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The Role of Imatinib Mesylate in the Treatment of Metastatic Dermatofibrosarcoma Protuberans: A Case Report and Literature Review

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Abstract **Case Report**

Dermatofibrosarcoma of Darier and Ferrand is a rare cutaneous tumor characterized by its local aggressiveness and high potential for recurrence. It rarely metastasizes, but when it does, the prognosis is poor. Surgery plays a crucial role in the management of these tumors, while targeted therapy is beneficial for metastatic or unresectable forms. Here, we present the case of a 50-year-old female patient who was admitted to our hospital for the management of metastatic dermatofibrosarcoma in the liver. The patient underwent wide excision surgery followed by treatment with imatinib. One-year follow-up showed a good response.

Keywords: Dermatofibrosarcoma, metastasis, cytogenetics, imatinib.

INTRODUCTION

Dermatofibrosarcoma of Darier and Ferrand (DFS) is a low to intermediate grade soft tissue sarcoma originating from the dermis of the skin. It is a rare fibrous cutaneous tumor, accounting for 0.1% of malignant skin tumors and 2 to 6% of all soft tissue sarcomas [1]. Its aggressiveness is primarily local, with no lymphatic dissemination, and the rate of distant metastases is less than 5% [2]. The cytogenetics of DFS are characterized by chromosomal rearrangements resulting in the formation of a specific fusion gene, COL1A1-PDGFB.

The expression of the fusion protein COL1A1-PDGFB appears to activate the PDGFB receptor signaling pathway in an autocrine and paracrine manner, leading to cell proliferation [3]. The treatment of DFS is based on surgery with wide margins of 3 to 5 cm to reduce the rate of local recurrence [1,2]. Imatinib mesylate, a tyrosine kinase inhibitor, has recently proven to be effective in the management of DFS in locally advanced, unresectable, transformed into a higher grade sarcoma, or metastatic forms [4].

CASE PRESENTATION

We present the case of a 50-year-old female patient with a medical history of cardiac arrhythmia under treatment and hypertension managed with a low-salt diet. She was admitted to the Oncology Center of CHU Mohammed VI in Marrakech for the management of a cutaneous tumor on her right thigh. The clinical symptoms began 14 years ago with the appearance of a painless nodular skin lesion of whitish-yellow coloration on the inner side of the right thigh. Over time, the lesion progressively increased in size without any other associated signs. The patient remained in a good general condition with no fever. During the initial examination, the patient was stable hemodynamically and respiratorily, and her overall general condition was good with an OMS score of 0.

The skin examination revealed a poorly defined, mobile mass of 4 cm in size along the deep and superficial planes. The mass was soft in consistency, painless, and showed no signs of inflammation. It was located on the inner side of the right thigh. A skin biopsy was performed by a dermatologist, and the histopathological study of the biopsy revealed a dermal-hypodermal spindle cell tumor proliferation. An additional immunohistochemical study confirmed the diagnosis of dermatofibrosarcoma of Darier and Ferrand. The patient underwent a large excision. The histopathological showed a small yellowish induration measuring 1x0.6 cm. It was situated 0.6 cm from the deep margin, 4 cm from the upper and lower margins, 6 cm from the posterior margin, and 6.5 cm from the anterior margin a postoperative MRI of the right thigh was performed, showing no abnormalities.

An extension assessment was performed, including a thoraco-abdomino-pelvic CT scan that revealed a normal-sized liver. A hypodense mass with continuous peripheral enhancement in an annular halo pattern measuring 58x34 mm was identified in segment VII. A hepatic MRI was requested to further characterize the hepatic lesion. It showed a normal-sized liver with regular contours, presenting a nodular formation in segment VII measuring 46.2x38.2 with T1 hyposignal, T2 hypersignal, and peripheral enhancement (figure 1). The case was discussed in a multidisciplinary team meeting, and the decision was made to initiate the patient on a daily dose of 400 mg of imatinib. After one year of treatment, the patient exhibited good clinical and biological tolerance with a positive radiological response. A follow-up hepatic MRI showed a significant reduction in the size of the lesion described in the initial MRI.

