Primary Renal Malignant Fibrous Histiocytoma Four-Case Report and Review of the Literature

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OBJECTIVE To evaluate the diagnosis and treatment for primary renal malignant fibrous histiocytoma, a rare tumor arising from the kidney.

METHODS The clinical and pathological data from 4 cases of malignant fibrous histiocytoma of the kidney detected in our hospital are described. One case of special interest involved a giant cell subtype, the first to be reported in the oncology literature. The clinicopathologic features and prognostic factors of this tumor were analysed and summarized after reviewing 55 documented cases in the English and Chinese literature.

RESULTS A palpable mass (71.2%), emaciation (54.2%) and pain (54.2%) were common manifestations in renal MFH. Of all the cases, 51 were identified as a storiform-pleomorphic subtype by pathologists. In consideration of all the prognosis related factors, the residual tumor and high TNM stage predicted a shortened survival duration, but the symptom of a fever served as a better prognostic factor.

CONCLUSION Malignant fibrous histiocytoma which arises from the kidney is a rare pathologic type, and possesses a high tendency towards local recurrence and distant metastasis. Despite the poor prognosis, early detection and radical surgery can prolong survival in selected cases.

KEYWORDS: kidney, malignant, fibrous histiocytoma.

Malignant fibrous histiocytoma (MFH) is considered to be the most common soft tissue sarcoma in adult life.[1] Typical sites are the extremities(67～75%), and retroperitoneum (6～16%). Even though involvement of the genitourinary tract is rare, isolated cases of involving the urinary bladder, prostate, penis, and spermatic cord have been described.[2] A primary malignant fibrous histiocytoma of the kidney is very rare. Through the end of 2003, we found only 38 patients with renal MFH reported in the English literature, and only 17 cases have been mentioned in the Chinese. Here we discuss four additional cases of primary renal malignant fibrous histiocytoma including one giant cell subtype, which is the first published report. In addition, we reviewed the literature to discuss the diagnosis, morphology, prognosis, and therapeutic approaches of this infrequent tumor.

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CASE REPORTS

Case 1

A 53-year-old woman presented with a 10-month history of fatigue, a slight fever of 38℃, and weight loss of about 15 kg. Physical examination revealed a palpable mass in the left flank with a mild left flank tenderness. Hematological tests showed an anemia (hemoglobin 7.9 g/dl), an elevated white blood count (9.8×10^9/ L), and a raised erythrocyte sedimentation rate (140 mm/hr). Serum biochemistry was normal except for an elevated alkaline phosphatase at 376 U/L. Urinalysis was normal. The excretory urogram showed deformity of a bifid ureter on the right side, and a large mass arising from the upper pole of the left kidney. Ultrasound examination confirmed the presence of an upper pole mass on the left side which had a mixed echo pattern consistent with a renal cell carcinoma. A radical nephrectomy was performed through a transperitoneal approach. A solid, whitish mass, 8 cm in greatest dimension projected from the upper pole of the kidney and extended through the Gerota's fascia, but with no invasion of the renal parenchyma. The cut surface exhibited local hemorrhage and necrosis. Histologically, the tumor was composed of spindle-shaped cells frequently in a storiform pattern. The cell nuclei were hyperchromatic and pleomorphic. The incomplete fibrous capsule was infiltrated with histiocytes and lymphocytes. A 2 cm swollen lymph node resected from the left renal artery was negative. Immunohistochemically, there was strong reactivity for vimentin, lysozyme, CD68, and negative for the epithelial membrane antigen (EMA), the cytokeratin and S-100 protein. The pathological diagnosis was storiform-pleomorphic MFH (Fig.1). After nephrectomy, the levels of the erythrocyte sedimentation rate, alkaline phosphatase and white blood count were all normalized as well as the patient's temperature. Afterwards the patient received a course of 5,000 cGy over five weeks to the left upper abdominal quadrant. The patient was rehospitalized seven months later for an afternoon low-grade fever that persisted for a week. Computerized tomography (CT) revealed multi-focal liver and lumbar vertebrae metastases, and the patient expired 4 months later.

