Virchows Arch [Pathol Anat] (1983) 399:89–104

Virchows Archiv A

Mesenchymal chondrosarcoma in the young

A clinicopathologic study of 19 patients with explanation of histogenesis

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Summary. It has been almost a quarter of a century that this rare, still poorly understood and to date insufficiently studied, cartilage neoplasm was described. Based on 19 cases in the young representing 26 percent of chondrosarcoma patients under the age of 21 years, this study found equal sex distribution with the youngest patient being a 6-year old boy. Twelve lesions occurred between the ages of 16 and 21 years. All but one of the tumors arose in the skeleton with nearly half of them involving the lower extremity. Pain was inconsistent and rare at presentation in contrast to the regularity of swelling or a painless mass. Survival analysis revealed a 46 percent 2-year and a 35 percent 5-year survival rate, whereas at 10 years only 20 percent of the patients were still alive.

This study attempts to establish the likeliest evolutionary pathway of neoplastic cell differentiation and traces the origin of this tumor to a neoplastic caricature of embryonal endochondral osteogenesis.

Key words: Bone neoplasms – Diagnosis – Pathology – Chondrosarcoma – Diagnosis – Pathology – Histogenesis

It has been almost a quarter of a century since this rare and distinctive cartilage neoplasm has been initially described in 1959 among a varied group of unusual cartilage and chondroid tumors, both benign and malignant (Lichtenstein and Bernstein 1959). The original report contained two examples of a unique hard to classify neoplasm designated as mesenchymal chondrosarcoma, so named because of a highly cellular primitive spindle cell

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Presented in part at the Seventy-first Annual Meeting of the International Academy of Pathology (U.S.-Canadian Division), Boston, Mass. March 1–5, 1982

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0340-1227/83/0399/0089/$03.20

stroma displaying focal chondroid differentiation. Since this time no stark changes in the original assessment of this tumor have been noted and no serious professional dissent has been registered while it became well accepted that this lesion was of cartilage derivation. Various names and appelations have been applied to mesenchymal chondrosarcoma among which "primitive multipotential primary sarcoma of bone" (Hutter et al. 1966), "hemangiopericytoma with cartilaginous differentiation" (Reeh 1966), "polyhistioma: a pluripotential small round cell sarcoma" (Jacobson 1977), "poorly differentiated chondrosarcoma" (Azar 1976) and "atypical chondroblast tumour" (Salzer-Kuntschick 1969) were the most prominent.

Material and methods

In a comprehensive review of all patients with malignant cartilage tumors of the skeleton and of extraosseous sites diagnosed and treated at Memorial Hospital for Cancer and Allied Diseases between 1921 to 1981, 35 had mesenchymal chondrosarcoma, 19 of whom were 21 years or younger. Patients referred as consultations only, similarly to those with insufficient clinical or pathologic material were eliminated. All cases included in this study were histologically verified. Regularly conducted annual follow-up was maintained by the hospital's Cancer Registry. Due to these well focused efforts none of the patients were lost to follow-up. Survival functions were estimated using the actuarial life table method which incorporates all survival information accumulated up to the termination of the study (Cutler and Ederer 1958). Survival duration and length of disease-free intervals were measured from the date of definitive therapy.

Results

There were 35 examples of mesenchymal chondrosarcomas, 19 of which occurred in individuals 21 years of age or younger. This represents approximately one-fourth of those chondrosarcomas which afflict the young. There were 10 males and 9 females with the youngest male being 6 and the youngest female 15 years of age, respectively. Only 2 boys were younger than 10 years with 7 patients being between 11 and 15 years (Fig. 1). While 6 of the males were 15 years or younger only 3 women were in this age group. This male to female predominance was reversed for patients over 15 years of age but still younger than 21. Here there were 7 women for 3 men.

Pain, considered by many the cardinal symptom to accompany malignant cartilage tumors, was notably absent in the young mesenchymal chondrosarcoma patients. Fifteen patients experienced their tumor mass to be totally painless and only 4 had some degree of pain (3 mild and one severe). The most common presenting sign was swelling or a painless mass.

All but one of the 19 tumors arose in the skeleton (Fig. 2). The long tubular bones of the appendicular skeleton were involved in 8 instances while the ribs and the ilium in two each, and the calcaneus in three. Among the craniofacial bones, 1 lesion each arose in the occiput and maxilla. The sole extraosseous example was located in the soft tissues of the upper arm. The bones of the lower extremity were affected in 44%, while the pelvis and femur in 28% of all cases.

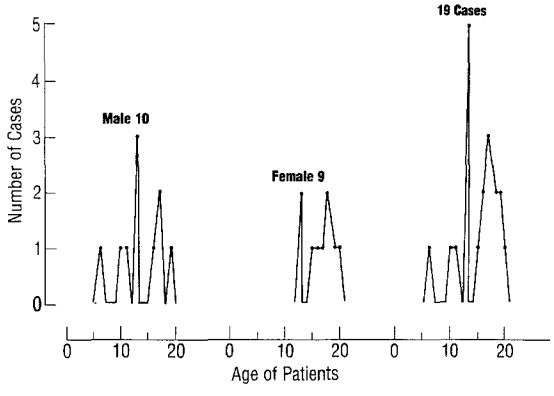

Fig. 1. Age and sex distribution in 19 young patients with mesenchymal chondrosarcoma

