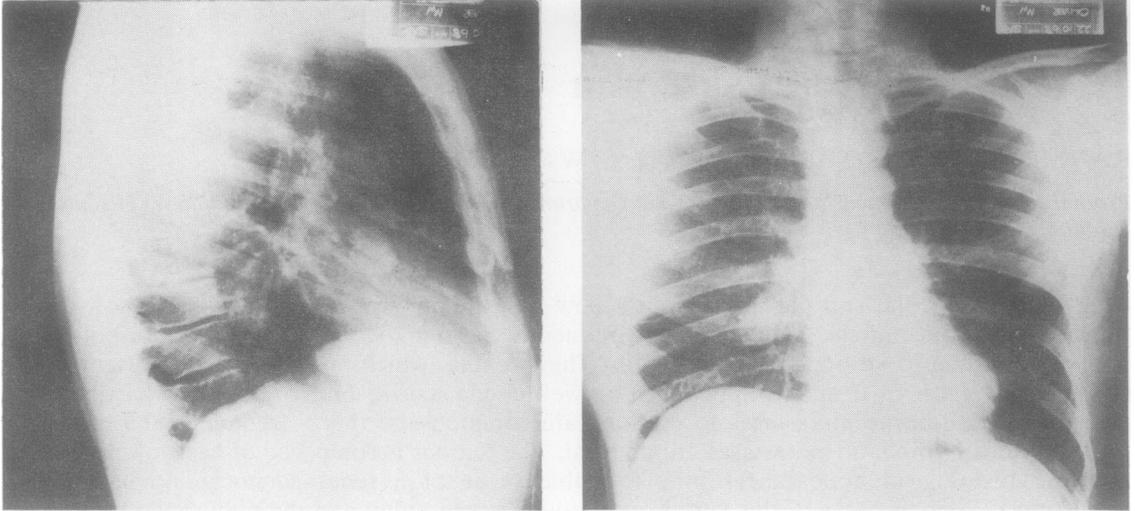


Fig 1 Case 1: lateral and posteroanterior radiographs showing well-defined rounded and uncalcified lesion in right mid-zone, found at operation to be in middle lobe.

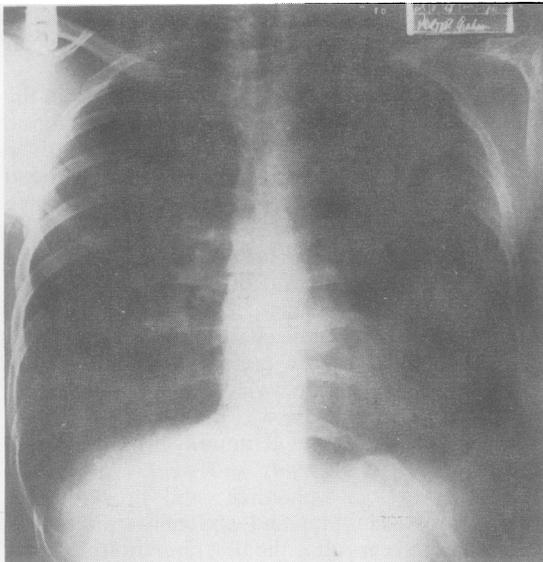


Fig 2 Case 2: radiograph showing multiple opacities in both lungs, one in the right lung and two behind the heart in the left lung.

cm, was excised from the quadriceps muscle. It was well encapsulated and was extremely vascular. Histological examination showed it to be an alveolar soft-part sarcoma and in retrospect it was seen to be identical to the lung tumour. The lung lesions enlarged and he died five years after the initial radiograph, 14 years after the thigh tumour had first been noticed. No local recurrence occurred in the thigh during the two years before his death.

