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Bone Marrow Involvement in Adult Soft Tissue Sarcomas

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Abstract—*Bone marrow biopsy was performed as part of the initial assessment in 74 patients with soft tissue sarcoma. Infiltration of the marrow by tumour was present in four cases, all from the group of 56 patients who had other evidence of metastatic disease, giving an overall incidence of 7%. The histological subtypes were pleomorphic rhabdomyosarcoma, angiosarcoma, synovial sarcoma and myxoid liposarcoma, of which the first three were high-grade tumours. Although it was not possible to determine whether response to chemotherapy was influenced by marrow involvement, haematological toxicity seemed excessive.*

INTRODUCTION

A VARIETY of metastatic manifestations of soft tissue sarcoma have been reported in the literature and typical patterns of dissemination, determined by a review of autopsy material from 156 patients, have been described [1]. Although these tumours have a predilection for pulmonary metastasis, other less common sites such as the brain and bone marrow may have clinical relevance in patients treated with chemotherapy. Gercovich *et al.* [2] first suggested that intracranial relapse was more common following successful chemotherapy for sarcoma and this was confirmed by Espana *et al.* [3].

Bone marrow involvement suggests widely disseminated disease, may impair tolerance to chemotherapy and might be expected to carry a poor prognosis. This is certainly true in childhood rhabdomyosarcoma, in which bone marrow involvement assigns the patient to the most advanced stage and is associated with a median survival in the order of 13 months, despite aggressive chemotherapy [4].

In contrast with embryonal rhabdomyosarcomas, there are no large series of adult sarcoma in the literature which include bone marrow biopsy as part of the staging investigations. We report an incidence for bone marrow involvement in adult soft tissue sarcoma based on a series of 74 patients, the majority of whom had advanced local or metastatic disease.

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MATERIALS AND METHODS

Patients with soft tissue sarcoma presenting to the Christie Hospital, Manchester, between October 1976 and June 1981 had a bone marrow biopsy performed prior to chemotherapy. Aspirate and trephine biopsies were taken from the posterior iliac crest, avoiding areas within radiotherapy fields or sites of obvious bony metastasis. Follow-up biopsies were performed in three out of four of the positive cases.

RESULTS

Seventy-four patients had adequate pre-treatment bone marrow biopsies. The histological types of sarcoma are shown in Table 1 and the sites of disease in Table 2. Four patients had tumour infiltration of the marrow, demonstrated by aspirate and trephine in two cases and by trephine biopsy only in the other two cases. The salient clinical features are described in Table 3, and illustrated in Figs. 1–5.

DISCUSSION

Although bone marrow biopsy is a routine staging process in childhood rhabdomyosarcoma, it is rarely performed in adult soft tissue sarcoma. Treatment of sarcoma is primarily surgical and since cure may be effected by wide local excision or amputation, investigations for metastases are

Table 1. Soft tissue sarcoma—histological types

Leiomyosarcoma	20
Neurofibrosarcoma	9
Undifferentiated	9
Malignant fibrous histiocytoma	7
Liposarcoma	7
Rhabdomyosarcoma	6
Synovial sarcoma	4
Fibrosarcoma	3
Angiosarcoma	3
Miscellaneous:	6
mixed mesenchymal uterus	3
endometrial stromal uterus	1
metastasising fibromatosis	1
epithelioid	1

Table 2. Soft tissue sarcoma—sites of disease

Locoregional disease only	12
Metastases ± local recurrence:	56
lymph nodes	5
skin/subcutaneous	12
bone	7
pulmonary	40
intra-abdominal	13
hepatic	7
other	9
No residual disease	6

often limited and usually do not include a bone marrow biopsy. Reports of metastatic disease in the bone marrow have usually been incidental findings, either at post-mortem or when marrow biopsy has been performed for some other reason. However, in advanced disease marrow invasion may be more common. As part of a larger series including a variety of tumours, Jonsson and Rundles [6] reported 5 positive marrow aspirates in 11 patients with sarcomas of unspecified type which may have included embryonal rhabdomyosarcomas. This high incidence probably reflects patient selection and the authors' policy of performing aspirates from clinically or radiologically involved bony sites.

