FULL PAPER
Pathology

Malignant Histiocytosis in Cattle

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ABSTRACT. Malignant histiocytosis was diagnosed in 4 cows. In all cases the tumor tissues were composed of cytologically atypical histiocytes with evidence of erythrophagocytosis. The tumor in case 1 appeared highly anaplastic with marked nuclear pleomorphism, and had areas of spindle cell differentiation, but had no relation to malignant fibrous histiocytoma. The neoplastic tissue in case 2, characterized by cohesive growth of tumor cells, was distinguishable from anaplastic carcinoma cells by cytokeratin immunostaining. There were many hemosiderin-laden neoplastic cells suggestive of high phagocytic activity in a lymph node of case 3. The neoplastic cells in case 4, frequently multinucleated, were less atypical than in the other cases. All cases expressed histiocyte-associated markers (lysozyme and HAM56), and were negative for cytokeratin, S100, and T- and B-cell lineage-specific markers (CD3 and CD79a). The most frequent HAM56 immunoreactivity was detected in case 4, and the giant, multinucleated forms, reminiscent of epithelioid cell differentiation, seemed not to indicate cytological pleomorphism as a result of neoplastic transformation.

KEY WORDS: bovine, erythrophagocytosis, HAM56, histiocytic marker, malignant histiocytosis.

Malignant histiocytosis is a rare disorder characterized by systemic progressive invasive proliferation of morphologically atypical histiocytes and their precursors [16]. This disease has been reported in human beings [1] and dogs [15], and only a few other cases have been recorded in cats [2, 4] and a filly [10]. Its histiocyctic nature was demonstrated by erythrophagocytosis and/or immunohistochemistry for lysozyme [13]. Here we describe the morphological and immunohistological characteristics of 4 cases of bovine malignant histiocytosis.

RESULTS

The clinical histories of the 4 cows, and gross pathological findings, are summarized in Table 1. The most noticeable gross feature was enlargement of lymph nodes. The bone marrow was not investigated in any cases.

Histological findings: In all cases, neoplastic cells proliferated mainly within lymphatic sinuses of the enlarged lymph nodes. The nodal architecture was effaced but groups of residual lymphocytes were detected in places (Fig. 1). There were many necrotic foci or widespread areas of necrosis in 3 cases. The neoplastic cells in the remaining case (case 3) were often pyknotic or necrotic but did not form distinct areas of necrosis. The neoplastic cells in the remaining case (case 3) were often pyknotic or necrotic but did not form distinct areas of necrosis. Although present in noncohesive sheets in 3 cases, the tumor cells tended to form closely packed masses in case 2 (Fig. 2). The large tumor masses in cases 2 and 3 were lymph nodes, the architecture of which was almost completely replaced by tumor cells. In case 4, the spleen was displaced by tumor tissue, and neoplastic cells were found in unencapsulated masses in the liver. Several tumor cells were also detected in hepatic sinusoids, and some were in the lumina of alveolar capillaries.

The tumor in case 1 was exceedingly anaplastic, the cells being large or very large with great variations. The nuclei were vesicular and frequently irregular or binuclear, with prominent nucleoli. Nuclear pleomorphism was marked, and larger cells tended to have larger nuclei. The cytoplasm was...
eosinophilic and abundant, and phagocytosed erythrocytes and their remnants looking like hyaline droplets were easily recognized, especially in hemorrhagic foci (Fig. 3). Phagocytosis of small lymphocytes or neutrophils was rare, and mitotic figures were numerous. In parts, the tumor cells showed transition into spindle-shaped cells (Fig. 4).

In case 2, the neoplastic cells resembled those in case 1, but were somewhat less atypical and pleomorphic. Some cells had prominent nucleoli, and cells showing erythropagia were few. In case 3, the tumor was moderately anaplastic, resembling a large cell lymphoma (Fig. 5). Larger tumor cells contained 2 to 5 bizarrely shaped nuclei, which were usually similar in size and shape to those of mononuclear cells. Erythrophagocytosis was infrequent, but many tumor cells containing hemosiderin deposits were present in a lymph node (Fig. 6). The tumor in case 4 appeared to be well differentiated, but atypical nuclei were confirmed in some of the tumor cells. Multinucleated giant cells were often observed (Fig. 7). Occasional tumor cells phagocytosed red blood cells, hemosiderin, neutrophils, smaller tumor cells or lymphocytes (Fig. 8). There were frequent mitoses, including abnormal forms.

