

# A Comparative Ultrastructural Study of Chondrosarcoma, Chordoid Sarcoma, and Chordoma

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## ABSTRACT

A morphologic and electron microscopic study was made of two chordoid sarcomas. These lesions were compared with two classical chondrosarcomas and two chordomas. The chondrosarcoma cells showed many features common to chondrocytes, such as abundant RER, well-developed Golgi complexes, and microvillous cytoplasmic membranes. The chordoid sarcomas bore a close morphologic resemblance to the chordomas but the ultrastructural features revealed a close relationship to the chondrosarcomas. The chordoid sarcoma and chondrosarcoma cells had scalloped cytoplasmic membranes, variable amounts of glycogen, round or oval nuclei and microfibrils, collagen, and electron-dense granules in the ground substance. The chordoma was characterized by the presence of stellate and physaliphorous cells, as well as many transitional cells, with varying nuclear morphology; dilated and irregular RER in contact with mitochondria and morphologically varied vacuoles are the main features in the cytoplasm. This study suggests that chordoid sarcoma represents a variety of the chondrosarcoma rather than a form of chordoma. These findings also support the suggestion of Weiss that chordoid sarcoma is an extraskeletal myxoid chondrosarcoma.

## INTRODUCTION

Chordoid sarcoma is a comparatively rare neoplasm that was first described by Stewart<sup>30</sup> in 1948. It may arise from soft tissues and bone and exhibits a less aggressive behavior than classic chondrosarcoma of bone.<sup>2</sup> It has been reported under different names such as “chordoma periphericum”,<sup>17,18</sup> “giant chordoma-like tumor”,<sup>32</sup> “chondroid chordoma”,<sup>13</sup> “parachordoma”,<sup>2</sup> and “chordoid sarcoma”,<sup>21,24,30</sup> The origin of chordoid sarcomas is not clear; although Stewart<sup>30</sup> believed that it is a chondrosarcoma, Laskowski<sup>18</sup> thought that the tumor arose from notochord-like cells occurring in an extramidline position. This controversy has not been solved until now.

Chondrosarcoma varies greatly in growth potential and morphology.<sup>3,7,11,14,16,20,28,33</sup> It may present a considerable variation in metastatic potential.<sup>22,26</sup> Unusual histologic variants of chondrosarcoma are clear-cell chondrosarcoma,<sup>34</sup> mesenchymal chondrosarcoma,<sup>4</sup> and extraskeletal myxoid chondrosarcoma.<sup>6</sup>

Chordoma is a malignant tumor that appears in areas where the primitive notochord existed and probably arises from remnants of the embryonic notochord.<sup>5,9,15-29,35</sup> Chordoma has a characteristic morphologic pattern, but it presents some pathologic and histochemical similarities with chondrosarcoma; islands of chondrosarcoma in chordomas of the sphenoid-occipital region are not unusual.<sup>3</sup>

The purpose of this report is to present a comparative light and electron microscopic study of chondrosarcoma, chordoid sarcoma, and chordoma in order to better understand the possible relationship of these tumors and provide additional evidence that the chordoid sarcoma is a cartilaginous tumor.

## MATERIALS AND METHODS

Specimens from two cases of chondrosarcoma, two of chordoid sarcoma, and two of chordoma were fixed in phosphate-buffered 10% aqueous solution of formaldehyde (formalin), dehydrated, and embedded in paraffin. Fresh material was stained with oil red O stain. Formaldehyde-fixed tissues were stained with hematoxylin and eosin, PAS, PAS-diastase, alcian green, mucicarmine, and toluidine blue.

Material from the cases, in most instances obtained at the time of frozen section diagnosis, was minced into 1-mm slices and fixed in cacodylate 2% glutaraldehyde for 2 hours. The specimens were then rinsed in buffer and postfixed in 1% osmium tetroxide, dehydrated in a graded ethanol-propylene oxide series, and embedded in epon-araldite. Thin sections were stained with uranyl acetate followed by lead citrate and examined in a Siemens Elmiskop electron microscope.

Case 3 has been reported previously.<sup>24</sup>

## **RESULTS**

### **Chondrosarcoma: Cases 1 and 2**

Microscopically, both cases have the typical malignant appearance of a cartilaginous tumor. Case 1 showed a lobular pattern and cystic degeneration in the center of the largest lobules. The matrix was abundant and the cells had one or several nuclei with a few mitoses. It was diagnosed as Grade 1 chondrosarcoma (Fig. 1). Case 2 showed focal lobulation with cystic and myxoid degeneration. There were areas with scanty cartilaginous matrix. Myxoid degeneration had morphologic similarities to chordomas. The neoplastic cells were pleomorphic and the mitotic index was higher than in Case 1. It was diagnosed as Grade 2 chondrosarcoma.

Neoplastic cells and ground substance were PAS, mucicarmin and alcian blue positives and stained with oil red O. Ground substance showed metachromasia with toluidine blue stain.