It has been recognised that bone marrow involvement in childhood rhabdomyosarcomas is common in generalised disease and has prognostic significance, although the bone marrow is rarely investigated in other types of paediatric sarcomas. Pratt *et al.* [7] reported a series of 153 children with rhabdomyosarcoma presenting to St. Jude's Hospital between 1962 and 1978, 20 (13%) of whom had marrow involvement and 19 of whom were dead. Delta and Pinkel [8] demonstrated marrow involvement on aspirate only in 3 of 13 children with embryonal rhabdomyosarcoma, 2 of 6 with osteosarcomas and 1 of 8 with Ewing's sarcomas.

The prognostic significance of the histological grade of the primary sarcoma has been recognised and a new staging system, incorporating this feature, has been proposed [9]. The metastatic potential of high-grade tumours is apparently greater, and 3 of the 4 cases cited here would have been expected to metastasise widely. Although several early biopsies in case 1 showed benign histological features and were interpreted as diffuse haemangiomatous malformation, increasing prominence of the dense network of small capillary vessels with actively proliferating endothelium suggested a diagnosis of angiosarcoma at the time of mastectomy 4 yr later. Angiosarcoma of the breast is an extremely aggressive tumour and long-term survivors are rare [10–13]. In contrast, the widespread dissemination, including bone marrow infiltration,

Table 3. Clinical features of patients showing marrow involvement

	Case 1	Case 2	Case 3	Case 4
Age/sex	36/F	50/F	18/M	37/M
Primary site	Right breast	Right triceps	Dorsum left foot	Left thigh
Histological type	Angiosarcoma	Pleomorphic rhabdomyosarcoma	Monophasic synovial	Myxoid liposarcoma
Histological grade	H	H	H	L
Sites of metastases	Bone	Lung	Bone Extradural D11 Lung	Liver Intra-abdominal Lymph nodes Skin
Blood count: Hb g/dl	10.2	12.1	10.7	12.9
(at time of WBC × 10^9/l	9.6	5.5	5.2	8.4
marrow platelets × 10^9/l	303	216	225	248
biopsy)				
Chemotherapy	CYVADIC*	CYVADIC*	CYVADIC*	Carminomycin
Response to chemotherapy	PD	PD	PD	PR
Survival: from diagnosis	60	52	36	34
(mos) from marrow biopsy	4	20	5	21

Abbreviations: M, male; F, female; H, high; L, low; PD, progressive disease; PR, partial remission.
*CYVADIC = cyclophosphamide/vincristine/adriamycin/DTIC.