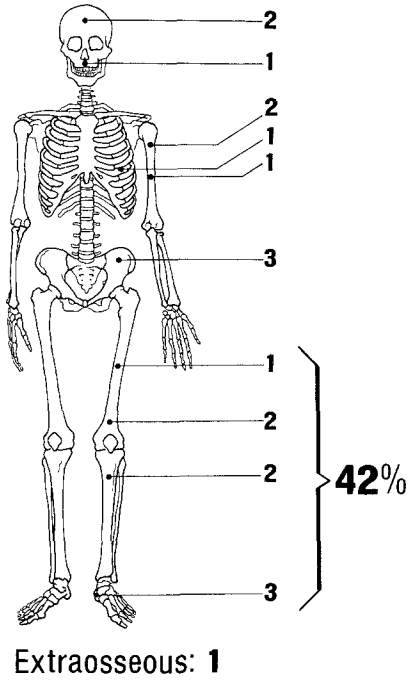

Fig. 2. Skeletal location in 19 patients

Since the number of cases are relatively small in this study, it is difficult to discern skeletal distribution trends in mesenchymal chondrosarcomas arising in patients 21 years old or younger. The skeletal locations of the 18 cases correspond in general to chondrosarcoma afflicting the young. To wit, approximately 40% of both ordinary and mesenchymal chondrosarcomas afflict the bones of the lower extremity. The same proportion of both types of chondrosarcomas involve the craniofacial bones (13% versus 11%). In contrast to a prominent participation of pelvic bones in giving

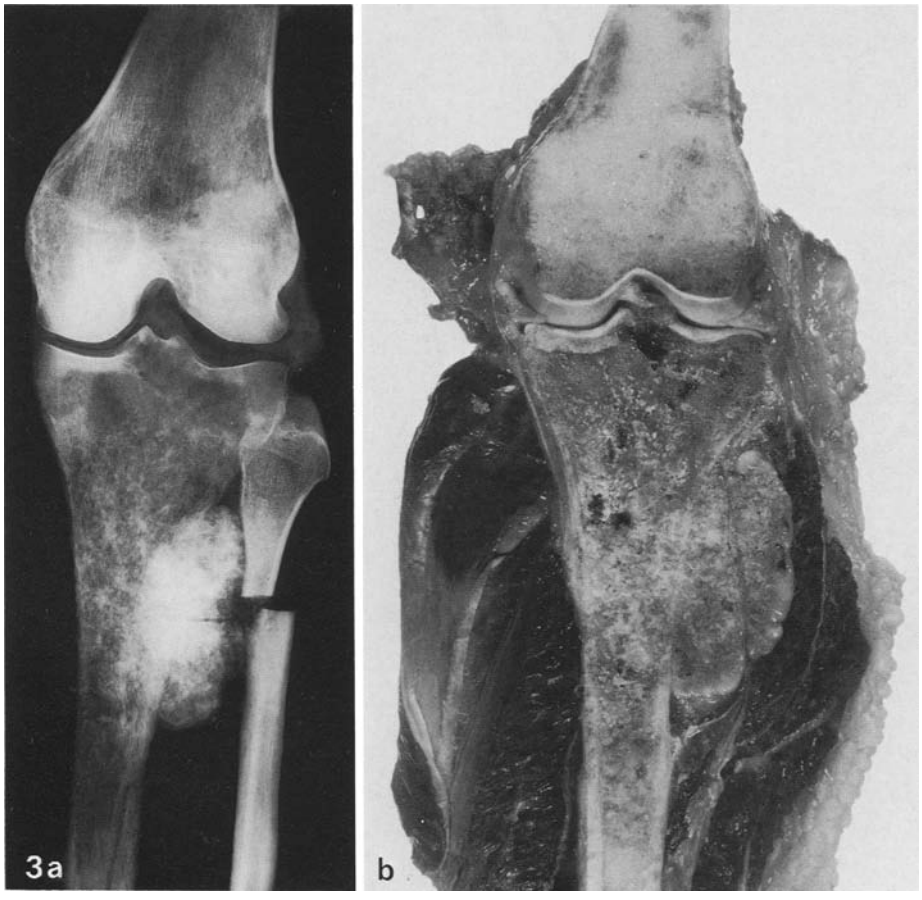

Fig. 3. (**A**) Mesenchymal chondrosarcoma of the proximal tibia in a 21 year old woman with bone destruction and adjacent calcified soft tissue tumor mass. (**B**) The gross specimen reveals extensive solid cartilaginous tumor involvement with both osseous and lobulated soft tissue involvement. The soft tissue component is partially surrounded by a pseudocapsule

rise to malignant cartilage tumors in adults (31%) as well as in the young (20%), this rarely occurs with mesenchymal chondrosarcomas. The calcaneus is rarely the site for chondrosarcomas except when it is of the mesenchymal type as in the three examples we reported.

In general, radiologically these tumors are most difficult to identify, as there is no unifying appearance or special diagnostic features to distinguish mesenchymal from ordinary chondrosarcoma of bone or soft tissues (Wilner 1982). Only rarely, in about one-fourth of cases, was the exact diagnosis established clearly and unmistakably and frequently merely a primary malignant osseous tumor was suggested. Most of the mesenchymal chondrosarcomas were predominantly lytic, irregularly outlined destructive lesions (Fig. 3A). The long tubular bones of the appendicular skeleton

