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Extraskeletal Ewing's Sarcoma

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Summary. Clinicopathologic study of five cases of soft tissue tumors revealed distinct differences from skeletal Ewing's sarcoma in preferential localisation and mean age. The cases examined here are similar to cases described earlier as "extraskeletal Ewing's sarcomas". They show light- and electronmicroscopical features analogous to skeletal Ewing's sarcoma. The term extraskeletal Ewing's sarcoma appears to be appropriate for this type of soft tissue tumor.

Key words: Extraskeletal Ewing's sarcoma – Clinicopathological with ultrastructural findings.

Zusammenfassung. Eine klinisch-pathologische Studie von fünf Patienten mit sogenannten extraskelettalen Ewingsarcomen ergab deutliche Unterschiede in bezug auf die Vorzugslokalisation und das Durchschnittsalter, gegenüber dem Ewingsarcom des Skelettsystem. Die licht- und elektronenmikroskopischen Befunde rechtfertigen jedoch den Begriff extraskelettales Ewingsarcom.

Introduction

Revising the AFIP-material during a period ranging from 1957–1969 Angervall and Enzinger (1975) discovered 39 cases of a malignant extraskeletal neoplasm bearing a close resemblance to Ewing's sarcoma of bone. The authors gave a detailed description of the history of these cases as well as of their clinical, roentgenologic and histologic findings and treatment. Wiggers et al. published an additional case report with the title "Extraskeletal Ewing Sarcoma" (1977) and compared the ultrastructural features with those of bony Ewing's sarcoma.

The present report deals with the clinicopathologic features and the fine structural findings of 5 cases of "extraskeletal Ewing sarcoma" (EES) which were observed within the last 12 months.

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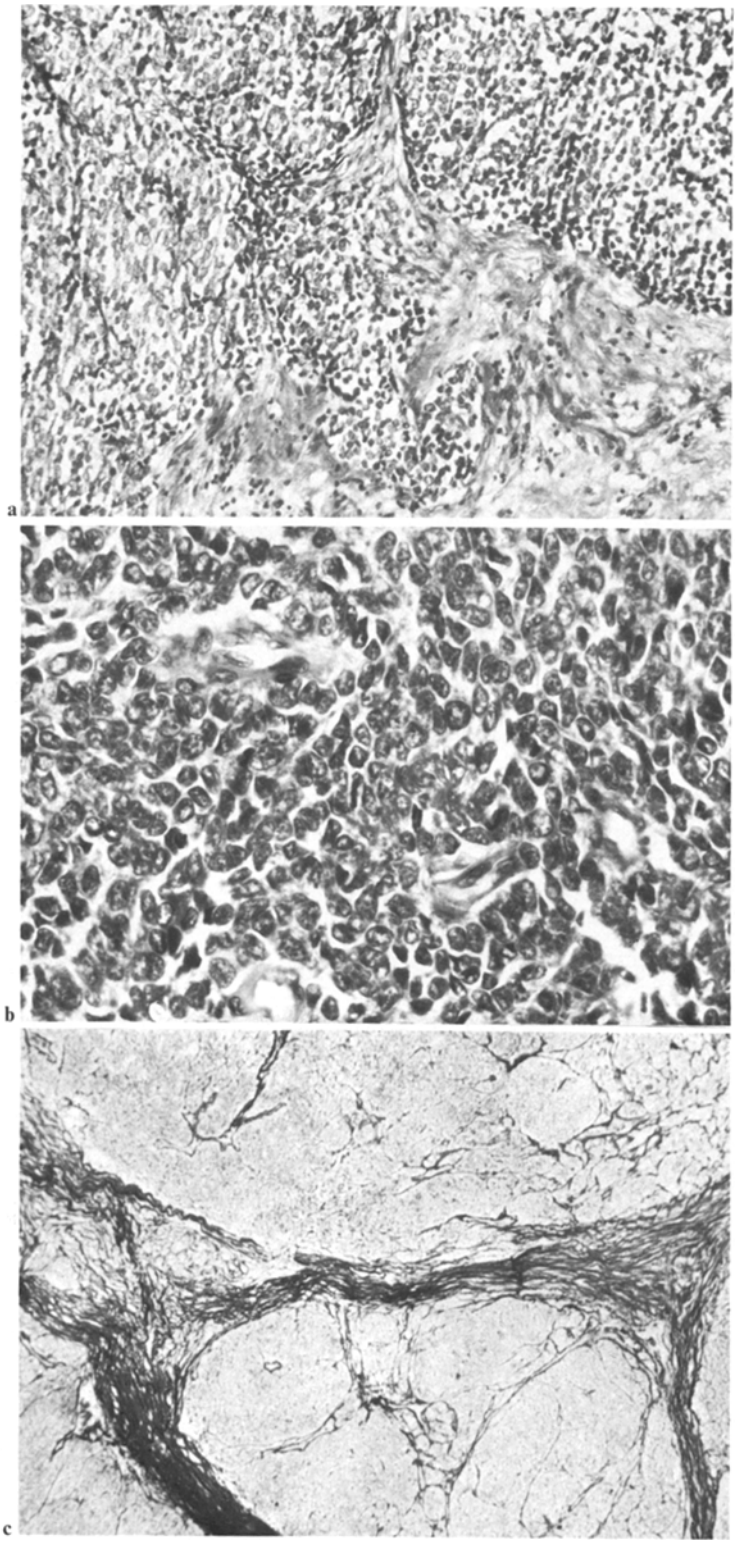

