A Correlative Cytologic and Histologic Study of Malignant Fibrous Histiocytoma: An Analysis of 40 Cases Examined by Fine-Needle Aspiration Cytology
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A correlative cytologic and histologic study of 40 cases of histologically highly pleomorphic malignant fibrous histiocytoma (MFH) is presented. The fine-needle aspiration biopsy was performed preoperatively, and a diagnosis of malignant soft-tissue tumor could be established in all cases. The cytologic and histologic features corresponded well with each other. The two main cell types were mono- and multinucleated, large polymorphic, often bizarre, histiocyte-like cells and atypical fibroblast-like cells. For a correct diagnosis of pleomorphic MFH, it is important to recognize atypical large polymorphic tumor cells showing signs of phagocytosis: prominent cytoplasmic vacuolization, cell debris or even well-preserved cells within the tumor cell cytoplasm. Phagocytic activity was easily demonstrated in air-dried and May-Grünwald Giemsa-stained material. The differential diagnosis of MFH as opposed to other soft-tissue sarcomas and pleomorphic carcinomas is discussed. Diagn Cytopathol 1986;2:46–54.

Key Words: Fine-needle aspiration cytology; Sarcoma; Soft-tissue tumor; Malignant fibrous histiocytoma

Malignant fibrous histiocytoma (MFH) is the most common soft-tissue sarcoma.1,2 MFH has a broad cellular spectrum and is characterized by varying proportions of fibroblast- and histiocyte-like cells.3–4 The pleomorphic variant of MFH3 is composed of elongated fibroblast-like and round, ovoid, or polygonal histiocyte-like cells, often arranged in a storiform and fascicular pattern, and accompanied by large, polymorphic uni- and multinucleated (pleomorphic) tumor cells and inflammatory cells. This is the most common variant of MFH. Another variant of MFH is predominantly myxoid but has, in principle, the same appearance as the pleomorphic variant. It is described as a myxoid variant of MFH5 or myxofibrosarcoma of high grade.6 Low-grade myxofibrosarcomas have a less polymorphic appearance and consist predominantly of fibroblast-like cells.7 An inflammatory type,8 a giant-cell variant,9,10 and an angiomatoid type of MFH11,12 have also been described.

The appearance in cytology of the myxoid variant as well as the giant-cell variant of MFH has been described previously.13,14 Only single cases or very small series of the pleomorphic variant have been reported.15–21

The aim of this investigation was to describe the cytologic findings in a large series of histologically highly malignant, pleomorphic fibrous histiocytomas in order to define the cytologic criteria for its preoperative diagnosis.

Materials and Methods
Forty cases of highly malignant pleomorphic malignant fibrous histiocytoma with preoperative cytologic material were studied. They were obtained from the National Swedish Series of soft-tissue sarcomas reported to the Swedish Cancer Registry between 1958 and 1965 and from the files of the laboratory of clinical cytology, Sahlgren Hospital, Göteborg, for the years 1964–1984. Clinical histories were obtained from the hospitals where the patients had been treated.

Histologic Methods
Four- to five-micron sections were cut from paraffin blocks and stained with hematoxylin and eosin (H&E) and according to van Gieson's trichrome method. The silver impregnation technique according to Gordon and Sweet was used to demonstrate reticulin and the periodic acid-Schiff reaction (PAS) according to McManus was used for the demonstration of glycogen and other glycogens. In
selected cases Sudan black B was used to demonstrate fat, and Prussian blue was used for hemosiderin.

**Cytologic Methods**

In all cases a fine-needle (diameter, 0.6-0.7 mm; 23-22 gauge) aspiration biopsy had been done before the surgery for the primary or recurrent tumor. The content of the syringe was deposited on glass slides as cell smears, then air-dried and stained according to the May-Grunwald Giemsa method (MGG). In seven cases, alcohol-fixed smears were stained according to the Papanicolaou method.

**Results**

**Clinical Data**

The most pertinent data are summarized in Table I and Fig. 1. The mean age of the 17 women was 67 yr, while the mean age of the 23 men was 64 yr (range, 31-88 yr). In most patients, the tumor had produced symptoms for some months. Only a few patients had had symptoms for more than 1 yr or less than 1 mo. All patients were surgically treated, and some patients were given postoperative x-ray treatment and/or adjuvant chemotherapy. The tumors recurred in 27 patients between 1 and 53 mo after surgery. Twenty-three patients died from metastasis within a time period of a few months to more than 6 yr after the primary operation. Seventeen patients are still alive with a follow-up period of from 1 to 63 mo after the primary operation.

