DEVELOPMENT OF DYSPLASTIC NEVI AFTER DERMATOFIBROSARCOMA PROTUBERANS TREATMENT WITH IMATINIB: A CASE REPORT

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Summary

Dermatofibrosarcoma protuberans is a very rare tumor, but it is considered the most common skin sarcoma. It originates in the dermis and tends to infiltrate underlying structures. Due to a high rate of misdiagnosis, it is usually discovered with local invasions, but metastases are rare. Wide local excision and adjuvant therapies such as Imatinib (Tyrosine Kinase Inhibitor) are used to both prevent and limit recurrences. Long term follow-up is strongly recommended.

We present the case of a 51-year-old man who presented with multiple atypical nevi. The patient was diagnosed with dermatofibrosarcoma protuberans and mediastinal adenopaties seven years ago. The primary lesion was excised and he was prescribed chemotherapy with Paclitaxel and Carboplatin. Subsequent, he was diagnosed with a dermatofibrosarcoma protuberans pulmonary metastasis with fibrosarcomatous development, thus beginning treatment with Imatinib. From the patients`s history, he was also diagnosed with in situ melanoma on the back which was excised, developed after initiating the treatment with Imatinib.

Patients with fibrosarcomatous dermatofibrosarcoma protuberans may need adjuvant therapy such as Imatinib in order to avoid a possible recurrence or to treat metastases. Dysplastic nevi proliferation may be associated with Imatinib therapy. Therefore, regular follow-ups are required in order to monitor both dermatofibrosarcoma protuberans recurrences, as well as atypic nevi at a patient with history of melanoma.

Keywords: *Dermatofibrosarcoma, metastases, Imatinib, dysplastic nevi, atypical nevi.*

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Introduction

Dermatofibrosarcoma protuberans is a rare, low-grade soft tissue tumor originating in the dermis and subcutaneous tissues, which accounts for approximately 1% of all soft tissue sarcomas. It is locally aggressive, with a tendency for local recurrence, but rarely metastasizes. [1]

It usually affects young to middle aged patients, and can be found on the trunk, extremities, neck or head. It is usually a very slowly growing skin-colored tumor without epidermal invasion but with intracutaneous and subcutaneous spread. Sometimes the tumor presents as a reddish, flat elevated, firm lesion with irregular borders or it may exhibit a multinodular growth. Rapid modifications of the lesion may suggest a fibrosarcomatous transformation. [1]

The early clinical symptoms of dermatofibrosarcoma protuberans are non-specific, making diagnosis difficult and leading to a high chance of misdiagnosis. Therefore, pathological and immunohistochemical examinations are the gold standard for diagnosing dermatofibrosarcoma protuberans. [2] Dermatofibrosarcoma

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protuberans is histopathologically divided into classical and non-classical types. Classical-type dermatofibrosarcoma protuberans typically shows diffuse infiltration of the dermis and the subcutaneous fat by densely packed, spindle-shaped, CD34-positive tumor cells, characterized by cytological uniformity, arranged in a radial pattern and forming a honeycomb-like structure. [1] Atypia is minimal, and mitoses are rare. [3] Non-classical dermatofibrosarcoma protuberans comprises at least 10 subtypes, of which the most common include pigmented type, mucus type and fibrosarcomatous type. [4] Fibrosarcomatous dermatofibrosarcoma protuberans typically displays increased mitotic rate and cytological atypia which may develop gradually or appear de novo. [1] Mitotic count, necrosis and areas of fibrosarcomatous change should be mentioned in the histopathological report as they are associated with aggressive clinical behavior and a lower overall survival rate. [3]

Pathologically, the most important differential diagnoses of dermatofibrosarcoma protuberans are benign atypical variants of dermatofibroma and dermatomyofibroma, and more severe diseases, such as pleomorphic sarcoma of the skin, leiomyosarcoma, Malignant Peripheral Nerve Sheath Tumors (MPNST) and rare variants of spindle-cell malignant melanoma. Therefore, immunostainings (CD34, factor XIIIa, stromelysin-3) are recommended in all cases of suspected dermatofibrosarcoma protuberans. [1]

Dermatofibrosarcoma protuberans is a locally aggressive tumor and local recurrences can be relatively common. As distant metastases are extremely rare, an extensive workup is not routinely indicated unless clinical examination indicates it or in case of recurrences or fibrosarcomatous transformation. Diagnosis of metastatic disease requires lymph node ultrasound, chest X-ray and abdominal ultrasound or CT scans. [1]