#### CASE 3

A 50-year-old man presented in 1970 with a month's history of producing blood-stained sputum. Four years previously a left "adrenal" tumour had been removed, together with the spleen, left kidney, and tail of the pancreas. The tumour had been diagnosed as a phaeochromocytoma. A chest radiograph showed a well-defined shadow occupying most of the left lower lobe, best seen on tomography (fig 3). Bronchoscopy showed tumour in the apical segment of the left lower lobe but no firm diagnosis could be made from the biopsy specimen. A left lower lobectomy was carried out. Histologically the tumour in the left lower lobe and the previously resected "adrenal" tumour were both alveolar soft-part sarcomas. Lymph nodes were not affected. The patient died two years later from a recurrent growth in the thorax.

#### CASE 4

An Italian woman aged 21 years was referred to hospital in 1977 for investigation of a four-month history of amenorrhoea and lassitude. There was a firm swelling in the quadriceps muscle of the right thigh, which had been present for two years, and a swelling in the left lower chest wall below the axilla. A chest radiograph showed erosion of the 11th rib under the swelling and also a large mass in the right chest posteriorly, tomograms of which (fig 4) showed calcification. A biopsy specimen of the chest wall lesion at another hospital had first been reported as rhabdomyosarcoma and then subsequently as "normal muscle." A biopsy of the swelling in the thigh, which was situated in the substance of the quadriceps

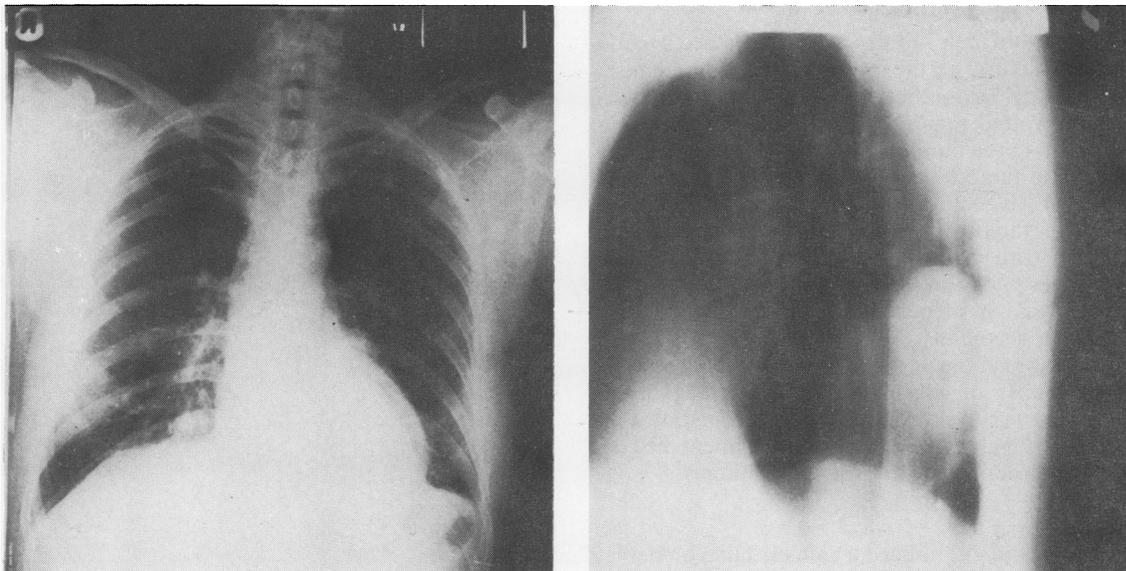


Fig 3 Case 3: radiograph (left) showing well-defined shadow in left lower lobe, best seen on a tomogram (right).

