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Central Nervous System Involvement in Sarcoma

A Presentation of 12 Cases, a Review of the Literature, and a Discussion of Possible Changing Patterns with the use of Chemotherapy, Placing Special Emphasis on Embryonal Tumours

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Abstract—*Secondary central nervous system involvement is a rare event in the natural history of sarcoma, the one exception to this occurring in alveolar soft part sarcoma where there is a reported incidence of 15%. A number of workers have reported an increased incidence of cerebral metastases following the introduction of chemotherapy into the management of these diseases. In a review of 744 cases of sarcoma treated at the Royal Marsden Hospital, 12 cases of secondary involvement of the brain were found. These 12 patients are discussed in relation to the literature, together with a possible association of an increasing incidence, with particular emphasis on embryonal tumours.*

INTRODUCTION

DESPITE the common haematogenous route of dissemination, sarcomata rarely metastasise to the central nervous system, the one exception to this being alveolar soft part sarcoma in which there is reported incidence of up to 15% of cerebral deposits [1]. This is an atypical sarcoma in a number of ways, not the least of which is its proclivity towards long survival, sometimes over 20 yr, even in the presence of overt metastatic disease, and its eventual inevitably fatal outcome.

It is also interesting to note that for tumours with this pattern of blood-borne spread, bone marrow infiltration is exceedingly rare except in embryonal tumours, a fact which may take on greater significance later.

According to Stortebecker, secondary deposits constitute between 13.5 and 37% of all intracranial tumours [2]; Courville puts the number at 20.5% [3], a figure agreed with by Russell and Rubinstein [4]; yet in two large series reported by Stoier [5] and Willis [6] no case of sarcoma was seen.

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It is the purpose of this paper to underline the rarity of cerebral metastases as a part of the natural history of sarcomata, whilst confirming the exception to this rule, namely alveolar soft part sarcoma; to record the basic data of these patients to compare with other cases where the clinical course may have been altered by the addition of chemotherapy to their management, and to suggest the possible emergence of an increase in the incidence of cerebral metastatic spread, particularly in embryonal tumours.

The 12 cases reported here are from a total of 744 patients with sarcoma treated at the Royal Marsden Hospital, including a retrospective study of 517 cases presenting between the years 1961–70 [7] and are represented in Table 1.

MATERIALS AND METHODS

A brief summary of the patients is shown in Table 2.

Of the 12 cases 3 had the diagnosis of alveolar soft part sarcoma, and these were from a total of only 8 patients with this sarcoma type giving an incidence of 37.5%

Table 1. *Frequency of occurrence of sarcomata type within* 517 *patients treated at the Royal Marsden Hospital between* 1961 *and* 1970

Histological type	Total No. of cases	No. with cerebal metastases
Alveolar soft part sarcoma	8	3
Embryonal rhabdomyosarcoma	85	2
Undifferentiated sarcoma	50	2
Fibrosarcoma	179	1
Leiomyosarcoma	139	1
Liposarcoma	51	1
Epithelioid sarcoma	3	1
Giant cell tumour of soft parts	2	1
Total	517	12

Table 2. *Summary of patients*

Case No.	Age/sex	Histology	Primary site	Previous therapy	Time in months diagnosis to: brain	2°/death
1.	28/F	Liposarcoma	Pleura	Surgery Chemo. Radiation	12	12
2.	54/F	Giant Cell Soft Parts	(L) Thigh	None	1	1
3.	49/F	Leiomyosarcoma	Small Bowel	Surgery	12	12
4.	22/M	Undifferentiated	Wrist	Surgery Radiation	13	14
5.	56/F	Fibrosarcoma	Clitoris	Surgery Radiation	5	5
6.	29/M	Epithelioid	(L) Hand	Surgery	3	5
7.	61/M	Undifferentiated	?	Surgery Radiation	3	4
8.	24/F	Alveolar Soft Part	Axilla	Surgery Radiation	84	96
9.	29/M	Alveolar Soft Part	(L) Thigh	Surgery Radiation	72	84
10.	21/M	Alveolar Soft Part	(L) Pelvis	Surgery Radiation Chemo.	48	60
11.	15/F	Embryonal Rhabdo.	Nasopharynx	Radiation Chemo.	12	$12\frac{1}{2}$
12.	4/M	Embryonal Rhabdo.	Mandible	Radiation Chemo.	12	14

which is rather higher than that of Lieberman *et al.* [1], albeit in a smaller series. It does, however, seem to set this tumour apart from other sarcomata in producing a high proportion with cerebral spread.

