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Extraskeletal Ewing's Sarcoma: A Clinical, Morphological and Ultrastructural Analysis of Five Cases with a Review of the Literature

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Abstract—*In* 1969 *it was recognised that tumours with light microscopic appearances indistinguishable from Ewing's sarcoma of bone may arise in extraskeletal sites (extraskeletal Ewing's sarcoma). Here, we review the available literature and report five new cases. All five received combined modality therapy with combination chemotherapy and radiotherapy to the primary site followed by surgical excision in two. All attained complete remission; after a median follow-up of* 26 months, *three remain disease-free but two have relapsed and died. Our experience, in accord with previous series, suggests that extraskeletal Ewing's sarcoma compared with its bony counterpart tends to occur in older subjects, has a similar incidence in males and females, usually presents with a painless mass and readily responds to combined modality therapy. We detected no light or electron microscopic features to denote a histogenetic origin. However, we suspect extraskeletal Ewing's sarcoma may occur more frequently than previously supposed.*

INTRODUCTION

EWING'S sarcoma of bone, first described in 1921 [1], accounts for about 30% of all paediatric primary malignant bone tumours [2] and is second only to osteosarcoma in incidence. The peak incidence occurs in subjects younger than 20 yr [3, 4], but falls rapidly to a very low level after the age of 25 [5]. Ewing's sarcoma occurs rather more frequently in males than females [4–6], but there are more distinct racial and geographic variations: it is a disease of Caucasians, being rare in Negroes [2, 7, 8] and Chinese [9]. The most common presentation is a painful bony swelling, and the most frequent primary sites are the femur, pelvis, humerus, fibula, rib and scapula [10, 11].

Histologically, Ewing's sarcoma of bone is a highly cellular tumour, traversed by fibrous tissue septa. The cells are small and fairly uniform with sparse cytoplasm and indistinct cytoplasmic borders. In cellular areas, reticulin is scant and areas of haemorrhage and necrosis are common. Glycogen is frequently, but not always, identified by special stains. The nuclear chromatin pattern is finely granular with inconspicuous nucleoli. Mitoses, however, are rarely frequent. A large cell variant of Ewing's sarcoma has been described in which the nuclei are larger and less regular than those seen in the typical example [12].

By electron microscopy, the principal cell of Ewing's sarcoma of bone is generally round or polygonal [13–16] and may be connected to its neighbours by occasional junctions of rudimentary appearance. The nucleus is round or ovoid, but may be indented and chromatin is finely dispersed. The sparse cytoplasm contains few organelles, which show no specialised features. Characteristically, glycogen forms large focal deposits, variable in amount and distribution. "Secondary cells" probably represent degenerate forms [14, 15] and are smaller and less regular in shape than principal cells and show condensation of their nuclear and cytoplasmic components. An atypical variant has coarser nuclear chromatin and a greater number of cytoplasmic organelles including intermediate filaments [14, 16]. Well developed desmosomes may also be apparent in atypical tumours [14].

Tumours to be considered in the differential diagnosis of Ewing's sarcoma are lymphoma, acute leukaemia, neuroblastoma, alveolar rhabdomyosarcoma, haemangiopericytoma and other soft tissue sarcomas, small cell carcinoma and "malig-

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nant small cell tumours of the thoracopulmonary region in childhood" [17]. Differentiation from other small round cell tumours on light microscopic examination may be difficult or even impossible, but definitive tumour typing may be achieved by ultrastructural examination [13, 16, 18].

Tumours reported in extraskeletal sites with large microscopic appearances indistinguishable from those of Ewing's sarcoma of bone were first described in 1969 [19] and are subsumed under the term "extraskeletal Ewing's sarcoma". No histological characteristics have been described that allow differentiation of extraskeletal from skeletal Ewing's sarcoma [20]. Although Wigger *et al.* [21] regarded the paucity of glycogen, "immaturity of tumour cells" and absence of secondary cells as important points of distinction in their single case, most authors [16, 18, 22–25] have considered extraskeletal Ewing's sarcomas to be indistinguishable ultrastructurally from their more common bony counterparts. The precise incidence of extraskeletal Ewing's sarcoma is unknown, although one series noted 11 such tumours compared with 75 primary Ewing's sarcoma of bone seen during a 5-yr period [26].