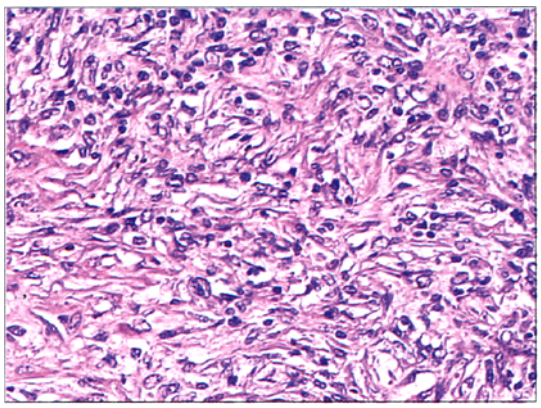

Fig.1. Microscopic appearance of the tumor was composed of spindle-shaped cells, frequently in a storiform pattern. The cell nuclei were hyperchromatic and pleomorphic H&E× 200.

Case 2

A 48-year-old woman was admitted to the department of chest surgery because of a cough, fatigue, 10 kg weight loss over a 6-month period, and an afternoon fever (37.5℃～38.3℃) which she had for one week. There was no history of flank pain or hematuria. Physical examination showed a large, fixed, non-tender mass in the left flank. The hemogram showed an anemia (hemoglobin 11.2 g/dl). Both erythrocyte sedimentation rate (72 mm/hr) and alkaline phosphatase (112 U/L) were over the normal range. Ultrasonography and computerized tomography of the abdomen revealed a 5 × 4 cm size, well-demarcated mass in the lower pole of the left kidney. There was no involvement of the renal vein, inferior vena cava or lymphadenopathy. Chest X-ray and CT showed multi-focal metastatic nodes in the right lung. Suspecting a stage IV renal carcinoma, the patient underwent a left nephrectomy. Grossly, the tumor was solitary, sharply defined, and the cut section was solid and gray-yellowish. The pyelocaliceal system, renal vessels, Gerota's fascia were free of tumor involvement. Microscopically, the tumor was composed of pleomorphic spindle cells arranged in fascicles or in a storiform pattern, intermixed with more rounded histiocytic appearing cells. The nuclei were enlarged and hyperchromatic with considerable variation in size and shape. More than 20 mitoses were observed in 10 high power fields. Lympho-plasmacytic

infiltrates and neutrophil granulocytes were deposited between the tumor cells. Neoplastic cells were positive for vimentin and lysozyme, and negative for EMA, S-100 and CEA. The microscopic and immunohistochemical findings thus indicated an inflammatory type of MFH (Fig.2). She died of a further widespread bilateral lung metastasis 2 months after nephrectomy.

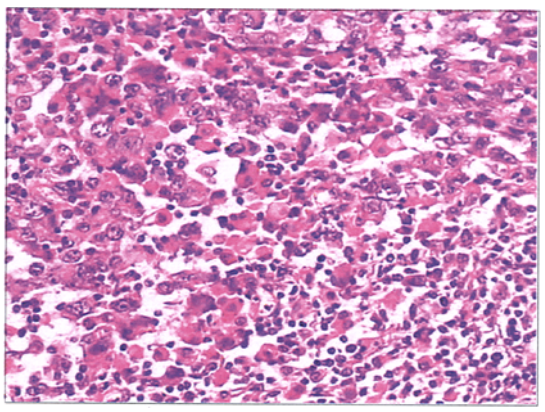

Fig.2. Microscopic appearance of the tumor was intermixed with more rounded histiocytic appearing cells. The nuclei were enlarged and hyperchromatic with considerable variation in size and shape. Lymphoplasmacytic infiltrates and neutrophil granulocytes were deposited between the tumor cells H&E× 200.

Case 3

A 46-year-old man presented with a 3-month history of right loin pain and weight loss. He had also noticed a "lump" in his right flank. Examination confirmed the presence of a fixed mass in the right renal area. Hematological and biochemical tests and chest X-ray showed no abnormality. Abdominal computerized tomography revealed a 8 × 6 cm tumor in the upper part of the right kidney and the area of the right adrenal gland. The right kidney was removed together with the right adrenal, but the mass was found to involve the pancreas, so about 2 cm of residual tumor remained. Pathologically, the cut surface had a variegated appearance varying from tan to white with reddish-brown necrotic areas. The tumor compressed and infiltrated the surrounding adipose tissue and intimately associated with the right adrenal gland. Microscopic examination of the tumor disclosed a predominantly storiform structure which consisted mostly of fibroblast-like cells with marked pleomorphism. Other cells resembling giant histiocytes were noted. Mitoses were frequently present. Immunohistological staining was positive for vimentin, CD68 and lysozyme, and negative for EMA, cytokeratin and S-100. The histopathlogical diagnosis was storiform-pleomorphic MFH. Adjuvant chemotherapy with cyclophosphamide, cisplatin, and adriamycin was instituted 3 weeks postoperatively. However, a lung metastasis was founded by the routine examination before the next course of chemotherapy, and he died 2 months later of widespread disease.

