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Clinical Oncology: Case Presentations from Oncology Centres 1. Ewing's Sarcoma

The London Bone Tumour Service

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The management of a case of Ewing's sarcoma of the left proximal humerus in a 15-year-old girl is presented, and the radiological and pathological findings are described. The chemotherapeutic, radiotherapeutic and surgical management of Ewing's sarcoma are discussed with reference to the case.
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AN INTELLIGENT, right-handed, 15-year-old schoolgirl was first seen in early 1991 with 4 months of pain and swelling in her left shoulder. A plain radiograph of her shoulder arranged by her local physician showed radiological features suggestive of a tumour arising in the proximal left humerus. She was referred for further management to the London Bone Tumour Service.

Clinical assessment

The patient was a well and normally developed 15-year-old. There was a firm diffuse swelling overlying the upper third of the left humerus. External rotation of the left shoulder was reduced by 25% because of pain. There was no other limitation of movement but the rhythm of abduction was markedly abnormal with most of the movement being scapulothoracic rather than glenohumeral.

Investigation

The plain radiograph (Fig. 1) shows that the proximal part of the humerus was intact but abnormal changes were present in the shaft just beyond the metaphysis. These consisted of a permeating destructive change involving the medulla and the cortex on its lateral aspect. As a consequence of the formation of reactive periosteal new bone, the cortex on the medial side of the humerus was thickened. The medullary destruction had a wide zone of transition between normal and abnormal bone, a feature of a rapid and aggressive process; however, not all the changes were lytic as some central sclerosis was indicative of a limited endosteal reactive response.

A needle biopsy from an anterior approach, just inferior to the surgical neck of the humerus, was performed. Histological examination of the needle biopsy specimen following rapid decalcification (Fig. 2) showed a focally necrotic malignant round cell tumour permeating the marrow spaces of cancellous bone, showing associated reactive changes. The tumour cells contained intracytoplasmic glycogen and gave a negative reaction with a panel of antibodies, including cam 5.2, *pD7*, NSE and S100, confirming a classical Ewing's sarcoma.

Further imaging was then performed to assess the extent of the tumour. The radionuclide scintigram (^{99m}Tc MDP) (Fig. 3) showed increased uptake in the proximal half of the humerus, confirming the length of the lesion. Computed tomography (CT) (Fig. 4) showed the medullary involvement and the formation of periosteal new bone; the extent of the lesion can be determined by the assessment of serial slices with measurement of attenuation. The scans showed the soft tissue extension was mainly on the lateral aspect of the humerus. A magnetic resonance (MRI) examination (not illustrated here) showed altered signal in the marrow in T1-weighted images, confirming the extent of the lesion as similar to that depicted at bone scintigraphy. The extent of the tumour extension and peritumoural oedema was also depicted well on the T2-weighted images.

The initial investigations staged the lesion of the left upper humeral metaphysis and diaphysis as stage IIB, the tumour

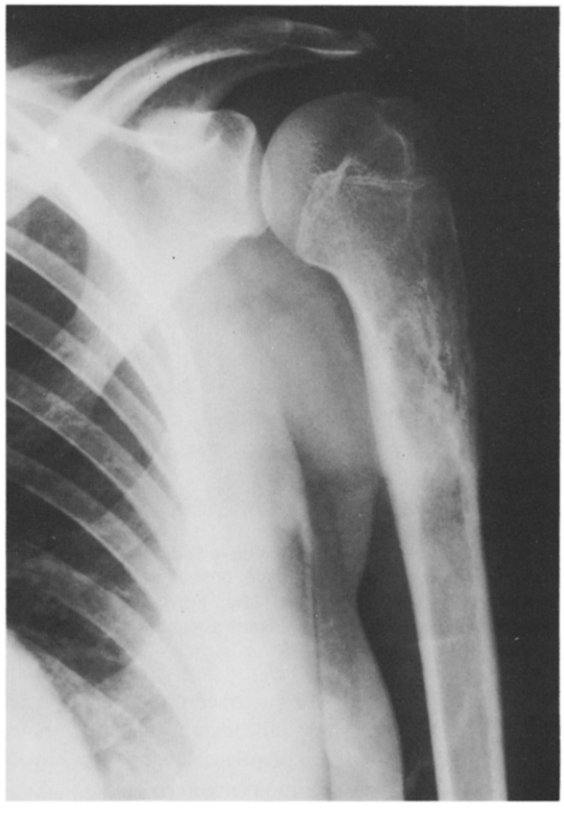

Fig. 1. Initial plain X-ray of the left humerus showing a permeating lesion consistent with Ewing's sarcoma.

