COEXISTENCE OF DERMATOFIBROSARCOMA PROTUBERANS AND MULTIPLE CUTANEOUS MELANOMAS: DIAGNOSTIC AND THERAPEUTIC CHALLENGES

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Summary

Dermatofibrosarcoma protuberans (DFSP) is a rare cutaneous sarcoma characterized by slow growth but significant local infiltrative potential and a high risk of recurrence, while fibrosarcomatous transformation represents an event associated with increased biological aggressiveness and metastatic capacity [1,2]. In parallel, the occurrence of multiple primary cutaneous melanomas constitutes a relatively rare phenomenon, suggesting increased individual susceptibility determined by genetic, immunologic, or environmental factors [6,15]. The coexistence of these two histogenetically distinct neoplastic entities in the same patient is uncommon and raises significant challenges in diagnosis, staging, and therapeutic management.

We present the case of a 56-year-old patient with a history of dermatofibrosarcoma protuberans initially diagnosed in 2015, subsequently complicated by local recurrence and pulmonary metastasis histopathologically confirmed as DFSP with fibrosarcomatous transformation, treated with targeted therapy using imatinib [3,8], with favorable evolution under treatment. During oncologic surveillance, the patient successively developed three distinct melanocytic neoplasms: melanoma in situ (2017), ulcerated primary cutaneous melanoma (2024, stage IIB [6,12]), and a melanocytic tumor initially diagnosed as MELTUMP (Melanocytic Tumor of Uncertain Malignant Potential), later reclassified following histopathological and immunohistochemical reassessment as non-ulcerated primary cutaneous melanoma (pT2a). Sentinel lymph node biopsy of the latter lesion revealed suspicious subcapsular melanocytic proliferation, subsequently confirmed by immunohistochemistry as a capsular melanocytic nevus, with no evidence of nodal metastasis, resulting in a final stage IB. Molecular analysis revealed absence of BRAF mutation, with prognostic and therapeutic implications [11].

This case highlights the complexity of differential diagnosis in borderline melanocytic lesions, the importance of histopathological reassessment in specialized centers, and the essential role of clinicopathologic and immuno-histochemical correlation in avoiding staging errors. It also underscores the need for rigorous multidisciplinary monitoring in patients with multiple primary cutaneous neoplasms to optimize therapeutic management and long-term prognosis.

Keywords: *dermatofibrosarcoma protuberans; melanoma; MELTUMP; sentinel lymph node; multiple cutaneous neoplasms.*

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Introduction

Dermatofibrosarcoma protuberans (DFSP) is a rare cutaneous sarcoma of fibroblastic origin, with an estimated annual incidence of 0.8 to 4.5 cases per million inhabitants[1]. This neoplasm is characterized by slow progressive evolution but marked local infiltrative potential, responsible for a significant recurrence rate after surgical excision. Literature data indicate that 10–15% of cases undergo fibrosarcomatous transformation (FS-DFSP), a biological event associated with substantially increased tumor aggressiveness and systemic metastatic risk [2], predominantly pulmonary. The introduction of tyrosine kinase inhibitors, particularly imatinib, targeting the characteristic t(17;22)(q22;q13) translocation involving the COL1A1 and PDGFRB genes, has significantly improved the prognosis of advanced or inoperable forms [3,8].

Multiple primary cutaneous melanomas are reported in approximately 1–8% of patients diagnosed with melanoma and are frequently associated with genetic predisposition factors, including CDKN2A gene mutations [6,15]. The coexistence of DFSP and melanoma in the same patient represents a rare association [9], raising hypotheses regarding possible shared pathogenic mechanisms, genetic susceptibility, or the influence of immunologic and therapeutic factors.

The diagnosis of melanocytic lesions with intermediate histopathological features, such as melanocytic tumors of uncertain malignant potential (MELTUMP), represents a major challenge in dermatopathology practice, requiring careful correlation of morphologic, immunohistochemical, and clinical parameters to avoid under- or overdiagnosis while establishing optimal therapeutic management[4,5,13].