Ultrastructurally, chondrosarcoma was composed of irregularly oriented chondrocytes. Most of the chondrocytes occupied recognizable lacunae and were large, round, or spindle-shaped. The cytoplasm contained an electron-dense amorphous matrix and prominent, oval, occasionally indented nuclei (Fig. 2). In many instances two or more nuclei were found in a single cell. The chromatin pattern was finely dispersed. The nucleoli were often prominent with dense, homogeneous nucleolar material. Mitochondria had few cristae and contained electron-lucent matrixes, which resembled large, clear vacuoles. The Golgi apparatus was prominent. Free ribosomes were distributed throughout the cytoplasm. Abundant RER were seen, and some cisternae were dilated. Glycogen particles were seen in variable amounts, in small clusters, or diffusely in the cytoplasm. Lipid droplets and vacuoles were numerous in some cells. Myelin figures were evident. Most of the malignant chondrocytes had scalloped filiform membranes or microvilli and occasional apposition of marginal densities. The intercellular stroma surrounding the lacunae consisted of fine fibrils (80-120 Å thick) mixed with matrix vesicles and electron-dense granules (Fig. 3). Collagen fibers with periodicity were scarce.

### **Chordoid Sarcoma: Cases 3 and 4**

Both cases showed lobular patterns. Neoplastic cells were large, round, spindle-shaped, or polygonal. Cytoplasm was clear and vacuolated, sometimes with indistinct boundaries (Fig. 4). Tumor cells showed marked variation of nuclear size. Nucleoli were prominent. Mitotic figures were few. Ground substance was scarce and consisted of small eosinophilic strands. Large vacuolated and physaliphorous cells were frequently seen. In areas, masses of mucus contained syncytial strands of neoplastic cells. Case 4 has a small island of ordinary Grade 2 chondrosarcoma.

Neoplastic cells were PAS, mucicarmin, and alcian blue positives. The ground substance was PAS positive. Oil red O stains of these cases were not performed.

On electron microscope, tumor cells showed marked variation in size and shape, but it was clear that there was a single cell type. The nuclei had a slightly irregular round or

oval shape. The chromatin was granular with peripheric condensations. Solitary or multiple bizarre nucleoli characterized the nuclei of these cells (Fig. 5). The cytoplasm had few mitochondria with electron-lucent matrix. These mitochondria showed swelling and a variable number of cristae. The RER was composed of short branching segments (Fig. 6). The Golgi complex was well developed in some tumor cells and contained electron-dense membrane-limited granules. Glycogen granules were seen forming clusters or rosettes.

Rounded vacuoles, probably with lipid contents, were numerous (Fig. 7). The cytoplasm also contained a few fine filamentous fibers (40-60 Å thick). Rare myelin figures were present. Plasma membrane condensations were pronounced in some of the neoplastic cells. The cytoplasmic membranes were often interdigitated by

lamellar expansions and microvilli (Figs. 5 and 7). Desmosomal attachments between cells were rarely found. The intercellular matrix was composed of fibrillar (Fig. 7) and/or granular amorphous material (Fig. 6). In some areas, the matrix was condensed around the tumor cells. The matrix fibers were of variable thickness (80-180 Å) but had no periodicity. Thicker fibers showed the typical 640 Å periodicity of the collagen (Fig. 7).

### **Chordoma: Cases 5 and 6**

By light microscopy, sections of both tumors showed lobulated masses that contained irregularly distributed ovoid, stellate, and physaliferous cells (Fig. 8). The nuclei were hyperchromatic and of variable size and shape. The stroma was either thin-fibrous or mucoid. In some areas, cell boundaries were indistinct, lying in a mass of mucus.

The ground substance was strongly PAS positive. Neoplastic cells were PAS mucicarmin and alcian green positives.

Ultrastructurally, the cellularity and amount of inter-cellular substances varied widely both in different parts of the same tumor as well as in both chordomas. All the different types of chordoma cells were clearly distinguishable: stellate, ovoid, physaliferous, and transitional cells (Fig. 10). The tumor cells showed irregularly shaped nuclei with a coarse granular chromatin and multiple nuclear bodies. Chromatin granules were condensed at the nuclear margin (Fig. 9). Nuclei of physaliferous cells were peripheral, containing finely granular chromatin and prominent nucleoli. The cytoplasm had a clear matrix. Mitochondria were few and small and had an electron-lucent matrix and few cristae. The amount of RER was variable, appearing as dilated cisternae filled with electron-dense contents. Frequently mitochondria appeared to be completely surrounded by the dilated RER (Fig. 10). Many chordoma cells had large and numerous Golgi structures. Dense membrane-bound bodies (150-300 Å diameter) were seen, sometimes related to Golgi structures. There was an abundance of glycogen granules. Pinocytotic vesicles and vacuoles of variable size in the cytoplasm were numerous, especially in the physaliferous cells. Some vacuoles were lined by microvilli and some contained an amorphous granular material. Microfilaments were noted in the cytoplasm of many cells. Plasma membrane had infoldings and microvilli ultrastructurally similar to those of the vacuoles (Fig. 11). Few desmosomes were seen. The matrix was scarce and finely granular or amorphous.

## DISCUSSION

The differentiation of chordoid tissue from embryonic cartilage and of chordoma from chondrosarcoma is not always easy or clear-cut.<sup>13,28</sup> Some primitive animals have cartilage, chordoid tissues, and a series of different intermediate tissues.<sup>27</sup> It suggests a close relationship among these tissues. Why do some sacrococcygeal chordomas occasionally have foci of chondrosarcoma? Why are chordomas more unusual in dorsal and lumbar vertebral regions than in other areas of the spinal column? Why is not notochordal tissue found in nuclei pulposi of the adults? The description of chordoid sarcoma<sup>2,17,18,21,24,25,30,32,35</sup> has added more confusion to these unresolved questions.

