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Skin Involvement in Dupuytren's Disease

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Keywords

Dupuytren's; Disease; Contracture; Fibromatosis; Fasciectomy; Dermofasciectomy; Skin; Graft; Recurrence; Dermis; Dermal; Outcome; Risk

Abstract

Whether the palmar skin has a role in the development, propagation or recurrence of Dupuytren's disease remains unclear. Clinical assessment for skin involvement is difficult and its correlation with histology uncertain. We prospectively biopsied the palmar skin of consecutive patients undergoing single digit fasciectomy (for primary Dupuytren's disease without clinically involved skin) and dermofasciectomy (for clinically involved skin or recurrence), in order to investigate this relationship. We found dermal fibromatosis in 22 of 44 ~~(50%)~~ patients undergoing fasciectomy and 41 of 59 patients (70%) undergoing dermofasciectomy. Dermal fibromatosis appeared to be associated with greater pre-operative angular deformity, the presence of palmar nodules and occupations involving manual labour. Dermal fibromatosis exists in the absence of clinical features of skin involvement and we hypothesise that the skin may have a greater role in the development and propagation of Dupuytren's disease than previously thought.

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INTRODUCTION

Dupuytren's disease is a common fibroproliferative disorder with a worldwide prevalence of up to 321.6% (Lanting et al., 2014). Despite its morbidity and associated costs to health services (Gerber et al., 2011) many aspects of the pathogenesis, classification and management remain strongly debated. In particular, the role of the palmar skin in the development, propagation, surgical management and risk of recurrence remains uncertain.

There are numerous treatment modalities available for patients with Dupuytren's disease (Eaton, 2014). Mild disease may be observed. Intralesional collagenase injections, percutaneous needle fasciotomy or selective aponeurectomy are suitable for palmar disease proximal to the metacarpophalangeal joints (MCPJs), although progression or recurrence affects up to 85% of cases (Betz et al., 2010; Mehta and Belcher, 2014; Mickelson et al., 2014; van Rijssen et al., 2012; Verheyden, 2015). Limited fasciectomy (Hueston, 1961) is the most common primary procedure for moderate to severe disease, although again up to 100% of patients experience recurrence or extension (Kan et al., 2013; Werker et al., 2012). In the 1960s, Hueston suggested that recurrent Dupuytren's disease should be managed by skin replacement (Hueston, 1962; Hueston, 1969). This hypothesis was developed by Logan and colleagues, compounding the importance of radically excising all pre-axial tissue (skin, fat and fibrous tissue) and covering the defect with a full thickness skin graft (FTSG) (Logan et al., 1985; Searle and Logan, 1992). The same group later showed that fibromatosis was present in the skin of patients with recurrent Dupuytren's disease and therefore suggested dermofasciectomy to be the most appropriate surgical option (McCann et al., 1993). Since then, dermofasciectomy and FTSG have been shown to reduce the risk of recurrence by up to 33% (Abe et al., 2004; Armstrong et al., 2000; Brotherston et al., 1994; Ebelin et al., 1991; Hall et al., 1997; Hueston, 1984; Kelly and Varian, 1992; Ketchum and Hixson, 1987; Tonkin et al., 1984). The current clinical indications for dermofasciectomy include recurrent disease and clinically involved skin. However, clinical assessment for skin involvement is difficult and

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of debatable reliability. Moreover, the relationship between clinical assessment and histological involvement is unclear. To-date, there is limited literature comparing the clinical and histological features of Dupuytren's disease in the skin (Chen et al., 2009; Hall et al., 1997; Hindocha et al., 2011; Iqbal et al., 2012; Logan et al., 1985; McCann et al., 1993) and no reports on microscopic examination of clinically uninvolved skin.

As the palmar skin may be involved by Dupuytren's disease more often than the clinical assessment suggests, our objective was to compare the histological characteristics of the palmar skin with clinical outcomes, for patients undergoing fasciectomy and dermofasciectomy.

