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A Perplexing Malignant Bone Tumor

Highly Malignant So-Called Adamantinoma or Non-Typical Ewing's Sarcoma

U. J. G. M. van Haelst and A. H. de Haas van Dorsser

Department of Pathology and Department of Orthopedic Surgery, St. Radboud Hospital, University of Nijmegen, The Netherlands

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Summary. A malignant tumor of the second metatarsal in a thirteen-year-old girl with trouble-some clinical and especially light- and electronmicroscopical aspects is described. The findings are discussed in relation to each of the two possibilities to be considered: highly malignant, extra-cranial so-called adamantinoma (poorly differentiated or basaloid type) or Ewing's sarcoma with focal squamous differentiation, the latter being a most remarkable observation.

Key words: Extra-Cranial So-Called Adamantinoma — Ewing's Sarcoma — Light- and Electronmicroscopy.

In general the distinction between Ewing's sarcoma and so-called adamantinoma is no matter of debate. The purpose of this communication, which concerns the peculiar light- and electronmicroscopic observations on a malignant tumor involving a small foot-bone of a 13-year-old girl, as well as some clinical aspects, is to focus attention on the contingencies which can arise when dealing with these tumors.

Case Report

A thirteen-year-old caucasian female was presented to the Department of Orthopedic Surgery in December 1971, with complaints of pain and swelling in the right foot for about two years.

At physical examination a circumscript swelling of the dorsum of the right foot could be palpated. The temperature of the overlying skin was elevated. The patient was slightly limping. The function of the ankle-joint and foot was normal. The remaining physical examination was unremarkable.

Extensive examination for a primary tumor elsewhere was negative.

Laboratory tests were normal, except for a slightly elevated alkaline phosphatase (252 U/l). X-ray examination showed shortening of the second metatarsal bone with destruction of the shaft (Fig. 1). On chest X-ray examination there were no signs of pulmonary metastases.

On February 2, 1972, the second metatarsal bone was biopsied.

Primary Histological Diagnosis. Presumably adamantinoma. Considering this primary diagnosis, amputation in the Chopart joint was felt to offer the best possible treatment and was performed on February 16, 1972.

The postoperative course was unremarkable. As the slides revealed tumorous invasion of the skin adjacent to the amputation level and *re-evaluation* of the slides showed evidence of non-typical Ewing's Sarcoma, the patient was treated accordingly with local radiotherapy (5000 rads Co-60) in combination with Actinomycin-D (7.5 gamma/kg/day × 5, IV).

A chest X-ray on June 20, 1972 was positive for extensive metastases in both lungs (Fig. 2). A bone survey was negative for metastases. It was felt that the patient might benefit

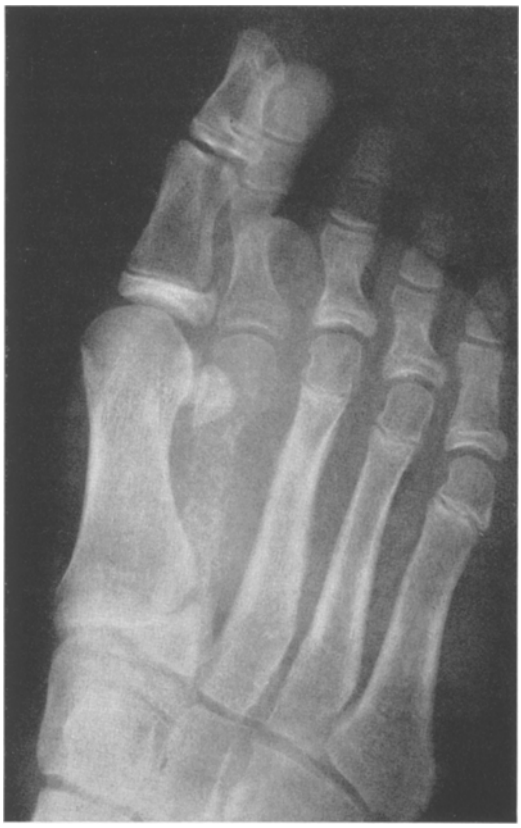


Fig. 1. Roentgenogram of the foot demonstrates mottled destruction of the cortex and medullary cavity of the second metatarsal bone with slight periosteal reaction of the third metatarsal bone

from a combination of radiotherapy (2100 rads) to both lung fields and Actinomycin-D (5 gamma/kg/day/IV), followed by a combination chemotherapy with Cytoxan and Vincristin according to schedule.