By light microscopy, there is a clear-cut similarity between chordoma and chordoid sarcoma. But reported chordoid sarcomas have a great morphologic variability within the same tumor and between different tumors. The cases reported by Dabska<sup>2</sup> are very suggestive of chondrosarcoma, but others reported that chordoid sarcomas<sup>24,25,32,36</sup> have a morphologic pattern indistinguishable from chordomas. This histochemical study, however incomplete, shows a close relationship of chordoid sarcoma with chondrosarcoma. But more extensive histochemical studies does not support a definite cartilaginous or chordoid origin for the chordoid sarcoma.<sup>21</sup>

Electron microscopy of chordoid sarcoma is inconclusive, but shows a great similarity to chondrosarcoma. Both tumors have condensations of cytoplasmic membrane, similar morphology of mitochondria and nuclei, variable amounts of glycogen and lipid droplets, microfibrils and collagen in the ground substance.

The granules found in the extralacunar matrix of both chondrosarcoma and chordoid sarcoma are probably produced by the neoplastic cell s. They are very characteristic of cartilaginous tissue. Similar granules are found associated with matrix calcifications in normal epiphyseal cartilage.<sup>1</sup> These are proteoglycan granules, which hold sulphated mucopolysaccharides.<sup>7,10,23,31</sup> Martin<sup>21</sup> has found histochemically that the ground substance of chordoid sarcoma contains great amounts of acid mucopolysaccharides of the chondroitin type, which resists hyaluronidase as well as beta-glucuronidase hydrolysis.

Dilated RER in close relationship with mitochondria was considered very characteristic of chordomas by Erlandson et al.<sup>8</sup> This morphologic pattern of RER does not appear in cases of chordoid sarcoma, but it has been described as Grade 1 chondrosarcoma.<sup>7</sup>

Electron microscopy may help differentiate these tumors, especially by the characteristics of the ground substance. Ground substance of chondrosarcoma contains fine fibrils, vesicles, and granules: the stromal matrix of chordoid sarcoma has a fibrillar and/or granular amorphous material. Finally, the ground substance in chordoma is scarce and finely granular or amorphous in character.

The different neoplastic cell types described as chondrosarcomas<sup>33</sup> suggest the great morphologic variability of this tumor.<sup>3</sup> Two different cartilaginous tumors have been described that share many characteristics of chordoid sarcomas. The first one is clear-cell chondrosarcoma.<sup>19,34</sup> Chordoid sarcoma is very similar to this tumor. Both tumors usually have islands of classic chondrosarcoma.<sup>19,34</sup> Ultrastructurally, an important difference is the absence of desmosomes in chordoid sarcomas;<sup>19,33</sup> however, Robertson

and Hogg<sup>25</sup> describe the presence of numerous desmosomes a distinctive ultrastructural feature of chordoid sarcoma. The clear-cell pattern of chondrosarcoma described by Unni et al.<sup>34</sup> has been justified by the presence of great amounts of glycogen in the cytoplasm.<sup>19</sup> Erlandson and Huvos<sup>7</sup> only found decreased amounts of glycogen in the more undifferentiated chondrosarcomas. Chordoid sarcoma could be a clear-cell chondrosarcoma with scanty and variable amounts of glycogen.<sup>24</sup> Its relatively good prognosis supports this hypothesis.

The second tumor that shares many characteristics with chordoid sarcoma is the extraskeletal myxoid chondrosarcoma.<sup>6</sup> Based on ultrastructure, Weiss<sup>36</sup> considers both as the same tumor. Age of onset, anatomic location, and prognosis are very similar in both tumors. Morphologic differentiation of extraskeletal myxoid chondrosarcoma from chordoid sarcoma is very difficult.<sup>6,10</sup> Ultrastructure of both tumors is also very similar.<sup>10</sup>

Hajdu et al.<sup>12</sup> and Robertson and Hogg<sup>25</sup> consider that chordoid sarcomas, as epithelioid and clear cell sarcomas, have a synovial origin. The authors are unable to contradict this hypothesis. Nevertheless, the theory is compatible with a morphologic identity of chordoid sarcoma and extraskeletal myxoid chondrosarcoma, whose origin is not yet well established.<sup>6,10</sup>

In conclusion, it is believed that chordoid sarcoma is a special type of chondrosarcoma. The similarities among chordoid sarcoma, clear-cell chondrosarcoma, and extraskeletal myxoid chondrosarcoma seem to indicate that variants of the same tumor are being dealt with. The relationship between chordoid sarcoma and chordoma is inconclusive. Reported cases of extramidline chordomas are probably chordoid sarcomas.<sup>36</sup>