Comparing extraskeletal Ewing's sarcoma with Ewing's sarcoma of bone, few clinical differences, apart from the primary site, have been noted. However, extraskeletal Ewing's sarcoma tends to occur in older patients, has a similar incidence in females and males, and presents with pain less frequently than Ewing's sarcoma of bone [20]. As for Ewing's sarcoma of bone, extraskeletal Ewing's sarcoma metastasises most frequently to lung and bone [20, 26, 27]. The prognosis for extraskeletal Ewing's sarcoma is poor: the largest series [20] reported tumour related deaths in 22 of 35 patients, (12 within 1 yr of diagnosis) despite surgery. However, with combined modality therapy 50% of patients or more may be long term disease-free survivors [26, 28].

The largest series of extraskeletal Ewing's sarcoma described 39 patients [20], but other smaller series exist [16, 18, 19, 21–35]. Combining the data from these reports provides information on a total of 149 patients: sex was recorded in 122 cases [16, 18–27, 29–35]; 67 (55%) were male and 55 (45%) female; age was stated in 101 patients [16, 18–27, 29–35] and the median age at presentation was 20 years (range newborn–83 yr). Mean ages at presentation were similar for males (25 yr) and females (26 yr). Race was reported in only 30 patients and all were Caucasian [18, 20, 22, 23]. The site of the primary tumour was described in 136 patients (Table 1); the most frequent sites were: an extremity (44 patients, 32%), paravertebral or epidural (21 patients, 15%), head and neck (15 patients, 11%) or chest wall (15 patients, 11%).

Table 1. The primary site of extraskeletal Ewing's sarcoma in 136 patients

Site	No. of patients		Reference
Extremity	44	(32%)	18,20,24,26,27,28,30
Paravertebral/Epidural	21	(15%)	19,20,22,26,27,31,33
Head and neck	15	(11%)	20,23,26,28,30
Chest Wall	15	(11%)	20,24,26,27,30,35
Pelvis	9	(7%)	20,21,27,28,31
Retroperitoneum	8	(6%)	16,20,26
Buttock	6	(4%)	16,20,29,30
Axilla	6	(4%)	18,20,26,27,30
Shoulder	3	(2%)	27,29
Mediastinum	3	(2%)	16
Scrotum/Perineum	2	(1%)	27,34
Inguinal	1	(1%)	18
Hip	1	(1%)	20
Lung	1	(1%)	25
Abdominal Wall	1	(1%)	27
	136		

MATERIALS AND METHODS

Patients

Between October 1979 and January 1984, five patients subsequently diagnosed as having extraskeletal Ewing's sarcoma were referred to our adult oncology units for further management (Table 2). Three were male and two female. Mean age at presentation was 33 yr (range 26–38). Three patients presented with painless masses but two with leg pain. The sites of the primary lesion were: an extremity (two patients), the pelvis (one patient), the axilla (one patient) or the retroperitoneum. At presentation, two patients had disease restricted to the primary site but two patients had tumours locally invading bone. The remaining patient had an abnormal radioisotopic bone scan suggestive of bony metastases. However, in these three patients with tumours invading bone or abnormal bone scans, none exhibited radiological features suggestive of a primary bone tumour, and each was classified as having a Ewing's sarcoma of extraskeletal origin.

Morphological review

Histopathological material from each case was reviewed. Paraffin blocks were available from each patient, but from patient 3 (Table 2) the only material available prior to chemotherapy was derived from a fine needle aspirate. Sections were stained with: haematoxylin and eosin, silver stain, periodic acid Schiff and periodic acid Schiff with diastase. The fine needle aspirate was stained using a modified Papanicolou method.