Case Presentation

We present the case of a 56-year-old patient, a chronic smoker with prolonged occupational exposure to industrial toxins and a family history of melanoma, undergoing regular dermatologic follow-up due to multiple previous cutaneous malignancies.

The patient was diagnosed with dermatofibrosarcoma protuberans in 2015, located in the right supraclavicular fossa, treated by surgical excision followed by systemic chemotherapy (8 cycles of carboplatin and paclitaxel). In 2016, DFSP recurred locally, leading to repeat surgical intervention. In 2017, PET-CT examination revealed metabolically active mediastino-hilar lymphadenopathy, which was biopsied; histopathological examination was negative for tumor infiltration. Given the disease course, the oncologist initiated targeted therapy with imatinib 400 mg (2 tablets/day), administered until 2019. In 2020, imaging investigations identified a pulmonary secondary lesion, histopathologically confirmed as dermatofibrosarcoma protuberans with fibrosarcomatous transformation. In this context, imatinib therapy was resumed.

Parallel to the course of dermatofibrosarcoma protuberans, the patient developed multiple melanocytic neoplasms.

In 2017, he was diagnosed with melanoma in situ located on the posterior thorax, for which re-excision with 5 mm margins was performed.

Subsequently, in February 2024, the patient was diagnosed with ulcerated primary cutaneous melanoma located in the left deltoid region, with a Breslow thickness of 3 mm. Re-excision with 2 cm margins and sentinel lymph node biopsy were performed. Histopathological examination of the lymph node was negative, establishing a final stage IIB. At the time of diagnosis, according to the European guidelines in force, adjuvant immunotherapy for stage IIB melanoma had not yet been incorporated as a standard recommendation. Consequently, clinical, biological, and imaging surveillance was chosen, in accordance with the therapeutic recommendations valid at that time.

In June 2025, the patient noticed the appearance of a new tumor on the posterior aspect of the right calf. Initial histopathological examination classified the lesion as a melanocytic tumor of uncertain malignant potential (MELTUMP), raising diagnostic challenges in differentiating between an atypical melanocytic neoplasm and an incipient melanoma. Given the patient's complex oncologic background, the

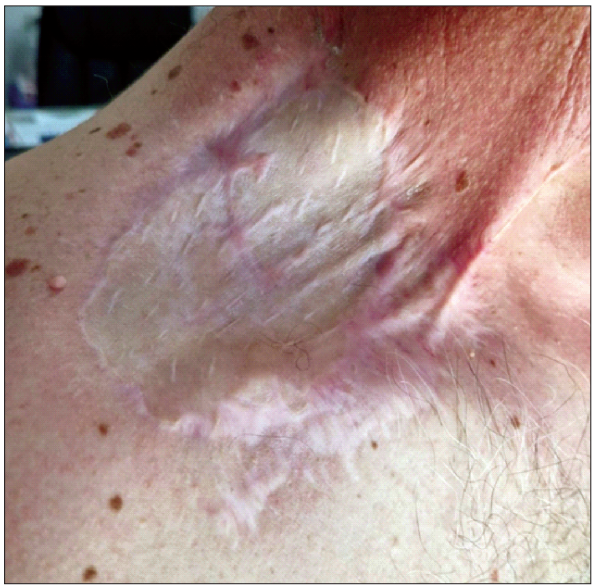

Figure 1. Post-excision scar following dermatofibrosarcoma protuberans DFSP resection (personal archive of Prof. Dr. Magda Constantin).

