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Can an osteoblastoma become malignant?

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Summary. A rare case of an osteoblastoma in the clavicle is reported, that became malignant within $3^1/_2$ years, after two recurrences. The clinical course of the disease and a comparison of tissue sections removed during a total of four operations point to a secondary malignant transformation of an osteoblastoma, such as has been described by Schajowicz, among others. Six years after the first diagnosis was reached and $3^1/_2$ years after the last resection of the clavicle and the removal of a tumour from definitely healthy surrounding tissue, and after long-term chemotherapy, the now 17-year-old youth is free of metastases and there is no sign of a recurrence of the tumour. The problem of differentiating this kind of tumour from other types is discussed in light of international literature on the subject, and therapeutic recommendations are made.

Key words: Osteoblastoma – Osteosarcoma – Malignant osteoblastoma – Malignant transformation

Introduction

Osteoblastomas are generally considered to be benign bone tumours. In certain cases considerable diagnostic difficulties can arise in distinguishing an osteoblastoma from an osteosarcoma. In light of the relatively frequent observation of local recurrences and the existence of locally aggressive but never metastatic intermediate forms, Schajowicz (1976) defined the so-called malignant osteoblastoma. Since only 12 cases of malignant transformation have been reported to data in the medical literature, a further case observed by the authors is described in the following article. The problems of classification, determination of malignancy or benignancy, and differential diagnosis between osteoblastoma and osteosarcoma will also be discussed.

This article is dedicated to Prof. Dr. med. Dres. h.c. mult. Wilhelm Doerr in honor of the 70th birthday

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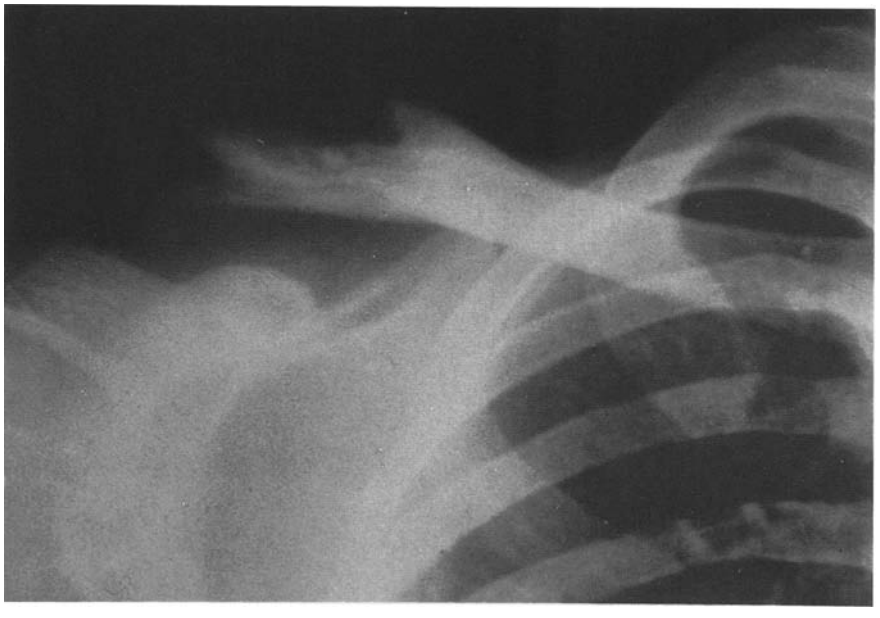

Fig. 1. Cystic defect in the structure of the lateral part of the right clavicle (first X-ray evidence of the tumour, June 1978)

Case report

On June 1, 1978, M. M., an 11-year-old boy, was admitted to the City Hospital in Fürth for the treatment of an "undefined tumour of the right clavicle".[1] The right clavicle had been painful when touched for three months. An *X*-ray showed a cystic tumour in the clavicle (see Fig. 1). Laboratory tests done before the operation yielded no abnormal results, with the exception of a slight elevation in the alkaline phosphatase level (142 I.U., the normal range includes values up to 100 I.U.). When the patient was examined, a tumour 5×3 cm was discovered, an X-ray showed the bone to be club-like with a subcortical cyst. During the curettage of the tumour on June 2, 1978, crumbly yellowish-whitish masses were found in the hollow areas in the cyst. They were completely removed clinically. The alkaline phosphatase level now measured 74 I.U..

