

Cowden's Syndrome: a rare case report

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Abstract: Cowden syndrome is a rare autosomal dominant disorder that is characterized by multiple hamartomas in a variety of tissues and this is associated with germline mutations in the phosphatase and tensin homologue (PTEN) gene, which is the tumor suppressor gene located on chromosome 10q23.3. It is characterized by multiple hamartomatous neoplasms of the skin, oral mucosa, gastrointestinal (GI) tract, bones, central nervous system, eyes, and genitourinary tract. Clinical features of Cowden's disease are explained by the mutation of the PTEN tumour suppressor gene, whose modification leads to an uncoordinated growth of tissues. The importance of this disease lies in the increased susceptibility to malignization of some lesions, specially breast, thyroid and genito-urinary tract lesions. As a result, the disease has been considered a preneoplastic condition. Despite its varied phenotypic expression, this disease is generally unknown. Consequently, many cases are undiagnosed or diagnosis comes at a late stage, what points out the importance of an early diagnosis of the disease so the patient can have periodic check-ups to prevent malignant diseases. We present a case of a 28 year old female with Cowden's disease. The patient had facial papules, intra oral lesions multiple GI hyperplastic polyps, oesophageal glycogenic acanthosis and, goiter.

Key words: Cowden's disease, Hamartoma, Hyperplastic polyp, PTEN gene,

I. Introduction:

Cowden Syndrome (CS) is a rare autosomal dominant disorder characterised by multiple hamartomas and an increased risk of breast, thyroid and endometrial carcinomas^[1,2] Germline mutations in the tumour suppressor gene PTEN (phosphatase and tensin homolog) chromosome 10q23.2, which codes for a lipid phosphate mediating cell cycle arrest and apoptosis, were first described in Cowden Syndrome^[3]. Mucocutaneous lesions have been reported in the literature with a high frequency (99-100%) and are the most characteristic features of the disease. They include multiple facial papules (trichilemmomas), acral keratoses and oral papillomatosis^[4,5]. Multiple hamartomas and neoplasms of other organs, including thyroid tumors (benign and malignant), fibrocystic disease of the breast, breast carcinoma, neoplasms of the female genital tract and gastrointestinal polyps have also been reported^[5,6]. In female patients the syndrome is associated with up to 50% lifetime risk of developing breast cancer, 5-10% risk of developing endometrial cancer, and 10% lifetime risk of developing follicular thyroid cancer^[7]. In recent reports the elevated lifetime cancer risk in Cowden syndrome patients or in individuals with germline PTEN mutations is up to 85% for breast cancer, up to 35% for thyroid cancer, and up to 28% for endometrial cancer^[8,9]. Lifetime cancer risks are now extending to kidney cancer and colorectal cancer (up to 33% and 16%, respectively). Other features of the disorder include macrocephaly, gastrointestinal polyps, benign breast, thyroid and endometrial manifestations, and characteristic mucocutaneous lesions. The diagnosis of CS in most cases is primarily based on the presence of mucocutaneous features, estimated to have 99% penetrance before the age of 30^[2].

Communication of this case is considered important given the rarity of the disease, the pathological significance of its progression for affected patients and the responsibility of the dentist in its diagnosis through the clinical knowledge of the oral lesions.

II. Case report

A 48-year-old female was admitted to the hospital for soft papules affecting both upper and lower limb. The physical examination was notable for isolated multiple soft papules on the legs, arms and neck. The oral mucosa showed the echymotic lesions in the vestibule and lower lip. Her thyroid gland was enlarged and a recent ultrasound had revealed multiple goitre. The thyroid function was normal and auto antibodies were negative. Upper GI endoscopy revealed extensive nodularity of the oesophagus, a micropolypoid appearance of the stomach (body and antrum) and a duodenal ulcer. The second part of the duodenum was normal. Laboratory investigations including renal biochemistry, liver function tests and thyroid hormones (T4, T3, and thyroid-stimulating hormone (TSH)) were normal. Results of a complete blood count showed iron-deficiency anemia. Based on these clinical and pathological findings, the patient was diagnosed as a carrier of Cowden's syndrome and is being followed up

III. Discussion

Cowden's syndrome, or multiple hamartoma syndrome, is an unusual autosomal, dominant, inherited disease with characteristic mucocutaneous lesions combined with gastrointestinal polyps and abnormalities in other organs with high frequency of malignant transformation, especially in the breast and thyroid^[5,6]. The disease is associated with a germ line mutation of the PTEN gene (10q 22-23)⁷. This rare clinical entity is well known to dermatologists and stomatologists because mucocutaneous lesions are the most obvious and characteristic features of the disease^[4]

The hamartomatous lesions observed in Cowden syndrome can arise in any of the three embryonic germ cell layers and thus it may be ectodermal, mesodermal or endodermal in origin^[1]. These lesions can arise in the derivatives of any of the three embryonic germ cell layers^[1,2]. The cardinal manifestations of Cowden syndrome include facial trichilemmomas, which are hamartomas of the infundibulum of the hair follicle, acral keratoses and mucocutaneous papillomatous papules^[10,11]. The incidence of Cowden syndrome was estimated to be 1:1 000 000^[12]. However, after identification of the relevant gene, the estimate for the prevalence of Cowden syndrome has been increased to between 1 in 200 000 and 1 in 250 000^[13].

