Treatment of dermatofibrosarcoma protuberans with fixed Mohs micrographic surgery: 225 consecutive cases

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ABSTRACT :

Introduction: Dermatofibrosarcoma protuberans (DFSP) is a tumor of intermediate malignancy characterized by its aggressive local growth due to pseudopodum-like outgrowths and its marked propensity to recur after surgical excision. To achieve complete cure with conventional surgery, surgical margins of up to 5 cm are required, leading to wide scars in young patients. Mohs' micrographic surgery (MMS) is used for the removal of certain malignant tumors, ensuring both complete excision by examination of all margins and minimal normal tissue loss. However, differentiating minimal residual tumor from normal skin can be difficult on the frozen section used in MMS. Our aim was to develop a MMS procedure in conjunction with rush formalin-fixed, paraffin-embedded sections to treat DFSP.

Patients and methods: Two hundred and twenty five (225) consecutive cases (203 primary and 22 recurrent) were prospectively treated between 1998 and 2014. Under local anesthesia in the majority of cases, the tumor was first excised including a lateral margin of 1 cm and a deep margin extending to the

underlying muscle aponevrosis. A 3-mm thick horizontal layer of the surgical bed was then removed, rush-formalin-fixed, paraffin-embedded, tangentially sectioned, hematoxilin-eosin stained and, if necessary, stained with an anti-CD 34 monoclonal antibody. While awaiting pathology results, the surgical bed was closed when possible with direct suture along the micrographic marks. If excision was incomplete, an oriented additional excision was performed a few days later. In some samples, RNA was extracted from the tumor and the Mohs' layer and RT-PCR aimed at the fused COL1A-PDGFR gene was performed.

Results: Patients' characteristics were: mean age 41,2 years, sex-ratio 1.16 (121 women, 104 men). Median size of the tumor was 33,8 mm X 23,1 mm. Excision was complete after the first stage of MMS in 206 patients and incomplete, always exclusively at the deep margin, in 19 patients, all of whom were treated with only one more stage. Lateral surgical margins were reduced to 1.3 cm in all patients, facilitating wound closure: direct suture (147 cases), wound healing by secondary intention (42 cases), skin graft (26 cases) or flap (10 cases). Not a single recurrence has been observed after a mean duration of 62 months with 80 % of follow-up.

Discussion: The use of MMS reduced surgical margins to 1.3 cm in all 225 cases. This technique is of particular interest in difficult sites such as the head and neck , the genitalia, the breast or the periarticular regions. The standard surgical procedure is modified, with a Mohs' layer rush-formalin-fixed and paraffin-embedded for a more accurate histological reading. Other cases and longer follow-up are necessary to validate this procedure but the

number of treated patients and the long follow-up period provide some evidence here as to the efficiency of this procedure.

Dermatofibrosarcoma protuberans (DFSP), first described by Darier and Ferrand in 1924 (1), raises a difficult therapeutic problem. Its subclinical extension, which may be wide, asymmetrical and unpredictable, leads to a high recurrence rate of about 20% after surgical excision despite a 2 to 3 cm safety margin (2). Margins of 5 cm are therefore currently recommended. These effectively prevent recurrence (0% at 5 years in 60 primary DFSP) (3) but leave extensive 10-cm defects in addition to the diameter of the tumor. The patients, who are often young (mean age 35 years in the literature), carry major scar sequelae from a tumor which is generally not aggressive (4% of metastases in a review of 913 patients) (4) nor life-threatening. This locally spreading tumor is a good indication for Mohs micrographic surgery (MMS). Using this technique, the 5-year recurrence rate is 2% with « made-to-measure » margins which are reduced to a mean of 2 cm (2, 5, 6, 7, 8). However, cytologic analysis of this sarcoma is difficult on frozen sections of fresh tissue, and so is immunolabeling with monoclonal antibodies (9, 10, 11).

For these reasons, we prospectively used in this indication a modified MMS technique in which the Mohs layers were embedded in paraffin. (9, 10, 12, 13). This procedure, called fixed MMS, combines the benefits of Mohs surgery (markedly reduced lateral surgical margins and visualization of the margins in their entirety) with the quality of histologic examination after

fixation and paraffin embedding, and the possibility of immunolabeling with an anti-CD34 antibody.

Patients and Methods

This was a prospective study of all cases treated using this technique in our department between October 1998 and December 2014. Treatment by MMS was decided in the pluridisciplinary tumor clinic because of the extensive repair which would have been necessary with the usual 5 cm margins. None of these cases had prior carcinologic treatment in our department. A standardized report form was filled out recording demographic information, the primary or secondary nature of the tumor, its site and its size measured by marking the visible borders and above all by palpation.