A chest X-ray on July 10, 1972 was negative for pulmonary metastases. Owing to gastrointestinal toxicity from the combination therapy with Cytoxan and Vincristin, the patient was admitted to the Haematology Ward of the Department of Internal Medicine, September 1972. On physical examination there were lymphnode metastases in the right popliteal fossa, the mid-dorsal area of the right tibia and below and above the right inguinal ligament. A chest X-ray and a bone survey were negative for metastases at that time.

The patient was treated with local radiotherapy to the lymphnode metastases (2500 rads Co-60) in combination with Actinomycin-D (5 gamma/kg on 5 consecutive days), with good local results.

October 20, 1972 the patient was readmitted to the Department of Orthopedic Surgery for combination chemotherapy with Actinomycin-D (5 gamma/kg/day $\times$ 5), Cytoxan (10 mg/kg/day $\times$ 5) and Vincristin on day 1 and 15, IV. There were no signs of osseous metastases. On chest X-ray 2 small metastases in the right lung were noticed. Due to bone marrow depression (leucocytes 2700/mm^3, thrombocytes 97000/mm^3), treatment was discontinued. The patient was discharged in relatively good general health.

In the beginning of November 1972 a tumor-mass in the right calf muscle was noticed and treated with local radiotherapy (2500 rads Co-60 in 2 weeks). Chest X-rays obtained in December 1972 and January 1973 were again positive for pulmonary metastases. The patient received systemic chemotherapy according to schedule, but only for 3 days due to bone marrow toxicity. The patient complained of a sore throat and for a few days a generalized rash, probably due to Actinomycin-D, was noticed. The patient was discharged in general good health and a chest X-ray obtained in April showed no change in the pulmonary metastases.

A chest X-ray in May 1973 showed a marked increase in pulmonary metastases (Fig. 3). The patient complained periodically of a slightly productive cough. On physical examination the liver was enlarged on percussion. There were no peripheral lymphnode metastases palpable. A liver and spleen scan were negative for metastases.

The patient was readmitted to the Orthopedic Ward in the beginning of June and started on Adriamycin (75 mg/m^2 body surface; IV to repeat every 3 weeks). She was discharged in general good health. A chest X-ray obtained at the end of June showed a marked decrease in pulmonary metastases; the results of the laboratory analysis were unremarkable and as there were no signs of bone marrow toxicity again 110 mgs of Adriamycin were administered, IV, June 26. The patient had to be readmitted July 10, due to severe bone marrow depression: leucocytes 800/mm^3 and thrombocytes 85000/mm^3. There was a marked alopecia.

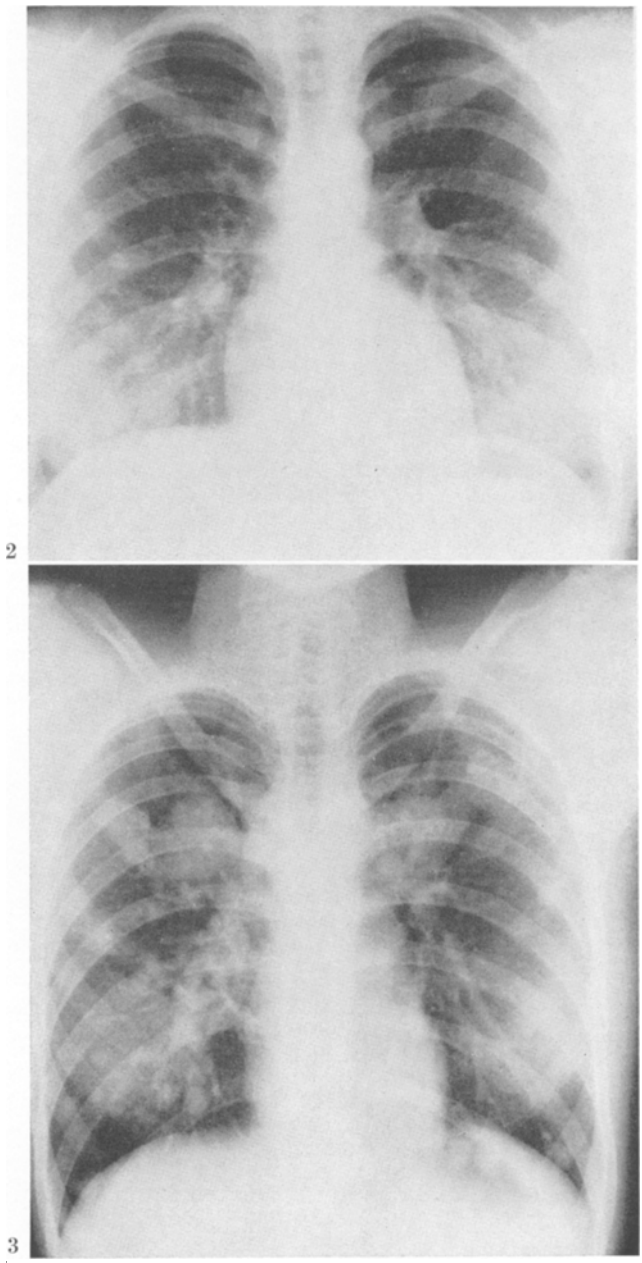
There were no signs of generalized metastases. A chest X-ray was negative for pulmonary metastases (Fig. 4). The patient received ampicilin and was discharged July 14 (leucocytes 1600/mm^3, thrombocytes 137000/mm^3).

