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Complete Remission of Metastasised Clear Cell Sarcoma of Tendons and Aponeuroses

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Clear cell sarcoma of tendons and aponeuroses is a rare disorder which originates from migrated neural crest cells. It tends to local recurrences and dissemination and the prognosis has to be considered as poor. Based on a small series of patients, a wide surgical excision of the primary tumour or amputation are the therapies of choice. Radiotherapy might be of some value as an adjuvant treatment but radiotherapy and chemotherapy are of little value in the treatment of the advanced disease. Because of the lack of treatment alternatives we treated a 40-year-old female patient with disseminated clear cell sarcoma with interferon-alpha 2b (IFN-α_{2b}) perilesionally after several courses of systemic chemotherapy and radiotherapy had failed. After 4 months of therapy the patient came into a complete pathological remission which lasted for 17 months. A relapse of round cell sarcoma on both tumour sites was then noted. This outcome shows that IFN-α_{2b} was able to induce a complete remission in clear cell sarcoma and might have altered the natural course of the disease. IFN-α should be studied as adjuvant therapy after surgery of primary clear cell sarcoma and as a first-line palliative treatment in disseminated disease.

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INTRODUCTION

CLEAR CELL sarcoma as a tumour entity was first defined and described by Enzinger in 1965 when he reported on 21 cases [1]. Since then, 230 additional cases have been published. This tumour originates from tendons, aponeuroses and fascial structures with a predilection of the lower extremities. Because of its capacity to produce melanin, some authors prefer the name "melanoma of soft parts". Clear cell sarcoma is described to occur more often in females than in males and occurs predominantly in younger patients. Prognosis of generalised clear cell sarcoma is poor and therapeutic approaches like radiotherapy or chemotherapy have poor results so far [2, 3].

These facts and the known sensitivity of malignant melanoma to biological response modifiers like interferon [4], as well as the lack of treatment alternatives, prompted us to treat a patient with metastasised clear cell sarcoma with interferon-alpha 2B (IFN-α_{2b}), after she had failed surgical interventions followed by radiotherapy and intensive chemotherapy.

CASE REPORT

The patient's tumour history revealed the first appearance of a tumour-like lesion on the medial left ankle in 1979. Because the colour changed to bluish-red, this lesion was surgically removed in 1985 and the diagnosis of clear cell sarcoma was histologically established. Staging procedures showed four involved lymph nodes in the left inguina which were also excised. In January 1986 the patient noticed a palpable mass in the left inguina and was therefore transferred to our unit.

Staging procedures of the 40-year-old woman revealed lymph node metastases of six cm in diameter in the left inguina and involvement of the left parailiacal lymph nodes. Tumour biopsy showed the presence of clear cell sarcoma with small spots (about 5%) of cells of an undifferentiated round cell sarcoma. Immunohistochemical stains showed S-100 protein (neuronal marker) and vimentin (mesenchymal marker) positive reactions, Leu-5 (epithelial marker) and neuron-specific enolase weak positive reactions, and melanin negative reaction.

Chemotherapy with high-dose methotrexate, bleomycin and doxorubicin according to the schedule of the Memorial Sloan–Kettering Institute for osteogenic sarcoma and malignant synovialioma [5] was initiated and a minor response could be achieved. Because of disease progression in the left inguina and the development of a local recurrence, therapy was changed to the CYVADIC (cyclophosphamide, vincristine, doxorubicin and dacarbazine) regimen. Additionally, photon beams to the ankle and to the iliacal and parailiacal lymph nodes were given. Despite this polypragmatic treatment tumour regression could not be induced. Further surgical intervention was rejected by the patient. In January 1987 physical re-examination showed an exulcerated aching nodule of 3.5 cm in diameter on the medial left ankle, as well as palpable lymph nodes in the left inguina.

Interferon treatment

Starting in mid January 1987 we administered 2.5 MU IFN-α_{2b} (Introna®, AESCA, Traiskirchen, Austria) daily intralesionally to the local recurrence. This route was chosen because of positive reports for malignant skin cancers in the literature [6]. Interferon therapy was tolerated by the patient without any side-effects, whereupon the dose was escalated to 5 MU. Half of the dose was administered intralesionally to the local recurrence and half perilesionally to the inguinal lymph nodes. Dose escalation resulted in fever up to 38.2°C for one day and nausea lasting two days. The patient was taught the self-application of interferon and was put on an outpatient status with monthly controls.

