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*Original Article*

# Malignant fibrous histiocytoma of visceral organs: clinicopathologic features and diagnostic value of ezrin and HMG-CoA reductase

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**Abstract:** Malignant fibrous histiocytoma (MFH) of the breast and visceral organs is extremely rare. There is an incomplete understanding of the clinical pathology of the primary MFH originating from the breast and visceral organs, especially in comparison with other soft tissue sarcomas. As a consequence we searched and analyzed the clinical and pathological records of all the nine patients with diagnosed breast and visceral MFH in our hospital. Immunohistochemical staining was performed for ezrin and HMG-CoA reductase in these MFH cases and relevant mesenchymal sarcomas. The 9 MFH cases presented with nonspecific symptoms and imaging manifestations. 6 cases were classified as storiform-pleomorphic MFH, 2 cases as inflammatory MFH, and the remaining 1 case as giant cell MFH. The results showed that ezrin expression, as well as HMG-CoA reductase expression, was significantly stronger in MFH cases than other non-MFH sarcomas. Poor prognosis seemed to be associated with younger age. Certain characteristics and clinicopathologic features can help us making the diagnosis of MFH. In conclusion, our study provided the potential value of ezrin and HMG-CoA reductase for diagnosis and differential diagnosis of MFH located in the breast and visceral organs. More accurate prognostic information of this rare disease needed to be further investigated.

**Keywords:** Malignant fibrous histiocytoma, visceral organs, breast, ezrin, HMG-CoA reductase

## Introduction

Malignant fibrous histiocytoma (MFH) was first described by O'Brien and Stout in 1964 [1], and has generally been regarded as one of the most common soft tissue sarcomas in adults [2]. The most frequent primary sites of MFH are the extremities, and less commonly the retroperitoneal spaces, abdominal cavity, or other sites [3]. MFH has been considered to originate from undifferentiated mesenchymal cells capable of multidirectional differentiation [4]. For many years, it accounted for more than 30% of all soft tissue sarcomas. However, with the development of immunochemistry, the number of cases defined as MFH has declined. Nowadays, the histogenesis of MFH still remains controversial, and the term is reserved for a small group of sarcomas which, by current technology, shows no definable line of differentiation, accounting for no more than 5% of adult soft tissue sarcomas [5]. According to the 2002 edition WHO classification of soft tissue tumors, MFH can be categorized into three morphological subtypes: storiform-pleomorphic MFH (undifferentiated high-grade pleomorphic sarcoma), giant cell MFH (undifferentiated pleomorphic sarcoma with giant cells), and inflammatory MFH (undifferentiated pleomorphic sarcoma with prominent inflammation).

Primary MFH located in the breast and visceral organs, such as the liver, pancreas, esophagus, lung, and so on, are extremely rare. There is an

unclear understanding of the clinical pathology of the primary MFH originating from the breast and visceral organs, especially in comparison with other MFH from the soft tissue, other non-MFH soft tissue sarcomas, and with the more common primary carcinomas of the breast and visceral organs. Hence for diagnosis, primary MFH needs to be distinguished with undifferentiated carcinomas and other sarcomas with a similar degree of cellular pleomorphism.

Ezrin, a novel cytoskeleton linker protein, has been reported to be actively involved in regulating cellular growth and metastatic potential of various types of malignant carcinomas and sarcomas, including soft tissue MFH [6-8]. An *in vitro* study performed in hepatocellular carcinoma cells showed that inhibition of Rho kinase resulted in a blockade of Ezrin phosphorylation, implicating Rho kinase-ezrin signaling in hepatocellular carcinoma cell invasion [9]. Statins, an inhibitor of the hepatic 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, inhibit Rho activation and have been shown, for example in an *in vitro* model of pancreatic cancer invasiveness, to prevent cancer cell invasion [10]. And based on lots of epidemiological studies, including meta-analysis, statins use is associated with reduced risk of various malignancies, such as hepatocellular cancer, colorectal cancer, esophageal cancer and so on [11-13]. So we wonder whether statins can reduce the risk of soft tissue sarcomas, including MFH, through Rho kinase-ezrin signaling.

In the past decade, there were 10 diagnosed MFH cases located in the breast and visceral organs in our hospital. Here in our article we described the clinical manifestations, imaging, histological features, immunohistochemistry, and follow-up data of all the cases. Immunohistochemical staining of ezrin and HMG-CoA reductase were also performed to confirm their diagnostic and prognostic value in MFH from different organs. We aimed to provide a better understanding of the clinicopathologic characteristics of this rare malignancy from the breast and various visceral organs with an emphasis on its diagnosis and differential diagnosis.