Case 4

A 56-year-old male presented with fatigue and a 9-kg weight loss over a 6-month period. He also had an intermittent fever of 38.8℃. A mass was palpated in the left hypochondrium. Blood studies showed an anemia (hemoglobin 7.0 g/dl), an elevated white blood count (50 × 10^9/L), an elevated platelet count (780 × 10^9/L), and a raised erythrocyte sedimentation rate (126mm/hr). Serum glutamic-oxaloacetic transaminase (SGOT) was elevated to 78 IU/L and alkaline phosphatase to 515 U/L, but BUN and creatinine were normal. Urinalysis results were within normal limits. Plain and enhanced CT depicted a 10 × 12 cm left renal mass with areas of necrosis (Fig.3). Findings on bone scan and chest CT were negative. On suspicion of a large renal cell carcinoma, a tumor nephrectomy was performed with extensive lymphadenectomy. This procedure revealed infiltration of the psoas musculature, and four enlarged lymph nodes (φ 1.5～2.5 cm) around the renal artery. Microscopically the tumor consisted of spindle-shaped cells with marked pleomorphism, elliptic or rounded histiocyte-like cells, and frequent multinucleate or mononucleate giant cells. Storiform structures could be seen in several area. The nuclei of multinucleate giant cells mostly were located on the cellular margin, and present as a floral hoop. There existed many inflammatory cells, but no tumor cells in the four resected lymph nodes. Masson, cytokeratin, EMA and S-100 were negative, with only vimentin and lysozyme showing positive immunostaining. The tumor was diagnosed as a giant cell type of MFH (Fig.4). After nephrectomy, the

levels of the erythrocyte sedimentation rate, alkaline phosphatase, platelet and white blood count were all normalized as well as the patient's temperature. The patient received a course of 5,600 cGy to the left renal area, and then was treated with interferon α -2a for 4 months. Seven months after the operation, he was rehospitalized for an intermittent fever similar to that occurring pre-operation. Computerized tomography revealed widespread bilateral lung metastasis. The patient died 6 weeks later.

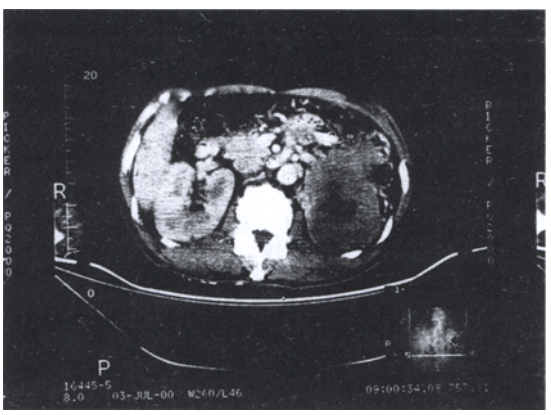

Fig.3. Abdominal CT of case 4 revealing a 10× 12 cm mass with areas of necrosis in the left kidney.

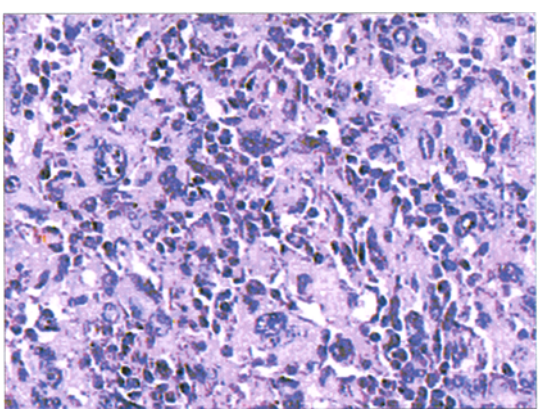

Fig.4. Microscopic appearance of the tumor consisted of spindle-shaped cells with marked pleomorphism, rounded histiocyte-like cells, and frequent multinucleate or mononucleate giant cells. The nuclei of multinucleate giant cells were mostly located on the cellular margin, and present as floral hoop H&E× 200.

DISCUSSION

Primary sarcomas of the kidney are rare tumors in adults, accounting for approximately 1% of all primary renal malignancies reported in 2 large series. [3,4] Histologically, leiomyosarcoma was the most frequent type followed by the rarer liposarcomars and fibrosarcomas. In newer statistics from the M.D. Anderson Cancer Center, leiomyosarcoma was also the most common tumor, accounting for 47% of 17 cases. Except for 5 unclassified sarcomas, the next histologic type was MFH (2 cases). In our hospital, 11 cases of renal sarcoma were diagnosed from 1970 to 2000, including 4 leiomyosarcomas, 4 MFHs, 2 liposarcomas, and 1 case of poorly-differentiated sarcoma.