During the following weeks a decrease in pain intensity of the

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left malleolar region and a considerable decrease in size of the local recurrence as well as of the metastases were noted. Complete remission was documented by CT scan after four months of interferon therapy and was confirmed by biopsy. The patient was therefore kept on interferon with the same dose level.

17 months after initiation of interferon treatment relapse on both tumour sites was noted. Histological investigation showed the presence of an undifferentiated round cell sarcoma. The patient refused further therapy and died in March 1989 due to the disease progression.

DISCUSSION

Clear cell sarcoma has now been widely recognised as a distinct tumour entity. It is a rare malignant disorder and only 251 cases have been published so far. Summarising the reports, incidence of metastases appear to be as high as 60–70% with regional lymph nodes and the lung as the most common sites of dissemination. Nevertheless, almost all other organs can be involved and malignant effusions have been also described [7]. The reports that clear cell sarcoma occurs predominantly in the lower extremities of younger people and is more common in females than in males are confirmed by our review: the median age of the 252 reported cases is 29 years (range 7–83) and the sex ratio males:females is 1:1.3. In 174 patients clear cell sarcoma was located on the lower extremities; in 54 patients the upper extremities, and in only 24 cases are other sites of the primary tumour described.

The period of time from onset of symptoms to diagnosis is variable but can be as long as 19 years with reported mean durations between 2 and 5.5 years [1, 8]. This might be due to the fact that clear cell sarcoma still poses diagnostic problems for many pathologists and is often misdiagnosed for some other type of soft tissue sarcoma and also malignant melanoma. Histogenesis of clear cell sarcoma has not yet been definitely established. Some authors considered it as a variant of synovial sarcoma [8] but, since the S-100 protein, a neuroectodermal marker, is positive in many of these cases and neuron specific enolase and melanin can be demonstrated in a high percentage of the tumour stains, most of the reviewers have recognised clear cell sarcoma as a tumour of neural crest origin [2, 3, 9]. This obvious capacity for producing melanin supports the thesis of origin from migrated neural crest cells. Therefore some authors prefer to use the term "malignant melanoma of soft parts" to describe this tumour entity.

First therapeutic approaches of clear cell sarcoma consisted mainly in simple or wide excision of the tumour but since there is a fairly high incidence of local recurrences following primary surgical treatment, extended excision, amputation or even radical extracompartimental resection is recommended as the treatment of choice [2, 3]. Adjuvant radiotherapy after initial wide excision was reported in some patients [10 ,11] and good results were documented in terms of decreased incidence of local recurrences. Although the number of patients is small and although non-standardised radiation therapy techniques were used, adjuvant radiotherapy is recommended by several authors [1, 2, 10]. Radiotherapy to metastases as palliative treatment resulted in poor outcome [3]. Chemotherapy was employed as a pallative adjunct in patients with local recurrences or metastasised disease. Only two short lasting minor responses are reported out of six patients where this therapy was applied [3, 12].

Prognosis of patients with clear cell sarcoma has to be considered as poor. The mean period from diagnosis to death is 39 months (7 months to 10 years) in patients with widespread tumour and 88 months (35 months to 14 years) in patients with initially localised tumour. This is the first report of a complete remission which lasted for 17 months induced in a patient with generalised clear cell sarcoma after failure of surgical treatment as well as radiotherapy and chemotherapy. The fact that IFN-α was able to induce a complete remission and altered the natural course of the disease points to a possible role of biological response modifiers in the treatment of this tumour entity. Two explanations for the exclusive presence of cells of a round cell sarcoma in the biopsy of the local recurrence after treatment with IFN-α have to be discussed. There could have been a selection of round cell sarcoma cells, which had been present in small number in the primary tumour and were insensitive to IFN-α, or the change of the histological pattern might have been due to dedifferentiation of clear cell sarcoma to undifferentiated round cell sarcoma resistant to interferon therapy (Fig. 1).