## Materials and methods

### *Ethics statement*

The research was approved by the local Ethics Committee (the Ethics Committee of Nanjing Drum Tower Hospital the Affiliated Hospital of Nanjing University Medical School). Each patient involved in the study provided the written consent. Our ethics committee was formally responsible for ensuring that informed written consent was obtained from each involved patient. In addition, the committee approved the informed consent forms and specimen collection procedures.

### *Diagnostic criteria*

The following clinicopathologic criteria were used to define MFH located in the breast or visceral organs: (1) detected solitary or multifocal neoplasm; (2) histologically compatible with the spectrum of soft tissue MFH; (3) immunohistochemical evidence of mesenchymal differentiation (vimentin positive, keratins negative) with < 5% of tumor cells indicating any well-defined line of derivation.

### *Study design*

Clinical records of all the 9 patients with diagnosed MFH treated from 2003 to 2013 at Nanjing Drum Tower Hospital of Nanjing University Medical School were reviewed, of which one was pulmonary metastatic MFH from the breast. Routine examinations (physical examination, blood tests, ultrasonography, CT and/or MRI) and relevant tumor marker tests had been carried out. After we selected the cases, the diagnosis was pathologically confirmed by two pathologists (S.J. & Y.J.). Clinical, radiologic, and follow-up data were retrieved from medical records and communication with attending surgeons or physicians.

Immunohistochemical staining was performed on 4 μm thick sections cut from the formalin-fixed, paraffin-embedded blocks from the 9 selected cases using a panel of commercially available antibodies including ezrin and HMG-CoA reductase. Color was developed by streptavidin-biotin-peroxidase technique using 3'-diaminobenzidine as the chromogen. Appropriate positive experiments for all antibodies were performed. And negative controls were included in each case by omitting primary antibodies. Besides, we selected the non-MFH high-grade malignant sarcomas located in each relevant organ (breast, uterus, liver, lung, bladder, and intestine) we could find from Department of Pathology as controls. All of the immunohistochemically stained slides were reviewed inde-

**Table 1.** Clinical features of the nine cases of malignant fibrous histiocytoma located in the breast and visceral organs

| Case No./Age/Sex | Location | Presentation | Size (Largest Dimension, cm) | Therapy | Follow-up/Outcome |
|---|---|---|---|---|---|
| 1/59 male | Liver | Abdominal pain, malaise, nausea | 12.1 | Right lobectomy | 3 months/died of tumor |
| 2/60/male | Liver | Abdominal pain, malaise, nausea | 5.2 | Right lobectomy | 3 months/died of tumor |
| 3/62/female | Lung | Recurrent cough | 6.6 | Right pneumonectomy | Unknown |
| 4/76/male | Lung | Cough, expectoration | 5.4 | / | 3 months/died of tumor |
| 5/46/female | Breast | Painless breast mass | 3.5 | Modified radical mastectomy | Unknown |
| 6/79/male | Bladder | Gross hematuria | 5 | Palliative cystectomy | 4 years/alive, no recurrence |
| 7/37/female | Intestine | Abdominal pain | 10 | Right hemicolectomy, sigmoidectomy | 6 months/died of tumor |
| 8/79/male | Esophagus | Dysphagia | 7 | EMR | 2 years/alive, no recurrence |
| 9/48/female | Lung | / | 4.6 | / | 3 months/died of tumor |

pendently by 2 pathologists (S.J. & Y.J.). Based on the percentage of positive neoplastic cells, staining intensity was assessed by an arbitrary value of 0 (no staining, < 5%), 1 (weak staining, 5-33%), 2 (moderate staining, 33-66%), or 3 (strong staining, > 66%). Discrepancy in scoring was resolved by consensus.

After compiling the immunohistochemical data from our series, we divided the patients into two groups: one group as MFH originating from the breast and visceral organs, and the other group as non-MFH malignant breast or visceral sarcomas. Then we used a T test to compare the immunoreactivity of ezrin and HMG-CoA reductase between the two groups. SPSS software was used throughout (version 18.0) and $P < 0.05$ was considered to be statistically significant for this test. Besides, a 2-tailed Fisher exact test was performed to explore the association between the clinicopathologic variables (age, sex, ezrin expression, and HMG-CoA reductase expression) and patients' prognosis, and $P < 0.1$ was considered to be statistically significant for this test.

## Results

### *Clinical characteristics*

The detailed information of all the 9 patients is summarized in **Table 1**, of which 1 was pulmonary metastatic MFH from the breast. Of the remaining 8 primary MFH patients, 2 were hepatic MFH, 2 were pulmonary MFH, and the other 4 were respectively located in the breast, esophagus, bladder, and the ileum. Ages of the patients ranged from 37 to 79 years (average 60.7 y) at the time of diagnosis. There were 5 men and 4 women.

