

Short reports

Malignant mesenchymoma of the lower leg

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Abstract

A 24 year old man had a two year history of a painless mass on his right popliteal region. Magnetic resonance imaging demonstrated a 6 × 8 cm tumour mass in the lateral gastrocnemius. Histological examination of the tumour resected by radical surgery revealed that it consisted of myoblastic sarcoma and chondrosarcoma. Immunohistochemical studies were positive for Ki-67 and p53 throughout the area and for S-100 protein in the chondrosarcomatous area; in addition, they showed partial positivity for muscle common actin (HHF-35), smooth muscle actin, and myoglobin in the spindle cells. The percentages of Ki-67, p53, and p21/WAF1 positive cells in the spindle cell component were 34%, 65.7%, and < 0.1%, respectively. In addition, staining was negative for pancytokeratin, desmin, and glial fibrillary acidic protein. The SYT-SSX, TLS-CHOP, and EWS-FLI1 fusion genes were not detected using the reverse transcription polymerase chain reaction. Given the results, the definitive histological diagnosis is malignant mesenchymoma. This is the first report of malignant mesenchymoma of the lower leg with immunohistochemical and molecular studies.

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Malignant mesenchymoma is a rare soft tissue tumour consisting of two or more different histological components of malignant mesenchymal tumour. Stout first described malignant mesenchymoma in 1948.¹ This definition has been generally accepted, and further cases of malignant mesenchymoma have been reported in the literature using these criteria. However, other mesenchymal tumours with different phenotypes such as dedifferentiated liposarcoma, dedifferentiated chondrosarcoma, malignant Triton tumour, and myoblastic differentiation in liposarcoma or chondrosarcoma should be excluded for the diagnosis. Electron microscopic²⁻³ or immunohistochemical studies⁴⁻⁶ can help in making a more accurate diagnosis. Nevertheless, malignant mesenchymoma, as an independent disease entity in soft tissue tumours, is controversial. Tumours are frequently located in the trunk (for example,

the chest wall and retroperitoneum), and tumours are usually high grade with a poor prognosis. We present here a relatively rare case of malignant mesenchymoma in the lower leg, which was diagnosed by immunohistochemical and molecular studies.

Clinical history

A 24 year old man had a painless mass on his right popliteal region, which over two years had gradually increased in size. On physical examination, he had a tumour, 6 × 6 cm in diameter on his popliteal region. Axial T2 weighted magnetic resonance imaging (MRI) demonstrated a 6 × 8 cm tumour in the lateral gastrocnemius, which had an inhomogeneous high signal intensity (fig 1). Histological examination of the incisional biopsy revealed a diagnosis of high grade sarcoma composed of spindle cells. Synovial sarcoma and leiomyosarcoma were suspected. However, chemotherapy was not given because he complained of frequent tachycardia as a result of cardiovascular disease (Wolfe-Parkinson-White syndrome). The patient provided written informed consent for surgery and investigation of tumour samples. Wide excision was performed 12 days after the biopsy. There has been no recurrence or distant metastases in the one year that has passed since surgery.

Material and methods

The specimen was fixed with 20% neutral formaldehyde and embedded in paraffin wax. Sections (4 µm thick) were stained with

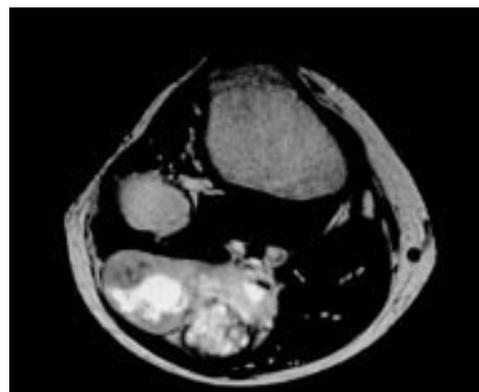


Figure 1 Axial magnetic resonance imaging scan showing the tumour in the lateral gastrocnemius, which had an inhomogeneous intensity on T2 weighted image.

