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Skin Cancer (T Ito, Section Editor)

Dermatofibrosarcoma Protuberans in Children

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Opinion statement

Paediatric dermatofibrosarcoma protuberans (DFSP) is a rare soft tissue malignant tumour which displays aggressive local behaviour and has low metastatic potential. The diagnosis is often delayed as DFSP is usually mistaken for other skin conditions, particularly in the early stages of disease. DFSP tends to follow an indolent course after the initial presentation with what is often described as a "rubbery lump". As the disease progresses, the lump tends to enlarge, change colour, and exhibit a more nodular consistency. In rare cases, DFSP can present as an ulcerated exophytic lesion or a depressed area of skin, making diagnosis even more challenging. A high index of suspicion is warranted for early diagnosis, and referral to a specialist unit with expertise in both oncologic resection and reconstruction. DFSP tumours arise from the dermis and grow with finger-like projections. Therefore, in cosmetically sensitive or functionally important locations, an excision and analysis technique that assesses all excision margins is the gold standard of care. Slow Mohs technique performed with en bloc excision is a well-tolerated option for oncologic resection of the tumour. Mohs technique can also be considered but can be challenging in children for reasons explained below. As an alternative, depending on the anatomical location, tumours can be excised with a wide local excision. While an excision technique that incorporates the deep fascia with a 3-cm peripheral margin is acceptable in adults,

planning of the excision margin in children should involve consideration of preoperative imaging with MRI, site of the tumour, age, and physical built of the child. Patients should be offered all treatment options considering the local outcomes, available expertise, and cost. A multidisciplinary approach and good communication between team members is crucial. Close collaboration with a pathologist who is familiar with sectioning technique that allows margin control is of paramount importance. Soft tissue reconstruction should be performed immediately after oncologic clearance, although a staged approach may be required. Adjuvant radiotherapy should be avoided in children due to the long-term risk of secondary malignancies and potential for growth disruption.

Introduction

Dermatofibrosarcoma protuberans (DFSP) is considered a rare type of cancer of fibroblastic origin arising in the dermis [1]. It may be managed by skin, or sarcoma surgeons.

This article discusses the current trends in diagnosis and treatment of paediatric DFSP highlighting new evidence-based developments.

In the USA, 451 paediatric patients were diagnosed with DSFP between 1973 and 2010. The incidence was reported to be higher among children with darker skin and adolescent age group (15–19 years old) [2]. In Wales, with a population of approximately three million, only five paediatric cases were reported over 15 years [3]. Similarly, small case series published in the literature highlight the rarity of this group of tumours [4, 5, 6•, 7•].

Although uncommon, paediatric DFSP has been diagnosed in infancy with lesions identified as early as 7 weeks old [8]. DFSP is more common in adulthood and patients are usually diagnosed between the second and fifth decades of life.

DFSP was first described by Hoffman in 1925 [9]. An earlier report of similar lesions was documented by Darier and Ferrand, who described the disease as "progressive and recurring dermatofibroma [10, 11]".

Clinical features

Paediatric DFSP is a slow-growing tumour with a high risk of local recurrence but with low metastatic potential. It is more commonly located on the trunk and proximal extremities, rarely found in the head and neck, and is slightly more predominant in males [5].

DFSP may start as a scar-like area (atrophic variant) that subsequently develops a growth described as a "nipple like projection" (nodular variant). DFSP is usually a slowly growing lesion; however, a duration of few weeks to many years have been described [5, 6•, 11]. The atrophic variant may be present for many years before suspicion is raised when a nodule develops.

The nodular lesion can be pink, reddish, flesh coloured, or even bluish in colour. Hence, it may be confused with vascular malformations and haemangiomas in children [6•, 8, 11] (Fig. 1a). It is typically firm, well circumscribed, fixed to the skin but mobile relative to underlying structures.

A change in size, tenderness, or new ulceration is sometimes reported in a previously known lesion. DFSP is associated with trauma and this had been well described in the literature. However, it is difficult to ascertain whether trauma is a predisposing factor or purely coincidental.

