Cowden syndrome- Clinico-radiological illustration of a rare case

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Abstract

Cowden syndrome (CS) or multiple hamartoma syndrome is an infrequent genodermatoses, which is inherited as an autosomal dominant trait resulting from the mutation in the Phosphatase and Tensin homolog gene on the arm 10q and is principally characterized by multiple hamartomas with an increased risk of development of malignancies. Facial and oral signs are remarkable in the form of multiple papules and trichilemmomas on the face. We report one such rare case of CS in a 19-year-old patient who was diagnosed on the basis of her oral mucosal lesions and was further investigated and diagnosed with other hamartomas. The present case report signifies the responsibility of the oral physician in the early diagnosis of this progressive pathological syndrome as it leaves its footmark in the oral cavity in the form of oral mucosal lesions.

Keywords: Cowden syndrome, fibroadenoma breast, gastrointestinal tract polyps, hamartomas, multinodular goiter, oral papules, trichilemmomas

Introduction

Cowden syndrome (CS) or multiple hamartoma syndrome is an infrequent genodermatoses which was first described by Costello in 1940.[1] It was defined and named by Llyod and Dennis in 1963, after their patient Rachel Cowden, a 20-year-old female.[2,3] It is an autosomal dominant condition showing a high degree of penetrance and a range of expressivity.[4] Usually the syndrome results from mutation in the Phosphatase and tensin homolog gene on the arm 10q[4] and is principally characterized by multiple hamartomas of ectodermic, mesodermic or endodermic origin.[5] Some of these lesions are prone to malignization, hence the disease belongs to "paraneoplastic hereditary syndrome".[6] Until now approximately 300 cases have been reported in the English literature,[3] the number of reports increasing owing to the greater awareness of this disorder.[5]

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Case Report

A 19-year-old female patient reported to our Department with the chief complaint of swollen lower lip since 1 year. Her medical history revealed history of surgical treatment of a lump in the breast 2 years back. History also revealed presence of dysmenorrhea, frequent diarrhea and generalized body ache since 3 years. Her parents and other siblings were normal. On general examination, the patient appeared thin built. Her left palm and left thumb showed presence of lobulated nodules [Figure 1].

Extra-oral examination revealed presence of multiple skin colored flat papules (trichilemmomas) on her face involving the bridge of the nose, forehead region and on the upper lip measuring around 1-5 mm in diameter [Figure 2]. Lower lip also showed multiple non-tender papular growths around 1-3mm in diameter, clustered at certain places [Figure 3].

Intra oral examination revealed smooth whitish papillomatous lesions involving the dorsal surface of the tongue and the buccal mucosa measuring 1-5 mm in diameter [Figures 4 and 5]. On the basis of history and clinical examination, the patient was provisionally diagnosed as a case of CS.

Several investigations were performed for this patient to rule out other hamartomas and malignancies that included complete blood investigations, thyroid profile and thyroid scan, ultrasonography of breast, thyroid, ovaries and nodules of palm, mammography, orthopantomogram, Magnetic Resonance Imaging of brain, Digestive endoscopy and Fine needle aspiration cytology from the lesions of the breast and thyroid along with incisional biopsy from the tongue and the lip lesions.

Hematological investigations of the patient and the thyroid profile (T3, T4.Thyroid stimulating hormone did

not reveal any changes from the normal reference values. The mammography and orthopantomogram of the patient revealed normal findings. MRI of brain did not reveal any lesions in the cerebellum. The ultrasonographic examination of the thyroid gland showed multiple nodules in the both lobes of the thyroid gland, which were mostly echogenic. Few cysts were also seen within the thyroid with internal finger like solid projections showing increased vascularity (intracystic papillary mass) which gave the impression of multinodular goiter [Figure 6]. Similarly, the Tc-99 m pertechnate thyroid scintigraphy scans were suggestive of euthyroid multinodular goiter with a dominant cold nodule present at the lower pole of the right lobe of the thyroid

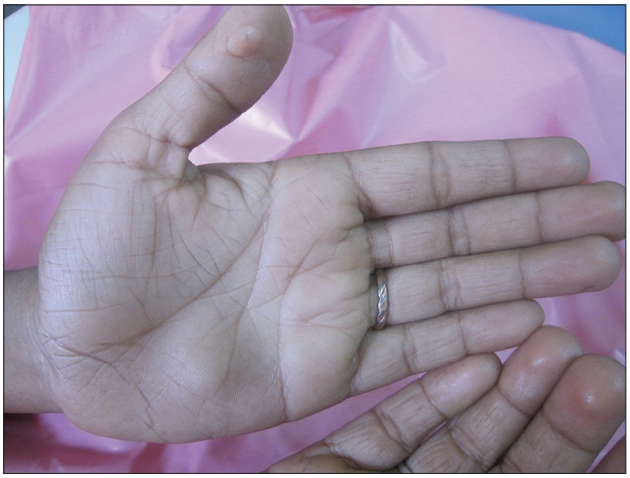

Figure 1: An arterio venous malformation present on the left palm and thumb diagnosed as arterio-venous malformation on ultrasonography

