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Dermatofibrosarcoma protuberans: Our experience of 37 cases, a Single institutional review at NCI, Egypt

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ABSTRACT

Background: DFSP is a rare slow growing locally malignant skin tumor. It is the commonest cutaneous stromal tumor arising in young & middle-aged adults with rare occurrence in paediatrics. It arises as a firm slow-growing nodule that infiltrates deeply with in apparent finger projections beyond clinical margins. Commonly it recurs but rarely metastasizes unless there is a fibrosarcoma component diagnosed by open biopsy & IHC with CD34. Surgery is the main stay of treatment with wide clear margins of 2-3 cm or more beyond clinical borders & down to fascia. Mohs micrographic surgery plays a role especially when wide resection would result in poor cosmetic or functional outcome as on face or ears. Margins of first resection are the main factor to affect local recurrence rates & prognosis. With LNs metastases regional lymphadenectomy offers survival benefit. Lung metastases are rare & occur with multiple local failures after multiple compromised surgeries. Metastasectomy is justified in isolated oligo-metastatic resectable lesions mainly in lungs. CTH is rarely used & RT may be used adjuvant to surgery reducing recurrence when clear margins are not obtained. Imatinib may be considered an option for locally advanced & recurrent lesions. *Aims:* To study clinicopathological features of all cases of DFSP, presentations, diagnosis, surgical management, complications, reconstructive methods & outcome 'DFS' & 'OS'. *Materials & Methods*: A single institution prospective analysis of all cases presented to NCI-Cairo University with DFSP candidates for surgery over a period of 5 years from Jan 2015 until Dec 2019. 37 cases included. Data collected from patients archives then analyzed. *Results:* Mean age was 36.5ys ranging (6-65ys). Males predominated (40 cases, 54.1%). Most lesions were on the trunk (14 cases, 37.9%). Protruding type was the commonest (26 cases, 70.2%). All cases were denovo at initial presentation. 8 cases (21.6%) were on top of previously injured skin. Post resection least diameter ranged (0.5-5.5cm) with mean (2.01±1.36 SD) while largest diameter ranged (0.5-14cm) with mean (3.79±3.08 SD). +ve or close margins (<1cm) encountered in (10 cases, 27%). Local recurrence appeared in (11 cases, 29.7%) for 1st time, in (5 cases, 13.5%) for 2nd time & in (2 cases, 5.4%) for 3rd time. Local recurrence occurred in (12 cases, 32.4%) of primary clear margins & among (7 cases, 18.9%) of primary close margins even after re-resection. Median & mean survival times were 4ys & 4.1yrs respectively. Most patients survived 3 or 4 years (43.2% or 35.1%, respectively). The only significant survival parameter was tumor free margins above 4 cm as free-margin lesions survived longer than those with close-margin lesions (<1cm).

Keywords: Dermatofibrosarcoma protuberans, prognosis, NCI, EGYPT

1. INTRODUCTION

Dermatofibrosarcoma protuberans (DFSP) is a rare slowly growing locally malignant cutaneous neoplasm of mesenchymal origin. Its incidence ranges from 0.8 to 5 per 10^6. Despite rarity, it is the commonest cutaneous stromal tumor. Usually arises in young & middle-aged adults on the trunk, proximal limbs, head & neck (H&N) regions with rare affection of fingers. It is characterized by aggressive local recurrence power if not promptly excised (Llombart et al., 2009). DFSP has a higher incidence to occur between ages of 20s & 50s with male/female ratio of 3/2 in most studies. Others suggest equal distribution among males & females or even predominance in men with a male-to-female ratio of approximately 3:2. It is rarely found in paediatric ages although some consider giant cell fibroblastoma as the juvenile form of DFSP (Abbott et al., 2006; Sung et al., 2017).

Locally, DFSP grows by asymmetrical inapparent fingers that spreads horizontally beyond apparent clinical margins as well as infiltrates deeper structures. Commonly it recurs but rarely metastasizes (<1%). About 90% of DFSP are low grade locally aggressive cutaneous STS, the remaining contains often high-grade fibrosarcoma components (DFSP-FS). This fibrosarcomatous variant is an aggressive progressive form of DFSP with high rate of spread (Sachdev and Sundram, 2006; Liang et al., 2014). Clinically it arises as firm, slow-growing nodules. Accurate diagnosis is achieved by open biopsy & IHC staining. On microscopy, it appears uniform, spindle-shaped cells with prominent nuclei and high mitotic index, grouped in short storiform fascicles. Cells are immunoreactive positive to CD34 (broad spectrum endothelium associated marker), hyaluronate, vimentin, and negative for XIIIa & S100. However, this CD34 positivity is nonspecific & can occur in benign fibrohistiocytic lesions or other sarcomas (solitary fibrous tumor, sclerotic fibroma, superficial acralfibromyxoma, cellular digital fibromas, dermatofibromas & nuchal-type fibroma). Cytogenetically, cells show a specific pathognomonic translocation between chromosome 17 & 22 (McNiff et al., 2005).

