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Does chondroid chordoma exist?*

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Summary. The existence of chondroid chordoma (CC), initially described in 1973, has remained controversial. Since the antigenic profiles of both chordoma (CD) and cartilaginous (chondroid) lesions have been well characterized, we decided to study chondroid chordoma immunohistochemically. Our hypothesis was that chondroid chordoma should display a hybrid or mixed pattern of staining: chordomatous areas with an epithelial phenotype and cartilaginous areas with a mesenchymal (non-epithelial) phenotype. An analysis of CC (seven cases) was performed and compared with results obtained on notochord, cartilage, classic CD (18 cases), peripheral chondromas (two cases), and peripheral chondrosarcomas (CS, eight cases). Four epithelial markers were employed: MKER and AE-1 (both monoclonal antibodies to cytokeratin); PKER (a polyclonal antibody to cytokeratin); and, EMA (epithelial membrane antigen). In addition, selected cases were tested for the presence of neurofilament (NF) and glial fibrillary acidic protein (GFAP). All 18 CD's exhibited the expected epithelial immunophenotype – MKER+, AE-1+, PKER+, and EMA+ – a reaction pattern nearly identical to that found in fetal notochord. This reinforced the importance of the growth pattern in assessing the presence of chordomatous elements. All chondromas and CS's failed to express any of the epithelial markers studied and contained only S-100 immunoreactivity, like cartilage. Chondroid chordoma resembled cartilaginous tumors immunohistochemically; no mixed pattern with even focal epithelial marker reactivity was identified. All CC tested were also NF and GFAP negative. We conclude that CC either does not exist or is extremely rare and that these tumors are cartilaginous in nature. We propose abandoning the term chondroid chordoma and replacing it with "low grade chondrosarcoma". Distinction from CD is still imperative due to the clear difference in natural history; we provide histological definitions and an immunophenotype to aid in this distinction.

Key words: Chordoma – Chondroid chordoma – Chondrosarcoma – Base of skull lesions – Immunohistochemistry

When pathologists at the Mayo Clinc (Heffelfinger et al. 1973) first proposed the existence of chondroid chordoma (CC), they based their argument upon morphological features. Chondroid chordoma was defined as a tumor exhibiting histological features common to both chordoma and cartilaginous tumors. Vacuolated cells in "cords" accompanied foci of often malignant-appearing cartilage. Practically all CC were located at the skull base and the vast majority of previously diagnosed chondrosarcomas were renamed CC. The importance of distinguishing CC from chordoma (CD) was accentuated by the fundamental difference in the natural history of these lesions. Compared to CC, CD were far more aggressive biologically with metastatic capability and much shorter patient survival. Since its definition, CC has not only become an accepted diagnosis, but seems to be the preferred terminology for most chondroid-appearing lesions at the skull base. However, differentiating CC from pure cartilaginous tumors is difficult at best. Further, the relationship between CD, CC, and well-differentiated chondrosarcoma continues to be the subject of debate.

More recently, immunohistochemical studies have proven CD to be epithelial in nature and easily dis-

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tinguished from cartilaginous lesions by its antigenic profile. On the basis of these previous findings, we concluded that the existence of chondroid chordoma could be tested. Our hypothesis was that such a hybrid neoplasm should display a hybrid or mixed immunohistochemical staining pattern. Specifically, using epithelial markers, chondroid chordoma should contain positive epithelial (chordomatous) regions admixed with negative non-epithelial (cartilaginous) regions. A panel of epithelial markers [epithelial membrane antigen (EMA) and three different cytokeratin antibodies] was employed in this investigation to ascertain the reactivity of each tumor. To evaluate the existence of central or peripheral nervous system cell types within these tumors, antibodies to other cell-specific polypeptides [the intermediate filament proteins, neurofilament (NF) and glial fibrillary acidic proteins (GFAP)] were also used. A group of chordomas, chondroid chordomas, and chondrosarcomas was assembled and the results with the panel were compared.

Methods

Cases of chordoma and chondroid chordoma were collected from three sources: the Surgical Pathology files at the Hospital of the University of Pennsylvania, referred consultation files, and the files of the local Suburban Pathology Society. Only cases with paraffin-embedded fixed tissue available for immunohistochemical studies were included. In all cases, hematoxylin and eosin stained sections were reviewed. In addition, selected cases of peripheral chondromas and chondrosarcomas were included as controls.

