Pyogenic Skin Infections as a Presentation of Papillon-Lefèvre Syndrome: Phenotypic Variability or Under-Reporting?

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Papillon-Lefèvre syndrome (PLS) is a rare autosomal recessive condition characterised by palmoplantar keratoderma and severe prepubertal periodontitis. Increased susceptibility to both pyogenic skin infections and liver abscesses have been reported in a minority of cases. Haim-Munk syndrome, reported in only two families worldwide, shows a constellation of periodontitis, keratoderma, skin infections, arachnodactyly, acro-osteolysis and onychogryphosis. Allelic mutations in the Cathepsin C (CTSC) gene are reported in PLS and HMS.

We report a boy presenting with recurrent staphylococcal abscesses at four months of age. Prepubertal periodontitis was noted at two years nine months, with additional thickening and cracking of his palms and soles. His father and two paternal aunts are similarly affected, his father being edentulous since the age of 18. Mutation analysis in the CTSC gene confirmed a homozygous R272P mutation in the proband and his father, his mother being heterozygous. The periodontal management strategy has aimed to eliminate periodontal pathogens from the child and parents using non-surgical periodontal therapy and adjunctive systemic antibiotics. The skin has been treated with emollients and topical antiseptics.

Our patient has features of PLS and highlights the susceptibility to skin infections as an important presenting sign. The R272P mutation has been previously noted in families with PLS without documented skin infections, suggesting either phenotypic heterogeneity or under-reporting/lack of awareness of this feature. Tendency to skin infections has been reported in both PLS and HMS, whereas acro-osteolysis, arachnodactyly and pes planus appear unique to the two families with reported HMS. PLS and HMS may represent opposite ends of a phenotypic spectrum of allelic CTSC mutations, with factors including polymorphisms in disease-modifying loci and environmental influences underpinning the heterogeneity. However, given the previously reported co-inheritance of PLS with albinism, it is also possible that HMS is a variant of PLS, arising following co-inheritance of a further, yet to be identified gene mutation in the vicinity of the CTSC gene locus.

Key words: cathepsin C, Haim-Munk, keratoderma, Papillon-Lefèvre, pre-pubertal periodontitis, pyogenic skin infections

INTRODUCTION

Papillon-Lefèvre syndrome (PLS) was first described in 1924 (Papillon and Lefèvre, 1924). It is a rare autosomal recessive condition with a prevalence estimated between one and four per million, characterised by palmoplantar keratoderma and severe pre-pubertal periodontitis, leading to premature tooth loss and alveolar bone destruction (Gorlin et al, 1964). Tendency to pyogenic skin infections (Haneke et al, 1975; Marandian et al, 1979; Borroni et al, 1985; Bergman and Friedman-Birnbaum, 1988) and liver abscesses (Tosti et al, 1988; Oguzkurt et al, 1996; Khandpur and
Reddy 2001; Anuradha et al, 2002; Almuneef et al, 2003) has been reported in a minority of cases of PLS. Haim-Munk syndrome (HMS) was first described in 1965 in a Jewish family from Cochin, India (Haim and Munk, 1965), and more recently in a Brazilian family (Cury et al, 2005). In addition to keratoderma and periodontitis, features reported in both families with HMS include:
- pyogenic skin infections
- arachnodactyly (long, slender fingers)
- acro-osteolysis (osteolysis of distal phalanges)
- onychogryphosis (curved thickening of nails)
- pes planus (flat feet/fallen arches of the feet).

Patients with PLS and HMS demonstrate allelic homozygous mutations in the Cathepsin C gene (CTSC) located at 11q14.1-14.3. This 47 kb gene comprises seven exons (Toomes et al, 1999). Forty-five different mutations have already been identified in PLS (University of Pittsburgh Genetics Research Group Mutations Database, 2002; Selvaraju et al, 2003; Hewitt et al, 2004), the majority being missense mutations occurring within exons 5 to 7, important domains for enzyme activity (Turk et al 2001).

Cathepsin C is a lysosomal cysteine protease, widely expressed in gingival and palmoplantar epithelium, immune cells including neutrophils and macrophages, osteoclasts, lung, kidney and placenta (Rao et al, 1997). It is responsible for activation of protease enzymes. The precise mechanisms of disease underlying PLS and HMS remain incompletely understood. However, immune mechanisms including dysregulation of phagocytic activity and chemotaxis, cytotoxic T lymphocyte and cytokine responses may underpin the tendency towards aggressive periodontitis and pyogenic abscesses (Firatlı et al, 1996; Ghaffer et al 1999; Liu et al 2000; Kabashima et al 2002; de Haar et al, 2004; Ullbro et al 2004; Pham et al 2004). The role of cathepsin C in the regulation of keratinocyte differentiation and desquamation, perhaps via desmosomal proteins including desmoglein-1, may partly explain the keratoderma (Horikoshi T et al, 1999). Here we present a case that highlights susceptibility to skin infections as an important aspect of PLS. Clinicians should actively explore for the additional clinical features associated with this condition. Specifically, dental surgeons managing pre-pubertal periodontitis should ask for a history of skin infections and keratoderma, dermatologists should assess for periodontal problems in patients with keratoderma and skin infections, and paediatricians should consider PLS in children with recalcitrant skin infections. Possible reasons for the apparent phenotypic heterogeneity of CTSC mutations are discussed.

