

Original Research Article

Prevalence of factors influencing recurrence and/or metastasis in dermatofibrosarcoma protuberans

Abstract

Introduction: Dermatofibrosarcoma protuberans (DFSP) is a slow growing tumour with limited metastatic potential. It acquires aggressive attributes as it enlarges or if it recurs following excision. The fibrosarcomatous (FS) variant of DFSP has increased propensity for local and distant recurrence.

Aim: To determine the prevalence of markers of aggressive disease including FS-DFSP in patients presenting with DFSP.

Methods: A review of histopathology records of patients diagnosed with DFSPs was undertaken. Data retrieved included patients' demography, tumour site, size, biopsy type, excision margin, CD34 stain result, mitotic count, presence of necrosis and evidence fibrosarcomatous change.

Results: 75 histopathological records were found of which 25.3% were recurrent. Majority 57.3% (43/75) were from female patients. All were black Africans. Their average age was 39.7 years and 66.7% were from the trunk with an average size of 8.1cm (range: 1.5cm-19.5cm). Excision was performed for 57.3% (43/75) and resection margin was adequate in 5.7%.

FS-DFSP was reported in 16.0% (12/75) overall and in 27.9% (12/43) of DFSPs which were excised. Most 75.0% (9/12) of patients who had FS-DFSPs were females. Only 9.7% of classical DFSPs involved limbs whereas 25.0 % (3/12) of FS-DFSPs were in extremities. Average age of patients who had FS-DFSPs was 44.7 years and their average size was 10.4cm. Mitotic count of 5 and above per 10 high-power fields was reported in 74.9% (9/12) of FS-DFSPs.

Conclusion: Majority of DFSPs are larger than 5cm at presentation. FS-DFSP variant is common and affects older patients compared to the classical DFSP. Adequate tumour resection margin is rarely achieved, especially for FS-DFSP.

Keywords: [Dermatofibrosarcoma protuberans, fibrosarcomatous variant of DFSP and resection margin]

1. INTRODUCTION (ARIAL, BOLD, 11 FONT, LEFT ALIGNED, CAPS)

Dermatofibrosarcoma protuberans (DFSP) is a nodular subcutaneous slow growing tumour which commonly affects individuals in early to middle adulthood^{1,2}. It is more common in black Africans³. In the early stage DFSP starts as a plaque-like lesion which may be confused with common dermatological conditions such as warts or keloids. It grows slowly before entering a phase of rapid growth during which it enlarges, becomes infiltrative and may develop satellite nodules. It is the infiltrative growth which increases the chance for incomplete surgical resection and therefore high rate of local recurrence²⁻⁷.

Factors associated with aggressive behaviour in DFSP include older age (>50 years), large tumour size (>5cm), recurrent tumour, tumour location (head and neck region) and aggressive histological sub-types^{8,9,10,11,12}. The fibrosarcomatous (FS-DFSP) variant of DFSP is aggressive and has a higher propensity for local recurrence and metastatic spread^{10,13}. Diagnostic criteria for FS-DFSP include tumour differentiation, degree of cellular atypia, pleomorphism, number of mitotic counts, the presence of tumour necrosis and CD34 expression⁹. What is required for confirmation of FS-DFSP is demonstration of evidence of sarcomatous change in at least 5% of the tumour^{13,14}.

Dermatofibrosarcoma protuberans is amongst the commonest soft tissue sarcoma seen in South Africa¹⁵. This study was conducted to determine the prevalence of features associated with aggressive behaviour of DFSP such as size greater than 5cm, recurrent tumour and fibrosarcomatous change in our setting.

2. MATERIAL AND METHODS / EXPERIMENTAL DETAILS / METHODOLOGY (ARIAL, BOLD, 11 FONT, LEFT ALIGNED, CAPS)

Patients and Methods: The study was based on an audit of histopathological reports of patients who presented and were treated for DFSP at CHBAH between January 2009 and June 2013. Only patients who had a core needle, incision or excision biopsy and whose specimens were analysed at the Department of Anatomical Pathology of the National Health Laboratory Services (NHLS) in University of the Witwatersrand's circuit were included. All primary and recurrent DFSPs were included. Data retrieved included patients' demography, recurrence or primary, tumour site and size, biopsy type, excision margin, CD34 stain result, mitotic count, tumour necrosis and report on presence of fibrosarcomatous change. Fine needle aspiration cytology result was not relied on to confirm the diagnosis. Recurrent DFSPs were included.