The surgical and histopathologic procedures were also standardized and recorded on a pre-established form. Most often under local anesthesia, or under general anesthesia for tumors whose diameter exceeded 6 cm, the tumor was first resected in one piece with a surrounding 10 mm margin of healthy skin. This 10-mm margin was determined based on publications about standard MMS in DFSP, where an average 2.5 steps were required to obtain clear margins, resulting in lateral margins of around 10 mm. Our idea was therefore to aim at a complete excision upfront with the debulking excision at 10 mm, the additional 3-mm Mohs layer simply added on for histological confirmation of clear margins. In depth, this debulking removes the hypodermis down to the underlying aponeurosis. In some cases, the tumor was no longer grossly visible because of a previous excision which was incomplete or carried out for diagnostic purposes without margins. In these cases, the

whole scar was entirely resected with a 10 mm latéral margin and to the aponeurosis at the deep margin. This operative specimen was sent for conventional histopathologic analysis.

A 2 to 3-mm thick layer was then removed from the entire surgical defect and deep into the muscular aponeurosis or even the underlying muscle. This layer, which encompassed all margins of the tumor, was fixed on a polystyrene board and oriented with the aid of a schematic showing the micrographic marks around the excision. The specimen was sent to the histopathologists for rush processing, fixed in 10% buffered formol, embedded in paraffin and sectioned « en face » tangentially to the surgical margin, stained with hematoxylin-eosin-saffron and if necessary immunolabeled at the histopathologists' request with an anti-CD34 monoclonal antibody (11). The slides were promptly read.

The surgical defect, which was systematically measured, was immediately closed by an oriented direct suture, if possible. If excision was complete, this suture was also the definitive closure. In cases where direct suture was not feasible, the surgical defect was healed by secondary intention while awaiting the pathology results, then by an additional closure technique if needed (skin graft or flap). Further excision was only performed if residual tumor remained, and was limited and oriented by the schematic. Depending on the pathology results, it was restricted to the surgical bed or the borders. In these cases, definitive repair was only considered after the pathology results showed completely clear margins.

Patients were followed annually by us or by her dermatologist. Every patient of this cohort was reached by phone or underwent systematic clinical examination between February and April 2015.

Results

We treated 225 patients with DFSP (221 primary tumors, including 92 which had been previously incompletely excised and 24 recurrences) according to this protocol. Mean age of the patients was 41,2 years, sex-ratio 1.16 (121 women, 104 men). Median size of the tumor was 33,8 mm X 23,1 mm. Site of the tumor was as follows ; trunk (139) proximal extremities (68)
neck (6) forehead (2) cheek (2) nasal ala (2) other (6)

The lateral surgical margin was limited to 13 mm in all our cases. In only 19 cases (8,4 %), secondary excision was necessary because of incomplete initial excision. Residual tumor was always present only at the deep margin. The secondary excision involved only the underlying muscle in most of the cases ; in rare cases, the second mohs layer involved a fraction of peripheral skin for optimal orientation of the sample and did not much widen the defect. The postoperative defect, measuring on average 70 by 56 mm, was larger than the sum of the tumor diameter and twice the surgical margin, because of internal tension due to the elasticity of the surrounding skin.

Mean time to histopathology results for each stage was 4 days. Immunolabeling with an anti-CD34 antibody for better visualization was necessary in only 3 cases

Because of this reduced margin, immediate direct suture was possible in 147 patients. Suture in the deep plane using monocryl 2/0 with separate sutures and reverse knots allowed good approximation of the borders, followed by a running intradermal suture using monocryl 4/0. The orientation of this suture allowed pin-pointed re-excision if pathology revealed a positive margin.

In 78 patients, the defect could not be sutured and was left to heal by secondary intention (42 cases) : moist dressings were changed every 48 hours by an outside nurse and monitored weekly in the department until complete healing was obtained at 1 to 2 months..The remaining 36 patients had more extensive surgical defects which were treated either by a graft (26 patients) or a flap (10 patients), carried out by a plastic surgeon (AT) under general anesthesia.

There were no infectious complications or bleeding and no notable postoperative complications except for one hemorrhage in a maxillary DFSP which required hemostasis in the operating suite.

During the follow-up visits, the scar resulting from healing by secondary intention was smaller than the initial surgical defect because of contraction. In all cases it remained fairly visible but in no way hindered joint movement. Direct suture and healing by secondary intention, in addition to their simplicity, allowed easy surveillance of the scar and, consequently, better oncologic follow-up.

No recurrence has been observed after a median follow-up of 62 months . Only 20 % of patients were lost to follow-up .