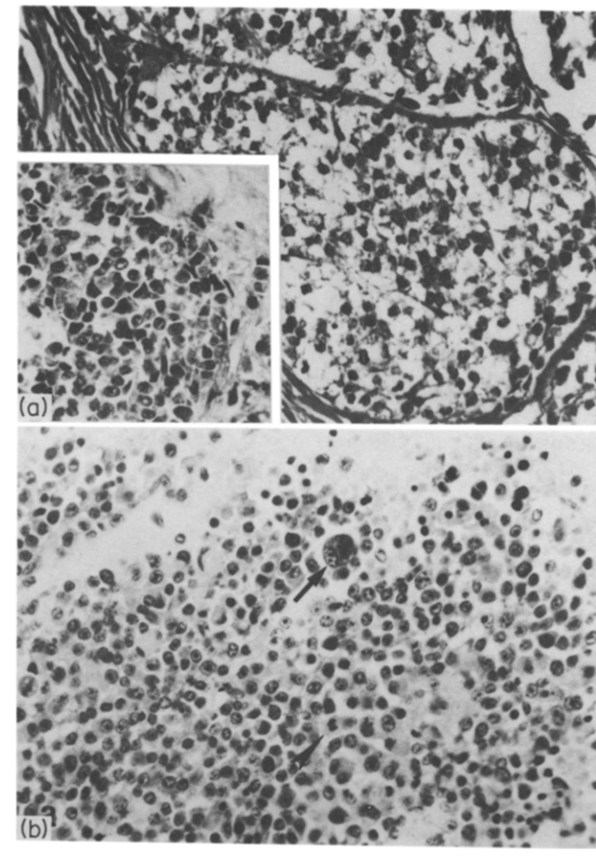

Fig. 1. Lymph-node metastasis of clear cell sarcoma (haematoxylin/eosin, ×140) before IFN-α_{2b} therapy (a), inset shows round cell sarcoma, and after treatment (b) (arrow = multinucleated tumour cell; arrow-head = mitosis).

Clear cell sarcoma represents a rare tumour entity and the clinical course varies and is unpredictable. Radiotherapy and chemotherapy are of little value in the palliative treatment and therefore prognosis of patients with disseminated clear cell sarcoma is poor. Because of the rarity of this kind of tumour controlled clinical trials with large numbers of patients are not possible. Therefore, due to our observation, IFN-α should be considered as adjuvant treatment after adequate surgery as well as first line palliative treatment in disseminated disease.

1. Enzinger FM. Clear-cell sarcoma of tendons and aponeuroses. An analysis of 21 cases. *Cancer* 1965, **18**, 1163–1174.
2. Chung EB, Enzinger FM. Malignant melanoma of soft parts. *Am J Surg Pathol* 1983, 7, 405–413.
3. Pavlidis NA, Fisher C, Wiltshaw E. Clear cell sarcoma of tendons and aponeuroses: a clinicopathological study. *Cancer* 1984, **54**, 1412–1417.
4. Martinelli G, Cavalli F. Alpha-interferon alone or in combination with chemotherapy in the treatment of malignant melanoma, renal cell carcinoma and other solid tumours. In: Smyth JF, ed. *Interferons in Oncology—Current Status and Future Directions*. Berlin, Springer, 1987, 33–38.
5. Rosen G, Nirenberg A. Chemotherapy for osteogenic sarcoma. *Cancer Treat Rep* 1982, **66**, 1687–1697.
6. Taguchi T. Clinical studies of recombinant interferon alpha-2a (Roferon-A) in cancer patients. *Cancer* 1986, **57**, 1705–1708.
7. Nguyen GK, Shnitka TK, Jewell LD, Wroblewsky JA. Exfoliative cytology of clear-cell sarcoma metastases in pleural fluid. *Diagn Cytopathol* 1986, 2, 144–149.
8. Tsuneyoshi M, Enjoji M, Kubo T. Clear cell sarcoma of tendons and aponeuroses: a comparative study of 13 cases with a provisional subgrouping into the melanotic and synovial types. *Cancer* 1978, **42**, 243–252.
9. Kindblom LG, Lodding P, Angervall L. Clear cell sarcoma of tendons and aponeuroses, an immunohistochemical and electron microscopy analysis indicating neural crest origin. *Virchow Arch (A)* 1983, **401**, 109–128.
10. Eckardt JJ, Pritchard DJ, Soule EH. Clear cell sarcoma. A clinicopathological study of 27 cases. *Cancer* 1983, **52**, 1482–1488.
11. Suit WD, Russell WO, Martin RG. Sarcoma of soft tissue: clinical and histopathological parameters and response to treatment. *Cancer* 1975, **35**, 1478–1483.
12. Radstone DJ, Revell PA, Mantell BS. Clear cell sarcoma of tendons and aponeuroses treated with bleomycin and vincristine. *Br J Radiol* 1979, 52, 238–241.