Of the remaining 9 patients, there were 7 adults with discrete cerebral lesions and two children with presumed 'malignant meningitis', with malignant cells identified in the cerebrospinal fluid, but with normal brain scans.

The adult patients comprised 2 undifferentiated sarcomata, one fibrosarcoma, one leiomyosarcoma, one liposarcoma, one giant cell tumour of soft parts, and one epithelioid sarcoma. The diagnosis was made purely on clinical grounds in 2 cases, one of which was subsequently proven at post mortem examination, by brain scintiscan in 3 cases, by computer-assisted tomographic scan in one case, and was found as an incidental finding at post mortem in the remaining patient. In all, 4 of these 7 cases had histologically proven cerebral deposits at post mortem examination; in the other 3 cases permission for autopsy was refused.

Initial treatment to the primary lesion consisted of either radiotherapy or surgery, or a combination of both. One patient who presented with metastatic disease was treated with chemotherapy from the outset. Only two other patients received chemotherapy at any time during the clinical course of their disease. The interval between diagnosis and onset of cerebral metastases varied from one week to 20 months.

Both of the children with 'malignant meningitis' had presented with embryonal rhabdomyosarcoma of the head and neck. Both received radiotherapy as initial treatment to the primary lesion, followed by adjuvant chemotherapy. One developed a solitary lung lesion treated successfully with small volume high dose 'postage-stamp' radiotherapy, chemotherapy continuing without interuption. This patient subsequently developed bone marrow infiltration in addition to the CNS disease. The other patient had no evidence of secondary spread outside the central nervous system. In this patient, weekly intrathecal injections of methotrexate alternating with cytosine arabinoside via an ommaya valve relieved the symptoms and rendered the cerebrospinal fluid free of malignant cells.

RESULTS

The 3 patients with alveolar soft part sarcoma with CNS involvement survived 3, 7 and 9 yr from diagnosis, and in each case the interval between discovery and death was 1 yr or longer. Of the 8 patients with this tumour, none remains alive.

In the remaining 7 adult patients survival after cerebral spread ranged from 4 days to 2 months. Treatment on the whole was symptomatic with only one patient receiving cerebral irradiation, and one chemotherapy, neither with any demonstrable effect. Six of the 7 patients also had evidence of metastases outside the central nervous system, and of the patients who had received chemotherapy, none had shown a response or stabilisation of their disease, 2 dying within 2 weeks of commencing drug therapy. There was no significant interval between the occurrence of cerebral metastases and those in other sites, most appearing concurrently.

Of the two children with malignant meningitis, both died within 2 months of the onset of cerebral symptoms, one after only 2 weeks. Post mortems were not performed as both were of the moslem faith.

DISCUSSION

It is now accepted that cerebral metastasis in alveolar soft part sarcoma is seen as a part of the natural history of the tumour, but there are few reports in the literature regarding other sarcomata. Harding and Courville [8] cited one case of a primary osteosarcoma of the femur with a solitary radio-opaque deposit in the occipital region. In Stout's series of 41 liposarcomata [9] one patient had documented cerebral deposits, and in the same tumour, Enterline *et al.* [10] reported 2 out of 53 cases. Rather more recently Dal Canto *et al.* [11] published a single case of fibrosarcoma of the renal capsule with brain secondaries, although LiVolsi [12] suggested that this might have been a spindle cell variant of renal carcinoma.

In a series of 456 patients from the South West Oncology Group (SWOG) referred for treatment of disseminated disease, only 6 (1.3%) had cerebral deposits at presentation [13]. Within this group there were 2 fibrosarcomata, one leiomyosarcoma, one liposarcoma, one Ewing's sarcoma and one rhabdomyosarcoma. Adachi *et al.* [14] recorded a case of leiomyosarcoma metastasising to the brain from a primary in the thyroid, but the case of Sato *et al.* [15] appears to be one of local extension from the skull into brain tissue. In a series of 167 cases of malignant fibrous histiocytoma reported by Kearney *et al.* [16] only 3 patients developed cerebral metastases.