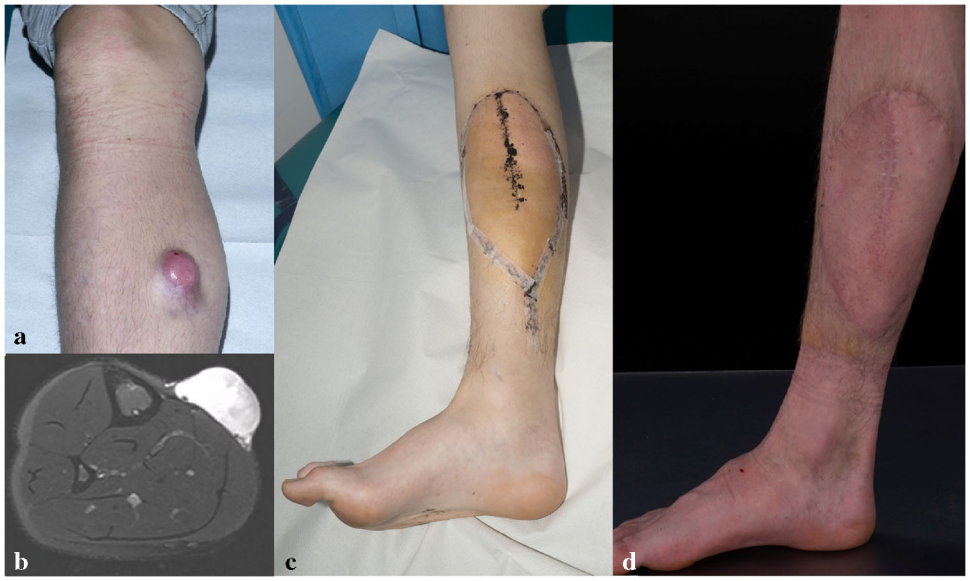

Fig. 1. **a** Photograph showing nodular type of DFSP on the anteromedial aspect of the right lower limb. **b** MRI scan demonstrating hyperintense lesion on T2W/STIR images. **c** Complex soft tissue reconstruction with free tissue transfer using free scapula/parascapular flap. **d** After 52 months follow-up.

The clinical differential diagnoses include morphea, vascular malformations, haemangiomas, dermatofibroma, morphoeic basal cell carcinoma, and granuloma annulare [5, 6•, 8, 11].

Imaging

DFSP tumours often have finger-like projections that extend into deeper tissues. Imaging is helpful, particularly an MRI with contrast, to delineate anatomical extension which in turn may affect surgical management and planning. This is especially true in recurrent, extensive, and atypical lesions [12–14].

On MRI scans, DFSP tumours are demonstrated as hypointense lesions compared to adjacent subcutaneous fat on T1-weighted images and a variable intensity compared to that of the skeletal muscle. When T2-weighted images are obtained, they usually show a hyperintense or similar intensity signal compared to subcutaneous fat. The tumour enhances to gadolinium either uniformly or in patches [12, 13] (Fig. 1b).

Histopathologic features

There are many histopathologic variants of DFSP including the classic, sclerosing, Bednar's tumour (pigmented), myxoid, atrophic, and fibrosarcomatous type. The classic type is seen more commonly in the general population. However, children show increased incidence of the atrophic variant, together with most of the diagnoses of giant cell fibroblastoma, a tumour closely related to DFSP [5, 11, 15–18].

DFSP tumours typically appear to have uniform spindle-shaped cells with infrequent mitotic figures arranged in storiform or cartwheel-like patterns on

microscopy, a feature not exclusive for this entity [5, 11, 15, 16]. This morphology and the infiltrative pattern of growth warrant the use of further tests, including immunohistochemistry to confirm the diagnosis. DFSP typically stains positive for CD34 in about 90% of tumours and negatively for factor XIII [17, 18].

Giant cell fibroblastoma is also associated with a high tendency to recur locally after excision. It is less cellular than classic DFSP and is characterised by giant cells and perivascular lymphocytes set in a wreath-like arrangement. Intralesional haemorrhage is also a feature of giant cell fibroblastoma. Giant cell fibroblastoma stains positively for CD34 and vimentin and negatively for smooth muscle actin, desmin, HMB-45, keratin, and S100 protein [19, 20].

The histopathologic differential diagnosis of DFSP includes dermatofibroma (most dermatofibromas stain negatively to CD34), solitary fibrous tumour, plaque-like CD34-positive dermal fibroma, and spindle cell tumours that stain positively for CD34. It has been reported that healing tissue can be difficult to distinguish from residual DFSP in a re-excision sample when looking for residual tumour [6•, 21, 22].