Microscopic examination of the tumour tissue after removal (E-Nr. Fürth 5205/78, see Fig. 2), showed small, irregularly arranged osteoid trabeculae in some areas. In other areas regularly arranged osteoid trabeculae were found. Next to them stroma consisting of long, spindle-shaped cells with slender nuclei, as well as isolated giant cells of osteoclastic type were discovered. A rich blood supply was a conspicious feature. A diagnosis of osteoblastoma with no sign of malignancy was made.

The patient was discharged with the recommendation that an X-ray be taken every three month, but neglected further check-ups. The patient was not readmitted until April 28, 1981. For two months the now 13-year-old boy had noticed increasing tumour growth at the place where the first tumour had been curetted. A clinical examination revealed a growth of 6×4 cm. It was firm and immobile. The X-ray findings mere of irregular radiolucent lesions, most of which were sharply defined by thin layers of lamellar bone. The character of the changes was distinctly spotty, the former bone structure had disappeared.

Selective angiography of the right subclavian artery revealed one larger caliber blood

1 We are thankful to Dr. F. Kleinfeld, medical superintendent of the Second Surgical Ward of City Hospital in Fürth, West-Germany, for allowing us to evaluate the clinical and X-ray findings

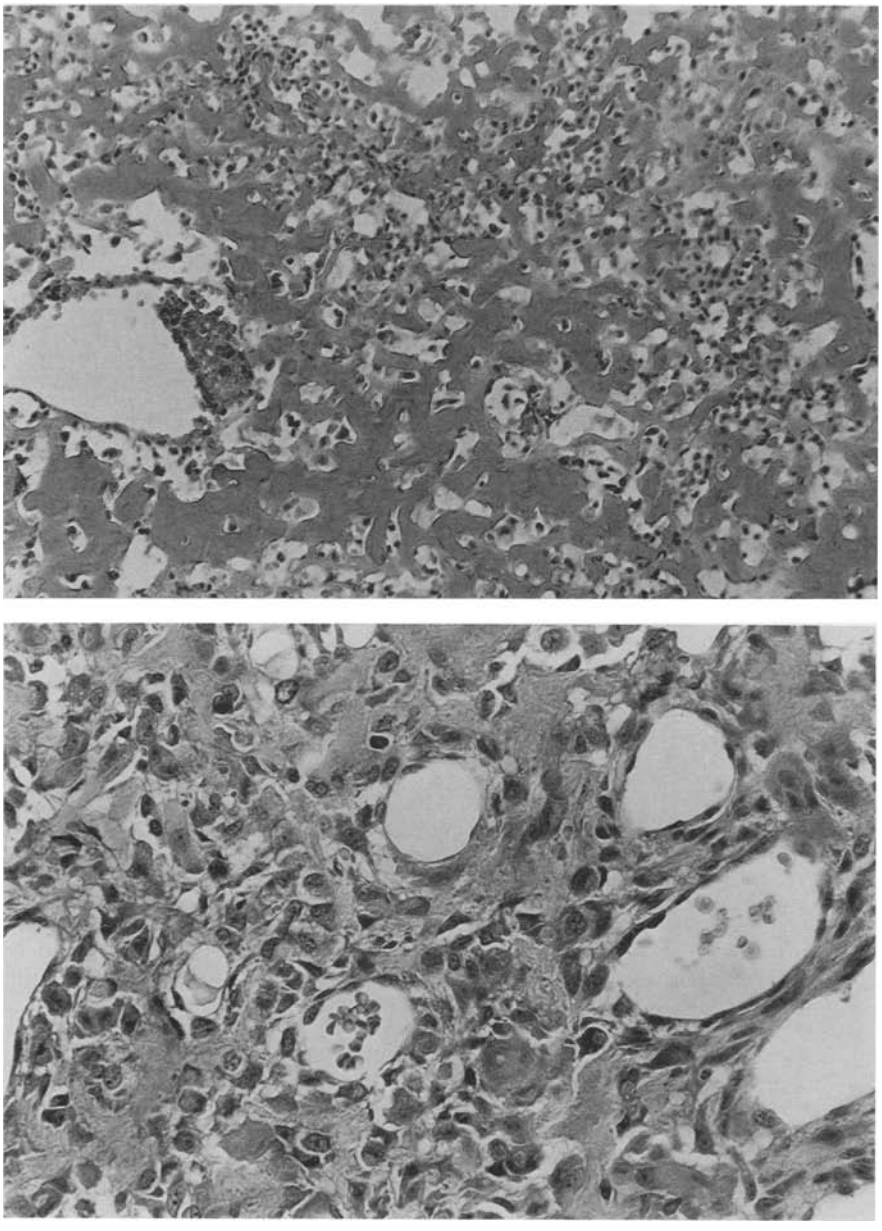