CASE REPORT

Our patient is a five-year-old boy, born to consanguineous Pakistani parents. He presented initially with repeated infections from birth, including several episodes of tonsillitis and otitis media, and most notably, staphylococcal abscesses. He developed a breast abscess at four months of age, followed by recurrent submandibular abscesses caused by methicillin-resistant Staphylococcus aureus (MRSA) at two years of age, requiring prolonged courses of antibiotics and surgical incision and drainage. In view of suspected underlying immunodeficiency, an extensive series of immunological investigations were performed, including serum immunoglobulins, T and B cell markers, and enhanced chemiluminescence and specific antibody responses. All results were normal, other than an isolated suboptimal antibody response to Haemophilus influenzae B.

At two years nine months old he was noted to have periodontitis, manifest by recession of the gingival margins, mobility and alveolar bone loss affecting the anterior deciduous incisors (Fig 1). At the same time, he was noted to have mild uniform thickening and cracking of the palms and soles,
extending to the sides of the fingers (transgrediens) (Fig 2 and 3). The hands were otherwise normal. Specifically, there was no evidence of arachnodactyly or nail dystrophy.

**Family History**

The high degree of consanguinity within the family is reflected by the fact that the proband’s father and two paternal aunts are similarly affected. His father was edentulous by 18 years of age. At present he demonstrates keratoderma affecting predominantly the weight-bearing surfaces of the soles of his feet (Fig 4) and skin creases of the palms (Fig 5), with a suggestion of mild toenail dystrophy. The proband’s mother has been troubled by a recalcitrant right breast abscess, requiring several hospital admissions during 2004. Breast reconstructive surgery has been proposed. However, she had no signs of keratoderma of the palms or soles and no periodontitis, although generalised gingival inflammation was evident, consistent with local risk factors (calculus).

**Genetic Investigations**

Mutation analysis of CTSC performed at St. Mary’s Hospital, Manchester has demonstrated a homozygous missense mutation of guanine to cytosine at position 815 within exon 6, resulting in a substitution of arginine to proline (R272P), both in the proband and his father. The proband’s mother is heterozygous for the same mutation.

**Management**

The periodontal management has comprised full mouth non-surgical periodontal therapy with adjunctive amoxicillin and metronidazole for the proband and his mother (father is edentulous), in
an effort to eliminate the putative periodontal pathogens associated with PLS. A rigorous six-weekly periodontal maintenance regime in both our patient and his mother has been implemented and two additional courses of adjunctive oral antibiotics (metronidazole and amoxicillin) have been necessary during this period. At four years of age the child’s periodontitis had remained relatively well-controlled, and he had lost only the deciduous anterior two upper incisors prematurely, which may be considered to be almost within normal limits. However, recently the lateral deciduous incisors and canines have demonstrated early mobility and abscesses have developed beneath his deciduous mandibular first molars. Topical treatment for the keratoderma has included emollients and antiseptics. Current treatment planning is to involve early extraction of the deciduous lateral incisors and first molars and extraction of the remaining deciduous teeth prior to eruption of the permanent incisors. The use of systemic retinoids is also being considered for his keratoderma and periodontitis.

The parents have been informed of the 50% recurrent risk for subsequent offspring being heterozygous for the CTSC mutation and thus phenotypically affected (Fig 6). The father, in particular, experienced significant guilt at the time of his son’s diagnosis, and this is reflected in the couple’s positive decision to avoid further children. However, prenatal diagnosis remains a possibility for the future.