There is no standard staging system for dermatofibrosarcoma protuberans. In general, the primary tumor is considered stage I, lymph node metastasis is stage II and distant metastasis, stage III. [1] Although, the potential for metastasis of the classic form of dermatofibrosarcoma protuberans is low, metastatic dermatofibrosarcoma protuberans can occur, especially with fibrosarcomatous transformation or after multiple recurrences due to inadequate surgical excisions. The lung appears to be the most common site of involvement, although other sites such as the brain, pelvis, and non-local lymph nodes (rarely), have been cited. [4]

Surgical excision with safety margins is the main therapeutic option. [2] If initial margins are invaded, secondary excision is recommended. Regarding lateral safety margins, 3 cm is advisable. Moreover, the excision of the deep fascia should be performed in order to remove any infiltrating tumor cells. Mohs micrographic surgery is the optimal way to achieve complete tumor resection. However, for locally advanced and metastatic dermatofibrosarcoma protuberans, Imatinib (Tyrosine Kinase Inhibitor), chemotherapy and radiation therapy have been used as adjuvant therapy. [1]

Imatinib is a tyrosine kinase inhibitor that selectively targets the platelet derived growth factor (PDGF) receptor and is indicated for treating inoperable primary tumors and recurrences as well as metastatic dermatofibrosarcoma protuberans. Approximately 50% of patients respond to Imatinib and it has also been prescribed as neo-adjuvant, for preoperative tumor size reduction. [1]

Radiation treatment is an option for primary inoperable tumors, incomplete resections and prior multiple recurrences, but standard chemotherapy regimens are no longer recommended due to the fact that there are no proven benefits. [5]

In case of fibrosarcomatous dermatofibrosarcoma protuberans, the main treatment option is complete surgical excision with 3 cm safety margins, taking into consideration adjuvant radiation or targeted therapy in inoperable tumors or metastatic disease. [1]

Follow-ups for local recurrences every six months are advised. Imaging examinations are required for recurrent dermatofibrosarcoma protuberans and fibrosarcomatous dermatofibrosarcoma protuberans. [1]

Case

We present the case of a 51-year-old man who was sent to us for a dermatological consult from his oncology team regarding multiple pigmented macules. From the medical history we found out

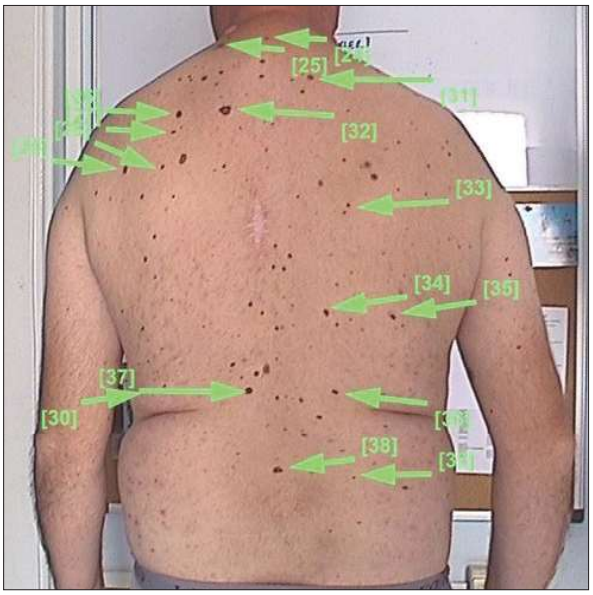

Figure 1. Multiple pigmented nevi on the back, many of them with atypical appearance.

that the patient had a skin-colored, indurated supraclavicular nodule 7 years ago, which was misdiagnosed as a cyst. The biopsy revealed dermatofibrosarcoma protuberans for which he underwent surgical excision. Due to the fact that the PET-CT revealed multiple mediastinal adenopathies which were thought to be caused by the initial tumor, he was prescribed 8 doses of chemotherapy using Paclitaxel and Carboplatin.

Subsequent, due to the fact that the patient had metabolically active mediastinal adenopathies described on PET-CT, he was diagnosed with dermatofibrosarcoma protuberans pulmonary metastasis with fibrosarcomatous development and he started Imatinib 800 mg/day treatment for 2 years. Concurrently, he was also diagnosed with in situ melanoma (S100+, HMB45+, MELAN A+, Ki67+) on the upper trunk which was surgically removed.

