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Dedifferentiated chondrosarcoma of bone

An immunohistochemical and lectin-histochemical study

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Summary. Ten cases of dedifferentiated chondrosarcoma (DCS) were immunohistochemically and histochemically compared with 12 de novo malignant fibrous histiocytomas, 10 osteoblastic osteosarcomas, 9 conventional chondrosarcomas, and 4 fibrosarcomas (all of bone or soft tissues), in order to discern similarities and differences in the immunophenotypes of these neoplasms. All cases of DCS and malignant fibrous histiocytoma were reactive for alpha-1-antichymotrypsin, and several examples of both tumor types bound peanut agglutinin, and expressed positivity for alpha-1-antitrypsin and lysozyme. None of these four cellular markers was observed in de novo osteosarcoma and fibrosarcoma; in addition, conventional chondrosarcoma lacked all of them except for peanut agglutinin receptors. S100 protein reactivity and binding of wheat germ agglutinin were detectable in conventional chondrosarcomas and in rare cells of the anaplastic components of primary DCS, but not in malignant fibrous histiocytoma arising ab initio and the other sarcomas. These results suggest the evolution of a second neoplastic cellular clone in DCS, with primitive morphological and phenotypic characteristics.

Key words: Chondrosarcoma – Sarcomas of bone – Immunohistochemistry – "Histiocytic" markers

The concept that chondrosarcoma may alter its microscopic appearance, and assume the characteristics of an anaplastic neoplasm without overt chondrogenesis, is now well-accepted (Astorino and Tesluk 1985; Braddock and Hadlow 1966; Brooks 1986; Campanacci et al. 1979; Dahlin 1978; Dahlin and Beabout 1971; Eyre-Brook and Price 1969; Johnson et al. 1986; Kahn 1976; McCarthy and Dorfman 1982; McFarland et al. 1977; Mirra and Marcone 1974; Rockwell and Enneking 1971; Sanerkin and Woods 1979). This phenomenon has been termed "dedifferentiation", (Dahlin and Beabout 1971) and is thought to occur in approximately 10% of all chondrosarcomas. Tumors that reach a large size, or repeatedly recur, seem to be particularly prone to display dedifferentiated foci (Dahlin 1978). Although the process in question is not actually "de-"differentiation, but rather an arrest in the maturation of neoplastic cells, the modifier "dedifferentiated" is widely-used in the literature on chondrosarcoma, and will be retained in the ensuing discussion for that reason.

Various reports on dedifferentiated chondrosarcoma (DCS) have classified its high-grade histologic component as osteosarcoma, fibrosarcoma, or malignant fibrous histiocytoma (Braddock and Hadlow 1966; Dahlin 1978; Dahlin and Beabout 1971; Eyre-Brook and Price 1969; Johnson et al. 1986; McCarthy and Dorfman 1982; McFarland et al. 1977; Mirra and Marcone 1974; Rockwell

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and Enneking 1971; Sanerkin and Woods 1979). In an attempt to discern whether this element is indeed heterogeneous in its differentiation products, we have studied ten examples of DCS immunohistochemically, using a panel of antibodies directed against epithelial and mesenchymal antigens. The immunophenotype of these cases was compared with those of twelve malignant fibrous histiocytomas, ten osteosarcomas, and four fibrosarcomas of bone and soft tissues.

Materials and methods

The surgical pathology files of the University of Minnesota and the University of Virginia were searched for examples of dedifferentiated chondrosarcoma. Clinical records, microscopic slides, and radiographs were reviewed, in all cases that were retrieved. For comparison, ten cases of conventional osteosarcoma and nine of Broders' grade 2 to 3 chondrosarcoma were also studied, along with two malignant fibrous histiocytomas (MFH) of bone, ten MFH of soft tissues, one fibrosarcoma of bone, and three fibrosarcomas of soft tissues. The latter group of neoplasms was randomly chosen from available examples in the institutional files of one of the authors (MRW).

Microscopic sections were cut at 5 microns from formalin-fixed, paraffin-embedded tumor tissue in each case, and were stained with hematoxylin and eosin. In addition, immunohistochemical analyses were performed for eight antigens with the PAP or ABC methods, as previously described (Hsu et al. 1981; Sternberger et al. 1970). These antigenic determinants were chosen to reflect the characteristics of epithelial and mesenchymal cell lines, and are listed in Table 1. In addition, the binding of three lectin preparations (peanut, wheat germ, and concanavalin-A agglutinins) was assessed in all cases, using biotinylated reagents (Vector Laboratories, Inc., Burlingame, CA, USA) and the ABC method. In order to determine the possible effect of differing technical procedures on immunohistochemical results, selected immunostains (for S100 protein and alpha-1-antichymotrypsin) were performed in the laboratories of two of the authors (MRW and GPS).

All immunohistochemical analyses were done in a phosphate-buffered saline system (pH 7.4), without prior digestion of tissue sections by proteolytic enzymes. Negative controls were represented by sections of each neoplasm stained by substitution of nonimmune rabbit serum or mouse ascites fluid for primary antibodies. Positive controls consisted of stock tumors or tissues known to contain the determinants of interest.