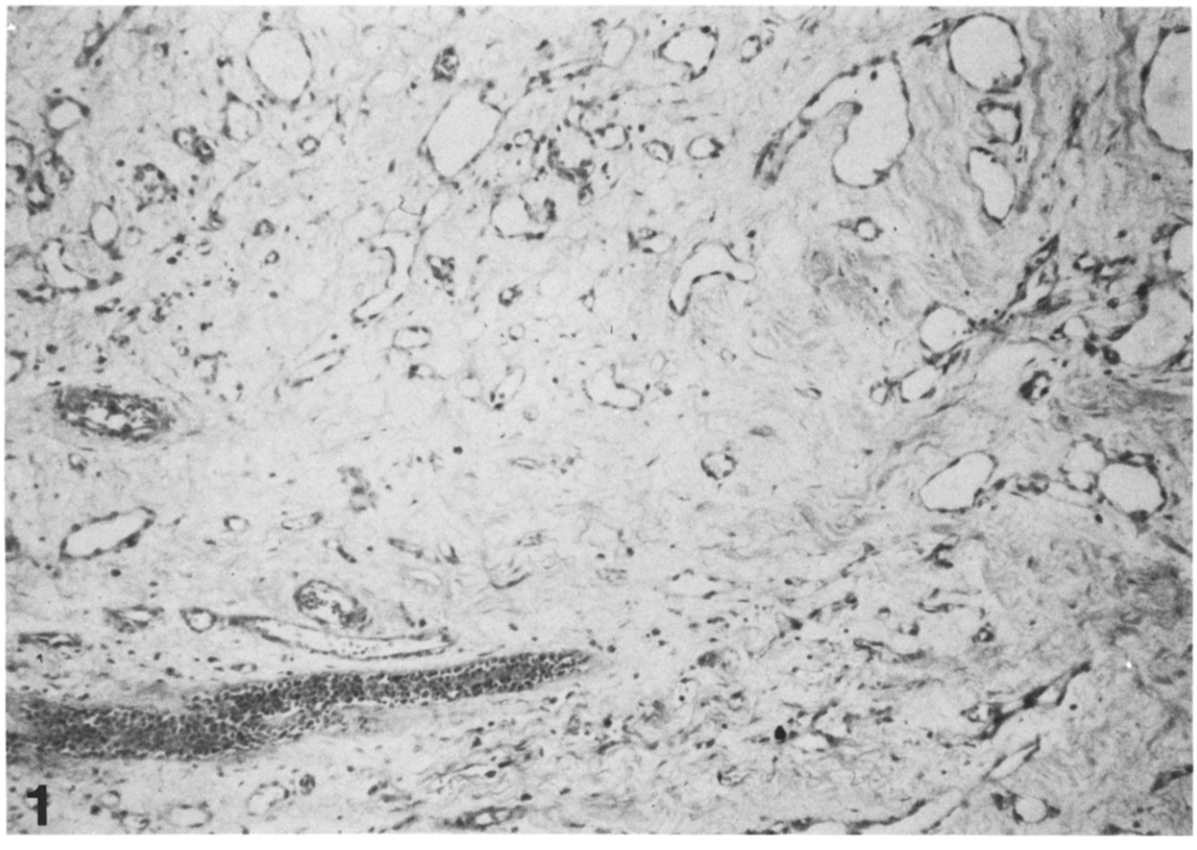

Fig. 1. Case 1: primary tumour: angiosarcoma right breast; haematoxylin and eosin; × 57.