The patient was seen at regular intervals in the orthopedic clinic for re-evaluation. A third dose of Adriamycin of only 40 mgs because of bone marrow depression was administered August 21. Chest X-ray examinations showed possible hilar metastases and progression of these secondary deposits later on. The patient's general health was deteriorating with increasing productive cough and periodically haemoptysis. A bone survey at regular intervals was negative for metastases. There were no signs of lymphnode, liver and spleen metastases. Due to a persisting thrombopenia (80000/mm^3), deteriorating general condition and increasing pulmonary metastases on chest X-ray (Fig. 5), no further chemotherapy was considered on October 30, 1973. After consulting the general practitioner the patient was admitted to her local hospital and given supportive care. She died November 1973.

No autopsy was performed.

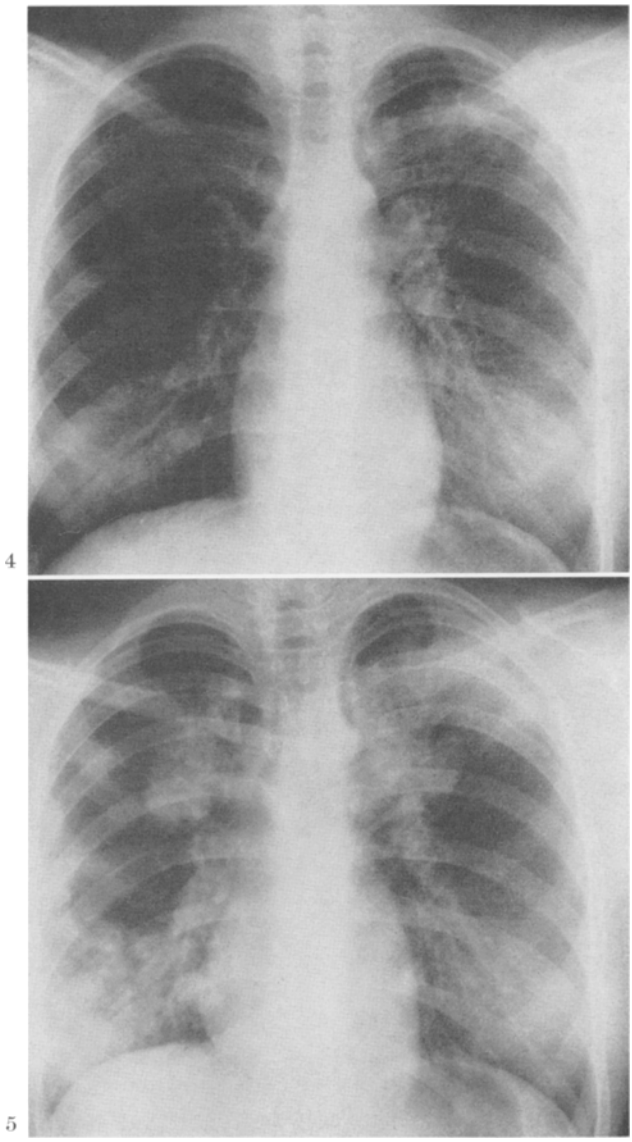
Pathology

Light Microscopy. Haematoxylin and eosin stained sections show irregular but sharp delimitated, compact masses of small cells with a basaloid pattern (Fig. 6), in the periphery of which cubic cells can be found in palisade formation (Fig. 7). The solid collections of tumor cells are separated from each other by fibrovascular septa or pre-existent bone spiculae and frank necrosis can be seen in the central parts of large nests. The nuclei are round or ovoid and slightly basophilic with scarcely visible nucleoli. The tumor cells have scanty cytoplasm and cell membranes are indistinct (Fig. 8). A fair number of mitoses can be detected. There is no pseudo-rosette formation. Glycogen