METHODS

Between November 2009 and November 2012, an electronic database was prospectively completed in order to capture the details of all consecutive patients undergoing fasciectomy or dermofasciectomy for Dupuytren's disease, under the care of the senior author (AF). This database was retrospectively reviewed and supplemented by written and electronic notes.

According to our Hospital's funding protocol, surgery is offered when the disease adversely affects day-to-day activities with pain or when a digital contracture in any joint(s) is >20°. Skin involvement was defined by the presence of palmar pits, with or without firm and deficient skin tethered to a nodule or cord (Townley et al., 2006). Recurrence was defined by the return of nodules or cords in a previously operated area in association with recurrent contracture(s) >20° (Kan et al., 2013). We offer dermofasciectomy when there is obvious clinical evidence of skin involvement or in the presence of recurrent contracture(s). Otherwise, we offer a fasciectomy as the primary procedure in all cases.

This study was originally designed as an audit of surgical outcomes on Dupuytren's disease (Institutional registration number PS2013009). In order to minimise confounding variables and biases, we appraised only patients undergoing surgery on one digit of one hand for Dupuytren's disease. We felt that this would allow more reliable comparisons and conclusions to be drawn, ie. range of motion would not be adversely effected by surgery on adjacent digits or the palm, all the grafts would be of a similar size as only one digit was covered, etc. Therefore, at baseline we excluded patients undergoing bilateral, multi-digit or simultaneous non-Dupuytren's surgery (eg. carpal tunnel decompression). At baseline we also excluded those who declined the offered/advised procedure and those presenting with a ~~2nd~~ second recurrence within a previously operated ray (ie. requiring a ~~3rd~~ third surgery to the same ray), as we felt that this would further increase the heterogeneity of the cohort. We also retrospectively excluded those patients with unavailable/unclear histological diagnoses

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(Figure 1). Patients were grouped as fasciectomy or dermofasciectomy for comparative analysis.

Within the study period, all consecutive patients were counselled, consented and operated on by the same author (AF). Fasciectomy involved either Bruner or Skoog incision(s), followed by careful dissection and excision of pathological tissue whilst preserving neurovascular structures. For patients undergoing fasciectomy, a sliver of skin from the margin of the incisions (mean size 3x11 mm) directly overlying a cord or nodule on the palmar aspect of the involved finger, was excised and sent for histological analysis. According to Logan and colleagues (Hall et al., 1997; McCann et al., 1993), dermofasciectomy was performed by excising the palmar skin and underlying subcutaneous tissue from the distal palmar crease up to the distal interphalangeal joint (DIPJ) crease as necessary, following mid-lateral incisions. The entire specimen was sent for histological analysis. FTSGs were harvested from the ipsilateral medial arm and inset with absorbable 4-0 braided sutures (Vicryl rapide™) and a tie-over dressing. The hand was wrapped in soft dressing without splintage (Jerosch-Herold et al., 2011; Kemler et al., 2012). All operations were planned as day case procedures and patients only stayed overnight for social reasons or pain relief.

Data including age, sex, occupation, handedness and medical history were recorded alongside the degree of digital deformities and presence of palpable cords or nodules. We classified builders, plumbers, factory workers and similar roles as manual labourers. Angular deformities at the MCPJs, proximal interphalangeal joints (PIPJs) and DIPJs were measured with a standard office goniometer placed on the dorsum of the digit, by an independent Hand Therapist before surgery and ~~6~~ six months after surgery (Ellis and Bruton, 2002). The cumulative flexion deformity was calculated as the sum of the deformities measured at the MCPJ, PIPJ and DIPJ for the given digit. For the purpose of statistical analysis, the IPJ of the thumb was categorised as a PIPJ. Preoperative clinical assessment for skin involvement

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was undertaken and recorded by the senior author during the first consultation. Tissue samples were sectioned into multiple slices for H&E stain microscopy by experienced specialised skin histopathologists. The diagnosis of dermal fibromatosis was binary and based on overall morphology. We considered a partial graft failure as necrosis of less than ten percent~~<10%~~ of the graft. Complex Regional Pain Syndrome was diagnosed according to the International Association for the Study of Pain criteria (Harden et al., 2007). Follow-up ranged between ~~6~~ six and ~~26~~ twenty six months ~~with (a~~ mean ~~of~~ 12~~.4~~ months~~)~~.