Malignant fibrous histiocytoma is a primitive and pleomorphic mesenchymal tumor with some histiocytic and fibroblastic differentiation first discribed by O'Brien and Stout in 1964.[5] MFH is the most frequent soft-tissue sarcoma in adults, but primary renal malignant fibrous hitiocytoma is an unusual presentation with only 59 cases reportd to date. [6-17] Our report adds 4 further cases as a contribution to our understanding of this tumor, including preoperative diagnosis, pathologic characteristics, specific therapy and prognosis.

The patients ages ranged from 3 to 87 years at the time of diagnosis with a mean age of 55 years (Table 1). We found a significant male preponderance in the current series, whereas several prior series reported an equal sex distribution. Both kidneys were equally affected. The clinical symptoms of renal malignant fibrous histiocytoma usually appear late and are non-specific. The common presenting symptoms and signs were a palpable mass, weight loss, and abdominal or flank pain. Hematuria, present only in 9 cases, was rare in contrast to being the commonest symptom of renal cell carcinoma. Only 3 asymptomatic patients were discovered incidentally on ultrasound screening. Pain and palpable mass reflect the aggressive nature of renal MFH. Fifteen cases including 3 of our patients had a concomitant fever, elevated white blood count and a raised erythrocyte sedimentation rate, features which were apparent in most of these cases. These symptoms possibly associate with rapid growth, internal necrosis or hemorrhage, and peripheral inflammatory reactivity of the tumors. These MFH features were identified by

extensive histologic and cytologic analysis. Raised alkaline phosphatase was detected in 3 of the present cases and in 6 other reports, and all were normalized after nephrectomy, possibly due to the paraneoplastic syndrome, however this could not be confirmed.

Table1. Clinicopathologic features for all patients

Characteristic	No.of patients(%)
Age(years)	
0-10	1(1.7)
11-20	3(5.1)
21-30	2(3.4)
31-40	3(5.1)
41-50	12(20.4)
51-60	18(30.5)
61-70	14(23.7)
>70	6(10.2)
Gender	
Male	39(66.1)
Female	20(33.9)
Symptoms	
Hematuria	9(15.3)
Mass	42(71.2)
Pain	32(54.2)
Weight loss	32(54.2)
Fever	15(25.4)
Asymptomatic	3(5.1)
Site	
Left	29(49.2)
Right	27(45.8)
Bilateral	1(1.7)
Unknown	2(3.4)
Tumor size	
≤5 cm	2(3.4)
≤10 cm	22(37.3)
≤15 cm	18(30.5)
>15 cm	11(18.6)
Unkown	6(10.2)
Pathologic subtype	
Storiform-plemorphic	51(86.4)
Inflammatory	6(10.2)
Myxoid	1(1.7)
Giant cell	1(1.7)

In our cases, preoperative differential diagnosis from a renal cell carcinoma is impossible with imaging techniques. The majority of diagnostic imaging included ultrasound and computerized tomography. Ultrasound in most of the cases showed a well-defined mass with a rather complex internal pattern. Computerized tomography showed a solid mass often with areas of necrosis, and adjacent muscle or organ invasion. The lungs are the most frequent metastatic site. Three of our 4 patients died with lung metastases, and in our review of the literature we found only 4 patients who had documented metastases at the time of diagnosis, all located in the lungs. Due to the tendency of this tumor to develop pulmonary metastases, a thoratic CT scan is recommended.

As with most other types of renal sarcomas, the tumors arise from the connective tissue capsules and compressed renal parenchyma. The average diameter of our cases was 8 cm, but over 60% of the previously reported cases were in excess of 10 cm at the time of diagnosis. The tumors were described by various authors as firm, gray-white to fleshly pink-tan, often with areas of hemorrhage and necrosis and occasionally calcification. Typical histologic appearance of this tumor included "storiform" or whorl-like arrangements of spindle-shaped fibroblast-like cells, conglomerations of histiocyte-like cells, multinucleate giant cells, xanthoma cells, inflammatory cells, mitotic figures and nuclear pleomorphism.