Results

Clinical features

Among the ten patients with DCS included in this study, seven were men and three were women, ranging in age from 37 years to 85 years at diagnosis. Nine complained of pain in the affected bones, while one case presented with a nonpainful mass. Three tumors involved the ilium, three occurred in the humerus, and one each arose in the scapula, femur, tibia, and radius. All were clearly malignant radiographically, and were represented by large, lytic, focally calcified masses which expanded the bone and breached its cortex (Fig. 1). Pathologic fracture was present in two cases. The therapies employed, and clinical outcomes of cases of DCS

Table 1. Immunohistochemical and histochemical reagents used in the study of dedifferentiated chondrosarcoma and other sarcomas of bone and soft tissue

Antibody/Lectin	Source	Working dilution
Polyclonal anti-S100	DakoPatts Co., Inc.	1:1000
Monoclonal anti-S100[a]	Dr. G.Y. Gillespie University of North Carolina-Chapel Hill	1:20
Anti-lysozyme	DakoPatts Co., Inc.	1:700
Anti-alpha-1-antitrypsin	DakoPatts Co., Inc.	1:800
Anti-alpha-1-antichymotrypsin	DakoPatts Co., Inc.	1:800
Anti-vimentin (Clone PK-V)[a]	Lab Systems, Inc.	1:40
Anti-cytokeratins:		
Clones AE1/AE3[a]	Hybritech Labs, Inc.	1:160
Clone PKK1[a]	Lab Systems, Inc.	1:200
Clone EAB 902[a]	Enzo Biochem, Inc.	1:6400
Anti-epithelial membrane antigen[a]	DakoPatts Co., Inc.	1:160
Anti-desmin	DakoPatts Co., Inc.	1:200
Biotinylated peanut agglutinin	Vector Laboratories, Inc.	1:1600
Biotinylated wheat germ agglutinin	Vector Laboratories, Inc.	1:3600
Biotinylated concanavalin-A agglutinin	Vector Laboratories, Inc.	1:800

[a] Murine hybridoma antibodies

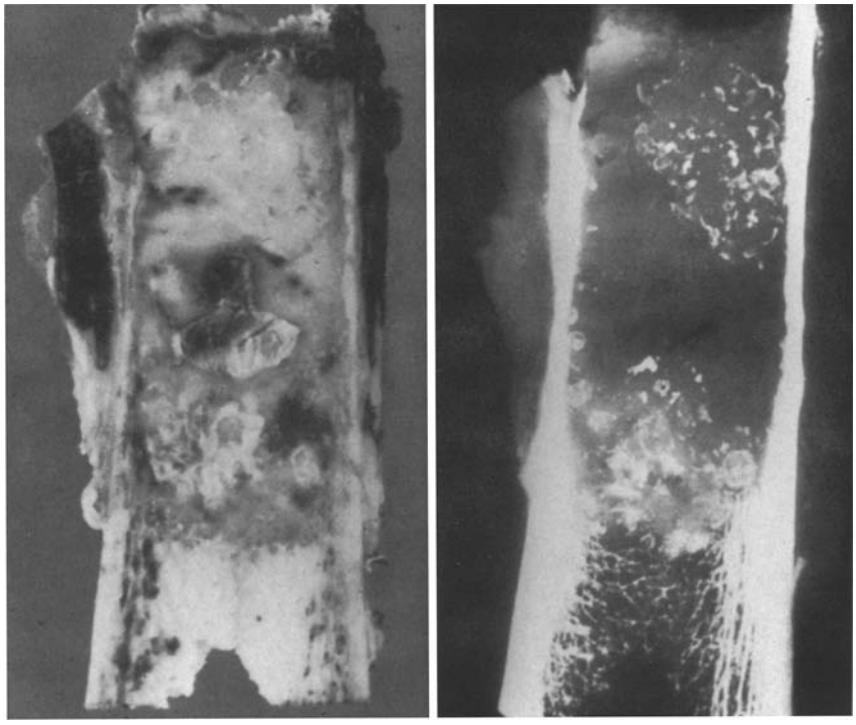

Fig. 1. Gross specimen and specimen radiograph of dedifferentiated chondrosarcoma. The tumor expands the affected bone and breaches its cortex

are summarized in Table 2. The other osseous and soft tissue sarcomas presented as masses, with or without pain.

