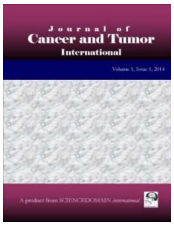

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Occurrence of Factors Influencing Recurrence and/or Metastasis in Dermatofibrosarcoma Protuberans

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Authors' contributions

This work was carried out in collaboration between all authors. Author AYB designed the study as part of MMed (Surg), wrote the protocol, collected data, did initial statistical analysis and wrote the first draft of the manuscript. Author PSK co-supervised the MMed, was involved during protocol development, application for regulatory approval, drafting of initial draft and review of the manuscript. Author MJH co-supervised the MMed, was involved during protocol development, application for regulatory approval and review of the manuscript. Author JBLK was involved in data analysis including statistical analysis, drafting and review of the manuscript, preparation for submission and response to the reviewers. Author TEL conceived the idea, designed the study, co-supervised MMed, analyzed data, drafted and revised the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Dermatofibrosarcoma protuberans (DFSP) is a slow growing tumour with limited metastatic potential. However it acquires aggressive attributes as it enlarges or if it recurs following excision. The fibrosarcomatous (FS) variant of DFSP has a higher propensity for local recurrence and distant metastasis.
Aim: To determine the frequency of findings 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 of fibrosarcomatous change. The Pearson's chi-square was used to determine if there was an association between DFSP subtype and; gender, age and tumour site. Significance was set at below 5%.
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 8.1 cm (range: 1.5 cm-19.5 cm). 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. 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. The median age of patients who had FS-DFSPs was 40.5 years (IQR: 34-46) and their average size was 10.4 cm. Mitotic count of 5 and above per 10 high-power fields was reported in 74.9% (9/12) of FS-DFSPs. Gender, age, tumour site and tumour size did not significantly influence occurrence of classical DFSP and FS-DFSP. The difference in mitotic count for DFSP and FS-DFSP was however statistically significant.
Conclusion: Majority of DFSPs are larger than 5 cm at presentation. FS-DFSP variant is common and affects older patients compared to the classical DFSP. Mitotic count above 5 is likely in FS-DFSP as compared to classical DFSP. Adequate tumour resection margin of 2 cm and above is rarely achieved in our setting, especially for FS-DFSP.

Keywords: Dermatofibrosarcoma protuberans; fibrosarcomatous variant of DFSP; resection margin.

1. INTRODUCTION

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 Africans [3]. 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 recurrence of up to 40% even when an excision margin of 2 cm or greater is used, unless if Mohs micrographic procedure is undertaken [2-7].

Factors associated with aggressive behaviour of DFSP include older age (>50 years), large tumour size (>5 cm), recurrent tumour, location (head and neck region) and aggressive histological sub-types [8-12]. 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 necrosis and CD34 expression [9]. What is required for confirmation of FS-DFSP is demonstration of evidence of sarcomatous change in at least 5% of the tumour volume [13,14].

Dermatofibrosarcoma protuberans is amongst the commonest soft tissue sarcoma seen in our setting [15]. This study was conducted to determine the frequency of occurrence of features reported to be associated with aggressive behaviour of DFSP such as age, larger tumour size, recurrent tumour and fibrosarcomatous change in our setting.

2. MATERIALS AND METHODS

2.1 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 analyzed 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.

Data was entered into an Excel spreadsheet for analysis. Numbers and percentages were used to summarize categorical data whereas the mean, median with inter-quartile range or average with range was used for continuous data. Pearson chi-square test was used to establish if there was an association between gender, age and tumour site, and subtypes of DFSP. The the level of significance was set at less than 5%.

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.

3. RESULTS

A total of 75 records of DFSP were found of which 26.4% (19/75) were recurrent. Majority 57.3% (43/75) of patients were females. All were black Africans with an average age of 39.7 years (range: 6-70) and 58.6% were either 40 years old or younger. 56.0% (42/75) were reported as classical DFSPs and 16.0% (12/75) were FS-DFSPs. Tumour subtype in 28.0% (22/75) was not specified (Table 1).