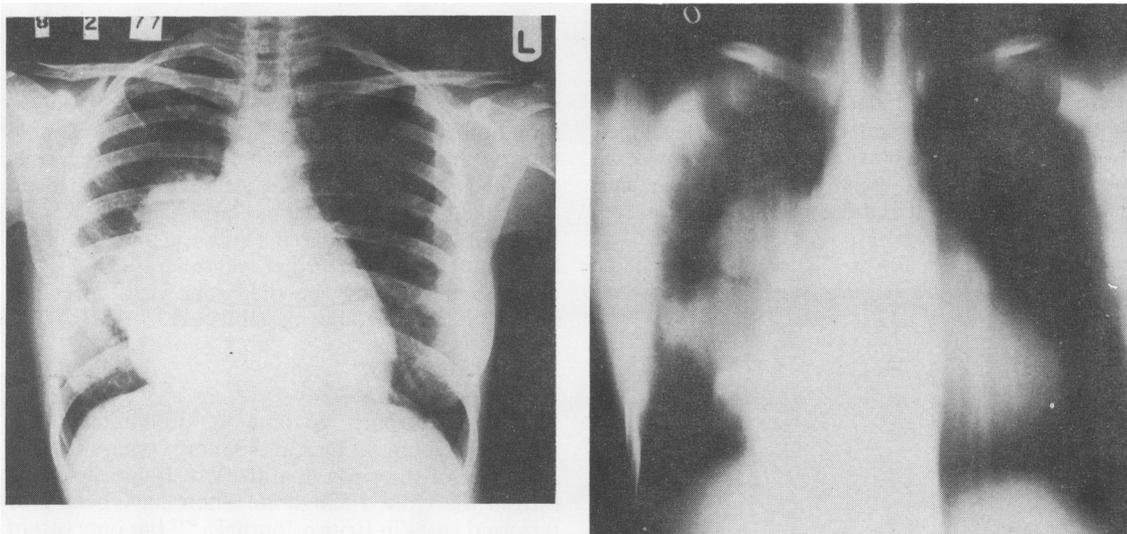


Fig 4 Case 4: radiograph (left) showing large mass in right chest, a tomogram of which (right) shows calcification.

muscle and was extremely vascular, showed alveolar soft-part sarcoma. There was a systolic murmur over the chest wall tumour and aspiration showed venous blood, indicating its extreme vascularity. For this reason biopsy was not attempted.

Treatment consisted of radiotherapy (five treatments of 400 rad (4 Gy) to each of the three lesions), with vincristine 1.5 mg/m<sup>2</sup>, actinomycin D 0.4 mg/m<sup>2</sup>, and intravenous cyclophosphamide 300 mg/m<sup>2</sup>

weekly for six weeks. One month later whole-lung irradiation to a total dose of 1950 rad (19.5 Gy) was given. Three months later it was apparent that the lung lesions were progressing and a further course of triple chemotherapy was given. A metastasis in the left sacroiliac joint and two cerebral metastases in the left frontal area both responded temporarily to radiotherapy, but the patient died 10 months after the diagnosis had been established.

## CASE 5

A 22-year-old male Greek Cypriot sustained a pathological fracture of the neck of the right humerus in 1979 (fig 5). A chest radiograph (fig 6) showed multiple round tumours in both lungs. A biopsy of the lesion in the humerus was interpreted as showing metastatic tumour, possibly hypernephroma, hepatoma, or alveolar soft-part sarcoma. A course of palliative radiotherapy to the humerus was given, together with medroxyprogesterone acetate 100 mg four times a day in view of the possibility that the tumour was a hypernephroma.

Further secondary deposits developed in the right femur, lower thoracic spine, and right thigh (quadriceps), biopsy of which confirmed the diagnosis of alveolar soft-part sarcoma. Courses of methotrexate and folinic acid had no effect and the patient died one and a half years after the onset of symptoms.

## CASE 6

A 22-year-old girl noticed a painless lump on her left thigh. No action was taken until two years later in 1976, when a complete excision biopsy was performed. Histological examination showed alveolar soft-part sarcoma. After operation monthly courses of vincristine 1 mg, adriamycin 5 mg, and methotrexate with calcium folinate rescue were given; but eight months later pulmonary metastases developed and the chemotherapy was changed to three-weekly courses of vincristine, bleomycin, adriamycin, and dacarbazine for a total of three months.