Microscopic findings

Nine cases of DCS showed the concomitant presence of typical chondrosarcoma and high-grade, noncartilaginous sarcoma in the same tissue specimen (Fig. 2). One neoplasm consisted only of anaplastic sarcoma, but occurred at the margin of a grade 2 myxoid chondrosarcoma, resected one year earlier. In nine cases, the high-grade sarcoma was composed of densely-packed, spindled, fibroblast-like cells, large uninucleated polygonal cells, and multinucleated tumor cells (Fig. 3). In one instance, it consisted only of spindled cells in a "storiform" arrangement. All three neoplastic cell

Table 2. Clinical features of ten cases of dedifferentiated chondrosarcoma

Case	Age/sex	Presenting complaints	Type of surgery	Adjuvant therapy/type	Clinical outcome
1	51/M	Painful mass left acetabulum	En bloc resection[a]	ChemoRx: ADR+DTIC	DOD:1 yr
2	59/M	Pain and pathologic fracture: right femur	En bloc resection	ChemoRx: ADR+DTIC	Metastases to lungs: AWD:25 months
3	40/F	Painful mass right ilium	En bloc resection	None	DOD:1 yr
4	37/F	Painful mass right tibia	Above-knee amputation	ChemoRx: ADR+DTIC	NED:21 months
5	85/M	Mass right radius	Below-elbow amputation	None	DOD:9 months
6	40/F	Painful mass right acetabulum	En bloc resection	ChemoRx: ADR+DTIC	DOD:17 months
7	84/M	Pain and pathologic fracture: left humerus	Biopsy only	None	DOD:4 months
8	74/M	Painful mass left humerus	En bloc resection	None	DOD:5 months
9	62/M	Painful mass right thigh	Hip disarticulation	None	DUC:4 months
10	54/M	Painful mass right scapula	Forequarter amputation	ChemoRx: ADR+DTIC	Metastases to lungs: AWD: 6 months

[a] Original tumor was grade 2 myxoid chondrosarcoma; recurrence was "pure" dedifferentiated chondrosarcoma: death 1 year after recurrence, 2 years after initial presentation

ChemoRx = Chemotherapy; ADR = Adriamycin; DTIC = Dithio-imidazole carboximide; DOD = Dead of disease; AWD = Alive with disease; NED = No evidence of disease; DUC = Dead of unknown causes

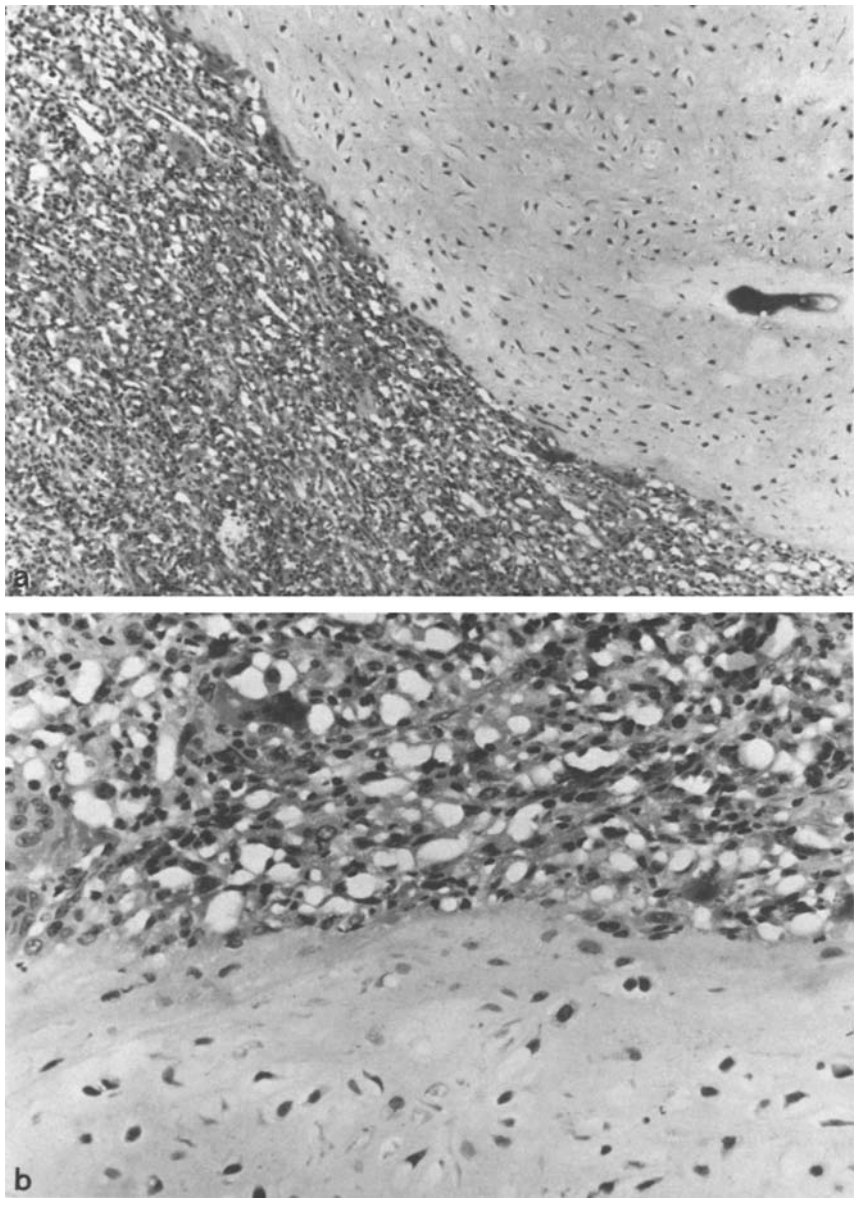

Fig. 2. a Overview of dedifferentiated chondrosarcoma. High-grade sarcoma is abruptly apposed to a well-differentiated chondrogenic component (H and E, ×70); **b** Low-grade chondrosarcoma, characterized by nuclear hyperchromasia and binucleation, is juxtaposed to a high-grade pleomorphic component in this dedifferentiated chondrosarcoma (H and E, ×140).