Case 1 and Case 2 were hepatic MFH. Both of them were male. They suffered from abdominal pain and discomfort in the right upper quadrant and other symptoms such as malaise and nausea. No history of previous operation or alcohol consumption was found. In Case 1, laboratory data showed increased glutamyltranspeptidase (γ-GT) (184.7 U/L; normal 11.0-50.0 U/L). In Case 2, laboratory data showed slightly increased glutamic-pyruvic transaminase (GPT) (84.8 U/L; normal 5-40 U/L), glutamic-oxaloacetic transaminase (GOT) (56.4 U/L; normal 8-40 U/L), and glutamyltranspeptidase (γ-GT) (97.7 U/L; normal 11.0-50.0 U/L). Serologic hepatitis B virus (HBV) surface antigens were positive in both patients, while serum alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA19-9) were within normal limits. In Case 1, preoperative abdominal computed tomography (CT) revealed a well-demarcated solitary heterogeneous mass (12.1 × 8.6 cm) with marked enhanced boundary in the right hepatic lobe. In Case 2, CT demonstrated multiple small nodules up to 1 cm in diameter and a well-demarcated solid mass (5.2 × 4.0 cm) with enhanced boundary in the right hepatic lobe. They both underwent right lobectomy of the liver, and unfortunately, died of their primary tumor within 3 months after the operation.

Case 3 and Case 4 were pulmonary MFH. Case 3, a 62-year-old woman, presented with recurrent cough. Physical examination revealed decreased breath sounds over the right basal lung field. Chest CT scan showed a large tumor of soft tissue density replacing the right hilus pulmonis (6.6 × 4 cm). Case 4, a 76-year-old man, presented with cough and expectoration with gasping out. Physical examination revealed moist rales over the left lung base. The sputum culture showed positive Candida albicans. Chest CT scan demonstrated well-demarcated hypodense mass with heterogeneous enhancement in the anterior mediastinum. Serum biochemistry and tumor markers were within normal limits in both patients. Under these circumstances, Case 3 was consented for surgery and a right pneumonectomy was performed. However we were unable to get follow-up information of this patient. Case 4 had only a needle biopsy on our record. And he died from his tumor within 3 months.

Case 5, a 46-year-old woman, was a breast MFH, presenting with a painless breast mass. The tumor mass was located in the right breast, with the size of 3.5 cm in diameter. She underwent modified radical mastectomy, and did not receive further treatment. Unfortunately she died with half a year after the surgery.

Case 6, a 79-year-old man, presented with a MFH arising in the bladder. He was admitted to our hospital due to a 6-week history of painless gross hematuria. Cystoscopy revealed a large tumor (4 × 5 $cm^2$) at the right side of the urinary bladder with focal ulceration of the mucosa. A biopsy indicated MFH of the bladder. CT scan

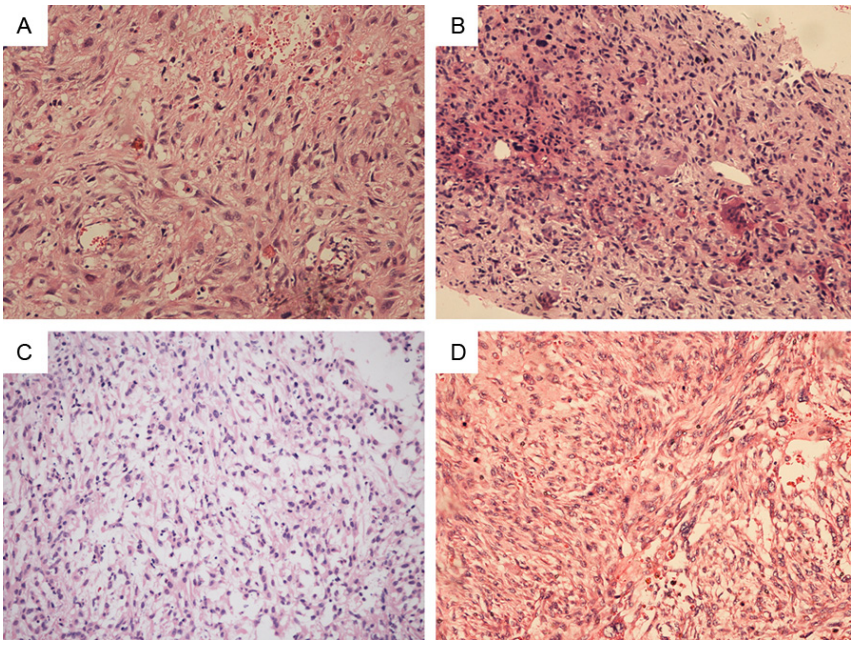


**Figure 1.** Histological spectrum of the visceral MFH. (H/E-stained slides). A. Case 1: primary hepatic MFH, classified as storiform-pleomorphic MFH. B. Case 4: primary pulmonary MFH, classified as giant cell MFH. C. Case 6: primary vesical MFH, classified as inflammatory MFH. D. Case 8: primary esophageal MFH, classified as storiform-pleomorphic MFH.

failed to yield any evidence of extravesical dissemination, so palliative cystectomy was performed. The patient underwent perfusion chemotherapy after the surgery and was still alive until now.

