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Cowden Syndrome: Study of Novel Features and a Diagnostic Overview

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***Abstract**: Cowden syndrome is a rare, autosomal dominant disorder which affects various organs of the body and characterized by high risks for malignant tumors of breast, thyroid and other organs. The case in the present study presented with certain novel features which were not reported earlier. These includes grossly enlarged tonsils, adenoid facies, dysphagia and difficult breathing (as presenting symptoms), H/O cataract surgery at the age of 18 years and ECG changes in the heart (tachycardia, T wave inversion in leads III, aVF, V1, V2 and V3). The signs and symptoms of Cowden syndrome are highly variable, non-specific and subtle. Nevertheless, clinicians should be able to identify the plethora of signs and symptoms associated with CS as the diagnosis of CS is still clinical, and the risk for development of malignancy in patiets of CS is very high. The life time risk of development of breast cancer in Cowden syndrome is 25% to 50%. Furthermore, with the current practice of identifying CS, based not only on the pathognomic mucocutaneous features, but also on the personal and family histories of cancer, and clinical experience with PTEN testing, it is likely that more novel features will come to light in future.*

Key words: Cowden syndrome, Cowden disease, Multiple hamartoma syndrome, PTEN hamartoma tumor syndrome (PHTS).

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I Introduction

Cowden syndrome (CS), also termed Cowden disease and multiple hamartoma syndrome, is a rare, autosomal dominant disorder which affects various organs of the body and characterized by high risks for malignant tumors of breast, thyroid and other organs. It is a rare disorder and until now approximately 300 cases have been reported in the English literature. This paper presents a case of Cowden syndrome with novel features which have not yet been reported. Furthermore, the disease involves multiple organs and present with highly variable, non-specific and subtle features, which if not recognized may lead to development of various malignancies. Therefore it is important that these features should be recognized early so as to avoid the morbidity and mortality associated with this disorder

II CASE

A 28 years old female had reported to the ENT OPD of our hospital with the complaints of hoarseness of voice, difficulty in breathing and eating, and swelling in the throat for the last 12 years. She gave a history of mouth breathing because of swelling in the throat. From the ENT OPD she was referred to the skin OPD as she also had mucocutaneous lesions which developed over the last 10 years. A history of slowly developing lumps in the breasts for the past 9 years, surgery for cataract of both the eyes when she was 18years, a delayed menarche at the age of 18 years and menorrhagia, was also elicited. There was no family history of similar complaints or malignancies.

General examination was within normal limit except for adenoid facies (elongated, elliptical face, hitched up upper lip, enlarged protruding upper incisors), macrocephaly (occipital frontal circumference 62 cms i.e., >97th percentile) and hugely enlarged tonsils (Fig. 1). Cutaneous examination revealed multiple tiny, skin colored, firm papules (1mm - 2mm) over forehead (Fig.2), nose, malar prominence, chin, eyelids & retro auricular area (trichilemmomas and facial papules). A large, firm, skin colored papule measuring 1 cm diameter was also present over forehead. Multiple, small, firm, coalescing, pink to slightly white, mostly smooth, 1–3 mm diameter, papillomatous lesions, imparting a characteristic cobblestone appearance, were seen on the lips (Fig. 3). These multiple papillomatous mucosal lesions were also seen over gingival and tonsilar surface. Gingival hypertrophy, a large epulus and a few dental caries were also noticed. Few tiny warty type of lesions were found

at the dorsum of hands and feet (acral keratosis). Multiple bilateral, soft to firm, nodulo-cystic lesions, measuring 1 – 2 cms in diameter were palpated in both the breasts.

She was anemic (Hb 6.3 gm), ECG revealed tachycardia (heart rate 100/minute) and inversion of T waves in leads III, aVF, V1, V2 and V3. The cardiac ECHO, however, was normal. Ultrasonography of breasts showed bilateral, multiple, enlarged, hetroechoic, nodular lesions suggestive of fibro adenomas with fibrocystic changes. FNAC of the nodular lesion in breast also suggested fibroadenoma. The ultrasound scan of thyroid suggested nodular lesions in both the lobes of thyroid. Thyroid profile was normal. Ultrasonography of uterus, ovaries and abdomen, MRI of brain and endoscopy of stomach were normal. Histopathology of one of the papillomatous lesions over face showed features suggestive of trichilemmoma and included verrucous epidermis, proliferation of cells around hair follicle with peripheral pallisading, and underlying thickened basement membrane (Fig 4).

