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Pulmonary metastasis of a Dermatofibrosarcoma of Darier and Ferrand treated by IMATINIB: a case report

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ABSTRACT

Dermatofibrosarcoma (DFS) described by Darier and Ferrand represents less than 5% of soft tissue sarcomas and metastases only very rarely.

We report the case of a 51-year-old patient followed for six years for a DFS of the right thigh root recurrent several times after non-optimal surgical resections. The occurrence of thoracic pain associated with a cough with dyspnea, motivated the realization of a thoracic computed tomography (CT) showing a right basal pulmonary mass with pulmonary nodules. CT biopsy of one of the pulmonary nodules confirmed the metastatic nature of these lesions. The search for translocation t (17,22) could not be performed. A treatment based on imatinib has been started. The evolution was marked by the disappearance of the respiratory symptomatology and a good radiological response.

The advent of targeted therapy with imatinib transformed the prognosis for this disease, which was considered incurable at the metastatic stage.

Keywords: Darierand FerrandDermatofibrosarcoma, Imatinib, Pulmonary Metastasis, Recurrence, Translocation.

Conflict of interest: The author declares that he has no conflict of interest

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Introduction:

Darierand FerrandDermatofibrosarcoma (DFS) is a fusiform cell skin sarcoma first described by Darierand Ferrandin 1924 under the name of progressive and recurrent dermatofibroma, also called by the Anglo-Saxon DFS Protuberans (DFSP)[1]. This slowly progressive tumor is characterized by a strong local aggressiveness and a real but weak metastatic potential: 5% of the patients will have a metastatic evolution in spite of an optimal surgery[2].

DFSare characterized by a specific translocation between chromosome 17 and chromosome 22: t (17,22) (q22; q13) which is at the origin of the malignant transformation in this pathology. This abnormality molecular of DFSP has diagnostic and especially therapeutic consequences. In vitro studies testing the antitumor activity of imatinib (inhibitor of PDGFR: platelet-derived growth factor receptor) have shown a regression of proliferation in the presence of platelet-derived growth factor [3, 4].

We report here the case of a patient followed for a metastatic DFS at the pulmonary level with a good evolution under treatment by Imatinib.

Case presentation

A 51-year-old man presented six years ago a nodule of the root of the right thigh relapsing on 3 surgical occasions. The last surgical procedure performed a year ago, allowed a resection with microscopic residual tumor (resectionR1). On the histological examination of the operative specimens, tumoral formation of a mesenchymal nature with fuso-cellular proliferation (figure 1) strongly expresses CD34 marker at the immunohistochemical analysis(figure 2), which is in favor of DFS. Resection limits were invaded deeply and sometimes dropped to less than 1mm. Six months ago, the patient developed respiratory symptoms that included chest pain associated with cough and dyspnea. Thoracic computed tomography showed a right basal pulmonary mass associated with disseminated nodules in the two lung fields (Figure 3). Due to the scarcity of DFS metastases, a scanned-biopsy was performed on one of the largest pulmonary nodules, confirming the metastatic nature of these lesions: appearance of a low-grade fuso-cellular sarcoma, marked by the PS100 and not the smooth muscle actin. Although a search for t (17,22) translocation could not be performed, an Imatinib-based treatment at 400 mg/day was initiated. The evaluation after two months of treatment was marked by a clear clinical improvement and an excellent radiological response estimated at 70% according to the criteria of the Response Evaluation Criteria In Solid Tumors (RECIST) (figure4).