Data was entered into an Excel spreadsheet for analysis. Numbers and percentages were used to summarize categorical data whereas the mean, median or average with range was used for continuous data. Chi-square test, Student t-test or Fisher's exact test was used for comparison depending on whether the data being compared were categorical or continuous. The level of significance was set at a p-value below 0.05.

RESULTS

A total of 75 records of DFSP were found of which 26.4% (19/75) were recurrent. Majority 56.9% (43/75) were females. All were black Africans with an average age of 39.7 years (Table 1). Most DFSPs (66.7%) were on the trunk and the overall average size was 8.1cm (range: 1.5cm-19.5cm) (Table 1).

Excision was performed in 59.7% (43/75) which was considered adequate wide local excision on clinical grounds in 81.4% (35/43). Resection margin was however adequate on histopathological analysis in only 5.7% (2/35). Only 9.7% of classical DFSPs involved limbs whereas 3/12 (25.0 %) of FS-DFSPs were in extremities (Table 2) and (please note that DFSP subtype in 22 records was not specified). Although the average age for the whole group was 39.7 years (range: 6-70), the average age for non FS-DFSPs and FS-DFSPs were 37.0 years and 44.7 years respectively. The average size of non FS-DFSPs was 6.4cm (range: 2-12.5cm) and for FS-DFSP 10.4cm (range: 2.5-19.5cm).

Average mitotic count per 10 high power field were 5.6 (range: 0-70), 3.0 (range: 0-13) and 15.8 (range: 3-70) for the overall group, non FS-DFSPs and FS-DFSPs, respectively. Mitotic count of 5 and above per 10 high power fields was reported in 74.9% (9/12) of FS-DFSPs. CD34 immuno-histopathological stain was positive in all DFSPs, irrespective of tumour subtype when it was reported (98.7%: 74/75).

DISCUSSION

The main aim of the current study was to determine the prevalence of markers of aggressive DFSP which include older age, tumour in the head and neck region, large size at presentation, recurrent tumour and histological subtypes other than the classical variant. We undertook the study because DFSP is the commonest soft tissue sarcoma in our setting¹⁵, which mirrors emerging reports from other parts of the world^{3,13,16}. Furthermore, care including resection of DFSP in our setting is often done by individuals who are the least experienced and without involvement of a multidisciplinary team. Results of this study confirm that DFSP is a disease of young adults below the age of 50 years^{1,3}.

Actually it is reported that some of the DFSPs start in childhood and perhaps during intra-uterine life but because of their indolent growth they present later during adulthood³. Majority of patients with DFSP in the current study were however above the age of 35 years and those who had FS-DFSP were even older (at least six years older than the ones who had the classical variant DFSP). It is not surprising that patients with FS-DFSP were much older as DFSP is known to remain indolent for a protracted period and acquires aggressive attributes as it enlarges or with each recurrence if it has been excised^{1, 14, 4,17, 18, 19,20}.

Most of the DFSPs in our study were larger than 5cm in diameter at presentation, irrespective of site and FS-DFSPs were on average significantly bigger. Larger tumour size of FS-DFSP as compared to classical DFSP is consistent with what has been reported that DFSP loses its innocence as it grows bigger¹². When DFSP reaches an as yet to

be determined size (probably greater than 5cm) it begins to grow at a rapid rate and becomes even more aggressive including conversion to the FS-DFSP variant^{10,11,19}.

The prescribed adequate circumferential and deep resection margin of at least 2cm was only realized in 5.7% of DFSPs in the current cohort of patients. One of the key challenges in the management of DFSP is high local recurrence rates even after wide local excision due to infiltrative growth pattern. The infiltrative growth pattern is enhanced by secretion of hyaluronic acid from the tumour³. Sometimes satellites nodules may develop around the main tumour.