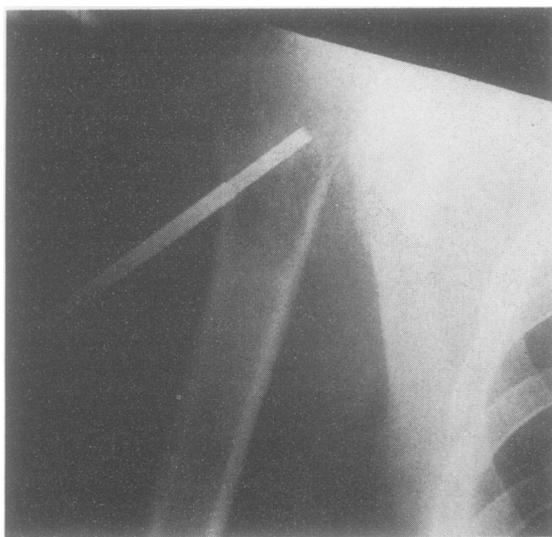


Fig 5 Case 5: radiograph showing pathological fracture of neck of right humerus, with the biopsy trephine.

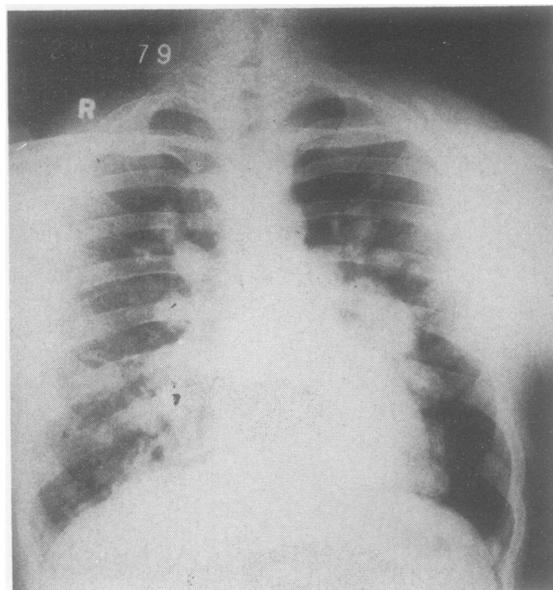


Fig 6 Case 5: radiograph showing "round" tumours in both lungs.

In 1978 the patient developed two small cerebral metastases, which were treated by whole-brain irradiation to a total of 5000 rad (50 Gy). She was able to return to work for a year but the cerebral deposits enlarged and in 1980 new metastases developed in the abdominal wall, right upper arm, and left tonsil. Later there was spread to the liver and the shaft of the left femur. Despite further radiotherapy and cytotoxic chemotherapy she died four years after the initial diagnosis had been established.

## Discussion

Alveolar soft-part sarcoma is predominantly a tumour of young women and is more common on the right side of the body than the left. It appears to be rare in the United Kingdom. There have been four reported cases in British Journals,<sup>4-7</sup> but only two of the patients actually lived in the United Kingdom.<sup>4,5</sup> This tumour was first recognised in 1952 by Christopherson *et al*,<sup>1</sup> who reported a group of 12 morphologically identical tumours which presented predominantly in women aged 15-30 years as slow-growing, painless masses in the arm or leg. In one case the first sign was a lung metastasis. A further 53 cases were collected by Lieberman *et al*<sup>2</sup> at the National Cancer Institute, Bethesda. In this series also the tumour occurred more commonly in women than in men (in a ratio of 2:1). The average age of the women was 20 years and the men 30 years. No other group of tumours has been reported in which the age of onset is

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younger in women than in men and a further unique feature of this series was that the tumour was three times as common on the right as on the left. The growth of the tumour in these two series was slow but almost always metastases developed in the lung, brain, or bones, often 10 or more years after primary resection. It was concluded that the course of the tumour was indolent but inexorably fatal.