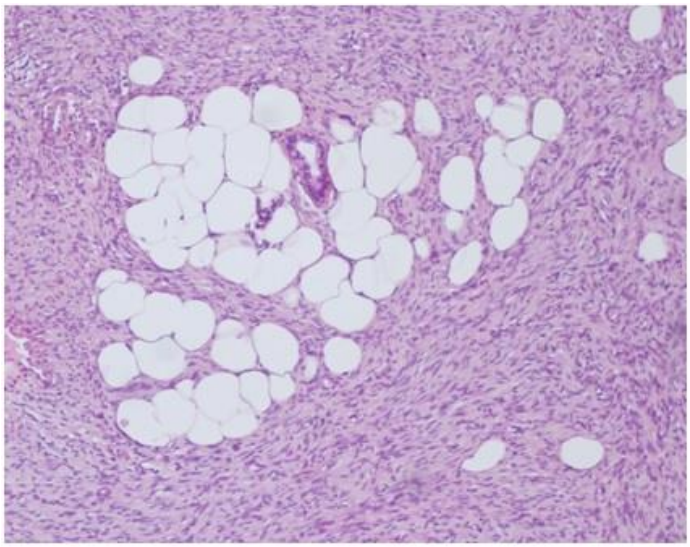

Figure 1: Fusiform cells with thin fibroblasts

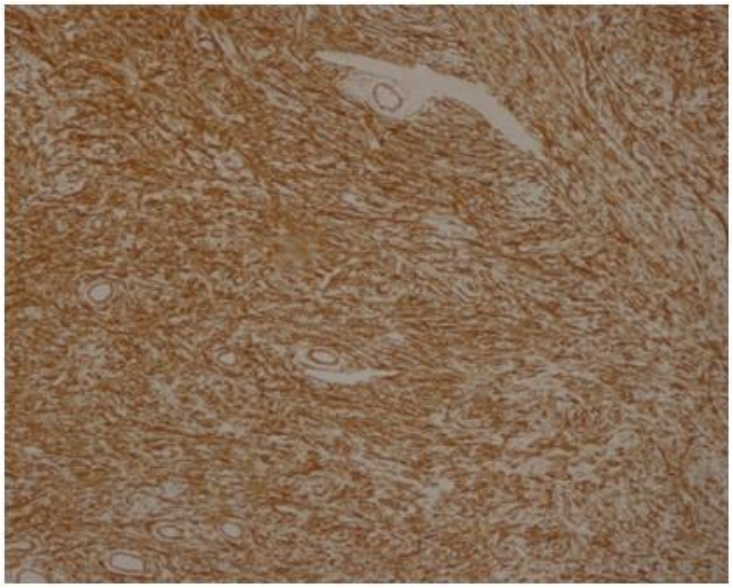

Figure 2: Positive immunohistochemical staining of CD34.

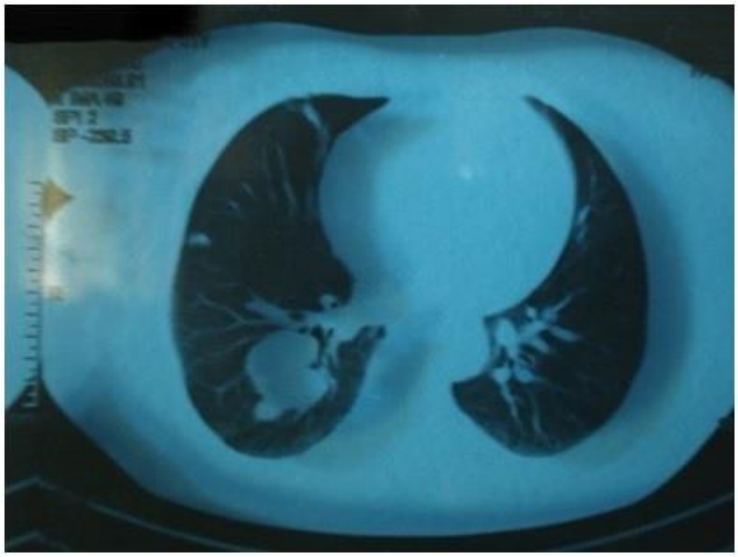

Figure3: CT image before treatment.