Molecular cytogenetic studies

Another distinguishing feature of DFSP is the presence of translocation between chromosomes 17 and 22; t (17;22) (q22; q13). This translocation leads to the fusion of the COL1A1 gene (Collagen type1 alpha1) on chromosome 17q21-22, and *PDGFB1* (platelet-derived growth factor beta) on 22q13. The resultant fusion protein activates PDGFB receptor and leads to tumour growth. This translocation is present in 86–96% of cases and can be identified using fluorescence in situ hybridization (FISH) analysis or multiplex reverse transcription polymerase chain reaction when the tissue fixed with formalin and embedded in paraffin [21–26].

For the above-mentioned reasons, molecular cytogenetic testing utilising FISH analysis is particularly helpful in situations where there is histopathologic and immune-histochemical overlap in diagnosis, as in the case of differentiating CD34-positive dermal fibroma [27].

FISH analysis is also theoretically helpful in situations where healing tissue from re-excision samples in slow Mohs technique (described below) is confused with residual tumour. In this situation, immunohistochemical testing with CD34 is usually beneficial in establishing a definitive diagnosis. However, confusion can persist as the non-neoplastic spindle cells normally present in the dermis and healing tissue can also sometime stain positively for CD34. Hence, further analysis with FISH in translocation-positive tumours can theoretically be used to confirm complete oncologic resection [6•, 28, 29].

Fibrosarcomatous DFSP

The fibrosarcomatous change is associated with tumour progression, occurring in up to 9% of adult patients. Histopathologically, the storiform pattern is lost in favour of a herringbone appearance, the mitotic index per 10 HPFs is higher and the tumour stains less commonly for CD34 (50%) compared to the classic DFSP [30–32].

The risk of tumour recurrence and metastasis from fibrosarcomatous DFSP is higher than classic DFSP but variable within the literature. This is probably affected by the duration of the lesion before treatment and may also be influenced by the excision technique used and margin control.

The fibrosarcomatous changes in DFSP are far less common in paediatric population but exhibit the same behaviour in terms of local recurrence and metastasis when compared to studies performed in adults [33].

A study by Hoesly et al. 2015 examined 188 adult patients with DFSP including 18 with fibrosarcomatous change and found there was no difference in age, race, duration of tumour before diagnosis, and clinical presentation when comparing DFSP with or without fibrosarcomatous change in their cohort. However, the histopathologic differentiation is important for prognostic values. The risk of 1- and 5-year recurrence-free survival in fibrosarcomatous variant was 86% and 42% respectively compared to 94% and 86% in conventional DFSP. Also, the risk of metastasis was 18% in the fibrosarcomatous group compared to no metastasis in the conventional DFSP group [30].

Treatment

Surgical excision of DFSP tumours is the preferred treatment option when feasible. Surgical excision can be performed by micrographic surgery or wide local excision. Micrographic surgery allows assessment of all excision margins and it includes Mohs and slow Mohs techniques. The differences between the two techniques are discussed below.

DFSP tumours are known to have deeper extensions and finger-like projections beyond the lesion on the skin surface. Hence, histopathological examination of all margins is recommended.

The conventional bread loafing technique of processing the specimen utilises vertical sectioning technique at various distances and only assesses less than 2% of the margin. Therefore, the risks of missing residual tumour when wide local excision (WLE) technique is used combined with vertical sectioning. In micrographic techniques, the specimens are sectioned horizontally, and all margins are assessed.

The National Comprehensive Cancer Network guidelines recommend tumour excision using Mohs micrographic surgery or other techniques of micrographic surgery. Alternatively, WLE is recommended if these techniques are not available with 2–4 cm margin [34].

The European consensus-based interdisciplinary guidelines also advocate an excisional technique that assesses all margins and recommended an initial peripheral excision margin of 1–1.3 cm using micrographic technique with excision of the deep fascia, preferably utilising the slow Mohs technique. They also recommend an excisional margin of 3 cm if conventional WLE and histopathological assessment are performed [35].

Micrographic surgery

Several studies performed mostly in adults showed Mohs technique is particularly useful to control all the margins and preserve tissue and has lower risk of tumour recurrence [36–41].