Case 7, a 37-year-old young woman, was an intestinal MFH. She suffered from recurrent right lower quadrant abdominal pain. At laparotomy, a tumor was found originating from the ileum with the size of 10 × 10 $cm^2$. A partial resection of the small intestine was performed followed by a right hemicolectomy, a sigmoidectomy, a right adnexectomy, and an omentectomy. She was not treated with chemotherapy or radiotherapy and died within six months.

Case 8, a 79-year-old man, was an esophageal MFH. He presented with dysphagia and underwent endoscopic mucosal resection (EMR) to relieve the symptom. Endoscopic pathology dissection revealed a MFH with the size of 2 × 7 $cm^2$. The patient suffered from dysphagia again in a year. EMR was performed followed by neither surgery nor chemotherapy. Fortunately the patient survived until now.

Case 9, a 48-year-old woman, was a metastatic lung MFH from the breast. She had underwent left modified radical mastectomy and been diagnosed with breast MFH. However a solitary tumor was found in the left lower lung after the surgery. A biopsy demonstrated a metastatic lung MFH. No surgery was performed and she died within 3 months.

*Pathological features*

H/E-stained slides were independently reviewed by two pathologists (S.J. & Y.J.). Diagnosis was made based on the WHO criteria (2002 edition). Six cases (Case 1, 2, 3, 5, 8, & 9) were classified as storiform-pleomorphic MFH, as they showed a classical microscopic appearance of apparent pleomorphic tumor cells and nuclei, mixed heteromorphic giant cells, spindle cells and round histiocytoid cells (**Figure 1A** and **1D**). One case (Case 4) was diagnosed as giant cell MFH, as the tumor showed many multinucleated giant cells and mononucleated giant cells except for the pleomorphic elliptical and spindle cells (**Figure 1B**). Two cases (Case 6 & 7) were classified as inflammatory MFH, as the tumor consisted of abundant atypical spindle cells, and acute and chronic inflammatory cells (**Figure 1C**). Areas of necrosis were presented in four of the cases (Case 1, 4, 6, & 7). And the tumor of Case 1 presented with vascular invasion. Neither epithelial components nor normal ductal components were observed in any of the tumors.

*Immunohistochemical analysis*

The immunohistochemical data of two of the cases (Case 5 & 9) were missing. The detailed immunohistochemical staining results of the remaining 7 cases in our series were summarized in **Table 2**. The tumors in all the 7 cases were positive for vimentin. CD68 was also positive in 3 of the cases (Case 1, 4, & 8). Tumor

**Table 2.** Immunohistochemistry results of the 9 cases of malignant fibrous histiocytoma located in the breast and visceral organs

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | Case 8 | Case 9 |
|---|---|---|---|---|---|---|---|---|---|
| Vimentin | +++ | + | + | + | | + | + | + | |
| CD68 | + | | - | + | | | | + | |
| Ki-67 (%) | | | | | | 20 | 30 | 40 | |
| SMA | | - | | | | | +++ | + | |
| CD163 | | ++ | | | | | | | |
| Actin | - | | | + | | - | | | |
| S100 | | + | - | - | | - | - | - | |
| CK88 | - | | | | | | | | |
| Hept1 | - | - | | | | | | | |
| CK | - | - | - | - | | - | - | - | |
| Desmin | - | - | | | | - | - | | |
| CK19 | - | - | | | | | | | |
| EMA | - | - | - | | | - | | | |
| CD34 | - | - | | - | | | - | - | |
| AFP | | - | | | | | | | |
| CD117 | | - | | | | | - | - | |
| HMB45 | | - | | | | | | | |
| A103 | | - | | | | | | | |
| αAT | | | + | | | | | | |
| ALK | | | | - | | - | - | | |
| Bcl-2 | | | | - | | | - | | |
| CK7 | | | | | | - | | | |
| CK20 | | | | | | - | | | |
| Myod1 | | | | | | - | | | |
| Myogenin | | | | | | - | | | |
| P53 | | | | | | - | | | |
| CD31 | | | | | | - | | | |
| CD34 | | | | | | - | | | |
| Inhibin | | | | | | - | | | |
| D2-40 | | | | | | - | - | | |
| CD35 | | | | | | | - | | |
| CD21 | | | | | | | - | | |
| CR | | | | | | | + | | |
| ROS | | | | | | | | - | |
| Ezrin score | 2 | 1 | 1 | 1 | 2 | 3 | 3 | 2 | 2 |
| HMG-CoA reductase score | 1 | 1 | 3 | 2 | 1 | 2 | 1 | 2 | 3 |