Immunohistochemistry

An avidin-biotin-complex immunoperoxidase technique was used (Hsu et al. 1981). Paraffin-embedded sections, 5 μm in thickness, were cut and carefully melted at 58–60° C. After deparaffinization, with two changes in xylene (10 min each), the slides were hydrated using graded alcohol to distilled water and incubated in 0.3% H_2O_2 in absolute methanol for 45 min. Sequential incubations in 20% normal goat serum (30 min), primary antisera (1 h at room temperature or overnight at 4° C), secondary biotinylated antibody (45 min), and avidin-biotin complex reagent (45 min) followed, with three 5-min washes in phosphate-buffered saline (PBS) interspersed (with the exception of the first step where only excess normal serum was removed). Sections were then exposed to the chromagen reaction solution (0.035% diaminobenzidine in 10 ml Tris buffer, filtered, and brought to 0.3% H_2O_2) for 5 min. After washing in tap water (5 min), the sections were counterstained in hematoxylin, dehydrated, cleared, and mounted.

With antisera to cytokeratin, sections were pretreated with a 0.1% solution of trypsin (Sigma Co.), and PBS with 0.1% CaCl for 30 min at 37° C.

Sources of reagents and dilutions of antisera were as follows: Avidin-Biotin reagents (Vector Laboratory System, Inc., Burlingame, CA); diaminobenzidine (Sigma Co.); monoclonal antibody to cytokeratin-MKER (PKK1, 1/100, Lab Systems); polyclonal antisera to cytokeratin-PKER (1/100, Dako); monoclonal antibody to cytokeratin-AE-1 (1/400, Hybritech); antibody to epithelial membrane antigen-EMA (1/75, Dako); antisera to S-100 protein (1/1500; Dako); monoclonal antibody to human NF (undiluted + 1/10); and monoclonal antibody to human GFAP (1/500). Both NF and GFAP monoclonals were originally produced to bovine NF and GFAP immunogens and were shown to be reactive with human NF 200-kDa protein and GFAP protein (Tremblay et al. 1985). Both negative and substitution serum controls were employed. Positive tissue controls were also inserted in each experiment. Sections were evaluated for the presence of internal controls and the approximate frequency of positive cells was recorded. In addition, particular attention was paid to the morphological appearance of regions of immunoreactivity and to the presence of a mixed positive and negative immunoreaction pattern. Importantly, for each epithelial marker all cases were tested in the same experiment.

Results

Light microscopy

With one exception, all chordomas were remarkably similar histologically (Fig. 1). Eosinophilic cells with cytoplasmic vacuoles (physaliphorous cells) were observed in cohesive sheets and nest-like formations within a myxoid ground substance. Here, the word "cohesive" is emphasized; cells were directly opposed one to another without intervening ground substance. A lobular growth pattern was noted in all cases. Vacuoles were clearly within cells and only occasionally adjacent to them within the ground substance. Further, when cells were found in cords, the cords were practically always two or more cells thick, providing the definition of *cord* used in this study. Only very rarely, in an otherwise classic chordoma with *nests* (circular or oval groups of cohesive cells greater than 4–5 cells wide) and cords, were thin *strings* (one cell thick) identified. No sacral chordomas contained cartilaginous foci. In the one exceptional case, a more poorly differentiated region existed side by side with classic chordoma; here, individual vacuolated cells were separated by a small amount of ground substance and no cords or nests were seen. This skull base tumor represented our only example of a chordoma with metastases (to the rib 2 years after diagnosis).