Reports<sup>8-13</sup> of a further 11 cases emphasised the incidence in young women and confirmed the features already described. The presence of a murmur over the tumour due to its extreme vascularity is recorded in several cases,<sup>4,6,8,14</sup> and in one patient excision had to be abandoned because of haemorrhage.<sup>6</sup> The tumour may present as a pulmonary metastasis while the site of the primary is never found.<sup>12</sup> Two studies<sup>2,15</sup> emphasise the much greater incidence of the tumour on the right side of the body. Reports of a further 20 cases<sup>16-19</sup> show similar features. The prognosis after local excision of the tumour is most difficult to determine, for although the growth may recur locally<sup>2,4,9,19</sup> one patient has remained well 10 years after a local removal of the tumour and no further treatment.<sup>20</sup> Some cases of the sarcoma occur in relation to the oropharynx, especially the mandible.<sup>21-25</sup> Twenty cases in which the site was the genital tract<sup>26,27</sup> or the orbit<sup>28-32</sup> have been reported. Other cases showing a presentation and natural history similar to those of the present series and of the cases already noted have been described,<sup>33-47</sup> the most remarkable of which is the case of a 14-year-old boy whose primary tumour was removed in 1968 and who seven years later had 40 secondary nodules removed from the right lung and 52 nodules from the left lung.<sup>40</sup> He had then been given quadruple chemotherapy of vincristine, actinomycin D, cyclophosphamide, and doxorubicin for two years and had remained well for a further three years. One Japanese report<sup>39</sup> cites 31 further recorded cases from that country, in nine of which there were cerebral secondary deposits; but most of these reports are in Japanese with no translation. Further pathological studies have been made,<sup>48-52</sup> with three short general reviews of the subject.<sup>53-55</sup>

These tumours are all related to skeletal muscles, usually in an upper or lower limb. Macroscopically they appear to be well circumscribed but nevertheless they infiltrate surrounding tissues; invasion of veins is very common and blood-borne metastases are frequent. Invasion of lymphatic tissue is unusual. In some cases bone has been affected by the primary tumour.<sup>4,14,17,34,35</sup>

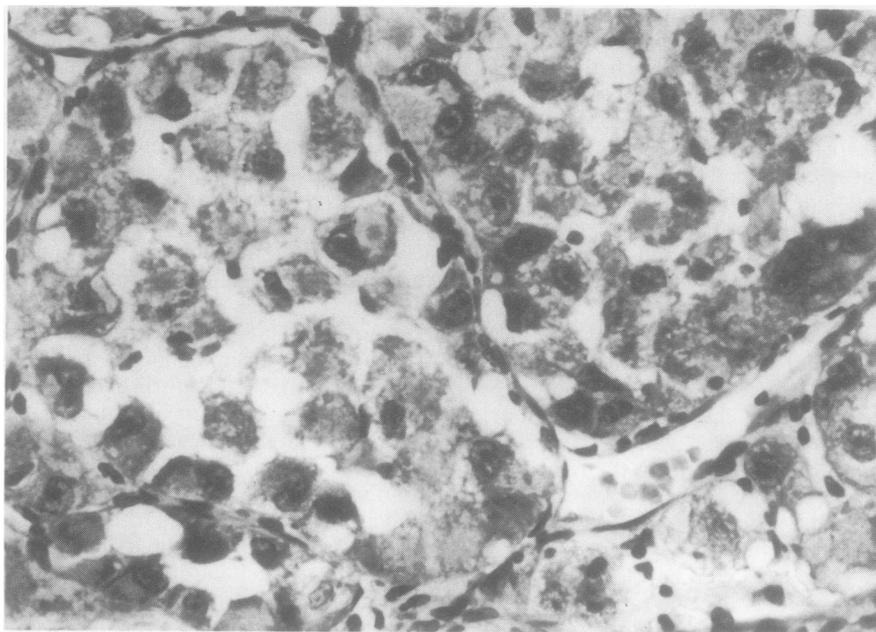
The histological appearances are characteristic<sup>1,51,52</sup> and are well illustrated by the present series. The tumour is composed of nests of large cells separated by delicate connective tissue septa

containing capillaries (fig 7). In some of the nests the central cells may become detached, giving an alveolar appearance (fig 8). The cytoplasm is abundant and eosinophilic and contains granules which stain with periodic-acid-Schiff (PAS) and are resistant to diastase digestion (fig 9). There may also be elongated intracellular crystals (fig 10), which are also PAS positive and diastase resistant and in which a periodic pattern of lines is demonstrable by electron microscopy (fig 11). The nuclei are fairly uniform but have prominent nucleoli. Mitotic figures are rare.