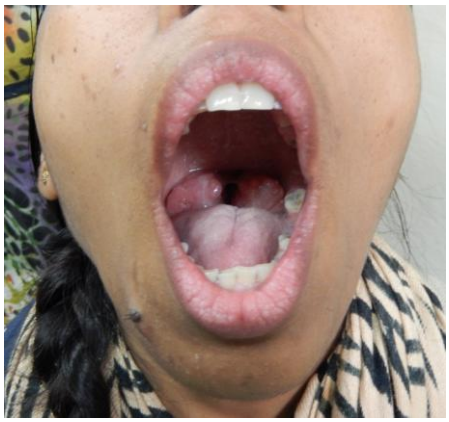

Figure 1 Hugely enlarged tonsils

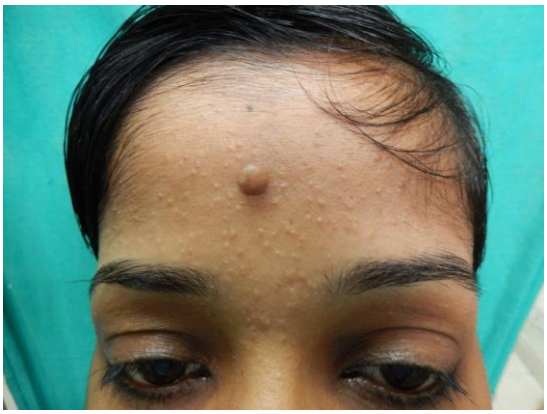

Figure 2 Multiple tiny, skin colored, firm papules (1mm – 2 mm), over forehead (tricholemmomas and facial papules). A large, firm, skin colored papule measuring 1 cm is also present over forehead.

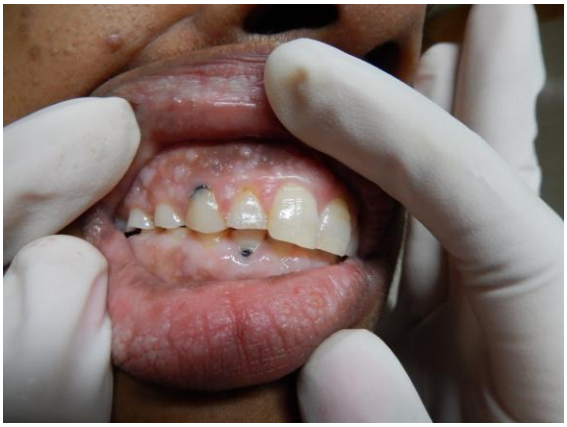

Figure 3 Multiple, small, firm, coalescing, pink to slightly white, 1–3 mm diameter, papillomatous lesions, imparting a characteristic cobblestone appearance over lips and gums along with dental caries.

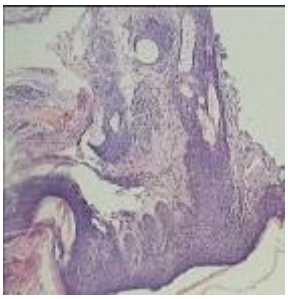

Figure 4 Hematoxylin and eosin stained section showing verrucous epidermis, proliferation of cells around hair follicle with peripheral pallisading, and underlying thickened basement membrane (H and E, × 10)

III Discussion

This hereditary cancer susceptibility syndrome results most commonly (80%) from a mutation in the *PTEN* gene on arm 10q[1]. Cowden syndrome is considered to be a part of the PTEN hamartoma tumor syndrome (PHTS) which includes Cowden syndrome, Bannayan-Riley-Ruvulcaba syndrome (BRRS), Proteus syndrome, and Proteuslike syndrome. All these syndromes have *PTEN* mutations[2,3]. Mutation in the *PTEN* gene, a tumor suppressor gene, in Cowden syndrome causes hamartomatous neoplasms in the various tissues and organs of the body including skin and mucosa, GI tract, bones, CNS, eyes, and genitourinary tract, and has a significantly increased risk of development of cancer . The prevalence is estimated to be between 1 in 200,000 to 1 in 250,000. The age at which CS is diagnosed varies between 13 and 65 years and there appears to be a female preponderance.

The case did not pose any diagnostic problem as it fits well into the diagnostic criteria of CS[4,5,6,7,8] (Table 1). Presence of pathognomic mucocutaneous features (trichilemmomas, facial papillomatous papules, oral mucosal papillomatous lesions and acral keratosis), macrocephaly (one of the major feature), fibrocyctic disease of the breasts and nodular lesions in thyroid glands establishes the diagnosis of CS in this case. The hallmark feature of CS is the trichilemmoma which is considered pathognomic when present in large numbers. Three facial lesions were biopsied, but only one of them showed features suggestive of trichilemmoma. All facial lesions may not show features of trichilemmoma. In one series, only 29 of 53 facial lesions showed findings diagnostic of trichilemmoma[5]