Most DFSPs (66.7%) were on the trunk and their average size was 8.1 cm (range: 1.5 cm-19.5 cm) (Table 2). Excision was performed in 59.7% (43/75) and was considered adequate wide local excision on clinical grounds in 81.4% (35/43). Resection margin was however adequate on histopathological analysis i.e. greater than 2 cm in only 5.7% (2/35).

The median age of the patients who had classical DFSP was 33.5 years (IQR: 25.5-44.5) and 53.5% (22/41) were males. 65.9% of classical DFSPs were from patients who were younger than 41 years old and 68.2% (28/41) of them had tumours situated in the trunk whereas 22.0% (9/41) were from head and neck region. The median size of classical DFSPs 6.0 cm (IQR: 2.75-9 cm) and 12.2% (5/41) was larger than 10 cm in diameter. Tumour size in 41.5% (17/41) of classical DFSPs was not specified. The median mitotic count was 2.0 (IQR: 0-8.8) and counts of 5 and above per 10 high power field were noted in 24.4% (10/41) of classical DFSPs. In 17.1% (7/41) mitotic count was not reported (Table 3).

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

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

NB: FS = Fibrosarcomatous dermatofibrosarcoma protuberans

Of the 12 patients who had FS-DFSP, 75.0% (9/12) were females. The median age of patients who had FS-DFSP was 40.5 years (IQR: 34-46). 58.3% (7/12) of DFSP patients were below 41 years. 66.7% of FS-DFSPs were found in the trunk region and 8.3% (1/12) from the head and neck. The median size of FS-DFSs 11.0 cm (IQR: 3.8-14.8) and the size of 41.7% (5/12) of the tumours was more than 10 cm. Tumour size was not specified in 25.0% (3/12) of FS-DFSPs which were diagnosed on core needle biopsy. The median for mitotic count in FS-DFSP was

10.0 (IQR: 3.8-14.8) and 74.9% had counts above 5 per 10 high power field. Mitotic count was not specified in 8.3% (1/12) of FS-DFSPs (Table 3).

The Pearson's chi-square p-values (p-value significant < 0.05) checking for the influence on occurrence of classical and FS-DFSP by gender, age, site, size and mitotic count were 0.21, 0.86, 0.27, 0.14 and 0.001 respectively.

91.7% (11/12) of FS-DFSPs were newly diagnosed and 75.0% (9/12) were diagnosed following excision. CD34 stain was positive in 91.7% (11/12) but was not specified in one case. In 75.0% (9/12) it was recorded that specimens were sent following wide local excision but a final tumour excision margin greater than 2 cm was not recorded in any of them (Table 4).

4. DISCUSSION

The main aim of the current study was to determine the prevalence of markers of an aggressive DFSP in our setting. These markers 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 setting [15], which mirrors emerging reports from other parts of the world [3,13,16]. Furthermore, care including initial 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].

Table 2. Average size of all DFSPs according to site

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

Table 3. Comparison between classical DFSP and FS-DFSP

	Classical (n=41)	FS-DFSP (n=12)	P-value
Gender	22 (53.7%)	3 (25.0%)	***0.21***
Male	19 (46.3%)	9 (75.0%)	
Female			
Age groups	2 (4.9%)	0 (0.0%)	***0.86***
<20 years	25 (61.0%)	7 (58.3%)	
20-40 years	11 (26.8%)	4 (33.3%)	
41-60 years	3 (7.3%)	1 (8.3%)	
>60 years	33.5 (25.5-44.5)	40.5 (34-46)	
Meadian **(IQR)**			
Site	28 (68.2%)	8 (66.7%)	***0.27***
Trunk	4 (9.8%)	3 (25.0%)	
Limb	9 (22.0%)	1 (8.3%)	
Head and Neck			
Size	7 (17.1%)	3 (25.0%)	***0.14***
<5cm	12 (29.3%)	1 (8.3%)	
<5-10cm	3 (7.3%)	3 (25.0%)	
10.1-15cm	2 (4.9%)	2 (16.7%)	
>15cm	17 (41.5%)	3 (25.0%)	
NS	6.0 (2.75-9)	11.0 (3.8-14.8)	
Median (IQR)			
Mitotic count			***0.001***
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)	