types displayed high nuclear-to-cytoplasmic ratios, coarse nuclear chromatin, prominent nucleoli, and numerous mitotic figures. There was marked variation in cellular size and shape in all but the purely spindle-cell tumor. Osteogenesis was questionably present in three of the 10 cases, and one neoplasm formed aneurysmal bone cyst-like blood "lakes" in its dedifferentiated component. The overtly chondrogenic portions contained binucleate chondrocytes in a lacunar background, with nuclear hyperchromasia and enlargement (Fig. 2). Overall cellular atypia in this component was slight to moderate, consistent with Broders' grades of 1 or 2.

The histologic appearances of the conventional chondrosarcomas, malignant fibrous histiocytomas, osteosarcomas, and fibrosarcomas in the comparative study group were as standardly described (Dahlin 1978; Meister et al. 1980). All osteosarcomas were of the osteoblastic type (Dahlin 1978), without areas resembling MFH.

Immunohistochemical findings

All tumors studied, including the ten cases of DCS, displayed immunoreactivity for vimentin, and lacked cytokeratin and epithelial membrane antigen. Vimentin was the only detectable antigen in

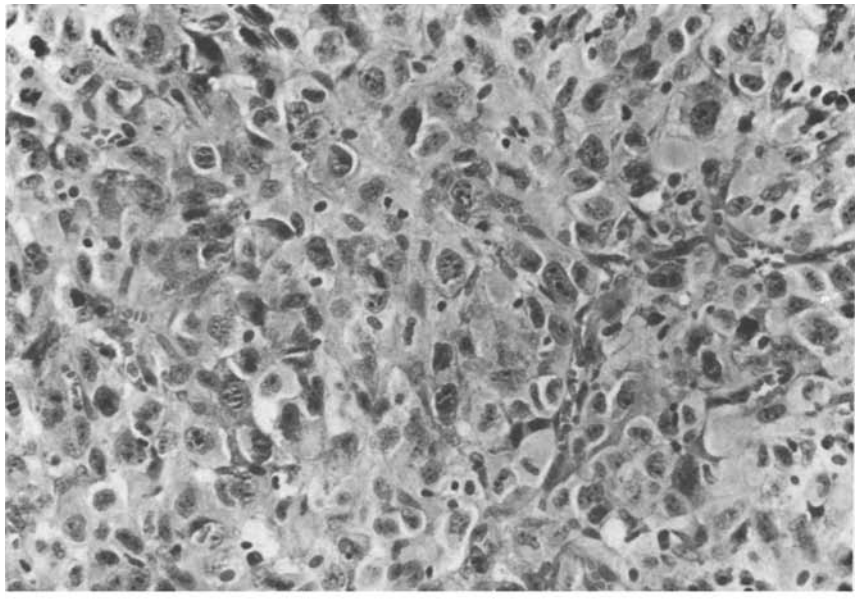

Fig. 3. Anaplastic portion of dedifferentiated chondrosarcoma. A mixture of polygonal and spindle cells in apparent (H and E, ×175)