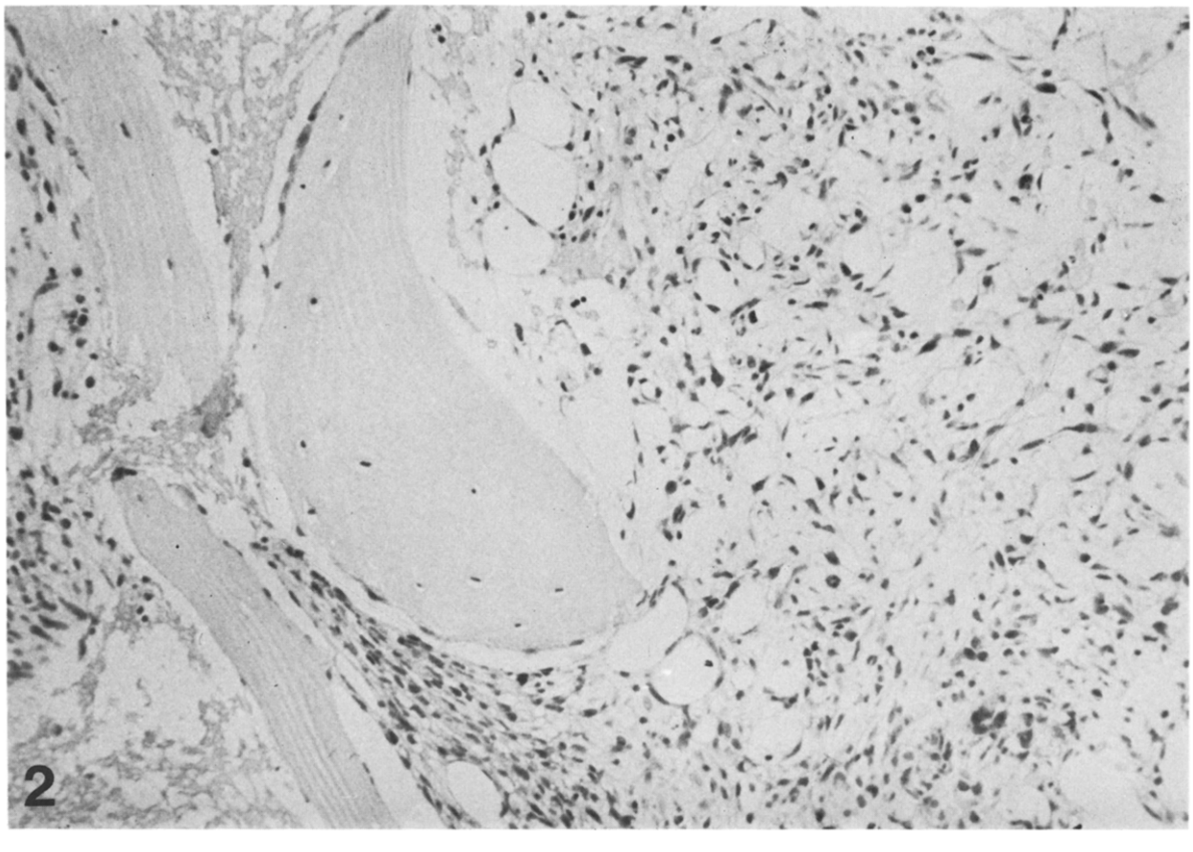

Fig. 2. Case 1: bone marrow trephine showing metastatic angiosarcoma; haematoxylin and eosin; × 57.