Chondroid chordomas were distinctly different (Fig. 2). Clear-cut cartilaginous differentiation was seen in every case. Coupled with this were eosinophilic cells in a loose myxoid ground substance; these cells occasionally contained intracytoplasmic vacuoles. However, vacuoles were commonly observed in an extracellular location directly adjacent to tumor cells or within the ground substance. Also, the tumor cell growth pattern differed from classic chordoma: cells grew either as individual cells within the matrix, or as strings; no cords or cohesive nests were noted. Even when cells were growing as *sheets*, the cells were not

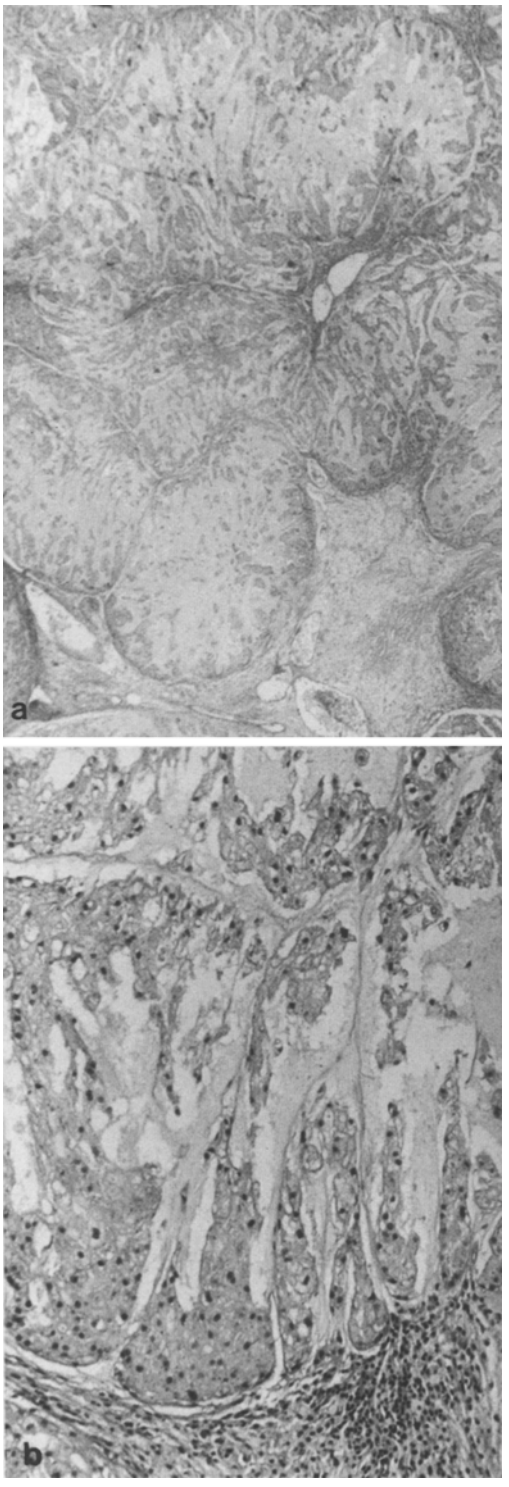

Fig. 1 a, b. Chordoma. The growth pattern; a lobular architecture (**a**) with cohesive nests and thick cords (**b**) was characteristic of all cases

directly opposed to one another. Rather, within discohesive sheets, cells were individualized by the presence of small quantities of ground substance around each cell. Nonetheless, these were acceptable cases of chondroid chordoma based upon criteria in the literature.

Vacuolated cells, as well as growth in discohesive sheets and strings, were noted in the control peripheral chondrosarcoma cases (Fig. 3). The importance of the above definitions, which greatly aided in differentiating chordoma from non-chordomatous lesions, was reinforced by the immunohistochemical results.

Immunohistochemistry

The results of the immunohistochemical analysis are contained in Table 1. Fetal notochord and fetal cartilage of 9 and 12 week gestational age were tested immunohistochemically and the reactions compared. As reported by others (Salisbury and Isaacson 1985), fetal notochord expressed cytokeratin; all three of our cytokeratin reagents (PKER, MKER, and AE-1) gave a strong reaction. We were unable to confirm the presence of EMA in fetal notochord reported by others (Salisbury and Isaacson). No S-100 immunoreactivity was seen in notochordal tissue. In contrast, fetal cartilage lacked cytokeratin and EMA staining and exhibited only S-100 reactivity.

All 18 chordomas displayed strong and diffuse reactivity with each of the three cytokeratin reagents, and in this respect resembled normal notochordal tissue (Fig. 4). Within each case, all tumor cells stained positively. Unlike notochord was the additional expression of EMA and S-100 in chordomas, again diffusely in all tumor cells. No differences in staining characteristics were observed between sacral and skull base neoplasms.

