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CASE REPORT

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Multiple cutaneous myxofibrosarcoma on the right arm: Clinicopathological features and differential diagnosis

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Key Clinical Message

The clinical presentations and pathological features of low-grade myxofibrosarcoma can be misleading, frequently resulting in diagnostic errors. An accurate diagnosis requires the application of immunohistochemistry techniques and the discerning diagnostic acumen of experienced pathologists. A 62-year-old male patient visited our outpatient clinic with multiple painful and rapidly enlarging subcutaneous nodules on his right forearm. Initially, the condition was misdiagnosed as multiple lipomas. The final pathology revealed characteristics consistent with low-grade myxofibrosarcoma.

KEYWORDS

cutaneous, differential diagnosis, myxofibrosarcoma, pathological histology, soft tissue sarcoma

1 | INTRODUCTION

Myxofibrosarcoma (MFS) is a rare malignant mesenchymal neoplasm originating from fibroblasts and developing within a myxoid matrix.[1] It is classified as a distinct pathological entity in accordance with the 2002 World Health Organization tumor classification system. Most tumors are typically found in the lower limbs (77%), trunk (12%),

retroperitoneum or mediastinum (8%), and head (3%).[2] It mostly affects elderly patients more than 60 years of age with a slight predominance in males.[1] On histopathological examination, MFS is characterized by its prominent myxoid matrix, the proliferation of fusiform or stellate fibroblasts, and the curvilinear arrangement of blood vessels.[3] Morphologically, these tumors can be categorized as high-grade, intermediate-grade, or low-grade. Furthermore, MFS typically presents as either a deep or superficial tumor (20%–70%), cutaneous or subcutaneous, usually solitary, with deceptively infiltrative borders, making complete surgical resection challenging and leading to a high local relapse rate after surgery.[1,3] In this article, we discuss a case involving a 62-year-old man with multiple MFSs on his right forearm. This case is characterized by atypical clinical presentations, leading to its initial misdiagnosis as multiple lipomas.

2 | CASE REPORT

A 62-year-old male with no significant medical history visited our outpatient department with a 3-month history of experiencing multiple painful and rapidly enlarging subcutaneous masses on his right forearm. According to the patient, he first noticed a subcutaneous nodule while bathing 3 months ago but initially did not pay it much attention. Initially, it was approximately the size of a red bean, but over time, both the number and size of these nodules steadily and progressively increased. The largest mass had grown to the size of a ping pong ball. There was no history of prior trauma or drug ingestion. Dermatological examination revealed multiple skin-colored, soft, and well-defined subcutaneous masses with limited mobility on his right forearm. These masses were often associated with local pain and tenderness (Figure 1). Laboratory examination results showed no abnormalities in blood counts, biochemical data, or infectious disease screening. Our initial diagnosis was multiple lipomas, and we recommended the removal of the largest subcutaneous mass, which was potentially impacting the patient's quality of life. However, during surgery, we encountered significant difficulties due to the mass's tight adhesion to the surrounding tissues, resulting in increased bleeding.

Pathological analysis of sections from the surgically removed lesion revealed a neoplastic lesion characterized by a multinodular structure, interspersed with incomplete fibers and muscles. The neoplastic cells consisted of actively dividing, plump spindle and stellate cells embedded within an abundant myxoid matrix. Microscopically, curvilinear vessels were also observed within the tumor. The cells displayed a moderate degree of pleomorphism, and mitotic activity was evident (Figure 2). Immunohistochemical staining indicated positivity for smooth-muscle actin and weak positivity for desmin. However, CD34 and S100 protein staining yielded negative results (Figure 3). Due to the multiple tumors that could not be completely excised, the oncology department recommended radiation therapy for the patient. This patient was treated with multiple small doses (2 Gy) of radiotherapy (fractionated radiotherapy) up to total doses in the range of 50 Gy. No organ metastasis was found at the end of the follow-up.

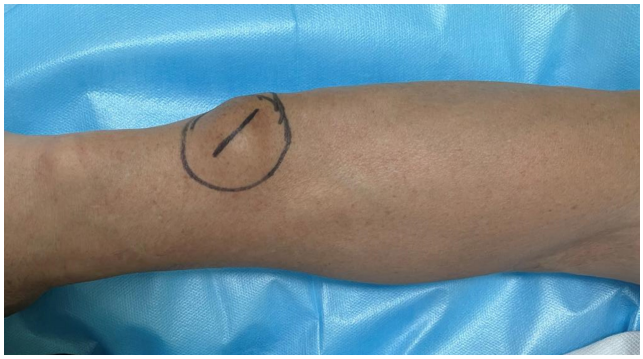

FIGURE 1 The patient exhibits multiple nodular formations within the subcutaneous layer of the right forearm, the most prominent of which measures approximately 3 cm in diameter.