granules, controlled by the PAS stain with and without diastase digestion, are present within some of the tumor cells. Reticulin fibers (Laguesse method) do not enclose individual or small groups of tumor cells but a basal membrane seems to surround each large nest of cells (Fig. 9). At places, particularly in the small tumorous areas, a most interesting histological feature can be seen. The more centrally located tumor cells become larger and polygonal and display evident squamous changes (Fig. 10). Besides this epidermoid appearance, a whirling of elongated cells with small, hyperchromatic nuclei suggestive of pearl formation and even central keratin



Figs. 2 and 3

Figs. 2—5. These four roentgenograms of the chest illustrate the effects of the therapy on the course of the metastatic lesions in both lungs. The roentgenograms were made respectively on June 20, 1972; May 22; July 10; October 30, 1973



Figs. 4 and 5

formation can be detected (Fig. 11). In sections of the amputation specimen cell strands can be seen breaking through cortical bone and penetrating into small blood vessels as well as into the surrounding (muscle and subcutaneous fat).

Electron Microscopy. Since ultrastructural examination had not been anticipated at the time of biopsy, this study is made on material which had been initially fixed for a few days in 4% formaldehyde and postfixed in a 2% osmium tetroxide solution in Palade buffer, so that the preservation is less than optimal.

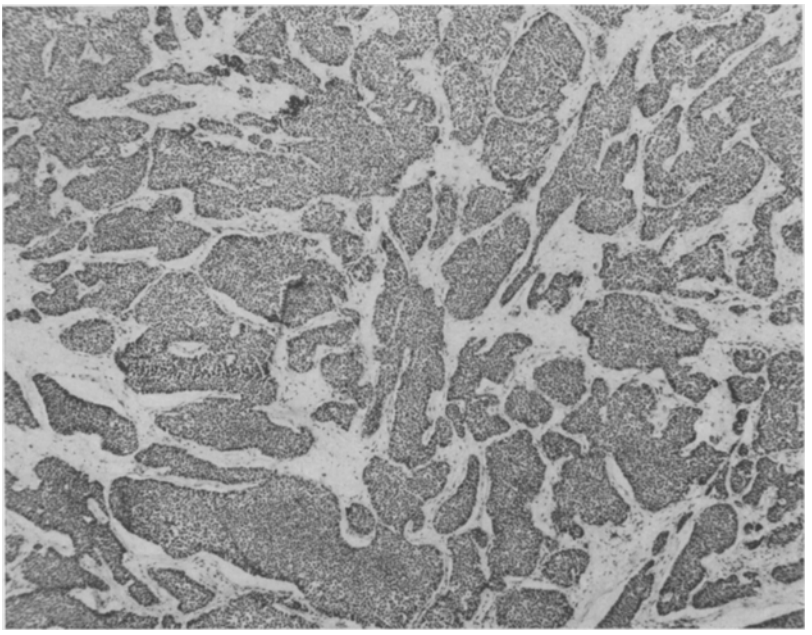


Fig. 6. Low-power view showing sharply demarcated, solid fields of tumorous tissue. Haematoxylin and eosin. × 44

