Original Article

Primary or recurring extra-abdominal desmoid fibromatosis: Assessment of treatment by observation only

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KEYWORDS
Desmoid fibromatosis; Soft tissue tumor; Surgery; Conservative treatment; Simple observation

Summary

Introduction: Extra-abdominal desmoid fibromatosis (EADF) is a benign tumoral condition, classically managed by more or less radical and sometimes mutilating excision. This treatment strategy is associated with a recurrence rate of nearly 50% according to various reports.

Hypothesis: EADF may show spontaneous stabilization over time.

Methods: A retrospective series of 26 cases of EADF managed by simple observation was studied to assess spontaneous favorable evolution and identify possible factors impacting evolution. Eleven cases were of primary EADF with no treatment or surgery, and 15 of recurrence after surgery with no adjuvant treatment. MRI was the reference examination during follow-up.

Results: Twenty-four cases showed stabilization at a median 14 months; there were no cases of renewed evolution after stabilization. One primary tumor showed spontaneous regression, and one recurrence still showed evolution at end of follow-up (23 months). The sole factor impacting potential for evolution was prior surgery. No radiologic or pathologic criteria of evolution emerged from analysis.

Discussion: The present series, one of the largest dedicated to EADF managed by observation, confirmed recent literature findings: a conservative "wait-and-see" attitude is reasonable and should be considered when large-scale resection would entail significant functional or esthetic impairment.

Level of evidence: Level IV, retrospective study.

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Extra-abdominal desmoid fibromatosis (EADF) or aggressive fibromatosis is a rare tumor developing in the musculo-aponeurotic structures. It is a low-grade soft tissue tumor, which is systematically benign, without potential malignancy or remote dissemination, but showing severe local aggression and unpredictable evolution following treatment. The reference attitude is extensive surgical resection which, however, entails a risk of functional sequelae and significant morbidity with a high rate of recurrence even when resection extends to neighboring healthy tissue, due to the infiltratory character of EADF [1—5].

The literature contains certain reports of short series or occasional cases showing stabilization or regression of non-operated primary or recurrent EADF managed by simple surveillance [3,6—8]. These reports encouraged us to try simple wait-and-see surveillance in 26 of the EADF patients managed in our center between 1989 and 2009.

The study sought to assess the reality and frequency of spontaneous favorable evolution in the series, and to identify predictive factors for evolution so as to improve treatment strategy.

Material and methods

Material

The main inclusion criterion was confirmed presence of all anatomopathologic diagnostic signs of EADF on biopsy of non-operated tumors or in the exeresis specimen in case of recurrence after surgery:

- architectural criteria: tumor proliferation of fibroblastic or myofibroblastic spindle cells, without areas of necrosis, over a collagen ground rich in broad divergent bundles and a few vessels surrounded by clear space. At the periphery of the tumor, there may be small lymphoid islands. These tumors are poorly contoured, invading fat and muscle;
- cytologic criteria: myofibroblasts showing monomorphic nuclei with between one and three small nucleoli and an occasional mitosis.

Immunomarking: systematic exploration for smooth-muscle actin, beta catenin, desmin, caldesmon, AE1, AE3, EMA, PS100 and CD34 markers.

All included patients had been managed in the department for EADF between 1989 and 2009.

Data were collected by systematic retrospective harvesting of all historical, clinical and surgical records. Slides and MRI slices were systematically reassessed.

All patients with complementary medical treatment or radiochemotherapy (Glivec, Tamoxifen, anti-TNF alpha, Indocid, etc.) were excluded.

All patients were lost to follow-up.

In all, 45 patients were treated for EADF, 26 of whom (57%) underwent simple radioclinical surveillance. Two subgroups could be distinguished:

- primary EADF (11 cases), with no surgical or medical treatment;
- recurrent EADF (15 cases), undergoing surveillance after one or more surgical operations: 14 of the 34 EADF patients operated on once or more during the study period were cured; five recurrences were managed medically and 15 underwent simple radioclinical surveillance and were included in the present study.

The choice between surgery and simple surveillance was based on the feasibility of sequel-free marginal resection.

