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CURRENT CONCEPTS REVIEW

Treatment of aggressive fibromatosis : A multidisciplinary approach

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INTRODUCTION

Desmoid tumours are dense fibroblastic tumours occurring in any mesenchymal tissue at the site of a fascia. It is usual to distinguish extra-abdominal and abdominal forms, although they are microscopically similar. The extra-abdominal variety is also called aggressive fibromatosis (AF). Abdominal desmoid involves either the abdominal wall, particularly the lower part of the rectus abdominis muscle, or the abdominal cavity where it arises in the mesentery or from any muscular structure. The abdominal variety tends to occur more frequently in women of child-bearing age. This review will only focus on the extra-abdominal variety.

AF is a tumour with many contrasts: it is a purely benign process but it may infiltrate vital structures and cause severe morbidity. The growth potential can be high in some cases, with early recurrence, whereas spontaneous regression can be observed in others.

Owing to such a disconcerting tumoral behaviour, the treatment has been a matter for debate and is the subject of this article.

EPIDEMIOLOGICAL, GENETIC and CLINICAL ASPECTS

AF is a rare occurrence with a prevalence of about three persons per million individuals *(4, 25)*. There is no racial predisposition. It occurs slightly more frequently in females and may concern a broad age range from 3 to 70 years but with a predilection for patients between 20 and 40 years *(5, 24, 28)*. AF is a fibroproliferative disorder characterised by a monoclonal proliferation of fibroblast-like cells. A similar excessive proliferative stage is also observed in wound healing. AF occurs most frequently as a sporadic lesion, but it may also occur as part of familial adenomatous polyposis coli, a rare disease caused by an autosomal hereditary condition due to mutation of the adenomatous polyposis coli (APC) gene on chromosome 5. The disease is associated with osteoma, aggressive fibromatosis and other soft tissue tumours, and polyposis of the colon. Interestingly, the APC gene helps regulate the cellular level of beta-catenin, a signal protein secreted by fibroblasts, which binds transcription factors. In AF, beta-catenin is elevated and causes cell proliferation. In a transgenic mouse strain having a genetically modified beta-catenin metabolism, AF will develop *(6)*. AF may also develop after removal of a Gardner's fibroma which appears as a first symptom of a Gardner's syndrome *(30)*. AF displays various chromosomal alterations with trisomies in chromosome 8 and 20 and deletion on parts of chromosome 5 *(8)*. Fifteen

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percent of sporadic cases of AF display somatic APC mutations and 60 % of those without APC alteration have a mutation in the beta-catenin genes that impair its degradation *(1, 29)*.

Cyclooxygenase-2 (Cox-2) is an enzyme involved in prostaglandin synthesis and is dependent on the presence of beta-catenin. Cox-2 is overexpressed in AF. Cox-blocking drugs might decrease the cell proliferation in AF *(22)*.

AF has been observed appearing in surgical scars (*14*) or in a previously traumatised area *(12)*. Clinically, the most frequent complaint is a non painful deep mass that is slowly growing. Symptoms may be caused by compression on adjacent structures. The tumour is firm on physical examination. It is a plain mass. AF may affect the limbs, the head, the neck and the trunk. In the limbs, it shows a predilection for the shoulder and the buttock. More rarely, AF may be multicentric. AF is benign with a strong propensity to recur locally, even after wide resection. It can cause significant morbidity owing to its ability to infiltrate any anatomical structure. Desmoid tumour is a benign tumour but not a benign disease *(23)*.

Magnetic resonance imaging (MRI) is the most appropriate imaging modality to demonstrate the lesion extension or recurrence.

HISTOLOGY

AF is a proliferation of well-differentiated fibroblasts arranged in parallel rows separated by variable amounts of collagen. It is a dense fibrous tumour which lacks a capsule and which infiltrates along fascial planes and may invade any adjacent structures. Mitoses, cellular atypia and necrosis are not observed *(5)*.

TREATMENT OPTIONS

Desmoid tumours can be frustrating to manage because no one treatment offers a high likelihood of achieving remission. There are several options to treat desmoid tumours : surgery, radiotherapy, chemotherapy, isolated tumour perfusion and hormonal therapy. Randomised studies on treatment modalities are lacking and current recommendations are based on retrospective studies or reviews. Even more, the aggressiveness of the disease appears highly variable : spontaneous regressions have been reported *(3, 7)* whereas some patients left with contaminated margins after surgery did not experience recurrence. No one single treatment emerges as most effective and modern trends rely on a customised algorithm for treatment.

Surgery alone

Because of its marked propensity to recur, wide local excision has been the preferred treatment. It is meant that surgery will remove the pathologic tissue with a margin of at least 10 mm of healthy tissue. In a non encapsulated and infiltrative pathology, the surgical achievement of a healthy, uncontaminated margin is of importance. One of the difficulties associated with surgery is the adequate assessment of the extent of AF. The infiltrative nature of the tumour makes it difficult to assess during surgery the true microscopic extent of the pathologic process. Reflecting this difficulty, the reported rate of a contaminated margin after surgery is high, ranging from 44 % *(31)* to 61 % *(17)*.