Surgical excision is the mainstay of treatment. Because of its infiltrating growth pattern, DFSP commonly extends far beyond clinical apparent margins resulting in a high recurrence rate after standard surgical excision. Hence, wide excision of 2-3 cm or even more is justified beyond clinically identifiable borders & down to include fascia. Mohs surgery plays a role in its management, especially when normal tissue conservation is at a premium and wide surgical resections may lead to poor cosmetic or functional results as on the face or ears (Lowe et al., 2017). For patients with LN metastases, most studies recommend formal regional control to offer a long-term survival. Distant hematogenous metastases are rare and likely to occur with multiple local failures after multiple compromised surgical resections. Lungs are most affected, but brain, bone & other soft tissues can be affected. Metastatectomy may be offered in situations with isolated oligo-metastatic resectable lesions especially when occurring in lungs (Lal et al., 2004).

Conventional chemotherapy (CTH) is rarely used in treatment of DFSP. Radiotherapy (RT) had also limited role in the past but recently it is used as adjuvant to surgery reducing its risk of recurrence when clear margins can not be obtained. This is usually justified when adequate surgical excision may result in major cosmetic or functional deficits (face & near neurovascular bundles). RT dosing ranges (50-70 Gy) with an overall low risk of severe complications. Close follow-up is needed after RT as some tumors may recurs in a more aggressive form (Lemm et al., 2009).

This work aims to evaluate the clinicopathological features of DFSP, present their clinical features, work-up, surgical management & outcome of such treatment with addressing main factors affecting the local recurrence & DFS rates.

2. MATERIALS AND METHODS

Data of Patients

This is single institution prospective study of all cases presented to NCI-Cairo University with DFSP candidates for surgery from Jan 2015 until Dec 2019. 37 cases were recruited. Data collected from patients' archives at the statistical department. Data included demographic features (age & sex), tumor characters (size & margins), surgery done & sequalae, reconstuction if needed, adjuvant treatments (CTH, RT) & outcome (Local recurrences & Disease free survival 'DFS' rates).

Methodology

Surgical treatment was done by standard WLE including skin, subcutaneous & fascia. Margins were not compromised in areas where more wider excision was impossible (nose, cheek, upper eyelids). We considered margins <1 cm as close ones & needed further interference. Specimens fixed with formalin and sent to the pathology department for histopathology & IHC. IHC staining done included (CD34, Vimentin, S100, CD 68 and Perl's iron stain).

Follow up

It was ranged from 36 to 84 months with a mean follow-up time of 70 months. Again, surgery was needed for adequate margins & gapped wounds, including reexcision with just resuturing for primary intention or reconstruction (skin grafts, local rotational flaps or remote pedicled flaps). CTH or RT was not used in this work either as a neoadjuvant or adjuvant protocol. Ethical clearance for the conduction of this study was obtained from our institute ethical committee.

3. RESULTS

This study included 37 patients with DFSP. Males predominated (40 cases, 54.1%). Age ranged from (6-65 ys) with mean of (36.5±14.4 ys). Most lesions presented on the trunk (anterior abdominal wall, back, anterior or lateral chest wall) (14 cases, 37.9%) followed by LL. The protruding type was the commonest (26 cases, 70.2%). 8 cases (21.6%) appeared on top of previous injured skin, wounds, scars, lentigo simplex, actinic keratosis & giant pigmented nevus. All cases were denovo (not recurrent) at time of initial presentation (table 1).