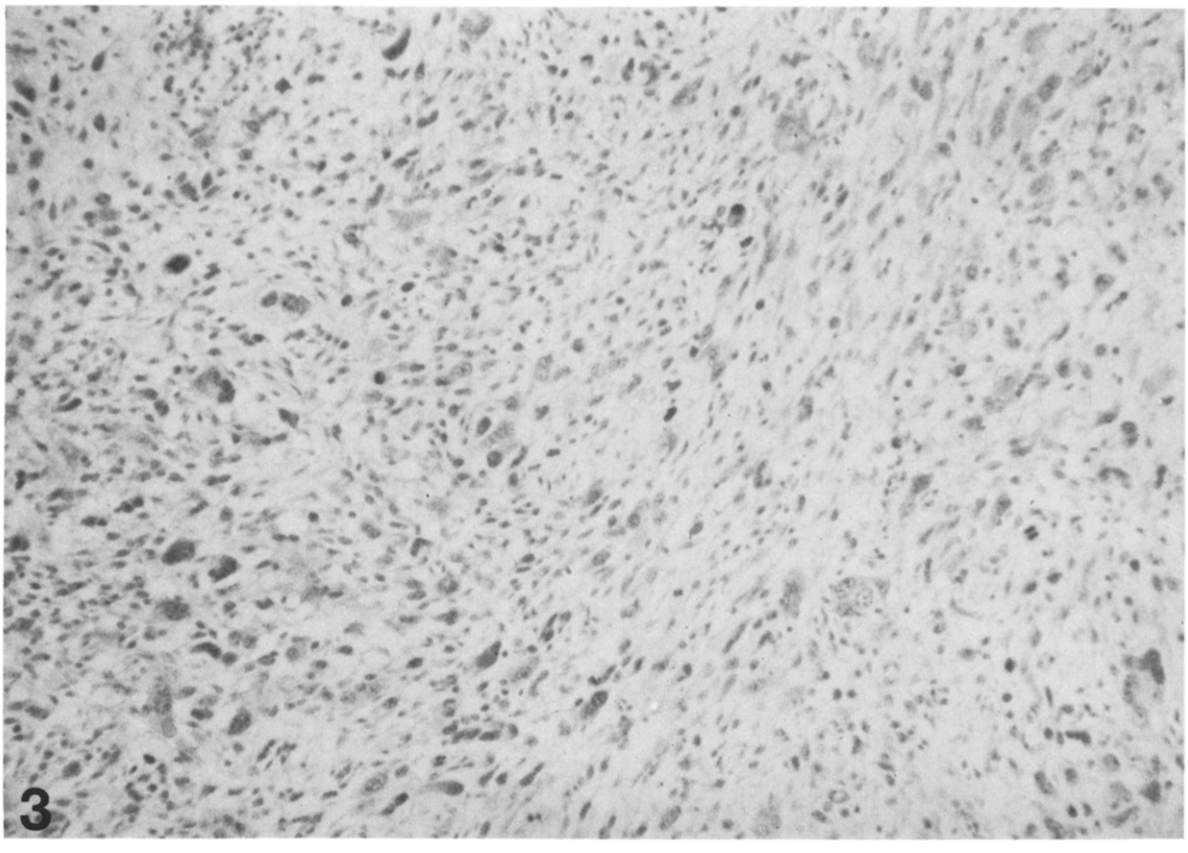

Fig. 3. Case 2: primary tumour: pleomorphic rhabdomyosarcoma right triceps; haematoxylin and eosin; × 57.

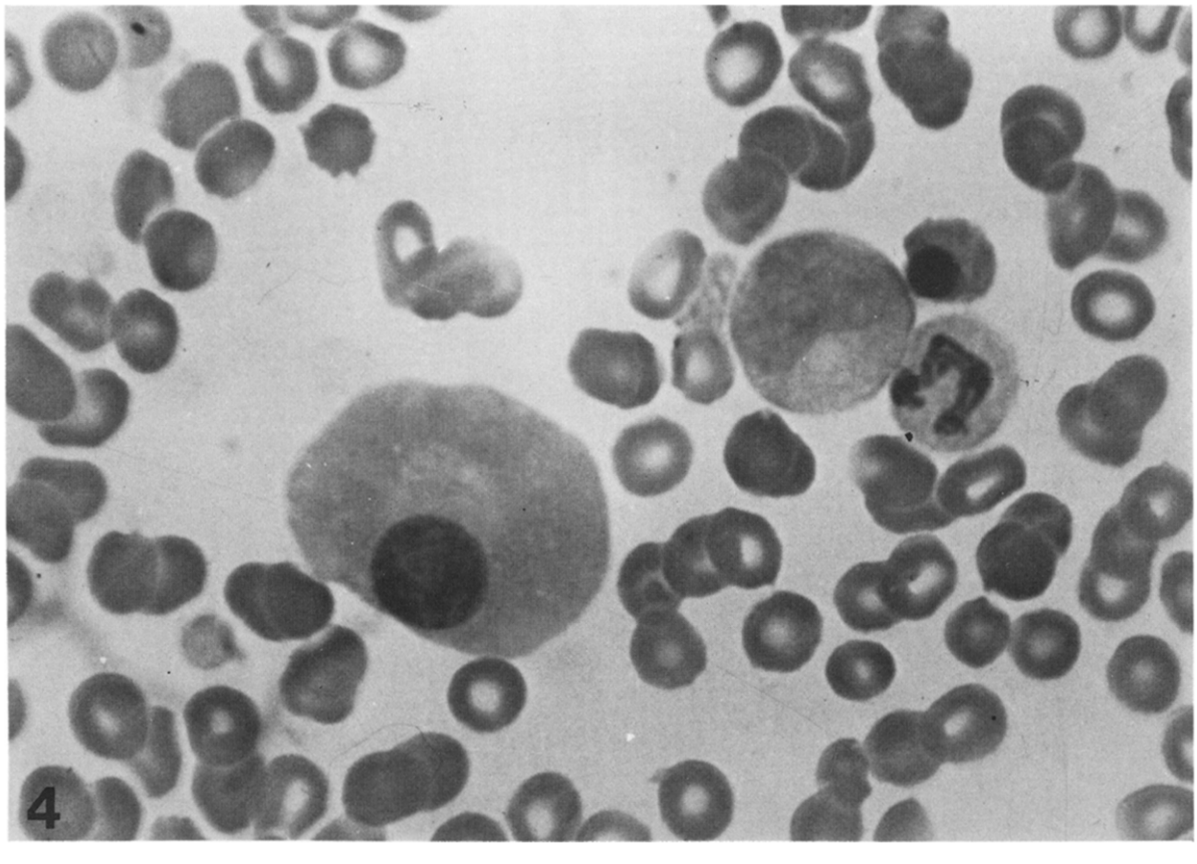

Fig. 4. Case 2: bone marrow smear showing tumour cell; May-Grünwald-Giemsa; × 1092.

