

Cowden Syndrome: A Result of Mutation in the PTEN Tumour Suppressor Gene

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Cowden syndrome, also known as multiple hamartoma and neoplasia syndrome or PTEN (phosphatase tensin homologue) hamartoma syndrome, was first described in 1963. Cowden syndrome has a genetic basis in a novel mutation in the transforming growth factor (TGF)-regulated and epithelial cell-enriched phosphatase (PTEN) tumour suppressor gene located on 10q23.3. It characteristically gives rise to lesions from all three germ layers (ectoderm, endoderm and mesoderm), which commonly affect the skin, mucous membranes, breasts, gastrointestinal tract and thyroid gland. Certain lesions have been shown to undergo malignant change, e.g. adenocarcinomas may arise in the breasts, thyroid and gastrointestinal tract. Other associated conditions such as macrocephaly and kyphoscoliosis have also been reported.

The reported case is of a 22-year-old female who presented with gingival overgrowth/hyperplasia. Her medical history revealed that she had previously had a follicular adenoma of the thyroid, angioliomas affecting the leg and forearm and hydrocephalus as a child. The patient underwent routine hygiene phase therapy for her periodontal condition, and later also underwent gingivectomy. The patient has only recently been diagnosed with Cowden syndrome, which highlights the importance of recognising how apparently unrelated medical conditions may form pieces in the jigsaw puzzles that underpin rare syndromes, and which include oral lesions as manifestations of those syndromes. Long-term review of the oral cavity will be essential in this patient, to monitor potential oral tumour development.

Key words: Bannayan–Riley–Ruvalcaba syndrome, Cowden syndrome, multiple hamartoma syndrome, PTEN (phosphatase tensin homologue) gene

INTRODUCTION

Cowden syndrome is a rare mucocutaneous autosomal dominant disorder with incomplete penetrance and variable expression, which is equally common in both sexes and tends to arise in patients of Caucasian origin (Migogna et al, 1995). It was first described by Lloyd and Dennis in 1963 (Lloyd and Dennis, 1963; Chaudhry et al, 2000) and is now known to arise from a novel mutation in the transforming growth factor (TGF)-regulated and

epithelial cell-enriched phosphatase (PTEN, phosphatase tensin homologue) tumour suppressor gene, which encodes a 403 amino acid protein. Approximately 80% of patients fulfilling the diagnostic criteria for Cowden syndrome have been found to have germline mutations in the PTEN tumour suppressor gene (Gorlin et al, 1992; Nelen et al, 1996; Marsh et al, 1998; Marsh et al, 1999). The gene has been located to chromosome 10q3.3 and fine mapping has localised the Cowden-critical region of the gene to be between



Fig 1 View of labial gingivae showing papillary appearance to free and attached gingivae. Fibrous and well circumscribed lesion on labial gingivae 21.



Fig 2 Palatal view demonstrating papillary hyperplasia of palate and marginal gingival overgrowth.

D10S1761 and *D10S541*. PTEN encodes a 403 amino acid dual specificity phosphatase (protein tyrosine phosphatase), which behaves as a tumour suppressor by mediating apoptosis or cell cycle arrest, or indeed both. It is important in cell proliferation and cell differentiation and is comparable to the tumour suppressor gene p53. Mutations include missense and nonsense point mutations, deletions, insertions, deletion/insertion and splice site mutations. In Cowden syndrome, exon 5 (the gene has 9 exons) appears to be a particularly common site for mutations. Another syndrome, known as Bannayan–Riley–Ruvalcaba syndrome, is allelic to Cowden syndrome, and has also been found to have germline mutations of the PTEN gene. This disorder is characterised by macrocephaly, lipomatosis, haemangiomas and pigmented macules of the glans penis. Proteus syndrome, characterised by hamartomatous overgrowth of connective tissue, epidermal naevi and hyperostoses, has also been found to have PTEN germline mutations, but is not as closely linked as Cowden and Bannayan–Riley–Ruvalcaba syndromes (Pilarski and Eng, 2004). Cowden syndrome causes multiple hamartomatous lesions of many organs [hence giving rise to an alternative name for the syndrome of 'multiple hamartoma and neoplasia syndrome' (Swart et al, 1985)], which are derived from ectodermal, mesodermal and endodermal tissues. The lesions may involve the skin, mucous membranes, breasts, gastrointestinal tract and thyroid gland (Bathi et al, 2002). Lesions of the skin are histologically benign tumours of the hair follicles or trichilemmomas. There