3 | DISCUSSION

Myxofibrosarcoma is a well-recognized pathological entity, accounting for approximately 5% of all soft tissue sarcomas.[3] Typically, the clinical presentation involves a slowly enlarging, painless dermal or subcutaneous mass, which is often solitary.[1] Approximately one-third of these lesions involve the fascia and skeletal muscle.[4] In our case, the clinical manifestations included multiple subcutaneous masses and nodules on the right upper limb, which are easily misdiagnosed as multiple lipomas due to their deceptive nature. The metastatic potential of MFS is closely linked to its grade, with patients harboring high-grade tumors having a three to four times higher risk of metastasis compared to those with low-grade tumors. The lung is the most common site for metastasis, followed by the pleura, lymph nodes, skin, soft tissue, and bone.[3]

The diagnosis of MFS relies on pathological histology, and tumors are classified into a grading system, which includes low-, intermediate-, and high-grades.[4] Low-grade tumors are identified by features such as low cellularity, cells with pleomorphic and hyperchromatic nuclei, and a prominent myxoid matrix.[5] These tumors typically exhibit thin-walled elongated vessels surrounded by the infiltration of tumor cells and inflammatory cells. In low-grade lesions, signs of mitosis and other distinctive malignant features may be less

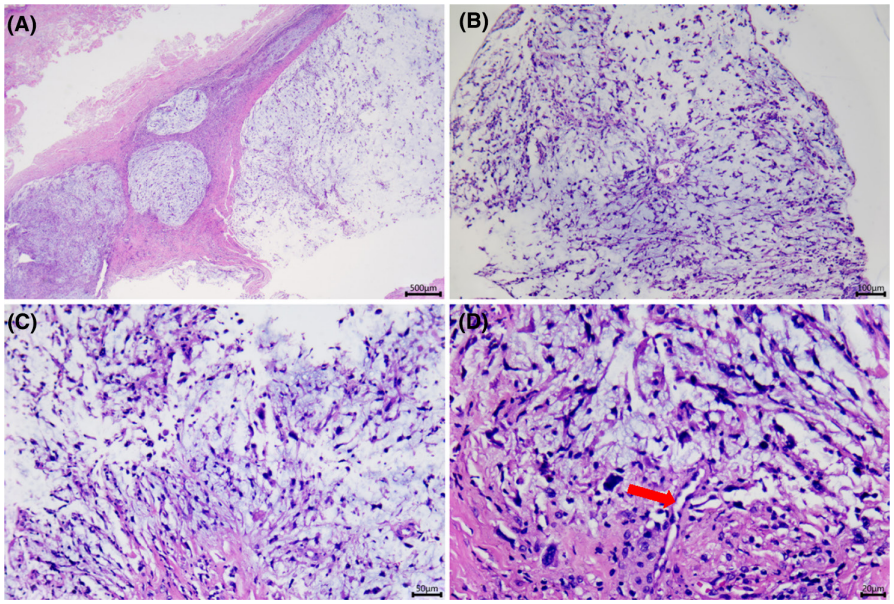

FIGURE 2 Histopathological manifestations. (A) The tumor shows nodular growth with a prominent myxoid matrix at low power (hematoxylin–eosin, ×25). (B) The tumor shows fusiform or stellate fibroblasts (hematoxylin–eosin, ×100). (C) Cells showed moderate degree of pleomorphism and mitotic activity can be seen (hematoxylin–eosin, ×200). (D) Elongated, curvilinear, thin-walled blood vessels (hematoxylin–eosin, ×400).

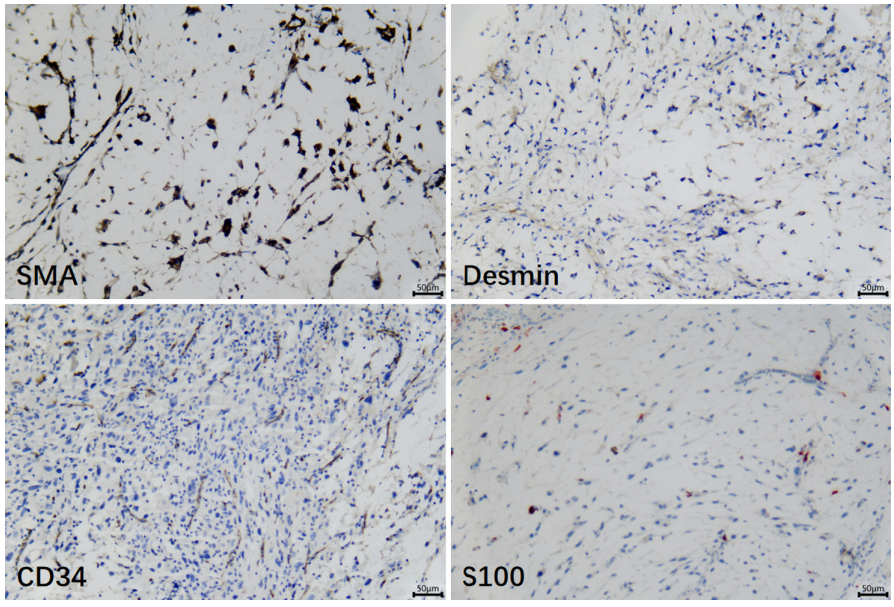

FIGURE 3 Immunohistochemical analysis of the tumor tissue was positive for SMA, and weak positive for desmin. CD34 and S-100 protein stain were negative.