Table 1 Clinicopathological features of our patients (37cases, 100%)

Sex:	
Male	13 cases, 35.1%
Female	24 cases, 64.9%
Age: mean age (36.5 ± 14.4 ys)	
<18years	6 cases, 16.2%
>18years	31 cases, 83.8%
Presentation:	
Protruding type	26 cases, 70.2%
Morphea- like	5 cases, 13.5%
Atrophoderma-like	3 cases, 8.1%
Pigmented type	2 cases, 5.4%
Angioma-like	1case, 2.7%
Site:	
Trunk	14 cases, 37.9%
LL	11 cases, 29.7%
UL	7 cases, 18.9%
H&N region	5 cases, 13.5%
Origin:	
On top of normal skin	29 cases, 78.4%
On pigmented/injured skin	8 cases, 21.6%
Margins:	
Clear margins	27 cases, 73%
Close (<1cm) or +ve margins	10 cases, 27%
Histological variants:	
Classic type	27 cases, 72.9%
Bender tumor	4 cases, 10.8%
Fibroblastoma	3 cases, 8.1%
Atrophic	2 cases, 5.4%
Fibrosarcoma	1 case, 2.7%
Skin closure:	
Primary intention	25 cases, 67.6%
Reconstruction (grafts or flaps)	12 cases, 32.4%
Wound dehiscence	13 cases, 35.1%

The least diameter post resection ranged from (0.5 to 5.5 cm) with mean (2.01±1.36 SD) while the largest diameter ranged from (0.5 to 14 cm) with mean (3.79±3.08 SD). Positive or close margins of resection (<1cm) were encountered in (10 cases, 27%). Tumors

recurred locally in (11 cases, 29.7%) for the 1st time post resection, in (5 cases, 13.5%) for the 2nd time & in (2 cases, 5.4%) for the 3rd time. Local recurrence of our cases did not show significant correlations with patient age, sex or tumor site & size, although these local recurrences tended to appear among older age groups & females (table 2). Again, tumors of UL & abdominal wall tended to have more local recurrence rates than other sites. Only margins of the first resection were found to influence the local recurrence rates & affect prognosis. Collectively, local recurrence occurred among (12 cases, 32.4%) of primary clear margins & among (7 cases, 18.9%) of primary close margin lesions even after re-resection.

Table 2 Local recurrences in our cohort (37 cases, 100%)

Factor:		Local Recurrence		Total no & %	p-value
		No	Yes		
Age (Mean ± SD)		35.3 ± 13.5	39.3 ± 17.3		0.464
		No & %	No & %		
Sex	Male	15 cases, 75%	5cases, 25%	20,100%	0.483
	Female	10 cases, 62.5%	6 cases, 37.5%	16, 100%	
Site	H & Neck	5 cases,100%	-----	5, 100%	0.259
	UL	2 cases, 40%	3 cases, 60%	5, 100%	
	Chest wall	2 cases, 100%	-----	2, 100%	
	Abdominal wall	2 cases, 40%	3 cases, 60%	5, 100%	
	Back	5 cases, 71.4%	2 cases, 28.6%	7, 100%	
	LL	8 cases, 72.7%	3 cases, 27.3%	11, 100%	
Size	Least diameter	2.05 ± 1.44	1.94 ± 1.29		0.851
	Largest diameter	1.10 ± 1.29	0.83 ± 0.29		0.363
Margin	Free margin	18 cases, 66.6%	9 cases, 33.4%	27, 100%	0.046
	Close margin	8 cases, 80%	2 cases, 20%	10, 100%	

The median survival time in our study was 4 ys while the mean survival time was 4.1 ys. The majority of patients survived for 3 or 4 years (43.2% or 35.1% respectively) (table 3).

Table 3 Survival time (years) among our patients

Survival (years)	No & %
3 ys	16 cases, 43.2%
4 ys	13 cases, 35.1%
6 ys	4 cases, 10.8%
7 ys	4 cases, 10.8%
Total no.	37 cases, 100%
Mean ± SD	4.11 ± 1.37
Median (95% CI)	4.0 (3.62 – 4.378)

Survival time of DFSP did not show significant associations with age, sex, tumor site or size. However, female patients survived less than males. Also, survival time was inversely correlated with age and tumor size (table 4). Patients with tumor lesions on their back or chest wall survived less than patients with other tumor sites. The only significant association was with tumors with free margins above 4 cm where patients with free-margin lesions survived longer than those with close-margin lesions (<1cm) (figure 1 & 2).