Four tumours had been examined by electron

Table 2. Clinical features of five patients with extraskeletal Ewing's sarcoma

Patient No.	Sex	Age	Primary site	Presenting symptom	Metastases
1	Male	37	(L) Thigh	Painless Swelling	Bone
2	Female	26	(R) Axilla	Painless Swelling	Locally invading bone
3	Male	32	(R) Thigh	Painless Swelling	Absent
4	Female	31	Retroperitoneum	Leg Pain	Absent
5	Male	38	(L) Pelvis	Leg Pain	Locally invading bone

microscopy (patients 1, 3, 4, 5, Table 2) and the records of these examinations were reviewed. In three cases glutaraldehyde fixed biopsy samples were postosmicated, treated *en bloc* with uranyl acetate, dehydrated and embedded in Spurr's resin. Ultrathin sections were contrast stained with uranyl acetate followed by lead citrate. The fine needle aspirate from patient 3 was processed as described by Lazzaro [36]; the open biopsy following chemotherapy was also prepared for electron microscopy after fixation in phosphate buffered formalin.

Treatment

Details of treatment are summarised in Table 3. All patients received combined modality treatment with systemic chemotherapy and radiotherapy to the primary tumour. In three patients (patients 1, 2, 3) the chemotherapy preceeded the radiotherapy, but one (patient 4) received radiotherapy prior to chemotherapy, while the remaining patient received radiotherapy and chemotherapy concurrently. The primary tumour was excised from two patients, prior to chemotherapy in patient 2 but following chemotherapy in patient 3.

In three patients, chemotherapy was administered according to a protocol for Ewing's sarcoma of bone, developed by the St. Jude Children's Research Hospital, Tennessee. This protocol is described fully elsewhere [37], but briefly, therapy consists of an induction phase comprising alternating courses of cyclophosphamide (orally, days 1–8) and doxorubicin (i.v. day 8). At week 14, radiotherapy is given to the primary lesion and maintenance chemotherapy given with weekly vincristine and fortnightly actinomycin-D. After week 27, the induction regimen of chemotherapy is reintroduced and continued until week 43. Patients with localised disease cease therapy at this date, while those with metastatic disease continue chemotherapy with the maintenance regimen between weeks 47 and 57.

Two of the three patients entered onto this protocol completed treatment but one (patient 3) was withdrawn after completion of induction because only minor tumour regression had been obtained. This latter patient subsequently received intra-arterial *cis*-platinum and doxorubicin given over 34 weeks, prior to radiotherapy and surgical excision of the primary.

The remaining two patients (patients 4 and 5) were treated before the St. Jude protocol was adopted. One received vincristine, doxorubicin, cyclophosphamide and actinomycin-D given at 3-weekly intervals for 6 months, and the other vincristine, bleomycin and actinomycin-D at monthly intervals for 6 months.

Table 3. Treatment and response in five patients with extraskeletal Ewing's sarcoma

Patient No.	Primary excised	RT to primary site	Chemotherapy	Overall Response	Relapse	Alive	Follow-up (months)
1	No	Yes	St. Jude Regimen*	CR	No	Yes	26
2	Yes	Yes	St. Jude Regimen	CR	No	Yes	18
3	Yes	Yes	Induction—St. Jude Regimen; Intra-arterial CDDP and DOX	CR	No	No	15
4	No	Yes	VCR, DOX, CTX, ACT-D	CR	No	Yes	45
5	No	Yes	VCR, BLEO, ACT-D	CR	Yes	No	86

*See text; RT = Radiotherapy; CDDP = *cis*-platinum; DOX = doxorubicin; VCR = vincristine; CTX = cyclophosphamide; ACT-D = actinomycin-D; BLEO = bleomycin; CR = complete remission.