Methods

Survival comprised 6-monthly clinical examination and systematic MRI. MRI comprised sagittal, frontal and coronal T1, T2 and gadolinium-enhanced sequences. The evolution criteria were tumor size on the longest axis and change in tumor signal.

Events were dated according to age on the day of initial diagnosis. Surveillance of primary EADF was referenced by the date of initial diagnosis and of recurrent EADF by the date of the diagnosis of recurrence.

Exeresis quality was assessed on the Union Internationale Contre le Cancer (UICC) R classification [9].

Data submitted to analysis concerned tumor location, size and MRI signal.

Statistical analysis

Survival was analyzed using the Kaplan-Meier method. The event considered was recurrence. Mean values were compared by Fisher’s F-test; the significance threshold was set at 5%.

Results

General series characteristics

The series comprised 26 cases, with an M/F sex-ratio of 1/10 for primary EADF and 1/2 for recurrent EADF, or 1/3.3 for the series as a whole. In recurrent EADF, mean age on the day of diagnosis of recurrence was 36 years (range, 14—67 years) and, in primary EADF, mean age on the day of diagnosis of primary tumor was 35.5 years (range, 21—73 years).

In primary tumor cases, discovery involved tumefaction in all cases, with associated pain in four. In previously operated patients, recurrence was diagnosed on control MRI in all cases, with associated tumefaction in seven. There were no histories of Gardner syndrome; trauma was noted in seven cases, but could not be formally linked to the tumoral pathology (shoulder, thigh or calf).

Surveillance found stabilization at a median 14 months: by month 14, tumor evolution had stabilized in half of the patients; Fig. 1 shows the cumulative incidence curve for evolution arrest.

Mean follow-up after case-by-case stabilization was 12.7 months (range, 2—27 months) in the primary EADF group (Figs. 2 and 3) and 19.1 months (range, 1—80 months) in the recurrence group. No surgery was required in any patient during surveillance.
Results in primary extra-abdominal desmoid fibromatosis

Table 1 presents the characteristics of the primary EADF patients. One patient (case 8) showed total regression at 6 months, and the others all showed arrest of evolution. Mean evolution to stabilization was 13.2 months (range, 6–30 months) (Figs. 2 and 4). No patients showed renewed progression after stabilization.

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/age</th>
<th>Location</th>
<th>Date of diagnosis on 1st MRI</th>
<th>Date of 1st MRI without evolution</th>
<th>Evolution/tumor growth duration (mo)</th>
<th>FU (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/73</td>
<td>Shoulder</td>
<td>10/2004</td>
<td>03/2007</td>
<td>Stable/29</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>F/21</td>
<td>Buttock</td>
<td>6/2008</td>
<td>12/2008</td>
<td>Stable/6</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>F/28</td>
<td>Buttock</td>
<td>07/2008</td>
<td>12/2008</td>
<td>Stable/6</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>F/28</td>
<td>Thigh</td>
<td>06/2006</td>
<td>08/2007</td>
<td>Stable/11</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>F/27</td>
<td>Shoulder</td>
<td>10/2005</td>
<td>04/2008</td>
<td>Stable/30</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>F/31</td>
<td>Hip</td>
<td>10/2006</td>
<td>5/2008</td>
<td>Stable/19</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>F/33</td>
<td>Hip</td>
<td>12/2005</td>
<td>06/2006</td>
<td>Regressed/7</td>
<td>26</td>
</tr>
<tr>
<td>9</td>
<td>F/43</td>
<td>Thigh</td>
<td>06/2008</td>
<td>12/2008</td>
<td>Stable/6</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>F/38</td>
<td>Shoulder</td>
<td>03/2008</td>
<td>09/2008</td>
<td>Stable/6</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>F/35</td>
<td>Shoulder</td>
<td>02/2005</td>
<td>11/2005</td>
<td>Stable/9</td>
<td>27</td>
</tr>
</tbody>
</table>

F: female; M: male.