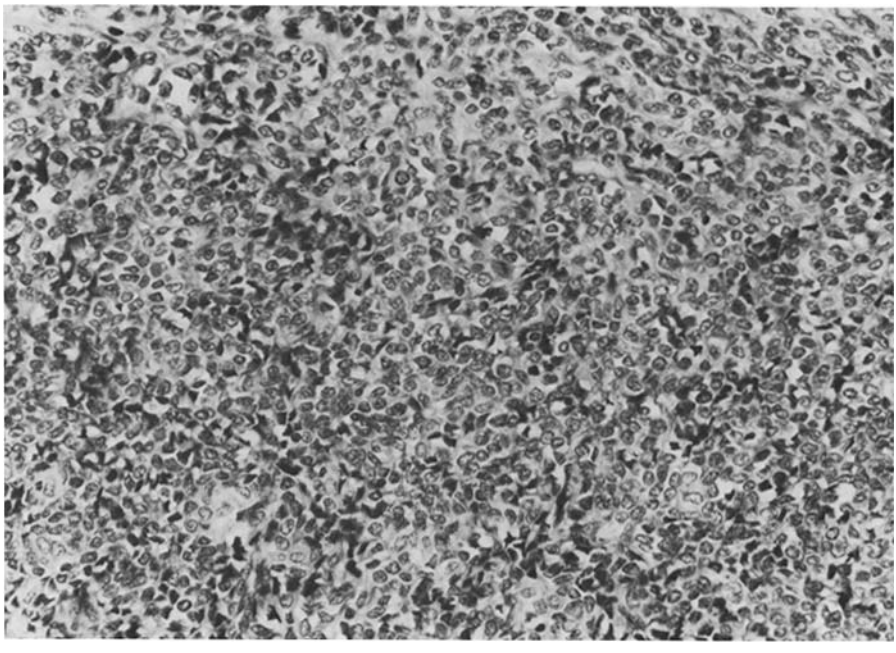

Fig. 4. Richly cellular field of predominantly round tumor cells. (H&E ×400)

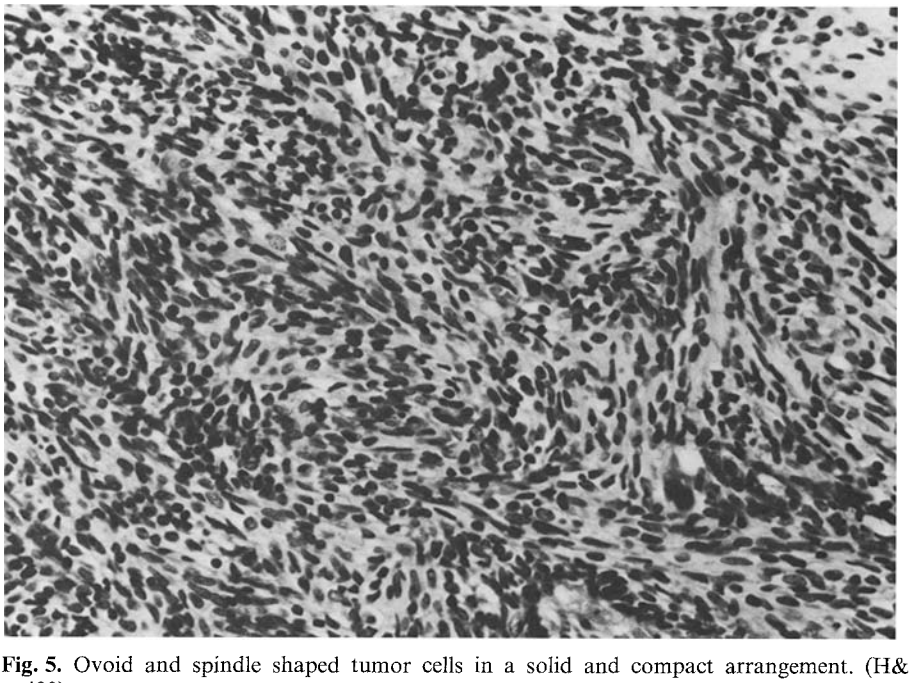

Fig. 5. Ovoid and spindle shaped tumor cells in a solid and compact arrangement. (H&E ×400)

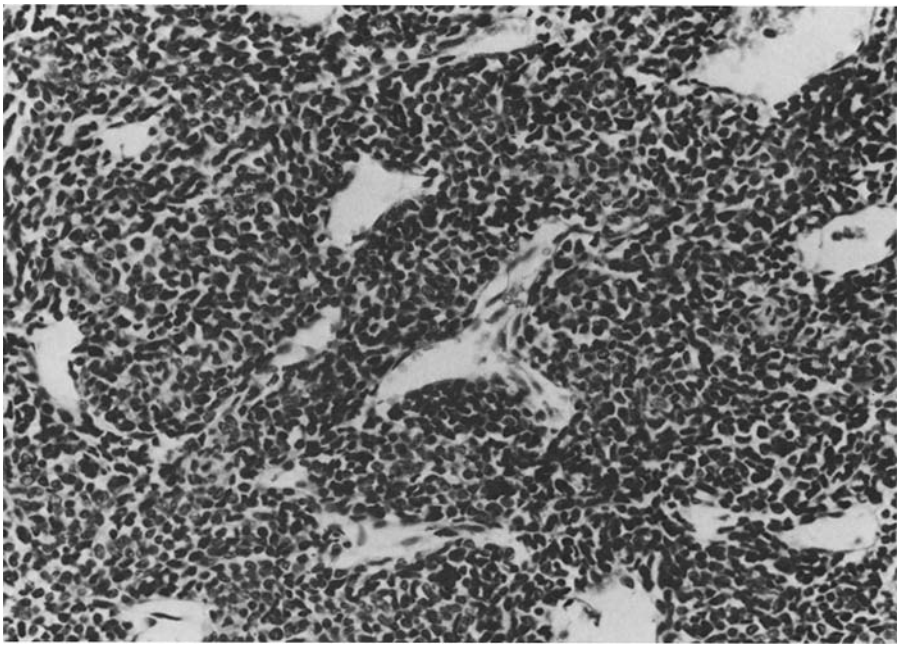

Fig. 6. The hemangiopericytoma-like growth pattern representing mesenchymal tissue organization with cleft formation in a solidly growing tumor tissue without matrix production. (H&E × 300)

become expanded in the region of tumor involvement with cortical penetration and circumferential periosteal reaction. Zones of intralesional sclerosis could also be occasionally seen. Lesional demarcation was sharp in some while in others the transition zone was wide, indistinct and gradually melding. Epiphyseal-diaphyseal location was most frequent. Midshaft cortical saucer-like cortical destruction was sometimes displayed with adjacent medullary spread. Central, irregular vertical spiculation could be seen where the tumor directly extended beyond the cortex and periosteum into nearby soft tissues. The advancing tumor margin may show a solid laminated periosteal cuff. The soft tissue tumor whether the tumor was primarily extraosseous or it represented soft tissue penetration by an initially osseous lesion showed an irregularly calcified tumor mass (Fig. 3 B).