Fig. 2. a Section of the material removed during the curettage of the "original tumour" (E-Nr. 5205/78) with the histological characteristics of an osteoblastoma: Haematoxylin eosin. Magnification 150× with additional magnification. **b** Shows an area of the same section in a close-up view with many vessels and less osteoid

vessle in the area of the tumour with a number of fine netlike blood vessels, but neither pathological blood vessels, nor AV-shunts, nor blood-pools were found. Laboratory tests yielded normal results with the exception of an elevated alkaline phosphatase level (1531 I.U.).

When the tumour was exposed surgically to do a biopsy a bone hollow was found, filled with soft whitish-yellowish tumour tissue, completely surrounded by very dense, sclerosed

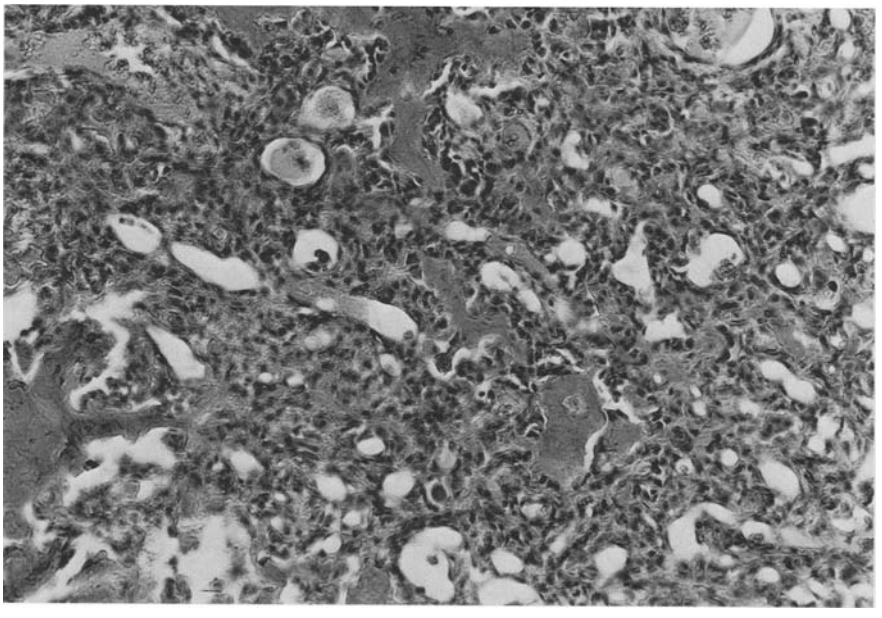

Fig. 3. Histological section from the first recurrence of the osteoblastoma (E-NR. 6430/81) approximately three years after the curettage of the original tumour. There is abundant formation of osteoid, isolated giant cells of osteoclastic type were seen. The cells are still well-defined; the hypertrophic osteoblasts, which are regular in appearence, dominate the picture. The number of mitoses has not increased. A large amount of osteoid is present. Haematoxylin eosin. Magnification 160 × with additional magnification

bone. An examination of the microscopic tissue structure (see Fig. 3) showed that the tumour was somewhat less sharply defined, but still gave the appearance of being an osteoblastoma. There was no indication of malignancy.