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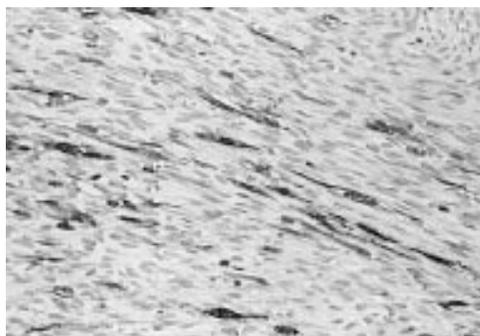


Figure 2 The spindle cell component of the tumour with occasional atypical mitoses. The tumour cells express myoglobin (ABC method). Original magnification, $\times 50$.

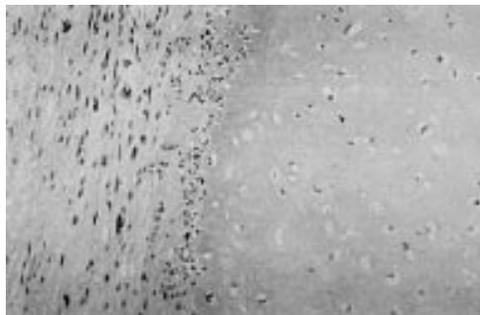


Figure 3 The chondrosarcoma (grade 2) region with moderate cellular atypism. Note also the adjacent area of spindle cell sarcoma. Haematoxylin and eosin stain; original magnification, $\times 50$.

haematoxylin and eosin. Immunohistochemistry was performed using the avidin–biotin–peroxidase (ABC) technique (Vectastain ABC kit; Vector Laboratories) using antibodies to the following molecules: Ki-67 (Mib 1) (Immunotech, Marseille, France; 1/100 dilution; antigen retrieval by autoclave), p53 protein (Dako, Glostrup, Denmark; 1/100 dilution; antigen retrieval by autoclave), p21/WAF1 protein (Calbiochem Darmstadt, Germany; 1/100 dilution; antigen retrieval by autoclave), S-100 protein (Immunon, Pittsburgh, USA; 1/400 dilution), HHF-35 (muscle common actin) (Dako; 1/50 dilution), pancytokeratin (Euro-Diagnostica, Malmö, Sweden; 1/600 dilution; antigen retrieval by proteinase K), smooth muscle actin (Sigma, St Louis, Missouri, USA; 1/500 dilution), desmin (Dako; 1/200 dilution; antigen retrieval by microwave), GFAP (glial fibrillary acidic protein) (Immunon; 1/400 dilution), and myoglobin (Lipshaw; Pittsburgh, USA 1/600 dilution).

Total RNA was extracted from a frozen specimen as described previously.⁷ A 5 μ g sample of the extracted RNA was reverse transcribed using 200 U of M-MLV reverse transcriptase and 50 pmol of oligo dT primer according to the manufacturer's recommendation (reverse transcription polymerase chain reaction (RT-PCR) kit; Takara, Kyoto, Japan). The samples were heated at 95°C for five minutes to terminate the reaction. The PCR amplification was carried out as described previously,⁷ using the primer sets for SYT-SSX1, SYT-SSX2, TLS-CHOP, and EWS-FLI1.

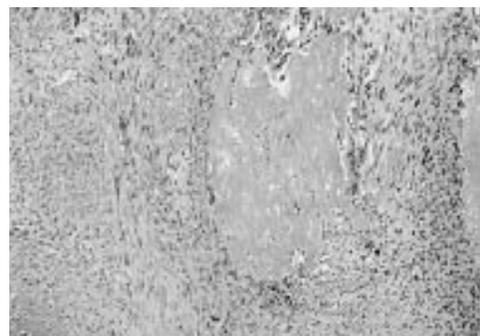


Figure 4 Area of bone formation in the spindle cell component. Haematoxylin and eosin stain; original magnification, $\times 25$.

Pathological findings

The tumour removed measured 6 \times 6 \times 8 cm; the axial cut surface was smooth, myxoid, whitish yellow, and without a capsule. Histological examination of the tumour resected by radical surgery revealed that the tumour consisted of four components, as follows: (1) spindle cells with high cellularity (leiomyosarcoma-like region) (fig 2); (2) proliferation of anaplastic cells with large nuclei (pleomorphic sarcoma-like lesion); (3) cartilaginous cells with nuclear atypism and extracellular matrix (grade 2 chondrosarcoma region) (fig 3); and (4) neoplastic bone and osteoid formation (fig 4).

In the spindle cell component, mitoses were frequent (30/10 high power fields) and nuclear atypism was high. There was little necrosis (< 1%) in the whole area.