The tumors differed greatly in their appearance from case to case. Those of soft tissue location were well demarcated, exhibited pushing borders often having a cleavage plane with a seeming fibrous investment, a pseudocapsule on the external surface of the neoplasm (Fig. 3 B). Many displayed a nodular external contour. Tumors originating in bones usually expanded the bony outlines resulting in thinning of the adjacent cortex or in turn often invading them.

On cut surface, the normal bony architecture became replaced by a bluish-white cartilaginous tissue with frequently opaque yellow-gray or pink-

Fig. 7. Solidly growing tumor tissue with abrupt chondrification and endochondral ossification. (H&E × 64)

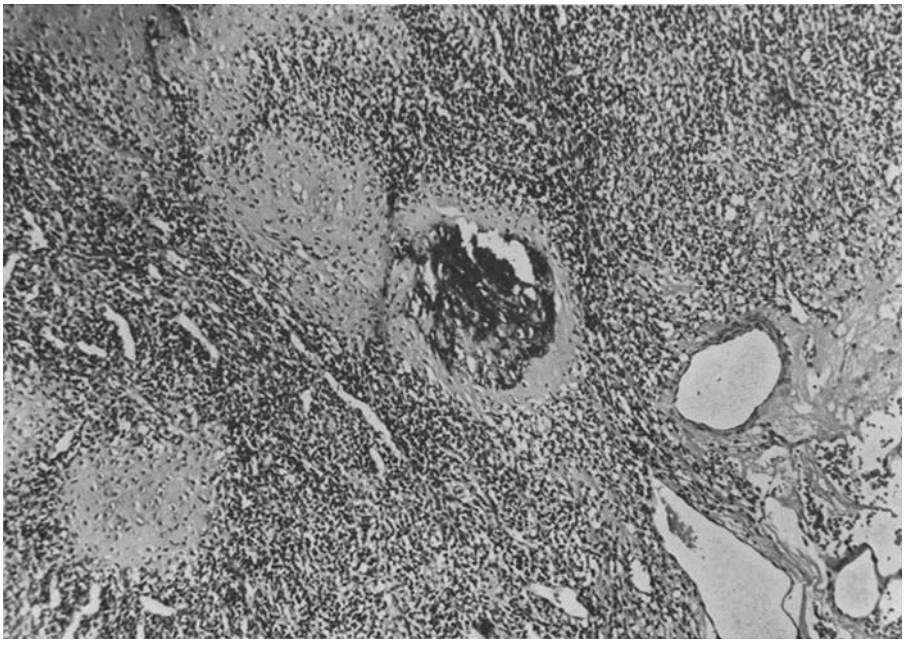

Fig. 8. Typical lesional tissue with islands of well differentiated cartilage in a "hemangiopericytomatoid" pattern. (H&E ×160)

gray patchy inlays of ossified or calcified material imitating marble. Small foci of hemorrhages and areas of cystification were prominently featured by some lesions. Peripherally, the tumor was often lobulated and here the lesional consistency became soft and gray-pink. In six cases the tumor mass was hard and well ossified suggesting an osteoblastic rather than a chondroblastic neoplasm. The tumors varied in size considerably and ranged from 3 cm to 10 cm in greatest diameter. In one unusual instance there were two separate tumor masses; one in the epimetaphyseal region of the proximal tibia while the other involved the soft tissues adjacent to the lateral aspect of the tibial periosteum (Fig. 3A and B).

The most common microscopic feature of mesenchymal chondrosarcoma is the presence of solid masses of undifferentiated cells growing without any pattern. Four distinct cell types can be identified among the proliferating cellular elements. The small lymphocyte-like stem cells, and the larger round cells with a small rim of cytoplasm (Fig. 4). In addition to these, there are elongated, spindly cells with cigar-shaped nuclei (Fig. 5) and others with the characteristics of "reticulum cells". Further study reveals a fine network of capillaries with narrow or occluded lumina permeating the fields of neoplastic mesenchymal cells which in some areas grow in lose aggregates featuring an alveolar growth pattern (Fig. 6). The increasing degree of cellular differentiation is manifested by the creation of small empty cleftlike spaces or sinusoids traversing and subdividing the solid cell masses closely imitating a hemangiopericytoma. This peculiar and unusual "pericytic"