**Tumor Location and Gross Findings**

The most frequent tumor sites were the thighs, back, and buttocks (27 cases; Table I). The tumor size varied from about 3 to 20 cm. Eighteen tumors were 10 cm or larger in diameter. At gross examination, the tumors often appeared circumscribed. The tumors were often lobulated and showed white, firm-to-soft friable yellow cut surfaces. In 30 of the 40 cases, necrotic and hemorrhagic areas were seen. Nine of the 40 cases were partly cystic.

**Histologic Findings**

The malignant fibrous histiocytomas were all of high-grade malignancy (grade III-IV). They characteristically showed cosinophilic, polymorphic histiocyte-like cells and fibroblast-like cells haphazardly arranged or in a storiform or fascicular pattern (Figs. 2-4). In addition to the dominating mononuclear cells, there were many large polymorphic multinucleated giant cells (Fig. 5). The nuclei of the giant cells showed one or several large prominent nucleoli. There were also multinucleated tumor cells resembling Touton's giant cells. Many of the large polymorphic cells showed phagocytic activity and contained ingested cells, cell debris, and vacuoles. Often, xanthoma cells were seen, both atypical forms and cells resembling benign and reactive lipid-loaded foam cells. The amount of hemosiderin in histiocyte-like tumor cells varied from tumor to tumor. Fat stains showed that there were mononucleated, as well as multinucleated, giant cells that contained small lipid droplets. Cytoplasmic hyaline, cosinophilic, and PAS-positive globules were occasionally seen in histiocyte-like tumor cells (Fig. 6). The mitotic activity was generally high, and atypical mitoses were common (Fig. 5).

Reticulin fibers encircling individual cells were seen in silver-impregnated sections. Inflammatory cells, lymphocytes, and plasma cells were present in varying amounts. Granulocytes occurred preferentially in or near necrotic areas. All cases could be classified as storiform-pleomorphic according to Enzinger and Weiss (1983), and no case was a myxoid (myxofibrosarcoma), giant-cell, angiomaticoid, or inflammatory variant of MFH.

![Fig. 1. Sex and age distribution in 40 patients with malignant fibrous histiocytoma.](image-url)
Fig. 2. Malignant fibrous histiocytoma showing storiform pattern with mono- and multinucleated tumor cells. Many of the mononucleated cells are fibroblast-like (H&E, x 125).

Fig. 3. Tumor area in MFH dominated by fibroblast-like tumor cells with a few giant cells (H&E, x 200).

Fig. 4. Tumor area in MFH dominated by histiocyte-like tumor cells with one or more nucleoli in vesicular nuclei (H&E, x 200).
Cytologic Findings

In general, the material was cellular, but occasional cases were dominated by tissue fluid, necroses, and/or blood. In six cases, the tumors gave the impression of a cyst or an abscess at fine-needle aspiration because the aspirated material was mainly fluid. In the smears, however, the material was representative of the tumor.

The background frequently contained fibrillar mucous material, occasionally accompanied by capillary fragments and collagen fibers. The main cell constituents were atypical mono-, bi-, and multinucleated, sometimes bizarre, histiocyte-like and plump spindle-formed fibroblast-like cells (Figs. C-7 and C-8). Relatively small mononucleated, finely vacuolated xanthoma cells could be seen cytologically in about half the cases. It was often difficult to decide whether these cells were neoplastic.

Large, atypical, mono-, bi-, or multinucleated histiocyte-like cells were predominant in most cases. They occurred singly or in small unorganized groups. Tightly cohesive fascicles were not seen. The cells tended to be rounded but showed an extreme variation in size and shape (Figs. C-8–C-10).