Fig. 1. **a** Extraskeletal Ewing's sarcoma showing characteristic lobular pattern and mostly tumor cells with typical pale nuclei. HE, ×100. **b** Pale nuclei with fine chromatin particles are seen and occasional "dark cells". No cell borders are recognizable. HE, ×400. **c** Distinct lobulation of the tumor, but only scanty and irregular reticulin fibers are seen within the lobules. Silver impregnation, ×40

Clinical Details and Pathological Findings

At the time of biopsy the 3 male and 2 female patients had an average age of 23.2 years, the youngest being 18 and the oldest 39 years old. In 3 cases the trunk (including the neck) was affected, typically by an intercostal tumor. In the remaining two cases the tumor was located in the upper extremities. The neoplasm always manifested itself initially as a tumor mass, while tenderness was only observed in one case. Clinical symptoms usually lasted a few weeks. At surgery all cases presented an ill-defined, deep seated soft tissue tumor measuring from 3.5 to 9.0 cm. In 3 cases the tumor-mass was attached to the periostium.

Macroscopy generally revealed a withish cut surface with small areas of cystic degeneration. Constant findings upon microscopic examination were a highly cellular tumor with a coarsely lobular pattern due to small septa of connective tissue (Fig. 1a), necrotic foci of varying size and areas of marked vascularity with a peritheliomatous pattern.

High power magnification of the tumor cells showed a clear or vacuolated cytoplasm without distinct cell borders and pale, oval nuclei with chromatin particles located peripherally. Mitoses were scanty; irregularly distributed tumor cells with a smaller and more darkly stained cytoplasm were occasionally found (Fig. 1b). Silver impregnation revealed hardly any reticulin fibres within the "tumor lobules" and no special perivascular cell-arrangement (Fig. 1c). Some positive cytoplasmic granules could be demonstrated by PAS-reaction in all our cases. None showed positive granules by ASD-chloracetate reaction.

Fine structural analysis of material re-embedded for electron microscopy from paraffin blocs (Hübner, 1970) disclosed closely packed polygonal tumor cells limited by thin, distinct cytoplasmic membranes of 50–60 Å (Fig. 2a). Occasionally desmosome-like attachment sites were observed (Fig. 2b). The nuclei were round to oval, sometimes irregular, with indentations. The regularly distributed chromatin was aggregated at the nuclear membrane. A relative paucity of organelles was found to be a characteristic feature of the tumor cells. Only a few polyribosomes were present. Fibrils and lipid vacuoles appeared only rarely. Glycogen deposits could not be proved at all. Sometimes small areas of "empty cytoplasm" were observed. Fine breaks in the membranes of nuclei, cytoplasm and cell organelles were frequently discovered. Intermingled with this common cell type were "dark cells", with nuclei and cytoplasm of increased electron-density.