+: positive; -, negative. CD: cluster of differentiation; SMA: smooth muscle antibody; CK: cytokeratin; EMA: epithelial membrane antigen; AFP: alpha-fetoprotein; ALK: anaplastic lymphoma kinase; BCL: B-cell lymphoma; CR: calretinin; ROS: reactive oxygen species; HMG-CoA: hepatic 3-hydroxy-3-methylglutaryl coenzyme A.

cells were variably positive for Ki-67 in 3 different cases with the estimated percentage of positive cells ranging from 20% to 40%. SMA was positive in 2 cases (Case 7 & 8). The tumors of Case 2 stained positive for S100 and CD163. αAT was positive in Case 3, actin was positive in Case 4, and CR was positive in Case 7. The broad spectrum cytokeratins were negative in all the remaining 7 cases.

Ezrin immunoreactivity was detected in the membrane or cytoplasm of tumor cells in our series. Three cases (Case 2, 3, & 4) showed a weak staining of ezrin expression (**Figure 2E**).

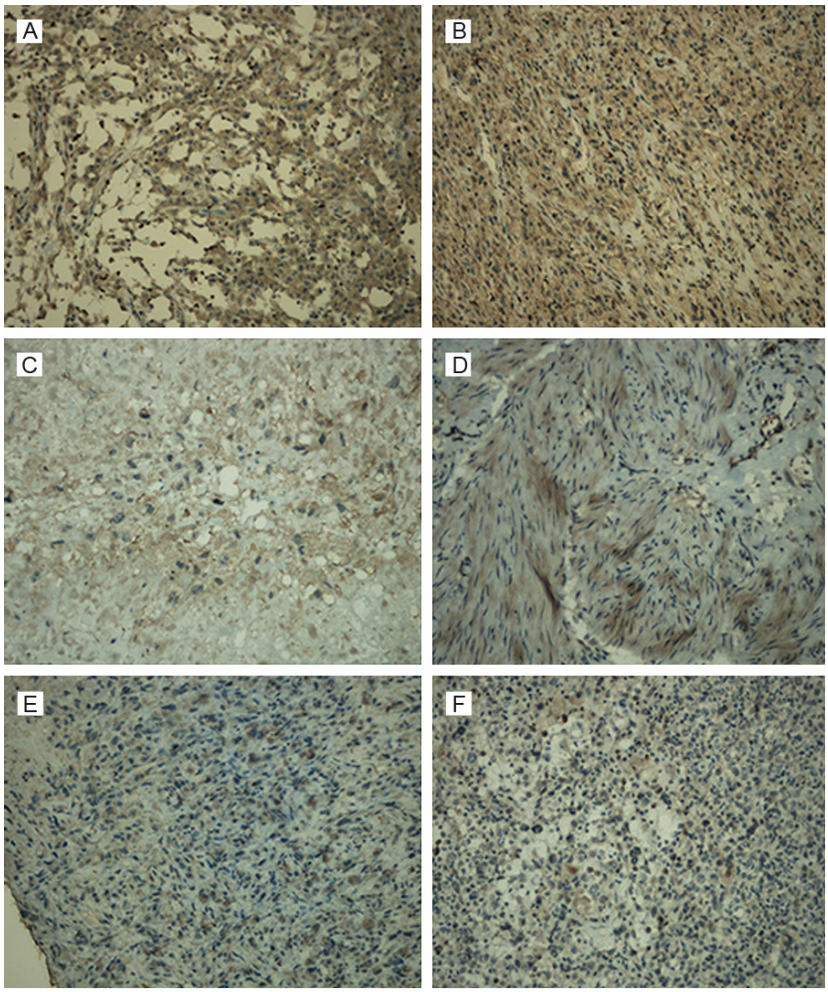


**Figure 2.** Immunohistochemical expression of ezrin and HMG-CoA reductase in MFH cases located in different organs. A. Ezrin expression in vesical MFH (Case 6, +++). B. HMG-CoA reductase expression in pulmonary MFH (Case 3, +++). C. ezrin expression in hepatic MFH (Case 1, ++). D. HMG-CoA reductase expression in vesical MFH (Case 6, ++). E. ezrin expression in pulmonary MFH (Case 4, +). F. HMG-CoA reductase expression in breast MFH (Case 5, +).

