Title: five years local control of subscapularis aggressive fibromatosis managed by surgery and imatinib: a case report

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Five years local control of subcapularis Aggressive Fibromatosis managed by surgery and imatinib: a case report

Abstract:

Introduction Imatinib, a tyrosine kinase inhibitor, was a major therapeutic option for management of unresectable Aggressive Fibromatosis (AF) [1]. Unfortunately, for most patients of low or very low average income countries, surgery often is the first treatment option. This related to unavailability molecules of chemotherapy or targeted therapy, the lack of financial resources or surgeons unknowledge of other therapeutic options.

Case presentation: A young Moroccan male, born in 1984 (26 year-old in 2010), single, carpenter was referred to oncology and radiotherapy center by his surgeon for the management of a recurrent tumor of right subscapularis muscle. Before his assessment in our center, two resections were performed by his surgeon after performing an incision biopsy and magnetic resonance imaging (MRI). Postoperative MRI was performed and notified a right axillary nodule size 2.1cm regarding a collection with a residual tumor. We decided to administrate imatinib 400mg daily per os. Clinical and MRI evaluation were performed regularly and reported a stable tumor. We didn’t report any imatinib’side adverse effects regarding Common Terminology Criteria for Adverse Events (CTCAE) grading.

Conclusion: Recurrences were high during AF management. Systemic treatment with imatinib for unresecable or recurrent tumors with positive ckit could be a best therapeutic option. In our case report, the patient was stabilized with imatinib for 30 months and had very good quality of life.

Keywords: aggressive fibromatosis-subscapularis-surgery-recurrence-imatinib –local control.
Introduction

Imatinib, a tyrosine kinase inhibitor, was a major therapeutic option for the management of unresectable Aggressive Fibromatosis (AF) or desmoids tumors [1]. These tumors are non-malignancy aggressive tumor, which can occur anywhere in the body. Its Extra-abdominal forms are usually confined to the musculature and the overlying aponeurosis or fascia but the neoplasm may infiltrate the surrounding tissue up to 2 or 3 cm outside the palpable tumor [2]. Management of these tumors is not standardized but relies on the combination of surgery, radiotherapy and or systemic therapy. Local control is the main goal of treatment and there has been a change in the management of these tumors from aggressive surgical resection to function preservation [3]. Surgical resection rate regarding primary treatment modality for desmoids tumors when functionally and cosmetically acceptable with reported local control is 75 to 80% [3]. For surgery alone, local recurrence rates have varied from 24 to 77% which was justifying the use of other therapeutic options. Systemic therapeutic has been reported regarding cytotoxic agents [4] but with documented cardiotoxicity and myelosuppression. Regarding the relative toxicities of cytotoxic agents, hormonal therapy and tyrosine kinase inhibitors are increasingly reported as therapeutic options [5]. Imatinib mesylate (Gleevec) is a specific tyrosine-kinase inhibitor highly used for targeting ckit, breakpoint cluster region-abelson gene (bcr-abl), platelet-derived growth factor receptors and macrophage-colony stimulating factor receptor (M-CSFR). Longtime disease stabilization occurred with this molecule have been reported in different series of patients with relapsing desmoids tumors, with one-year progression-free survival (PFS) rates close to 60–70% [6;7;8]. Unfortunately, for most patients of low or very low average income countries, surgery often is the first treatment option. This is related to the unavailability molecules of chemotherapy or targeted therapy, the lack of financial resources or surgeons acknowledges of other therapeutic options. Previously a best management, despite benign nomenclature of AF, multidisciplinary approach should be required to plan local control with acceptable morbidity.
**Case presentation**

A young Moroccan male, born in 1984 (26 year-old in 2010), single, carpenter was referred to oncology and radiotherapy center for management of recurrent tumor of right subscapularis. No pathological medical or surgical history was reported and no alcohol or tobacco habits. One year before, he had presented to his surgeon with subscapularis’ tumor which had appeared gradually and increased size during six month without associated pain or other symptoms. Physical examination reported a mass size 10 cm, palpated in right subscapularis region. First resection was realized. Histopathological analysis demonstrated spindle-shaped cells with no identifiable nuclear pleomorphism or mitotic activity. There was no necrosis. A conjunctival fusocellar with no sign of malignancy tumor was suspected. In immune-histo-chemistry, the cells stained positive for anti-smooth muscle actin (ASMA), favoring a smooth muscle origin. The diagnostic of aggressive fibromatosis was retained. Unfortunately, the mass, recurred within a period of ten months and continued to increase in size reaching 13 cm on Computed Tomography Scanner (CT Scan) and MRI (figure1) without regional structures involved (bone, muscle or vascular). A second tumor and lymph nodes resection were performed by another surgeon that reported “a very hard resection without cleavage plane”. Histological analysis regarding two fragments size 4x3cm and 14x10x8cm concluded to aggressive fibromatosis tumor; hormonal receptor was not found. Resection of margins were narrowed and lymph nodes resections regarding 4 nodes were not involved. At assessment time in our oncology and radiotherapy center after this second resection, patient’s Performans status of World Health Organization (WHO) was quoted zero, weight 84kg, size 177 cm. There was no induration or palpable mass. MRI performed after this repeat surgery was normal. During following up, a recurrence was suspected one year after the second resection. Axillary MRI (figure 2A-B) was performed and found a large mass in the last tumor site, measuring 12.6 cm involving deltoid muscles and extending to axillary area. Third resection was realized and histopathological exam showed the same Aggressive Fibromatosis tumor with a low positivity of ckit. Margins were narrowed. Postsurgery MRI (figure 2C-D) was performed and notified a right axillary residual tumor measuring 2.1cm. Diagnosis of recurrent AF tumor with positive ckit and without hormonal receptor was retained. The decision to administrate imatinib 400mg daily per os was taken. The Follow-up was performed by clinical examination and was normal during six months. When we stopped imatinib administration during one month, tumor had growed to a size of 4 cm. Retreatment with imatinib was decided. Clinical and MRI evaluation were performed
regularly and they reported a stable tumor. Last MRI (figure 3A) performed on January, 2014 reported a stabilized tumor and many intra-tumoral calcifications. We didn’t report any side effects regarding Common Terminology Criteria for Adverse Events (CTCAE). Currently the patient is feeling well but keeps an ankylosis (90 degree) in right upper limb due to particular localization of AF and surgery (figure 3B).