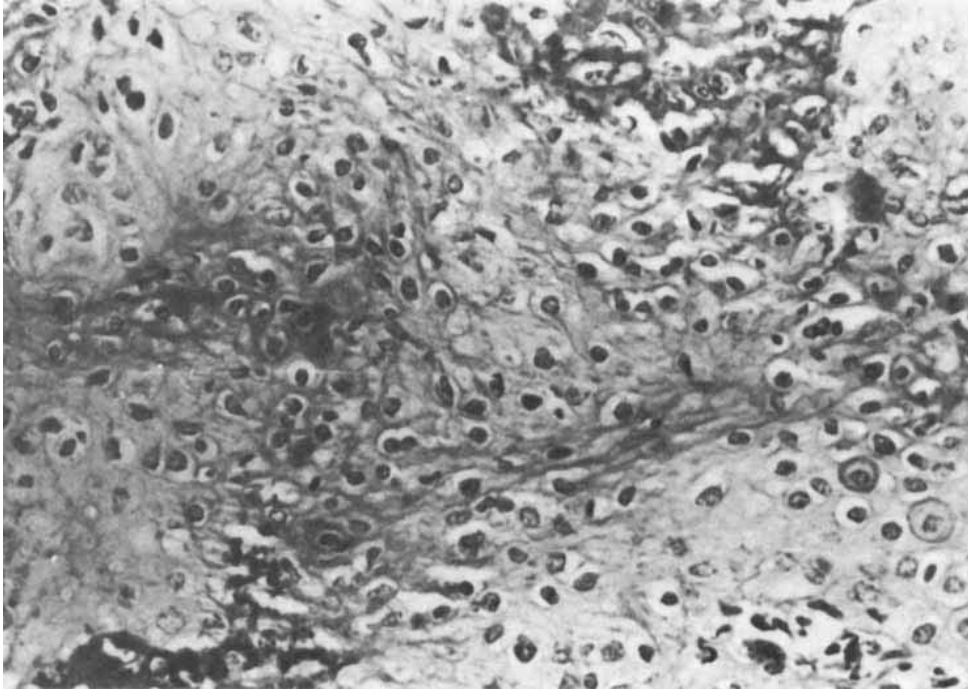
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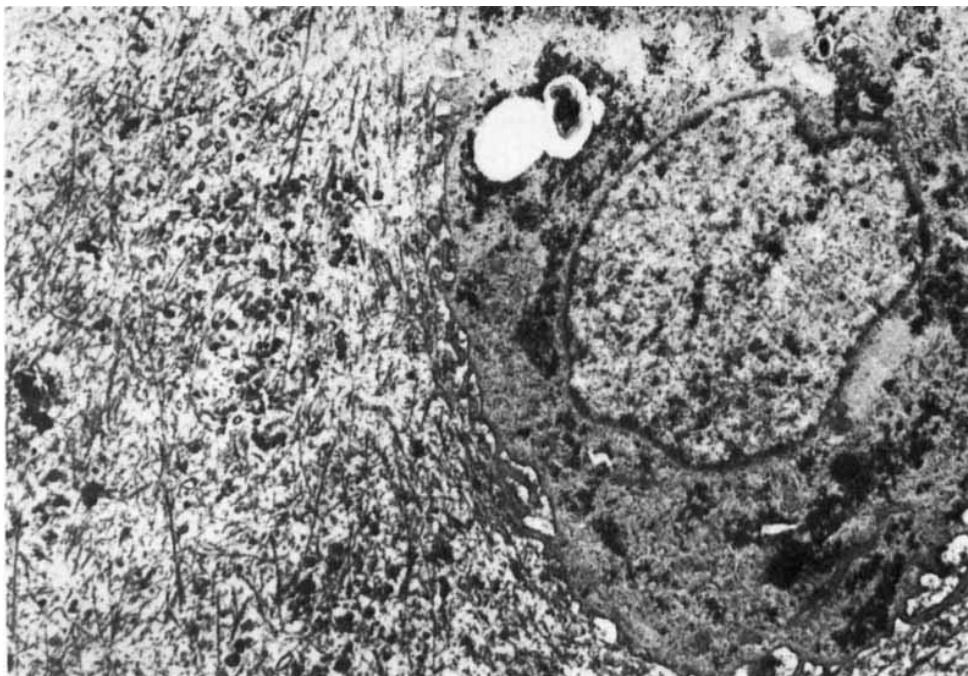
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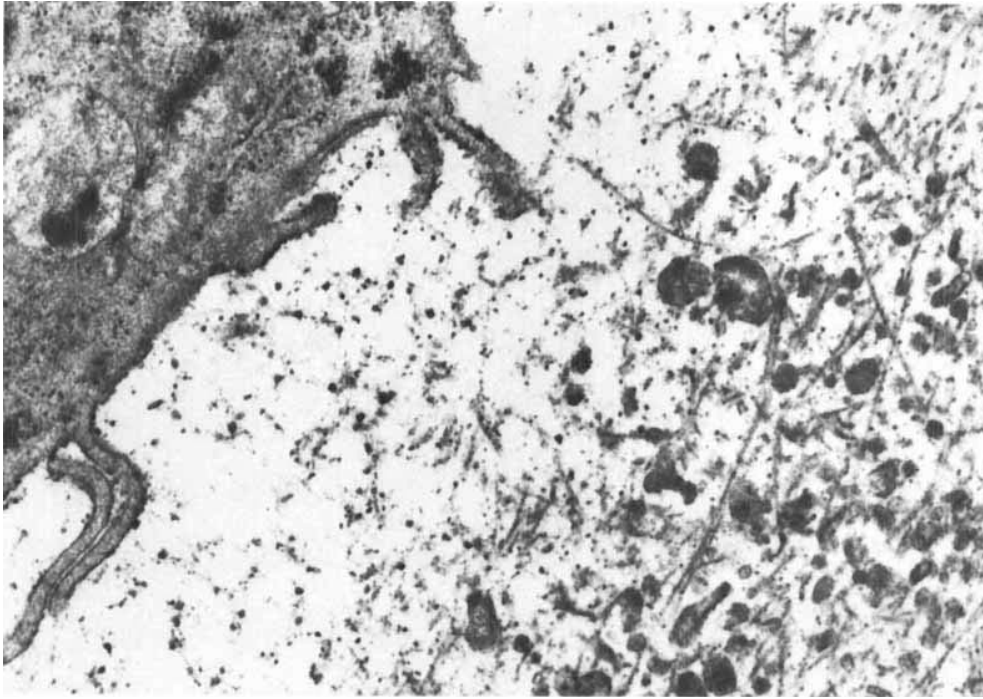