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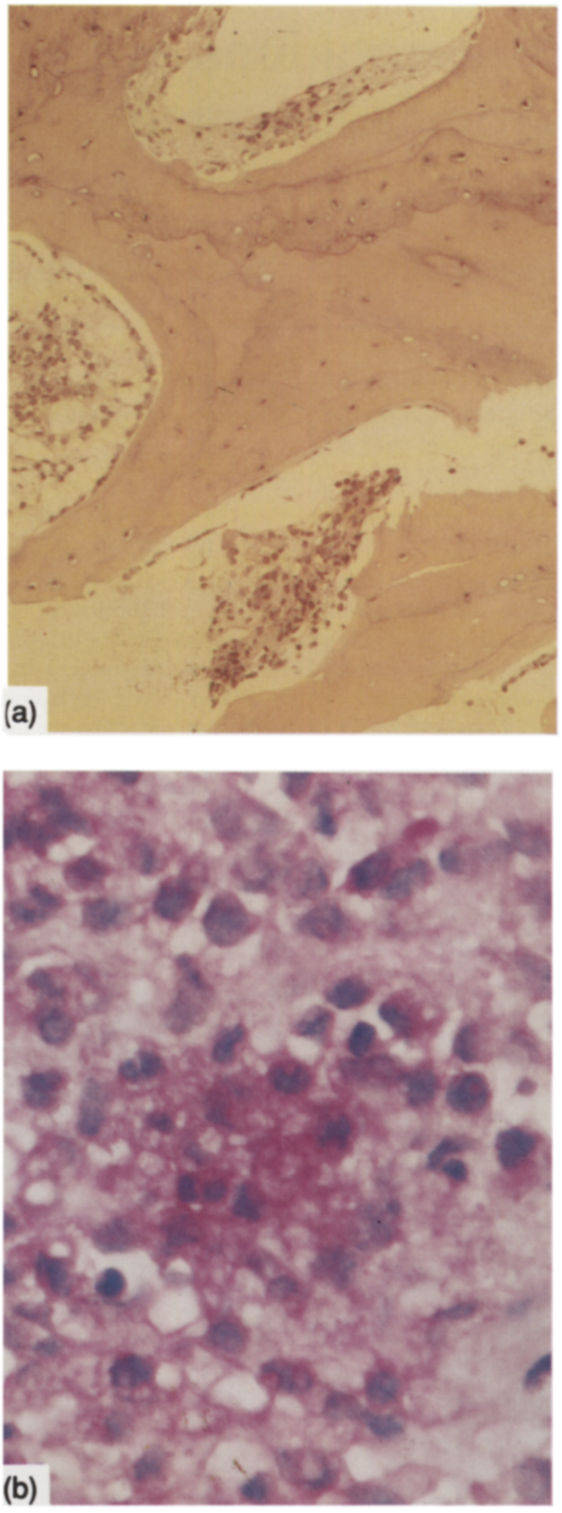

Fig. 2. (a) Low power (haematoxylin–eosin) of the needle biopsy core showing necrotic and reactive bone and islands of Ewing's sarcoma in the marrow spaces. (b) High power (PAS) of the tumour cells showing copious intracytoplasmic glycogen in the tumour cells.

being of high grade and being extracompartmental in nature. From the staging radiology, the extent of the tumour was established and a transection plane marked at 5 cm beyond the furthest extent of apparent tumour involvement.

Full blood count, liver function tests, base measurements of glomerular filtration rate by ^{51}Cr-EDTA clearance and left

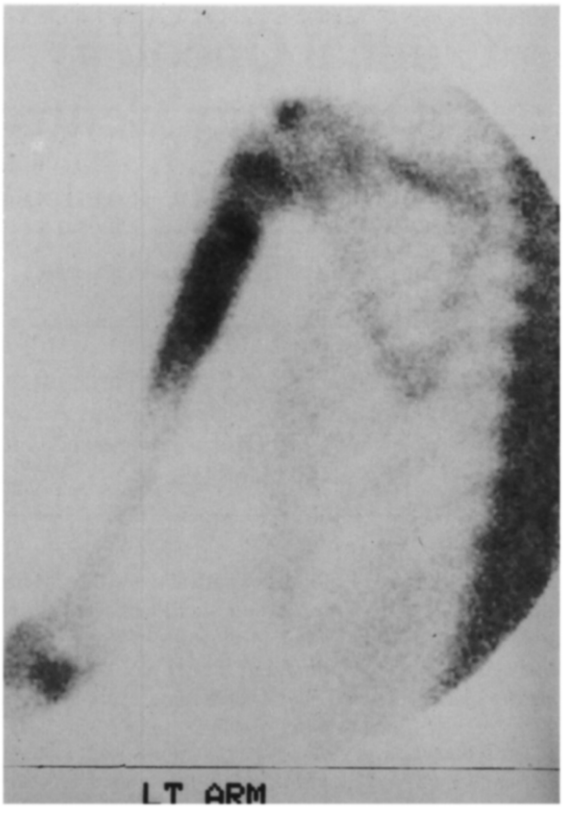

Fig. 3. Bone scan showing the extent of abnormal uptake by the tumour in the left humerus.

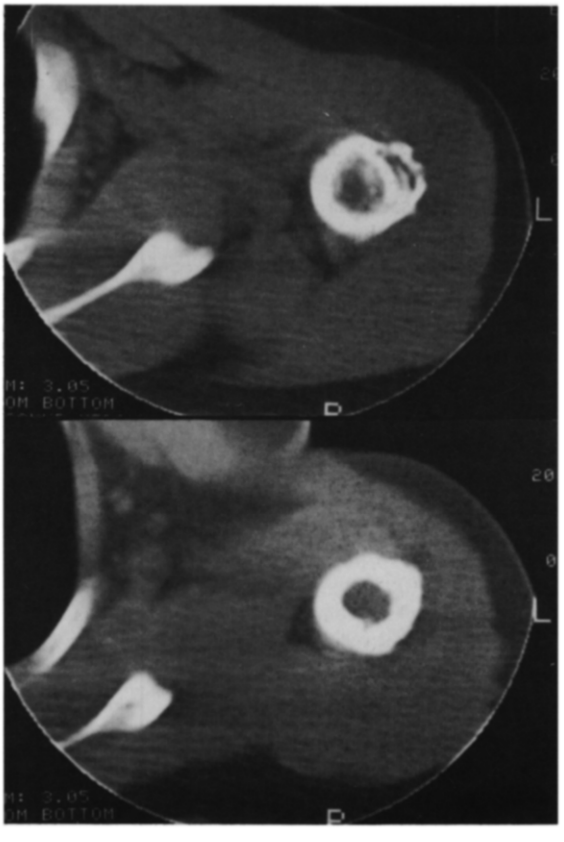

Fig. 4. CT through the tumour at two levels showing penetration of the cortex with lateral spread into the soft tissues.

ventricular function by MUGA scan performed prior to chemotherapy were all normal.

Differential diagnosis and investigation

At this age, the main differential diagnosis would include atypical Ewing's tumour where the tumour cells would have no glycogen, and primitive neuroectodermal (PNET) tumour where, in addition to absence of glycogen, the tumour cells would demonstrate neural features—positive reaction with markers such as neurone specific enolase NSE (Figs 5a,b), and S100 protein, and dense core granules with electron microscopy [2].

