



Multiple Pilomatrixomas: Review of Genetic Associations – The Surgeon Perspective

Adeeb Paddy Naasan¹, Hannah Naasan² and Anas Naasan^{1*}

¹Department of Plastic Surgery, Institute of Ninewells Hospital, UK

²Department of Dermatology, Institute of Ninewells hospital, UK

Abstract

Pilomatrixoma, or calcifying epithelioma of Malherbe, was first described in 1880 by Malherbe and Chenantais. It is a benign neoplasm arising from hair follicle matrix cells. It usually presents as a hard subcutaneous slowly growing mass. It accounts for 1.04% of all benign skin lesions. The overlying skin is mostly skin-coloured but could be pigmented. The mass is either deeply subcutaneous and invisible or superficial with possible erosion. Bullous appearance has also been described but is rare. Multiple pilomatrixomas is found to be associated with several genetic conditions, most commonly myotonic dystrophy, Turner's syndrome, and Gardner's syndrome. Recent associations with MYH-associated polyposis, Rubinstein-Taybi syndrome, Trisomy 9, Sotos syndrome and sarcoidosis have also been reported in the literature. A review of the literature assessing the genetic implications for multiple pilomatrixomas is analysed. Areas for future research into some of these associations currently suggested by the literature are highlighted.

Keywords: Multiple pilomatrixomas; Pilomatrixoma; Pilomatrixoma; Genetic; Skin

Introduction

Pilomatrixoma, sometimes spelled as 'pilomatrixoma', is also known as a calcifying epithelioma of Malherbe, since it was first described in 1880 by Malherbe and Chenantais [1]. It was thought initially to be a calcified tumour of sebaceous glands. However, Forbis and Holwig demonstrated in 1961 that the benign tumour originates from hair cell matrix, thus the term Pilomatrixoma was introduced [2]. Lesions usually present as a solitary, skin-coloured or pigmented cystic or firm nodules on the head, neck or upper extremities [1]. It lies either deeply subcutaneously and invisible or superficial with possible erosion (Figure 1 and 2). It is characterised by calcification within the lesion, which accounts for the firm feel, and often results in an angulated shape (the 'tent sign'). Bullous appearance of pilomatrixomas is rare (Figure 3) [3]. The fluid has been shown to be lymphatic. Aetiology remains debatable, although various theories have been proposed as possible explanation. Multiple lesions are found in 3.5% of cases [4]. Familial pilomatrixomas and multiple familial pilomatrixomas are even rarer [5]. Four distinct morphological stages have been proposed: early small and cystic, fully developed or large lesions, early regression and late regression with calcification [6]. A study in the 1970s by Moehlenbeck found that pilomatrixomas accounted for 0.12% of 140000 skin tumours [7]. A case review of 107 pilomatrixomas found that the mean age of patient is 13.2 years, while the location of Pilomatrixoma is most commonly in the head (64.5%), neck (14.0%) and upper extremities (12.2%) [8]. The two commonest ages for Pilomatrixomas are the under-20s (>60%) and the elderly [9]. Hence it should be considered in the differential diagnosis of any solitary skin lump in the head, neck and upper extremities [2]. Malignant transformation is rare, but should be considered in a patient with multiple recurrences. Sau et al. [9] reported 43 pilomatrix carcinoma. It has been found that clinicians have a poor diagnostic prediction for this condition; the literature has reported correct pre-operative diagnosis in 35.5% [9] and 28.9% [10] in studies consisting of 107 cases and 346 cases respectively. Surgical excision is the treatment of choice [9], although local recurrences may occur [3].

Literature Review

Sporadic pilomatrixomas are commonly associated with mutations in the beta-catenin (CTNNB) gene, which is only found within the tumour itself. The Beta-catenin gene is located at the 3p22-p21.3 locus, and functions as a cell-cell adhesion molecule and transcription factor. It is a mediator in the Wnt signal transduction pathway [11]. These mutations have a similar role in the pathogenesis of

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*Correspondence:

Anas Naasan, Department of Plastic Surgery, Ninewells Hospital and Medical School, Dundee DD1 9SY
01382660111, Scotland, UK,
E-mail: anaasan@doctors.org.uk

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Figure 1 and 2: Lesions usually present as a solitary, skin-colored or pigmented cystic or firm nodules on the head, neck or upper extremities. It lies either deeply subcutaneously and invisible or superficial with possible erosion.



Figure 3: Bullous appearance of pilomatrixomas is rare.

pilomatrixoma in sporadic and multiple tumours [12]. A few cases of multiple pilomatrixomas have been reported in the literature in the past. Most notably, the case of a 68-year-old Caucasian woman with a total of 4 pilomatrixomas (1 facial and 3 upper extremity) was reported [11]. Another case of a 23-year-old black woman with lesions on her face and back was clinically suggestive of calcified sebaceous cysts or lymph nodes, but on histopathology were found to be pilomatrixomas [12]. A similar case of an 18-year-old Indian man found a history of 4 current and 2 past pilomatrixomas, which were initially suspected to be neurofibromata. The incidence of multiple pilomatrixoma is estimated to be 3.5% [5]. The most widely reported association of multiple pilomatrixomas is with myotonic dystrophy. Myotonic dystrophy is an autosomal disease with variable penetrance. It is a dysfunction of skeletal muscle, and also involves cardiac conduction tissues, smooth muscle, the eyes and central nervous system. The clinical severity varies from death in utero to a mild asymptomatic condition [13]. The clinical features may appear in early childhood and include: muscle wasting, weakness, frontal balding, cataract, expressionless facies, mental retardation, diabetes mellitus, heart block and hyperostosis frontalis externa. The molecular basis is an expansion of the unstable trinucleotide repeat in a gene coding for a novel protein kinase [14]. The association of multiple pilomatrixomas and myotonic dystrophy was first described in the literature in 1965, by Cantwell and Reed [15]. That this association was also familial was reported by Harper, in 1971 [16]. The number of lesions reported in association with myotonic dystrophy varies between 1 and 31 [17]. The recognition of the potential for use of multiple pilomatrixoma as a cutaneous marker for myotonic dystrophy was recognised in 1978. They may precede the signs of myotonic dystrophy, and as such may be a potential early cutaneous marker [18]. In these cases genetic