Analysis of predictive factors for evolutivity

Analysis of factors relevant to evolutivity found a significant time difference in evolution to stabilization between primary and recurrent EADF ($P = 0.0417$). Similarly, within the recurrence group, patients reoperated on several times.
Extra-abdominal desmoid fibromatosis managed by observation

showed significantly longer evolution before stabilization than those in whom recurrence was not managed by surgery ($P=0.0203$). On the other hand, no significant time difference in evolution to stabilization emerged between resection into healthy or contaminated tissue at last operation ($P=0.4099$).

Radiological analysis failed to identify any factors predictive of evolution. In fact, radiology was consistently normal. No bone invasion was found. Initial MRI at diagnosis found lesions with hypo- or iso-intense periphery on T1-weighted image. On T2, lesions were consistently hyperintense in the center. After gadolinium injection, there was systematic progression of hypointense signal in the periphery.

Table 2  Characteristics of patients with recurrent extra-abdominal desmoid fibromatosis.

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/age</th>
<th>Location</th>
<th>Date of 1st operation</th>
<th>Number of operations</th>
<th>Margin quality at last operation</th>
<th>Date of last non-operated recurrence</th>
<th>Date of 1st MRI without evolution</th>
<th>Evolution/tumor growth duration (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>F/18</td>
<td>Calf</td>
<td>05/2004</td>
<td>2</td>
<td>R2</td>
<td>02/2006</td>
<td>In growth</td>
<td>Stable/14 6</td>
</tr>
<tr>
<td>13</td>
<td>F/42</td>
<td>Calf</td>
<td>1999</td>
<td>1</td>
<td>R1</td>
<td>04/2007</td>
<td>06/2008</td>
<td>Stable/19 75</td>
</tr>
<tr>
<td>14</td>
<td>F/42</td>
<td>Calf</td>
<td>1989</td>
<td>1</td>
<td>R1</td>
<td>06/2000</td>
<td>03/2002</td>
<td>Stable/24 1</td>
</tr>
<tr>
<td>15</td>
<td>F/44</td>
<td>Ankle</td>
<td>2004</td>
<td>2</td>
<td>R0</td>
<td>01/2007</td>
<td>01/2009</td>
<td>Stable/6 12</td>
</tr>
<tr>
<td>16</td>
<td>F/42</td>
<td>Calf</td>
<td>1999</td>
<td>1</td>
<td>R0</td>
<td>04/2007</td>
<td>12/2007</td>
<td>Stable/6 12</td>
</tr>
<tr>
<td>18</td>
<td>M/39</td>
<td>Thigh</td>
<td>2002</td>
<td>4</td>
<td>R2</td>
<td>08/2007</td>
<td>06/2008</td>
<td>Stable/6 12</td>
</tr>
<tr>
<td>19</td>
<td>F/23</td>
<td>Shoulder</td>
<td>03/2002</td>
<td>1</td>
<td>R0</td>
<td>10/2004</td>
<td>03/2005</td>
<td>Stable/5 40</td>
</tr>
<tr>
<td>20</td>
<td>M/30</td>
<td>Thigh</td>
<td>1994</td>
<td>3</td>
<td>R0</td>
<td>07/2003</td>
<td>01/2007</td>
<td>Stable/41 20</td>
</tr>
<tr>
<td>21</td>
<td>M/32</td>
<td>Calf</td>
<td>09/2007</td>
<td>1</td>
<td>R1</td>
<td>07/2008</td>
<td>01/2009</td>
<td>Stable/6 1</td>
</tr>
<tr>
<td>22</td>
<td>F/50</td>
<td>Forearm</td>
<td>2007</td>
<td>1</td>
<td>R2</td>
<td>03/2008</td>
<td>09/2008</td>
<td>Stable/6 5</td>
</tr>
<tr>
<td>23</td>
<td>M/51</td>
<td>Shoulder</td>
<td>1981</td>
<td>8</td>
<td>R2</td>
<td>11/2004</td>
<td>01/2009</td>
<td>Stable/48 1</td>
</tr>
<tr>
<td>24</td>
<td>F/14</td>
<td>Foot</td>
<td>1998</td>
<td>3</td>
<td>R2</td>
<td>03/2004</td>
<td>03/2006</td>
<td>Stable/24 12</td>
</tr>
<tr>
<td>25</td>
<td>F/16</td>
<td>Leg</td>
<td>1999</td>
<td>2</td>
<td>R1</td>
<td>04/2002</td>
<td>04/2004</td>
<td>Stable/24 12</td>
</tr>
<tr>
<td>26</td>
<td>F/43</td>
<td>Buttock</td>
<td>05/2007</td>
<td>2</td>
<td>R2</td>
<td>01/2008</td>
<td>02/2009</td>
<td>Stable/13 0</td>
</tr>
</tbody>
</table>