Discussion

Mohs micrographic surgery allows histologic control of the entire margins of the tumor. Surgical cutaneous removal in layers yields macroscopic sections which orient the microscopic sections. These perfectly horizontal histologic sections enable two-dimensional control of a cutaneous area which, with its thickness, makes up a three-dimensional space. MMS has been called « 3D histology », giving greater reliability to the histologic report of a « complete excision ». In the standard MMS technique, histologic analysis is carried out by examination of fresh frozen sections. We used paraffin fixation, which enables better cytologic analysis (9, 10, 12, 13). This modified technique applies less pressure on the pathologists than standard MMS. In particular, there is no longer the urgency of giving an immediate reply which adds strain to the frozen section examination. If further excision is required, it is done a few days later. However, we stress that revision surgery must be carried out rapidly, before scar formation leads to a marked fibroblastic reaction that can be difficult to distinguish from the DFSP itself. We used immunolabeling with an anti-CD34 monoclonal antibody when necessary (11). This modified technique is known as « slow Mohs » or « fixed Mohs » in the English literature.

With this procedure, we have been able to considerably reduce the size of the surgical margins (13 mm in our 225 cases). It must be remembered that the « standard » 3 to 5-cm surgical margins necessarily create a defect 6 to 10 cm in diameter, to which tumor size must be added. This requires complex reconstruction using musculocutaneous flaps which leave major scar sequelae. The reduced margin was particularly valuable in periarticular areas where a

large flap, mandatory after a wide margin, would no doubt have hindered mobility (shoulder, proximal thigh). Similarly, in the breast region the disfigurement was markedly reduced and in the groin, considerable sacrifice of genital tissue was avoided. The same goes for the head and neck

Reduced margins also enabled us to carry out most of the excisions under local anesthesia with a simple wound reconstruction technique, greatly increasing the cost-effectiveness of the procedure.

No recurrence has been observed in this cohort after a median follow-up of 62 months with only 20 % lost to follow-up.

In Foroozan et al.(14) a systematic review of the literature comparing the efficacy of Mohs Micrographic Surgery versus Wide Large Excision, the Recurrence Rate (RR) was 1.11% (95% Confidence interval: 0.02-6.03) in MMS-treated patients and 6.32% (95%CI: 3.19-11.02) for WLE .

At the University of Wisconsin Mohs Surgery Clinic (15), 29 patients were treated by MMS with more than 5 years of follow-up: there were no local recurrences.

In another study of 76 patients (16) treated with frozen-section MMS, nine were lost to follow-up. In the remaining 67 (67/76) cases, the recurrence rate was 1.5% during the mean follow-up period of 50 months (2–132).

In Wide Local Excision (WLE)-treated patients, RR varies from 1% up to 50%. The discrepancies between RR in the different studies can be explained by the technique used for pathologic evaluation of resected tumours. In a recent retrospective review of 204 patients treated by WLE between 1991 and 2008, Farma et al. (17) found 1% RR after WLE using 1-2 cm margins at a median

follow-up of 64 months: histological evaluation in this study included en face tangential sectioning of the entire margins. A similar technique was used in the Dubay et al.(18) study that reported a RR of 0% in 44 patients with this modified WLE. The surgical technique used in both trials is a modified WLE, similar to the one used by Mohs surgeons and not commonly used in conventional WLE. This confirms the hypothesis that meticulous evaluation of all peripheral and deep margins is the mainstay of DFSP treatment.

Recurrence of DFSP is due only to the presence of residual tumor foci resulting from incomplete initial resection. As the margins are visualized in their entirety with great reliability of pathology readings in slow Mohs, we may hope to achieve truly complete excision and, consequently, definitive cure.
7 recurrences were described after MMS (14) in DFSP. The mean time to recurrence was specified in 5 cases and was 68 months on average. 50% of these local recurrences occurred by 3 years and 75% by 5 years post-surgery. 25% of local recurrences appeared late, after the recommended 5-year follow-up period. Considering these late recurrences, more than 5-year follow-up time should be considered for MMS-treated DFSPs.
In "classic" WLE (conventional histology without careful evaluation of all peripheral and deep margins) fifty percent of recurrences develop in the first 12 months and 80% in the first 36 months (8)

To the best of our knowledge, only one other study has published the results obtained with the « slow Mohs » technique (19) in DFSP. No recurrence was observed, but the series was small (only 35 patients) with a follow-up of only 29,5 months.

Randomized controlled trials with extended follow-up periods should be encouraged to definitively determine the role of MMS in the treatment of DFSP. However, considering the very low RR for MMS-treated patients, planning such trials may raise technical and ethical difficulties (20)

Conclusion

This procedure is a very promising approach to the surgical treatment of dermatofibrosarcoma protuberans and provides multiple benefits (efficiency , better cosmetic and functional outcome and cost-effectiveness). The number of treated patients and the long follow-up period provide some evidence here as to the efficiency of this procedure.

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