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Normally distributed data are presented as means with standard deviations (SD) and compared by the independent samples t-tests. Skewed distributions are presented as medians with interquartile ranges (IQR) and compared by the the Mann-Whitney U-Test. Categorical variables (as frequencies with percentages) were compared with Chi Square or Fisher's exact tests to generate odds ratios (OR) with 95% confidence intervals (CI). As we changed the focus of our study (from the planned audit of surgical outcomes to focus on the high rate of skin involvement), we performed multiple analyses; therefore, in order to address this we have generated a family wise error rate according to the Bonferroni method and our significance level is set at $p<0.002$.

RESULTS

During the study period, 169 surgical procedures for Dupuytren's disease were performed. Of these, 103 cases were included and the reasons for exclusion are shown in Figure 1. There were 44 fasciectomies (432.7%) and 59 dermofasciectomies (57.3%).

Table 1 shows participants' demographics. Dermofasciectomy appeared to be more common amongst participants who had previously required surgery for Dupuytren's disease on the same hand (732.8% vs. 52.3%, p=0.039). Of the dermofasciectomies, 29 were for recurrent disease (49.2%).

The mean total anaesthetic time for dermofasciectomy and FTSG was significantly greater than fasciectomy (2 hours 36 minutes vs. 1 hour 49 minutes, p<0.001). Thirty-two patients (31.1%) stayed overnight.

Outcomes are shown in Table 2. Histopathologically, dermal fibromatosis was present in 61.2% of cases. Further, out of 44 patients with dermal involvement ~~This included~~ 22 ~~patients (50%) with~~had no clinical features of skin involvement ~~who~~ and so underwent fasciectomy, as per protocol.

Pre-operative angular deformity appeared to be greater in the dermofasciectomy group, although this was not statistically significant after statistical correction. ~~Similarly, both~~ Both groups attained a straighter finger post-operatively, although again there were~~as~~ no statistical differences between groups. Histologically proven dermal fibromatosis was not related to the post-operative range of movement.

Complications were not different between groups although partial graft failure appeared to be more common amongst smokers (mean 20.0 vs. 1.25 pack years, p=0.050).

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During the study period, ten patients (9.7%) underwent two operations and one required four operations. After fasciectomy, six patients (143.6%) developed early recurrence of whom four elected to undergo revision dermofasciectomy. There were no early recurrences in the dermofasciectomy group.

Table 3 shows the 29 patients who underwent dermofasciectomy for recurrent disease. Clinical assessment of their skin did not correlate with the histopathological diagnosis in 9 nine cases (31%). It is important to notice that when we clinically assessed the skin and felt it was involved, we were incorrect 4 four times (243.5%), giving a positive predictive value of 776.5%. However, when we felt the skin was not involved clinically we were incorrect 5 five times (421.7%), giving a negative predictive value of 58.3%. In our experience, clinical assessment has a sensitivity of 72.2% and specificity of 643.6%..

Positive predictors of dermal fibromatosis included an occupation involving manual labour and the presence of palpable palmar nodules (Table 4).