On May 16, 1981, a subtotal resection of the right clavicle took place. A rib was inserted and fixed in place with the help of a plate. Microscopic examination of the tumour tissue confirmed the initial diagnosis based on the results of the biopsy. The bone edges on both sides of the resection were free of tumour from a histological standpoint. On October 27, 1981, the patient was readmitted to the same hospital for removal of the plate. Conspicious was considerable hyperaemia in the entire area of the operation was well as singular "granulations", which were removed for a histological examination. In view of post-operative X-ray examination a recurrence of the tumour appeared likely. Structures lacking sharply defined edges with alternating defects and sclerosing consolidations were found. Microscopic examination showed a large number of mitoses and capillaries well filled with blood. Patholgogical mitoses were not found at the time of this examination. There was marked pleomorphism in the cell nuclei and atypical nuclei in comparison with previous biopsies as well as a relationship between nuclei and cytoplasm. Large amounts of irregularly ordered osteoid deposits were found. No tumour bone and no cartilage were found (see Figs. 4 and 5). A diagnosis of low-grade osteosarcoma was done.

Prof. Schajowicz, Buenos Aires, who examined sections prepared in our hospital, confirmed this diagnosis. In light of the previous examination it was considered to be an osteoblastoma with malignant transformation.

On November 19, 1981 the now 14-year-old male patient was transferred to the University Childrens Hospital in Erlangen. Staging examinations showed no signs of metastases in other parts of the body. Laboratory tests yielded normal values with the exception of a clearly elavated alkaline phosphatase level (876 I.U.), but there was a local tumour recurrence of 8 × 3 cm. A computerized tomogram showed a partly compact, partly spongy, dense tumour.

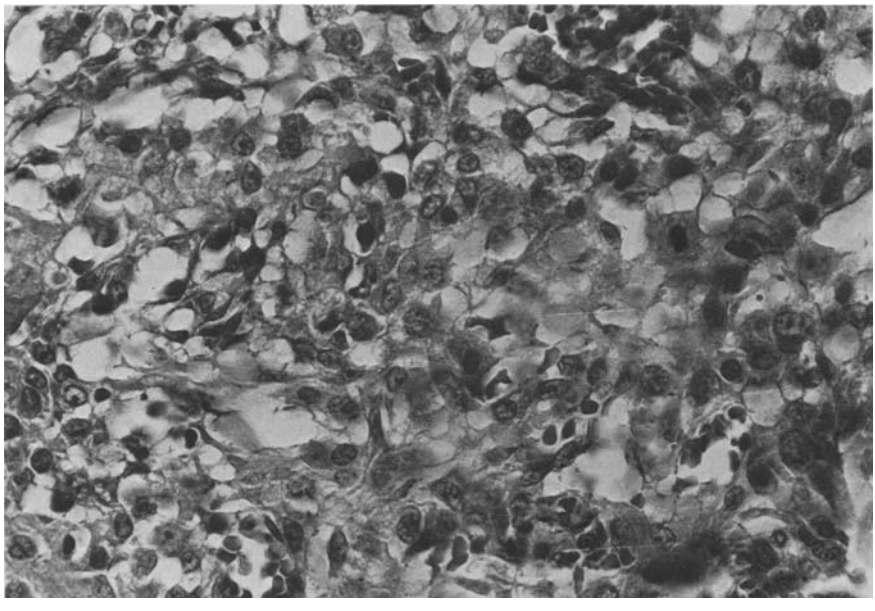

Fig. 4. The tumour now has the appearence of a low-grade osteosarcoma (E-Nr. 13199/81). Haematoxylin eosin. Magnification × 360 with additional magnification