RESULTS

Morphological review

In the four patients for whom paraffin blocks prior to therapy were available, the histological appearances were consistent with those described for Ewing's sarcoma of bone. Each specimen exhibited a positive reaction for the presence of glycogen, although the number of positive cells varied between the different cases. Reticulin was scant and tended to surround aggregates of cells rather than individual cells, in a pattern similar to Ewing's sarcoma of bone.

Definitive tumour typing was not possible from the fine needle aspirate from patient 3. However, review revealed a round cell malignant tumour, suggestive of a soft-tissue sarcoma and the diagnosis of Ewing's sarcoma was favoured. Examination of the post chemotherapy paraffin blocks indicated considerable necrosis and degeneration but residual viable tumour cells similar to those from the fine needle aspirate were also seen.

Electron microscopy of the four tumours studied revealed a compact pattern of polygonal or rounded smooth surfaced cells in close apposition with their neighbours (Fig. 1). Occasional short processes were present. In two specimens rudimentary intercellular junctions were seen, appearing as symmetrical focal thickenings of the two plasma membranes separated by a uniform narrow gap (Fig. 2); these were "desmosome like", in that converging filaments and an intermediate line were lacking. No basal lamina was visible and the sparse extracellular stroma consisted of amorphous material of low electron opacity with a few collagen fibrils or glycogen particles. The cell nucleus was mostly ovoid and fairly smooth in contour (Fig. 1), but in areas of one specimen was much more convoluted (Fig. 3). Nuclear chromatin was fine and dispersed, apart from a tendency to margination at the nuclear membrane. There were one or more nucleoli that, although small, appeared prominent because of their density or skein-like structure (Fig. 1). Occasional spherical fibrillary nuclear bodies were also seen.

The cytoplasm of most cells contained glycogen (Figs. 1, 3, 4), variable in amount and distribution, but in each specimen large glycogen aggregates could be found, often with the peculiar "hole" noted by Ghadially [13] (Fig. 4). Other cytoplasmic organelles were sparse (Figs. 1, 3), consisting mainly of free ribosomes and polyribosomes, together with a few mitochrondria, occasional cisternae of rough and smooth surfaced endoplasmic reticulum, an inconspicuous Golgi zone and rare lipid droplets. A few cells contained lysosomes. In one tumour intermediate filaments were arranged in short parallel bundles; this specimen was also distinguished by the presence of parallel microtubules or a few dense core neurosecretory-type granules of 80–100 nm diameter (Fig. 5). Smaller, irregular, stellate cells with the nuclear and cytoplasmic density characteristic of secondary cell were present in two specimens.

Much of the biopsy specimen obtained from patient 3 following chemotherapy was degenerate, but apparently viable elements showed much more irregularity of nuclear contour than in the previous sample, together with the loss of glycogen. Secondary cells were also more numerous.

Treatment

Details of treatment and overall response to combined modality therapy are summarised in Table 3. Of the two patients completing the St. Jude regimen, both achieved complete remission and remain free of disease 18 and 26 months respectively after the start of therapy. Although the third patient receiving this regimen achieved minor tumour regression (< 50%) with the induction phase, treatment was changed to intra-arterial *cis*-platinum and doxorubicin which resulted in partial tumour regression (> 50%). Following radiotherapy, the primary tumour was excised completely. However, shortly after surgery widespread metastases to lung and abdominal lymph nodes were detected. The disease failed to respond to further chemotherapy with single agent VP16 and the patient died 15 months after the start of treatment.

The fourth patient achieved a complete response to radiotherapy to the primary lesion followed by vincristine, doxorubicin, cyclophosphamide and actinomycin-D for 6 months and remains disease free 45 months after the start of therapy. The remaining patient (patient 5) achieved a complete response to combined therapy with vincristine, actinomycin-D, bleomycin and radiotherapy, but relapsed at the primary site 54 months later. Further chemotherapy with vincristine and bleomycin and later, vincristine, doxorubicin, actinomycin-D and cyclophosphamide failed to induce response and death occurred 32 months after recurrence. Thus, overall, all five patients achieved complete remission with combined modality therapy; three remain disease-free but two have relapsed and died despite further chemotherapy. The median duration of follow-up for the group was 26 months.