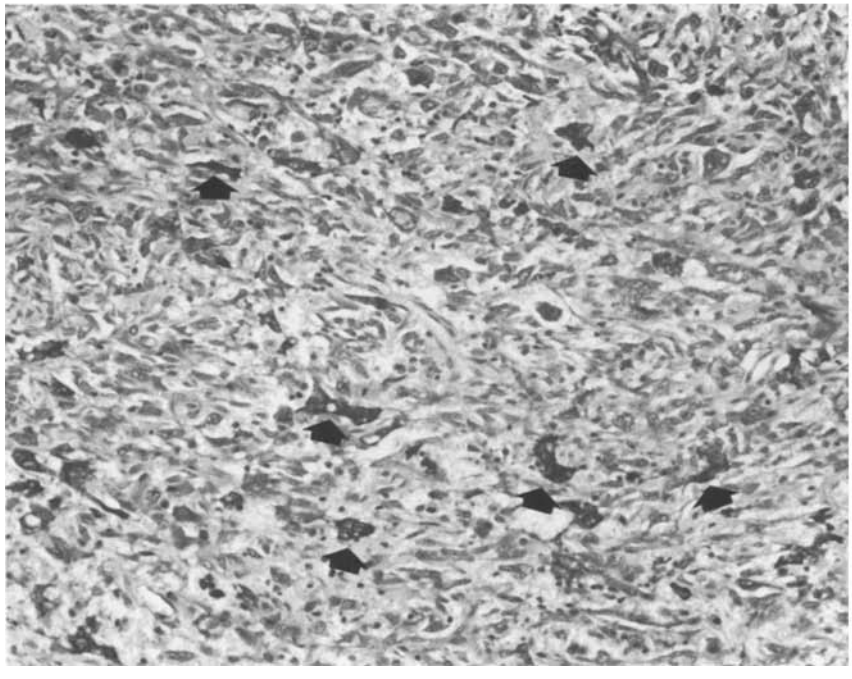

Fig. 4. Scattered immunoreactivity for alpha-1-antichymotrypsin in anaplastic portion of dedifferentiated chondrosarcoma (*arrows*) (PAP stain, ×95)

cases of fibrosarcoma and osteosarcoma of bone and soft tissues.

All examples of DCS and MFH exhibited positivity for alpha-1-antichymotrypsin, which was present in spindled, polygonal uninucleated, and multinucleated tumor cells. However, the last two of these cell types contained the strongest and most uniform reactivity (Fig. 4). Eight of 12 malignant fibrous histiocytomas and 8 of 10 dedifferentiated chondrosarcomas contained alpha-1-antitrypsin, with a similar cellular distribution to that of alpha-1-antichymotrypsin (Fig. 5). Lysozyme was observed in occasional tumor cells of three DCS and four MFH. This reactant was invariably seen only in uninucleated polygonal cells. Desmin was expressed by rare spindled cells with atypical nuclei, in 5 DCS and 6 MFH. Conventional chondrosarcomas were nonreactive for all of these antigens.

S100 protein-positivity was present in the low-grade chondrosarcomatous component of all nine DCS containing this element. Rare cells of the dedifferentiated elements stained with a polyclonal

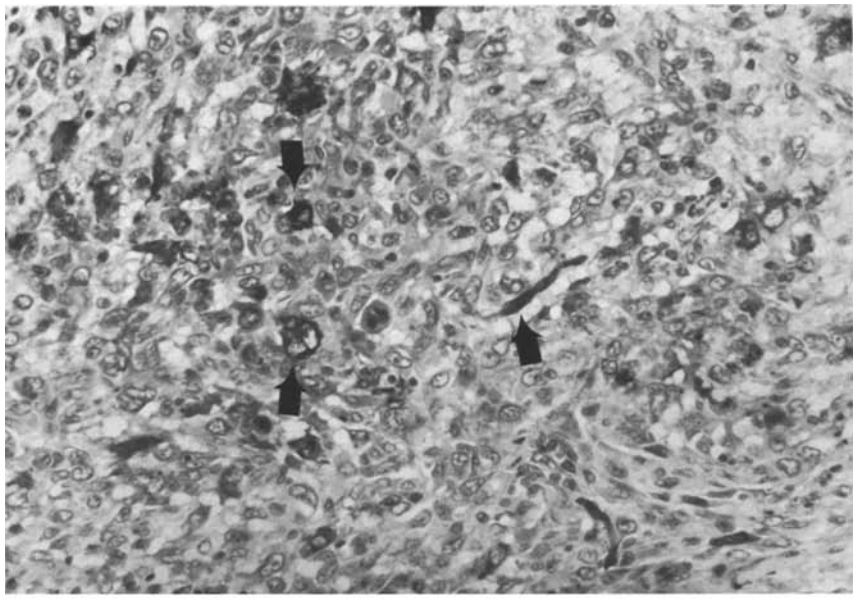

Fig. 5. Positivity for alpha-1-antitrypsin (*arrows*) in anaplastic component of dedifferentiated chondrosarcoma (PAP stain, ×175)