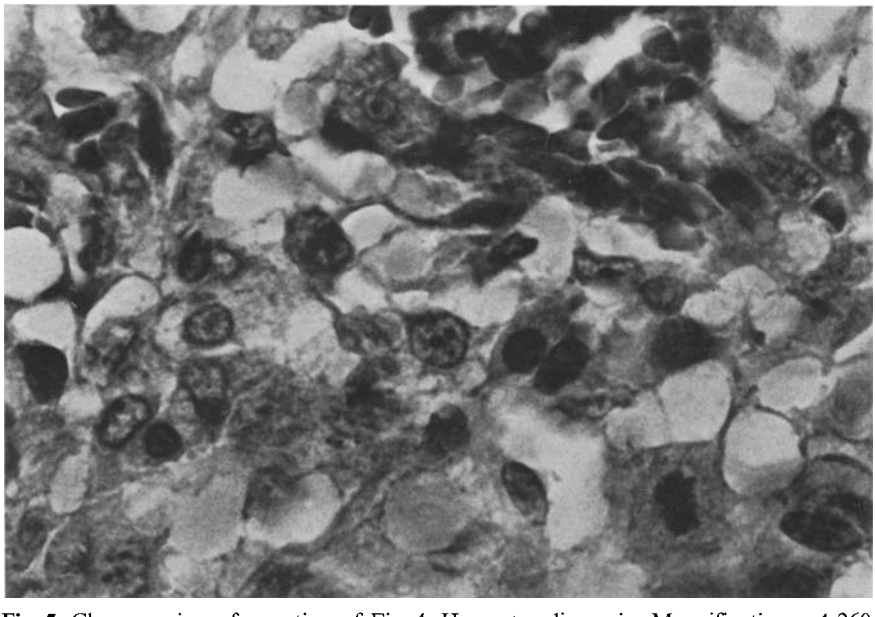

Fig. 5. Close-up view of a section of Fig. 4. Haematoxylin eosin. Magnification × 1,260 with additional magnification

Despite cystostatic chemotherapy the tumour grew rapidly, reaching the size of 15 × 8 cm on January 18, 1982, when it was surgically removed (see Fig. 6).

We thank Prof. Hermanek for letting us evaluate the results of the pathological-anatomical and patho-histological examinations that he carried out. A comparison with the sections of our last examinations offered no indication of a fundamental change in the findings. Chemo-

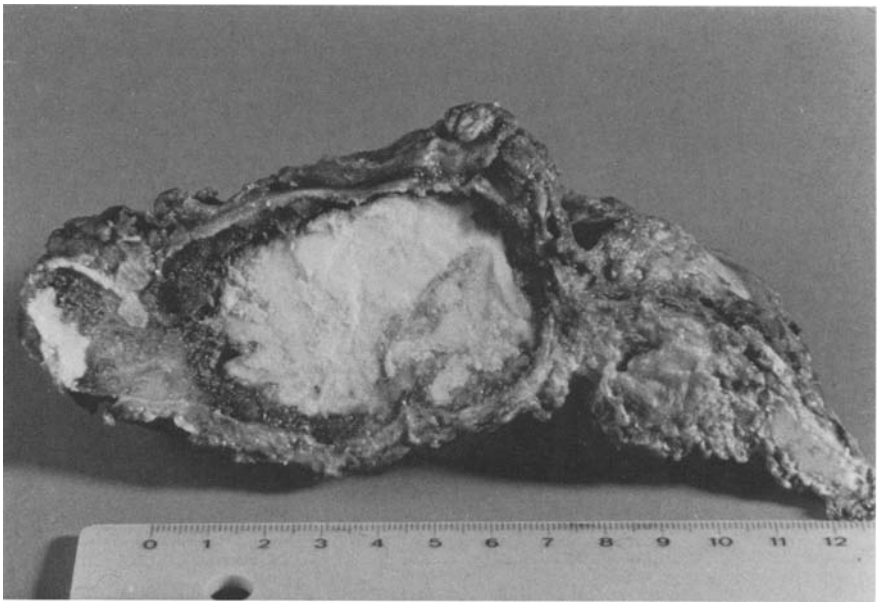

Fig. 6. Sawed-off section of the tumour prepared from bone removed during the operation (Surgical Hospital Erlangen, E-Nr. 6336/82). We wish to thank Prof. Dr. P. Hermanek, medical director of the division of Clinical Pathology at the University Hospital in Erlangen, FRG, for permitting us to use this picture