DISCUSSION

The information in the literature concerning extraskeletal Ewing's sarcoma comes largely from small series, reflecting the rarity of this tumour. However, extraskeletal Ewing's sarcoma is a distinct clinico-pathological entity and the diagnosis

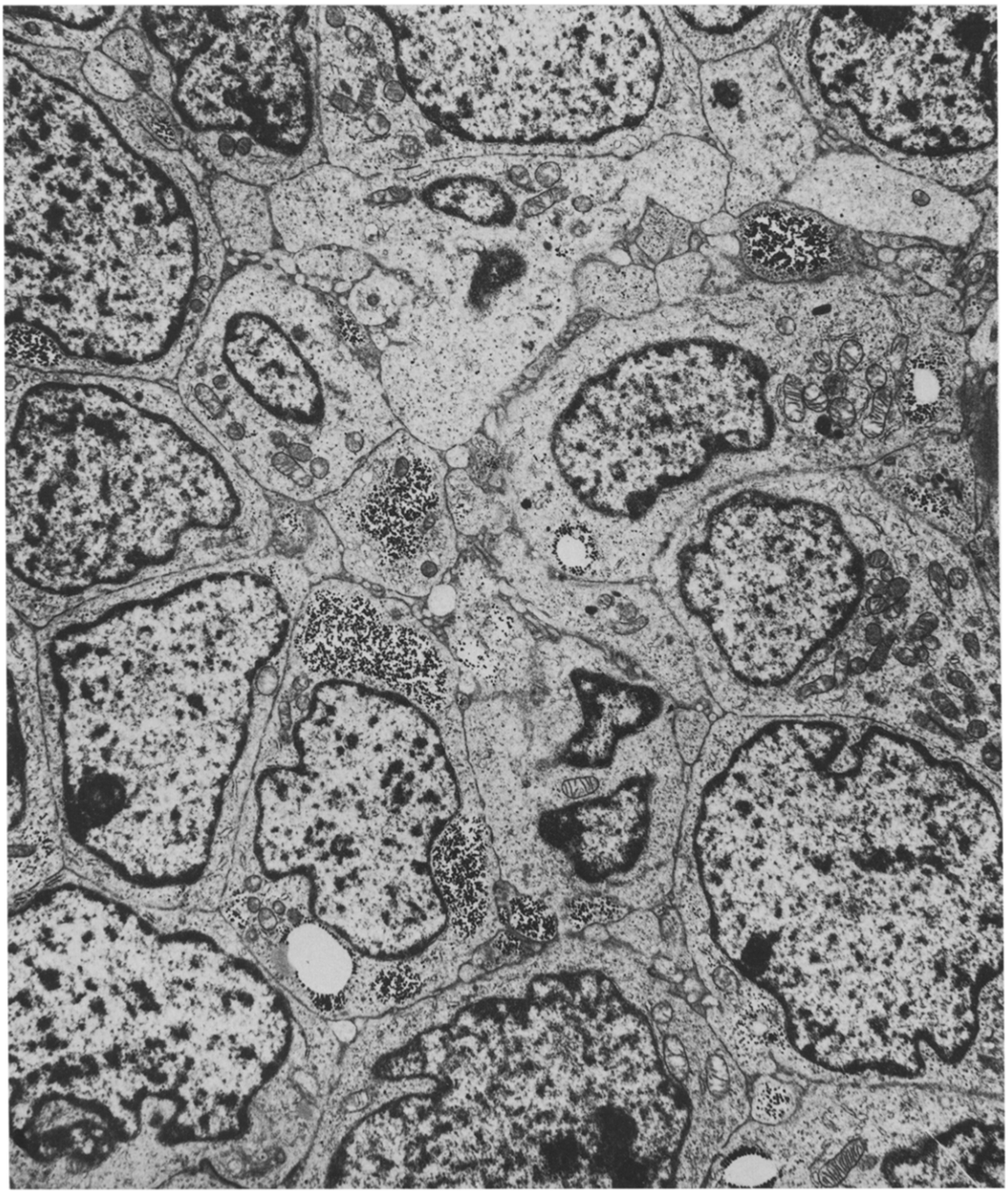

Fig. 1. ***Survey electron micrograph of extraskeletal Ewing's sarcoma. Tumour cells in close apposition and contain rounded or ovoid nuclei with small nucleoli. Glycogen is present in large aggregates in some cells but other cytoplasmic organelles are sparse.*** *(Electron micrograph* × 8000).