In adolescents, particularly if the X-ray is atypical for Ewing's, and the cells show some pleomorphism, the rare small cell osteosarcoma can be excluded by enzyme cytochemistry for bone alkaline phosphatase on air-dried imprint preparations [3]. Occasionally, with lesions in thin or flat bones such as fibula or scapula, there may be doubt as to whether the tumour has arisen in bone or soft tissue. Embryonal rhabdomyosarcoma particularly should then be considered in the differential diagnosis. In this situation desmin should be included in the panel of antibodies used.

Lymphoma presenting in bone was formerly included in the category malignant round cell tumour of bone under the name reticulum cell sarcoma/reticulosarcoma. The distinction from Ewing's rested on absence of glycogen and presence of reticulin fibres surrounding individual tumour cells. The nuclei often stained less densely and indented/bilobed forms could be identified. An older age group was affected. Lymphomas presenting in bone can be diagnosed with immunohistochemistry/ cytochemistry using common leucocyte antibody and B and T cell markers.

In young children, metastatic neuroblastoma should be considered in the differential diagnosis. Imprint preparations are again needed for detection of catecholamines in the neuroblastoma cells.

The plain radiograph remains the best imaging method for demonstrating permeation, cortical erosion and periosteal reaction, and newer imaging methods are supplementary. CT, but especially MRI, will show the soft tissue extension of the tumour which, in Ewing's sarcoma, occurs through a relatively intact cortex, and indicates a high grade of malignant behaviour. MRI shows in any selected plane the altered signal of tumoural spread within the marrow cavity. With CT, one is limited to the interpretation or reformatting of transaxial slices. Only when the presence of calcific features assumes diagnostic importance, e.g. in mineralising tumours such as chondrosarcoma, or when a subperiosteal egg-shell of bone persists, can CT be said to have any advantage over MRI and some of these features are discernible on the plain radiograph. It therefore seems likely that it may prove possible to dispense with CT examination in many tumour cases, although as these entities are rare and therefore dealt with in a few centres, the patient may already have had this investigation by the time of referral. CT retains its unique position for the demonstration or exclusion of pulmonary metastases. MRI is also the best method for accurate surgical staging in limb-salvage and other cases [1] and has, wherever it is readily available, replaced CT.

Bone scintigraphy, although showing some evidence of dynamic activity in a tumour, is of little value in diagnosis, being non-specific in its results. Because of peritumoural vascular activity, the region of increased uptake of the tracer tends to be more extensive than the actual tumoural involvement; the major use of this investigation remains the exclusion of other bony lesions—skip or metastatic. A plain chest radiograph and CT of the thorax showed no evidence of pulmonary metastases; similarly the bone scan showed no additional bone lesions.

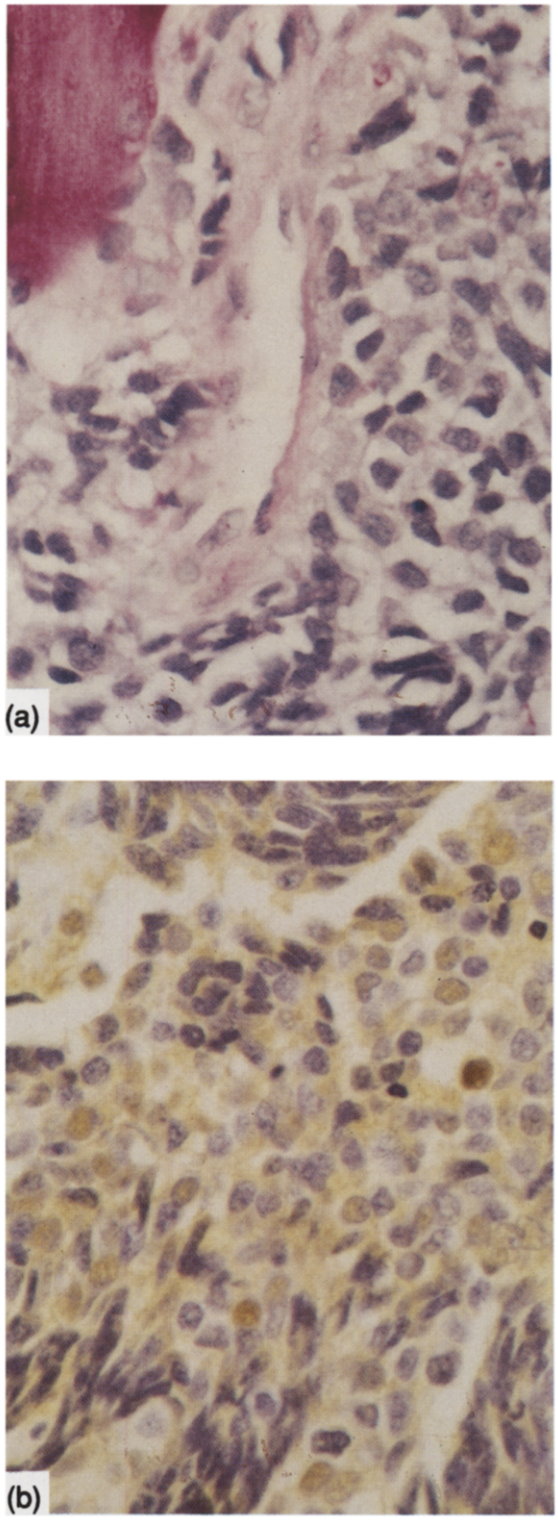

Fig. 5. (a) PNET tumour showing glycogen in a muscle fibre (top left) but no glycogen in the tumour cells. (b) Immunocytochemical staining showing positive reaction of the tumour cells for NSE.