Mohs micrographic surgery (MMS) involves an initial tumour excision with a small margin (not standardised in DFSP). The specimen and operative site are marked to orientate the excised tumour. The specimens are sectioned and inked in a specific way to maintain the orientation of the growth. Fresh frozen sections are inspected under the microscope, after horizontal sectioning so all margins are examined, ideally by the same dermatologic surgeon. Following this, another three-dimensional piece of tissue is removed from areas of residual tumour while the patient is waiting. This process is repeated until no further residual tumour is seen. The procedure is time consuming and requires a laboratory with appropriate equipment to process and analyse the specimens near the operation room [40].

In children, Mohs micrographic surgery is challenging because of the following reasons.

1. Children usually require general anaesthesia to perform the procedure and MMS will predispose them to a long operative duration [7, 42••, 43•].
2. Patient cooperation: In cases where local anaesthesia is considered, it is difficult to predict patient cooperation in this age group for a long period of time [42••]. This can be especially dangerous while operating in the head and neck area as precision is needed when the tissue is excised. Also, the children may face behavioural and anxiety-related issues that may leave a long-term effect.
3. In extensive lesions, it will be difficult to assess and prepare the slides for all margins in a timely manner [8].
4. Environmental factors: MMS requires a lab that is supplied with appropriate equipment to prepare the slides. This setting is not usually available in paediatric hospitals [42••].
5. Frozen sections that are used to prepare the slides in MMS may also cause difficulty in interpreting the histopathologic specimens due to crystallisation [6•, 40–42••].

Brough et al. 2021 have described their experience of treating seven patients under general anaesthesia utilising Mohs micrographic surgery. The mean excision margin was 1.45 cm. The number of layers excised ranged from 1 to 5 layers. Interestingly, the total duration of general anaesthesia was not reported in their publication [43•].

Whereas oncologic resection utilising slow Mohs and WLE performed under general anaesthetic is the usual method of resection. Utilising Mohs technique under general anaesthetic predisposes the child for long operation that may take many hours. There are concerns regarding child development and duration of anaesthesia in children.

Slow Mohs is an alternative option in children. The term slow Mohs refers to techniques that use en bloc excision of the lesion with a margin of normal-looking tissue in a staged approach. The tissue is fixed in formalin and embedded in paraffin instead of the frozen sections utilised in MMS. The specimens are analysed off-site by a specialist pathologist rather than by a Mohs surgeon. The process takes more than 24 h as it requires more time to fix and embed the specimens [38]. The wound is dressed, and another stage is awaited. If the

margin is involved, another layer is removed from the involved area and sent to the pathologist. If the margin is negative, then the defect is reconstructed. This allows a significantly less operative time, less anaesthetic time with assessment of all margins

Margin strip techniques are used in sectioning the specimens in slow Mohs and they include Tubingen and Muffin techniques. The Tubingen technique is used for larger tumours while the Muffin technique is used for smaller lesions. The difference lies in the method of sectioning and analysing the tumour to allow complete margin control [40, 44].

The use of slow Mohs technique in extensive tumours usually entails a staged approach and the wound needs to be temporised with dressings while histopathologic analysis is achieved with a plan for a secondary operation to either remove the incompletely excised tumour or reconstruct the defect.

The procedure is usually well tolerated as the duration of anaesthesia is short and there are no significant issues while the results are awaited [6•]. However, there could be problems with compliance with dressings in the meantime.

A recent study by Lee et al. showed there were no differences in recurrence rates between techniques performed with paraffin embedding compared to frozen sections [45].

Wide local excision

In adults, WLE with 2–4 cm margins is an alternative option for oncologic resection. In children, the excision margin should consider preoperative imaging with MRI, site of the tumour, age, and physical built of the child. The reported rate of tumour recurrence in the literature following WLE is variable

A recent large study from the UK by Durack et al. 2021 examined the outcomes of 494 adult patients (of those 483 were primary DFSPs) treated in 11 plastic surgery units and 15 dermatology units. Most patients with primary DFSP (75%, 362 patients) underwent WLE while 97 patients (20%) underwent MMS. The tumour recurrence rate following WLE was 1.2% (6 patients) while none of the patients who underwent MMS had recurrence with a follow-up duration of 25.5 months. The recurrence rate in this large study is very small compared to the published literature. Most of the published guidelines favour MMS over WLE because of significantly higher risk of recurrence published in the literature [46••].

