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Pleomorphic Rhabdomyosarcoma of the Adult Thigh: An Uncommon Aggressive Soft Tissue Sarcoma With Overlapping Morphology and Distinctive Immunohistochemical Features

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Abstract

Pleomorphic rhabdomyosarcoma is a rare and aggressive mesenchymal malignancy that occurs predominantly in adults, with no standardised therapeutic protocol and a poor prognosis. We describe a 47-year-old woman who presented with a three-month history of a painful, enlarging mass of the right thigh, initially suggestive of liposarcoma on magnetic resonance imaging. Core needle biopsy established the diagnosis, with immunohistochemical positivity for desmin, myogenin and myoD1 confirming skeletal muscle differentiation. After three cycles of neoadjuvant chemotherapy, wide surgical resection was carried out. The resection specimen showed no dimensional response to treatment, with 75% viable residual tumour. Histological examination confirmed a post-therapeutic residual pleomorphic rhabdomyosarcoma (World Health Organization Classification 2020), graded 3 according to the French Federation of Cancer Centers Sarcoma Group criteria, with a focally positive lateral margin (R1 resection). Negative murine double minute 2 (MDM2) immunohistochemistry argued against dedifferentiated liposarcoma with heterologous rhabdomyoblastic differentiation. Local recurrence developed three months after surgery, before planned adjuvant radiotherapy could be delivered, requiring surgical re-excision; the patient was subsequently lost to follow-up and died one year after diagnosis. This case highlights the diagnostic value of a comprehensive immunohistochemical panel and the prognostic importance of complete surgical excision.

Categories: Pathology, Oncology, Orthopedics
Keywords: adult, immunohistochemistry, local recurrence, myogenic differentiation, pleomorphic rhabdomyosarcoma, soft tissue sarcoma, surgical margins

Introduction

Rhabdomyosarcoma is a malignant mesenchymal neoplasm originating from skeletal muscle precursors that represents approximately 3% of adult soft tissue sarcomas [1]. As reported by Oancea and Mirică [2], the World Health Organization 2020 classification defines four histological subtypes, namely embryonal, alveolar, pleomorphic, and spindle cell/sclerosing. Pleomorphic rhabdomyosarcoma is a distinct clinical entity, unlike embryonal and alveolar subtypes, which predominantly affect younger patients [3]. It arises predominantly in the extremities, which account for approximately 60% of cases, the lower limb alone representing 48%, followed by the trunk (36%), the upper limb (12%), and the head and neck (4%) [1].

Histologically, it has pleomorphic rhabdomyoblasts, multinucleated giant cells, and abundant atypical mitotic figures [4,5]. Its diagnosis is challenging because of marked morphological overlap with other high-grade pleomorphic sarcomas. Immunohistochemical co-expression of desmin, myogenin, and myoD1 is critical to show myogenic differentiation to rule out morphological mimics, especially undifferentiated pleomorphic sarcoma and pleomorphic leiomyosarcoma [4,6]. Dedifferentiated liposarcoma with heterologous rhabdomyoblastic differentiation represents a more insidious pitfall, as the heterologous component expresses desmin, myogenin, and myoD1 identically, and its exclusion relies on Mouse Double Minute 2 homolog (MDM2) assessment rather than on myogenic markers. Pleomorphic rhabdomyosarcoma has a poor prognosis: five-year survival rate of 68.3% in localized disease, 15.4% in metastatic settings [1]. No standard therapeutic approach has been developed for adult pleomorphic rhabdomyosarcoma and early local recurrence continues to be a significant clinical obstacle [1,3].

Case Presentation

A 47-year-old woman, with no significant past medical history, presented with a painful, progressively enlarging mass of the right thigh, evolving over three months. Physical examination revealed a large, firm, deep-seated soft tissue mass of the right trochanteric region (Figure *1*).

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FIGURE 1: Clinical presentation of the mass in the right thigh

Clinical photograph showing a large, firm, deep-seated soft tissue mass of the right trochanteric region, with visible bulging of the overlying skin.