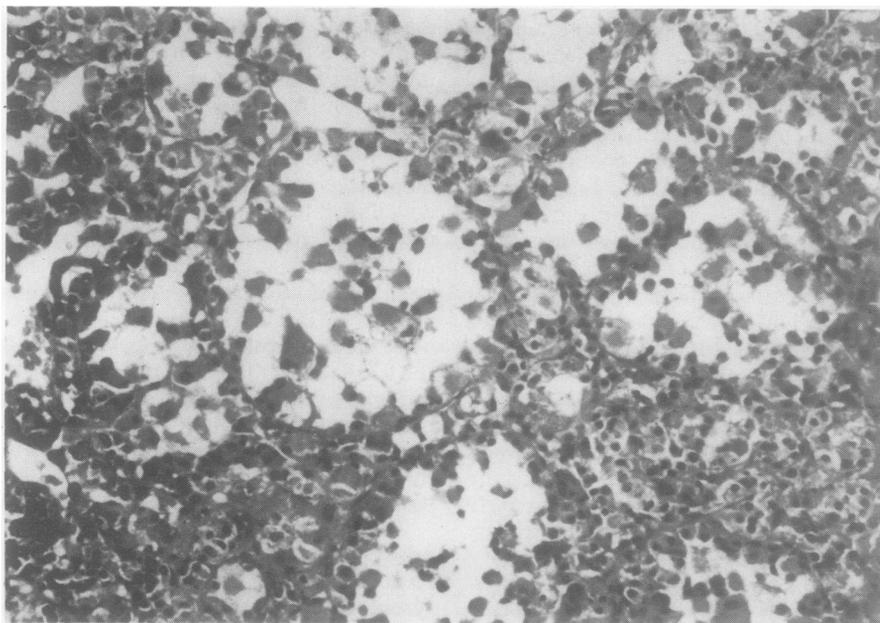
The histogenesis of alveolar soft-part sarcoma was obscure until 1982. It had been suggested that the tumour represents a malignant form of granular cell "myoblastoma,"<sup>56-62</sup> a distinct variant of rhabdomyosarcoma,<sup>63,64</sup> or a malignant paraganglioma<sup>65-69</sup>; but there were convincing objections to all these theories.<sup>34,70</sup> It is now suggested<sup>71</sup> that the tumour arises from modified smooth muscle cells of the vascular media and that the crystalline secretion product is a form of renin. The characteristic cytoplasmic granules and crystals react with specific antiserum to renin and have other histochemical and ultrastructural features found in renal juxtaglomerular cells and juxtaglomerular cell tumours. Since hypertension has not been recorded, the renin is presumably inactive or is not secreted.

The six cases presented in this paper closely resemble those previously described, except for the preponderance of men over women (4:2). All but one patient was under 36 years when the tumour was first diagnosed. The tumour was on the left side in four and on the right side in two. In three cases single or multiple pulmonary metastases were the presenting feature. In five cases the growth had spread to the lung at the time the initial diagnosis was made—three patients had a single metastasis and two had multiple metastases. In case 1 a solitary lung deposit developed 10 years before the primary growth was discovered and removed and the patient did not die until 19 years after the original lung metastasis had been noticed. In case 2 the primary growth had been present in the thigh for 10 years before the patient presented with multiple deposits in the lung. In case 3 the left "adrenal" tumour presumably arose from the left crus of the diaphragm. In case 4 the presence of calcification in the lung metastasis was unexpected. In case 5 the site of the primary growth was probably the right thigh, this being recognised only after the pathological fracture had developed.