Concerning cartilaginous lesions, two chondromas and eight chondrosarcomas exhibited reaction patterns identical to fetal cartilage; the epithelial markers cytokeratin and EMA were negative and only S-100 immunoreactivity was expressed.

Within the seven chondroid chordomas, the majority of cells were decorated with the S-100 reagent. In particular, cells both in cartilaginous foci as well as in more myxoid areas with the string pattern stained. However, in no instance were any regions stained with any of the epithelial markers (Fig. 5). Sections from five of these cases were available for testing with antibodies to NF and GFAP and none contained any staining for these two intermediate filament proteins. This finding argues against the emergence or inclusion of neuronal or glial cell types in these tumors.

Discussion

Credit for the immunohistochemical definition of chordoma as an epithelial neoplasm must be given to Miettinen and colleagues (Miettinen et al. 1983). They

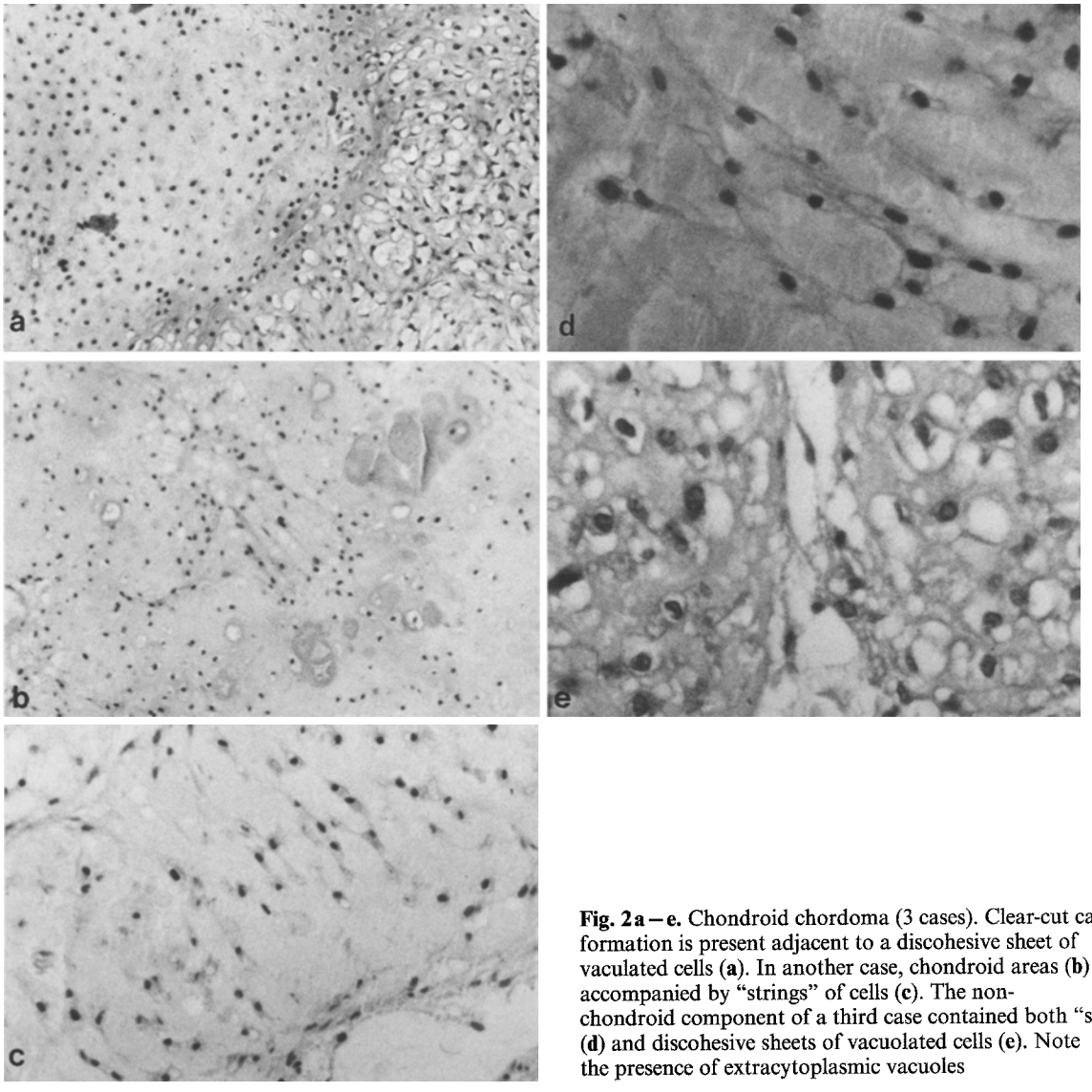

Fig. 2a–e. Chondroid chordoma (3 cases). Clear-cut cartilage formation is present adjacent to a discohesive sheet of vaculated cells (**a**). In another case, chondroid areas (**b**) were accompanied by "strings" of cells (**c**). The non-chondroid component of a third case contained both "strings" (**d**) and discohesive sheets of vacuolated cells (**e**). Note the presence of extracytoplasmic vacuoles

