Clinics of Surgery

Breast Desmoid Tumor with Spectacular Evolution : A Case Report and Review of Current Treatment Options

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1. Abstract

Desmoid tumors or aggressive fibromatosis of the breast, are a rare entity, representing less than 0.2% of all primary breast tumors. The clinical presentation and evolution can mimic a malignant carcinoma, with the notable difference that a desmoid tumor cannot generate distant metastases. The aim of the treatment is to achieve local control of this tumor, which can be highly aggressive by deeply infiltrating surrounding structures, and frequently reoccurs after resection. Both the tumor and its treatment may cause significant morbidity, causing a real therapeutic challenge.

We here report the case of a 63-year-old woman who underwent a tumorectomy for left breast cancer and developed six years later a large desmoid tumor in the same breast. First medically treated with selective estrogen receptor modulators and non-steroidal anti-inflammatory drugs, it progressed to an ulcerative exophytic and necrotic tumor requiring surgery. To our knowledge, this is the first description of such a spectacular evolution in the literature.

After reporting on this uncommon evolution of a rare disease, we will provide a short review of current treatment options.

2. Introduction

Desmoid tumors (DTs), or aggressive fibromatosis, are a sub-type of a mesenchymal neoplasm originating from a monoclonal proliferation of fibroblasts. According to the World Health Organization Classification of Soft Tissue, DTs are classified in three groups: abdominal wall fibromatosis (AF), extra-abdominal fibromatosis (EAF), and intra-abdominal fibromatosis (IAF). The incidence of EAF and AF is 2.4-4.3 new cases per 10^6 individuals per year. It accounts for 3% of the soft-tissue neoplasms and is even more uncommon when occurring in the breast. The breast location is included in EAF and represents less than 10% of all cases [1].

The pathogenesis of these DTs is multifactorial. Mutations in the beta-catenin and adenomatous polyposis coli (APC) genes, leading to abnormalities in the WNT pathway, are responsible for the development of most desmoid tumors. This explains the association between Familial Adenomatous Polyposis (FAP) and a minority of DTs, caused by germline mutations of the APC gene. Most DTs however are sporadic and occur in women of reproductive age, indicating an effect of the hormonal environment.

Approximately 85%-90% of DTs are associated with somatic beta-catenin gene mutations, leading to nuclear accumulation of beta-catenin. Beta-catenin and APC mutations seem to be mutually exclusive in DTs. The detection of a somatic beta-catenin mutation may thus help to exclude a syndromal condition, and conversely, beta-catenin wild type status justifies more extensive clinical work-up to exclude a FAP syndrome (e.g. by colonoscopy). A traumatic event, most often surgery, is another potential risk factor for this condition [2].

DT is classified as a benign neoplasm because, unlike sarcoma, it has no distant metastatic potential and no impact on overall survival. This disease can nonetheless cause high morbidity due to its high recurrence rate and subsequent treatment sequelae.

Before 2000, wide excision surgery with negative margins was the front-line treatment of DTs [3], inspired by the treatment of soft-tissue sarcoma [3, 4]. However, despite adequate surgery with negative margins, the local recurrence rate remains unacceptably high.

Based on new evidence detailed further, a paradigm shift has

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taken place since several years, moving away from radical surgical treatment towards an observational strategy called « wait and see ».

Of note, several studies have been conducted with medical therapies, thanks to a better understanding of the physiopathology of the tumor and the signalization pathways involved.

3. Case Presentation

A 63-year-old woman followed-up for a personal history of left breast cancer presented in September 2017 after palpating a mass in her left breast.

Her primary breast cancer was treated in June 2011 with conservative surgical excision (left lumpectomy) and sentinel lymph node biopsy. Anatomopathological results at the time showed a 6x9 mm grade 3 in situ ductal carcinoma associated with atypical ductal hyperplasia. Two sentinel lymph nodes were negative. The patient subsequently underwent adjuvant radiotherapy, followed by endocrine therapy with tamoxifen until January 2017.