Discussion

Extraskeletal Ewing's sarcoma (EES) differs from skeletal Ewing's sarcoma by the following features: 1) It does not show the distinct male predilection shown in bony Ewing's sarcoma, being equally distributed among both sexes. 2) The patients suffering from EES are older than those having bony Ewing's sarcoma: the average age of about 20 years in cases with EES is about 10 years higher than that of bony Ewing's sarcoma. 3) EES does not primarily affect the lower extremities preferentially, as does bony Ewing's sarcoma, but affects the trunk more frequently.

In all these respects our cases resemble those reported by Angervall and Enzinger (1975).

EES is usually located deep in the soft tissues. In 10 of the 39 cases examined by Angervall and Enzinger (1975) and in 3 of our cases, periosteal changes in the underlying bones were evident. However, none of these changes resembled the roentgenographic changes of typical bony Ewing's sarcoma and there was never any evidence for a primary bony localization of the tumor.

Despite these differences EES reveals striking similarities to typical bony Ewing's sarcoma on light and electron microscopy; that is to say the cytoplasm appears clear or pale in light microscopy and few organelles are visible with

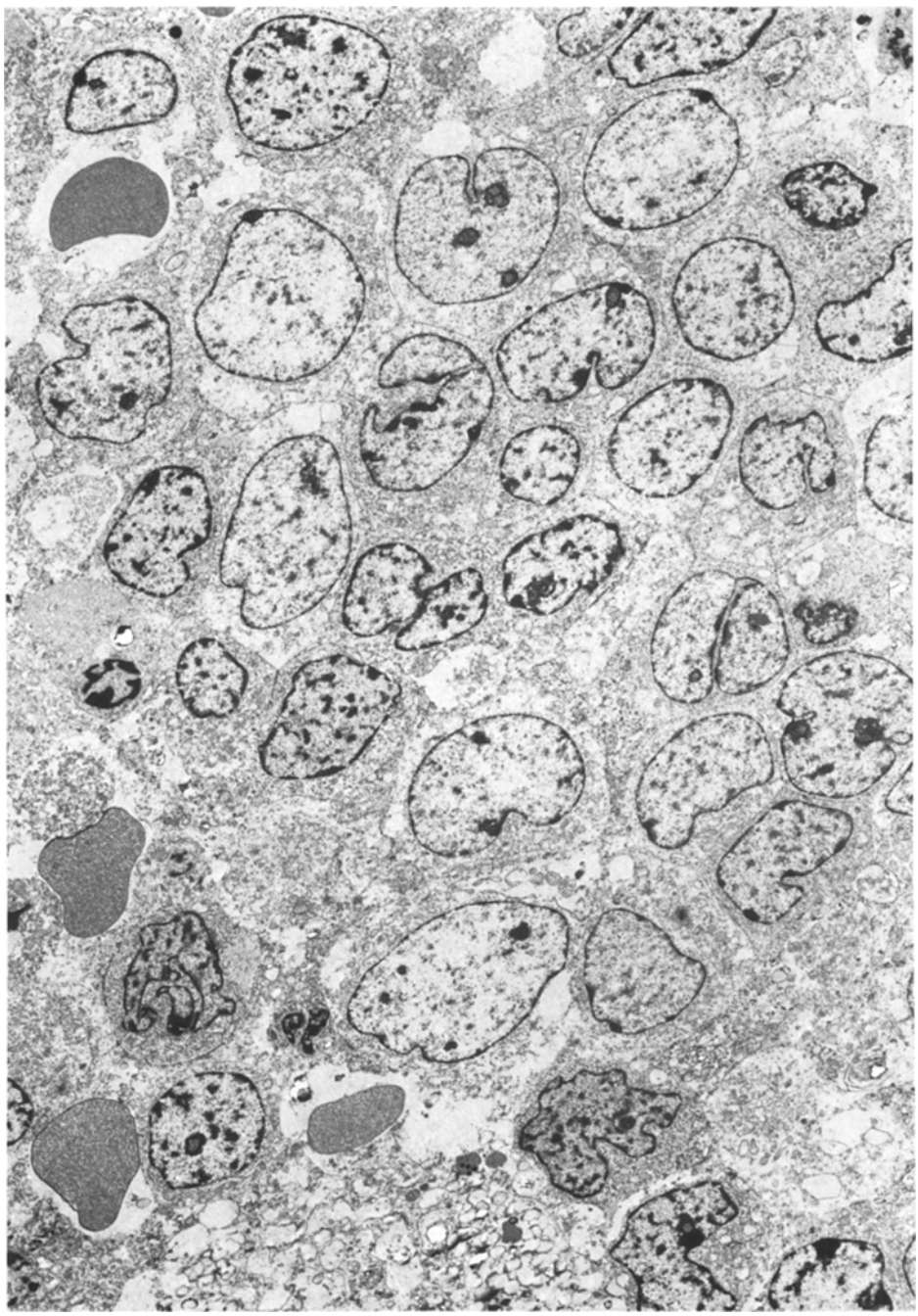

Fig. 2. a Survey electron micrograph: dense collection of large polygonal electron-lucent tumor cells defined by distinct cytoplasmic membranes. In the lower part are a few smaller electron-dense cells with condensed and irregular nuclei. Arch. Nr. 16367, ×3000. **b** Tumor cell of extraskeletal Ewing's sarcoma showing scanty cell organelles and desmosome-like attachment sites (arrows). *N* Nucleus, *M* Mitochondria, *P* Polyribosomes. Arch. Nr. 18078, ×53,000