APPRAISAL

Radiology

The radiological diagnosis of a bone tumour still depends primarily on the plain film. In this case, the radiograph showed

a permeative lesion indicating spread that was sufficiently rapid to prevent the host bone from producing a reactive response. If one excluded the possibility of a solitary metastasis, rare at this age, the radiological diagnosis lay between a highly malignant primary tumour of bone and acute or subacute osteomyelitis. The age of the patient, diaphyseal location and permeation was certainly in keeping with the diagnosis of Ewing's sarcoma; the long history, limited formation of reactive bone and absence of sequestration militated against osteomyelitis. An entirely lytic osteosarcoma with failure to mineralise the tumour osteoid was a possible alternative, but less likely in the light of other features so characteristic of Ewing's sarcoma.

Staging

A single staging system is in common use for all malignant musculoskeletal neoplasms [4]. This combines information derived from histology and radiology to grade the tumour (as low or high grade), and from radiology to define the local extent of the tumour (as intra or extracapsular and intra- or extracompartmental) and to determine whether distant metastases are present. Stage I lesions are generally of low grade malignancy and are usually treated locally. Stage II lesions are generally of high grade malignancy and require radical local excision and adjuvant chemotherapy. Distant metastases are present in stage III lesions and, in the case of bone tumours, where radical treatment is contemplated, it may be possible to resect metastatic lesions in addition to local and systemic treatment. Most Ewing's sarcoma are stage II or III. In cases of Ewing's involving the axial skeleton, radiotherapy is frequently the only feasible local treatment option.

Biopsy technique

Although, worldwide, open surgical biopsy remains the common definitive diagnostic procedure, its poor record in respect of complications, often making amputation rather than limb salvage mandatory [5], has made needle or trephine biopsy increasingly attractive, and in our unit is the method of choice for the patient with a bone tumour [6, 7]. Such a restricted biopsy avoids significant contamination and problems with wound healing. Although, ideally, any biopsy should follow full radiological staging, in practice a needle biopsy rarely causes artefact in subsequent imaging procedures. In certain situations, a CT-guided needle biopsy may be the method of choice. The production of such small samples does place a premium on the expertise of the pathologist and supporting technicians.

In specialist centres, needle biopsy has a 95% success rate [5, 7]. The use of imprint/touch cytological preparations is an enormous advantage as there is excellent preservation of glycogen and, if required, enzyme cytochemistry for bone alkaline phosphatase and catecholamines may be carried out where osteosarcoma or neuroblastoma are suspected. If a rapid diagnosis is needed, immunocytochemistry is also possible on imprint preparations. The majority of osteosarcomas and Ewing's sarcomas can be diagnosed on rapid imprint cytology, avoiding any delay between needle biopsy and chemotherapy [7].

TREATMENT

The patient was entered into the UKCCSG/MRC phase II trial of treatment of Ewing's sarcoma (Fig. 6). Treatment was commenced with intensive chemotherapy consisting of ifosfamide, vincristine and doxorubicin given over 3 days (IVAD). The chemotherapy was administered in a purpose-

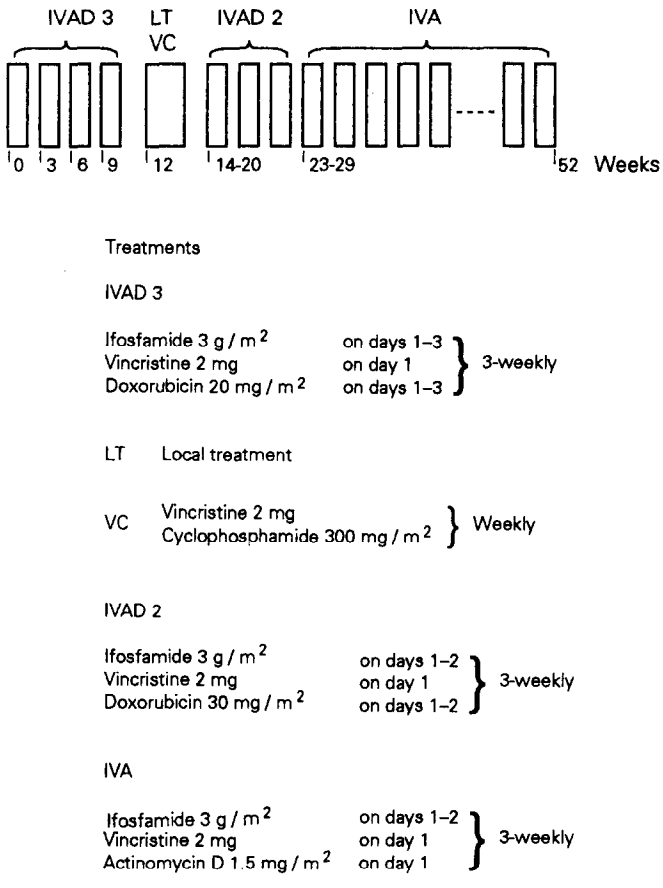

Fig. 6. UKCCSG Ewing's sarcoma protocol.

built ward designed to cater for the special needs of adolescent patients undergoing cytotoxic treatment for cancer. Her first course of IVAD was complicated by a confusional state induced by lorazepam and high-dose metaclopromide given as prophylactic antiemetics, and by an episode of severe neutropenia with fever requiring emergency readmission for broad spectrum antibiotics. Subsequent treatment cycles were better tolerated as a result of the use of ondasetron for antiemetic prophylaxis and a 20% dose reduction. During the 3-week intervals between treatments the patients continued with preparations for her school examinations. After four treatment cycles there had been a dramatic reduction in the clinical size of her tumour. Repeat plain radiographs and CT of her humerus showed a marked shrinkage of the soft tissue component of the tumour and an improvement in the appearances of the bone. A further chest CT again showed no evidence of lung metastases.