Clinical examination in September 2017 confirmed the appearence of a firm 4 cm mass in the upper outer quadrant of the left breast, without any palpable adenopathies. Ultrasound examination revealed a suspicious-looking hypoechogenic mass of 41x24x33 mm with irregular borders and a strong Doppler sig-nal. A core needle biopsy revealed a histological and immunohistochemical (IHC) profile compatible with desmoid fibromatosis. Microscopic examination showed fusiform cells in a collagenous matrix without any mitoses. IHC was positive for beta-catenin, negative for cytokeratin, desmin, Sox 10 and CD 34.

A CT-scan of the chest and of the abdomen did not find any signs of metastasis.

The multidiscipinary board recommended medical treatment as first-line therapy. The patient received tamoxifen (20mg orally daily) and non-steroidal anti-inflammatory drugs (NSAIDs; diclofenac 75mg orally daily) with a close clinical follow-up.

In September 2018, after twelve months of medical treatment, the patient was seen in the emergency clinic for ulceration of the tumor. Clinical examination discovered a 10 cm mass, with small skin erosion and necrosis in front in the summit of the tumor. Magnetic resonance imaging (MRI) of the breast confirmed the growth of the mass, measuring it at 105x80x76 mm, and demonstrating close contact with the chest wall and infiltration of the pectoralis minor muscle (**Figure a**). Less than one month later, the tumor was almost completely exteriorized, forming a huge exophytic necrotic lesion (**Figure b & c**).
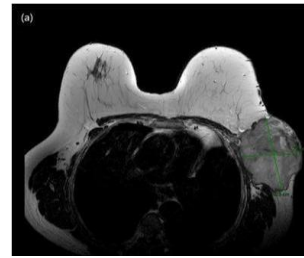
Figure a: Magnetic resonance imaging (MRI) of the breast in Sept 13th 2018, confirming the growth of the mass, measuring 10,5x8x7cm, and demonstrating close contact with the chest wall and infiltration of the pectoralis minor muscle.

Figure b: Desmoid tumor exteriorizing through the skin (picture taken Oct 10th 2018)..

Figure c: Desmoid tumor showing a progression outside the skin and an increasing of the necrotic part. (picture taken Oct 24th 2018).

Figure d: One month post-operative result.

Given the lack of local control of the tumor, the multidiscipinary board agreed to perform a surgical excision of the tumor to relieve the patient of the discomfort caused by this necrotic tumor. The aim was to clean the area and close the skin and not to have complete R0 resection.

At the time of surgery, the tumor was deeply attached to the fascia of the pectoralis major and pedicle of the latissimus dorsi, leading to a macroscopic incomplete resection (R2). Fortunately though, the skin could be closed after resection of the tumor. Anatomopathological results confirmed the desmoid nature of the tumor, which measured 11x10,5x5,5cm. The exophytic transcutaneous part measured 6x5x3cm, with partial necrosis (**figure e**). Margins were all positive for desmoid tumor except superficial margin. IHC studies confirmed the positivity for beta-catenin.

Figure e: Macroscopy of the desmoid tumor, measuring 11x10,5x5,5cm in total with an exophytic transcutaneous part measuring 6 x 5 x 3cm.

Next generation sequencing of the beta-catenin (CTNNB1) and APC genes was performed. No CTNNB1 mutation was found in the tumor, but a somatic APC mutation was found. These results could be in favor of FAP but the patient has no familial history of colorectal cancer or polyps. Additionally, FAP is usually associated with IAF, which does not include breast DTs.

A supplemental surgical procedure was necessary one month af-ter the initial procedure because of a small cutaneous dehiscence of the scar. The recommendation of the multidisciplinary board was to continue tamoxifen as a maintenance treatment and to perform close follow-up.

At 4 months of follow-up, clinical examination shows no sign of recurrence.
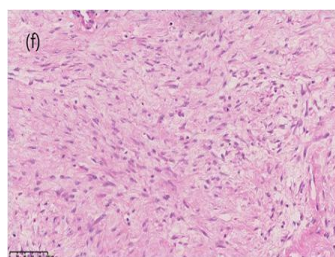
Figure f: Micro.