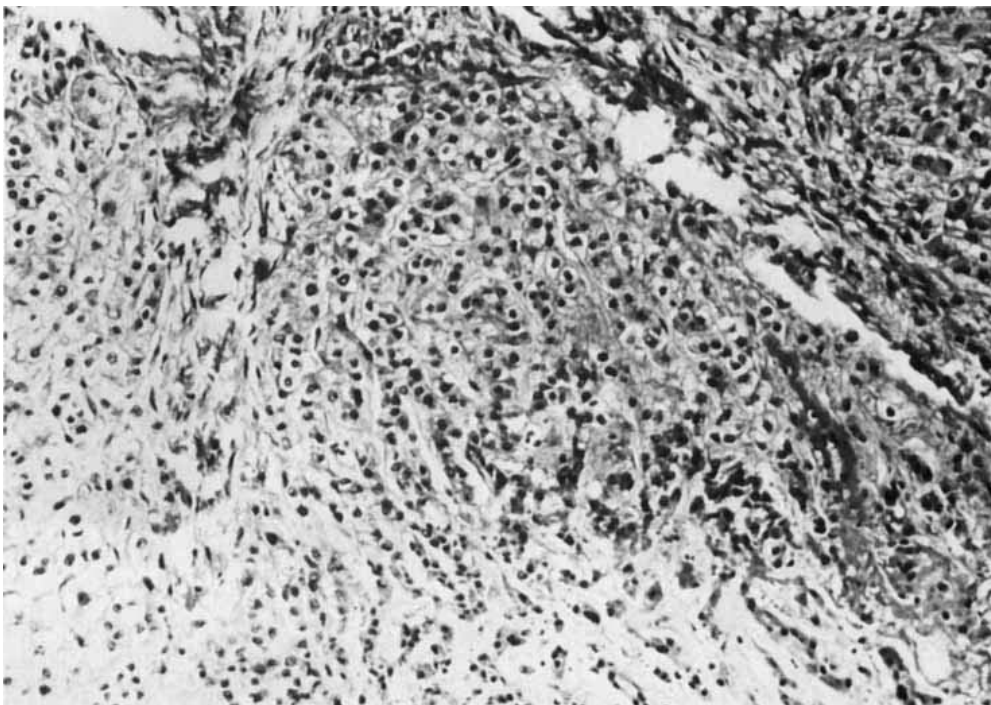
**Figure 1.** Chondrosarcoma, Grade I. Hypercellularity and foci of calcification in the ground substance (H & E, x312).



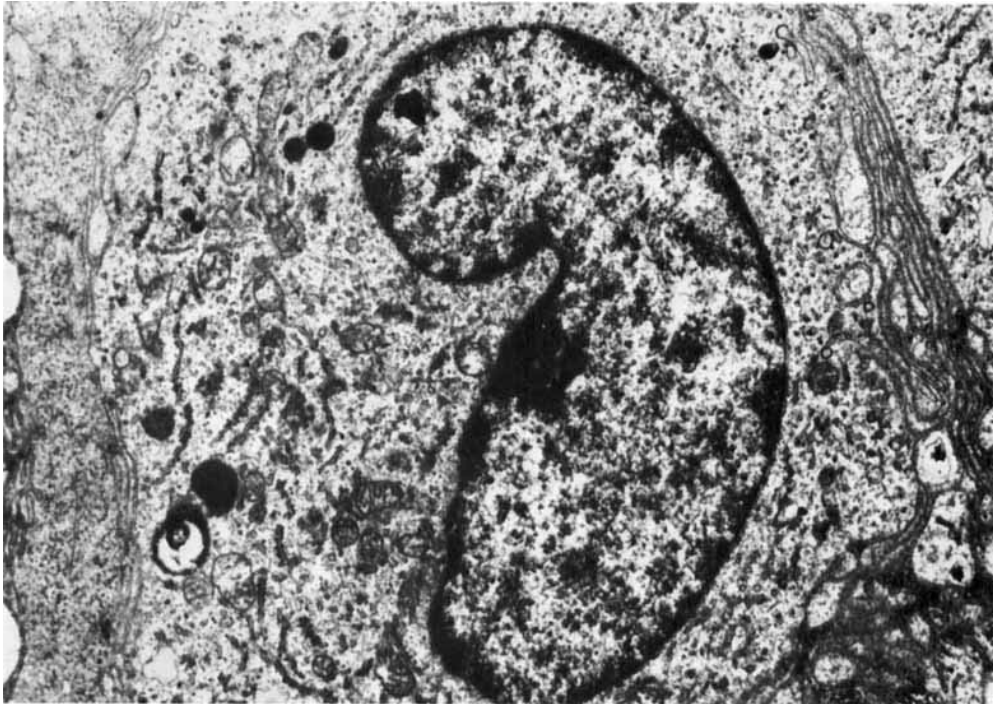
**Figure 2.** Chondrosarcoma, Grade I. Neoplastic chondrocyte that shows round nuclei, clusters of glycogen granules, and myelin figures. Fibrillar and vesicular matrix are typical of cartilaginous tumor ( x 9000).