is a propensity for lesions affecting these tissues to undergo malignant change, leading to the development of adenocarcinomas of the thyroid gland, breasts and colon. Polyps affecting the colon are also present in a number of cases that have been subjected to endoscopic investigation, but as they tend to be asymptomatic, the reported prevalence of polyps varies widely. Other malignancies have also been reported, such as acute myelogenous leukaemia, malignant melanoma and liposarcoma. There have also been multiple angiomas and lipomas associated with the condition (Ortonne et al, 1980; Ruschak et al, 1981). Some authors have also reported nervous system involvement, with neuromas and coordination disturbances (Weary et al, 1972; Leiber and Olbrich, 1981). A range of other conditions have also been reported: macrocephaly, kyphoscoliosis, pectus excavatum, diverticulitis, liver and pancreatic diseases, cholecystitis, uterine hypoplasia and pathological fractures of bone (Nuss et al, 1978; Ortonne et al, 1980; Rosenberg-Gertzman et al, 1980; Leiber and Olbrich, 1981). Multiple miscarriages may be another feature. A separate disorder, known as Cowden/ Lhermitte-Duclos disease shares many of the same features of Cowden syndrome, but cerebellar hypertrophy is also present (Porter et al, 1996). The majority of cases of Cowden syndrome have been reported in the dermatological literature. Lesions on the skin and oral mucosa are often the first manifestation of the syndrome. The first signs of the condition normally appear in the second and early parts of the third decades of life (Swart et al,



1985). Skin lesions appear as papules and nodules, which are skin coloured and appear around the ears, neck and face and around the eyes, mouth and nostrils. Lesions may arise on the palms and soles of the feet and may coalesce.

Within the oral mucosa, lesions present as papular and verrucous lesions. These are seen on the lips, buccal mucosa, tongue, palate, pharynx and gingivae (Figs 1 and 2). The tongue may be fissured or show papular enlargements (Fig 3). Other associated features reported in the literature include: rampant caries (Lloyd and Dennis, 1963; Gentry et al, 1974; Ortonne et al, 1980; Leiber and Olbrich, 1981), macroglossia (Nuss et al, 1978; Ruschak et al, 1981), gingivitis (Kuffer et al, 1979), presence of a high arched palate (Ortonne et al, 1980; Leiber and Olbrich, 1981), hypoplasia of the soft palate and uvula (Lloyd and Dennis, 1963; Leiber and Olbrich, 1981), and mandibular and maxillary hypoplasia (Ortonne et al, 1980; Leiber and Olbrich, 1981; Ruschak et al, 1981).

CASE REPORT

A 22-year-old female was referred to Birmingham Dental Hospital's Department of Periodontology in August 1998 by her general dental practitioner (GDP), for an opinion regarding the patient's worsening periodontal condition. She had initially presented to the GDP with a painless, red buccal gingival swelling, but had not been referred at that time as she was receiving treatment for a thyroid condition. However, when seen subsequently by the referring practitioner, it was noted that the patient had overgrowth of the gingival tissues especially around the upper anterior intercanine region, which gave rise to false pocketing. Medically, the patient had had surgery for a follicular adenoma of the thyroid gland for which she had undergone a right thyroid lobectomy (Fig 4), and a below knee amputation of the right leg after developing an angiofibrolipoma in 1995. She had also had an angiolipoma on the right forearm, which had been excised in 2001. In addition to this, she had suffered from hydrocephalus as a child, which had arrested and had not left any neurological deficit, although there had been some increase in the circumference of her head (Fig 5). She suffered from menorrhagia, which had lead to iron deficiency



Fig 3 Dorsum of tongue demonstrating papillary nature of epithelial surface.



Fig 4 Neck scar following thyroidectomy.



Fig 5 Facial view demonstrating mild macrocephaly.



anaemia, and was mildly asthmatic. She was taking the oral contraceptive pill, iron tablets, diclofenac and citalopram (anti-depressant).

At her initial visit, it was noted that the patient had poor oral hygiene with extensive gingival overgrowth affecting the labial aspects of the upper intercanine region. It was also noted that the palate had a nodular appearance, also between the maxillary intercanine region. A clinical diagnosis of chronic hyperplastic gingivitis was made. It was decided at this stage that the patient would benefit from regular periodontal treatment and intensive oral hygiene instruction within the department and this was arranged. The patient was reviewed regularly and when seen in July 1999, although her oral hygiene had improved and she had CPITN scores of 0, there was still evidence of the swelling and granular appearance of the gingivae observed at initial presentation. At this visit, a smear was taken from the area for candida cytology, and in addition to this a blood test was performed for a full blood count and random blood glucose. An incisional biopsy was performed in the area of papillary hyperplasia affecting the hard palate. Blood results revealed a slight hypochromia, but there was no evidence of candidosis from the smear. The histopathology results of the biopsy taken from the hard palate showed a 'fibroepithelial hyperplasia'. A 12-month review appointment was arranged and the patient was subsequently reviewed in August 2001. At this visit there were no problems and she was therefore discharged.