Immunohistochemical staining was positive for Ki-67 and p53 throughout the area and S-100 protein in the chondrosarcoma region; it was partially positive for p21/WAF1 (< 0.1%), muscle common actin (HHF-35), smooth muscle actin, and myoglobin in the spindle cells. The percentages of cells positive for Ki-67, p53, and p21/WAF1 in the spindle cell component were 34%, 65.7%, and < 0.1%, respectively. In addition, staining was negative for pancytokeratin, desmin, and GFAP. The predicted 585, 585, 378, or 654, and 327 or 393 or 579 bp products, indicating the presence of the SYT-SSX1, SYT-SSX2, TLS-CHOP and EWS-FLI1 fusion genes, were not found. According to these results, the definitive diagnosis was malignant mesenchymoma.

Discussion

Malignant mesenchymoma is a unique tumour, which has two or more different phenotypes of malignant mesenchymal tumour, including osteosarcoma, chondrosarcoma, leiomyosarcoma, rhabdomyosarcoma, and liposarcoma. Although our case was histologically proved to be a high grade spindle cell sarcoma at the time of the biopsy, the definitive histological diagnosis was not known until the examination of the specimen at radical surgery. The pathological findings of the surgical specimens showed the presence of two malignant mesenchymal phenotypes: myoblastic sarcoma and chondrosarcoma. Immunohistochemically, the tumour cells were partially positive

for muscle common actin, smooth muscle actin, and myoglobin. Therefore, they showed myoblastic differentiation. The osseous region in the spindle cell component in our case was neoplastic and not reactive; however, the ossification pattern was different from conventional osteosarcoma.⁸ The differential diagnoses were spindle cell sarcoma with cartilaginous or osseous region included, malignant peripheral nerve sheath tumour (MPNST), fibrosarcoma, synovial sarcoma, and leiomyosarcoma. In MPNST, cartilage and bone formation is common⁹; however, these tumours are usually reactive and not neoplastic. In addition, S-100 protein, the most widely used neural marker, is seen in 50–90% of MPNSTs,⁹ but it was negative in the spindle cell component in our case. In other spindle cell sarcomas, ossification and cartilage formation are extremely rare. Moreover, this tumour was negative for SYT-SSX1 and SYT-SSX2 (fusion genes seen in synovial sarcomas) on RT-PCR and negative for pancytokeratin, results that exclude synovial sarcoma.

Other mesenchymal tumours with two or more phenotypes are malignant Triton tumours,¹⁰ liposarcoma with smooth muscle, cartilaginous, or osseous differentiation; dedifferentiated liposarcoma; and dedifferentiated chondrosarcoma. It is often difficult to distinguish these tumours from malignant mesenchymoma. However, myoblastic components in malignant mesenchymoma are not dedifferentiated and other distinct mesenchymal components such as regions of liposarcoma, chondrosarcoma, and osteosarcoma are neoplastic, regardless of their histological grades. Myosarcomatous differentiations in dedifferentiated chondrosarcoma¹¹ or liposarcoma¹² are similar to malignant mesenchymoma, so it is also difficult to distinguish them. Because the tumour consisted of various components, despite a uniformly macroscopic finding in the cut surface, it is essential to study all areas of the tumour by means of immunohistochemistry for an accurate histological diagnosis of malignant mesenchymoma. If molecular studies contribute little to the diagnosis, then further studies must be made for myoblastic sarcomas, including leiomyosarcoma and rhabdomyosarcoma.

These tumours are frequently located in the trunk (for example, the chest wall and retroperitoneum)^{4,6} and lower extremities^{2,4,6,13}—most

often the thigh^{11,13,14}—and there have been no reports of a case in the lower leg. To our knowledge, this is the first report of a malignant mesenchymoma of the lower leg.

It is generally thought that malignant mesenchymomas are high grade sarcomas with a poor prognosis.^{2,4,6,14} However, Newman *et al* reported seven low grade malignant mesenchymomas, which had a better prognosis.⁴ The previous reviews are isolated case reports and small series, and there are no clinicopathological studies of numerous cases, so the clinical and histological prognostic factors of malignant mesenchymoma are unknown. Because our case is also a high grade sarcoma (as assessed by the Ki-67 staining result and high rate of mitoses), we will carefully observe the patient for relapse.

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