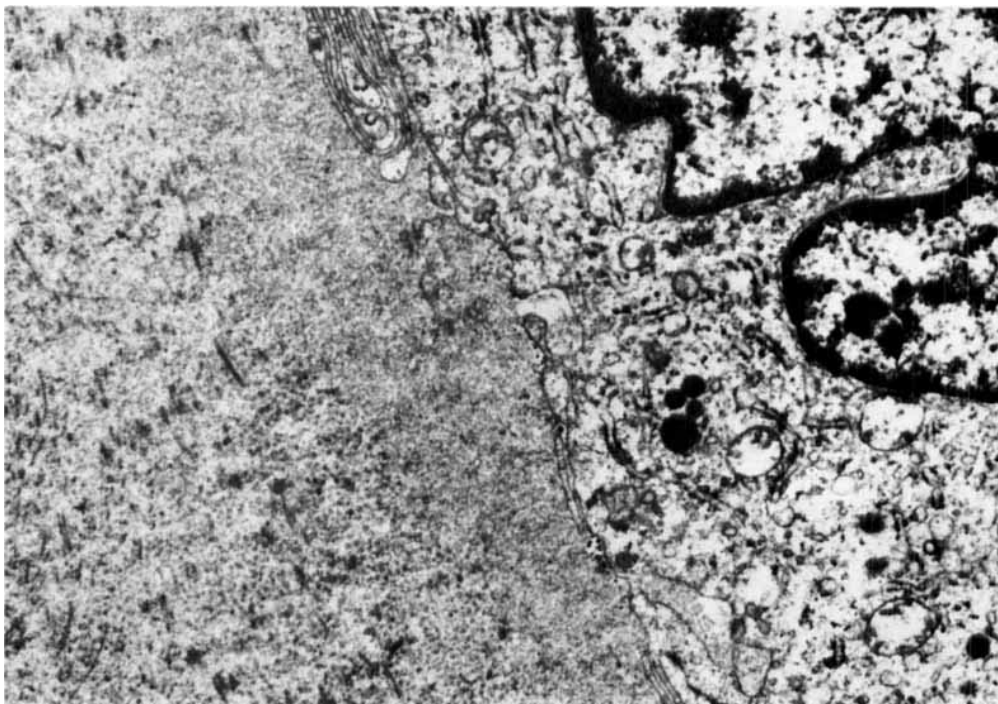
**Figure 3.** Chondrosarcoma, Grade I. Vesicular and fibrillar matrix. The vesicles are irregular and electron dense. Note the cytoplasmic microvilli with a granular border, probably glycogen ( x 28,800).



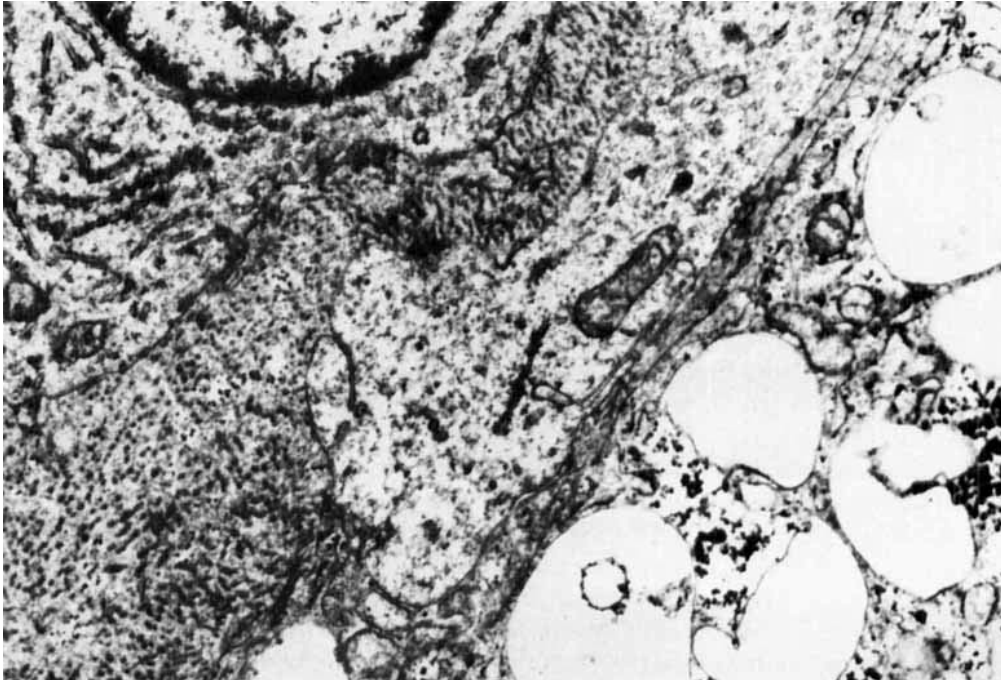
**Figure 4.** Chordoid sarcoma. Lobular pattern and mucus vacuoles in the cytoplasm of tumor cells (H & E, x 125).