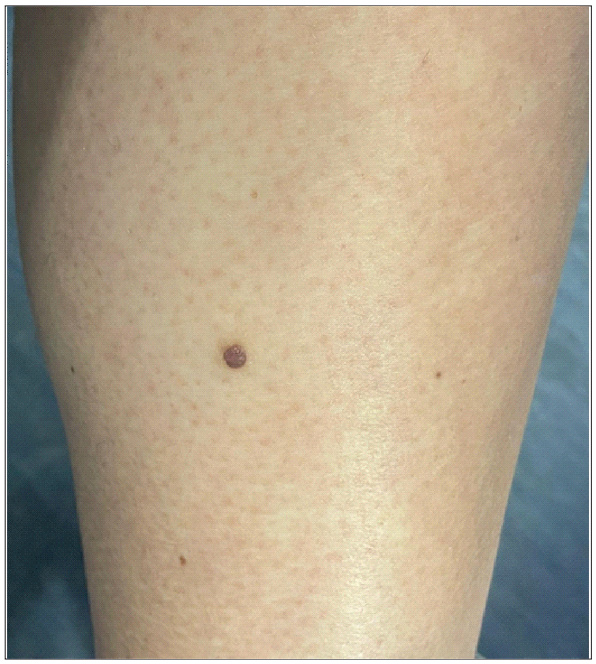

Figure 2. Clinical appearance of the lesion located on the posterior aspect of the right calf (personal archive of Prof. Dr. Magda Constantin).

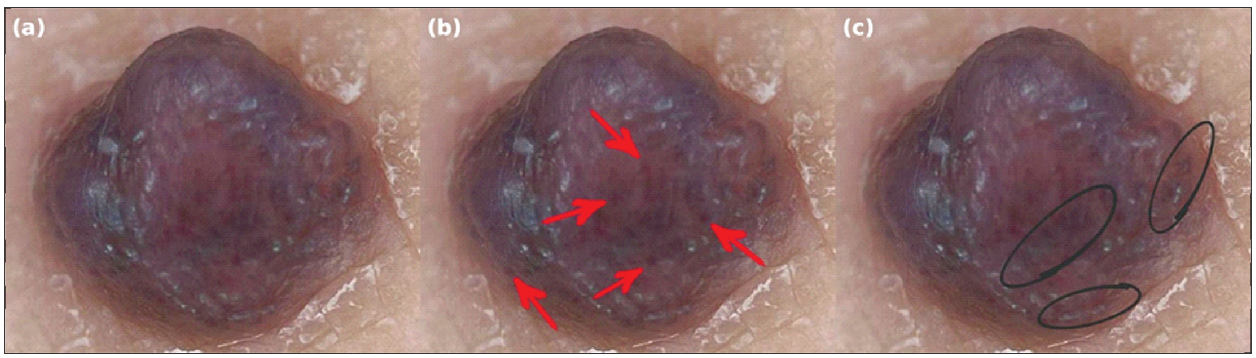

Figure 3. Dermoscopic appearance of the lesion located on the posterior aspect of the right calf. (a) erythematous-violaceous background;(b) irregularly distributed dotted vessels;(c) brown-blue globules(personal archive of Prof. Dr. Magda Constantin).

histopathological slides were re-evaluated. Reassessment established the diagnosis of non-ulcerated primary cutaneous melanoma with a Breslow thickness of 1.2 mm (pT2a), mitotic activity of 3 mitoses/mm², without evidence of lymphovascular invasion or neurotropism. Re-excision with 1 cm margins and sentinel lymph node biopsy were performed. Initial histopathological examination of the sentinel lymph node revealed suspicious subcapsular melanocytic proliferation; however, subsequent immunohistochemical analysis confirmed the presence of a capsular melanocytic nevus, with no evidence of nodal metastasis.

Molecular testing for BRAF mutation was negative. CT imaging performed in January 2026 showed no signs of locoregional progression or secondary lesions.

Discussions

The presented case illustrates the complexity of managing a patient with multiple cutaneous neoplasms, including dermatofibrosarcoma protuberans with fibrosarcomatous transformation and multiple primary cutaneous melanomas occurring at different time intervals. FS-DFSP represents a more aggressive variant, with a metastatic risk of up to 10–15% [2], compared to less than 1% in classic DFSP. The coexistence of these entities in the same patient is rarely reported and raises issues of differential diagnosis, therapeutic strategy, and long-term monitoring.