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Analysis of Tissue Platinum Distribution in Patients with Cancer of the Oesophagus

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The objective of this work has been to analyse the repartition of platinum (Pt) tissular levels within the tumour (T), the peritumoral adjacent non-tumoral area (P) and distant healthy tissue of the same anatomical zone (H) in oesophagus cancer. Forty-two biopsies (≃ 5 mg) have been performed under endoscopy and after informed consent in 11 patients (mean age 61 yr, range 43–74) with squamous cell carcinoma of the oesophagus treated by the neoadjuvant chemotherapy protocol including cisplatin (100 mg/m²) and 5-FU (1 g/m² × 5 days). Biopsies were done 34–36 h after cisplatin. Additional biopsies were obtained for histological controls. Pt was measured by flameless atomic absorption spectrometry. Considering Pt concentration in T, P and H there was no significant accumulation during repeated treatment (3 cycles). For all cycles, mean [S.D.] values (μg/g dry tissue) were 2.03 [2.39] for H, 2.75 [2.03] for P and 3.73 [2.3] for T (H vs. T, $P = 0.006$). In addition, Pt concentrations were found comparable between the upper and lower poles of the tumours (5 patients). Pt concentrations in T did not predict antitumour activity. These data complete the rather limited knowledge on tissular Pt levels in treated patients and suggest a decreasing gradient of Pt concentrations from tumour to healthy tissue in oesophagus cancer.
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INTRODUCTION

CISPLATIN (CDDP) is currently one of the most widely used chemotherapeutic agents. In addition to being used as a first line drug for testicular and ovarian cancers, cisplatin is given in combination with other cytostatics for other malignancies, including head and neck [1] and oesophageal cancers [2]. To date, the experimental data provided by pharmacokinetic and cellular pharmacological investigations strongly suggest that intratumoral platinum (Pt) is a determining factor for cisplatin activity. For example, animal studies have demonstrated that tissue Pt uptake is rapid, leading to persistent cellular concentrations higher than those in plasma [3–5]. In their pharmacokinetic study, Crom *et al.* [6] found that the transfer constant K12 (central to peripheral compartment) was six times higher than K21 (peripheral to central compartment). The physicochemical properties of cisplatin make this drug particularly reactive within the intracellular space, where the Cl concentration is 25 times lower than in plasma [7]. Nuclear DNA is the main, but not the sole, cellular target for cisplatin; the two molecular species form adducts which have been particularly well elucidated [8].

Numerous clinical pharmacokinetic studies have been performed on cisplatin in plasma [9]. In comparison, except for several experimental studies [3–5, 10, 11], current knowledge on tissue Pt concentrations in treated patients remains very limited [12–14]. Oesophageal cancers exhibit an interesting response rate to the cisplatin plus 5-fluorouracil (5-FU) [2]. Furthermore, these tumours lend themselves to biopsies under endoscopy.

In the present study, Pt concentrations were measured in 42 tissue samples obtained from 11 patients with oesophageal cancer treated by cisplatin–5-FU. Biopsies were taken in the tumours themselves, in the peritumoral mucosa, and at a distance, in non-tumoral healthy zones of the same anatomic site. Whenever posssible, biopsies were repeated during each treatment cycle.

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