MFH manifests a broad range of histological appearance of the soft tissue. Weiss and Enzinger [18] diveded MFH into 4 subtypes: storiform-pleomorphic, myxoid, giant cell, and inflammatory. There were 2 storiform-pleomorphic MFHs in our report, which was the most common histologic variant, as 51 of the 59 cases belonged to this subtype. The myxoid type is characterized by a prominent myxoid change of the stroma. It was identified as the second most common type in soft tissue , but only 1 with a kidney origin was reported from China. The last subtype was found to less common in soft tissue. The inflammatory type is characterized by a predominance of xanthoma cells and inflammatory cells. Six inflammatory renal MFH cases including 1 of ours have been published, however it is relatively more commonly located in the extremities. The giant cell type contained numerous

osteoclast-type giant cells. To our knowledge, this case from our hospital is the first report of this subtype of tumor originating from the kidney. At present clinical data indicated that storiform-pleomorphic MFH is the major subtype raised from the renal capsule, with myxoid and giant cell subtypes being rather rare.

The diagnosis of malignant fibrous histiocytoma continues to presuppose excellent sampling and evaluation of H&E stained sections. However, the most common and difficult problem in differential diagnosis is the distrinction of malignant fibrous histiocytoma from other malignant neoplasms showing a comparable degree of cellular pleomorphism. Although there is no specific mono-antibody for malignant fibrous histiocytoma, the application of multiple immunohistochemiscal markers has provided ample evidence that MFH is differentiated from other sarcomas and sarcomatoid carcinomas. In reviewing the immunohistochemical results from the literature, it may be noted that renal MFH is also positive for vimentin, lysozyme, antitrypsin and CD68, as well as lacking immunoreactivity for epithelial markers such as keratin and epithelial membrane antigen. On the other hand, focal immunostaining for substances such as desmin and S-100 is not sufficient in itself to alter the diagnosis, but should be corroborated by other light microscopic features. The limited role of electron microscopy reflects the fact that no ultrastructural features are uniquely specific for renal MFH, and cells with similar characteristics can be found in other tumors. Thus electron microscopy should be regarded as a confirmatory procedure that is best applied when the differential diagnosis has been narrowed by light microscopy.

Surgery is the mainstay of any treatment approach for a clinically localized primary renal tumor or soft tissue sarcoma. But the infiltrative nature and complex local anatomy make it is nearly impossible to achieve the type of wide or radical margins that would be considered standard when excising an extremital sarcoma. Incomplete resection or "debulking" of the tumor always results in a poor prognosis. Even following radical surgery, the margins achieved are merely regarded as the level of marginal excision, and often manifest local recurrence with subsequent distant metastases. After gross total resection of all visible tumor, 13 recurrent cases were reported among 34 patients who had a tumor located within Gerota's fascia. The mean recurrence time was 10 months. Except for 1 case of an inflammation type of lesion who replased 5 times during 6 years, the rest died with distant metastases at the time of their recurrences. Three cases with tumor localized inside the renal capsule obtained disease-free survival after nephrectomy. One additional patient had a partial nephrectomy, and had a recurrence 3 months later. Nineteen patients underwent regional lymphadenectomy, but only 3 cases of positive lymph nodes were demonstrated and existed no more than 10 months owing to widespread metastases shortly after operation. Aggressive surgery with a willingness to resect adjacent organs or perform a radical nephrectomy with regional lymphadenectomy, does not seem to benefit the patients or alter the course of the disease compared with nephrectomy alone.

Twenty-three patients received additional therapy including radiotherapy, chemotherapy and immunotherapy. Joseph et al.[6] reported 1 patient free of recurrence over 22 months after surgical excision and adjuvant radiation, but another 6 patients treated with radiotherapy were found to have a local recurrence or/and distant metastases in less than 7 months. Doxorubicin is the most commonly used cytotoxic drug for management of advanced MFH. This agent was reported to extend disease-free survival to 4 years as single-agent adjuvant chemotherapy for a case of bilateral renal MFH, however, randomized trials have demonstrated that additional doxorubicin does not improve survival compared with surgery alone for soft tissue sarcomas. From the report of Muretto et al.[7] multi-agent chemotherapy(adriamycin, vincristine, cyclophosphamide and dacarbazine) after nephrectomy seem to improve the chance for metastatic control. Ifosfamide is also an effective drug for MFH. Furthermore, Cole et al. [8] reported ifosfamide combined with etoposide and MTX could inhibit the recurrence of metastases for 16 months after development of resistance to adriamycin and

cyclophosphamide. Generally, MFH seems to be non-sensitive to immunotherapy, and has only limited sensitivity to chemotherapy and radiotherapy.