**DISCUSSION**

Our patient highlights recalcitrant skin infections as an important presentation of PLS. Both pyogenic skin infections (Haneke et al, 1975; Marandian et al, 1979; Borroni et al, 1985; Bergman and Friedman-Birnbaum, 1988) and liver abscesses (Tosti et al, 1988; Oguzkurt et al, 1996; Khandpur and Reddy, 2001; Anuradha et al, 2002; Almuneef et al, 2003) have been reported in PLS, although the paucity of publications would suggest the tendency to infection, aside from periodontitis, occurs in only a minority of cases. In particular, the R272P mutation has been previously noted in families with PLS without documented skin infections (Hart et al, 2000; Lefèvre et al, 2001; Selvaraju et al, 2003), suggesting either genuine phenotypic heterogeneity or under-reporting/lack of awareness of this aspect. Predisposition to recurrent pyogenic skin infections is unsurprising in PLS, given the neutrophil function defects associated with the syndrome and therefore clinicians should actively explore this area in patients with suspected PLS. Specifically, dental surgeons managing pre-pubertal periodontitis should ask for a history of skin infections and keratoderma, dermatologists should assess for periodontal problems in patients with keratoderma and skin infections, and paediatricians should consider PLS in children with recalcitrant skin infections.

Tendency to skin infections has been reported in both PLS and HMS, whereas acro-osteolysis, arachnodactyly and pes planus appear unique to the two families with full-blown HMS. PLS and
HMS may represent opposite ends of a phenotypic spectrum of allelic CTSC mutations (Hart et al, 2000). This is supported by identification of the Q286R mutation described in the original family with HMS (Hart et al 2000), additionally in PLS (Allende et al, 2001). More recently, a Brazilian family with HMS has demonstrated the L196P mutation (Cury et al, 2005), previously reported in PLS (Cury et al, 2002). However, given the previously reported co-inheritance of PLS with albinism (Hewitt et al, 2004), it is also possible that HMS is a variant of PLS, arising following co-inheritance of a further, yet to be identified gene mutation in the vicinity of the CTSC gene locus.

Whilst neutrophil dysfunction is likely to explain both the aggressive periodontitis and pyogenic skin infections in these subjects, the reasons for the phenotypic heterogeneity remain uncertain. Pham et al (2004) have demonstrated that impaired neutrophil killing is not a universal feature of gene mutations in PLS, which may explain in part, some of the reported heterogeneity. Genetic factors may include hitherto undetermined associated polymorphisms in disease-modifying loci. Environmental factors relating to the severity of periodontitis may include specific periodontal pathogens, but there are conflicting associations between bacteria such as Actinobacillus actinomycetemcomitans (Aa) and Prevotella intermedia and PLS (Kleinfelder et al, 1996; Springer et al, 1984), making targeted antimicrobial therapy difficult to justify. Anti-bacterial therapy therefore remains relatively non-specific and is aimed at reducing the bacterial load with good oral hygiene, involving rigorous removal of plaque and calculus. The strategy employed in the current family has been to treat the child and his mother, given the evidence for horizontal transfer of oral pathogens within family units (Van Steenberghen et al, 1993). Our patient's periodontitis was well controlled for two years with this approach, in keeping with recent reports (Lundgren and Renvert, 2004). Recent deterioration has coincided with lapses in oral hygiene within his mother, secondary to the inevitable rescheduling of hospital appointments and treatment delays due to her repeated hospital admissions for recalcitrant breast abscesses. This has led to the decision to ensure that the child has a period of deciduous edentulousness prior to the eruption of the permanent teeth and consideration of adjunctive retinoid therapy.

Other potential environmental influences may operate. In particular, the increasing number of reports of successful treatment of periodontitis and keratoderma in PLS with systemic retinoids (Bergman and Friedman-Birnbaum, 1988; Allende et al, 2001), with improvement in susceptibility to skin infections in some cases, suggests that vitamin A and its derivatives may be important cofactors. Indeed acitretin would be a potential therapeutic option for our patient in the future. Retinol has been shown to correct defective CD3-induced human T lymphocyte activation in vitro in PLS patients (Allende et al, 1997). Retinoids may directly regulate CTSC gene expression given that retinoic acid response elements have been identified in CTSC promoter regions of this gene (Rao et al, 1997). This also raises the possibility of dietary modification as a potential treatment strategy.

This family provides a further interesting observation. The proband's mother has suffered from a recalcitrant right breast abscess, raising the possibility that CTSC mutations may manifest in the heterozygous state. This may reflect the high degree of consanguinity in this family, with potentially additional disease-modifying or susceptibility genes inherited here. Whilst compound heterozygosity for PLS has been reported (Allende et al, 2001), our proband's mother is heterozygous for the R272P CTSC gene mutation, with no other mutations identified on either chromosome.

To summarise, this case highlights the different modes of presentation of CTSC mutations. In particular, patients may present to paediatricians with recurrent skin abscesses and suspected immunodeficiency, the diagnosis only becoming apparent at the onset of periodontitis or other manifestations.

The clinical heterogeneity of CTSC mutations emphasises the importance of careful history taking and examination of patients for other features. The reasons for this heterogeneity remain at present speculative.

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