All types of histiocyte-like cells showed indistinct cell borders and contained vacuoles and/or ingested material such as cell debris or even whole, presumably phagocytized, cells (Figs. C-11 and C-12). Sometimes the cytoplasm contained scattered acidophilic granules (Figs. C-9 and C-10). Large intracytoplasmic hyaline structures were seen in three of 40 cases (Fig. C-10). The nuclear atypia was generally pronounced in these tumor cells. The nuclei were single or multiple and polymorphous. They showed one or more nucleoli, which were often very large (Figs. C-11 and C-12). Nuclear “moulding” was also seen with several nuclei merging into one. The nuclear chromatin was clumped together and unevenly distributed. In two cases, there were nuclear impressions from cytoplasmic vacuoles, similar to that seen in liposarcomas.

Apart from histiocyte-like tumor giant cells, there were characteristic Touton-like giant cells in 24 of 40 cases (Fig. C-13). Osteoclast-like cells with several benign-looking nuclei were not observed except in aspirations from metastases in two cases, in which the primary tumors did not contain this element.

The fibroblast-like cells occurred singly or in clusters, but they seldom formed fascicles (four of 40 cases). In general, the fibroblast-like cells were less polymorphic than the histiocyte-like cells. They were elongated, spindle-shaped, and had a slender nucleus with tapering ends (Fig C-7). The cytoplasm, which stained an even blue in MGG, often had indistinct outlines in the smears. The nuclei had a coarse chromatin pattern and sometimes contained one or more nucleoli. Compared with normal...
Fig. C-7. Air-dried aspiration smear from malignant fibrous histiocytoma. The cellular part shows predominantly fibroblast-like cells with relatively slight anisokaryosis. One multinucleated giant cell is seen at the lower right (MGG, × 800).

Fig. C-8. Large histiocyte-like cells with hyperchromatic nuclei; the cytoplasm is vacuolated. Intermediate cell forms are seen (MGG, × 800).

Fig. C-9. Large spindle-formed histiocyte-like tumor cell. The cytoplasm is vacuolated and contains an abundance of acidophilic granules (MGG, × 1200).

Fig. C-10. Histiocyte-like tumor cell; the cytoplasm is vacuolated and contains a large hyaline structure in addition to acidophilic granules (MGG, × 2000).
Fig. C-11. Bizarre tumor giant cell with multiple prominent nucleoli. The cytoplasm contains cell debris, which is probably phagocytized material (MGG, × 1,200). Fig. C-12. Large tumor cell showing signs of phagocytosis with cell debris and even whole cells within the cytoplasm (MGG, × 800). Fig. C-13. Multinucleated giant cell similar to Touton's giant cell (MGG, × 800). Fig. C-14. Atypical mitosis in a histiocyte-like tumor cell (MGG, × 1200).
fibroblasts, these cells had an increased nuclear:cytoplasmic ratio and polymorphic, abnormal nuclei.

Mitoses, typical and atypical, were observed in all cell types, even in giant cells (Fig. C-14). The number of admixed inflammatory cells varied greatly, corresponding to the histologic findings.

Giemsa-stained smears were superior to Papanicolaou-stained ones, in the seven cases in which both stains were used, in demonstrating cytoplasmic details like vacuoles, granules, and ingested cell material. Stromal elements were also more easily identified in Giemsa-stained smears. The nuclear details could be seen in both types of staining.

The cellular atypia found at the cytologic examination led to the initial preoperative diagnosis of malignant tumor in all of the cases (Table II).

**Discussion**

All of the tumors in the present series were highly malignant and pleomorphic and can be classified as storiform-pleomorphic variants of malignant fibrous histiocytoma. Histologically, their main components were mono- and multinucleated large polymorphic (pleomorphic) histioyte-like cells, which were sometimes xanthomatous, and atypical fibroblast-like spindle cells. The tumor cells were often characteristic ally arranged in a storiform or fascicular pattern and accompanied focally by inflammatory cells.