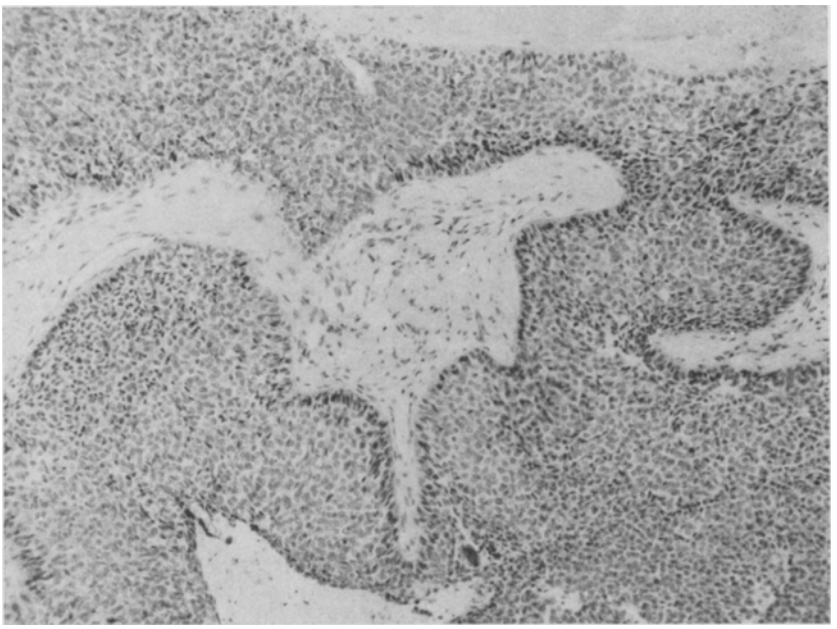


Fig. 7. Nests of tumor cells are separated by fibro-vascular tissue and show peripheral palisading. H. E. × 110

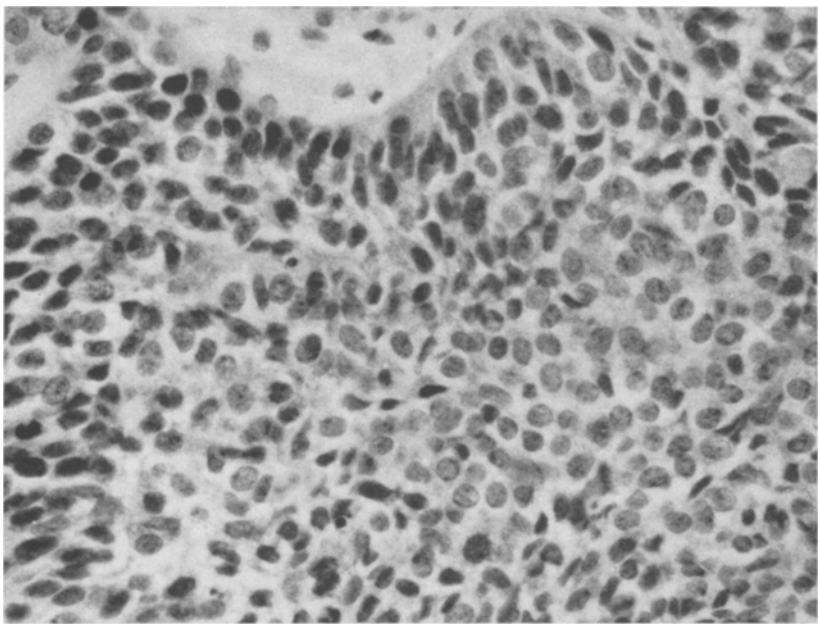


Fig. 8. This figure shows the general uniformity of cells; some nuclei are hyperchromatic and/or contain one or two nucleoli. H. E. $\times 437$

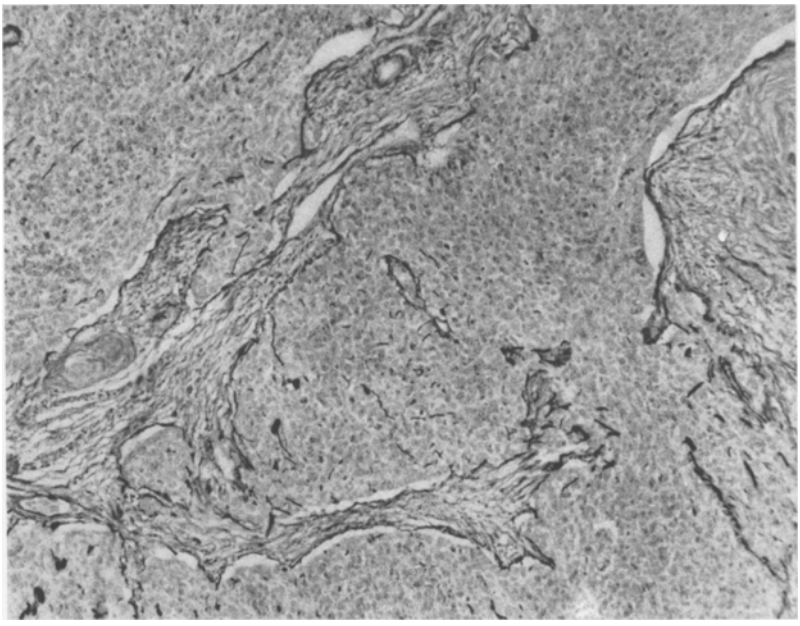


Fig. 9. Reticulum fibers are absent in zones of actual tumor, although they are seen at their periphery and in the intervening stroma. Laguesse's reticulin stain. $\times 110$