On this protocol local treatment is instituted after four cycles of IVAD. A Stanmore custom-built endoprosthetic replacement of the upper third of the humerus was inserted (Fig. 7). At the time of resection, a sample of marrow is taken from the bone beyond the transection point for histology to confirm clearance. If required, rapid imprints are done on this sample while the surgeon waits for the results before inserting the prosthesis. The resected bone, in this case the proximal 17.4 cm of the humerus, is inspected on the outside for any evidence of tumour and is then divided longitudinally in the plane of maximum tumour diameter using a band saw. A longitudinal slab slightly less than 0.5 cm thick is sawn and a fine detail X-ray of the slab is taken (Fig. 8a). This acts as a reference map for the histological blocks and and also gives a good indication of the extent of the

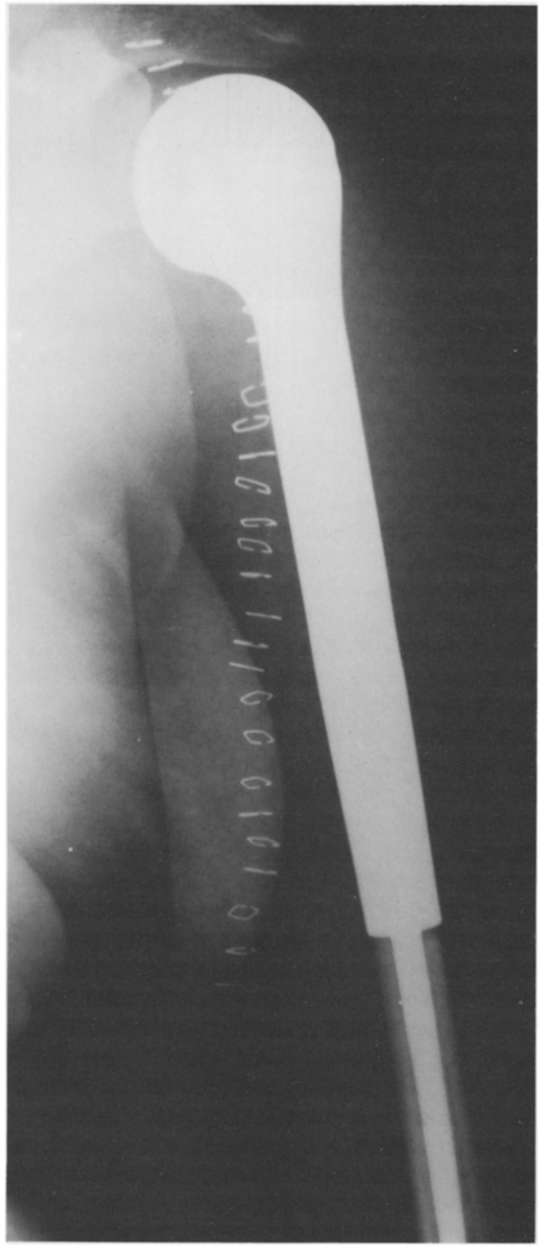

Fig. 7. Postoperative X-ray showing the Stanmore humeral endoprosthesis.

abnormality. Tumour-bearing bone shows a variety of response to pre-operative chemotherapy, usually with dense reactive sclerosis in Ewing's sarcoma. The rapid nitric acid method of decalcification is now used in cases where there is an urgent need to assess the clearance margins and the tumour resonse to chemotherapy. This is particularly so for Ewing's sarcoma as, in contrast to osteosarcoma, the tumour has usually extended beyond the periosteum (compartmental boundary) at the time of biopsy.

In this case 15 blocks were taken from the resected proximal humerus. The tumour response to chemotherapy was good but incomplete. The areas of residual viable tumour (Figs 8 b,c) are also indicated on the X-ray "map". None approached close to the bone or soft tissue margins. Low dose weekly chemotherapy with cyclophosphamide and vincristine was continued during the perioperative and postoperative period. Full-dose chemotherapy with scheduled dose modifications, to prevent cumulative toxicity, was recommenced 2 weeks postoperatively once the wound was adequately healed.

Chemotherapy continues for 1 year after the start of treatment. On completion of treatment, patients are seen at frequent intervals with regular chest X-rays especially during the first 3 years when the risk of relapse is high.

DISCUSSION

Ewing's sarcoma is rare. In Western nations the annual incidence in whites is 2 per million below the age of 16, rising to 4–6 between 16 and 22, then falling. It is exceptionally rare in blacks. Its rarity, as with most bone sarcomas, usually leads to a delay in diagnosis. Clinically detectable metastases are present in approximately 10–40% of newly diagnosed cases. Prior to the introduction of chemotherapy in the 1960s, the long-term survival rate reported in most series was less than 10% [8]. The most common sites of relapse in patients with adequately treated primary tumours are lung and bone, implying that micrometastatic disease is nearly universal. As with many malignant round cell tumours, Ewing's sarcoma shows a rapid response to chemotherapy and radiotherapy. Despite the improvement in long term survival recorded in cancer registry data since 1970 [9, 10], which probably stems largely from the introduction of routine chemotherapy, tumour recurrence, both locally and systemically is still frequent. The problems of early metastasis, drug resistance, and late local recurrence have, in recent years, led to a reappraisal of chemotherapy and methods of local treatment.

Chemotherapy

Ewing's sarcoma is the most chemosensitive of the bone sarcomas. A number of alkylating agents, particularly cyclophosphamide [11, 12], have shown to have useful activity in treating the disease. Similarly, vincristine [13], actinomycin [14] and doxorubicin [15, 16] are active drugs. These four drugs have formed the mainstay of most treatment programmes for many years.

Ifosfamide is the most promising of the newer cytotoxic drugs evaluated in Ewing's sarcoma; a response rate of 45% has been reported in heavily pretreated patients with recurrent disease [17]. Although direct comparisons with older alkylating agents have not been possible in Ewing's sarcoma, ifosfamide has been shown to be superior to cyclophosphamide in the treatment of soft tissue sarcoma [18]. Ifosfamide is now being used in place of cyclophosphamide in a number of recently initiated Ewing's treatment programmes. Etoposide has also been reported to have significant single-agent activity in relapsed disease [19]. The results of single-agent trials with cisplatin in relapsed disease are disappointing [20].