The fibrosarcomatous variant of dermatofibrosarcoma protuberans is recognized as having more aggressive biological behavior compared to the classic form, with a significantly higher risk of recurrence and metastasis. Identification of the pulmonary secondary lesion and histopathological confirmation of sarcomatous transformation required resumption of targeted therapy with imatinib. Favorable imaging evolution under treatment supports the essential role of tyrosine kinase inhibitors in controlling advanced or metastatic forms of the disease, representing the therapeutic standard in inoperable or systemic settings.

Regarding melanocytic pathology, the main critical point of the case was the lesion initially diagnosed as MELTUMP. This term is used for melanocytic tumors with histopathological features intermediate between nevus and melanoma, in which biological potential remains uncertain. In such situations, therapeutic management may be challenging, and clinical decisions depend significantly on the experience of the pathologist [5,13]. Histopathological reassessment allowed reclassification of the lesion as primary cutaneous melanoma, leading to application of a surgical strategy consistent with current recommendations, including adequate re-excision margins and sentinel lymph node biopsy. This step was essential for correct staging and for avoiding undertreatment.

Another potential moment of overstaging was the interpretation of findings at the sentinel lymph node level. Subcapsular melanocytic proliferations may represent a diagnostic pitfall, sometimes difficult to differentiate from melanoma micrometastases. It has been demonstrated that up to 20% of biopsied lymph nodes may contain benign nevic remnants (nodal nevi) [10], most likely resulting from arrest of neural crest cells during embryogenesis. These cells preferentially localize in the lymph node capsule and trabeculae. Confusion with melanoma micrometastases (which predominantly disseminate within the subcapsular sinus) is common on routine staining. The use of antibodies for S100 and Melan-A (positive in both), HMB-45 (generally negative in capsular nevi) [14], together with an extremely low Ki-67 proliferation index, spares the patient from overstaging to stage IIIC, maintaining stage IB and thus preventing completely unnecessary systemic treatment associated with considerable toxicity.

Furthermore, the negative molecular profile for BRAF mutation defines a tumor subset that would not benefit from targeted therapy with BRAF/MEK inhibitors, information relevant in the event of future recurrence or progression [11].

Conclusions

This case highlights the diagnostic and therapeutic relevance of the coexistence of distinct histogenetically primary cutaneous neoplasms, namely dermatofibrosarcoma protuberans with fibrosarcomatous transformation and metachronous multiple cutaneous melanomas. Their association in the same patient underscores the importance of recognizing a possible increased individual susceptibility to cutaneous neoplasms, determined by complex interactions among genetic, immunologic, and environmental factors.

The case emphasizes the essential role of specialized histopathological evaluation, particularly in borderline melanocytic lesions such as melanocytic tumors of uncertain malignant potential (MELTUMP). Histopathological reassessment in an expert center allowed establishment of the definitive diagnosis of primary cutaneous melanoma, facilitating appropriate therapeutic management and preventing undertreatment with potential negative prognostic impact.

The coexistence of cutaneous neoplasms derived from different cellular lineages (DFSP and multiple melanomas) requires a rigorous and strictly individualized therapeutic algorithm. Long-term careful monitoring is indispensable in these patients, given the increased risk of multiple cutaneous neoplasms and the heterogeneous biological behavior of each entity. Early identification and appropriate management of each lesion are essential for optimizing prognosis.

This case underscores the importance of a multidisciplinary approach, histopathological reassessment in expert centers, and appropriate use of immunohistochemical techniques to avoid both underdiagnosis and overtreatment. The patient's complex clinical course requires careful dermatologic and oncologic follow-up, considering the history of multiple primary cutaneous neoplasms and the distinct biological behavior of each tumor entity.

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Conflict of interest
NONE DECLARED

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