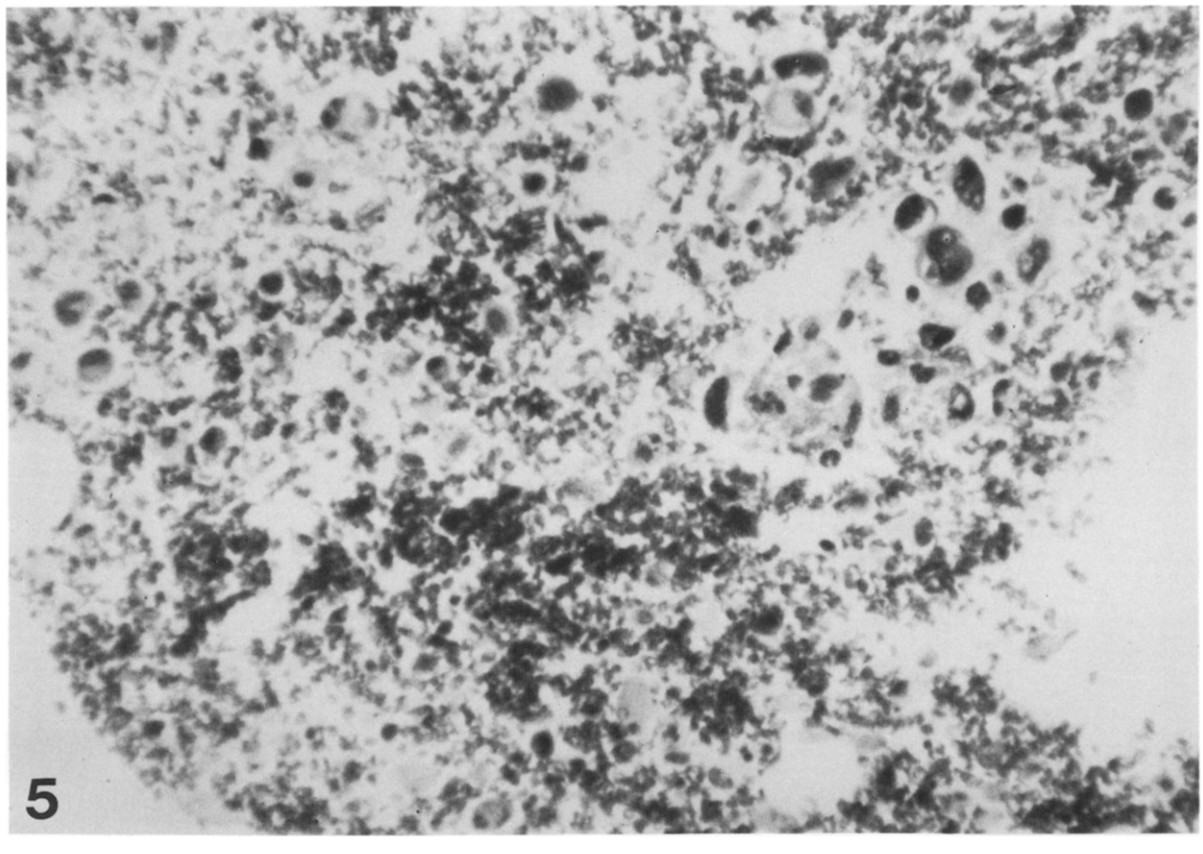

Fig. 5. Case 2: bone marrow clot section showing infiltration by pleomorphic tumour cells; haematoxylin and eosin; ×152.

by a low-grade myxoid liposarcoma (case 4) is unusual. The low mitotic activity and myxoid appearances noted in the primary tumour were also observed in the metastatic deposits. This illustrates that histological grading may not be a completely reliable indicator of metastatic potential, although it is possible that an exhaustive search of multiple sections may have revealed less well-differentiated areas within the tumour. Enterline *et al.* [14] reported a series of 53 cases of liposarcoma, 19 of which were of the well-differentiated myxoid type. Two of these metastasised widely, although marrow infiltration was not mentioned. Hosenpud *et al.* [15] reported bone marrow spread from a liposarcoma arising in a man suffering from hereditary multiple lipomata. In contrast with our case, this was a high-grade tumour showing numerous mitoses.