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DISCUSSION

Dupuytren's disease is hypothesised to begin within the palmar aponeurosis and progress axially to infiltrate fascial bands investing deep structures as well as the overlying skin. Occult fibromatosis within the dermis may be an important factor in recurrent disease (Abe et al., 2004; Armstrong et al., 2000; Brotherston et al., 1994; Ebelin et al., 1991; Hall et al., 1997; Kelly and Varian, 1992; Ketchum and Hixson, 1987; Logan et al., 1985; McCann et al., 1993; Searle and Logan, 1992) and therefore many surgeons have suggested that when there is evidence of skin involvement, dermofasciectomy may better treat the disease burden. For this reason, dermofasciectomy plays an important role in patients with obviously involved skin or recurrent disease (Abe et al., 2004; Armstrong et al., 2000; Brotherston et al., 1994; Ebelin et al., 1991; Hall et al., 1997; Hueston, 1984; Kelly and Varian, 1992; Ketchum and Hixson, 1987; McCann et al., 1993; Tonkin et al., 1984). Despite this general consensus, there is limited histhopathological data on the rate of dermal involvement in Dupuytren's disease and the paramount challenge remains in the clinical identification of those patients with skin involvement. Consequently, it is very difficult to say who may benefit from fasciectomy or dermofasciectomy with respect to the risk of recurrence. Whilst we are not the first to suggest that Dupuytren's disease exists in the skin (Chen et al., 2009; McCann et al., 1993) and subcutaneous tissue (Hindocha et al., 2011; Iqbal et al., 2012), we have demonstrated the presence of dermal fibromatosis in patients with no clinical features of skin involvement. These findings represent a novel and interesting opportunity for further research.

The most thought-provoking finding of our study is the overall rate of dermal fibromatosis (61~~.2~~%). Let us also consider that this prevalence is likely to be an underestimation of the actual percentage of dermal infiltration because only a small piece of skin was excised (mean size 3x11 mm) and the method of specimen preparation for microscopic analysis is likely to generate skip lesions. Therefore, we speculate that there is a substantially greater

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(sub-clinical) rate of skin infiltration than our study suggests. Furthermore, clinical assessment for skin involvement does not seem to be entirely reliable as we found 22 patients who had histologically involved skin, but underwent primary fasciectomy because the clinical assessment of their palmar skin was negative. This means that the occult skin disease was undetected and untreated, thereby raising the question should these patients have undergone primary dermofasciectomy? And if so, how can we identify these patients with sub-clinical disease in their palmar skin? Again, we cannot answer this question and can only speculate that pre-operative skin biopsy, with thorough microscopic analysis for dermal disease, may be valuable in stratifying patients for particular interventions. Additionally, skin biopsies for dermal involvement may be a useful variable in better understanding the otherwise unpredictable pattern of recurrence in this condition.

Histologically differentiating Dupuytren's fibromatosis from hypertrophic scarring is not always possible in limited/small skin biopsies. The morphological features are similar because the tissue shows increased cellularity and fibroblastic activity in both conditions. However, hypertrophic scars usually feature thick bundles of collagen and do not form 'burnt out' fibrotic nodules, which are frequently seen in late stage Dupuytren's disease. A potential differentiating method is nuclear staining with beta-catenin, which is typically positive in fibromatosis (Varallo et al., 2003). The diagnosis therefore relies heavily on overall morphology. Conversely, one may argue that it is not necessary to distinguish between dermal fibromatosis and excess scarring because the most important task is to excise all fibrotic tissue which results in digital contracture, regardless of the cause. Indeed, our data suggests that dermal fibromatosis was not associated to the severity of pre-operative flexion contracture nor a contributory variable to the amount of angular deformity corrected through surgery. Also, we have shown that by radically excising skin, fat, fascia, aponeurosis, scar and pathological tissue through dermofasciectomy (Logan et al., 1985), we were able to obtain a substantial greater improvement in range of motion. This gain in post-operative finger motion is likely to be related to the greater original deformity and the amount of

pathological tissue removed during dermofasciectomy. We are unable to comprehensively explain why our dermofasciectomy patients achieved a straighter digit and suggest that this is another topic to be further investigated.

Our total anaesthetic time for fasciectomy was longer than expected. Root-cause analysis revealed complications including ineffective blocks requiring conversion to general anaesthesia, difficult intubations and revision blocks for post-operative analgesia, which we do not believe are relevant to our outcomes.