The histological appearances resembled those described above and differed only in detail. There were clear-celled areas in cases 2, 4, and 5 but these represented degenerative changes; the bulk of the tumours consisted of the classical granular eosinophilic cells. The presence of clear cells creates a



**Fig 7** *Case 2: groups of large cells separated by delicate septa; the cells have abundant granular cytoplasm, uniform nuclei, and prominent nucleoli (haematoxylin and eosin,  $\times 520$ ).*



**Fig 8** *Case 5: loss of cohesion of central cells producing alveoli in place of solid nests (haematoxylin and eosin,  $\times 260$ ).*

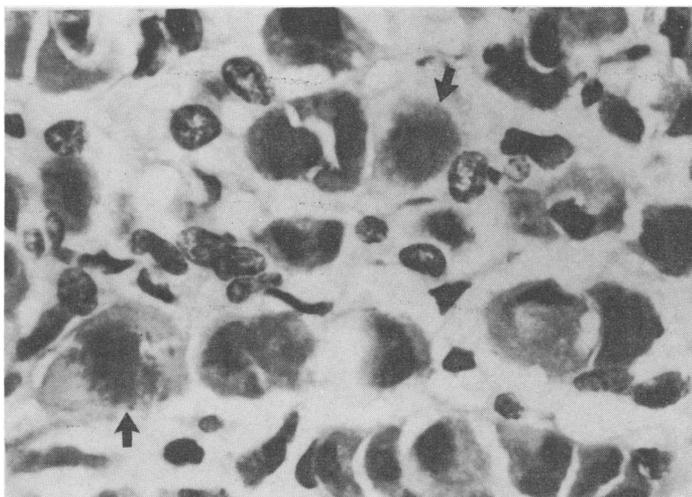


Fig 9 Case 6: PAS-positive, diastase-resistant granular material in cytoplasm of tumour cells (arrows). (PAS-diastase,  $\times 1560$ ).

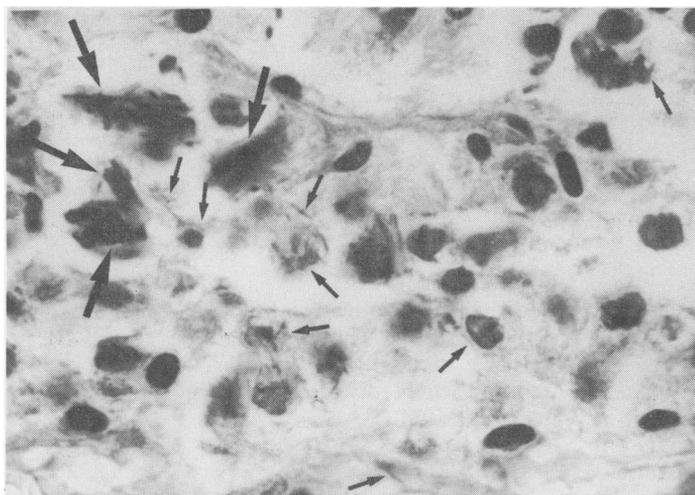


Fig 10 Case 1: large PAS-positive, diastase-resistant, shaped crystals (large arrows) and small crystals (small arrows). (PAS-diastase,  $\times 1560$ ).

resemblance to hypernephroma and other clear-celled adenocarcinomas and adds to the problem of establishing the histological diagnosis, especially when the site of the first biopsy is a metastasis. The distinctive intracellular crystals were seen in cases 1 and 5. These crystals are diagnostic of alveolar soft-part sarcoma<sup>52</sup> but occur in only some of the cases. The cells in cases 2, 3, and 4 contained glycogen in addition to the PAS-positive, diastase-resistant material, which was present in every case and is essential for diagnosis. Mitotic figures were common in case 3 (15/40 high-power fields) but were infrequent in the other cases (1/40 high-power fields in

cases 2, 4, 5, 6 and 3/40 in case 1). The scarcity of mitoses is in keeping with the slow progression of the disease in some cases and the high incidence of venous invasion with the invariably fatal outcome.