therapy was continued. Until the present time (August 1985) there have been no signs of a recurrence or of metastases.

Discussion

Osteoblastomata are relatively rare tumours. Jackson (1978) gives an account of 184 cases, Schajowicz (1981) reports 51 cases, Schreyvogel (1968) 49 and Dominok and Knoch (1982) 72 cases, the latter speaking of an osteoblastoma when the size of the nidus is greater than 1 cm. The clavicle was only affected in two of the cases described by Dominok and Knoch. According to Schreyvogel osteoblastoma is benign and relapses after complete removal do not occur, Dominok and Knoch are of the same opinion. Other authors (Literature, see Smith 1972) do not consider osteoblastoma so be a true bone tumour, but a specific, local response to injury with the possibility of spontaneous remission. They conclude that a partial excision is enough and that radical surgical procedures are superfluous.

Recurrences of so-called benign osteoblastomas are appearently not rare. Dahlin and Johnson (1954); Goidanich and Battaglia (1958); Lichtenstein (1959); Dunlop et al. (1970); Spjut et al. (1971), all report them. Canepa and DeFabiani (1965) report 11 recurrences among a total of 54 cases of osteoblastoma; Schajowicz (1981) reports 5 recurrences among 51 cases, even though long-term observations have not been made. Jackson (1978) surveyed 18 recurrences in 184 cases in which osteoblastoma had been diagnosed in medical literature in English-speaking countries, although no long-

term studies had been carried out in many of these cases. In view of periods of latency ranging from 3 month to 9 years, the actual number of recurrences is sure to be higher. During follow-up observations of 52 of a total of 197 osteoblastoma cases extending over a period of more than one year Marsh et al. (1975) had already observed 8 recurrences (=15,4%).

Recurrences occured most frequently in the spine and in the pelvis. A recurrence in the clavicle, such as we observed, has not yet been described. Interestingly enough all recurrences recorded by Jackson (as well as later malignant transformations) were preceeded by inadequate initial therapy (curettage, partial excision, etc.), while a recurrence has never been described after complete removal of the tumour. Thus Jackson demands the en bloc resection as a matter of course, with long-term check-ups afterwards.

Worldwide the possible malignant transformation of a so-called benign osteoblastoma has only been described twelve times in medical literature. These transformations occured after inadequate initial therapy (curettage and similar methods) and usually after several recurrences. Schajowicz and Lemos (1976) and Revell and Scholtz (1979) differentiate between osteoblastoma, which is generally considered to be benign and a special form, so-called malignant or aggressive osteoblastoma which grows aggressively locally, but never metastatizes. There is a variable appearence with blood-rich areas of a soft consistency but in the center areas which tend to be firmer and sclerosed are found. These are, however, never as hard as in the case of osteosarcoma. Thus X-ray pictures of malignant osteoblastomas vary greatly and are of no help in arriving at a diagnosis (see Pochaczevsky et al. 1960). A large osteolytic lesion is often observed at first, which is initially well-delineated and shows a bulging and thinning of the cortex. The cortex is not destroyed until later stages or until a recurrence, and is then accompanied by an invasion of the surrounding soft tissue or neighboring bones. Once in a while, as in the case under discussion, X-rays revealed spotty areas.