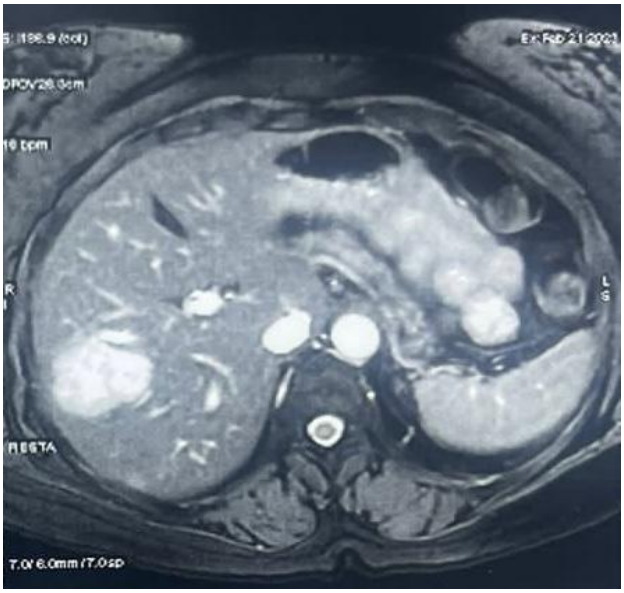

Figure 1: liver MRI showing a nodular lesion with T2 hyper signal and peripheral enhancement

DISCUSSION

DFS is an intermediate-grade mesenchymal dermal tumor [5]. It is a rare tumor, accounting for 0.1% of malignant skin tumors. The worldwide incidence is estimated to be between 0.8 and 4.2 cases per million per year [6]. The onset of DFS typically occurs between the ages of 20 and 50. DFS is extremely rare in children and newborns. It affects both sexes with a slight male predominance [7]. DFS can occur in any part of the body. According to literature data, there is a preference for the trunk, which is affected in 50 to 60% of cases. The limbs represent 20 to 30% of the locations, and 15 to 20% are attributed to the head and neck [8, 9].

Clinical diagnosis is challenging. In the infiltrative stage, the lesion appears as an indurated plaque. In a more advanced stage (nodular stage), the lesion extends and forms a multinodular mass over several months to years. However, this two-stage progression is not constant, as some forms can be unifocal or multifocal from the beginning. If left untreated, these lesions can become very large or ulcerate, leading to pain and bleeding [2, 10]. Histological examination is essential for diagnosis. The tumor consists of a dense, poorly defined, non-encapsulated cellular proliferation occupying the dermis, usually in its entirety. It sends extensions into the subcutaneous tissue without destroying its elements, while the epidermis is preserved. The cells are elongated, spindle-shaped, with varying amounts of cytoplasm and regular oval nuclei. Mitoses are variable with rare atypia. The stroma varies from one area to another.

Collagen and reticular fibers can be more or less abundant, while elastic fibers are pushed to the periphery of the tumor. Within the neoplastic cell clusters, a variable number of vascular spaces and perineural cell streams can be observed. Over time, there is a progressive decrease in the fibrous connective tissue component and an increase in cellular density. On an architectural level, the cells are arranged in radiating bundles ("wheel spoke" appearance) or swirling patterns. In all cases, the diagnostic criteria are based on a set of arguments, including the tumor's evolutionary history, strict dermal location of the proliferation, fusiform cytological configuration, swirling architecture, hypervascular stroma, and perineural cell streams [5]. Generally, the histological appearance guides the diagnosis.

In cases of uncertainty, immunohistochemistry helps distinguish DFS from other spindle cell tumors. It shows intense and diffuse positivity for CD34, focal positivity for smooth muscle actin (SMA), and consistent negativity for desmin and S100 protein [11]. Zones with sarcomatous transformation exceptionally

exhibit very weak or no expression of CD34 [10]. Cytogenetic analysis reveals the presence of supernumerary ring chromosomes composed of sequences derived from chromosomes 17 and 22, or more rarely, translocations t (17;22). These chromosomal rearrangements result in the formation of a specific fusion gene, COL1A1-PDGFB, detected in both ring chromosomes and translocations. To date, the COL1A1-PDGFB fusion gene remains the only identified fusion gene in this tumor.

The location of the breakpoint within PDGFB is remarkably consistent, placing exon 2 of PDGFB under the control of the COL1A1 promoter. On the other hand, the location of the breakpoint within COL1A1 varies widely between exons 7 and 47 in the region coding for the α-helix of collagen [12]. The COL1A1-PDGFB rearrangement leads to overexpression of PDGFB, resulting in permanent autocrine and paracrine activation of the PDGFB receptor called PDGFRβ and, consequently, a signal for cell proliferation [12]. From a diagnostic standpoint, the COL1A1-PDGFB fusion gene can be detected either by multiplex reverse transcription-polymerase chain reaction (RT-PCR) using a combination of forward primers targeting various exons of COL1A1 and a reverse primer for exon 2 of PDGFB, or by fluorescence in situ hybridization (FISH) on interphase nuclei of tissue sections.