Oral signs are very remarkable, therefore the dentist may be the first professional to come up with a presumptive diagnosis. Multiple papillomatous lesions are not common clinical findings in the oral cavity. Few other diseases present them; an example being Heck's disease, which has papillomatous lesions only in oral mucosa, it is etiologically and pathogenically linked to papilloma virus infection and generally observed in young people.

In Cowden's disease, the most significant dermal lesions are multiple facial trichilemmomas, typically occurring around natural orifices, as it occurred in this family members. As well as acral keratosis^[1,2,6] is another common finding.

Finally, as was the case with this patient, adequate screening for the organs known to develop malignancies in Cowden syndrome should be carried out in suspected patients. Even when benign lesions are suspected, the potential for malignant lesions must be kept in mind, and further pathologic examination and surgical resection should be aggressively performed without reservation.

IV. Conclusion

In conclusion, this case is a reminder of the importance of early screening for patients suspected of having Cowden syndrome, and female patients should be evaluated for lesions in the breasts and thyroid. Even if benign lesions are suspected, there have been published reports on cases diagnosed with cancer postoperatively; consequently, the possibility of malignancy should always be considered.

References

- [1]. Eng C: Will the real Cowden syndrome please stand up: revised diagnostic criteria. *J Med Genet* 2000, **37**:82830.
- [2]. Eng C: PTEN: one gene, many syndromes. *Hum Mutat* 2003, **22**:183-98.
- [3]. Liaw D, Marsh DJ, Li J, Dahia PL, Wang SI, Zheng Z, Bose S, Call KM, Tsou HC, Peacocke M, Eng C, Parsons R: Germline mutations of the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome. *Nat Genet* 1997, **16**:64-7
- [4]. Starink TM. Cowden disease. Analysis of fourteen new cases. *J Am Acad Dermatol* 1984; **11**:1127-1141.
- [5]. Williard W, Borgen P, Bol R, Tiwari R, Osborne M. Cowden disease: a case report with analyses at the molecular level. *Cancer* 1992; **69**:2969-2974.
- [6]. Thyresson HN, Doyle JA. Cowden disease (multiple hamartoma syndrome). *Mayo Clin Proc* 1981; **56**:179.
- [7]. Pilarski R: Cowden syndrome: a critical review of the clinical literature. *J Genet Couns* 2009, **18**:13-27.
- [8]. Riegert-Johnson DL, Gleeson FC, Roberts M, Tholen K, Youngborg L, Bullock M, Boardman LA: Cancer and Lhermitte-Duclos disease are common in Cowden syndrome patients. *Hered Cancer Clin Pract* 2010, **8**:6.
- [9]. Tan MH, Mester JL, Ngeow J, Rybicki LA, Orloff MS, Eng C: Lifetime cancer risks in individuals with germline PTEN mutations. *Clin Cancer Res* 2012, **18**:400-407.
- [10]. Salem OS, Steck WD. Cowden's disease (multiple hamartoma and neoplasia syndrome). A case report and review of the English literature. *J Am Acad Dermatol* 1983; **8**: 686-696
- [11]. Kovich O, Cohen D. Cowden's syndrome. *Dermatol Online J* 2004; **10**: 3
- [12]. Nelen MR, Padberg GW, Peeters EA, Lin AY, van den Helm B, Frants RR, Coulon V, Goldstein AM, van Reen MM, Easton DF, Eeles RA, Hodgson S, Mulvihill JJ, Murday VA, Tucker MA, Mariman EC, Starink TM, Ponder BA, Ropers HH, Kremer H, Longy M, Eng C. Localization of the gene for Cowden disease to chromosome 10q22-23. *Nat Genet* 1996; **13**: 114-116
- [13]. Li FP, Abramson DH, Tarone RE, Kleinerman RA, Fraumeni JF, Boice JD. Hereditary retinoblastoma, lipoma, and second primary cancers. *J Natl Cancer Inst* 1997; **89**: 83-84
- [14]. Porter S, Cawson R, Scully C, Eveson J. Multiple hamartoma syndrome presenting with oral lesions. *Oral Surg Oral Med Oral Pathol* 1996; **82**:295-301.
- [15]. Seoane J, Aguado A, Vázquez J, Romero A, Iglesias P. Síndrome de Cowden: manifestaciones orales. Estudio clínico patológico de un caso. *Quintessence (Ed esp)* 1996; **9**:462-5.



Oral lesions of the patients



papules present on lower limb



Endoscopy revealing the papular lesion of distal oesophagus