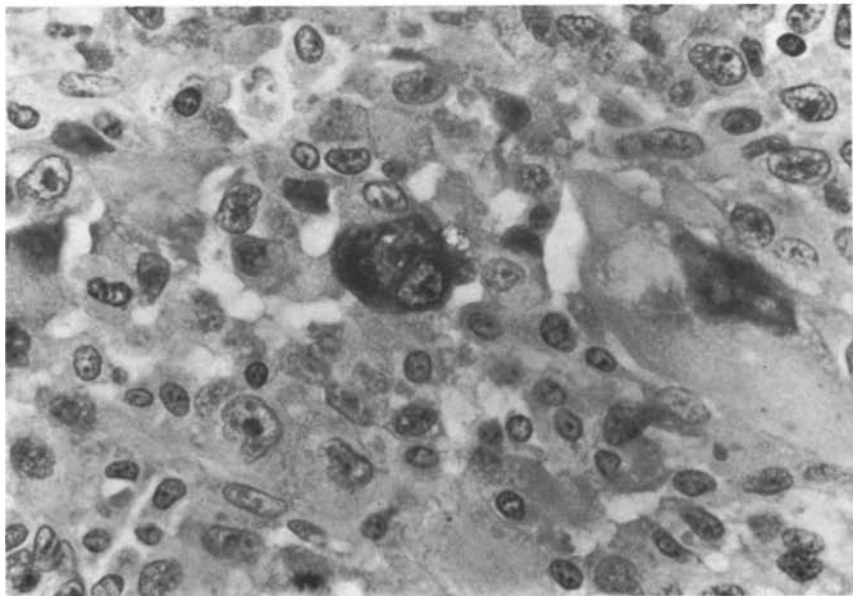

Fig. 6. Two isolated S100 protein-positive tumor cells, in high-grade portion of dedifferentiated chondrosarcoma. One cell manifests only nuclear reactivity (*right*), while the other contains cytoplasmic staining as well (*center*) (PAP stain, ×280)

rabbit antiserum to this determinant in 9 of 10 cases (Fig. 6). High-grade metastatic deposits of 2 DCS (both with S100-reactive primary lesions) were S100-negative. In contrast, only four of seven cases displayed immunoreactivity with a murine monoclonal antibody to S100, in high-grade areas. In these examples, fewer positive cells were seen than in the stains done with rabbit antiserum. The latter labelled spindled, polygonal, and multinucleated cells in the 9 positive cases, whereas monoclonal anti-S100 was reactive with polygonal cells only. All cases of conventional chondrosarcoma contained S100 protein, but none of the cases of osteosarcoma, fibrosarcoma, or de novo MFH expressed this determinant.

Histochemical stains demonstrated cell membrane binding of concanavalin-A agglutinin in all conventional chondrosarcomas and the low-grade components of DCS cases, and in 8 dedifferentiated foci of the latter. Eight of 12 examples of MFH, 6 of 10 osteosarcomas, and 3 of 4 fibrosarcomas showed similar binding patterns with this lectin. Wheat germ agglutinin labelled conventional chondrosarcomas, and the low-grade, as well as the anaplastic portions of primary DCS, with a characteristic, punctate, perinuclear cytoplasmic

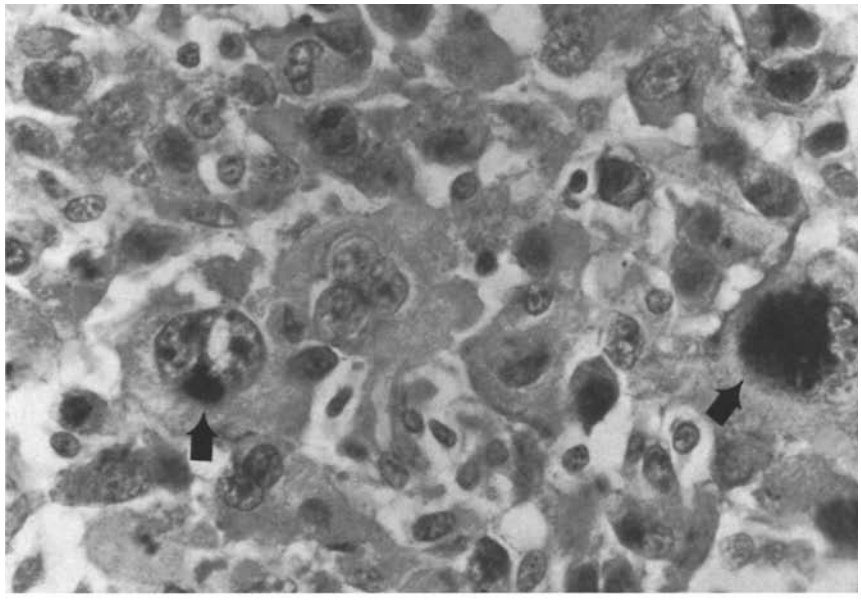

Fig. 7. Punctate perinuclear binding of wheat germ agglutinin (*arrows*) in dedifferentiated chondrosarcoma (ABC stain, ×280)