Multidrug chemotherapy was introduced into the treatment of Ewing's sarcoma approximately 20 years ago. Because of the rarity of the disease, very few randomised trials of treatment have been performed. Consequently, it is difficult to compare the results of the various treatment regimens. All reports, however, emphasise the extreme initial chemosensitivity of the disease with most reporting in excess of a 90% response rate.

Rosen [21] developed a series of treatment protocols over a 10-year period. In the earliest study patients were treated with sequential actinomycin, doxorubicin, vincristine and cyclophosphamide started concomitantly with radiotherapy and continued for 18 months. Subsequently additional drugs were introduced, treatment was given in alternating combinations prior to local irradiation, and postirradiation single-agent treatment was

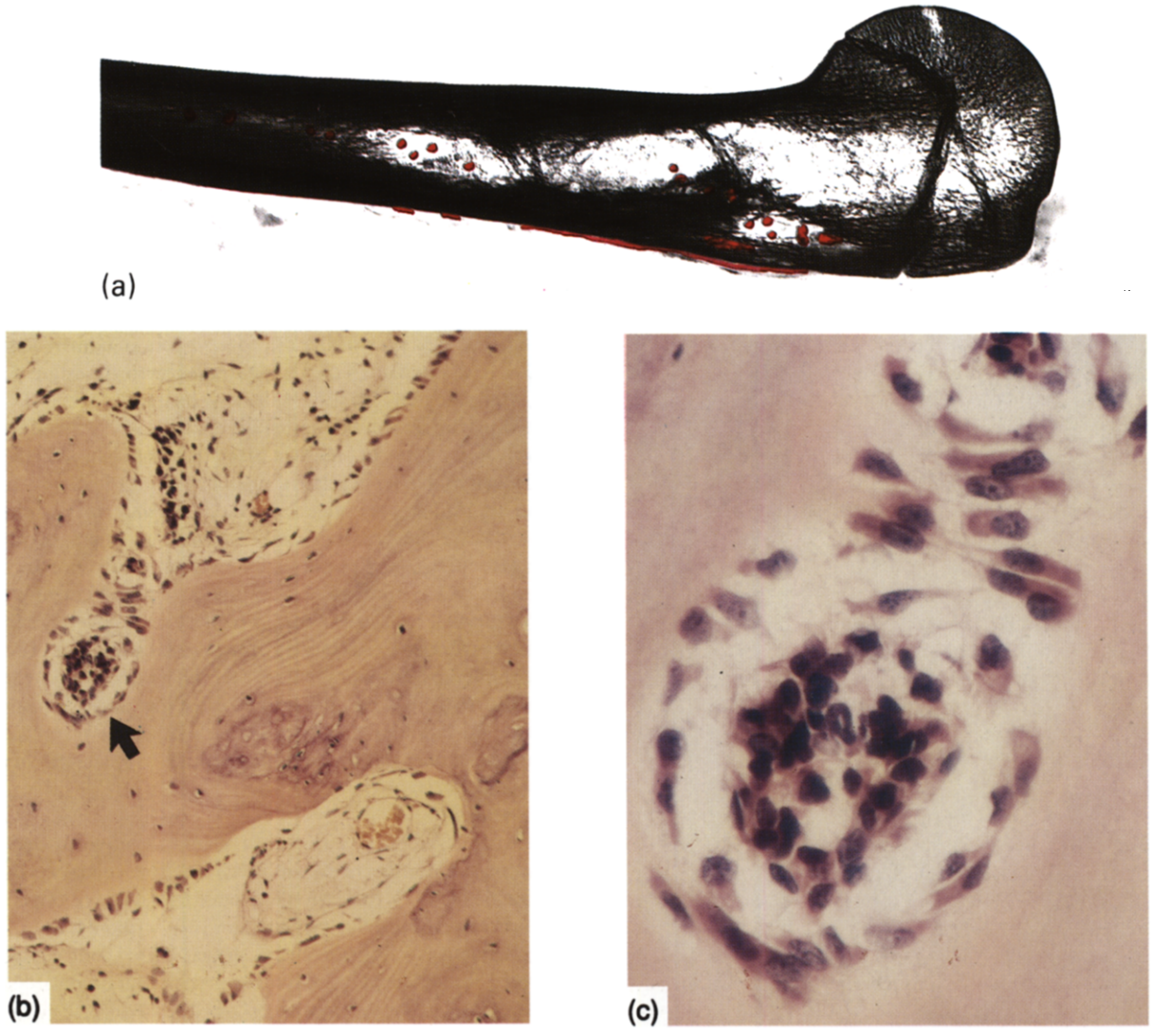

Fig. 8. (a) Fine detail X-ray of resected proximal humerus showing marked reactive sclerosis of the bone. Areas of residual viable tumour indicated by red dots. (b) Medium power of area from resected proximal humerus showing two islands of residual Ewing's sarcoma and associated reactive changes in the bone. (c) High power of area indicated in (b) showing hyperchromatic staining of Ewing's tumour cells in contrast to the reactive osteoblasts which have more open nuclei with prominent nucleoli.

replaced by combination treatment given over a shorter (9-month) period. The overall 2-year disease-free survival for children treated on these programmes was 79%.

Similarly Hayes *et al.* [22] treated patients with sequential cyclophosphamide and doxorubin prior to irradiation, followed by further treatment with vincristine and actinomycin and sequential cyclophosphamide and doxorubicin, in a programme lasting 10 months. 17 of their 52 patients relapsed, the majority within 3 years. The influential IESS I study [23] was able to enter 342 patients into a complex randomised trial in which it was shown that the addition of doxorubicin to the combination of vincristine, actinomycin and cyclophosphamide resulted in a significant prolongation of relapse-free survival (60% vs. 24% at 5 years).

European treatment programmes resemble North American programmes in using the same basic four-drug combinations, with chemotherapy started prior to local treatment and continued for a total of 10–18 months [24, 25]. The results are comparable to those of the IESS I study.