MRI of the right thigh revealed a well-lobulated deep soft tissue mass of the subtrochanteric region, measuring approximately 10 cm, with heterogeneous signal intensity and internal septations. The mass was hypointense on T1-weighted images and hyperintense on T2-weighted fat-suppressed images; its deep-seated location within the subtrochanteric fatty tissue and its internal septations initially suggested liposarcoma as the leading radiological diagnosis (Figure *2*).

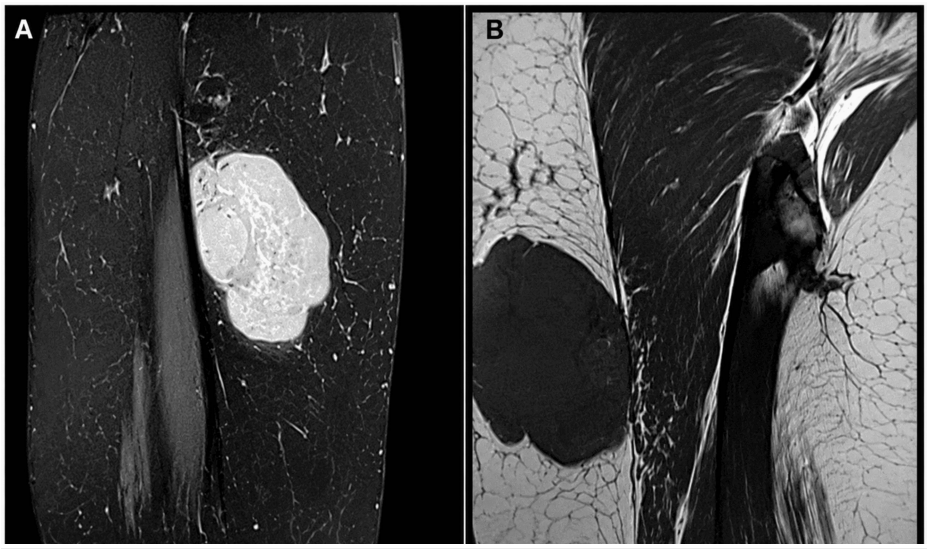


FIGURE 2: Magnetic resonance imaging of the mass in the right thigh

(A) Sagittal T2-weighted fat-suppressed MRI demonstrating a well-defined hyperintense solid mass with lobulated contours, located within the deep soft tissues of the right subtrochanteric region; (B) Coronal T1-weighted MRI showing a well-lobulated heterogeneous hypointense soft tissue mass of the right thigh with internal septations, measuring approximately 10 cm in its greatest dimension.

No inguinal lymphadenopathy or metastases were identified. Core needle biopsy showed marked pleomorphism with spindle, epithelioid, and bizarre giant cells, numerous atypical mitotic figures, focal necrosis and haemorrhagic changes. Immunohistochemistry showed positivity for desmin, myoD1, and myogenin, with negativity for smooth muscle actin, h-caldesmon and S100 protein, establishing the diagnosis of pleomorphic rhabdomyosarcoma.

The patient received three cycles of neoadjuvant chemotherapy before wide surgical resection. Baseline MRI before chemotherapy had shown a mass measuring approximately 10 cm in greatest dimension. The resection specimen measured 10 × 8.5 × 6 cm, indicating absence of any dimensional response to treatment.

Figure *3* shows the resection specimen contained the tumour, abutting the lateral margin and lying 4 mm from the deep margin.