Table 2 enumerates the commonly reported manifestations of Cowden Syndrome[6]. A wide range of other clinical findings have also been reported in patients with CS, which include periodontitis and dental caries, skeletal abnormalities, high arched palate, developmental problems or mental retardation, lipomas, neuromas, hamartomatous vascular malformations, haemangiomas, meningiomas, xanthomas, vitiligo, acanthosis nigricans etc.[4,7]. To the best of our knowledge, the grossly enlarged tonsils found in this case were not reported before in the Cowden syndrome. Our case was unusual for it revealed several novel features:

1. Grossly enlarged tonsils and adenoid facies
2. Presenting symptoms were dysphagia and difficult breathing
3. H/O cataract surgery at the age of 18 years.
4. ECG changes in the heart (tachycardia, T wave inversion in leads III, aVF, V1, V2 and V3.

The signs and symptoms of Cowden syndrome are highly variable, non-specific and subtle. Nevertheless, clinicians should be able to identify the plethora of signs and symptoms associated with CS as the diagnosis of CS is still clinical, and the risk for development of malignancy in patiets of CS is very high. The life time risk of development of breast cancer in Cowden syndrome is 25% to 50%. Furthermore, with the current practice of identifying CS, based not only on the pathognomic mucocutaneous features, but also on the personal and family history of cancer, and clinical experience with PTEN testing, it is likely that more novel features will come to light in future. Identification & validation of these features will help in diagnosing CS at an early stage. Once the diagnosis of CS is made these patients can be kept on surveillance and managed as per the NCCN (National Comprehensive Cancer Network) guidelines for management of CS[8].

Table 1: Diagnostic criteria for Cowden syndrome[4]

Pathognomonic criteria	**Major criteria**	**Minor criteria**
1. Adult Lhermitte-Duclos disease (LDD), defined as the presence of a cerebellar dysplastic gangliocytoma. 2. Mucocutaneous lesions: ○ Trichilemmomas (facial)	1. Breast cancer 2. Epithelial thyroid cancer (non-medullary), especially follicular thyroid cancer 3. Macrocephaly (occipital frontal circumference ≥97th percentile)	1. Other thyroid lesions (e.g., adenoma, multinodular goiter) 2. Intellectual Disability (IQ ≤75) 3. Hamartomatous intestinal polyps 4. Fibrocystic disease of the breast

○ Acral keratoses ○ Papillomatous lesions ○ Mucosal lesions	4. Endometrial carcinoma	5. Lipomas 6. Fibromas 7. Genitourinary tumors (especially renal cell carcinoma) 8. Genitourinary malformation 9. Uterine fibroids
An operational diagnosis of CS is made if an individual meets **any one** of the following criteria: 1. Pathognomonic mucocutaneous lesions combined with one of the following: ○ Six or more facial papules, of which three or more must be trichilemmoma ○ Cutaneous facial papules and oral mucosal papillomatosis ○ Oral mucosal papillomatosis and acral keratoses ○ Six or more palmo-plantar keratoses 2. Two or more major criteria 3. One major and three or more minor criteria 4. Four or more minor criteria **In a family** in which one individual meets the diagnostic criteria for CS listed above, other relatives are considered to have a diagnosis of CS if they meet **any one** of the following criteria: 1. The pathognomonic criteria 2. Any one major criterion with or without minor criteria 3. Two minor criteria 4. History of Bannayan-Riley-Ruvalcaba syndrome		

Table 2: Commonly Reported Manifestations of Cowden Syndrome[6]

Manifestations	**Prevalence**
Mucocutaneous lesions	90–100%
Trichilemmomas	
Acral keratoses	
Verucoid or papillomatous papules	
Thyroid abnormalities	50–67%
Goiter	
Adenoma	
Cancer	3–10%
Breast lesions	
Fibroadenomas/fibrocystic disease	76% of affected females
Adenocarcinoma	25–50% of affected females
Gastrointestinal lesions	40%
Hamartomatous polyps	
Macrocephaly	
Genitourinary abnormalities	44% of females
Uterine leiomyoma	Multiple, early onset

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Figure 1 Hugely enlarged tonsils (1272)

Figure 2 Multiple tiny, skin colored, firm papules (1mm – 2 mm), over forehead (tricholemmomas and facial papules). A large, firm, skin colored papule measuring 1 cm is also present over forehead (1276).

Figure 3 Multiple, small, firm, coalescing, pink to slightly white, 1–3 mm diameter, papillomatous lesions, imparting a characteristic cobblestone appearance over lips and gums along with dental caries. (1293)

Figure 4 Hematoxylin and eosin stained section showing verrucous epidermis, proliferation of cells around hair follicle with peripheral pallisading, and underlying thickened basement membrane (H and E, × 10).