| Case number | Primary cytologic diagnosis | Primary histologic diagnosis | Year of diagnosis |
|-------------|----------------------------|-----------------------------|------------------|
| 1 | Sarcoma (neurofibrosarcoma? liposarcoma?) | Rhabdomyosarcoma, pleomorphic type | 1964 |
| 2 | Malignant soft-tissue tumor, nos | Malignant fibrosarcoma | 1969 |
| 3 | Malignant soft-tissue tumor, angiofibrosarcoma | Sarcoma; leiomyosarcoma | 1969 |
| 4 | Malignant soft-tissue tumor | Rhabdomyosarcoma, nos | 1971 |
| 5 | Poorly differentiated malignant tumor, probably rhabdomyosarcoma | Rhabdomyosarcoma, alveolar type | 1971 |
| 6 | Malignant soft-tissue tumor, nos | Rhabdomyosarcoma, pleomorphic type | 1971 |
| 7 | Liposarcoma, pleomorphic type | Liposarcoma, pleomorphic type | 1972 |
| 8 | Sarcoma, neurofibrosarcoma? | Neurofibrosarcoma | 1972 |
| 9 | Sarcoma, nos | Rhabdomyosarcoma or myxosarcoma | 1973 |
| 10 | Liposarcoma, myxoid type | MFH | 1974 |
| 11 | Malignant, pleomorphic soft-tissue tumor | Malignant fibroxanthoma | 1974 |
| 12 | Sarcoma, nos | Sarcoma, poorly differentiated, probably neurofibrosarcoma | 1975 |
| 13 | Sarcoma, nos | MFH | 1975 |
| 14 | Malignant soft-tissue tumor; probably rhabdomyosarcoma | Leiomysarcoma | 1975 |
| 15 | Malignant soft-tissue tumor; pleomorphic liposarcoma? | MFH | 1976 |
| 16 | Malignant soft-tissue tumor, nos | Rhabdomyosarcoma | 1977 |
| 17 | Malignant soft-tissue tumor, nos | MFH | 1978 |
| 18 | Malignant soft-tissue tumor, nos | Leiomysarcoma, poorly differentiated | 1979 |
| 19 | MFH | MFH | 1979 |
| 20 | Malignant soft-tissue tumor, probably rhabdomyosarcoma | MFH | 1980 |
| 21 | MFH | MFH | 1980 |
| 22 | MFH | MFH | 1980 |
| 23 | Poorly differentiated sarcoma, probably MFH | MFH | 1980 |
| 24 | MFH | MFH | 1981 |
| 25 | MFH | MFH | 1981 |
| 26 | MFH | MFH | 1981 |
| 27 | MFH | MFH | 1981 |
| 28 | MFH | MFH | 1982 |
| 29 | MFH | MFH | 1982 |
| 30 | MFH | MFH | 1982 |
| 31 | MFH | MFH | 1982 |
| 32 | MFH | MFH | 1982 |
| 33 | MFH | MFH | 1983 |
| 34 | MFH | MFH | 1983 |
| 35 | MFH | MFH | 1984 |
| 36 | MFH | MFH | 1984 |
| 37 | MFH | MFH | 1984 |
| 38 | MFH | MFH | 1984 |
| 39 | MFH | MFH | 1984 |
| 40 | MFH | MFH | 1984 |
The smears indicated a malignant tumor in all cases. The cytologic specimens were generally highly cellular, and the findings corresponded well with the histology; atypical mono- and multinucleated histiocyte-like tumor cells were predominant, but atypical fibroblast-like cells were also common. Both the cell types and the extreme polymorphism among the tumor cells correspond well with the findings of other authors in case reports and small series.\textsuperscript{15-19}

The tumor cells showed morphologic evidence of histiocytic differentiation, such as vacuolization, granulation, and ingested material. The acidophilic cytoplasmic granules may represent lysosomal structures, similar to the larger acidophilic bodies (Figs. 6 and C-10) seen cytologically as well as in histopathology and electron microscopy.\textsuperscript{23} In all cases, the atypical histiocyte-like cells contained cell debris, and in about half the cases, they contained well-preserved entire cells within the cytoplasm. These observations were more easily made in air-dried and Giemsa-stained smears than in alcohol-fixed and Papanicolaou-stained smears and were well demonstrated in cases where both types of material were available. Special stains for macrophage enzyme activity (e.g., muramidase) were not used in our series.

Benign-looking osteoclast-like giant cells were rare in the cytologic material from the primary tumors. In two cases, however, aspirated material from the metastases contained many osteoclast-like giant cells while the primary tumors showed none. These observations indicate that it is difficult to maintain a distinction between different subvariants of highly pleomorphic MFH.