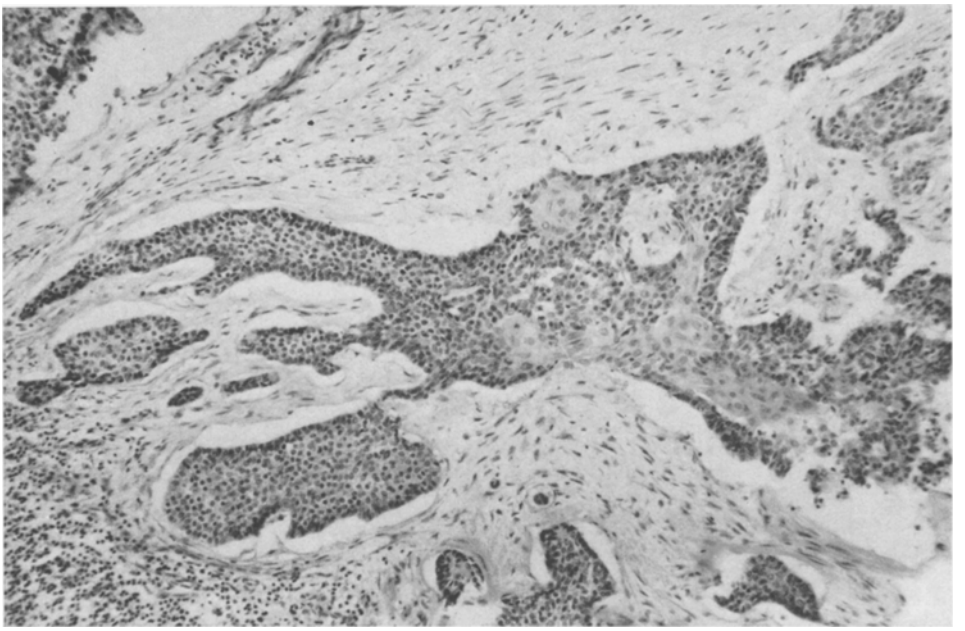


Fig. 10. This photomicrograph illustrates in the center of the cell groups a collection of cells which resemble, or in fact seem to be, squamous epithelium. H. E. × 110

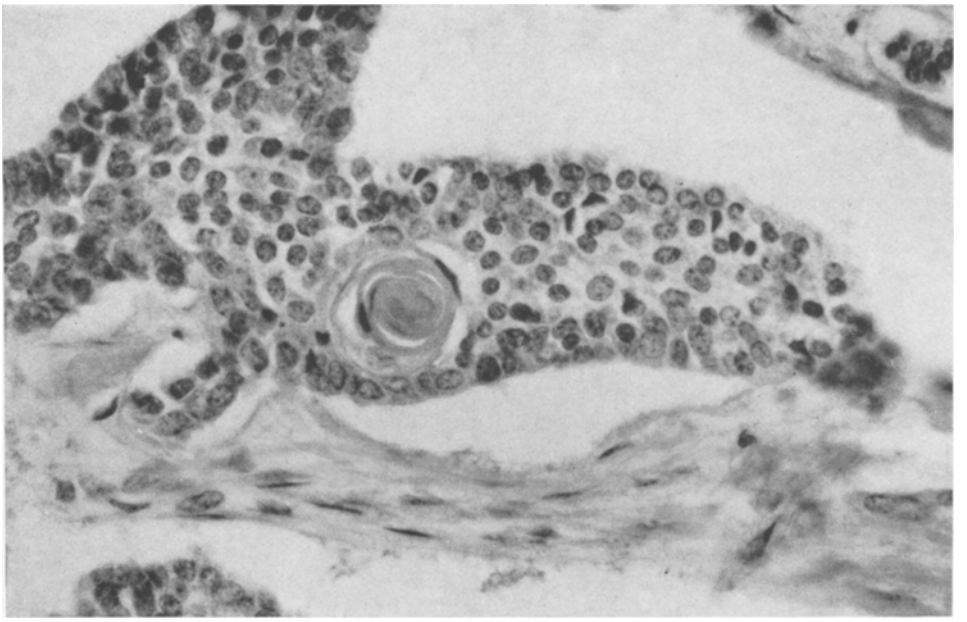


Fig. 11. Pearl formation with keratinisation is evident in some of the small cell nests. H. E. × 437