F: female; M: male; R0: extensive or radical exeresis; R1: marginal exeresis; R2: intralesional exeresis.
enhancement of the lesion (Table 3). On follow-up MRI, new readings found no change in signal intensity in a given tumor. Tumor size was very variable, independently of location and evolutivity.

Anatomopathology found no differences in architecture between primary and recurrent tumors. On immunohistochemistry, smooth-muscle actin and beta catenin muscle markers were consistently positive in the periphery, and desmin, caldesmon, AE1, AE3, EMA, PS100 and CD34 consistently negative.

### Discussion

Desmoid tumors are notorious for local recurrence after surgical treatment, at a rate of 19% to 77%, depending on the report [1,10—15]. The present study shows initially strong evolutivity, whether spontaneous or secondary to surgical aggression, which subsequently resolves in most cases.

The present study analyzed evolution in terms of tumor size on MRI. In the literature, MRI is the reference examination in EADF surveillance, optimally detailing the relation to neurovascular structures and enabling objective and reproducible measurement. There are, however, difficulties inherent to the measurement of a lesion the contours of which may be fuzzy due to its infiltratory character. Dating is based on the date of the initial radiological diagnosis, which fails to take account of the interval of occult development but does provide the physician with a reference for time of evolution from initial diagnosis.

There are many reports of incidental cases or series showing tumor regression or stabilization. Rock et al. [1] reported a series of 68 recurrent desmoid tumors managed by surveillance: 60 had ceased to evolve at a mean 6.1 years’ FU, and six had regressed; only two continued to evolve. Lewis et al. [2] reported on 15 patients with desmoid tumor that was non-excisable without amputation and was managed medically (chemotherapy, hormone therapy, NSAID) or by radiotherapy: nine tumors stabilized, and two regressed. Dalén et al. [6] reported some cases of spontaneous regression at more than 20 years in non-reoperated recurrent tumor. The main limitation of these studies was that they reported only recurrent tumors, known from the literature to show strong evolutive potential following surgical aggression. Chatelard et al. [8] and Pignatti et al. [3], conversely, reported a case of primary EADF that was stable on long-term FU. Recently, Gouin et al. [7] performed a prospective study of a cohort of 17 primitive or recurrent EADF patients: 12 showed arrested tumor growth and three showed objective regression on MRI; there were no cases of renewed evolution after regression or stabilization. Likewise, Bonvalot et al. [15] reported 11 cases of EADF managed by surveillance in a series of 112 patients managed in their center: only three cases showed progression at 3 years’ FU. Fiore et al. [16], in a multicenter study including 83 cases of primary or recurrent desmoid fibromatosis managed by surveillance and 59 managed medically (chemotherapy, hormone therapy), reported arrested evolution in 49.9% of tumors managed by surveillance versus 58.6% of those managed medically at 5 years’ FU (P = 0.3).

In the present study, stabilization was at a median 14 months. There was, however, a significant difference in evolution time between primary and recurrent EADF (P = 0.0417). Gouin et al. [7] reported a mean 10 months’ evolution (range, 0—36 months), with no difference between primary and recurrent tumors. The evolutive potential of EADF thus seems to be limited after 36 months.

In the present study, surgery appeared as an aggravating factor for tumor evolution duration. In Bonvalot et al.’s series [15], at 3 years 44% of operated tumors showed growth, versus 68% of those managed by simple surveillance; the authors concluded that there was a non-significant (P = 0.07) trend towards better evolution in non-operated than operated tumors, as confirmed by the present findings. Fiore et al. [16], on the other hand, reported identical results for primary and previously operated tumors, and their multivariate analysis disclosed no predictive factors for evolution.