Generally, renal MFH has an unfavorable prognosis. After an initial operation of 55 reported patients, 24 (43.6%) died by 1 year, 12 others died during the period from 14 to 72 months, only 19 patients maintained disease-free survival with the follow-up duration from 6 months to 9 years, and only 5 cases were alive over 3 years. The small number of cases, and insufficient follow-up data, especially for some survivals, prevent coming to a final conclusion on the prognostic parameters of the tumor. The prognostic data for most reported cases are summarized in Table 2. There was no differentiation among the various groups divided by age or sex. Tumor size and histologic type are considered as the important prognostic factors in extremital MFH, but tumor size of renal MFH did not influence the survival duration. Myxoid and inflammatory subgroups are reported to have a better prognosis for soft tissue MFH, however, it is difficult to evaluate the significance of the histologic subtype for renal tumors owing to the absolute preponderance of the storiform-pleomorphic subtype.

There was no statistical significance between the nephrectomy and radical nephrectomy groups, but failure of radical surgical removal of the tumor always

Table 2. Analysis of prognosis-relateded factors

Factor	Total	No.of died patients	No. of disease-free	Mean survival duration(months)	*P*
Age(years)					
< 60	38	20	13	17.2	> 0.05
≥60	21	14	6	14.3	
Gender					
Male	39	22	14	17.9	> 0.05
Female	20	12	5	12.4	
Tumor size					
<10 cm	24	15	7	18.5	> 0.05
≥10 cm	34	18	12	14.4	
Surgery					
Radical	21	12	8	19.2	> 0.05
Nephrectomy	38	22	11	14.1	
Residual					
Yes	14	14	0	5.7	< 0.05
No	45	20	19	20.0	
Stage					
I	4	0	3	26.7	
II	34	13	16	21.4	< 0.05
III	4	4	0	6.8	
IV	15	15	0	5.5	
Fever					
Yes	15	11	3	26.2	< 0.05
No	44	21	16	11.6	
Weight loss					
Yes	32	19	8	15.3	> 0.05
No	27	13	11	16.3	

Note: Some of cases were ignored due to the deficiency of clinical or follow-up information.

results in a poor prognosis. We tried to divide the developmental process of renal MFH into 4 stages by following Robson's staging system of renal cell carcinoma. It is clearly evident that early detection of capsule-limited diseases and radical surgery may offer the best chance for long-term survival. Gerota's fascia also plays as an important barrier in limiting the diffusion of the tumor, as the survival duration of the stage II group was obviously longer than stage III and IV. A quarter of the patients were classified as stage IV, 10 of the tumors extended beyond Gerota's fascia and invaded the surrounding posas muscles, colon, peritoneum, spleen, liver, or pancreatic tail, and the other 5 patients were diagnosed as having lung metastases before surgery. Fourteen of these patients died in 1 year. Only 3 cases with lymph node metastasis and 1 case with caval involvement were reported, their prognoses being similar to stage IV. Some cases in stage III and IV were treated by aggressive radical surgery leaving no residual tumor, but even so, the prognoses were poorer than with intra-fascia diseases.

Hematogenous dissemination and local recurrence are the major causes of death. In that regard, 8 patients died of retroperitoneal recurrence, 19 died from distant metastasis, and 3 patients had a combination of both conditions. The lungs are the most common metastatic site. Fourteen cases were noticed, but the true incidence rate is thought to be even higher because 5 reports noted multifocus metastases but no exact sites. Weight loss is regarded as an independent prognostic factor for renal cell carcinoma, but in our studies of recent reports, we could not find an obvious significant relationship in cases of renal MFH. Fever is also considered as a poor prognostic factor in most kinds of tumors, but on the contrary, in our survey of the literature, it seemed to predict a longer survival for renal MFH patients compared to those with a stable temperature. We suggest that the fever may be associated with the surrounding inflammation of the tumor cells and the secretion of some cytokines such as IL-1, IL-6, TNF, etc.

Some other factors related to our review as potential prognostic indicators for renal cell carcinoma include anemia, elevated erythrocyte sedimentation rate, alkaline phosphatase and lactate dehydrogenase, however it is difficult to discuss their value for MFH due to the insufficient clinical information.

In conclusion, malignant fibrous histiocytoma rarely arises in the kidney. It possesses a high tendency toward local recurrence and distant metastasis. Despite the poor prognosis of the tumor, early detection and radical surgery might enable long-term survival in selected cases.

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