Malignant osteoblastomata have no areas of necrotic tissue and have no chondroblastic tissue unless callus tissue formed as a result of a pathological fracture. According to Mirra et al. (1976) relatively thick osteoid in the osteoblastoma with irregular edges, surrounded by well-vascularized stroma are helpful in differentiating it from an osteosarcoma. In the case of osteosarcoma the osteoid and the barely calcified tumour bones are present in forms of long strings. There is little stroma and few blood vessles present. See also Table 1.

Although there are similarities between our case and the cases of malignantly transformed osteoblastoma described by other researchers, there are a number of peculiarities. First, osteoblastomas, malignant osteoblastomas and osteosarcomas are extremely rare in the clavicle. The symptoms experienced by our patient were extremely unusual. This fact, together with the morphological findings, tells, in our view, against the supposition expressed by some pathologists to whom the case was referred, that we were dealing a priori with low-grade osteosarcoma for the period of more than $3^1/_2$ years before local recurrence and the lack of metastases would be very unusual. There are reports of cases in which metastases were found in the lungs

Table 1. Distinguishing characteristics of osteoblastoma and malignant osteoblastoma

Osteoblastoma	Malignant osteoblastoma
Main location: spine	Main location: long bones
Formation of abundant ostoid and immature bone trabeculae surrounded by a large number of active osteoblasts and osteoclasts	In addition fields with numerous multinucleated giant cells of the osteoclast type, formation of bone spicules of irrgular shape that stain dark blue with haematoxylin (blue spiculated bone) generally surrounded by normal osteoblasts
	Osteoblasts more abundant, larger in size often with plump hyperchromatic nuclei
	Greater nuclear atypism
Fewer normal mitoses	Frequent normal mitoses
No atypical mitoses	Small number of atypical mitoses possible
	Destruction of the cortex and invasion of the surrounding soft tissue in advanced cases

when the original tumour was only 2 cm in size. There were no cases of osteosarcoma among the 176 well-documented cases of tumours with spontaneous regression or cessation in growth compiled by Everson, quoted according to Mirra et al. (1976). After the tumour had grown slowly for $3^1/_2$ years, it grew extremly rapidly despite chemotherapy. This would be difficult to explain if we had been dealing ab initio with an osteosarcoma. Nevertheless the sudden growth of the tumour after it had grown very slowly over a period of years is hardly consistent with the diagnosis of a still benign osteoblastoma. Indeed from the standpoint of the clinical and morphological findings there was absolutely no sign of malignancy in 1978. At the time there were only isolated mitoses. Atypical cells and nuclei were still lacking at that time, as were microscopic signs of an osteosarcoma. Not until the end of 1981 and in 1982 did the tumour clearly contain pleomorphic cells and nuclei, and atypical cells, in contrast to all previous examinations. Chondroid areas, necrotic areas, atypical mitoses or blue spiculated bone, such as are typical for osteosarcoma, could not be found in the last sections prepared. The number of cells increased and the cells were less well-delineated from recurrence to recurrence until 1982. In 1981 and 1982 new morphological changes took place which convinced us that we were dealing with a malignantly transformed osteoblastoma. For us the changes in the morphological picture mentioned above are an expression of a change in the biological behavior of the tumour in the direction of malginancy.

In conclusion, the morphological differentiation of recurrences of an osteoblastoma, a malignant osteoblastoma and a low-grade osteosarcoma is extremely difficult, in some cases perhaps impossible. The morphological appearence and biological behaviour of the tumour are not necessarily in accordance with each other. The course of the disease will play a major role in the choice of therapy in individual borderline cases. Since there

are recurrences in up to 15.4% of all cases of osteoblastoma and since a malignant transformation has up to now always been preceeded by one or more recurrences, the initial therapy must strive for an extensive excision.

After the operation closely spaced follow-up check-ups over a long period of time are absolutely necessary. When there are 2 or more recurrences, preferably a bloc resection should be done. On the other side Pieterse et al. (1983) according to Lichtenstein (1977) accept the aggressive behaviour, however unusual, as part of the spectrum of osteoblastoma, but they warn against unnecessary aggressive treatment.

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