While a more diffuse intense pattern of staining was observed in the remaining six cases, especially in bladder and intestinal tissues (Case 6 & 7) (**Figure 2A** and **2C**). As is known to all, the conclusive diagnosis of breast and visceral MFH relies on histological examination only [14]. And sometimes it is extremely difficult for us to distinguish MFH from other soft tissue sarcomas. So we want to investigate whether the expression of ezrin is different between MFH and other non-MFH sarcomas. We selected the non-MFH malignant soft tissue sarcomas located in each visceral organ (liver, lung, intestine, and bladder) and the breast we could find from our database. We could not find any non-MFH malignant esophageal sarcoma. Then ezrin immunoreactivity was also detected in the 9 non-MFH soft tissue sarcomas (See **Table 3**). Some of these tissues showed a patchy faint staining pattern, while most of them demonstrated no staining of ezrin expression (**Figure 3A** and **3C**). Then we performed a T test between the two groups (MFH vs. other non-MFH mesenchymal sarcomas) to compare ezrin expression, and found that ezrin immunoreactivity was significantly much stronger in MFH group than that of non-MFH sarcomas ($P < 0.001$).

The immunoreactivity of HMG-CoA reductase was also detected in the membrane or cytoplasm of tumor cells. Four cases showed a weak staining (Case 1, 2, 5, & 7), (**Figure 2F**) while the remaining five cases showed moderate or strong staining pattern (**Figure 2B** and **2D**). A T test was also carried out to compare the expression of HMG-CoA reductase between the two groups. We found that HMG-CoA reductase immunoreactivity was significantly stronger in breast or visceral MFH cases than that of other non-MFH malignant soft tissue sarcomas ($P = 0.008$).

*Prognostic value of patients' age, sex, ezrin and HMG-CoA reductase expression*

The follow-up data of 7 patients in our series were available. And only 2 patients survived until now. (Case 6 and Case 8) Most of the remaining patients died within 3 months, and 1 patient survived up to 6 months (Case 7). Then we used a Fisher exact test model to detect whether patients' age, sex, ezrin expression, and HMG-CoA reductase expression were associated with the prognosis of these patients.

**Table 3.** Ezrin and HMG-CoA reductase expression score in relevant non-MFH soft tissue sarcomas

| Organ | Case | Histological types | Ezrin | HMG-CoA reductase |
|---|---|---|---|---|
| IntestineLiver | 1 | Leiomyosarcoma | 1 | 0 |
| | 2 | Stromal tumors | 0 | 0 |
| | 3 | Leiomyosarcoma | 1 | 2 |
| Bladder | 4 | Fibrosarcoma | 1 | 1 |
| | 5 | Rhabdomyosarcoma | 0 | 1 |
| Breast | 6 | Fibrosarcoma | 0 | 0 |
| Lung | 7 | Leiomyosarcoma | 0 | 1 |
| | 8 | Lipoblastoma | 0 | 1 |
| | 9 | Fibrosarcoma | 0 | 0 |

*2="++", 1="+", 0="-". HMG-CoA: hepatic 3-hydroxy-3-methylglutaryl coenzyme A; MFH: malignant fibrous histiocytoma.

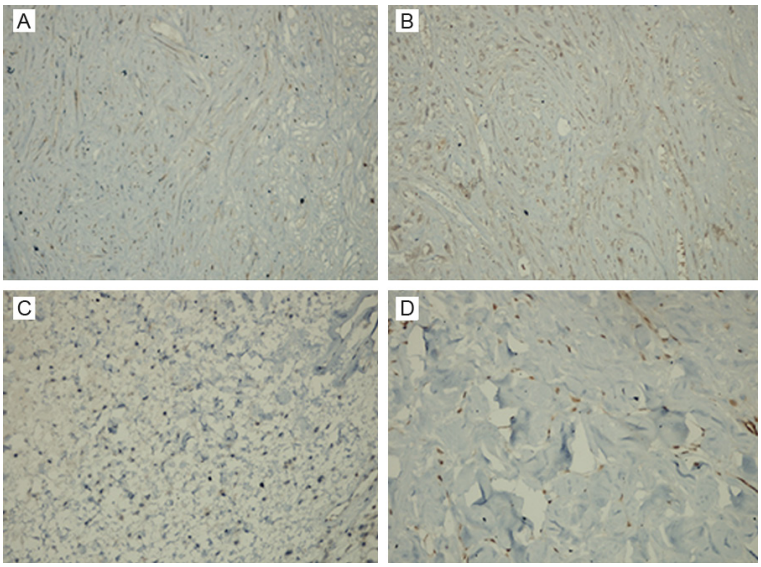


**Figure 3.** Immunohistochemical expression of ezrin and HMG-CoA reductase in other non-MFH malignant soft tissue sarcomas. A. ezrin expression in hepatic sarcoma (+). B. HMG-CoA reductase expression in hepatic sarcoma (+). C. ezrin expression in vesical sarcoma (-). D. HMG-CoA reductase expression in breast sarcoma (-).