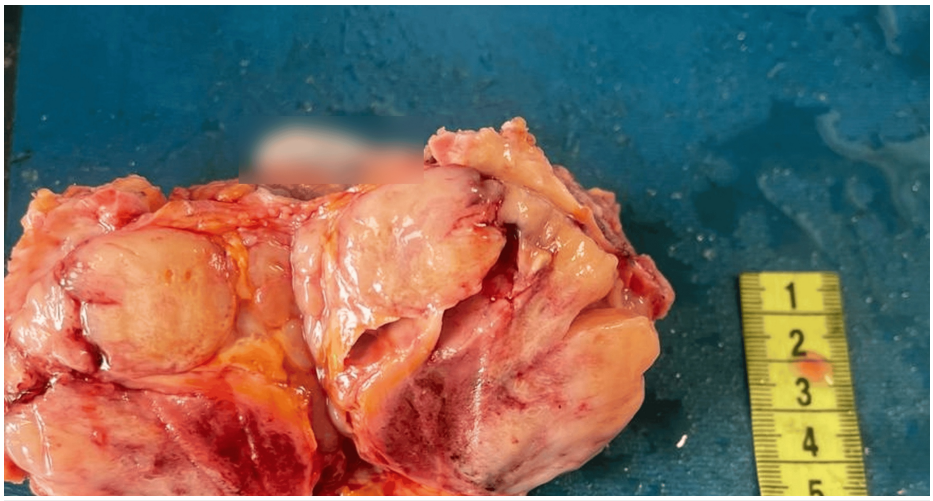


FIGURE 3: Gross examination of the surgical resection specimen

Gross examination shows a large, well-lobulated, firm soft tissue mass with a heterogeneous cut surface displaying areas of haemorrhage, necrosis and yellowish, fat-like areas, which corresponded histologically to entrapped non-neoplastic adipose tissue and post-therapeutic change.

Histological examination of the surgical specimen showed residual viable tumour accounting for 75% of the

tumour bed, with 20% necrosis and 5% post-therapeutic fibrous stroma. The tumour was composed of spindle and epithelioid cells arranged in broad fascicles and sheets, with eccentric hyperchromatic nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm. A high mitotic rate was observed, reaching 38 mitoses per 10 high-power fields. Lymphovascular invasion was identified. The lateral margin was focally positive, with tumour cells present at the inked surface, corresponding to an R1 resection; the deep margin was negative, with tumour lying 4 mm from the inked surface. Immunohistochemistry on the resection specimen confirmed the biopsy findings: Desmin showed diffuse cytoplasmic positivity in more than 80% of tumour cells with strong intensity; myoD1 showed diffuse nuclear positivity in more than 75% of tumour cells with strong intensity; Myogenin showed nuclear positivity in approximately 25-50% of tumour cells with moderate intensity. Smooth muscle actin, h-caldesmon and S100 protein were negative in tumour cells. MDM2 was consistently negative in tumour cell nuclei across all fields examined, including at the interface with the yellowish fat-like areas. Overall, the findings were consistent with the diagnosis of post-therapeutic residual pleomorphic rhabdomyosarcoma (World Health Organization Classification of Soft Tissue and Bone Tumours, 5th edition, 2020), graded 3 according to the French Federation of Cancer Centers Sarcoma Group system (differentiation score: 3, necrosis score: 1, mitotic score: 3) [7-9] (Figure *4*).

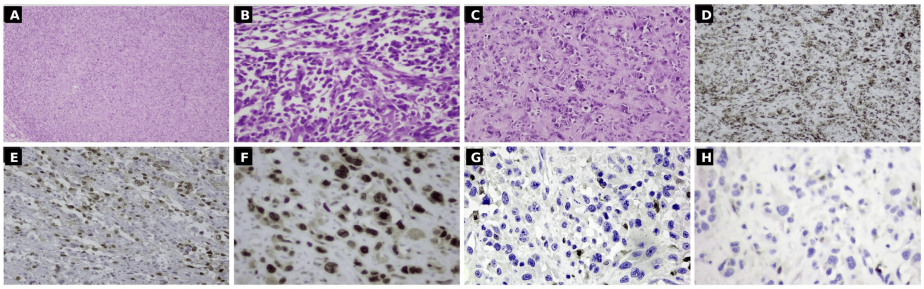


FIGURE 4: Histological and immunohistochemical findings in adult pleomorphic rhabdomyosarcoma

(A) Low-power view of the surgical specimen showing residual viable tumour within post-therapeutic fibrotic stroma (H&E); (B) Core needle biopsy showing pleomorphic sarcomatous proliferation within an inflammatory stroma (H&E); (C) High-power view demonstrating marked nuclear pleomorphism, prominent nucleoli, abundant eosinophilic cytoplasm, and atypical mitotic figures (H&E); Immunohistochemical stains (D-H); (D) Desmin: diffuse cytoplasmic positivity in more than 80% of tumour cells, strong intensity; (E) Myogenin: nuclear positivity in approximately 25–50% of tumour cells, moderate intensity; (F) MyoD1: diffuse nuclear positivity in more than 75% of tumour cells, strong intensity. (G) S100 protein: negative in tumour cells; (H) MDM2: negative in tumour cell nuclei.