Recurrence rate of 25.3% in this study is not surprising as it is within the reported range, and may sometimes be as high as 60%. Tumour recurrence implies that the margin of excision was not adequate which not unusual as large DFSPs often have finger-like extensions which are exceedingly difficult to detect during histopathological analysis. Additionally, wide local excision is sometimes not possible in cosmetically sensitive areas or when a DFSP is close to a vital structure^{3,5,7}.

Dermatofibrosarcoma protuberans becomes more aggressive with each recurrence²¹. The aggression includes changing to FS-DFSP or development of metastasis. Whether it is a “chicken and an egg” situation i.e. it was an FS-DFSP ab initio which would explain the recurrence and/or metastasis would be difficult to prove. Only one out of twelve (12) FS-DFSPs from this study was recurrent.

The behaviour of DFSP can be unpredictable as distant metastases may develop from a tumour that appears histologically “benign”. An additional finding from the current study is the challenge of differentiating classical DFSP from FS-DFSP. Diagnosis of FS-DFSP requires demonstration of sarcomatous change in at 5% of the tumour^{13,14}. Parameters used to determine sarcomatous change include alteration of growth pattern (from storiform to herring bone pattern), hyper-cellularity, atypia, high mitotic count and evidence of tumour necrosis.

Other features which are considered for diagnosis of FS-DFSP include evidence of loss of CD34 expression, Ki67 index and p53 expression^{9,14,17}. Diagnosis or exclusion of FS-DFSP therefore requires a more detailed histopathological assessment which may not be possible in under-resourced settings. Despite the challenge FS-DFSP was diagnosed in just 16% of our DFSPs which is amongst the highest reported rates¹⁴. The FS-DFSP variant is therefore not as rare as it has been reported by Prahbu et al in 2013¹². In a significant proportion of records the DFSP subtype was not specified. Additionally, the same parameters which are used to confirm FS-DFSP are commonly found in other relatively benign subtypes of DFSP including the classical DFSP as demonstrated in the present study^{1,17}.

Knowing the type of DFSP one is dealing with is critical for planning of appropriate treatment. Whilst it is not necessary to perform MRI for classical DFSP, MRI is mandatory in FS-DFSP and all recurrent DFSPs³. Logically MRI should ideally be requested for large DFSP (>5cm) as beyond this size the tumour is likely to have an infiltrative growth pattern. Tumour excision reliant solely on just a combination of gross inspection and palpation would almost inevitably lead to recurrence^{22,23,24}. And, with each recurrence it is as if the DFSP becomes angrier. Furthermore, when DFSP is irresectable, mutational analysis may be necessary if neoadjuvant treatment with imatinib is considered^{2,25}.

Some of the limitations of this study are that it is retrospective study and some records were incomplete. The number of cases was small for inclusion of inferential statistics. As the diagnosis of FS-DFSP requires thorough histological evaluation of the tumour at multiple sites, it highly likely significant foci especially in large tumours could have been missed and the number reported could be an underestimation. Furthermore, histological subtype in close to 30% of DFSPs was not specified which could have influenced sub-categorization by gender, age and site.

Conclusion

Majority of DFSPs are larger than 5cm at presentation and likely to have entered the rapid and infiltrative growth phase. FS-DFSP variant is common and is likely in patients who are above 40 years of age. Differentiating classical from FS-DFSP is difficult as parameters which are used to differentiate classical from FS-DFSP such as loss of CD34 expression and level of mitotic count are not reliable. Adequate tumour resection margin is rarely achieved.

Recommendations

Dermatofibrosarcoma protuberans should be managed by a dedicated multidisciplinary team especially for patients who are older than 40 years, if the tumour larger than 5cm in diameter and is recurrent. A search should continue for a reliable method to differentiate FS-DFSP from classical DFSP.

Declaration: The research was conducted by Dr. Albert Benneh for partial fulfilment of the requirements for the degree of Master of Medicine in Surgery (MMed Surg).

Ethics: Permission to conduct the study was received from the Human Research Ethics Committee of University of the Witwatersrand (M130974) and approvals were also obtained from Research Review Boards of Chris Hani Baragwanath Academic Hospital and Department of Anatomical Pathology of National Health Laboratory Services of the Republic of South Africa.