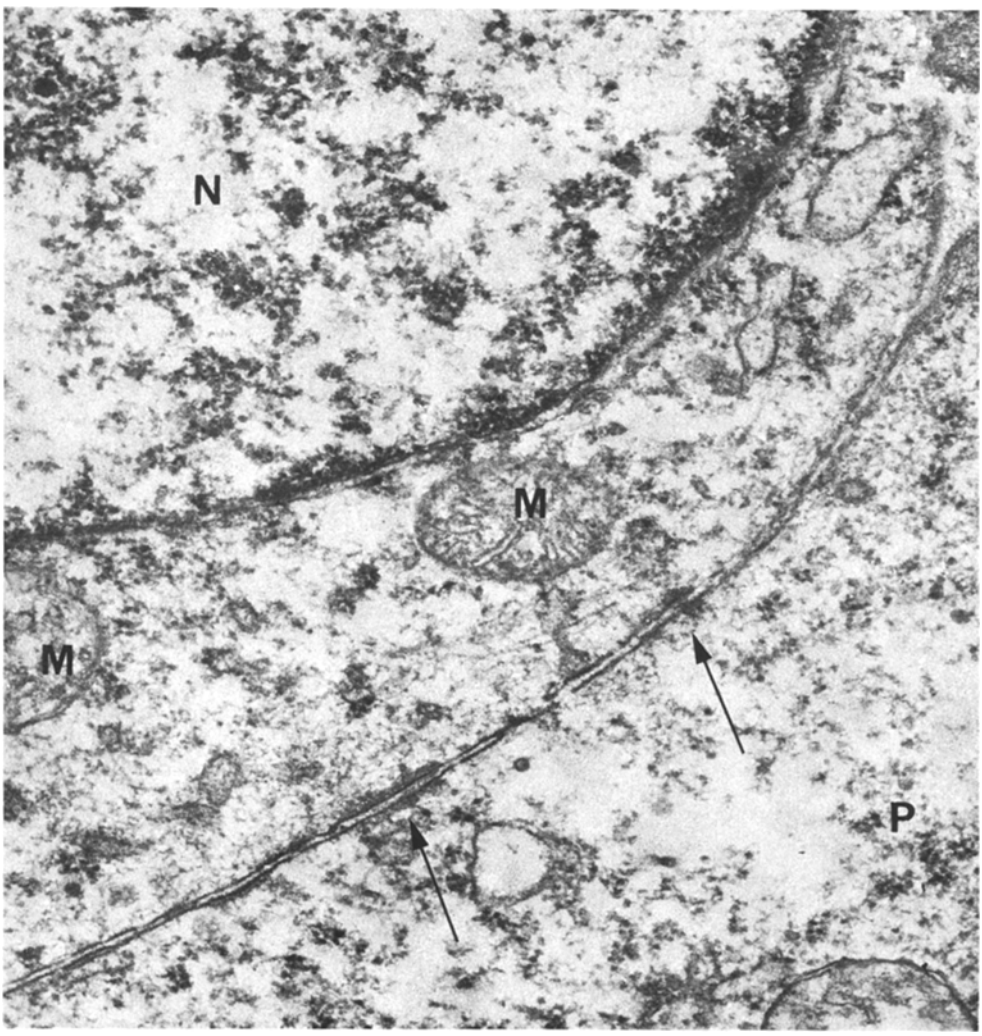

Fig. 2b

the electron microscope; on light microscopy the cytoplasmic membranes are indistinct, while thin cytoplasmic membranes become visible on electron microscopic examination. In contrast to the description of Wiggers et al. (1977) also smaller "dark cells" were found in our material. Friedman and Gold (1968) and Povysil and Matejovsky (1977) claimed these cells to be characteristic of bony Ewing's sarcoma. While PAS positive granules were regularly visable on light microscopy the existence of glycogen could not be demonstrated ultrastructurally. This discrepancy, however, is described in paraffin processed material re-embedded for electron microscopic examination (Friedman and Gold, 1968). It is possible that the areas of "empty cytoplasm" observed in our material represent former glycogen deposits.

Skeletal and extraskeletal Ewing's sarcomas are basically neoplasma of primitive mesenchymal cells. A positive alkaline phosphatase reaction, bound to the cytoplasmic membrane, was considered to be evidence for a possible angioplastic derivation of Ewing's sarcoma. In this context one should bear in mind that Ewing himself used the term "diffuse endothelioma of the bone" in his original report in 1921. Although a peritheliomatous cellular arrangement may predominate, the tumors lack other evidence of pericytic differentiation.

In differential diagnosis it is important to distinguish EES from neuroblastomas and malignant lymphomas. By light microscopy the former display rosettes and a fibrillary stroma (neuropil), have elevated levels of urinary catecholamine metabolites, and show secretory granules by ultrastructural examination (Mackay et al., 1976). It may prove difficult to differentiate between malignant lymphomas and EES especially if the material is not well preserved. EES may be recognised by their pale pink cytoplasm and their roundish