Bone marrow involvement has been reported in isolated cases of synovial sarcoma [16] and rhabdomyosarcoma [17]. Kaufman and Tsukada [16] demonstrated bone marrow infiltration at autopsy in a patient who had a synovial sarcoma of the right foot with widespread dissemination, including cerebral metastases. Several large series of synovial sarcomas have not mentioned bone marrow involvement [18–21]. A ten-year disease-free survival following successful chemotherapy for an abdominal rhabdomyosarcoma metastatic to the bone marrow has been reported by Sinkovics [17].

Tumour effects unrelated to direct invasion of normal structures are well documented, and many cases of anaemia seen in malignant disease may represent a distant non-metastatic suppression of haemapoiesis. However, partial marrow infiltration may result in a leuco-erythroblastic blood picture, although this was not evident in any of our patients. It is possible that partial marrow infiltration could impair recovery following chemotherapy. During treatment with anthracycline-containing regimes, 3 out of 4 of our patients became severely anaemic. Asymptomatic neutropenia following each course of chemotherapy was noted in one patient (case 4) and another (case 2) developed pneumonia and severe haemoptysis during an episode of myelosuppression. However, episodes of myelosuppression occurred in other patients with uninvolved marrows who received similar chemotherapy, and no statistical correlation can be made with such small numbers of patients.

In this series of 74 patients there were 4 with bone marrow infiltration—an incidence of 5%. Six patients, otherwise disease-free following removal of their primary tumour, had no evidence of marrow infiltration. The remaining 68 patients had advanced disease and 56 had proven metastases, giving an incidence of 7% for patients with metastatic disease. The marrow was never the sole site of involvement, although only two patients had evidence of concomitant bony metastases. In both these cases marrow biopsies were taken from sites remote from bony metastases demonstrated by radiographs or isotopic scans. It is important to recognise bone marrow infiltration as a separate entity from bone metastasis since the former may be clinically silent. Abnormalities recorded by radioisotope bone scan are usually determined by a change in periosteal activity, and this investigation could not be expected to demonstrate marrow deposits. It is possible, however, to perform radioisotope scans of bone marrow with [^{99m}Tc] sulphide colloid, which will show areas of tumour infiltration as reduced uptake or cold spots [22]. Alternatively, [^{111}Indium] chloride bone marrow scintography may be used to demonstrate the distribution of normal marrow elements. Although areas of hypoplasia, fibrosis or tumour infiltration were associated with decreased uptake of [^{111}Indium] in patients with lymphoma [23], tumour deposits from prostatic cancer showed inconsistent uptake of isotope [24]. Sampling errors may occur, particularly if infiltration is patchy, and the true incidence of marrow involvement by sarcomas may be higher. Both aspirate and trephine biopsies should be performed—in two of our patients tumour was detected by trephine only, while both aspirate and trephine showed infiltration in the other two. Monitoring bone marrow infiltration as an index of response may be misleading, as demonstrated by one of our patients (case 1) whose second marrow was normal at a time when her disease was progressive. Despite aggressive chemotherapy, disease progression occurred in 3 of our patients, while the other achieved a good partial response.

CONCLUSIONS

Our experience suggests that marrow involvement is unlikely to occur in the absence of other metastases, and it is usually associated with high-grade tumours. With such small numbers it is impossible to determine whether response is influenced by marrow involvement. The haematological toxicity of chemotherapy seemed to be in excess of that normally encountered. We would conclude that bone marrow biopsy is unlikely to be of value in localised disease but may be relevant in patients presenting with metastatic disease prior to entry into chemotherapy protocols.

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