The patient was re-referred in September 2003, as the patient was again suffering from chronic hyperplastic gingivitis, which had become more severe than when she had previously been seen. The gingivae were constantly sore and painful and this appeared to be getting worse. At this stage she was also being investigated for Crohn's disease (although it was later shown that she was suffering from irritable bowel syndrome). It was noted at this visit that the patient had become a severe bruxist, and also had marked erosion affecting the dentition, secondary to episodic haematemesis. The papillary hyperplasia of the palate seen previously was evident as was some localised swelling around the upper anterior teeth, especially around the upper central incisors. In addition to this, there were multiple papillomas over the dorsum of the tongue. She was provided with a hard occlusal guard to help with her bruxism and a gingivectomy was car-

ried out in the upper anterior region. Tissue taken from around the upper central incisors was again sent for histological analysis and was diagnosed as a fibrous epulis. She was also seen again by a hygienist for dietary advice in order to help with the erosion affecting the dentition.

After this course of treatment, the patient failed to attend and cancelled several appointments and was not seen again until 2004, when she presented in the department having lost her hard occlusal guard. She had also been referred to the department of oral surgery for removal of the lower left third molar, and removal of her upper left third molar and lower left third molars was carried out under local analgesia with intravenous sedation, in November 2004.

A diagnosis of Cowden syndrome led to further requests for periodontal review and the patient was seen in May 2006. The papillary hyperplasia of the palate was still evident and largely unchanged (Fig 2), as indeed was the tongue dorsum (Fig 3), but her attachment levels remained stable, despite the marginal gingival overgrowth in the palate and associated false pocketing. There was a sessile and firm fibrous area associated with the gingivae 21, in the region of the previous fibrous epulis, but this was asymptomatic and causing no aesthetic concerns. She had developed a degree of paraesthesia in her right arm associated with a recurrence of the angioliopoma, but was otherwise well. Long-term and regular review has now been arranged to monitor her oral mucosa and gingival tissues.

DISCUSSION

This report presents a case of Cowden syndrome presenting initially with gingival manifestations. It is interesting that several of the features of Cowden syndrome noted by previous authors were present in this patient, such as lesions affecting the thyroid gland, an angiofibrolipoma of the right leg and right arm and hydrocephalus during childhood, leading to subsequent macrocephaly. As the diagnosis of Cowden syndrome has only recently been made in this patient, regular review of her oral lesions has been arranged on a long-term basis, given the risk of tumour development. The patient also suffered from menstrual problems, which had led to anaemia, as has also been reported in pre-



vious cases (Bathi et al, 2002). Intraorally, she had a characteristic papillary hyperplasia of the palate. The chronic hyperplastic gingivitis affecting the anterior teeth may also have been a manifestation of the syndrome, and false pocketing along with bleeding on probing related to this has been previously reported (Greer et al, 1976). The histopathology report of the excised tissue from the palate of 'fibroepithelial hyperplasia' also fits with the experience of previous authors, who have carried out incisional biopsies in such cases (Chaudhry et al, 2000). At one of her subsequent review visits, it was also noted that there were multiple papillomas covering the dorsum of the tongue. This is a feature described by previous authors, who have stated that in any patient presenting with multiple papillomas of the oral cavity, Cowden syndrome should be considered as one of the differential diagnoses (Devlin et al, 1992; Bathi et al, 2002). Other differential diagnoses include: lymphangioma, pyogenic granuloma, fibroepithelial polyps, giant cell epulis, pyostomatitis vegetans, pseudoepitheliomatous hyperplasia and squamous cell carcinoma. The oral lesions of Cowden syndrome may be highly vascular, which should be appreciated if biopsy or removal of excess tissue/recontouring is planned (Devlin et al, 1992). Certainly the patient in this case reported marked post-operative bleeding after having a gingivectomy performed in the upper anterior region.

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CONCLUSIONS

This case highlights the importance in developing a multidisciplinary approach when a patient is referred with an unusual medical history made up of what appears at first glance to be a series of unrelated problems. Such a case should alert the practitioner to the possibility of the patient suffering from a rare syndrome. It is important to obtain a diagnosis of Cowden syndrome because such patients are at high risk for the development of malignant tumours, particularly of the breast and thyroid gland, both of which are more common in females with Cowden syndrome. As cutaneous and oral lesions are often early signs of the syndrome, and given the far from benign course of the syndrome in many individuals, dental practitioners should be aware of this syndrome. These patients require regular and appropriate monitoring. Oral papillomatosis should also alert the practitioner to the possibility of malignancy developing.



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