Adjuvant radiotherapy was planned, but within three months of resection, local recurrence developed at the primary site before it could be delivered, requiring surgical re-excision. The patient was subsequently lost to follow-up and died one year after diagnosis; the cause of death could not be documented.

Discussion

This case reflects three key challenges in the treatment of adult pleomorphic rhabdomyosarcoma: histological diagnosis based on systematic immunohistochemistry, wide tumour-free surgical margins, and the intrinsic chemoresistance of this highly aggressive entity. All of these challenges are evident directly in the clinical course of our patient. Pleomorphic rhabdomyosarcoma is an exceptionally rare sarcoma (approximately <3% of adult sarcomas) that shows a male predominance, with a median age at diagnosis of 63 years [1].

Our patient was notably younger and female, contrasting with the typical epidemiological profile [1,4], although the thigh location corresponds to the site of predilection of this tumour. Similar atypical demographic presentations have also been reported in the North African adult rhabdomyosarcoma literature [10]. In our patient, magnetic resonance imaging (MRI) revealed a deep heterogeneous mass involving the subtrochanteric fatty tissue, initially interpreted as liposarcoma, underscoring the limited specificity of imaging and the critical role of histopathological confirmation.

Core needle biopsy showed a pleomorphic sarcoma with myogenic differentiation. Immunohistochemical testing showed a positive result for desmin, myogenin, and myoD1, and the diagnosis of pleomorphic rhabdomyosarcoma was established. These findings are consistent with the immunohistochemical profile reported by Rekhi et al. [6] in pleomorphic rhabdomyosarcoma, in which desmin positivity was observed in all cases; myogenin expression was identified in 77.8%, and myoD1 expression was more variable. The histopathological findings in our case showed the characteristic histopathological features of pleomorphic rhabdomyosarcoma: highly pleomorphic epithelioid and spindle cells with abundant eosinophilic cytoplasm [4], and atypical multinucleated giant rhabdomyoblasts characterized by hyperchromatic eccentric nuclei and prominent nucleoli, with frequent atypical mitotic figures on histological analysis [2,4-

6]. Mitotic activity was notably brisk, 38 mitoses per 10 high-power fields, well above the average of 16 mitoses reported by Furlong et al. [4] and the median of 20 as reported by Stock et al. [5], reflecting the highly proliferative nature of the tumour. The co-expression of desmin, myogenin, and myoD1 allowed reliable exclusion of the two main histopathological mimics: undifferentiated pleomorphic sarcoma and pleomorphic leiomyosarcoma.

Undifferentiated pleomorphic sarcoma represents the most challenging differential diagnosis given significant morphological overlap, with distinction relying on skeletal muscle-specific markers [4,11,12]. Pleomorphic leiomyosarcoma presents as an expression of desmin but is characterized by smooth muscle appearance with constant negativity of myoD1 and myogenin [2,4].

Dedifferentiated liposarcoma with heterologous rhabdomyoblastic differentiation deserves particular consideration in our case, given the initial radiological impression of liposarcoma and the yellowish, fat-like areas seen on gross examination. Myogenic markers alone cannot exclude this diagnosis, since a heterologous rhabdomyoblastic component expresses desmin, myogenin and myoD1 identically [13,14]. Several morphological arguments support its exclusion here: extensive sampling of the resection specimen showed no well-differentiated liposarcoma component and no atypical lipomatous areas; no lipoblasts or atypical stromal cells were identified; there was no fibrous or myxoid septated background typical of atypical lipomatous tumour; myogenic marker expression was uniform and diffuse throughout the entire neoplastic population rather than confined to a discrete heterologous nodule; and the yellowish gross areas corresponded histologically to entrapped non-neoplastic adipose tissue and post-therapeutic change rather than to an adipocytic neoplastic component. S100 protein was negative in tumour cells, which is concordant with the absence of a neoplastic adipocytic component, although not discriminant in itself. MDM2 immunohistochemistry was negative in tumour cell nuclei in all fields examined, including those adjacent to the yellowish fat-like areas, further supporting the exclusion of dedifferentiated liposarcoma [13,14].