demonstrated the presence of cytokeratin (CK) in six chordomas. Since then, a number of other studies have confirmed the epithelial nature of this lesion (Miettinen 1984; Salisbury and Isaacson 1985; Sibley 1985; Abenoza et al. 1985). In addition to cytokeratin, CD have been shown to express EMA (Miettinen 1984; Salisbury and Isaacson 1985) and carcino-embryonic antigen (CEA) (Sibley 1985; Abenoza et al. 1985). With the exception of one unusual case, a "dedifferentiated chordoma" with areas resembling malignant fibrous histiocytoma (Miettinen et al. 1984), all CD have lacked vimentin immunoreactivity. Chordoma and cartilaginous lesions were alike only in S-100 protein expression (Nakamura et al. 1983). As Miettinen et al. also showed, CD can easily be distinguished from chondrosarcoma (CS) immunohistochemically. Unlike CD, CS failed to express cytokeratin and contained vimentin instead (Miettinen et al. 1983). Chondrosarcomas have subsequently been shown to lack EMA (Salisbury and Isaacson 1985; Abenoza et al. 1985) and CEA (Abenoza et al. 1985). Here, we confirmed the immunophenotypes of chordoma (S-100+, CK+, EMA+) and CS (S-100+, CK−, EMA−). In addition, our results using three different types of CK antibodies revealed adequate staining of CD with all three.

The immunophenotype of CC was determined here, for the first time, to be S-100+, CK−, EMA−, NF−, and GFAP−. Our cases of CC, as documented pictorically (Fig. 2), were acceptable cases and indeed resembled those previously reported in the literature.

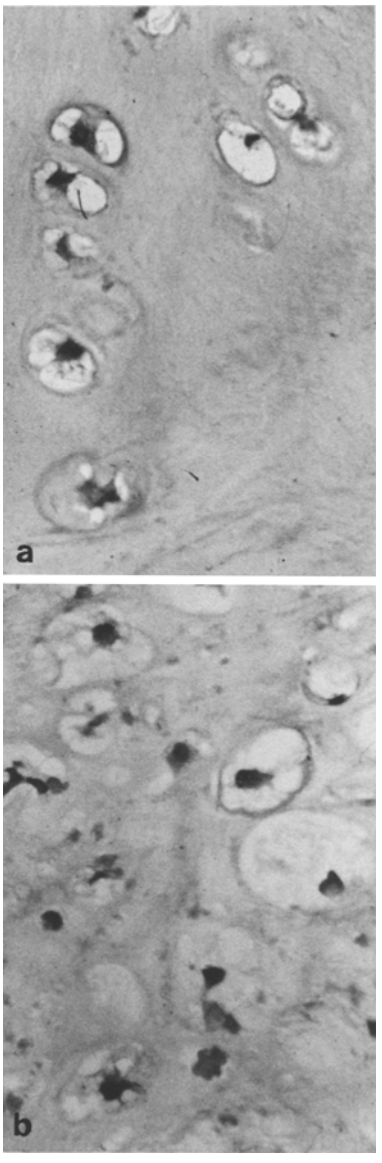

Fig. 3a, b. Cartilaginous tumors. Intracytoplasmic vacuoles were seen in chondroma (**a**) and chondrosarcoma (**b**)