(**Table 4**) We found that poor prognosis was associated with younger age ($P$ = 0.074). Disappointedly, no other statistically significant results were found. ($P$ = 0.327 for patients' sex, $P$ = 0.327 for ezrin expression, and $P$ = 0.180 for HMG-CoA expression).

## Discussion

In the most recent WHO classification (2013 edition) of soft tissue tumors, the terminology "malignant fibrous histiocytoma (MFH)" has been abandoned. Such lesions, after exclusion of specific lines of differentiation, are now classified as the quite separate and new category of "undifferentiated/unclassified sarcomas" [15]. Nevertheless the diagnosis of "MFH" had been widely used for many years before 2013. The cases discussed in our paper were all diagnosed before 2013. So in this study we still used "MFH" to define this rare and special group of sarcomas.

Primary nonepithelial malignant sarcomas of mesenchymal origin are rare in the breast and visceral organs. While primary MFH, which is an aggressive tumor with high potential of local relapse and distant metastases, is exceedingly rare. In the past decade we only obtained 9 diagnosed MFH cases located in the breast and visceral organs in our hospital. So here in this paper we took into account MFH originating from the breast, liver, lung, bladder, intestine, and esophagus together.

Primary hepatic MFH is a disease of adult patients without sex predilection. The diagnosis of this disease is often delayed because of nonspecific symptoms such as malaise, anorexia and weight loss. Most reported cases were solitary lesions with tumor size ranging from 5.5 to 20 cm, demonstrating a well-defined mass with a complex pattern on radiology image studies [16]. About 32% of the tumors presented with local invasion, most commonly into diaphragm and lung.

Immunohistochemically, the absence of antigens for epithelial tumors of the liver or the lineage-specific mesenchymal markers, and the presence of immune reactivity for vimentin and CD68 might suggest the diagnosis of primary hepatic MFH [17]. There were two diagnosed primary hepatic MFH in our series. They both died within 3 months, indicating the strongly malignant feature of primary hepatic MFH.

**Table 4.** Association of clinicopathologic variables with prognosis

| | Survival Time | | *P* value* |
|---|---|---|---|
| | ≤ 1 y | 1 y | |
| Age | | | |
| ≤ 60 | 4 | 0 | 0.074 |
| 60 | 1 | 2 | |
| Sex | | | |
| Male | 3 | 2 | 0.327 |
| Female | 2 | 0 | |
| Ezrin score | | | |
| ≤ 1 | 2 | 0 | 0.327 |
| > 1 | 3 | 2 | |
| HMGCR score | | | |
| ≤ 1 | 3 | 0 | 0.180 |
| > 1 | 2 | 2 | |

*$P < 0.1$ was considered to be statistically significant. HMGCR: hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase.

Primary pulmonary MFH only accounted for 0.2% of the pulmonary neoplasms. And lung was reported to be the most common site for distant metastases from other primary MFH [18]. The majority of patients presented with chest pain, dyspnea, cough, and hemoptysis. In addition, some patients might be asymptomatic during their presentation. The radiologic manifestations seemed to have no differential significance from other lung tumors. Rates of local and distant recurrence remained high even after radical surgery. We got two primary pulmonary MFH cases and one metastatic lung MFH from the breast in our series. Regardless of the patient we were not able to contact with, the other two cases both died within 3 months.

Breast MFH has been reported to account for less than 1% of all primary malignancies of the breast [19]. The absence of epithelial markers like EMA and cytokeratin, and the strong positive staining for vimentin supported the mesenchymal origin of this kind of tumor. Neither could we obtain the IHC staining data from the breast MFH in our series, nor could we get her follow-up data. Prognostic factors for MFH of the breast remained uncertain because of the small number of cases presented and the short follow-up period in most studies [20]. A recent study investigated the prognostic significance of Ki-67 in 7 available MFH cases of the breast, and concluded that patients with high Ki-67 expression had a dramatically shorter life span than those with Ki-67 expression, suggesting that elevated expression of Ki-67 was associated with poor prognosis in MFH of the breast [21].

Primary MFH of the bladder was also a very rare disease predominantly affecting men in their fifties to eighties. Patients usually presented with gross hematuria [22]. A recent systematic review statistically evaluating the reported cases showed that all primary MFH cases of the bladder were devoid of distant dissemination at the time of first clinical presentation but ran a very aggressive clinical course regardless of the treatment options employed [23]. However, the bladder MFH case in our series underwent a palliative cystectomy followed with perfusion chemotherapy, and he was still alive until now.