4. Discussion

While traditional management of DTs used to consist in a wide surgical excision with clear margins, recent studies have demonstrated that desmoid tumors can spontaneously regress, or re-main stable without any treatment in 20-30% of the cases [5-7]. On the other hand, we know that a very high rate of recurrence after surgery is described for all locations of DTs (25 to 60%) [8]. In breast DTs, the overall recurrence rate after surgery ranges from 18 to 39%[9]. Moreover, trauma, and particularly surgery, can lead to de novo development of DT [10]. It is estimated that 30% of breast DTs occur at the site of a past trauma or breast surgery, performed both for cosmetic or carcinologic reasons [2, 11]. In our case-report, the patient had a personal history of lumpectomy in the same breast.

These observations have led to a new strategy for the management of DTs, called « wait and see » approach. It consists of initial clinico-radiological surveillance after diagnosis of DT, with or without adjunction of medical therapies such as NSAIDs or tamoxifen, while surgery or more aggressive treatments like che-

motherapy and radiotherapy are proposed in case of progression of the disease [3, 6, 7].

Current data show that progression occurs in the vast majority within the 3 first years after diagnosis [3, 7, 10]. Therefore, an observation period without treatment allows for the identification of the patients who really require surgery, while avoiding overtreatment of DTs that spontaneously regress or remain stable and paucisymptomatic.

The first studies which supported this « wait and see » policy were based on retrospective data on patients with various sites of DTs, including breast DT.

In the study of Fiore et al. [7], five-year progression-free survival (PFS) was 49.9% with this « wait and see » approach. In the study of Turner et al [12], watchful waiting was successful in 58% of patients with no progression in the first 3 years of follow-up (with the adjunction of NSAIDs and/or tamoxifen in 20% of the patients).

In the study of Roussin et al [2], focused on the results of a « wait and see » approach in breast DT, 91% of patients did not require any surgery or radiotherapy within 36 months of follow-up, and all of them had stable lesions (median tumor size change was -4 mm during follow-up (range to -13 to +20 mm). Recent prospective data by Penel et al [13] show a 2-years event-free survival, defined as the absence of progressive disease during observation, relapse after surgery or change in therapeutic strategy, of 58%. Studies have also shown that this « wait and see » period does not induce more morbidity to patients who progress and ultimately require treatment [12].

Predictive factors of progression during observation or recurrence after surgery are still under investigation. Young age, large tumor size, unfavorable location (chest wall, head and neck, up-per limb), or somatic mutations in the beta-catenin gene (CTN-NB1, in particular the S45F mutation) have been identified as factors of progression/recurrence [10, 13, 14].

In the surgical management of DT, resection margins remain a controversial issue because of conflicting data about their impact on recurrence after surgery [10, 15]. Numerous studies have shown no effect of microscopic margins on the recurrence rate [7, 12, 13, 16, 17]. Survival curves are not significantly different if the resection is microscopically complete (R0) or incomplete (R1), but R2 resections result in a significantly poorer prognosis. From these observations, guidelines now state that when surgical therapy is needed, wide local excision with microscopically negative margins is the goal of resection but should not be at the expense of organ or limb function [4, 18]. Conservative surgery rather than obtaining R0 resection is recommended, in order to avoid unnecessary morbidity and functional deficits attributable

to radical surgeries.

Local (radiation therapy) or systemic therapies are usually indicated in patients who have disease-related symptoms or progression of inoperable disease. Radiotherapy up to a dose of 56 Gy in 28 fractions of 2Gy has been shown to provide adequate local control in the majority of progressive patients [19]. In the adjuvant setting, a meta-analysis of retrospective studies has shown that radiotherapy may reduce the risk of local recurrence after incomplete surgical resection (R1/R2), especially in patients with recurrent disease [15].