NB: Subtype in 22 DFSPs was not specified

Table 4. 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

NB: T= Trunk, L=Limb, H&N= Head and Neck, F=Female, M=Male, E=Excision, C=Core biopsy, Y=Yes, NS= Not specified, FS = Fibrosarcomatous dermatofibrosarcoma protuberans, R1 = microscopically positive resection margin

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 end up presenting later during adulthood [3].

Majority of patients with DFSP in the current study were 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 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. 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 bigger [12]. When DFSP reaches an as yet to be determined size (probably greater than 5 cm) it begins to grow at a rapid rate and becomes even more aggressive which may include conversion to the FS-DFSP variant [10,11,19].

The prescribed adequate circumferential and deep resection margin of at least 2 cm 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 the infiltrative growth pattern which is enhanced by secretion of hyaluronic acid from the tumour [3]. Sometimes satellites nodules may develop around the main tumour.

Dermatofibrosarcoma protuberans becomes more aggressive with each recurrence [21]. The aggression includes sometimes changing to FS-DFSP or development of metastasis. It is another "chicken and an egg" situation i.e. was it an FS-DFSP ab initio (which would explain the recurrence and/or metastasis) or it de-differentiated, becomes difficult to prove. However in our study only one out of 12 FS-DFSPs was recurrent.

An additional finding from the current study is the challenge of differentiating classical DFSP from FS-DFSP. The same features which are used to confirm FS-DFSP such as high mitotic count and CD34 expression are common in both classical and FS-DFSP, as demonstrated in the present study [1,17]. Diagnosis or exclusion of FS-DFSP therefore requires a more detailed histopathological assessment. Furthermore, the behaviour of DFSP can be unpredictable as distant metastases may develop from a tumour that appears histologically "benign". However FS-DFSP is more common in females, is likely to be larger than 2 cm in size, have mitotic count above 5 per 10 high power field as demonstrated in this study. Additionally, the study also supports heightened suspicion of FS-DFSP for DFSPs in extremities.

FS-DFSP was diagnosed in over 16% of our DFSPs which is amongst the highest reported rates and is therefore not as rare as it has been reported [12,14]. Knowing the type of DFSP one is dealing with is critical for planning of appropriate treatment. For example, while it is not necessary to perform MRI for classical DFSP it recommended for FS-DFSP[3] as tumour excision reliant solely on just a combination of gross inspection and palpation would almost inevitably lead to recurrence; especially if the tumour is large in size or has other markers of aggressive disease [3,22-29]. Metastatic workup is also advised if diagnosis FS-DFSP is made pre-operatively [25].

Some of the limitations of this study are that it is retrospective and some records were incomplete. 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.

5. CONCLUSION

Majority of DFSPs especially FS-DFSPs are larger than 5 cm at presentation. FS-DFSP variant is relatively more common in our setting and affects older patients as compared to classical DFSP. Mitotic count of 5 and more per 10 high power field is likely in FS-DFSP. CD34 expression is not reliable for differentiating FS-DFSP from classical DFSP. Tumour excision margin greater than 2 cm is rarely achieved our setting.

6. RECOMMENDATIONS

Dermatofibroarcoma 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.

CONSENT

Individual consent from each patient was waived as the study was retrospective and based on audit of histopathology records. Access to records was done after receipt of approvals from the Human Research Ethics Committee of University of the Witwatersrand, Research Review Boards of CHBAH and Head of Department of Anatomical Pathology. The study was conducted in adherence with the Declaration of Helsinki.

ETHICAL APPROVAL

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.

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).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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