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BRIEF REPORT

X-linked recessive polyfibromatosis manifesting with spontaneous keloid scars and Dupuytren's contracture

Lena Ly[1,2] and Ingrid Winship[2,3]

[1]Department of Dermatology, The Royal Melbourne Hospital, [2]Department of Medicine, The University of Melbourne, and [3]Adult Clinical Genetics, Royal Melbourne Hospital, Melbourne, Victoria, Australia

ABSTRACT

We present a patient with keloid scars and Dupuytren's contracture comprising the polyfibromatosis syndrome; four members over three generations of his family are also affected. To our knowledge this is the first familial case reported of polyfibromatosis with this specific phenotypic presentation and probable X-linked recessive inheritance.

Key words: collagen, Dupuytren's, genetic, keloid, polyfibromatosis, recessive, X-linked.

INTRODUCTION

The simultaneous occurrence of keloid scars and Dupuytren's contracture is an unusual and rare finding. We present a patient with both conditions associated with a strong family history, in which four members spanning three generations are also affected, and discuss the possible inheritance mechanisms with reference to disease aetiology. This is the first familial case reported of polyfibromatosis with this specific phenotypic presentation and putative X-linked recessive inheritance.

CASE REPORT

A 40-year-old Australian man of mixed English, Irish and Lebanese ancestry presented with a history of multiple keloid scars with bilateral Dupuytren's contracture. He first developed two vaccination-related keloid scars at age 6 and 13 – the latter specifically in reaction to the small pox vaccine. Subsequently, he developed multiple keloid scars related to minor surgery. By his 20s, he was developing spontaneous generalised keloid scarring without trauma. Bilateral Dupuytren's contracture was noted at age 16. There was no history of Peyronie's disease. Additional medical history includes insulin-dependent diabetes mellitus diagnosed at 27 and osteoporosis.

Physical examination demonstrated bilateral palmar contractures of the hand with fixed flexion deformities of the fourth and fifth fingers. Nodules were noted on the same fingers bilaterally and on his left fourth toe. Multiple thick clusters of keloid scars were identified involving his limbs and trunk (Fig. 1).

The patient (III, 2) had a strong family history of both keloid scars and Dupuytren's contracture (Fig. 2). His father is unaffected (II, 1) and there is no associated paternal family history. However, several maternal relatives have had both keloid scarring and Dupuytren's, with varying severity. His mother developed mild features of both conditions (II, 2) in her 60 s. The patient has two brothers, one unaffected (III, 3), and one who developed both conditions at age 16 (III, 1). The patient's maternal uncle has been severely affected with both conditions since his teens (II, 3); this uncle has an unaffected daughter (III, 4) whose son, aged 17, has developed both keloid scars and Dupuytren's (IV, 1). The history relating to the previous generation is less clear. His maternal grandmother of Lebanese and Syrian descent is said to have developed Dupuytren's in her fifth fingers in her very late years (I, 1). Little is known about her family history. His maternal grandfather had a contracture of his left fifth finger from about age 40, attributed to a chiselling accident and described as an enlarged knuckle caused by injury and repeated reopening of a wound (I, 2). This grandfather (I, 2) belongs to a sibship of eight where none of the physical features described have been seen in any of the siblings or their offspring.

Abbreviations:

DC	Dupuytren's contracture
HLA	Human leukocyte antigen

Correspondence: Dr Lena Ly, The Royal Melbourne Hospital, Grattan St, Parkville, Melbourne, Vic 3050. Australia. Email: lenaly21@yahoo.com.au

Lena Ly, MBBS, BMedSci, DipSurgAnat. Ingrid Winship, MBChB, MD, FRACP, FACD.

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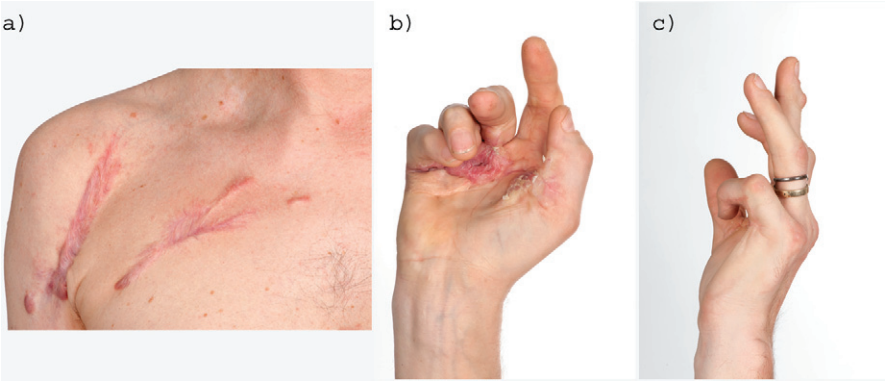

Figure 1 (a) Severe keloid scarring on trunk. (b) Severe Dupuytren's contracture (right hand, palmar view). (c) Severe Dupuytren's contracture and knuckle pad on third digit (left hand, ulnar view).