Anecdotally, some surgeons discourage the use of dermofasciectomy due to the alleged risk of graft loss, perceived surgical complexity and longer rehabilitation. To-date no studies have demonstrated a statistically or clinically significant risk of graft loss (Brotherston et al., 1994; Hall et al., 1997; Searle and Logan, 1992; Tonkin et al., 1984) and our series supports the concept that dermofasciectomy and full thickness skin grafting for Dupuytren's disease is a safe, effective and beneficial procedure (Armstrong et al., 2000; Brotherston et al., 1994; Hall et al., 1997; Searle and Logan, 1992; Tonkin et al., 1984). Anecdotally, these patients take longer to return to their normal daily activities and this should be balanced against a potentially lower rate of recurrence and revision surgery – a hypothesis, which certainly deserves more investigation (Rodrigues et al., 2014).

Surgery for Dupuytren's disease increases hand morbidity and may subtly increase mortality too (Wilbrand et al., 2005). In the UK, the annual cost of treating Dupuytren's disease exceeds £41 million (Gerber et al., 2011). In the USA, disability and treatments for Dupuytren's disease account for significant losses to the economy as well as adverse effects on health insurance (Macaulay et al., 2012). Therefore, we believe that the primary procedure aimed at treating this condition should be effective for the longest possible period, particularly for younger patients at risk of early recurrence. As we have shown that dermal disease is sub-clinically present in the majority of patients, we suggest that greater research

attention should be paid to the role of the palmar skin (specifically whether by surveying the skin through pre-operative biopsy and/or excision of clinically involved skin) we may reduce the disease burden and so, the risk of recurrence. Pre-operative skin biopsy would be particularly useful in understanding whether a heavy dermal disease burden relates to early recurrence and whilst our study is underpowered to answer this question, future researchers may wish to consider the matter. The balance between surgical morbidity, long-term outcomes, recurrence and cost is still unclear and histological detection of skin involvement may be an important piece of the puzzle.

We must acknowledge two substantial limitations to our study. This was originally designed as an audit of surgical outcomes and the finding of a high rate of skin involvement generated the idea for this paper. Therefore, we performed a generous number of statistical analyses (which some may call 'data mining') and fully accept the inherent risk of generating type 1 one errors. Consequently, we have attempted to adjust our cohort with the family wise error rate, which has rendered most our findings (albeit interesting), non-significant. Further, at baseline we excluded some patients which would have formed a potentially interesting subgroup (particularly those with multi-digit disease) and we are unable to correct this oversight. We hope that future researchers will take stock of our limitations and design studies to better investigate this fascinating and novel topic.

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CONCLUSIONS

We have demonstrated that dermal fibromatosis exists in the absence of clinical features of skin involvement. We have also shown that dermal invasion by Dupuytren's disease exists in the majority of patients, in our series. Therefore, we suggest that the skin may have a greater role in both the development and propagation of Dupuytren's disease than previously thought. This study may be a useful basis for future research on skin involvement in Dupuytren's disease, its role in the stratification of patients for surgery, and its association with long-term outcomes and recurrence.

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Conflict of interest

None declared.

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Ethical approval

This was designed and conducted as a prospective audit and so formal research and ethic committee approval was deemed unnecessary by the Chair of the Norfolk and Norwich Research and Ethics Committee.

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Figure Legends

Figure 1. A flow diagram of patient attrition.