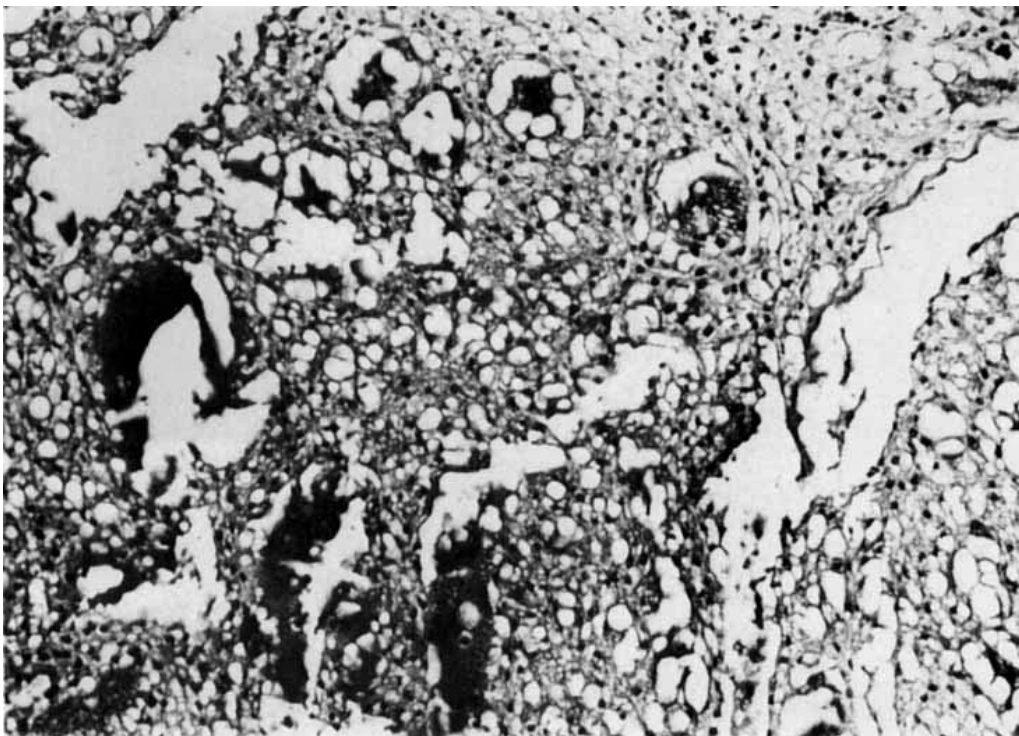
**Figure 5.** Electron micrograph of a chordoid sarcoma cell. Note the bizarre nucleoli and the granular, homogeneous, and electron-lucent cytoplasmic matrix. Indented nucleus, RER, mitochondria, and lipid droplets are apparent. The irregular interdigitations between two tumor cells are prominent ( x 9000).



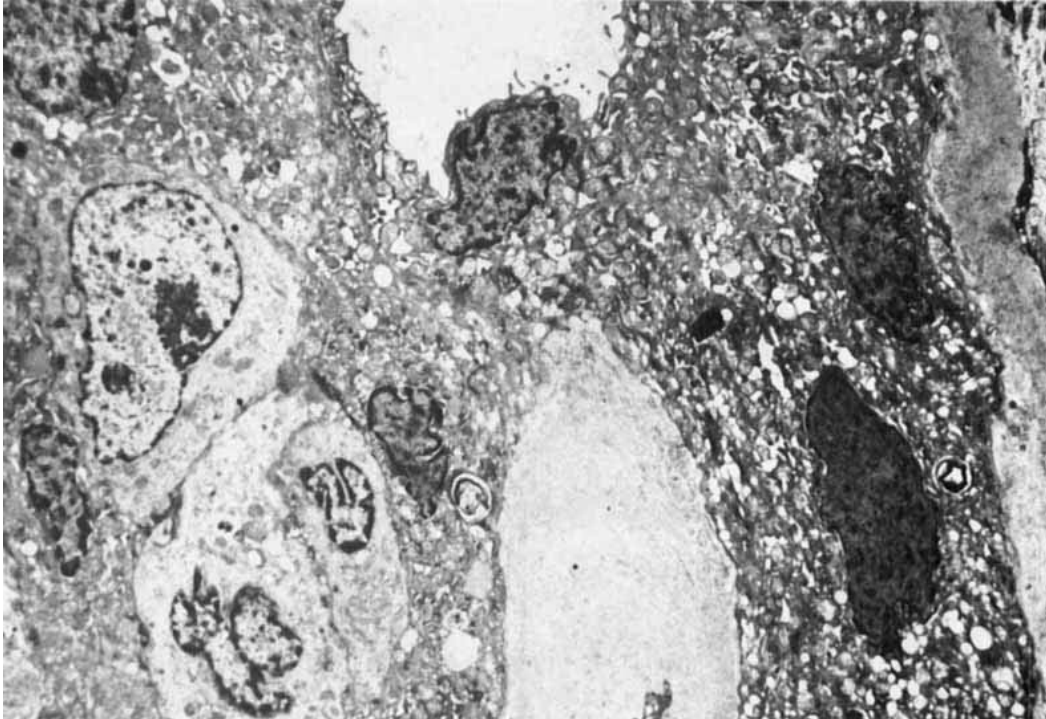
**Figure 6.** Chordoid sarcoma. Notice the homogeneous matrix adjacent to the irregular cellular border. Collagen fibers and finer fibrils are abundant. The neoplastic cell shows an indented nuclei and some electron-dense intracytoplasmic granules ( x 24,800).