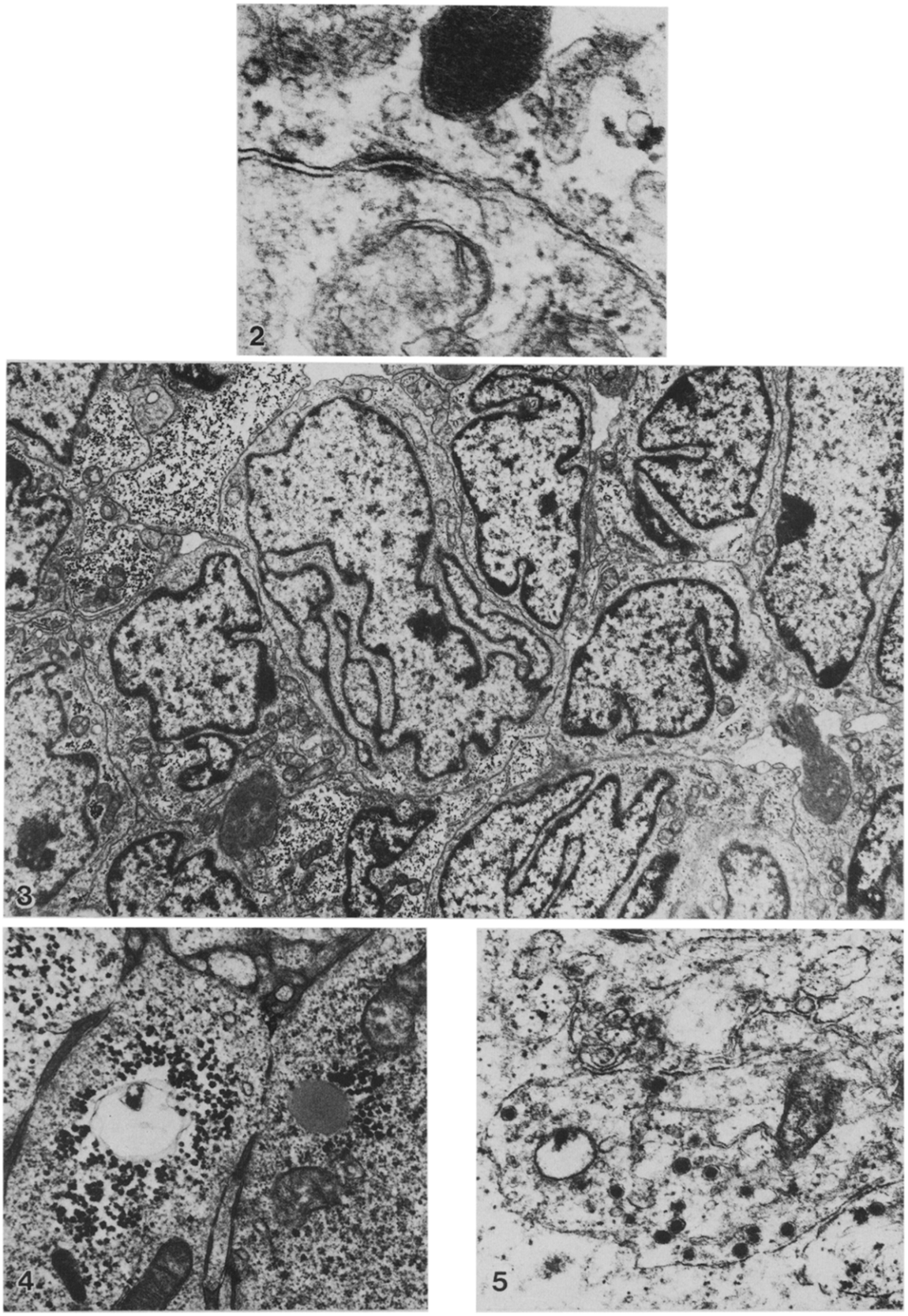

Fig. 2. *Rudimentary intercellular junction between two tumour cells.* (*Electron micrograph* × 70,000).
Fig. 3. *Tumour cells vary in size and several show marked irregularity of their nuclear contour.* (*Electron micrograph* × 8000).
Fig. 4. *Detail showing glycogen with a "hole" in the tumour cell to the left.* (*Electron micrograph* × 23,000).
Fig. 5. *Tumour cell process containing* 80–100 nm *dense core granules.* (*Electron micrograph* × 38,000).

should be considered in two situations: firstly, in the differential diagnosis of any soft tissue round cell tumour and secondly when Ewing's sarcoma of bone presents with an extensive soft tissue component. Clinical features such as the tendency of the tumour to present with a painless mass (reflecting its soft tissue origin), the older age of subjects and the similar incidence in males and females are useful points of difference between skeletal and extraskeletal Ewing's sarcoma [20] and the features of the patients in our small series reinforce these differences.

Our morphological observations confirm that extraskeletal Ewing's sarcoma shows essentially the same appearance by light and electron microscopy as Ewing's sarcoma arising in bone. We could not come to any conclusions with regard to histogenesis and, like others favour an undifferentiated mesenchymal cell as the cell of origin. However, a few ultrastructural findings are worthy of comment. The microtubules and dense core granules noted in rare cell processes in one of our cases have also been reported in Ewing's sarcoma of bone [38] and were regarded as evidence of a broader ultrastructural morphology of such tumours than has been supposed, rather than being unique to