nuclei of about twice the size of lymphocytes. A lobular pattern, PAS positive cytoplasmic granules, a positive alkaline phosphatase reaction and ultrastructural attachment-sites can serve as descriminants against most lymphomas (Lennert and Niedorf, 1969). Although Kadin and Bensch (1971) observed features characteristic for the development of myelocytes when examining cell cultures of Ewing's sarcoma, a myelogeneous origin of Ewing's sarcoma is not at all established. Differential diagnosis of EES should also include undifferentiated alveolar rhabdomyosarcoma. Finally, EES must be distinguished from primary and metastatic undifferentiated carcinoma as the age at which some cases of EES occur is within the range where these carcinomas develop.

The biological behaviour of EES can be evaluated from the follow-up data provided by Angervall and Enzinger (1975). Within a control period of 14 years 51% of the patients had died, the majority of them due to the rapid course of the neoplastic disease. 49% of their patients were alive, 26% without any evidence of tumor recurrence or metastases. In our group, which was followed-up from 6–12 months after the diagnosis had been made, one of the 5 patients had died. He had refused any treatment and exspired 3 months after the diagnosis had been made. The others have survived and are presently free of tumor.

The therapy of choice consists in total surgical excision of the tumor followed by x-ray treatment and/or chemotherapy. Lung metastases can frequently be found in incurable cases at an early stage of the disease. Lymph nodes and bones may also be affected (Angervall and Enzinger, 1975).

The rare and late occurrance of osseous involvement suggested to Angervall and Enzinger (1975) that it was unlikely that EES may be nothing but an initital soft tissue manifestation of a skeletal Ewing's sarcoma.

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