We have shown that the immunohistochemical profile of CC bears no relationship to that of chordoma and, in fact, is identical to that of CS. Therefore, our results do not support the existence of this previously described hybrid tumor. Instead, we have shown this tumor to be indistinguishable from chondrosarcoma and thus, we believe it to be firmly placed within the cartilaginous family of lesions. We recommend that the term chondroid chordoma be abandoned and replaced by "low grade chondrosarcoma". Naturally, this proposal does not in any way negate the recognized difference in natural history between "CC – low grade chondrosarcoma" and chordoma as originally documented by the Mayo Clinic authors (Heffelfinger et al. 1973). Rather, it underscores the rather indolent course of cartilaginous lesions of the skull base.

Table 1. Selected immunohistochemical results

	S-100	PKER	MKER	AE-1	EMA
Normal tissues					
Fetal notochord	0/2	2/2	2/2	2/2	2/2
Fetal cartilage	2/2	0/2	0/2	0/2	ND
Tumors					
Chondroma	2/2	0/2	0/2	0/2	0/2
Chondrosarcoma					
Typical	6/6	0/6	0/6	0/6	0/6
Myxoid	1/1	0/1	0/1	0/1	0/1
Mesenchymal	1/1	0/1	0/1	ND	ND
Chondroid chordoma	7/7	0/7	0/7	0/7	0/7
Chordoma					
Sacral	12/12	12/12	12/12	12/12	12/12
Base of skull	6/6	6/6	6/6	6/6	6/6

EMA: epithelial membrane antigen; ND: not done

Our immunocytological results also highlighted clear-cut morphological differences between "CC – low grade chondrosarcoma" and chordoma (Table 2). The histological feature which truly distinguished chordomas from all cartilaginous tumors was its growth pattern, which is so similar from case to case. Cohesive sheets, nests, and cords (as defined here) are emphasized as the key diagnostic findings for chordoma. Certainly eosinophilic vacuolated cells and a myxoid ground substance are necessary, but they are definitely not sufficient. Similar-appearing physaliphorous-like cells can be found in chondrosarcoma. Neither should the presence of a string-like pattern of single cells be confused with the cords of chordoma. This string pattern can occasionally be seen in typical CS and is classically identified in the myxoid CS subtype.

If the literature on CC is examined, approximately 42 cases can be found within 12 separate articles on the topic. Of these, 14 cases in 7 papers contained no photographic documentation (Chambers and Schwinn 1979; Harwick and Miller 1979; Hasegawa et al. 1985; Rich et al. 1985; Volpe and Mazabraud 1983; Wold and Laws 1984; Perzin and Pushparaj 1986). In the remainder, a recognizable chondroid component was commonly depicted photographically, but it was difficult to document the diagnostic growth pattern of chordoma. For example, the sheets of vacuolated cells depicted in two additional articles were discohesive with ground substance surrounding individual cells (Valderrama et al. 1983; Richter et al. 1975). Other reports, attempting to display tumor cells in cords, showed what we would interpret as strings (Heffelfinger et al. 1973; Spoden et al. 1980). Only in

one report (Heaton and Turner 1985) were thicker cords illustrated; here, however, we believe it is the chondroid component which was not convincingly demonstrated. In short, the classic features of chordoma, as redefined here, were not confincingly identified within the reported cases of CC.

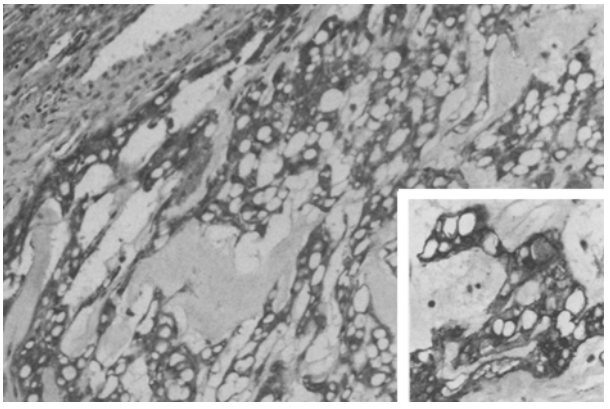

Fig. 4. Immunohistochemistry. Strong diffuse cytokeratin positivity within chordomas accentuated both the thick cohesive cord structures and the intracytoplasmic position of the vacuoles. Staining for epithelial membrane antigen (*inset*) also highlighted these features