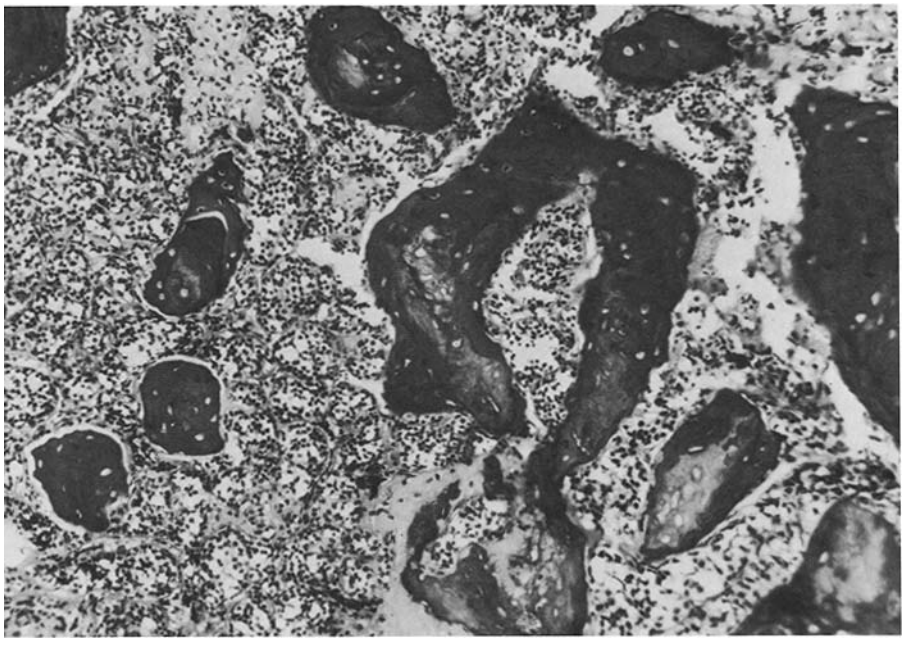

Fig. 9. Abrupt transition from small, dark tumor cells to cartilage and then to endochondrally formed bone (H&E ×160)

pattern of growth may be seen in other more or less differentiated mesenchymal tumors as well, like malignant fibrous histiocytoma, liposarcoma, or osteogenic sarcoma or even in synovial sarcoma, misleading or confounding the unwary diagnostician especially in limited biopsy specimens. The key to the accurate diagnosis here presupposes a careful and thorough search for scanty or on occasion larger microscopic fields of chondroid differentiation in the precartilage mesenchymal blastema. Cartilage may appear either diffusely without structural organization (Fig. 7) or as islands or nodular foci surrounded by vascular spaces or clefts (Fig. 8). These cartilage islands may be scattered throughout the lesional tissue in various proportions and the progressive differentiation of round mesenchymal cells into cartilage may be gradual, but more often it is abrupt and sharp (Fig. 9).

In some tumors, additional steps in the pathway of differentiation are represented by the transformation of cartilage into bone via endochondral ossification. In poorly differentiated tumor tissue the attempt at ossification is ultimately unsuccessful in that the bone formed here appears to be reactive and the osseous trabeculae occur immediately adjacent to a better differentiated well vascularized connective tissue. Notwithstanding this, prominent neoplastic endochondral ossification mimicking true osteogenesis was featured in six cases.

Although the latent potential of the neoplastic tissue to become cartilage and bone in some cases is quite evident, the actual development of such specialized tissues varied greatly from case to case. In instances in which

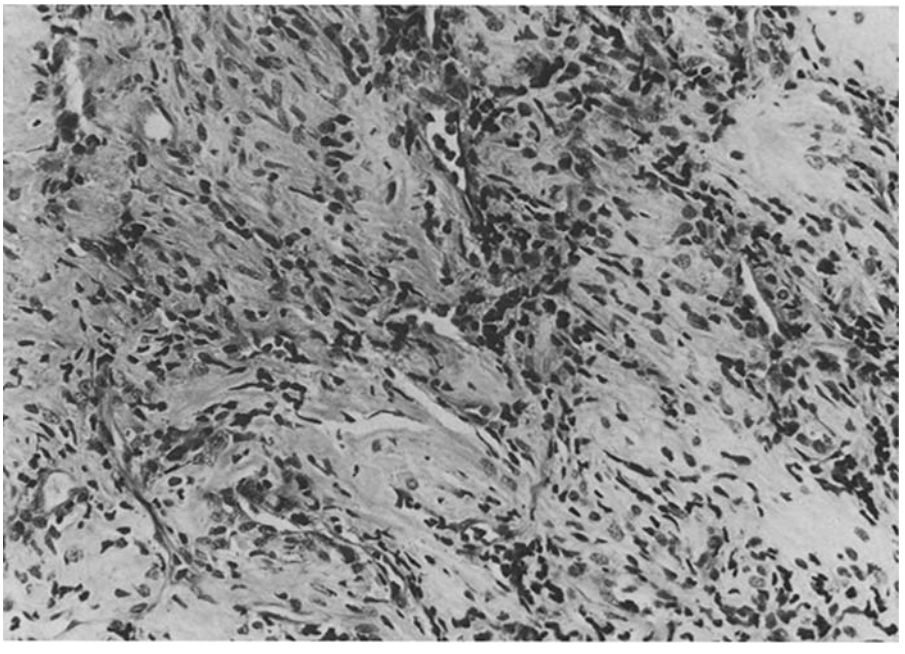

Fig. 10. Spindle shaped cells arranged in small clefts forming collagenous or fibrochondroid matrix interpreted as a peculiar chondroid differentiation. (H&E ×400)

the undifferentiated spindle cells predominated the neoplastic tissue, collagen fiber production was marked especially in organoid cellular growth areas, substituting for and obviating chondroid or fibro-chondroid matrix production (Fig. 10). In occasional cases the reticulum-like cells served as the main component of proliferating cell pool. These cells are somewhat larger than the round or spindle ones and display cytologic characteristics of malignant cells. In instances of reticulum-like cells differentiating into cartilage, the cartilage is always malignant, i.e., a chondrosarcoma, but ossification in these cases is never a feature. The pattern of growth is either diffuse with compact fields of reticulum like cells or an organoid growth trait is featured mimicking a hemangiopericytoma. In either case, the mitotic figures are numerous.