In the present study, resection margin quality in recurrence surgery did not appear as a predictive factor for evolution. For Bonvalot et al. [15], on the other hand, prognosis for surgical treatment correlated strongly with resection margin quality and with tumor location; for certain patients, they therefore recommend simple surveillance for a period of months, and that surgery, when performed, should extend into healthy tissue. Even so, their findings are open to discussion: two other studies, as well as the present, reported no link between resection margin quality and recurrence potential [4,8]. These various studies, however, are difficult to compare, as the definition of margins was not reproducible.

A conservative attitude is thus reasonable and may be considered when extensive resection cannot be performed without significant functional or esthetic impact. While the literature still considers extensive resection to be the most effective form of treatment, the associated recurrence rate is non-negligible [1,10—14], mainly within 2 years of surgery [1—3,5,6]. Surgery also entails a significant risk of functional and esthetic sequelae when resection aims to be extensive, as recommended by Leithner et al. [17] in their meta-analysis. The morbidity associated with surgery is non-negligible, and many series have reported amputation [1,7] or severe aftereffects [6]; moreover, amputation does not

### Table 3 Extra-abdominal desmoid fibromatosis MRI signal.

<table>
<thead>
<tr>
<th></th>
<th>T1</th>
<th></th>
<th>T2</th>
<th></th>
<th>Gadolinium uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypo</td>
<td>Iso</td>
<td>Hyper</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td>12</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>11</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

Hypo: hypo-intense signal; iso: iso-intense signal; hyper: hyperintense signal.
always prevent recurrence [1,7,8]. Morbidity, furthermore, increases the rate of revision surgery for recurrence. The associated mortality rate, however, remains less than 1% [1].

Thus, the high rate of recurrence, even after resection into healthy margins, combined with significant morbimortality and a non-negligible risk of sequelae point to the option of surgical abstention in favor of clinical and radiological surveillance. Surgical resection should be envisaged only if it can be complete.

In the present anatomopathological study, EADF always showed the same positive and negative markers. No histologic factors predictive of evolutivity emerged. There are, moreover, no studies in the literature on this issue.

Finally, MRI likewise found no factors predictive of evolutivity. Nakayama et al. [18] reported that three of the seven patients managed by MRI surveillance showed a significantly reduced signal on T2-weighted images. Likewise, Vandevenne et al. [19] reported that signal hyperintensity on T2-weighted images was initially heterogeneous, then diminished over tumor evolution, reflecting the reduction in tumor cellularity and collagen density. Gouin et al. [7] reported qualitative change in signal in some cases, with reduced hypersignal in T2 and the appearance of hyposignal in tumor cellularity and collagen density. Castellazzi et al. [20] analyzed 18 desmoid tumors managed by surveillance and 29 managed medically, to determine the correlation between tumor size, MRI signal and evolution of aggressive fibromatosis: size was stable in 79% of medically managed tumors and in 82% of those managed by surveillance. The initial signal was generally intense in tumors in which size was stable or reduced. The MRI signal of a given tumor, however, was generally stable over time, whatever the initial signal or size. Change in size did not correlate with initial signal. Reduction in size associated with reduction in signal was found in only three of the treated tumors. The authors concluded that tumor behavior cannot be predicted from the MRI signal.

Conclusion

EADF is a tumor that can stabilize spontaneously over time. The present study confirms that simple observation is a treatment option that can always be considered, being non-invasive, with low associated morbidity and satisfactory results. Stabilization was at a median 14 months. After diagnosis of EADF, if the tumor has no major functional impact and is not compressing neurovascular structures, surveillance is recommended, using clinical examination and 6-monthly MRI to assess spontaneous evolution before considering any other treatment. To date, no prognostic factors for tumor evolution have emerged. However, recurrence after surgery would seem to be associated with greater evolutivity than found in primary tumor.

Conflict of interest statement

None.

References