Table 4 DFS correlations in our cohort

		DFS	p-value
Sex	Male	4.2 ± 1.6	0.843
	Female	4.1 ± 1.0	
Age	Years	0.016	0.924

Site	Head & Neck	4.2 ± 1.6	0.967
	UL	4.4 ± 1.9	
	Chest wall	4.0 ± 0.0	
	Abdominal wall	4.4 ± 1.9	
	Back	3.7 ± 1.1	
	LL	4.2 ± 1.3	
Size	Least diameter	0.204	0.350
	Largest diameter	0.068	0.756
Margins	Free margin	4.15 ± 1.54	0.047
	Close margin	4.0 ± 0.82	
N.B. Data presented as Mean ± SD or Correlation coefficient. P-values <0.05 are considered significant			

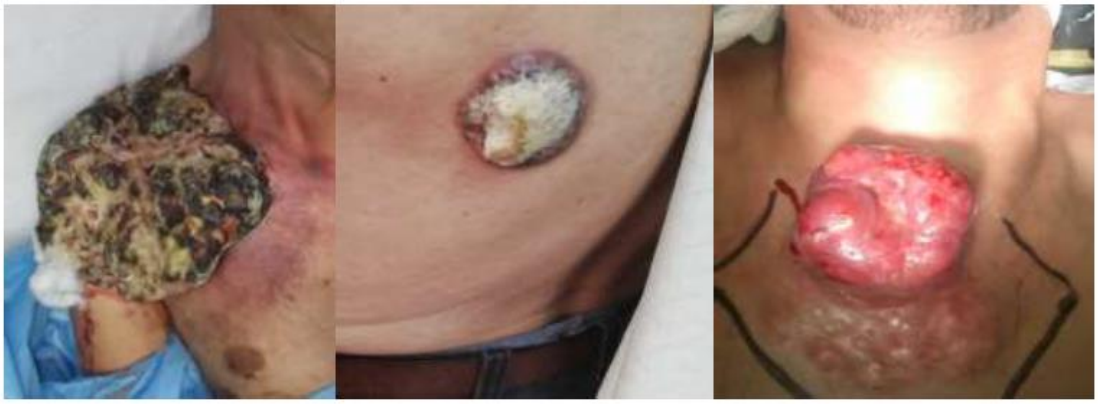

Figure 1 Clinical presentation of 3 of our cases with DFSP at different regions.

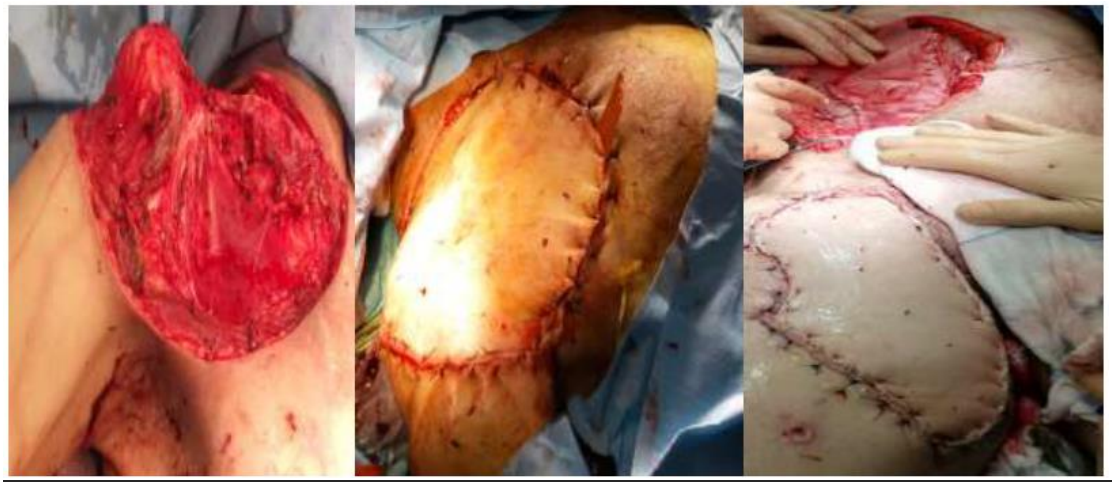

Figure 2 Intraoperative views of a recurrent DFSP of shoulder reconstructed by pedicled LD myocutaneous flap & another intraoperatve view of another case with 3rd groin reccurrence reconstructed by pedicled VRAM flap.