Over the last 3 years, the patient noticed an increase in pigmented lesions: 4 of them were atypical pigmented macules on the trunk and abdomen, with asymmetric irregular borders and variable pigmentation. Excisional biopsies were performed for all 4 atypical macules and histopathological examination described dysplastic nevi. He undergoes regular follow-ups every 3 months.

Discussions

Imatinib is a selective BCR-ABL tyrosine kinase inhibitor prescribed as adjuvant therapy for advanced dermatofibrosarcoma protuberans. I found one report describing dysplastic nevi associated with Radotinib therapy after chronic myeloid leukemia.

Eruptive melanocytic nevi is associated most frequently with immunosuppression. This syndrome is thought to result from a disarray in the regulation of melanocyte growth patterns caused by multiple foci of stimulation or immunosuppression. The tyrosine kinase inhibitors

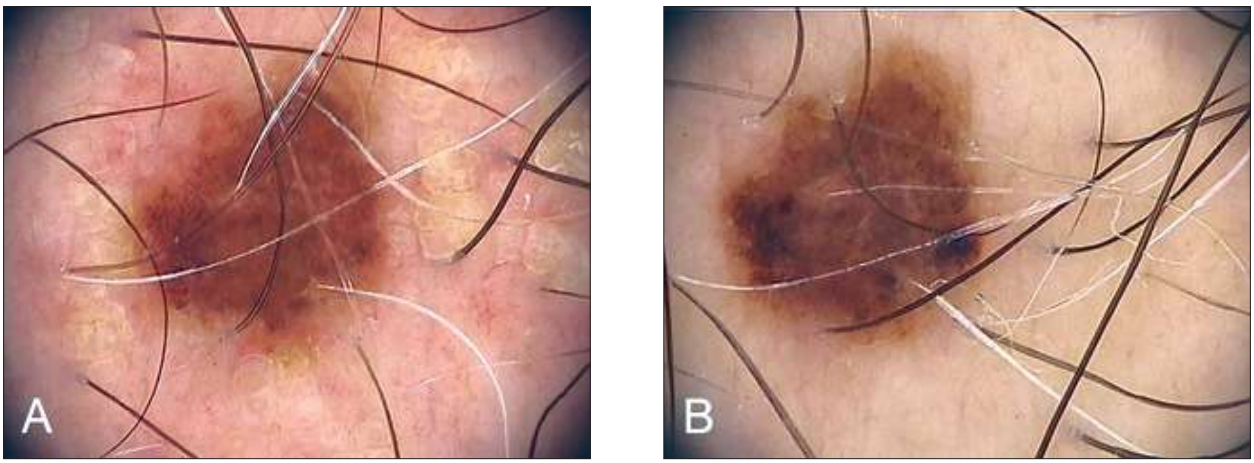

Figure 2. The evolution of a pigmented nevus on the anterior thorax during a period of 3 years, with irregular pigmented network and new globules. (A) The initial appearance. (B) The appearance after 3 years.

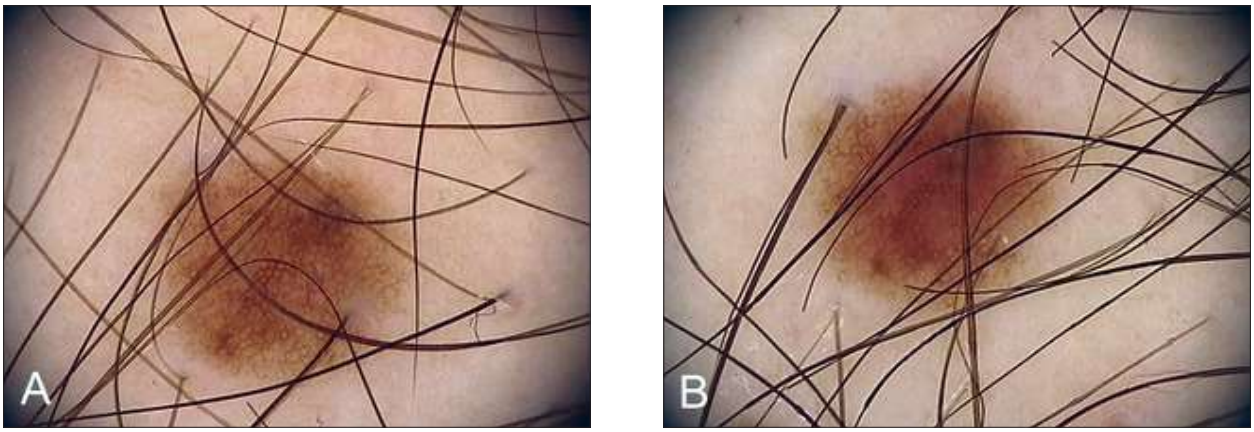

Figure 3. The evolution of a pigmented nevus on the abdomen during a period of 3 years, with irregular pigmented network and new globules. (A) The initial appearance. (B) The appearance after 3 years.