Immunohistochemistry: Many histiocytoid cells in cases 1 and 2 were positive for lysozyme, whereas almost all showed positivity in the other cases (Fig. 9). The spindled cells in case 1 exhibited occasional reactivity. All 4 cases showed positive staining for HAM56, and the number of cells showing immunoreactivity varied. The order of frequency was as follows: cases 4, 3, 1 (histiocytic), 2, and 1 (spindled).

Although readily discernible in the former 3 (Figs. 10-12), HAM56-positive cells were rare in case 2 and extremely rare in case 1 (spindled). There were several MAC387-positive cells in case 4, while no tumor cells bore this marker in the others. None of the neoplastic cells in any case stained for CD3, CD79a, S100, cytokeratin or SMA.

DISCUSSION

Malignant histiocytosis is morphologically characterized by phagocytosis, especially of red blood cells, by tumor cells, but this phenomenon is not usually a conspicuous feature in human beings [3], and has been observed in other hematopoietic neoplasms, such as monocytic leukemia, myeloblastic leukemia [5] and plasmacytoma [7]. Erythrophagocytosis was seen also in bovine monocytic [12] and myeloblastic [18, 19] leukemias, which had morphological features of immature monocytes and granulocytes, respectively, and which were quite unlike malignant histiocytosis. In our study, many hemosiderin-laden tumor cells were seen in case 3, and fair numbers of tumor cells showed erythrophagocytosis in hemorrhagic foci in case 1. These findings suggest that the tumor cells are highly phagocytic in bovine malignant histiocytosis, though this was inconspicuous in lesions lacking hemorrhage.

In human beings, staining for lysozyme is considered useful for the detection of cells of the myeloid and histiocytic series [20]. However, the presence of lysozyme is not specific for histiocytes, and there is no single immunopheno-
typic marker that identifies a cell as a histiocyte [1]. In this study we utilized not only lysozyme but also HAM56 and MAC387 as histiocyte markers, and all cases expressed lysozyme and HAM56 positivity. In addition, CD3, CD79a,
S100 and keratin staining was performed in order to differentiate malignant histiocytosis from large cell lymphoma, antigen-presenting cell tumors and anaplastic carcinoma [9], and these markers were entirely absent. Based on such immuno-
histochemical findings, the diagnosis of malignant histiocytosis was established.

Although there were many multinucleated giant cells in case 4, the neoplastic cells were less atypical than those in the other 3 cases, and showed the most frequent HAM56 positivity. The multinuclear giant cells seemed to be malignant counterparts of epithelioid cells, and not to be due to cytological pleomorphism. Traditional histiocytic markers such as lysozyme and alpha-1-antitrypsin are often positive in human histiocytic neoplasms, particularly among better differentiated cells [20]. In all our cases, great numbers of histiocyte-like tumor cells were positive for lysozyme, whereas the proportion of HAM56-positive cells tended to be higher in better differentiated neoplasms. A combination of staining for lysozyme and HAM56 may be helpful in confirming the histiocytic nature in bovine histiocytic neoplasms.

In bovine malignant fibrous histiocytoma, myofibroblastic differentiation was demonstrated by electron microscopy [17], and the myofibroblastoid element presumably stains positively for SMA [6]. In another case, the neoplastic cells showed no staining for lysozyme [14]. Spindle-shaped neoplastic cells, which displayed positivity for lysozyme and HAM56 but not for SMA, were present in case 1, and apparently differed from those of malignant fibrous histiocytoma. These cells could be interpreted as showing spindle cell metaplasia or spindle cell sarcoma-like change, which has been observed in human malignant histiocytosis cases [11] or true histiocytic lymphomas [1]. In contrast to the report of canine cases with features of both malignant histiocytosis and malignant fibrous histiocytoma [8], the view that malignant fibrous histiocytoma is not associated with histiocytes is dominant in human medicine [21].
REFERENCES