Discussion

In Lowaverage income countries like Morocco according to gross national income (GNI) of World Bank Atlas 2008, targeted therapies are not always accessible for all patients. For this case report we presented to our patient the advantages and disadvantages of imatinib versus iterated surgeries. During management of our case report, despite major surgery, two recurrences were reported within 12 months which justified the introduction of imatinib. In subscapularis region which is an unusual localization of desmoid tumor, surgery was very hard and margins were almost involved or narrow despite surgeon experience. Thus, the patient took imatinib during 2,5 years and he was stabilized with a good quality of life. Our patient received 400 mg orally daily. The daily dose of imatinib was controversial in literature. Some authors started with standard dose [9], other authors with low dose and raise it after two weeks [10] and another one started with high dose and previous decreasing dose when side effects occurred [7]. Varied dose was showed in table 1. We didn’t report any side effects within this case report. Imatinib is well tolerated in published series and only side effects grade I / II tiredness and edema were reported without no major effects (grade III / IV)” [7]. Joseph Mace has resumed imatinib pharmaceuticals action of Imatinib mesylate (Gleevec™; Novartis Pharmaceuticals, Hanover, NJ). Thus, imatinib “represents a selective tyrosine kinase inhibitor targeting bcr-Abl fusion protein in chronic myelogenous leukemia, multiple class 3 receptor tyrosine kinases (RTKs), including Platelet-Derived Growth Factor Receptor α and β (PDGFR-α and PDGFR-β), as well as the c-kit subtype. This agent blocks ligand activated receptor phosphorylation and mitogen-activated kinase activation and proliferation, resulting in the inhibition of cellular growth and proliferation”. Complete or even partial responses (PR) are documented in the literature in around 10% to 23% of patients treated with imatinib. Our patient have been treated with imatinib since 24 month. The mean follow up time in literature varied from 12 to 19.7 months. [7, 11]. However, not all clinical studies have been entirely positive regarding the use of imatinib. The French sarcoma group, in SARC trial, demonstrated positive initial results (nonprogression rates at 3 and 6 months of 90-80%, respectively.) but decreased at 12 months to 67%. The median time to progression
was 25 months in this study [6]. These results were confirmed in the SARC trial with initial progression-free survival of 94% and 88% at 1- and 2-months follow-up appointments but decreased significantly to 66% at one year [12]. In 2012 review [13] reported the increasing interest in the potential role for tyrosine kinase inhibitors in the treatment of extra-abdominal desmoid tumours despite a limited role for imatinib alone but recommended it as part of therapeutic options. Sunitinib, another tyrosine kinase inhibitor, could be useful in some cases of AF, especially if resistance to imatinib [11]. Other systemic therapy including Nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin and sulindac, translat were used without randomized trials.

Conclusion

The aggressiveness of desmoid tumors is related to their frequent recurrences despite surgical resection with clear margins. In their location subscapularis surgery is almost R1 (resection was narrowed or involved microscopically) and recurrences or progression were evident. Systemic treatment with imatinib for unresectable or recurrent tumors with positive ckit could be a best therapeutic option. In our case report, the patient was stabilized with imatinib for 30 months and had a very good quality of life.

Consent

Written informed consent was obtained from the patient's next of kin for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Abbreviations


Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

AD wrote this manuscript. NB gave clinical advice as an attending staff member. HJ performed images. AT: planed imatinib administrated and managed its side effects. TN, HJ, SS are members of radio-oncology team and they are finals lecture. AB Allowed this case to be published. All authors read and approved the final manuscript.
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References:


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**Legends:**

**Figure 1:** Thoracic CT axial cut (A) and sagittal cut (B)- Auxiliary MRI with Axial (C) and sagittal (D) cut showing mass measuring 130 mm. this mass was localized on the right chest wall, between scapula and chest wall, hypointensity T1, hypersignal T2; this mass displaces the muscle structures and odds; auxiliary vessels are permeable.

**Figure 2:** MRI axial and sagittal cut (A-B) showing Soft-tissue mass recurrences measuring 126 mm on high axis in right chest wall, hypo intensity T1 and hyper intensity T2, contact with axillaries pedicle and brachial vessels homolateral. These vessels remains permeable and are not involved; a second similar soft tissue mass of right chest wall in posterior areas measuring 61mm in high diameter was noted. After surgery, right auxiliary MRI (C-D) was performed and showed a residual tumor measuring 21mm.

**Figure 3:** Axillaries MRI (A) showing tumor and many intra-tumoral calcifications - B: patient with limited right upper member abduction to 90°