prominent.[6,7] On the other hand, intermediate-grade tumors are more cellular and often exhibit nuclear atypia. Both low- and intermediate-grade MFSs may display a "pseudo-lipoblast" appearance, characterized by significant intracytoplasmic vacuolization and a morphology reminiscent of lipoblasts.[5]

These cells represent a subtype of tumor cells characterized by the presence of acidic glycosaminoglycans in their cytoplasm, as opposed to lipoblasts that contain lipids.[1] Pseudo-lipoblasts can be a significant diagnostic feature of MFS, although they can also be found in myxoinflammatory fibroblastic sarcoma, pseudo-lipoblastic melanoma, and pseudo-lipoblastic perineurioma. High-grade tumors display densely packed, pleomorphic cells with numerous mitotic figures, as well as regions of hemorrhage and necrosis, resembling the morphology of pleomorphic malignant fibrous histiocytoma (MFH).[8] Immunohistochemistry revealed diffuse positivity for vimentin and, in a few cases, positivity for muscle-specific actin and smooth-muscle actin, indicating myofibroblast differentiation. CD68, S100 protein, HMB45, and epithelial membrane antigen (EMA) staining, however, yielded negative results.

The pathological presentation of our case was consistent with a low-grade MFS, initially misdiagnosed as a benign dermal tumor. Low-grade MFSs can often appear deceptively benign and need to be distinguished from noncancerous tumors, including cutaneous myxoma, superficial angiomyxoma, papular mucinosis, myxoid neurofibroma, nerve sheath myxoma, myxoid

pleomorphic fibroma, myxoid nodular fasciitis, among others.[1,5] However, benign tumors lack the pleomorphic cells and mitotic activity observed in low-grade MFS. Low-grade MFSs may also be histologically similar to other malignant tumors, such as low-grade fibromyxoid sarcoma (LGFMS), myxoid dermatofibrosarcoma protuberans (MDFSP), and myxoid liposarcoma (MLS). LGFMS is an indolent yet potentially metastasizing soft tissue tumor, characterized by a spiral or linear arrangement of spindle-shaped cells with minimal or absent mitotic activity, often accompanied by a mucous-like stroma.[9] Generally, thin-walled elongated vessels and pseudo-lipoblasts are not typical features of LGFMS. In contrast, MDFSP usually lacks the multinodular growth pattern, cellular atypia, and curvilinear vessels found in MFS. CD34 staining is typically diffusely positive in MDFSP but not in low-grade MFS.[10] On the other hand, MLS is typically hypocellular, comprised of bland spindle cells within a myxoid matrix, and frequently exhibits the presence of lipoblasts and mucin pools.[11] The capillaries in MLS tumors tend to be branched rather than elongated and curved. When it comes to intermediate- and high-grade MFSs, differentiation should be made from other high-grade malignant tumors, including spindle cell squamous carcinoma, spindle cell melanoma, and dedifferentiated myxoid liposarcoma.[12] In summary, dermatopathologists should have a thorough understanding of the pathological manifestations of each grade of cutaneous MFSs, including their potential to mimic benign processes.

The primary treatment of MFS typically involves wide surgical excision with a safety margin of at least 2 cm.[6] MFS is associated with a high local recurrence rate, ranging from 16% to 54%, particularly in cases with high tumor grade, tumor size exceeding 5 cm, and inadequate surgical margins.[4] In cases of intermediate to high-grade tumors and instances where complete tumor removal is not feasible, radiation and chemotherapy may be recommended as supplementary treatment options.[5] To optimize therapeutic outcomes, it is recommended to implement adjuvant radiotherapy for all deep-seated, high-grade tumors, irrespective of the status of surgical margins.[13] With an in-depth understanding of tumor pathogenesis and biology, promising results have been achieved in immunotherapy, such as the use of anti-programmed death-1 protein/anti-cytotoxic T-lymphocyte-associated protein 4 antibodies.[14] The overall 5-year survival rate for MFS is approximately 60%–70%.[4] Prognosis is strongly influenced by factors including the histopathological grade, initial tumor size, and depth. Low-grade tumors typically exhibit little to no metastatic potential.[15] In our presented case, surgical treatment was combined with adjuvant radiotherapy due to the presence of multiple tumors and the inability to achieve complete removal. The patient is currently undergoing follow-up.

In conclusion, we report a case of multiple low-grade MFSs with clinical presentations resembling multiple lipomas, which can easily be underestimated by clinicians. Additionally, the pathological features of these MFSs can be easily confused with benign tumors. The subtle malignant characteristics of low-grade MFSs may not be readily apparent, posing a diagnostic challenge in both clinical and histopathological assessments. Thorough histological examination and immunohistochemical analysis play crucial roles in enhancing the accuracy of diagnosis and prognosis for MFS.

AUTHOR CONTRIBUTIONS

Peng Zhang: Conceptualization; writing – review and editing. **Shi-Fan Ruan:** Writing – original draft. **Jinwen Huang:** Data curation; writing – review and editing. **Ting Gong:** Conceptualization; supervision; writing – review and editing. **Chao Ji:** Conceptualization; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest regarding the publication of this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Ethical approval is not required for this study in accordance with national guidelines.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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