The larger the tumors the more extensive were the areas of degeneration, cell necrosis and hemorrhages. In the immediate vicinity of necrosis, there was a zone of granulation tissue formation accompanied by islands of well differentiated fibrous connective tissue the center of which exhibiting scattered foci of well formed bony trabeculae. Dispersed throughout this reactive tissue there were numerous capillaries and cavernous spaces filled by blood. Adipose tissue differentiation as well as the presence of hematopoietic cell elements could be seen in an occasional case. Only rarely was an amorphous or spotty tissue calcification noted providing a stark contrast to a more frequent and pronounced intralesional ossification.

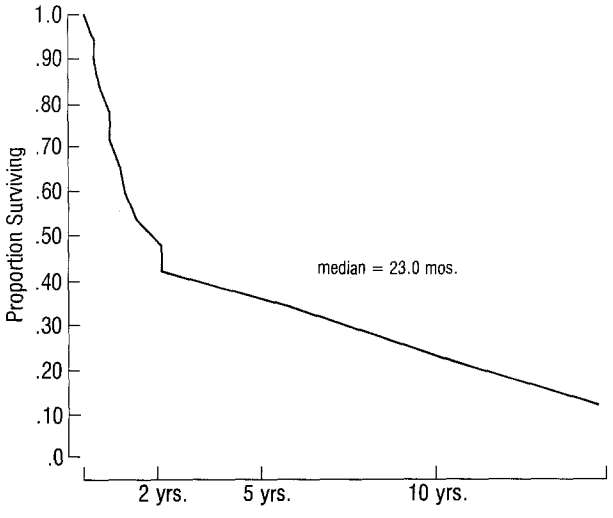

Fig. 11. Mesenchymal chondrosarcoma in the young. Survival rate in 19 patients

Survival analysis revealed a 46% 2 year, and a 35% 5 year survival rate, whereas at 10 years only 20% of the patients were still alive (Fig. 11). The median survival was 23 months. No statistically significant survival differences were evident between those young patients who were 15 years of age or younger and those older than 15 years ($P=0.4$).

Discussion

Since its original description, mesenchymal chondrosarcoma has been reported with ever increasing frequency and by now approximately 127 cases have been reported (Huvos et al. 1983). So far, Salvador and his associates have rendered the most complete histologic description (Salvador et al. 1971). The microscopic details here included small undifferentiated round and spindle mesenchymal cells accompanying foci of malignant cartilage. Only rarely did the reports however amount to more than one or very few case studies (Jacobson 1977; Salvador et al. 1971; Dahlin and Henderson 1962; Mazabraud 1974; Harwood et al. 1981).

One of the basic and intrinsic questions posed by mesenchymal chondrosarcoma is the presence of osseous tissue appearing within the lesion and how this fits in the evolutionary pathway of differentiation. Some attempted to explain the process of intralesional ossification as a reactive or metaplastic phenomenon (Salvador et al. 1971), while others like Jacobson ascribed it simply to an "osteoplastic element" (Jacobson 1977). Metaplasia is a transformation of a relatively mature tissue into another one. Since the middle of the 19th Century, following the lead of Virchow, this was considered to be a tissue change in which the original cells persist (Virchow 1853). Whether such an interpretation has direct application in mesenchymal chondrosarcomas remains to date controversial and unproven. A more plausible

explanation may invoke here the undifferentiated stem cell taking a different pathway of differentiation to become the "metaplastic" tissue type.

Mesenchymal chondrosarcomas represent an embryonal neoplasm composed of lymphocyte-like stem cells, in addition to round, spindle or reticulum-like cellular elements. Mitotic figures, except in cases with a predominant reticulum cell-like proliferation were sparse. All of the neoplastic cell lines exhibited a varied potential for differentiation into embryonal cartilage. This capacity to form cartilage varied from sparse to a moderate degree and was of the hyaline character. Fibrocartilaginous areas were also present formed directly by spindly mesenchymal cells. Abrupt changes from highly anaplastic cellular zones rather than gradual transition of these cells into cartilage were the rule and the cartilage formed was malignant.

The hemangiopericytomatoid growth pattern could be seen with or without cartilage differentiation but the organoid growth characteristics were on occasion obscured by diffusely aranged poorly differentiated mesenchymal cells displaying chondroid cellular traits. One of the most outstanding features of this neoplasm is the presence of endochondral ossification manifesting the osteoblastic faculty of the lesional tissue. A clear-cut demonstration of this potential is well documented in a patient with both an intraosseous and a simultaneous extraskeletal mesenchymal chondrosarcoma components of identical microscopic appearance attached to each other (Fig. 3 A and B). Both exhibited pronounced endochondral osteogenesis. The soft tissue tumor, in addition, displayed an imperfect caricature of embryonal skeletogenesis with high degrees of structural differentiation manifested by perfectly remodeled bony trabeculae, rimmed by normal osteoblasts, newly formed adipose tissue, hematopoietic cells enmeshed by a delicate network of blood vessels composing the medullary aspect of this skeletogenic bony structure (Figs. 12 and 13). Mesenchymal chondrosarcoma appears to originate from mesenchymal cells differentiating towards cartilage similarly to the cellular events seen in embryonal and fetal chondrogenesis.