neuroblastomas. The disappearance of glycogen following therapy has also been noted by others [39] and the presence of conspicuous secondary cells against a background of tumour necrosis in this specimen reinforces prior suggestions that such cells are degenerate [14, 15].

Ewing's sarcoma of bone has been associated with a poor prognosis when treated with either local radiotherapy or surgery, since even patients presenting with apparently localised disease usually develop metastases [40]. However, combined modality therapy with combination chemotherapy and surgery or radiotherapy appears to have improved disease-free survival [41]. The largest reported series of extraskeletal Ewing's sarcoma noted that the prognosis was poor also, as 22 of 35 patients died from the disease: all but one of the surviving patients were treated by radical surgery [20]. A more recent report, with a smaller number of patients noted that combined modality treatment may induce long-term disease-free remissions and suggested that with such treatment the prognosis for extraskeletal Ewing's sarcoma appeared similar to that for skeletal Ewing's tumours [26]. Our experience, albeit with an even smaller number of patients, supports this view, although the median duration of follow-up for our group is relatively short.

Since 1977, 18 patients with Ewing's sarcoma of bone and 5 with extraskeletal Ewing's sarcoma have been referred to our units. Our experience and that of others [26] suggest that extraskeletal Ewing's sarcoma may occur more frequently than previously assumed. We suggest, therefore, that the possibility of an extraskeletal origin of Ewing's sarcoma should be entertained more frequently.

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