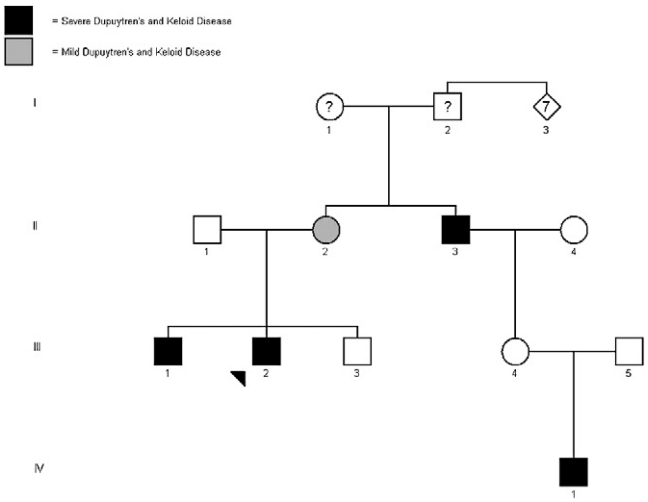

Figure 2 Pedigree.

The proband has two children, neither of whom is affected. His daughter has recently been diagnosed with type 1 diabetes mellitus at age 5.

Investigations included a normal karyotype, 46, XY. He was negative for HLA-DRB1*15.

The proband received multiple corticosteroid injections to the keloid scars as a young adult, and repeated surgical management with dermatofasciectomy and full thickness skin grafting, both providing little sustained relief.

DISCUSSION

This case demonstrates a clearly heritable genetic disorder with manifestations of two specific features comprising the polyfibromatosis syndrome. Clinical polyfibromatosis was first described by Touraine in 1945 and is characterized by: i) superficial fibromatoses – including palmar fibromatoses (Dupuytren's contracture, DC), plantar fibromatoses (Ledderhose's disease), penile fibromatoses (Peyronie's) and knuckle pads; and ii) deep fibromatoses – including extra-abdominal, abdominal, and intra-abdominal desmoids.[1] Aggressive forms associated with erosive arthropathy and osteolysis, spontaneous keloids, interstitial granulomatous dermatitis, and severe skeletal abnormalities have been described.[2–5] A positive association with diabetes has also been reported.[6] While considered to be an idiopathic or heritable disorder, an acquired form positively associated with phenytoin and epilepsy has been described.[7]

To our knowledge this is the first family described where the two features of Dupuytren's contracture and keloid co-segregate across three generations. Two other familial cases of polyfibromatosis have been described, however both without keloid disease.[8,9] Multiple cutaneous and visceral fibromas were noted in seven members of a German family spanning three generations, with apparent autosomal dominant inheritance possibly linked to a locus on chromosome one. Male to male transmission of Dupuytren's contracture and knuckle pads was reported in six members of a French family spanning three generations, supporting an autosomal dominant inheritance. The simultaneous occurrence of Dupuytren's contracture and keloid disease has been reported in a single Spanish man.[10]

The variable phenotype noted in this kindred suggests X-linked recessive inheritance, with some manifestation in heterozygotes (Fig. 2). Notwithstanding the lack of clarity about generation I, the pattern in generations II, III, and IV are highly suggestive of an X-linked recessive trait. Studies of the X chromosome would be valuable in delineating the pattern of inheritance.

The apparent paradoxical presentation of spontaneous keloid scarring and Dupuytren's contracture deserves some discussion. While both are fibroproliferative growths, distinct clinico-epidemiological features have been identified. Keloid scarring is common and occurs in response to minor trauma, sparing the palmar and plantar aspect of the hands and feet, respectively, with equal gender distribution and onset at any age. Higher prevalence rates between 15 and 20% are seen in black, Hispanic, and Asian people. By contrast Dupuytren's contracture is usually limited to the hands, occurs in response to ischaemia and anoxia, is much less common than keloid disease, and more frequently afflicts white men aged between 40 – 70 years. Despite these

differences, the accumulation of type III collagen demonstrated by both conditions makes a common molecular origin conceivable.[11,12]

More recently, there have been increasing genetic associations identified in both keloid and Dupuytren's disease. In white races, the human leukocyte antigen (HLA) subtype HLA-DRB1*15 has been independently linked with keloid development and Dupuytren's contracture.[13,14] The proband was negative for this HLA subtype. Furthermore, an autosomal dominant model of isolated Dupuytren's disease has been linked to chromosome 16q, although many cases occur sporadically.[15] Genetic susceptibility for Dupuytren's has also been demonstrated with the ZF9 gene polymorphism on chromosome 10p15, encoding a transcription factor that upregulates a fibrogenic cytokine transforming growth factor β1, implicated in fibroblast proliferation and extracellular matrix deposition.[16] It is therefore plausible that mutations in genetic susceptibility genes involving the common pathways of extracellular matrix, fibroblast and collagen synthesis, proliferation and apoptosis could be responsible for the development of both conditions in this syndrome.

CONCLUSION

This pedigree spanning four generations illustrates the interesting unusual simultaneous presentation of keloid disease and Dupuytren's contracture, probably inherited as an X-linked recessive trait. It is plausible that a common genetic mechanism may exist for these apparently disparate pathological entities.

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