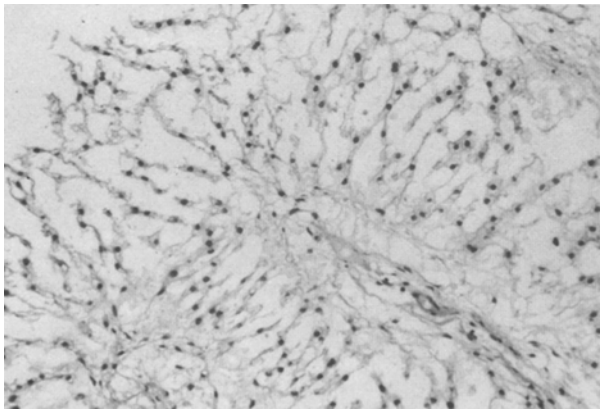

Fig. 5. Immunohistochemistry. In contrast to chordomas, chondroid chordomas (low grade chondrosarcomas) failed to stain with any epithelial markers; here, the stringing arrangement was negative for the cytokeratin AE-1

An elegant histochemical study (Bottles and Beckstead 1984) provided the initial hard evidence in the literature that CC were unrelated to chordoma. The presence of the enzyme 5′-nucleotidase was observed within chordomas but not within CC nor CS. These authors were the first to seriously question the entity of CC and noted that CC "appear similar histologically to CS and chondromas". They concluded that CC "may be better considered as cartilaginous tumors rather than as a subtype of chordoma".

The argument in favor of CC as a hybrid tumor was weak from the start. First, this was an entity introduced at the expense of the majority of previously diagnosed CS at the skull base (Heffelfinger et al. 1973). Very few CS in that region have been diagnosed within the past decade (Suit et al. 1982). Secondly, if one excludes the original description, there have never been any well-documented cases of CC in the sacral area; the site of many large bulky chordomas with more than adequate tissue for study. Thirdly, ultrastructural studies have not been critically examined. Desmosomes, certainly described in chordoma (Pena et al. 1970; Spjut and Luse 1964; Pardo-Mindan et al. 1981; Kay and Schatzki 1972) were also found in CC (Valderrama et al. 1983) and used as documentation of a chordomatous or epithelial feature. However, desmosomes or simple cell junctions are non-specific and can be found in a variety of non-epithelial lesions including CS (Weiss 1976; Pardo-Mindan et al. 1981; Robertson and Hogg 1980; Martinez-Tello and Navas-Palacios 1982). Our analysis further supports the non-specificity of this finding. Also, the peculiar crystalline tubular structures supposedly unique to CC (Valderrama et al. 1983) had been described in the myxoid CS (Wetzel and Reuhl 1980). More compelling ultrastructural support of the epithelial nature of chordoma was the finding of true tonofilaments (Miettinen 1984). Although tonofilaments were identified by Valderrama in CC, they were described as short and the illustration appeared to show a thick desmosome.

Morphological, histochemical, ultrastructural, and now immunohistochemical evidence has

Table 2. Defined histologic features[a]

Feature	Chordoma	Chondroid chordoma	Chondrosarcoma
Sheets	Cohesive	Discohesive	Discohesive
Nests	Present	Absent	Absent
Cords	Present	Absent	Absent
Strings	Rare	Common	Occasional
Eosinophilic cells	Yes	Yes	Yes
Vacuoles	Intracellular	Intracellular + Extracellular	Intracellular + Extracellular

[a] See text for definitions

accumulated against the existence of chondroid chordoma. We, like Bottles and Beckstead, propose these tumors be classified as low grade cartilaginous lesions, probably chondrosarcomas. Due to clear difference in behavior, these tumors should continue to be separated from chordomas; we have provided histological definitions and an immunophenotype to aid in this distinction.

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