The COL1A1-PDGFB fusion gene is not detected in approximately 8% of cases, suggesting the existence of a small proportion of DFS with variant genetic abnormalities yet to be identified [12]. Surgery plays a major role in the curative treatment of DFS. Two excision techniques achieve tumor control in over 90% of cases: wide local excision and Mohs micrographic surgery, which allows tumor excision with histological control of tumor-free margins. Classic wide excision involves performing deep and wide excisions, removing a peripheral margin of healthy skin measuring 3 to 5 cm and ensuring a healthy anatomical barrier in depth. It is evident that for certain locations, such as the face, this safety margin cannot be respected and becomes impossible. Surgical excision is then tailored based on considerations of anatomical territories, functional aspects, and aesthetic units.

Moreover, when there is recurrence, the excision margin should be increased. Reconstruction can be achieved through direct closure, directed healing, skin grafting, or flaps, depending on the size and location of the lesions. Systematic lymph node dissection is not beneficial [13,14,15]. Most authors report DFS as a radioresistant tumor. However, others have claimed that radiotherapy reduces local recurrence rates and allows for more limited surgery. Radiotherapy is recommended for multiple recurrences, insufficient or involved excision margins, very large tumors, and locations that prevent wide surgery. The combination of surgery and radiotherapy appears to be effective in preventing recurrences. Radiotherapy is recommended for multiple recurrences, insufficient or involved excision margins, very large tumors, and locations that prevent wide surgery.

The combination of surgery and radiotherapy seems to be effective in preventing recurrences. The recommended dose is 50 Gray for R0 surgery and 60 Gray for R1 surgery, divided into 2 Gray per fraction, 5 days a week. As for exclusive radiotherapy, it can be attempted in inoperable tumors, cases of patients who are unable to undergo surgery, or those who refuse surgical treatment, and the dose can go up to 66 Gray [16,17,18]. Imatinib mesylate (STI571) is one of the major targeted therapies for DFS. The use of imatinib in the management of these conditions is directly derived from its mechanism of action: tyrosine kinase inhibitor therapy targeting BCR/ABL (indicated in CML), KIT (indicated in GIST), FMS (receptor for colony-stimulating factor 1), and PDGFR alpha and beta (DFSP) [19]. Greco et al. conducted studies on the in vitro and in vivo effects of imatinib on cell lines transformed by the COL1A1-PDGFB fusion transcript [20].

The use of imatinib results in the blockade of cell proliferation and apoptosis of transformed cell lines. Imatinib was studied in three phase II non-randomized open-label clinical trials, providing a better understanding of the molecule's potential. The response rates and time to tumor progression did not differ significantly between these trials conducted at different dosages (400 mg per day or 400 mg × 2 per day), suggesting that 400 mg per day is as effective as 800 mg per day [21]. The optimal position and duration of neoadjuvant imatinib treatment have not yet been definitively established. Future studies will be necessary to determine its role in the preoperative setting as well as in the adjuvant setting after incomplete surgical excision. Alternative strategies with new molecules are currently being evaluated, such as pazopanib, which is being assessed in a multicenter study by the French Cutaneous Oncology Group [22].

This study evaluates the potential of pazopanib, whose efficacy on PDGFRβ is at least equal in vitro to that of imatinib and may overcome secondary resistance to the latter, while also possessing anti-angiogenic activity. The prognosis of DFS is characterized by its high potential for recurrence. The percentage of recurrences varies depending on the excision margins. Therefore, the initial radical surgical excision is the essential prognostic factor, determining the risk of local relapse. Several poor prognostic factors emerge from various published series, including incomplete excision, localization at the cephalic extremity where the principles of wide excision are more difficult to adhere to, the presence of fibrosarcoma areas within the tumor, and tumor depth

[23,24]. DFS rarely metastasizes, and the prognosis for these forms is poor. The 5-year survival rate is estimated at 20% [25].

CONCLUSION

Darier and Ferrand's dermatofibrosarcoma protuberans (DFSP) is a rare cutaneous tumor with a slow local progression over several years. It is characterized by diagnostic difficulty, a tendency for recurrence, and the rarity of metastases, which are primarily pulmonary. The diagnosis is often suspected clinically and confirmed histologically, with immunohistochemistry used in cases of diagnostic uncertainty. Targeted therapy with Imatinib Mesylate has proven to be effective in the treatment of unresectable or metastatic DFSP.

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