There is a large choice of systemic therapies available for DTs: chemotherapy, hormonal therapy, NSAIDs and tyrosine kinase inhibitors [20]. There is no accepted standard of care because data concerning these therapies originate from case reports and retrospective studies [21]. In the absence of randomized trials, it is difficult to identify if responses are attributable to the treatment or to the natural history of the tumor, which can spontaneously regress in the absence of any systemic therapy.

Cytotoxic chemotherapy is usually the first treatment option for rapidly growing, unrespectable disease that is either threatening limb function or symptomatic, a rare situation in a disease that usually has an indolent evolution. The most frequently used regimens are either a combination of methotrexate and vinblastine or an anthracycline-based chemotherapy [22].

Concerning endocrine therapy, the use of Selective Estrogen-Receptor Modulators (SERMs, tamoxifen) finds its rationale in the expression of hormonal receptors by DTs and has mainly been described in case reports and retrospective studies. However, in contrast with other locations of EAF, most breast DTs do not express any progesterone or estrogen receptors. Despite this fact, one case report has shown a significant decrease in size of a breast DT with the use of tamoxifen 20mg daily [23].

NSAIDs, often used in combination with tamoxifen, have also shown responses in retrospective studies [24]. Their mechanism of action targets the want pathway, via inhibition of cyclooxygen-ase-2 (COX-2) [25].

Targeted therapies such as tyrosine kinase inhibitors (TKIs) have been studied in DTs since the identification of c-kit and PDGFR in DF tissue. Targeting them with TKIs blocks proliferation and cell differenciation [26-28]. For example, sorafenib, an oral multitargeted receptor tyrosine kinase inhibitor, when administered at a daily dose of 400mg, has shown to have an acceptable safety profile and is associated with a response rate of 25% [29]. Recently, a prospective, randomized, double-blind, placebo-controlled phase 3 trial has shown a 2-years PFS rate of 81% with sorafenib versus 36% with placebo (p<0,001), after a median follow-up of 27 months [28]. Side effects were grade 1 or 2 rash,

fatigue, hypertension and diarrhea. These new results could be really practice-changing.

This case report illustrates the fact that although breast DT is a rare condition which is commonly indolent, it can also show spectacular progression after several months of expectant management and become locally aggressive. In accordance with the new European guidelines, we first observed a « wait and see » period, with the adjunction of medical treatments (tamoxifen 20mg and NSAIDs). After an uneventful follow-up of 12 months, the DT quickly progressed and became symptomatic. We used surgery as second-line treatment, with a suboptimal R2 resection, but we wanted to avoid a mutilating surgery. As discussed earlier, this period of observation, which led in this case to a progressive disease, did not cause any additional morbidity. As the patient had already received radiation therapy for her first breast cancer, we could not repeat this treatment modality for adjuvant therapy. We proposed to continue tamoxifen as a maintenance treatment, hoping that it would delay an unfortunately highly probable recurrence. At the time of writing this case report, we only had 4 months of follow-up, which is not sufficient to exclude that the tumor will relapse. However we have succeeded so far to relieve the symptoms without compromising limb function or esthetics.

5. Conclusion

Breast DT is a rare entity with a complex and unpredictable natural history, which ranges from spontaneous regression to aggressive progression. These variations in the clinical presentation and the multiple available treatments make the management of such tumors a real challenge, requiring the involvement of an experienced multidisciplinary team. European guidelines [4] now recommend an initial period of observation called « wait and see » approach, supporting the evidence that DTs observed for a period after diagnosis remain often stable, paucisymptomatic, or even regress, requiring no further treatment.

In case of progressive, symptomatic or disabling disease, surgery can be offered, with the lowest possible esthetic and functional impact, since it has not been proven that negative resection mar-gins decrease the risk of recurrence.

In case of unrespectable progressive disease (or if resection is associated with unacceptably high morbidity), or symptomatic disease, targeted therapy with tyrosine kinase inhibitor sorafenib has now proven its efficacy.

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