Comparing our cases with those reported in the literature, there seems to be no common pattern amongst the adult sarcomata, with the exception of alveolar soft part sarcoma, which might lead us to be able to predict which tumours are more likely to produce cerebral metastases. As one might expect, the three most common sarcomata are reported most frequently. The interval between the primary diagnosis and the onset of cerebral deposits is variable between immediate occurrence and nearly 5 yr, and the age of the patient between the early twenties and the late seventies. There also seems to be no difference between superficial and deep seated primaries, but the presence of deposits in other secondary sites is almost invariable. The only common denominator would appear to be the poor response to therapy, with only one of the SWOG patients showing tumour regression in the brain with adriamycin and DTIC in combination.

It may be, however, that our two children with embryonal rhabdomyosarcoma of the head and neck represent a different but pot-

entially more rewarding field for investigation. It has been suggested by Gercovich *et al.* [13] from the SWOG that the incidence of cerebral metastases in sarcoma is increased in patients relapsing after prolonged response to chemotherapy. Of their 14 patients who achieved either response or stabilisation of disease for at least 6 months, and then relapsed, 5 developed cerebral deposits as their only evidence of tumour progression. In a series of 20 cases of Ewing's sarcoma reported by Marsa and Johnson [17], two developed cerebral metastases following radiotherapy to the primary and adjuvant chemotherapy, again as the only manifestation of progressive disease, and Mehta and Hendrickson underlined this in a series of 27 patients in whom 15 developed CNS disease [18]. It is proposed by the authors that the improvement in chemotherapeutic response and the consequent lengthening of survival may be changing the observed pattern of metastatic disease. The analogy has been drawn with leukaemic patients where malignant cells within the central nervous system are protected by the 'blood - brain barrier' [19], and working on this hypothesis, adjuvant cranial irradiation, intrathecal drugs or the use of drugs such as nitrosoureas, that are known to penetrate the CNS, have been suggested [13].

In contradiction to the SWOG series, in two prospective studies of combined chemotherapy in adult sarcoma carried out at the Royal Marsden Hospital [19, 20], no patient developed CNS disease. However, when looking at embryonal rhabdomyosarcoma in children, the 2 patients reported here are from a series of only 15 patients treated with radiotherapy with or without prior surgery, followed by adjuvant chemotherapy giving an incidence of 13.3%, whereas in 46 patients treated in the past with surgery and radiotherapy alone, there were no documented cases of CNS involvement. This high incidence in treated rhabdomyosarcoma has recently been reported by Espana *et al.* together with a high incidence in malignant fibrous histiocytoma [21].

It is worthy of note that out of the 5 patients from the SWOG series who relapsed in the brain [13], 2 were reported as rhabdomyosarcoma in teenagers and were most probably embryonal tumours, and that the other two papers reporting an increased incidence [17, 18] in patients treated with chemotherapy dealt with Ewing's sarcoma which can also be regarded as an embryonal tumour. It may be, therefore, that we are beginning to uncover a natural affinity of all the embryonal tumours for the central nervous system by delaying death from other distant metastases with chemotherapy.

In conclusion, central nervous system involvement has now been recorded as an uncommon event in the natural history of a number of sarcomata. Apart from alveolar soft part sarcoma, no pattern has emerged with regard to histological type, primary site, tumour differentiation, or any other tumour characteristic which might help to predict secondary brain involvement. It may be found as an incidental finding at post mortem without prior clinical signs or symptoms which might suggest an actual incidence higher than observed, and that close examination of the brain at autopsy is necessary in all cases of sarcoma coming to post mortem.

Treatment on the whole is disappointing, but in alveolar soft part sarcoma where the prognosis may be more than 20 yr, radical palliative surgery with craniotomy and excision of the lesions is worth considering.

Being a more treatment-sensitive group of diseases, embryonal tumours may, however, offer a more rewarding therapeutic group. If this emerging pattern of CNS spread is confirmed, consideration might be given to prophylactic cerebral irradiation, and/or chemotherapy, as is now established in childhood leukaemia, with a reasonable expectation of a reduction in recurrences and an improvement in survival figures.

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