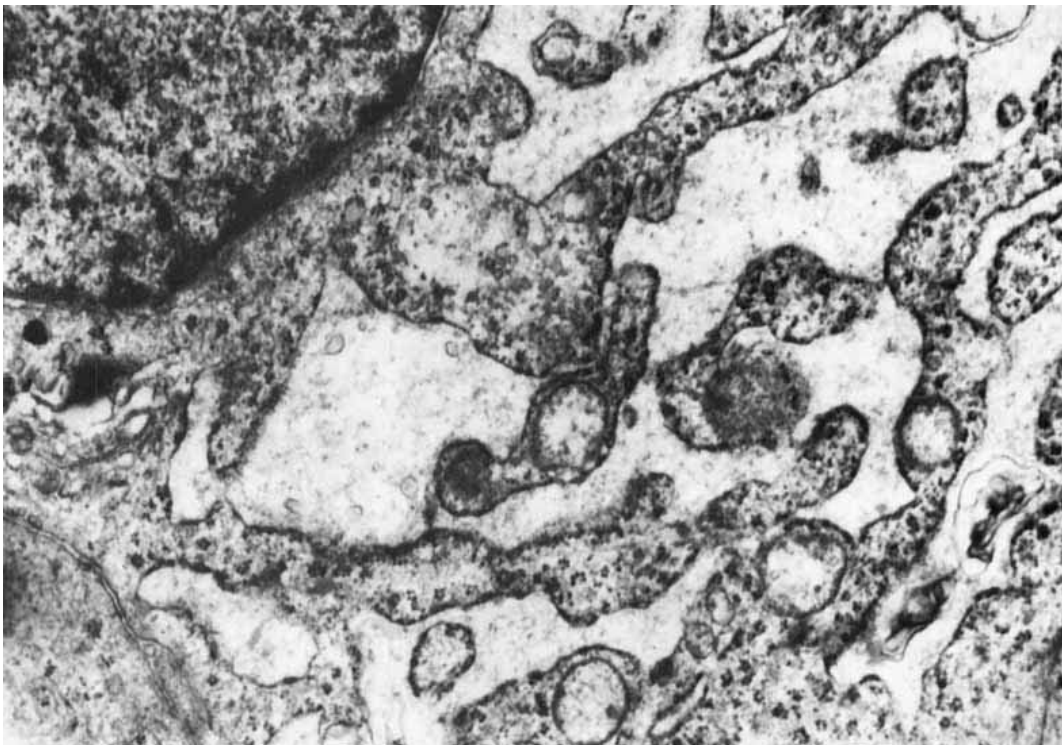
**Figure 7.** Chordoid sarcoma. The cytoplasm of some cells contains many large, clear vacuoles. Note the scarcity of intracytoplasmic organules. Contrast with Figure 3 ( x 14,400).



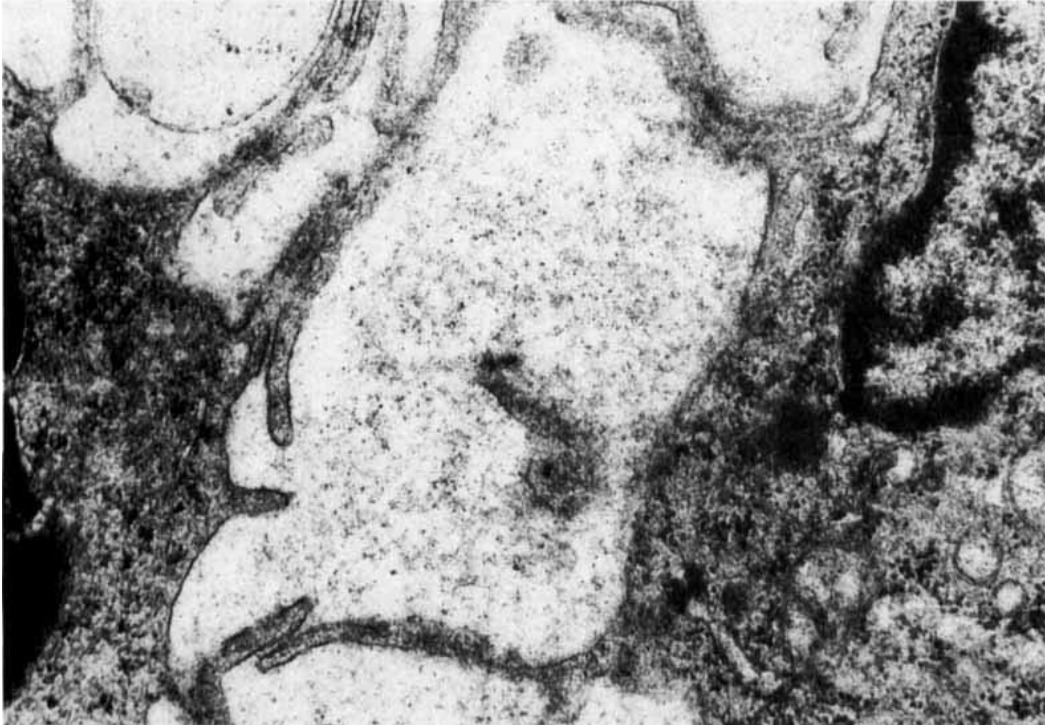
**Figure 8.** Vacuolated and physaliphorous cells in a background of mucus of chordoma. Compare cytoplasmic vacuoles with those of Figure 5 (H & E, x 125).



**Figure 9.** Chordoma. Low-power electron micrograph showing the irregular neoplastic cells. Ground substance is almost nonexistent, so the cells contact each other. Cytoplasm and nuclei of neoplastic cells are varied. Note several myelin figures and a large vacuole lined by microvilli ( x 3600).



**Figure 10.** Chordoma. Mitochondria surrounded by dilated RER. Note small vesicles within the cisternae of RER and a prominent Golgi complex ( x32,400).



**Figure 11.** Chordoma. Cytoplasm contains fine fibrils and is bordered by long microfilaments in contact with those of a neighboring cell (x32,400).