Primary esophageal MFH often presented in the middle and lower part of the esophagus in middle and old aged male, with the shape of polypus or mushroom. We could not get enough information about these patients through PubMed search. In our series, the esophageal MFH case underwent palliative EMR twice and fortunately survived until now without any recurrence.

Primary MFH of the small intestine was also an extremely rare condition with an aggressive biological behavior. Complete surgical resection was preferred, and adjuvant chemotherapy or radiotherapy might be advisable for these patients. The tumor cells of the intestinal MFH case in our series showed a strong positive staining for SMA and 30% positive staining for Ki-67. She underwent a partial resection of the small intestine, and died within 6 months.

It has been generally accepted that MFH is not a definable entity, but instead represents a wastebasket of undifferentiated pleomorphic sarcomas. The diagnosis of MFH from the breast and visceral organs has been a challenge for pathologists and clinicians because of the nonspecific symptoms, image examinations, and pathological features. The differential diagnosis between visceral MFH and epithelial carcinomas was not that difficult because MFH was of mesenchymal origin. However we could not reach a consensus of the way to distinguish MFH located in the breast

and visceral organs from other non-MFH mesenchymal sarcomas.

Ezrin was a member of the band 4.1 superfamily of proteins that, when activated, interact with both membrane proteins and the actin cytoskeleton [24, 25]. It was a component of cell surface structures involved in cell adhesion functions, interactions with the Rho-associated signal transduction, and the Akt-mediated apoptotic pathway [26-28]. Ezrin was proved to regulate cell activities such as survival, adhesion, migration, and invasion, all of which are important for tumor development and progression. Recent publications showed that ezrin was strongly expressed in a variety of invasive cancers, including pancreatic carcinoma, hepatocellular carcinoma, gastric and breast cancers [9, 29, 30]. And strong expression of ezrin was significantly correlated with poor prognosis of invasive carcinomas [31]. High ezrin expression was also shown in primary soft tissue sarcomas, and was strongly associated with development of metastases and poor survival [6]. A systematic review indicated strong expression for ezrin in primary hepatic MFH, and found that high ezrin expression was associated with poor prognosis of the patients. So we wanted to investigate whether ezrin expression could be of diagnostic and therapeutic value for those MFH of the breast and visceral organs. We found that ezrin expression was statistically significantly much higher in MFH than that in other non-MFH sarcomas located in relevant organs, suggesting that ezrin could be a potential differential diagnostic marker.

Statins, the inhibitor of HMG-CoA reductase, have been proved as chemopreventive drugs for variable malignancies. They were also shown to inhibit Rho activation, resulting in the repression of ezrin expression. Previous studies confirmed the expression of HMG-CoA reductase in most of the breast cancer cases, which was associated with an improved prognosis [32]. We sought to explore whether HMG-CoA reductase presented in these MFH cases. Interestingly, IHC staining showed significantly stronger expression for HMG-CoA reductase in visceral MFH patients than other relevant non-MFH sarcomas, suggesting that HMG-CoA reductase might also be of potential diagnostic value for MFH cases. Also, statins might be a potential drug for chemoprevention or chemotherapy of these MFH originating from the breast and visceral organs. The diagnostic and prognostic role of HMG-CoA reductase in MFH patients needed to be further investigated.

The prognostic value of some clinicopathologic variables, patients' age, sex, ezrin expression, and HMG-CoA reductase expression, was also investigated in our study. Young age seemed to be associated with a poor prognosis. However, we were not able to find any prognostic significance for ezrin and HMG-CoA reductase expression. A previous study reported that poor prognosis was associated with large tumor size, late clinical stage, and high ezrin expression in primary hepatic MFH patients, which was inconsistent with our findings [17]. Some reasons should be taken into account. The follow-up data of only 7 patients were available. And the clinicopathologic and prognostic features of these cases could vary among different organs.

There were also some limitations in our study. First, the number of MFH cases from the breast and visceral organs was rather small in our series. So we had to gather them together to analyze the clinical and pathological features. Second, the clinical stages of the cases and controls did not match with each other strictly, which could bring in the inaccurate difference of ezrin or HMG-CoA reductase expression between MFH and other non-MFH mesenchymal sarcomas.

In conclusion, we reported 9 cases of the breast and visceral MFH, and analyzed the clinicopathologic characteristics of this rare disease. However, the diagnosis and differential diagnosis remained difficult for pathologists and clinicians. Ezrin and HMG-CoA reductase might be of great value in distinguishing primary visceral MFH from relevant non-MFH malignant soft tissue sarcomas. Young age was associated with a poor prognosis. And the prognostic value of ezrin and HMG-CoA reductase needed further investigation.

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### Disclosure of conflict of interest

None.

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