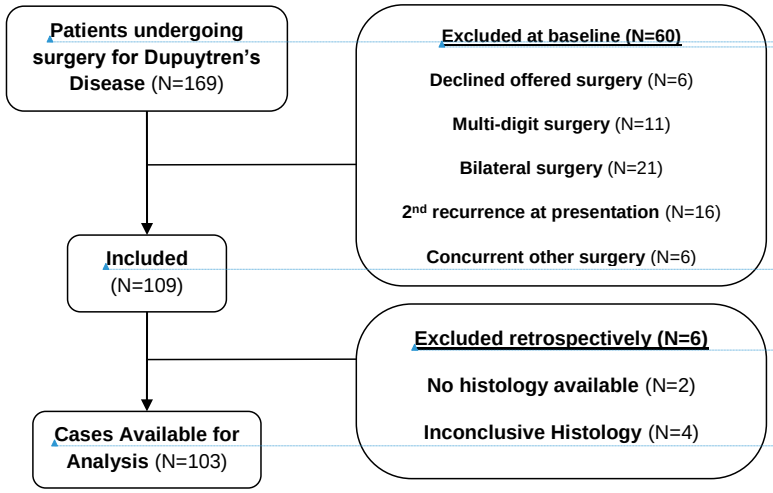

Figure 2.

An H&E stained section of skin overlying the proximal phalanx of the right little finger from a patient who underwent primary dermofasciectomy for clinical involved skin. **Upper panel:** an overview of the skin involved by fibromatosis showing destruction of the dermal adnexae and distortion of the normal dermal achitecture (low power). **Middle panel:** Dermal fibromatosis

reaching the mid-reticular dermis (medium power). **Lower panel:** A (high power) close up of the active area of Dupuytren's disease.

Figure 3.

Upper row: Pre-operative photographs of a 68 year-old right-handed man with Dupuytren's disease in the left little finger, involving the overlying skin. The PIPJ demonstrated 57 degrees of fixed flexion deformity. **Lower row:** Photographs one~~1~~ year post primary dermofasciectomy and full thickness skin grafting, showing a well-healed graft and corrected deformity.

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448 **Tables**

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Table 1. Baseline Characteristics		Fasciectomy (N=44)	Dermofasciectomy & FTSG (N=59)	p-value
Mean age (SD)		65.1 (9.03)	66.2 (8.10)	0.509
Gender (%)	Men	34 (33.0)	51 (5049.5)	0.226
	Women	10 (9.7)	8 (7.8)	
Handedness (%)	Right	36 (35.0)	58 (56.3)	0.004
	Left	8 (7.7)	1 (1.0)	
Manual Worker (%)		16 (165.5)	17 (176.5)	0.371
Family History (%)		22 (21.4)	21 (20.4)	0.142
Cords (%)		38 (376.9)	54 (52.4)	1.000
Nodules (%)		20 (19.4)	22 (21.4)	0.351
Skin clinically involved (%)		/	17 (176.5)	/

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Table 2. Outcomes		Fasciectomy (N=44)	Dermofasciectomy & FTSG (N=59)	p-value
Skin histologically involved (%)		22 (50.0)	41 (7069.5)	0.041
Median pre-operative flexion contractures in degrees (IQR)	MCPJs	25 (20-37)	39 (30-51)	0.015
	PIPJs	49 (26-64)	70 (56-90)	0.003
	DIPJs	1 (0-2)	30 (5-54)	0.190
Median post-operative flexion contractures in degrees (IQR)	MCPJs	0 (0-5)	0 (0-10)	0.413
	PIPJs	8 (0-20)	19 (0-33)	0.493
	DIPJs	0 (0-14)	0 (0-0)	1.000
Complications (%)	Infection	2 (4.54)	0 (0)	0.180
	CRPS	1 (2.327)	1 (1.769)	1.000
	Recurrence	3 (6.82)	2 (3.439)	0.649
	Total graft failure	/	0 (0)	/
	Partial graft failure	/	9 (15.3)	/
Median follow-up in weeks (Range)		39 (16-72)	51 (24-96)	0.117

Table 3. Dermofasciectomy for Recurrent Contracture		Histological Assessment of the Skin		
		Involved	Not Involved	p-value
Clinical Assessment of the Skin (%)	Involved	13 (454.8)	4 (1314.8)	0.119
	Not involved	5 (17.2)	7 (24.2)	

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Table 4. Positive Predictors of Skin Involvement

Risk Factor	OR	p-value	95% CI
Manual Worker	2.86	0.017	1.19, 6.86
Palmar Nodules	4.63	0.001	1.80, 11.9

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