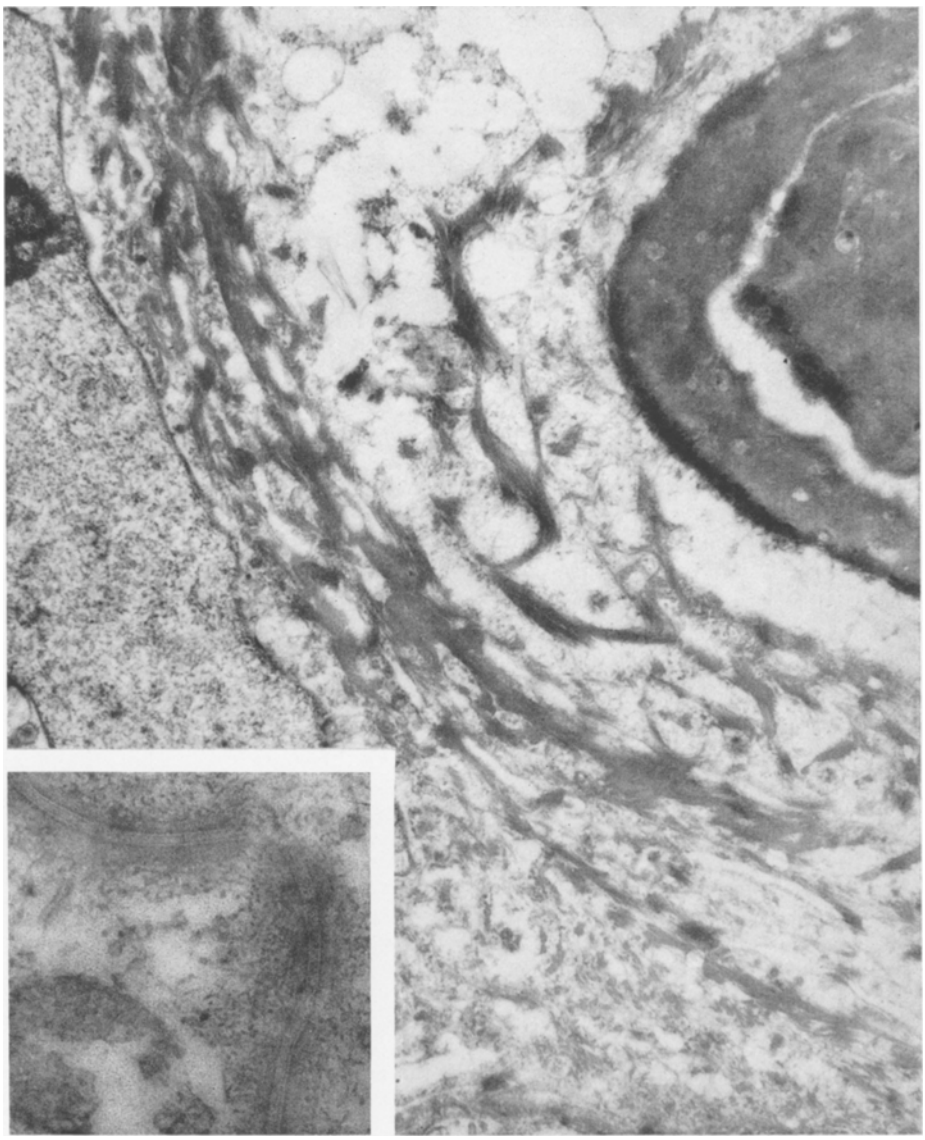


Fig. 12. Many bundles of tonofilaments can be found in the cells. Some of them converge upon desmosomes (inset.) Keratin is present in the right upper corner. × 12600; inset: × 60000

Valid ultrastructural features could as yet be observed in areas as depicted in Fig. 11. The cytoplasm of tumor cells contains abundant short and long bundles of tonofilaments with frayed ends (Fig. 12). Frequently, these filaments converge upon the cytoplasmic membrane and terminate into typical desmosomes. The latter show local condensation of the opposing cell membranes with inserted tonofilaments and thin, characteristic parallel lines can be seen in the intercellular

space (Fig. 12 inset). In the zones of lightmicroscopically visible pearl formation, there is a marked increase of intracytoplasmic bundled tonofilaments and also extracellular concentric accumulation of fine, undulating filaments, intermixed with remnants of cellular components and still recognizable desmosomes, can be demonstrated (Fig. 12). It is conceivable that these pictures represent keratinisation.