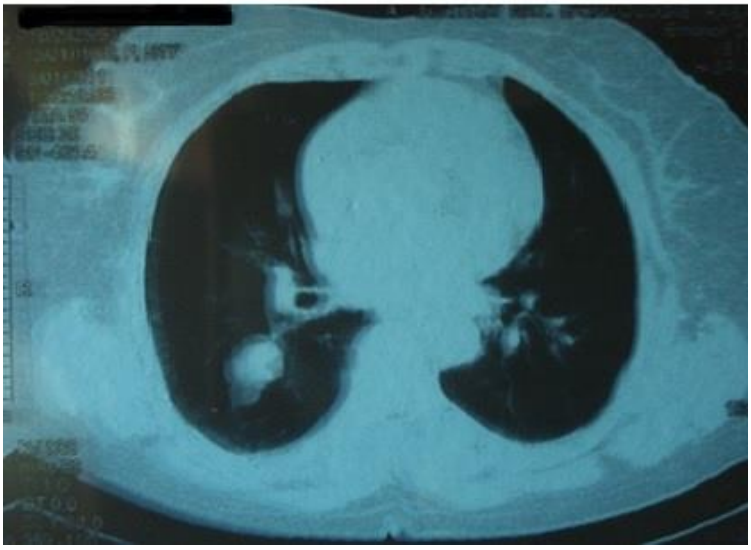

Figure 4: CT image after treatment.

Discussion:

DFS is a soft tissue sarcoma that accounts for about 0.01% of all malignant tumors and 2% to 6% of all sarcomas[3, 4]. DFS mainly affects patients aged 20 to 50, although it has been described in children and the elderly, congenital DFS is a recognized but rare entity [5]. It is a local aggressive tumor that originates in the dermis from fibrocytes that express on the surface the CD34 antigen commonly used as an immunohistochemical marker with detection sensitivity between 84 and 100% [6].

DFS is characterized by a genetic abnormality described in 1990 and is present in 90% of DFS cases. It is a reciprocal t (17,22) (q22, q13) translocation that produces a collagen gene for type 1 alpha1 COL1A1 collagen with the PDGFB growth factor B chain gene. This rearrangement leads to disruption of PDGFB expression with continuous activation of PDGF tyrosine kinase receptor that stimulates DFS growth [3].

DFS can be presented under two aspects: either as a fibrous plaque initially hard pinkish which extends progressively preceding the appearance of the nodules, or as a firm dermal nodule of coloration identical to that of the normal skin and whose evolution is characterized by the appearance of other satellite nodules, periphery which confluence to achieve a multi nodular closet characteristic of this lesion. The most frequent locations of DFS are: the trunk (47%) followed by the root of the limbs (inferior: 20% and upper 18%) and the neck (14%)[7].

DFS is a slowly evolving malignant tumor with a pronounced tendency to local recurrence, whereas it only gives distant metastases in 2 to 4% of cases: haematically in 2/3 cases or lymphatic 1/3 cases. Pulmonary, cerebral and bone metastases are the most described, whereas lymph node metastases are exceptional. These metastases occur late in the clinical course and usually after several local recurrences [7, 8].

The treatment of DFS is primarily surgical. Good surgery with satisfactory margins of healthy excision alone can cure this disease. Currently the reference technique is the Mohs technique. This surgery includes tumor fixation in situ by zinc chloride before excision or freezing of the excision piece horizontally allowing the analysis of 100% of the banks. Horizontal sections in series that guide the surgical procedure are performed during the procedure, this allows the tumor to be completely removed with the least sacrifice of surrounding healthy tissue [8].

Mohs surgery, named after its inventor Dr. Fredrick E. Mohs, is a microscopically controlled surgery, very effective for common types of skin cancers. This surgery decreased DFS recurrence rates from 53% to 11% and achieved a cure rate of 98%, even in recurrent DFS [7, 8]. A study comparing the wide resection of DFS with Mohs surgery showed that wide resection was associated with a recurrence rate of 13%, whereas Mohs surgery was not followed by any recurrence at 5 years [8].