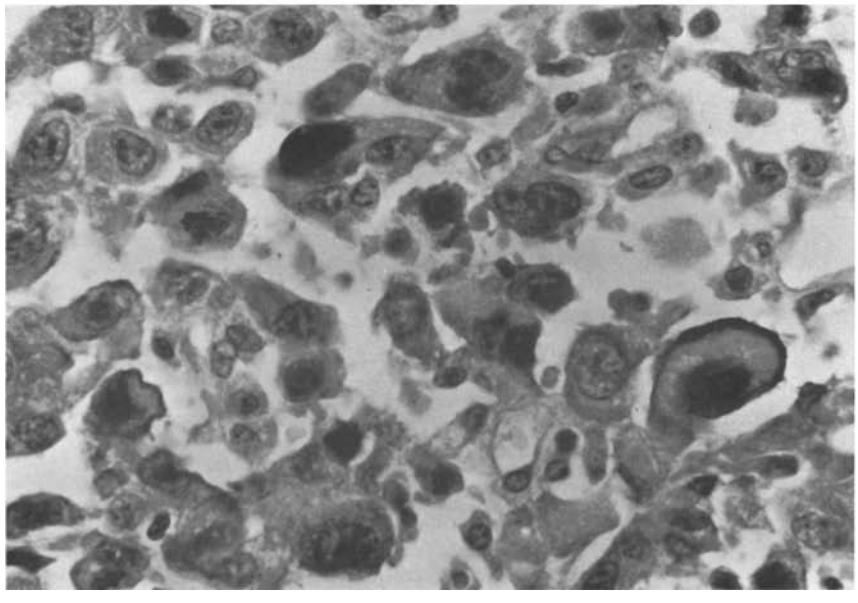

Fig. 8. Mixed cell-membranous and cytoplasmic reactivity for peanut agglutinin, in dedifferentiated chondrosarcoma (ABC stain, ×280)

pattern (Fig. 7). It did not bind to metastatic DCS cells in two cases, or to any of the other noncartilaginous neoplasms studied. Lastly, peanut agglutinin bound to polygonal and multinucleated tumor cells in the anaplastic foci of 6 DCS, and 7 of 12 MFH (Fig. 8). Labelling of the cell membranes and a discrete perinuclear cytoplasmic zone was seen with this reagent. All cases of grade 2 to 3 chondrosarcoma also bound peanut agglutinin in a purely membranous pattern, but examples of osteosarcoma and fibrosarcoma were negative.

Positive and negative control sections stained appropriately, and there were no interlaboratory differences in immunostaining results, using comparable antibodies. The immunohistochemical findings in the anaplastic components of DCS cases are summarized in Table 3.

Discussion

In light of the extremely aggressive clinical behavior of chondrosarcoma with dedifferentiation (Dahlin 1978; Dahlin and Beabout 1971; McCarthy and Dorfman 1982), it is essential that pathologists involved in the diagnosis of bone tu-

Table 3. Immunohistochemical and histochemical findings in ten cases of dedifferentiated chondrosarcoma

Case	*PS100*	*MS100*	*LYSO*	*AAT*	*AACT*	*VIM*	*CKER*	*DES*	*EMA*	*PNA*	*WGA*	*CON-A*
1	+	R+	+	+	+	+	0	R+	0	+	+	+
2	R+/0[a]	0/ND	R+/0	+/+	+/+	+/+	0/0	+/R+	0/0	0/0	+/0	+/+
3	R+	R+	R+	R+	+	+	0	0	0	+	+	+
4	R+	R+	0	0	+	+	0	R+	0	+	+	0
5	R+	0	0	+	+	+	0	R+	0	0	0	0
6	R+	0	0	+	+	+	0	0	0	0	+	+
7	R+	R+	0	+	+	+	0	0	0	R+	0	+
8	R+/0	ND/ND	0/0	+/0	+/+	+/+	0	0	0	+/+	+/0	+/0
9	R+	ND	0	0	+	+	0	0	0	+	+	+
10	+	ND	0	+	+	+	0	R+	0	0	+	+

[a] Results in primary tumor/results in metastases; + = Positive; R+ = Rare positive cells; 0 = Negative; ND = Not done; MS100 = Monoclonal anti-S100; PS100 = Polyclonal anti-S100; LYSO = Anti-lysozyme; AAT = Anti-alpha-1-antitrypsin; AACT = Anti-alpha-1-antichymotrypsin; VIM = Anti-vimentin; CKER = Anti-cytokeratin; DES = Anti-desmin; EMA = Anti-epithelial membrane antigen; PNA = Peanut agglutinin binding; WGA = Wheat germ agglutinin binding; CON-A = Concanavalin-A binding

mors be aware of the attributes of this neoplasm. Companacci et al. (1979), McCarthy and Dorfman (1982), and Johnson et al. (1986) have summarized the clinicopathologic and radiographic features of DCS, including its high rate of fatality within one year after diagnosis. Our series recapitulates the observations of these authors, as well as others (Dahlin 1978; Dahlin and Beabout 1971; McFarland et al. 1977; Mirra and Marcone 1974), with respect to the histopathology and biology of this tumor.

As mentioned previously, several examples of DCS have been described as "osteosarcomatous" or "fibrosarcomatous" transformations of low-grade chondrogenic neoplasms (Braddock and Hadlow 1966; Dahlin 1978; Dahlin and Beabout 1971; Eyre-Brook and Price 1969; McFarland et al. 1977; Mirra and Marcone 1974; Rockwell and Enneking 1971; Sanerkin and Woods 1979). A retrospective examination of the illustrations in these reports suggests to us that most express morphologic patterns like those of MFH, a conclusion also reached by other investigators (McCarthy and Dorfman 1982). Our own case material further supports this opinion.