The treatment of alveolar soft-part sarcoma is far from satisfactory and all the patients here reported have died. The tumour usually appears benign at operation but this belies its true nature and local recurrence develops in many cases within a few months.<sup>7</sup> For this reason very wide excision or even amputation has been advised. It is questionable whether such radical surgery has any effect on the natural course of the disease, however, for in cases 1,

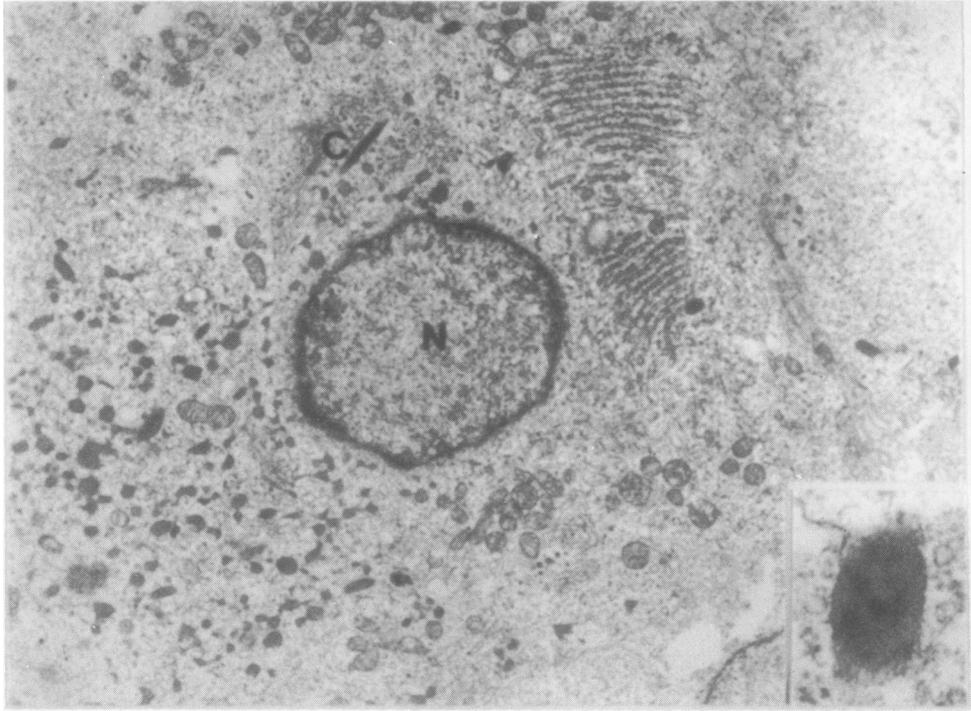


Fig 11 Case 5: Electron micrograph of alveolar soft-part sarcoma—tumour cell with long, thin crystal (C) above nucleus (N) ( $\times 12\,500$ ). Inset: a crystal from another cell, showing the characteristic pattern of regularly spaced parallel lines ( $\times 96\,000$ ).

2, and 3, in which the primary growth was excised completely, the patients lived nine, two, and six years without any local recurrence. This would suggest that the distant secondary deposits which ultimately caused the death of these patients were present at the time of the original surgery. The tumours are relatively radioresistant and cytotoxic treatment has little effect on the slow but relentless progress of the disease.

At present the treatment of choice would appear to be wide excision of the primary tumour, with radiotherapy and quadruple chemotherapy (cyclophosphamide, vincristine, methotrexate, and fluorouracil) for the secondary deposits.

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Mrs Joan Walters, of the Royal Society of

Medicine Library, made a Medline computer search of the literature. This has enabled us to include an extensive bibliography and a list of all the known recorded cases of this very rare tumour up to December 1981.

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