Several differential diagnostic problems can make the evaluation of this tumor difficult. In principle, the large pleomorphic histiocyte-like cells had the same cytologic appearance as those described in high grade (III-IV) myxofibrosarcoma\textsuperscript{13} and giant-cell tumor of soft tissue.\textsuperscript{14} Myxofibrosarcomas contain abundant mucoid material and arborized capillaries.\textsuperscript{13} Such elements were also present in some of the tumors in this series, but they were never predominant. Malignant giant-cell tumors of the soft tissue exhibit benign multinucleated giant cells of osteoelastic type, which are not present in MFH.\textsuperscript{14}

Differential diagnoses, other than variants of MFH, consist primarily of pleomorphic soft-tissue sarcomas. The most important cytologic criterion for a correct diagnosis of the pleomorphic variant of malignant fibrous histiocytoma is the recognition of atypical large polymorphic histiocyte-like cells that show signs of phagocytosis. Such tumor cells probably do not form part of any other soft-tissue tumor.

Pleomorphic liposarcomas may show patterns very similar to those seen in malignant fibrous histiocytomas.\textsuperscript{2} Atypical multivacuolated lipoblasts constitute the main diagnostic criterion for liposarcomas both histologically and cytologically.\textsuperscript{22} In two of the cases in this series, multivacuolated tumor cells similar to atypical lipoblasts were observed. However, in both of these cases, the cells also showed signs of phagocytic activity, favoring the MFH diagnosis.

Soft-tissue sarcomas showing areas of dedifferentiation may rarely mimic malignant fibrous histiocytoma histologically; these include, beside liposarcoma, extrasosseous osteosarcoma, chondrosarcoma, malignant schwannoma, and leiomyosarcoma.\textsuperscript{2} Little has been published on the cytology of extraskeletal osteosarcoma and chondrosarcoma, but the finding of osteoid and chondroid structures may help to establish the correct diagnosis. Cytologically, leiomyosarcomas\textsuperscript{24} show a fascicular arrangement of spindle cells that is not seen in MFH. Furthermore, the large polymorphic tumor cells that can appear cytologically in leiomyosarcomas do not show any evidence of phagocytosis.\textsuperscript{24}

Most authors mention pleomorphic rhabdomyosarcoma as an important cytologic differential diagnosis.\textsuperscript{15,16,19} According to Enzinger and Weiss,\textsuperscript{2} pleomorphic rhabdomyosarcoma in adult patients is an exceedingly rare tumor, and the presence of longitudinal striation in some tumor cells is not sufficient evidence of rhabdomyoblastic differentiation. Cross-striation by light microscopy and/or characteristic ultrastructural findings or specific tumor markers are necessary to establish the diagnosis.\textsuperscript{2} Alveolar rhabdomyosarcoma has been described in a correlative histologic and cytologic study;\textsuperscript{25} however, the tumor does not resemble MFH.

Pleomorphic (large-cell, polymorphic) carcinomas may also constitute a differential diagnostic problem of MFH, histologically as well as cytologically.\textsuperscript{3,33,34} However, tumor cell phagocytosis to the extent seen in MFH is rarely, if ever, a feature of pleomorphic large-cell carcinomas. In addition, carcinoma cells tend to occur cytologically in sheets and clusters, which are not seen in MFH. Furthermore, carcinomas seldom obtain the extreme cell variation that is characteristic of MFH.

We consider special stains for fat of very little value for differential diagnostic purposes, because fat can appear in several types of malignant tumor cell, e.g., in tumor cells of carcinomas, liposarcomas, and malignant fibrous histiocytomas.\textsuperscript{3,6} It can also occur as a degenerative phenomenon in many neoplastic cell types.

To summarize, this study emphasizes that the most important diagnostic criterion of MFH in cytology is the demonstration of atypical large polymorphic (pleomorphic) histiocyte-like cells. They are mono-, bi- or multinucleated, often bizarre, and show prominent signs of phagocytosis indicating their histiocytic differentiation. The other main cell component in MFH is atypical fibroblast-
like cells, which may resemble the tumor cells in other spindle-cell sarcomas. All components must be taken into consideration, but large polymorphic multinucleated phagocytic tumor cells are the most characteristic feature of MFH and help to rule out other pleomorphic soft-tissue sarcomas.

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