The latest National Comprehensive Cancer Network (NCCN) guidelines recommend 2 to 4 cm resection margins for conventional surgery.This tumor seems to be radiosensitive. Currently, radiotherapy is used to complete surgery in case of excision in the microscopic tumor zone, as well as palliative treatment [9].

The rate of distant metastases is 5% and the rate of local metastases is 1%[10]. The presence of metastases is associated with poor prognosis, with few patients surviving more than two years. Encouraging results in terms of response were obtained with Imatinibin DFS leading to improved prognosis even in case of metastatic disease[11].

The efficacy of Imatinibin the treatment of DFS is probably related to the tumor dependence of the PDGF pathway resulting from the t (17; 22) translocation inducing constitutive expression of the PDGF ligand. DFS is a unique example of a tumor that responds to a specific targeted

treatment that is not based on genetic amplification or mutation. The clinical development of Imatinibfor the treatment of DFS is limited by the fact that it is a benign to intermediate tumor for which complete surgical excision avoids the use of systemic therapy. Imatinib is likely to be applicable only to the treatment of a subset of patients with unresectable, recurrent or metastatic disease [11-13].

Imatinibmesilate has been developed to inhibit Abl kinase in the treatment of Philadelphia chromosome-positive chronic myeloid leukemia. The use of Imatinibfor the treatment of DFS has so far been limited, but has been encouraging. In one study, 10 patients with locally advanced or metastatic DFS presented varied responses to Imatinib. One patient with no t(17, 22) translocation did not respond to Imatinib [10]. Other studies have been published which show the success of this treatment in cases of metastatic or surgically unresectable DFS. This is the case of a patient with recurrent DFS at the upper back with metastases to the armpit and lung, in whom a response was observed after one month of treatment. After three months of Imatinib, the tumor was strongly regressed and the CT image showed almost complete disappearance of pulmonary metastases [12]. In a patient with DFS in the thigh with presence of vertebral metastases, Imatinibinduced a 75% decrease in tumor size in four months, making surgical resection of the tumor possible. The resected part showed no evidence of malignancy, indicating a complete histological response to the treatment [13]. Imantinib is now approved for the treatment of adult patients with unresectable, recurrent or metastatic DFS who are not good candidates for surgery.

Another study involving 15 patients with DFSP: initially locally advanced inoperable and 6 metastatic patients (two at the lungs, two soft tissues and two lymph nodes) with or without surgery, treated with Imatinib400-800mg. All patients had a cytogenetic diagnosis (fluorescent in situ hybridization). The two-year progression-free survival was 60%, and the two-year overall survival was 78% with 10 partial responses (67%), two stable diseases (13%) and three progressive diseases (20%). All of these studies confirmed the important anti-tumor effect of Imatinibin DFS harboring the t (17; 22) translocation [14-17].

Conclusion:

The DFS of Darier and Ferrand is a rare cutaneous tumor. It is characterized by its tendency towards recidivism andrarity of its metastases which are essentially pulmonary. The treatment of DFS is primarily surgical and must meet a double objective: a large excision passing between 3 and 5 cm of the banks depending on the location and the primary or recurrent nature of the tumor, while trying to be Ro (resection without microscopic tumor residue) in depth and cover the loss of substance caused by excision. An alternative to conventional surgical treatment is Mohsresection, which conserves healthy tissue based on extemporaneous examination of the operative piece. But this technique is not yet practiced in Morocco because of its high cost and theunavailability of specialized teams.

When the treatment is well conducted, the DFS has a good prognosis but nevertheless requires lifelong clinical supervision because of the risk of very late recurrences.

Conflict of interest:

The authors declare that they have no conflict of interest.

Authors' contributions

KE participated in the conception and design of the report and wrote the paper. IE and RB have made substantial contributions to acquisition, analysis and interpretation of patient’s data. MT has been involved in coordination and design of the report and revision of the manuscript. HE had overall responsibility for the report. All authors read and approved the final version of the manuscript.

Informed Consent:

Informed consent was obtained from the patient for publication of this case report.

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