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Table 1: Demography, clinical and histological findings of all patients with DFSP (N = 75)

Parameter	Number (%)
<i>Gender</i>	
Males:	32 (42.7%)
Females	43 (57.3%)
<i>Age groups</i>	
<20 years	4 (5.3%)
20-40 years	40 (53.3%)
41-60 years	23 (30.7%)
>60 years	8 (10.7%)
<i>Presentation</i>	
Primary	53 (70.7%)
Recurrent	19 (25.3%)
Not specified	3 (4.0%)
<i>DFSP subtypes</i>	
Classical	42 (56.0%)
FS-DFSP	12 (16.0%)
Unspecified	21 (28.0%)

NB: FS = Fibrosarcomatous dermatofibrosarcoma protuberans

Table 2: Average size of all DFSPs according to site

Tumour site	Number (%)	Average size (range)
Head and Neck	14 (18.7%)	6.2cm (2-13cm)
Trunk	46 (61.3%)	7.8cm (1.5-18cm)
Limbs	14 (18.7%)	10.9cm (2-19.5cm)
Not specified	1 (1.3%)	Not specified
Total	75 (100.0%)	8.1cm (1.5-19.5cm)

208 **Table 3:** Demography and histological findings in FS-DFSPs (n = 12)

Case no	Recurrent	Age	Sex	Race	Site	Size (cm)	Biopsy	CD34	Mitotic count per 10 high power field	WLE	Margins
1	n	45	F	B	T	3.6	E	+	3	Y	R 1
2	n	37	F	B	T	NS	C	+	16	NS	NS
3	n	64	F	B	L	19.5	E	+	11	Y	R 1
4	n	41	M	B	L	11.5	E	+	70	Y	5mm
4	n	34	M	B	T	11	E	+	8	Y	10mm
6	n	34	M	B	T	11	E	+	8	Y	10mm
7	n	56	M	B	T	16	E	+	4	Y	1mm
8	y	34	F	B	H&N	2.5	E	+	29	Y	R 1
9	n	40	F	B	T	NS	C	+	10	NS	NS
10	n	46	F	B	L	8.5	E	NS	NS	Y	1mm
11	n	27	F	B	T	NS	C	+	6	NS	NS
12	n	40	F	B	T	2.7	E	+	16	Y	R 1

209 **NB:** T= Trunk, L=Limb, H&N= Head and Neck, F=Female, M=Male, E=Excision, C=Core biopsy, Y=Yes, NS= Not
210 specified, FS = Fibrosarcomatous dermatofibrosarcoma protuberans, R1 = microscopically positive resection margin,
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213 **Table 4:** Comparison between Classical DFSP and FS-DFSP

	Classical (n=41)	FS-DFSP (n=12)
Gender		
Male	22 (53.5%)	3 (25.0%)
Female	19 (46.3%)	9 (75.0%)
Age groups		
<20 years	2 (4.9%)	0 (0.0%)
20-40 years	25 (61.0%)	7 (58.3%)
41-60 years	11 (26.8%)	4 (33.3%)
>60 years	3 (7.3%)	1 (8.3%)
Median (IQR)	33.5 (25.5-44.5)	40.5 (34-46)
Site		
Trunk	30 (73.2%)	8 (66.7%)
Limb	4 (9.8%)	3 (25.0%)
Head and Neck	9 (22.0%)	1 (8.3%)

Size		
<5cm	7 (17.1%)	3 (25.0%)
<5-10cm	12 (29.3%)	1 (8.3%)
10.1-15cm	3 (7.3%)	3 (25.0%)
>15cm	2 (4.9%)	2 (16.7%)
NS	17 (41.5%)	3 (25.0%)
Median (IQR)	6.0 (2.75-9)	11.0 (3.8-14.8)
Mitotic count		
0	11 (26.8%)	0 (0.0%)
<5	15 (36.6%)	2 (16.7%)
5-10	7 (17.1%)	4 (33.3%)
11-15	3 (7.3%)	1 (8.3%)
>15	0 (0.0%)	4 (33.3%)
Not specified	7 (7.3%)	1 (8.3%)
Median (IQR)	2 (0-8.8)	10.0 (3.8-14.8)

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NB: Subtype in 22 DFSPs was not specified