4. DISCUSSION

DFSP was first reported in 1924 by Darier & Ferrand. Hoffman described this tumor a year later as a skin neoplasm with a power to form protruding nodules & named them DFSP. Taylor & Helwig in 1962 described were the last to clarify its main histological features until 1992 where immunopositivity for CD34 & negativity for XIIIa was revealed. Finally, Simon et al. (1997) identified a translocation between chromosome 17 & 22 & made it clear that this cytogenetic alteration in cellular genome is the initiator of DFSP (Darier and Ferrand, 1924; Hoffman, 1925; Taylor and Helwig, 1962).

DFSP usually presents in the fourth decade, although it has been known that it can arise with a wide varying ages ranging 6 ys to 65 ys. Gender distribution still is a point of argue, where some suggest males predominate while others found females

predominated their work. In this cohort (6 cases, 16.2%) only were encountered in the paediatrics age groups, females predominated our work (24 cases, 64.9%) with females to males ratio of 1.8 (Tsai et al., 2014). Seven histological subtypes were encountered for DFSP. The *Classic type* (commonest [90%]; monomorphous spindle cells with large elongated nucleus, poor cytoplasm, low mitotic index & rarely metastasize [0.5%]). *Giant cell fibroblastoma* (giant multinucleated cells, sinusoidal vessels & myxoidstroma, common in children). *Bednar tumor* (melanocytes & melanin deposits, usually in Africans & black Americans). *Sclerotic* (rich stroma, layers of collagen & areas of dense cellularity). *Myxoid* (spindle cells grouped in nodules with eosinophilic cytoplasm). *Atrophic is* in atrophied dermis, subcutaneous tissue & epidermis of children. *Fibro sarcomatous* is most aggressive, highest potential of local and systemic failures, high mitotic index, high cellularity & marked nuclear pleomorphism. In this work, most cases were of the classic type (27 cases, 72.9%), while the fibrosarcomatous variant appeared only in a single case (2.7%) (Liang et al., 2014; Tsai et al., 2014).

The frequent causative agent most patients blamed for DFSP development is the exposure to recurrent skin trauma (scars of surgery, burns scars of trauma, radiation induced dermatitis, vaccines, insect bites and cannula sites). Most studies agreed with the prevalence of DFSP on LL than UL. In this cohort we found the trunk region either the anterior and lateral abdomen, the anterior and lateral thoracic cage or the backs were the commonest to be affected (14 cases, 37.9%). The prevalence of the disease on the LL was the same as most literatures (11 cases, 29.7%) versus only (7 cases, 18.9%) for UL (Bashara et al., 1992; Argiris et al., 1995; Green and Heymann, 2003; Tanaka et al., 2004; Bukhari et al., 2005).

Clinically, DFSP can appear as protruding lesions or non-protruding plaques making it difficult to suspect & often delays diagnosis. Three clinical variants were distinguished by Martin et al to describe clinically the non-protruding forms of DFSP; *Morphea-like* (white brown indurated plaque resembling scar, morphea, morphea form of BCC or dermatofibroma plaque in childhood). *Atrophoderma is like* soft depressed white brown plaque similar to atrophoderma usually congenital. *Angioma-like* (indurated red plaque similar to angiomatous malformations). In our work the protruding type was the commonest (26 cases, 70.2%) presenting as a large plaque in adults with numerous surrounding protruding nodules (Martin et al., 1998; Martin et al., 2005). There was no specific investigation regarding diagnosis of DFSP or staging in our work. All cases were diagnosed primarily based on clinical examinations. Only forms of tissue diagnosis besides preoperative routine labs were sufficient to send our patients for surgery. The commonest complications encountered in this cohort were those concerning wound closure. Skin flap discoloration as a result of partial ischemia from closure under tension were found in (13 cases, 35.1%) denoting a sign for reconstruction need. Surgeons should be more liberal & do not hesitate performing reconstruction whenever a question rises regarding flaps viability to save their patients wound dehiscence & need for a second surgery (Chang et al., 2004).

Tumor sizes varied from a few millimeters up to 15 cm in most studies before patients seek medical advice. One of the largest studies by Larbcharoensub et al. (2016) analysed tumor sizes at presentation found that most tumors ranged from 0.2–10 cm with mean of 3.2±2.3SD & median of 2.5 cm. In this work, the least tumor diameter ranged in size from 0.5 to 5.5 cm while the largest one ranged from 0.5 to 14 cm, which agrees with sizes of previous literature. Most series reported local recurrence rates widely ranging from 0% to 60%. In a series from Memorial Sloan-Kettering Cancer Center, local recurrence rates were 21% of cases studied, though there was a high rate of +ve margins (42%) & DFSP-FS variant (16%) in this study. The multivariable analysis of this series found DFSP-FS variant & positive or close (1mm) margins are of prognostic relevance for recurrence-free survival. Our results showed that local recurrences occurred in 30.6% of our patients for the first time, in 13.9% for the second time second & 5.6% for the third times, respectively. The overall local recurrence rate was 30.6% (Fiore et al., 2005).