No discussion on the histogenesis would be complete without mentioning several important studies as they relate to our concept of likely events during neoplastic cell differentiation in mesenchymal chondrosarcoma. Jacobson's term "polyhistioma" has been completely misunderstood by diagnostic radiologists, clinicians and some pathologists alike because it rightly connotes to many that it is a histiocytic neoplasm, which is clearly not the case (Jacobson 1977). Although the designation means "many tissues" its author is against calling it a mesenchymoma, which in our opinion is the proper interpretation. In contrast to Jacobson we feel mesenchymal chondrosarcoma can and should be diagnosed in biopsy material even in the absence of obvious cartilaginous differentiation if other histologic growth patterns strongly point to such a conclusion. The histologic differential diagnosis in extraskeletal lesions should include malignant hemangiopericytoma, synovial sarcoma and mesenchymal chondrosarcoma (Guccion et al. 1973; Pringle and Stoker 1980). In a thought provoking article in 1966 Hutter and his associates pioneered the concept of manifold histologic patterns of differentiation in small cell mesenchymal tumors of bone (Hutter et al. 1966). Their study clearly identified the malignant undifferentiated small

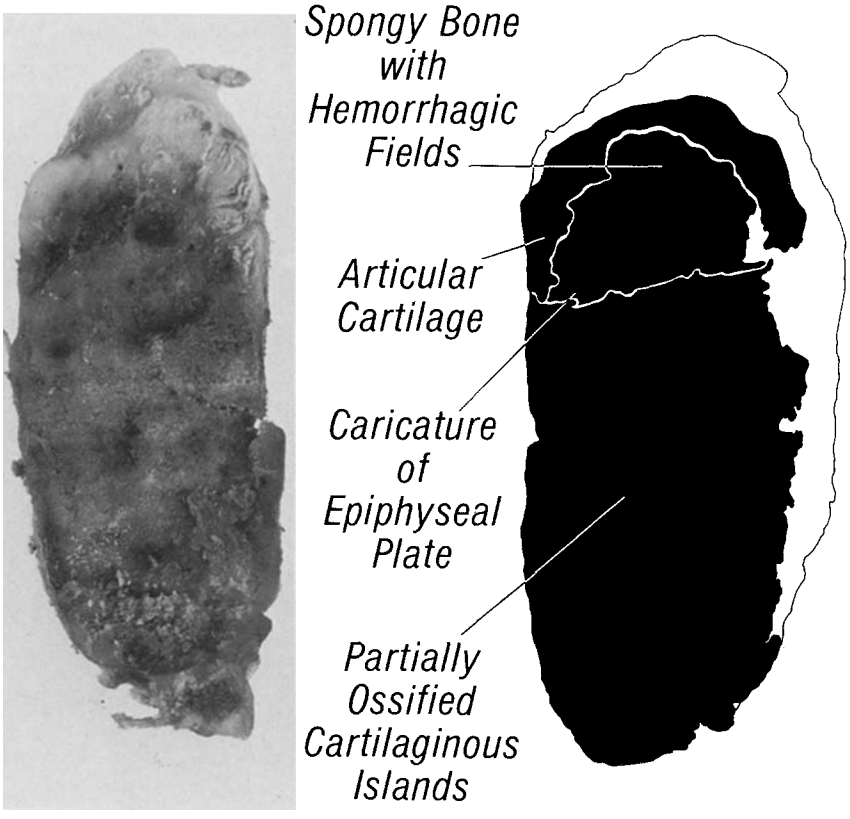

Fig. 12. Extraskeletal component of mesenchymal chondrosarcoma with attempt at embryonal skeletogenesis. (Same patient as Fig. 3A, B)

cell pattern as the common denominator in some chondrosarcomas, Ewing's sarcomas, osteogenic sarcomas, reticulum cell sarcomas and mesenchymal chondrosarcomas. In 12 of their cases chondroid matrix production or full fledged cartilage formation were noted. We share their view in that mesenchymal chondrosarcomas in their earliest stages of cellular differentiation may show a rather unspecific growth pattern, which only upon further differentiation will reveal the true diagnostic traits of the sarcoma.

The recently described embryonal chondrosarcoma which may arise congenitally or appear in children can involve both extraskeletal soft tissues and the nasoethmoidal bones (Albores-Saavedra et al. 1977). This lesion shares many microscopic similarities to myxoid type of chondrosarcomas and is distinct from mesenchymal chondrosarcoma (Dehner 1981; Jessurun et al. 1982). Similar conclusions have been reached by comparative ultrastructural studies of mesenchymal chondrosarcoma and myxoid chondrosarcoma (Fu and Kay 1974; Martinez-Tello and Navas-Palacios 1982). The ultrastructural study of Steiner et al. (1973) failed to find evidence of fibroblastic differentiation in the tumor cells which is in contrast to our findings and to those of Mandelenakis (1974).