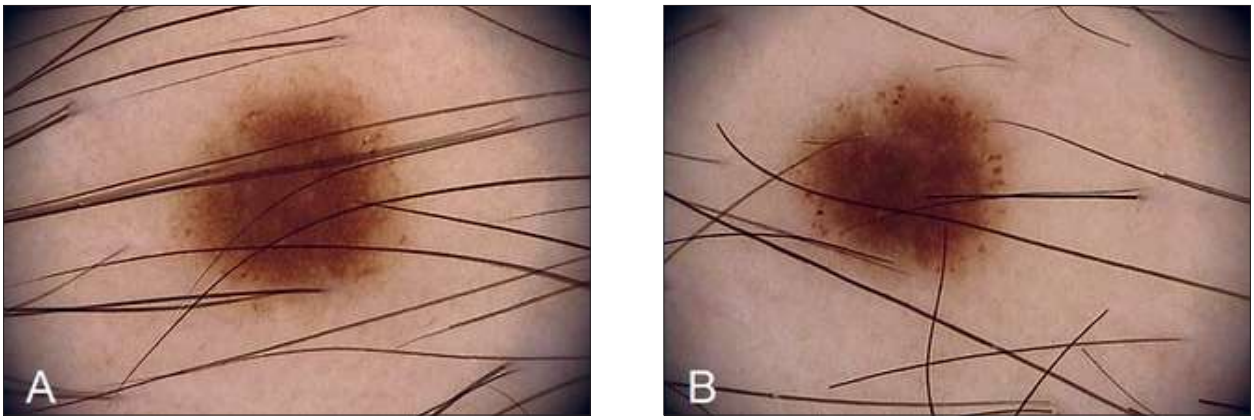

Figure 4. The evolution of a pigmented nevus on the back during a period of 3 years, with new peripheral globules. (A) The initial appearance. (B) The appearance after 3 years.

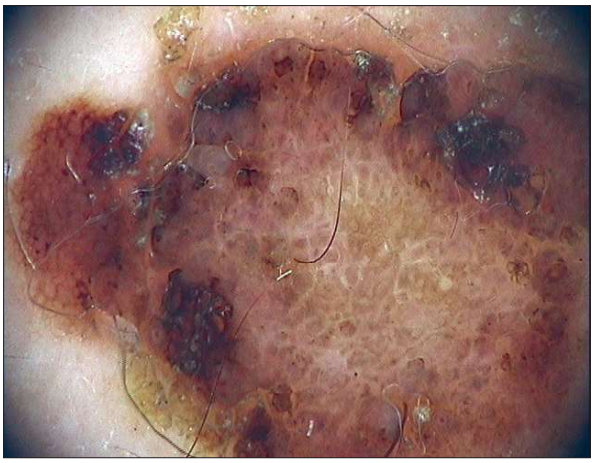

Figure 5. Excised atypical nevus diagnosed histopathologically as a dysplastic nevus.

inhibit not only BCR-ABL but also the c-kit signaling pathway, leading to diffuse hypopigmentation. However, paradoxical hyperpigmentation has been reported in imatinib. The mechanism is not entirely known, but it may be due to an aberrant activation of a c-kit mutant type. Moreover, because chemotherapeutic agents induce cytotoxic effects in epithelial cells, imatinib may exert cytotoxic effects in epidermal melanocytes, causing melanocytic dysplasia. [6]

Conclusion

In conclusion, we report a case where dysplastic nevi developed after Imatinib therapy for dermatofibrosarcoma protuberans. The pos-

sible occurrence of dysplastic nevi should be considered after tyrosine kinase inhibitors. Although most dysplastic nevi do not progress to malignancy, there is still a risk of malignant melanoma. Therefore, long-term follow-ups are essential for recording pigmented lesions, thus lowering the risk of malignant melanoma occurrence.

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Conflict of interest
NONE DECLARED

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