Another study by Farma et al. 2010 examined the outcomes of 206 patients diagnosed with DFSP and treated with WLE with an excision margin of 2 cm. They reported a recurrence rate of 1%. Only 4% of patients had adjuvant radiotherapy. The tumour recurrence rate was 1% with a mean duration of follow-up of 64 months. [47]

A systematic review by Foroozan et al. 2012 examined the recurrence rate following WLE versus Mohs in retrospective studies. The risk of local recurrence was 1% in MMS compared to 6% in WLE [37].

While it makes more sense to examine all margins following oncologic resection, patients should be offered all treatment options and discussion should consider local outcome measures, clinical expertise, and cost to the National Health Service.

Reconstruction may involve complex techniques utilising skin graft and local or free flaps (Fig. 1c, d).

Other modalities of treatment

In adults, adjuvant radiotherapy is considered if excision margins are less than 1 cm and WLE techniques were used, and further surgery is contraindicated. If Mohs or slow Mohs is utilised, then radiotherapy is not warranted. Radiotherapy should be avoided in children due to the lifetime risk of secondary malignancies and potential for growth retardation. However, its use has been reported in children in the literature [2, 48].

In recurrent disease, surgical resection is still the recommended modality of treatment. Radiotherapy is feasible if not used before usually in the form of adjuvant therapy but not recommended for the above-mentioned reasons. Alternatively, if surgery is contraindicated, then target treatment with imatinib is the modality of choice.

The use of imatinib mesylate has been described in adult population to treat the following situations: treatment of locally advanced or recurrent disease that is not amenable for resection or to avoid functional and cosmetic consequences, to treat distant metastasis and as neoadjuvant to decrease the size of the tumour pre-operatively if there are concerns about functional and cosmetic outcomes [49–54]. However, the use of imatinib in children is less well reported [5, 55–58]. Imatinib acts by blocking the platelet-derived growth factor beta receptor (PDGFB). Approximately 88–96% of DFSP patients show the translocation between chromosomes 17 and 22. This translocation leads to the fusion protein COL1A1-PDGF-B that is responsible of upregulation of platelet-derived growth factor beta and growth of the tumour [23–26].

There are few reports of using other types of targeted therapy in adult patients in imatinib refractory cases of unresectable tumours, e.g. sorafenib and sunitinib. However, their use in paediatric population is not reported to our knowledge [58, 59].

The use of chemotherapeutic agents in paediatric population is scarce. In one report, a child received a favourable outcome after administration of vinblastine and methotrexate [60].

Prognosis and follow-up

DFSP tumours usually have favourable prognosis. However, surgery may cause functional and cosmetic morbidity related to flap or graft failure, scar, involvement of major nerves, or operations near joints. The presence of fibrosarcomatous components is a feature predicating a poorer outcome. There is paucity of studies that examine outcomes of paediatric DFSP in the literature. A study reported on 451 paediatric patients in the USA showed an overall survival of 100%, 98%, and 97% in 5, 15, and 30 years respectively [2].

There is limited data on patient prospective regarding their journey with the disease. This is even more challenging in children for obvious reasons. A study published in 2019 that surveyed 218 patients or their relatives including children showed that 52.3% of the patients reported receiving misdiagnosis initially when presented with their skin lesions. The same study showed that

there was no difference in the size of the scar when WLE or Mohs was compared [61•].

Another study that surveyed adult patients showed that satisfactory cosmetic results were achieved in 50% of patients who underwent WLE compared to 71% of patients who underwent Mohs.

There is no agreed follow-up protocol that specifies interval or duration of follow-up for children diagnosed with DFSP. A systematic review performed by Foroozan et al. looked at rates of recurrence after WLE and MMS and found the mean time for recurrence to be 68 months [37].

It is reasonable to follow up these patients every 6–12 months for 5 years then annually for another 5 years [6•, 62].

Declarations

Conflict of Interest

Aseel Sleiwah declares that he has no conflict of interest. Thomas C. Wright declares that he has no conflict of interest. Tomas Chapman declares that he has no conflict of interest. Adam Dangoor declares that he has no conflict of interest. Francesca Maggiani declares that she has no conflict of interest. Rachel Clancy declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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