Discussion

Reconsidering the most relevant clinical data and part of the morphological findings, the conclusion could be drawn that we are dealing with Ewing's sarcoma. This applies to the age of the patient, the localisation of the tumor, the roentgenographic picture, most of the histo-cytological aspects, the metastatic lesions in the lungs with the initial good response upon treatment and, finally the rapidly progressive clinical course. However, some clinical and especially morphological points, which are not unique for Ewing's tumor or even more in favour of and compatible with so-called adamantinoma, remain for further discussion.

Up to now, more than hundred cases of extra-cranial so-called adamantinoma of the bones have been recorded and reviewed in the world literature (Baker *et al.*, 1954; Gloor, 1963; Moon, 1965; Mandard *et al.*, 1971). From the statistics there appears to be a widespread age range from 11 to 50 years for this tumorous condition, and even cases at the age less than 10 years have been recorded. As concerns the localization, it is well known that the great majority of the extracranial adamantinoma involves the midportion of the shaft of the tibia; the ulna, femur remaining less common sites. We are aware of only two localizations in short bones: in the first case the lesion arised in the capitate bone of the right wrist (Diepeveen *et al.*, 1960), in the second case the first cuneiform bone of the left foot was involved (Moon, 1965).

Regarding the malignancy of extra-cranial adamantinoma, careful study of the literature reveals a relative high incidence of metastasis. In their review, Baker *et al.* (1954) collected out of a series of 27 cases of adamantinoma of the long bones, 8 cases with metastasis proven by biopsy or roentgenographic examination. The inguinal lymphnodes were involved in 5 cases and lungmetastases were evident in 4 of these 8 cases. In turn, Moon (1965) reported on 10 additional cases: 7 patients had clinically suspected pulmonary metastatic lesions, and in 1 case there was evidence of inguinal node involvement.

Lack of complete information about the follow-up of the cases of adamantinoma and of uniformity of the treatment makes estimation of survival quite difficult. Reviewing the list of 91 cases reported by Moon (1965), one can state that the majority of the patients were well for several years, even with evidence of metastatic lesions. A number of patients died within one year.

The morphological findings, however, constitute the most puzzling point in the case we studied and deserve further comment. The basaloid pattern of the islands of tumor cells, the sharp delimitation into nests with palisade arrangement at the periphery as well as the differentiation into squamous epithelium or even focal pearl formation and keratinisation, are most unusual lightmicroscopic features of Ewing's sarcoma. In addition, the submicroscopical findings—the presence of intracytoplasmic packed tonofilaments, the highly specialized desmo-

somes, the structures resembling keratin and the presence of a basement membrane at the periphery of the cell nests—fit the findings well-known from the electron-microscopic studies on adamantinoma by Saavedra *et al.* (1968) and Rosai (1969) and could prove the epithelial nature of the tumor in question. Except in the case of a Ewing's tumor described by Takayama and Sugawa (1970), who observed some aggregated intracytoplasmic filaments and junction complexes between neoplastic reticulum cells, the presence of the specialized cellular structures, as observed in our case, is unmentioned or even denied in other, more extensive ultrastructural studies on Ewing's sarcoma (Friedman and Gold, 1968; Dick *et al.*, 1971; Kadin and Bensch, 1971; Sirsat *et al.*, 1971). In their recent study, Hou-Jensen *et al.* (1971) omit the term desmosome mentioning only the presence of atypical junction complexes with increased electron density in the neighbouring cytoplasm of the tumor cells. This finding confirms the previous observations by Takayama and Sugawa (1970) and those made by Mori and Lennert (1969) on long-branching desmosome-connected reticulum cells in lymphnode follicles. Epithelial characteristics, however, as the ones focally present in our material, have not yet been described. In addition, they are in contradiction with the current but not fully proven opinion on the cyto-histogenesis of Ewing's sarcoma, being a malignant mesenchymal stem cell tumor or neoplasm of myelogenous origin (Friedman and Gold, 1968; Kadin and Bensch, 1971). However, the possibility of "metaplasia" in Ewing's sarcoma, a phenomenon already described and sketchily illustrated by Gery (1935) years ago, cannot be excluded with certitude. Our findings too can point that way but further and extensive study of many slides of other cases of Ewing's sarcoma is needed. If from such a study the occurrence of focal squamous metaplasia would appear not to be infrequent, the histogenesis of Ewing's sarcoma and so-called adamantinoma located outside the jaws, seems to be closely related.

For the time being our opinion on the case in question is in favour of a highly malignant, *poorly differentiated so-called adamantinoma* of a small bone clinically simulating Ewing's sarcoma.

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Dr. U. van Haelst
Department of Pathology
University of Nijmegen
Geert Grooteplein Z 24
Nijmegen, The Netherlands