Since the original description of mesenchymal chondrosarcoma the mul-

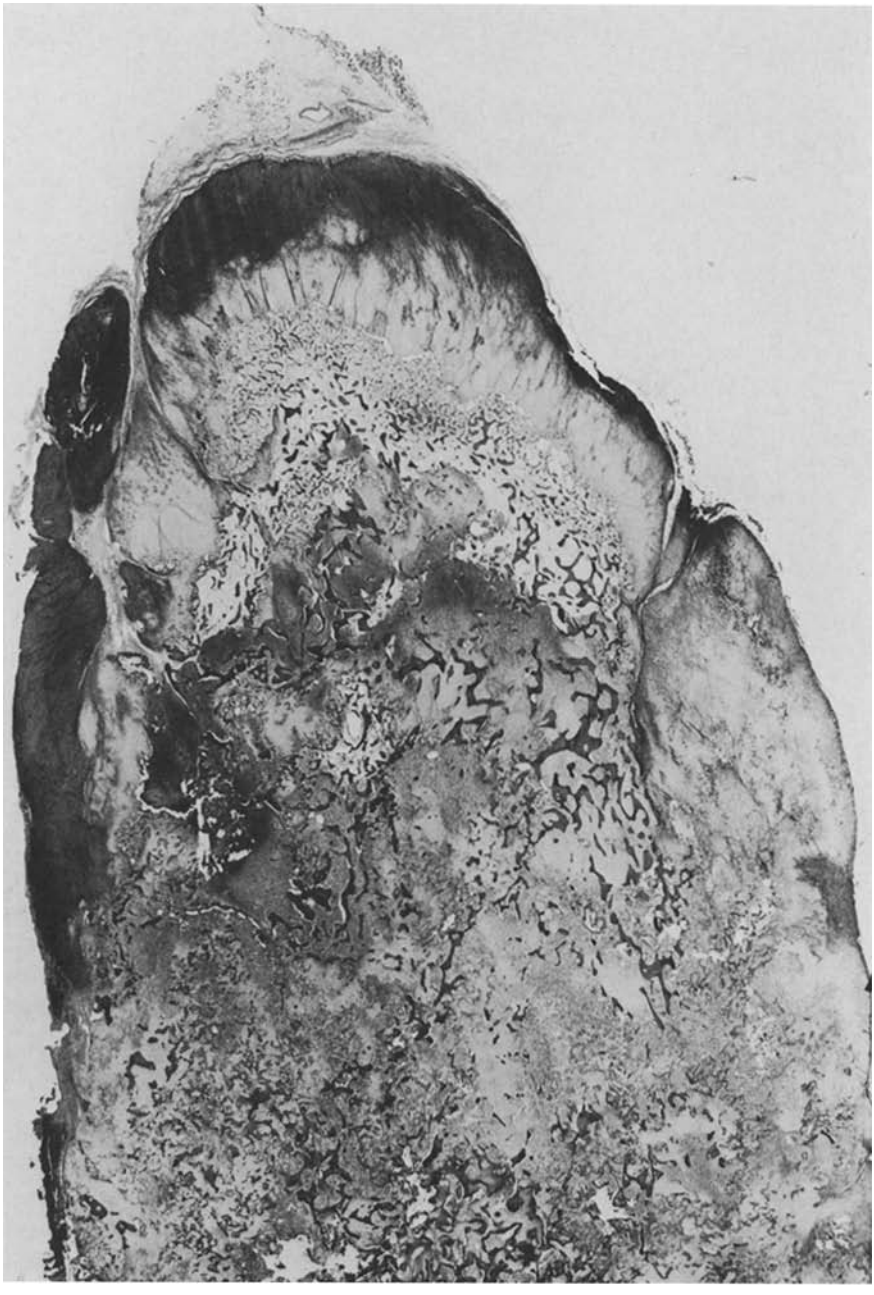

Fig. 13. The extraskeletal mesenchymal chondrosarcoma exhibits definite tendency of osteogenesis with a cartilage cap, epiphyseal region and endochondral bone formation. (H&E ×4) (Same case as Figs. 3A B and 12)

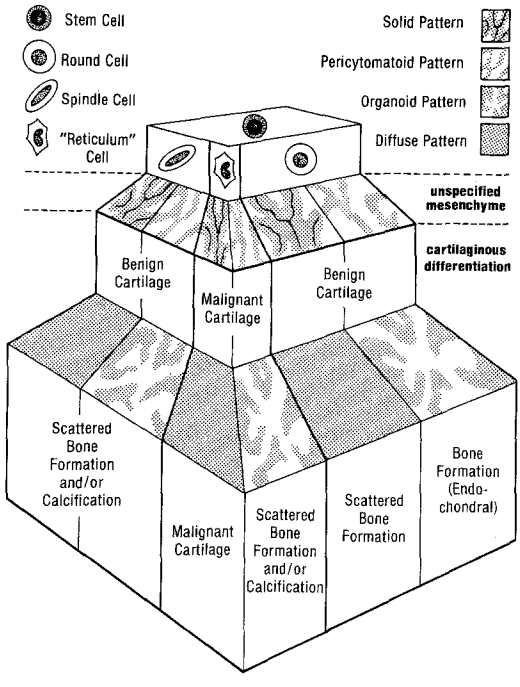

Fig. 14. The evolutionary pathway of mesenchymal chondrosarcoma

tiple osseous lesions were noticed and interpreted as being multifocal synchronous involvement. While this occurs in some cases, in others the presence of bone to bone metastases similarly to a pulmonary or other organ spread and soft tissue deposits are likelier explanations. This may be either synchronous or metachronous.

The roentgen presentation of mesenchymal chondrosarcoma provides difficulty and real challenge even for the most experienced diagnostic radiologist. The appearance varies widely and it is far from being specific. The major histologic components of the lesional tissue greatly influence the radiographic picture. All can be said in most instances that the lesion is a malignant tumor with features of an osteogenic sarcoma or a chondrosarcoma.

Similarly to previous studies this clinicopathologic analysis confirms that mesenchymal chondrosarcoma is a neoplasm of the primitive cartilage forming mesenchyme. In most cases the lesional tissue is composed of large masses of small anaplastic mesenchymal cells exhibiting only focal and the earliest stages of structural differentiation exemplified by minute fields of chondroid matrix formation. In others, however, the process of differentiation progressed to focal cartilage production, including various degrees of endochondral ossification resembling normal osteogenesis (Fig. 14). The ability of the tumor cells for further differentiation reaching the stage of endochondral osteogenesis is outlined and analyzed in this study. The scheme proposed by us appears to be an acceptable meaningful simplification of a hard to grasp problem, for one knows perfectly well that the differentiation patterns of a neoplasm of confusing complexity like mesen-

chymal chondrosarcoma, has far too many loosely related facets which are still poorly understood (Fig. 14). Nevertheless, employing the appealing, and hopefully correct, pyramidal representation in visually explaining the diversities of this lesion seemed to us to be desirable, justified and not unduly simpleminded.

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Accepted November 10, 1982