It seems quite logical that the number of recurrences is directly proportional to the need for skin reconstruction. As the recurrence times increases, each time it carries a more need for a method for skin closure. In this work skin reconstruction was needed in (5cases, 45%) of those 11 cases who recurred primarily, in (3 cases, 60%) of the 5 cases who recurred for the 2nd time and in the (2 cases, 100%) who suffered recurrence for 3rd time. This was done by thiersch grafting, local rotational skin flaps, pedicled latissimus dorsi (LD) myocutaneous flap or pedicled vertical rectus abdominis myocutaneous flap (VRAM) (Khatri et al., 2003). No adjuvant treatments were used for our recurrent cases (RT or CTH). All our cases were subjected to the 2nd or even 3rd time of resection. This precluded to rise the reconstructive stepladder gradually starting from just skin release and primary intention closure, passing by grafting with split thickness Thiersch graft up to the pedicled cutaneous or myocutaneous flaps (Chen et al., 2016).

Chang (2004) reported on 60 patients with DFSP who were treated with wide local excision: at least a 3-cm margin incorporating overlying skin and the underlying deep fascia. With a median follow-up of 59 months, the overall local recurrence rate was 16.7%. The mean time to recurrence was 38 months although the tumor reappeared after 5 years in 3 of the 10 patients with recurrent disease. The 5-years & 10-years DFS rates were 86% and 76%, respectively (Chang et al., 2004; Criscito et al., 2016). Fiore (2005) again reported their experience with 218 patients treated at the National Cancer Institute in Milan, Italy. Approximately 2/3 of

patients presented with primary DFSP & 1/3 presented with recurrent disease. The crude incidence of recurrence in the entire population was 3% at 5 years & 4.2% at 10 years, with a crude incidence of distant metastases of 1.7% at both 5 & 10 years. They found no difference in relapse rate was noted between patients with primary versus recurrent disease but that the most significant prognostic factor for relapse is the extent of initial resection with close margins (<2 cm) (Fiore et al., 2005; Farma et al., 2010).

Our work showed that local recurrence of DFSP did not show any significant associations with age, sex, site or size. However, local recurrence tended to occur more among older ages & females. Also, UL & abdominal wall lesions tended to have more local recurrence rates. The only statistically significant positive correlation with recurrence shown in this work was the initial wide margin of resection approaching 4 cm. The recurrence rate after DFSP excision varies in literature. Histologic subtype, high mitotic index, cellularity, size, location on H & N region & recurrent lesions are factors associated with higher recurrence rates. Clearly, the most important factor for local control is obtaining negative surgical margins. The median survival time of patients in this current study was 4 ys while mean survival time was 4.11 years. The majority of studied patients survived for 3 or 4 years (43.2% or 35.1% respectively). The survival time did not show significant associations with age, sex, site or size. However, female patients survived less than males. Also, survival time was inversely correlated with age and with size. Patients with tumor lesions on their back or chest wall survived less than patients with other tumor sites (Mendenhall et al., 2004; Kreicher et al., 2016).

Molecular targeted therapy with imatinib mesylate (tyrosine kinase inhibitor) may be considered as an alternative or adjuvant treatment option for locally advanced and recurrent lesions. In our work none of our cases was offered this treatment although it may carry a hope for those advanced cases (Kim, 2011; Rutkowski et al., 2011; Ugurel et al., 2014).

5. CONCLUSION

DFSP is a rare cutaneous mesenchymal neoplasm. Its presentation resembles benign skin lesions hindering early diagnosis. High index of suspicion should always rise towards any slowly growing nodules especially when there is a trauma history. Due to its high potentiality for local failure wide surgical excision with clear margins approaching 4 cm including fascia is the cornerstone for management.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

Ethical approval

This study was approved by the medical ethical committee (Institutional Review Board-IRB) of the National Cancer Institute/Cairo University on 15 of august, 2014 with an IRB number 07-2014-2316.

Data and materials availability

All data associated with this study are present in the paper.

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