However, achieving wide surgical resection does not necessarily ensure control of the disease and conversely, a positive margin does not imply a recurrence, emphasising the highly variable behaviour of the process. Recurrence rates ranging from zero to 28 % after wide excision with non contaminated margins have been reported *(3, 19, 31)*. Such occurrence becomes significantly higher when the resected specimen has contaminated limits, with recurrence rates in the range of 40 to 60 % *(3, 19, 31)*. Most but not all studies *(11, 18, 25)* agree that a positive margin at surgery will cause a higher recurrence rate. This finding has stimulated the combined use of radiotherapy as an adjuvant to control the disease. Recurrent disease has a worse prognosis than primary lesions with respect to the recurrence risk *(31)*.

Radiotherapy alone

Radiation is an effective option to treat AF, alone or combined with surgery. Radiation alone is at

least equal in controlling the disease to surgery alone with negative margins when assessed with the 5- and 10-year relapse rate *(3, 19, 31)*. The average dose is 50-60 Gy, whereas exceeding this range will cause a significant rise in radiation complication *(3)*. Approximately 20 % of the patients treated with radiation will develop complications *(3, 19)*. Fibrosis is the main complication but secondary sarcoma (0.7 %) has also been reported as a late complication *(19)*. Another problem is the delineation of the irradiation volume for a non encapsulated disease that propagates along the main axis of muscles and fascia. A margin of 5-8 cm in the main axis should be included in the radiation field *(3)*.

Combined surgery and radiotherapy

This association appears to be the most effective in controlling the disease. In cases with negative margins, the value of radiotherapy remains questionable whereas in cases with positive margins, the impact of external beam radiation is significant, with a recurrence rate falling from 52 % with surgery alone to 26 % with both treatments combined *(3, 16, 19)*.

Pharmacological agents

A large variety of molecules have been tried in the conservative treatment of AF. Most concern patients with a contraindication to surgery or radiation, or with relapsing disease. A review of this mode of treatment has been made recently *(4, 13, 26)*. No conclusive results have emerged so far from the literature. The most commonly reported agents are : anti-inflammatory drugs, hormonal therapy, interferons and chemotherapy.

Anti-inflammatory agents have been used successfully but conclusive results are lacking so far. Since two years, the role of cox-2 in the AF proliferation has been emphasised *(22)*. The use of anti-Cox 2 nonsteroidal antiinflammatory drugs in AF appears relevant and should be tried as an adjuvant therapy to slow down the tumour growth.

Tamoxifen, an oestrogen antagonist has often been used in unoperable cases on the assumption that this tumour can display oestrogen receptors. *In vitro* studies indicate however that this molecule has a growth inhibitory effect on these cells rather than an anti-oestrogen effect (*27*). This tumour lacks the oestrogen receptors when assayed by immunochemistry.

Chemotherapy has been advocated sporadically in desmoid tumours not amenable to surgery or radiation. Vinblastine-methotrexate or doxorubicine-dacabarzine are the most frequently reported regimens *(2, 4, 20, 26, 28)*.

Isolated limb perfusion appears to be one of the promising treatments of AF in the limbs. The isolated limb is perfused with melphalan and tumour necrosis factor, a potent anti-neoangiogenic molecule. Successful results have been reported at short term in recurrent desmoid tumours but need to be further confirmed *(9)*.

PROGNOSTIC FACTORS

There is no general agreement on the significance of various parameters. Among the reported significant factors for recurrence are: recurrent presentation *(23, 31, 29)*, positive margin *(2, 16, 18, 31)* and age below 18 years *(31)*. Among most reported non significant variables are : age, gender, site and size *(17, 18, 21, 31)*.

STRATEGY

Once confirmed with biopsy, the behaviour of the tumour should be monitored with MRI. Stable lesions can be observed at regular intervals with imaging studies. Anti-cox 2 drugs should be given. A progressing tumour needs to be treated. If AF is amenable to surgery, surgery with the aim of achieving negative margins should be the treatment of choice. When considering surgery, if an important functional deficit is anticipated for achieving negative margins, radiotherapy alone should be given. Mutilating or ablative surgery will be excluded. If the surgical margins appear contaminated, then postoperative radiotherapy should be given at a dose range of 50-60 Gy. In case of recurrence, surgery when possible will be associated with radiotherapy or radiotherapy alone can be performed. In case of recurrence after irradiation, iso-

lated limb perfusion will be considered. Medical treatment can be given after these first three lines have been considered.

CONCLUSIONS

AF should be managed with a multidisciplinary approach. Although curative surgery should be advocated first, the location, the size of the tumour, the patient history should be taken into consideration to decide which modality is most appropriate. The natural history of this benign tumour remains unclear. Some continue to grow while others are easily controlled. The growing capacity of the tumour should be documented with MRI.

Contemporary views still set surgery as a first line when appropriate. Radiotherapy should be used when doubt persists about the quality of the margin after surgical treatment. Isolated limb perfusion becomes a challenging option and is considered as third option. Other treatments such as adjuvants may be combined or not with surgery and /or radiotherapy.

Given the inconsistent behaviour of this tumour, treatment options should be based on a risk/benefit assessment for each patient.

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