Misclassification has direct therapeutic implications. The prognosis in pleomorphic rhabdomyosarcoma is worse than undifferentiated pleomorphic sarcoma [12], and it is less chemosensitive than in pediatric rhabdomyosarcoma subtypes, necessitating management based on adult soft tissue sarcoma guidelines rather than pediatric protocols [10,12]. Management of pleomorphic rhabdomyosarcoma generally requires a combination of surgery, radiotherapy, and systemic chemotherapy. Wide surgical resection along with negative margins is the mainstay of curative-intent therapy, and R0 resection alone is shown to benefit disease-free survival [3]. In our patient, the lateral margin was focally positive, corresponding to an R1 resection. Microscopically positive margins are a well-recognized risk factor for local recurrence [3] and likely contributed to the relapse that developed three months after surgery. Lymphovascular invasion, also identified in the resection specimen, is a further adverse prognostic factor and is consistent with the rapid clinical course observed. Although anthracycline-based neoadjuvant chemotherapy has shown response rates close to 50% in published series [3], in our case, the resection specimen showed significant residual viable tumour burden, typical of adult pleomorphic rhabdomyosarcoma due to limited chemosensitivity compared to pediatric subtypes [1,12]. Adjuvant radiotherapy is usually considered very important with borderline or positive margins, improves local control [15]. In our patient, local recurrence developed before planned adjuvant radiotherapy could be delivered, so that the R1 resection was never consolidated, which may have further contributed to the early relapse.

Molecularly, pleomorphic rhabdomyosarcoma presents a complex genomic background [3,11] comprising changes in tumour protein (TP)53 and Retinoblastoma transcriptional corepressor 1 (RB1), and no recurrent targetable gene fusions [3]. The local recurrence observed within three months of surgery, followed by death one year after diagnosis, illustrates the rapidly progressive clinical course of pleomorphic rhabdomyosarcoma, consistent with the aggressive behaviour reported in the literature [3,4].

Recent data from the Pushing Ultra-Rare Sarcomas Towards Hope (PUSH) consortium demonstrated clinically meaningful activity of anthracycline-based regimens in advanced pleomorphic rhabdomyosarcoma, with an overall response rate of 50% among 38 evaluable patients [12]. Rare but durable responses to Programmed Cell Death Protein 1 (PD-1) inhibitors have also been described [12], paving the way for future therapies in relapsed or non-responsive disease.

This report has several limitations. Cyclin-dependent kinase 4 (CDK4) immunohistochemistry and MDM2 fluorescence in situ hybridisation, the reference standard for detecting MDM2 amplification, were not available in our institution, and no molecular profiling was performed. Histological grading was performed on the post-treatment specimen and should be interpreted with caution. Finally, the patient was lost to follow-up after re-excision of the recurrence, and the cause of death could not be documented.

Conclusions

This case highlights the aggressive behaviour and rapid progression of adult pleomorphic rhabdomyosarcoma. It underscores the essential role of immunohistochemistry, particularly desmin, myogenin, and myoD1 expression, in confirming the diagnosis and distinguishing this tumour from its morphological mimics, as well as the contribution of MDM2 immunohistochemistry in addressing the differential diagnosis of dedifferentiated liposarcoma with heterologous rhabdomyoblastic differentiation. It

also emphasises the prognostic importance of achieving wide negative surgical margins, as an R1 resection not consolidated by adjuvant radiotherapy may contribute to early local recurrence. Given the absence of standardised therapeutic protocols, additional reported cases remain crucial to improve the understanding and management of this rare entity.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Bouchra Kouhkouh, Siham Mesmoudi, Sabrine Derqaoui, Kaoutar Znati, Zakia Bernoussi, Taha Yassine Aaboudech

Acquisition, analysis, or interpretation of data: Bouchra Kouhkouh, Siham Mesmoudi, Sabrine Derqaoui, Kaoutar Znati, Zakia Bernoussi, Taha Yassine Aaboudech

Drafting of the manuscript: Bouchra Kouhkouh, Taha Yassine Aaboudech

Critical review of the manuscript for important intellectual content: Bouchra Kouhkouh, Siham Mesmoudi, Sabrine Derqaoui, Kaoutar Znati, Zakia Bernoussi, Taha Yassine Aaboudech

Disclosures

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