It has become evident that a malignant fibrous histiocytoma-like morphologic appearance represents the "final common pathway" of other osseous and soft tissue tumors undergoing anaplastic transformation. Well-differentiated liposarcoma, synovial sarcoma, leiomyosarcoma, and chordoma are all capable of exhibiting such dedifferentiation (Brooks 1986; Hashimoto et al. 1986; Volpe and Mazabraud 1983). Recent data presented by Brooks (1986) support the contention that these lesions with divergent microscopic patterns also manifest dissimilar immunophenotypic profiles, with the expression of antigens associated with "fibrohistiocytic" proliferations. We initiated this study in an attempt to verify these observations immunocytochemically, and to determine whether any antigenic differences could be ascertained between DCS and de novo MFH.

The observed expression of alpha-1-antichymotrypsin, with or without alpha-1-antitrypsin, by the anaplastic components of DCS is in accord with the premise that they display "fibrohistiocytic" differentiation. With the exception of some epithelial neoplasms (Tahara et al. 1984), these enzymatic antigens are expressed by restricted mesenchymal cellular proliferations such as dermatofibrosarcoma protuberans, MFH, giant cell tumor of tendon sheath and nodular tenosynovitis, and malignant histiocytosis (duBoulay 1982; Kindblom et al. 1982; Meister et al. 1980; Meister and Nathrath 1981; Roholl et al. 1985a). The binding of peanut agglutinin by the tumor cells, with a combination of globular cytoplasmic and membranous positivity, has a similar association (Howard and Batsakis 1982; Roholl et al. 1985a). These immunocytochemical and histochemical features were not shared by examples of fibrosarcoma and osteosarcoma included in our study, and the unlikely possibility that the anaplastic components of DCS were epithelial was negated by their failure to react with antibodies to cytokeratin and epithelial membrane antigen (Gown and Vogel 1985; Pinkus and Kurtin 1985). Whether the cells of MFH are, in fact, histogenetically related to monocytes/histiocytes in a controversial topic (Roholl et al. 1985b; Wood et al. 1986; Strauchen and Dimitriu-Bona 1986).

It is our opinion that tumor-positivity for alpha-1-antitrypsin or alpha-1-antichymotrypsin

should not be equated with histiocytic differentiation in the absence of other data; however, our results do indicate that such determinants are of practical use in the diagnosis of fibro-"histiocytic" neoplasms in paraffin sections. Two caveats further pertain to this matter. First, tissue processing has a distinct impact on antibody reactivities, and the observations of this study thus may be dissimilar from others obtained with frozen tissue specimens (Löning et al. 1985; Roholl et al. 1985; Strauchen and Dimitriu-Bona 1986). Secondly, one must be careful to distinguish between the immunohistochemical reactivities of neoplastic and reactive cells, the latter of which may be abundant in some bone and soft tissue sarcomas.

We were able to detect some dissimilarities between the immunostaining profiles of DCS and de novo MFH. Nine of 10 primary examples of the former tumor contained scattered cells that were reactive for S100 protein, as detected by a polyclonal antiserum. Staining results with a monoclonal antibody to this protein (Loeffel et al. 1985) were less universally positive, but 57% of DCS cases did display reactivity in their high-grade components. Regardless of whether the rabbit antibody detected a cross-reacting antigen, or alternately, possessed greater sensitivity for S100 than its monoclonal counterpart, these data were not reproduced in the control group of malignant fibrous histiocytomas that arose ab initio. The affinity of tumor cells for wheat germ agglutinin also differed in these two lesions, in that it was only detected in DCS. The pattern of reactivity with this lectin, that of perinuclear cytoplasmic positivity, has been described in cells of the developing cartilaginous growth plate (Farnum and Wilsman 1984). Hence, the sum of these results suggests that the anaplastic portion of DCS retains some markers seen in cartilage and conventional chondrosarcomas (S100 and wheat germ agglutinin-reactivity (Farnum and Wilsman 1984; Kahn et al. 1983; Nakamura et al. 1983), while otherwise acquiring the immunohistochemical characteristics of MFH. This may involve the evolution of a second distinct neoplastic cellular clone with more primitive attributes (Brooks 1986).

Our results do not, of course, exclude the possibility that still other lines of differentiation may be expressed by DCS. Recent reports have convincingly demonstrated a rhabdomyosarcomatous component in such tumors, both in primary osseous lesions and their metastases (Astorino and Tesluk 1985; Têtu et al. 1986). We observed no microscopic evidence for such a transformation in our material; the desmin-reactivity present in 5 of our cases was seen in atypical spindle cells that lacked the morphologic features of rhabdomyoblasts. Whether or not these elements instead displayed smooth muscular differentiation is a matter of speculation, since specimens for ultrastructural studies were not available.

In summary, the paraffin-section immunophenotyping data generated in this study support the contention that the anaplastic portion of dedifferentiated chondrosarcoma displays "fibrohistiocytic" characteristics, and differs in this respect from de novo fibrosarcoma, osteosarcoma, and conventional chondrosarcoma. In addition, however, rare anaplastic cells of primary DCS appear to express markers that are shared by cartilaginous cells and tumors, such as S100 protein and wheat germ agglutinin receptors. These determinants are not found in de novo malignant fibrous histiocytomas.

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