Despite these encouraging results, the improved short-term results of treatment of Ewing's sarcoma did not result in a significantly improved long-term survival in the UK as a whole over the period 1972–1985 [10]. It is, possible that the intensification of chemotherapy in the newer treatment programmes will lead to an improved long-term outcome. Several programmes are now evaluating the use of high-dose chemotherapy with autologous bone marrow transplant in high-risk patients such as those with metastasis at presentation. The current UKCCSG protocol (Fig. 7) uses the four-drug combination of alkylating agent, vincristine, doxorubicin and actinomycin. The study is evaluating the effects of intensification of chemotherapy by the replacement of cyclophosphamide with high dose ifosfamide. As in many other Ewing's sarcoma protocols, initial treatment is with chemotherapy. Although response in bone is difficult to evaluate, Ewing's sarcomas almost invariably have a soft tissue component and the response of this to chemotherapy can readily be assessed by a combination of clinical examination and serial CT or MRI.

Initial chemotherapy has the additional benefits of reducing the tumour size, making effective local treatment easier, and in

cases where endoprosthetic replacement is considered, allowing time for manufacture of a prosthesis.

The toxicity of treatment remains substantial. On the UKCCSG protocol, alopecia is inevitable and the use of ifosfamide carries the additional burden of frequent inpatient episodes for treatment. The availability of $5HT_3$ antagonists, however, has greatly reduced the major short-term toxicity of emesis. The question of the effects of chemotherapy on the health of long-term survivors from treatment given in adolescence has only recently begun to be addressed and is now the subject of ongoing studies. It is possible that many patients experience subclinical organ damage, particularly renal and cardiac [26], which will become manifest in middle age, in addition to the known effects of alkylating agent treatment on fertility and the risk of secondary cancers. The long-term toxicity is a powerful argument in favour of reducing the total amount of chemotherapy in patients who can be identified as having a good prognosis.

Radiotherapy

Radiotherapy has clear advantages over surgery for local treatment in that loss of bone and muscle is avoided. Since the radioresponsive nature of this tumour was recognised by Ewing in 1921, radiotherapy was, wherever possible, the treatment of choice except in expendable bones. In recent years, however, following advances in surgery for osteosarcoma, radical surgery has been possible with maintenance of good limb function using prosthetic replacements. The fundamental issues in making a choice are those of local control, functional outcome and second malignancy.

Assessment of local control is confounded by several factors. There is a selection bias with smaller tumours undergoing surgery than those treated with radiotherapy alone [27]. Relapse rates, both local and distant, are higher in bulky tumours, being 10% in tumours less than 8 cm, rising to 30% in those greater than 10 cm [28].

There are considerable differences in results from multicentre groups compared with single institutions with control rates in pelvic tumours for example ranging from 85% [29], down to 70 or 30% [30, 31]. There are also variations due to technique. The introduction of centralised planning in the CESS study in 1983 reduced the local relapse rate from 51 to 20% [24]. Chemotherapy has a dual effect on recurrence rate. It contributes to local control but, by producing more long-term survivors, allows late local relapse to become apparent [32]. Local control rates from radiotherapy have risen from 50–70% before multimodality therapy to 67–95%, and local relapse was less in those with "inadequate" radiotherapy volumes with four than with a three-drug combination [33]. Finally the local control rate depends on the assiduousness with which local relapse is sought in patients who also have metastases. Necropsy studies increased local failure rate from 17 to 23% [34].

The functional results are a critical component of treatment strategy. In certain sites surgery remains, at present, either impossible or associated with poor function: the vertebral bodies especially with soft tissue extension, the upper scapula, the acetabulum and sacrum. At these sites radiotherapy remains the treatment of choice. In other sites, such as the femur, prosthetic replacement is well established with excellent function at least in the short term. In the humerus (as in this case) it is not clear if the advantage lies with surgery. Few data are available on late morbidity and limb function to allow a comparison.

Overall functional results following radiotherapy have been reported as excellent [35] or inferior to those produced by surgery [21]. They relate to multiple factors, including site, volume irradiated, dose, fractionation schedule, and sequencing with chemotherapy [33, 37]. The IESS 1 late effect study [32] suggested that the most profound effects are on the weight-bearing skeleton. Inequalities in the upper limb were on the whole well tolerated and of little significance. Postirradiation fibrosis and stiffness were also well tolerated and compatible with satisfactory function. Distal oedema was unusual, but problematical when it occurred. Whilst irradiation of the vertebral bodies was associated with a loss of height of 5–10 cm from projected height, this was also well tolerated. Treatment of the ilium however, where there had often been extensive destruction, was associated with stiffness and a limp. The most signficant problems were in the femur, with two thirds of the group having shortening and one third pathological fracture. Shortening was less in those with tibial lesions. Generally, function after radiation of hands or feet was not good. Butler [38] reviewed the skeletal consequences in 143 patients who had been irradiated in childhood, with 36% showing asymmetry of chest, and 16% significant pain at the site of radiotherapy. However, skeletal complications are less in those treated with more modern techniques.

It has been the practice to irradiate the entire long bone, following the observation of extensive marrow involvement [39]. In the growing child, this led inevitably to impaired growth. IESS II excluded the epiphysis furthest from the tumour with no loss of local control. Current recommendations are that provided there is a good margin a formal attempt to include the whole bone is not necessary.

The risk of second malignancy is perhaps the most cogent reason for a surgical rather than a radiotherapeutic approach wherever possible. Several studies have shown an increased risk of solid tumours in children irradiated for a variety of tumours. Radiotherapy alone is associated with a 2.7 risk [40] rising to 5.8 risk in sites receiving more than 50 Gy [41]. In Tucker's analysis of 9170 survivors over 2 years treated for various malignancies, 92% of second solid tumours were in or within 5 cm of the radiation field and the risks were dose related. Chemotherapy both with alkylating agents [40] and with dactinomycin [36] increases risk associated with radiation alone [40, 41].