testing may be warranted [19]. A figure for the number of cases of multiple pilomatrixoma which then go on to develop myotonic dystrophy is not available in the research; this may be an interesting area for future research into this association. Another association of multiple pilomatrixomas is with Gardner's syndrome. Gardner's syndrome is a variant of adenomatous polyposis coli (APC), and is an autosomal dominant disease characterised by gastrointestinal polyps, multiple osteomas, hypertrophy of the retinal pigment epithelium, and skin and soft tissue tumours. The APC protein is a negative regulator of Beta-catenin; the relationship of this with pilomatrixoma has already been mentioned [20]. A study analysing epidermal cysts excised from subjects with Gardner's syndrome found 63% had features histologically similar to those of a pilomatrixoma [21]. A case study of two familial cases of multiple pilomatrixoma leading to the diagnosis of Gardner's syndrome in one of the subjects suggests that multiple pilomatrixoma may be a cutaneous marker for Gardner's syndrome [22]. MYH-associated polyposis (MAP) is a recessive form of adenomatous polyposis coli (APC) associated with susceptibility to colorectal carcinoma [23]. A case report of two siblings found both had developed a low number of colonic lesions and early-onset colorectal carcinoma, and had a history multiple pilomatrixomas excised in childhood [24]. This study suggests that a history of multiple pilomatrixomas may predispose to MAP. There are 3 reports in the literature of an association with Turner's syndrome. One reports 2 cases of multiple pilomatrixomas in childhood associated with Turner's syndrome [25]. The second report is of a 10-year-old girl with Turner's syndrome who presents with multiple pilomatrixomas. The author suggests the predisposition may be due to abnormalities of hair-bearing skin in Turner's syndrome. The third report is of a 13-year-old girl with Turner's syndrome in association with 10 separate facial pilomatrixomas [26]. Most recently, a multicentre study demonstrated a high prevalence (2.6%) of pilomatrixomas among patients with Turner syndrome [27].

Trisomy 9 is a rare chromosomal disorder, characterised by facial anomalies, joint abnormalities, cardiac abnormalities, growth retardation and mental retardation, with a poor prognosis. Known skin abnormalities include deep palmar and plantar creases and hyperconvex nails [28]. One case report describes a four-year-old Japanese girl with trisomy 9 in whom a diagnosis of multiple pilomatrixomas was confirmed histopathologically after excision of the lesions from her left lower eyelid and median precordium [29]. To date, there are two further case reports in the literature with multiple pilomatrixoma in patients with Trisomy 9 [30,31]. The association of multiple pilomatrixomas with three cases of Trisomy 9 suggests the likely possibility of a link between them. Soto's syndrome is a very rare genetic disorder with excessive physical growth during the first 2-3 years of life, mild mental retardation, delayed motor, cognitive and social development, hypotonia and speech impairment [32]. Patients with Soto's syndrome have an increased risk of developing neoplasms. There is one report in the literature of an association between Soto's syndrome and multiple pilomatrixomas; although this may be an incidental finding [33]. Rubinstein Taybi syndrome is caused by an autosomal dominant mutation, and is characterised by short stature, learning difficulties, broad thumbs and first toes, small head and distinctive facies [34]. The association with multiple pilomatrixomas was first reported in 1994 [35]. Another case, reported in 2004, is that of multiple pilomatrixomas associated with both Rubinstein-Taybi syndrome and Churg-strauss syndrome [36]. Another case was reported in 2015 in the German literature [37]. There

has been one case report in the literature of an association of multiple pilomatricomas with sarcoidosis; however there are no other similar reports [38]. Sarcoidosis is characterised by the presence of non-caseating granulomas of unknown aetiology affecting two or more organs. It includes lung, skin, eyes, liver, cardiac and neurological manifestations. The skin is the second most commonly affected organ in sarcoidosis. Skin manifestations include hyperpigmentation, hypopigmentation, keloid reaction, lupus pernio, and erythema nodosum [39]. Recently, there is a single case report of a 15-year-old patient with gliomatosis cerebri- a rare primary brain tumour - developing four histologically-confirmed pilomatricomas on his face and upper arm in the course of 1 year [40]. This is hypothesised to be a new association and would represent an interesting area for further research.

Conclusion

Multiple pilomatricomas has been reported widely in the literature, with an incidence of 3.5%. Definite associations have been formed with myotonic dystrophy, Gardner's syndrome, MYH-associated polyposis and possibly Turner's Syndrome. Rarer associations with Trisomy 9, Soto's syndrome and Rubinstein Taybi syndrome have been mentioned in the literature, but have yet to be confirmed. The importance of the genetic associations must be taken into consideration when patients present with multiple pilomatricomas, to facilitate further investigation of the underlying cause.

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