Conventional fractionation with 55 to 60 Gy given over 6 weeks has usually led to a reduction in intensity of chemotherapy for several weeks, because of enhanced acute and late toxicities. However, as failure in Ewing's sarcoma is still primarily at sites of metastases, various attempts have been made to avoid this by alternating chemoradiotherapy or concomitent chemotherapy and hyperfractionated radiotherapy. The enhanced toxicity of the concomitant administration is mitigated in terms of late toxicity by the small dose per fraction and the acute by a planned gap. However, as two fractions per day are administered, overall radiotherapy treatment time is not increased. While this approach has produced acceptable acute toxicity to date, larger studies with assessment of late toxicity are required to ascertain if this approach offers advantage.

Local excision and reconstruction

There are a number of surgical options available in terms of reconstruction following a radical removal of the proximal humerus. These included the uses of an osteochondral allograft [42], the fashioning of an arthrodesis between the glenoid and the residual humerus, or the use of the prosthetic replacement, custom designed and manufactured for the patient. This latter

method was the one chosen in this particular case. The prosthesis was designed and manufactured in titanium at the Department of Biomedical Enginering at the Institute of Orthopaedics at Stanmore. At surgery, following cementation of the medullary component of the prosthesis into the distal humerus, some attempt is made to reconstruct the rotator cuff. The rotator cuff is now reattached directly into drill holes on the humeral head of the prosthesis which gives excellent stability of the head.

Definitive surgical treatment in this case consisted of a resection with a wide surgical margin. This is easy to determine in the case of bone as 5 cm clear of the most distal abnormality in the MRI on the prechemotherapy staging film. This point can be seen at approximately two thirds of the way down the humeral diaphysis. In terms of the soft tissue mantle this is more difficult to define. Ideally, 2 cm surgical clearance is required and certainly the rotator cuff must be sacrificed in order to be clear of the pseudocapsule of the tumour. The neurovascular bundle may encroach significantly closer than this 2 cm conceptual barrier, but this does not appear to significantly affect the long-term results. In this particular case the radial nerve appeared to be tethered to the tumour at approximately the mid diaphysis. Accordingly a proportion of the nerve was resected and re-anastomed.

Prosthetic replacement cannot be performed without risk of complications. The major risk is infection and despite precautions this is still in the order of 4.8%. Loosening of upper humeral prostheses is extraordinarily rare as the humerus itself is not a weight-bearing joint, and the lack of fixation of the humeral head means that tortional forces on the humeral shaft are significantly low. The major functional complication of the upper humerus is superior migration to lie beneath the acromioclavicular joint which causes some stiffening and loss of movement from that previously reported.

Prognostic factors

The major determinants of prognosis are the size of the primary tumour, the presence of detectable metastases, and, less certainly, neuroendocrine features. It has long been recognised that tumours in the pelvis have a worse prognosis than limb tumours [43]. Recent analyses have suggested that volume rather than site is the major determinant of these differences. Studies from St Jude's Hospital [22] and from the CESS group [24] have both shown the adverse effect of tumour volume on outcome. In the pelvis, in particular, tumours may reach a very large size and radiation therapy has been associated with a local failure rate of around 50% [25]. While new forms of fractionation and chemotherapy/radiotherapy combinations may improve these results there is also a need for exploration of surgical alternatives. With large pelvic tumours surgery may be associated with considerable functional disability and the long-term sequelae of radical operations is not known. Furthermore, with large tumours the resection margins are often not free of tumour [44] and there is then the need for radiation in addition with the attendent risks discussed previously. Large limb tumours may be resected with less morbidity after initial chemotherapy and limb conservation surgery is playing an increasing role in tumours at these sites.

Metastases are detectable at diagnosis in 25–40% of patients and in these patients the prognosis is much worse. Although cure is possible after presentation with pulmonary metastases, only 30% of patients are alive at 5 years [45]. Presentation with bone metastasis is almost invariably fatal. In these patients the prognosis will only be improved by more effective systemic treatment, either by new agents or intensification of chemotherapy using techniques such as autologous bone marrow transplantation (ABMT). There is as yet little evidence on which to judge the effectiveness of high dose chemotherapy and ABMT and, in such a rare tumour, international collaboration in trials may be necessary.

The histologically "atypical" Ewing's tumour, and possibly the neuroendocrine phenotype, seem to be associated with a worse prognosis [46]. The round cell tumours of the chest wall and pleural space described by Askin [47], although chemosensitive, often relapse quickly. Progress in management of these cases, as with metastatic Ewing's, awaits more effective chemotherapy regimens.

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Book Review

Autopsy in Epidemiology and Medical Research

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IN AN awkward preamble to radio and television interviews on environmental hazards, I have often had to explain what a professor of morbid anatomy is. It is useful, therefore, to find the thoughtful foreword to this IARC text by Tomatis begin with a reminder that autopsy means "seeing with one's own eyes".

Why, in the UK at least, do so few of those responsible for clinical care find this necessary? Many of them would contest any suggestion that they fail to care for their patient adequately if they do not ask for autopsy examinations to be performed, and if they fail to attend them when they are done. And yet nine major studies performed in the last 10 years have shown an almost constant 25–30% diagnostic error rate—errors which would have affected management. The identification of toxic or other adverse reactions to drugs has been delayed by failure of investigation. Coronial autopsies are an increasing proportion of all autopsies performed in the UK and are performed differently for different objectives and reasons; they do not fill the gap developing in our assessment of the natural history of disease and its management.

In this volume, many issues relating to the autopsy as an investigation are addressed. The start is not promising; in a review of secular changes in age at death and causes of death in Trieste (1901–1985), the data provide information similar to that found in other seqential studies but the reasons for the changes are the source of extravagant speculation in an overview. This is most emphatically not the flavour of the whole volume, however. Holzner's fine review of Austrian practice indicates why the European School of Pathology will base its autopsy teaching there; his observations on the use of autopsy data as