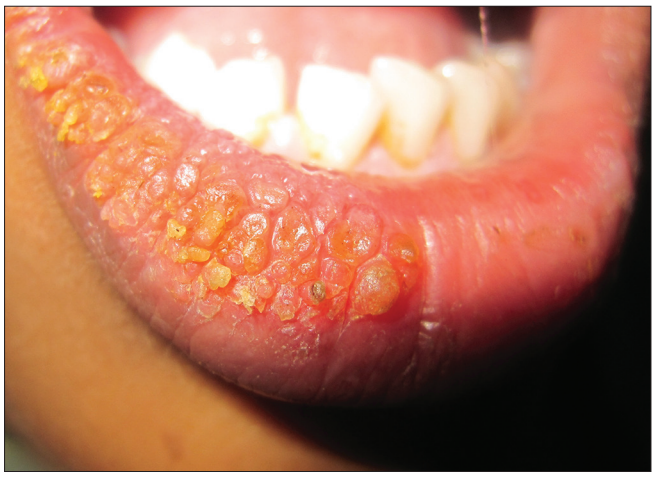

Figure 3: Cluster of papules on the lower lip

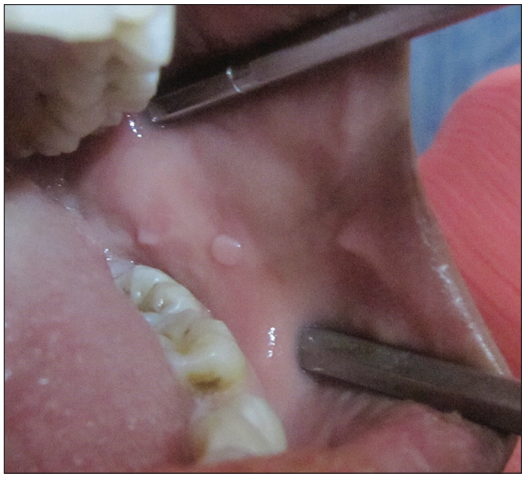

Figure 5: Papules seen on the buccal mucosa

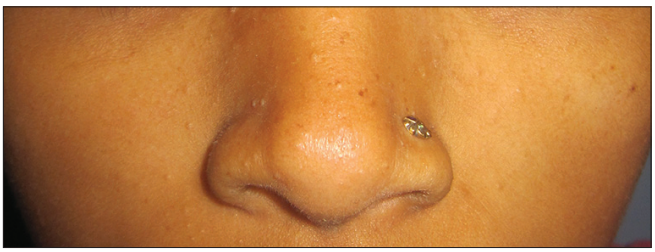

Figure 2: Multiple papules (trichilemmomas) on the bridge of the nose

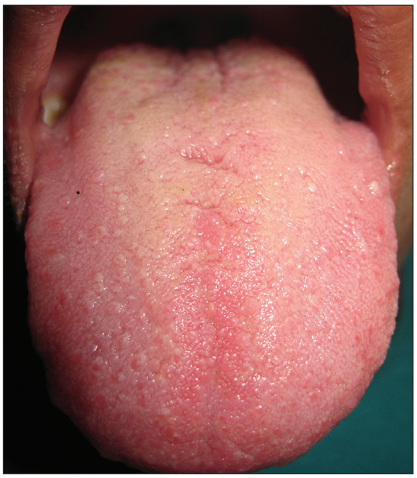

Figure 4: Papillomatous lesions on the dorsal surface of tongue

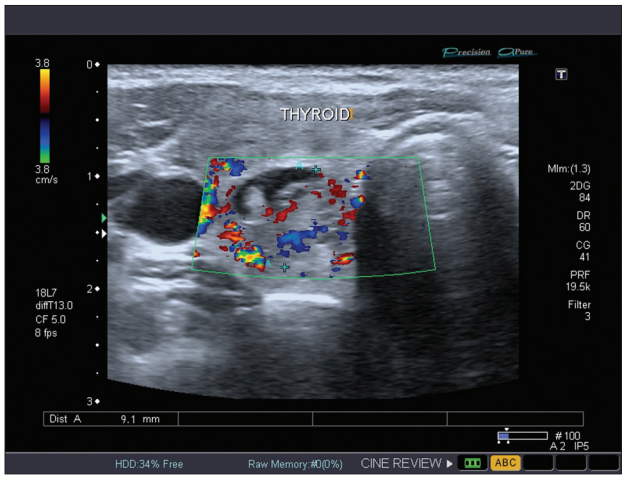

Figure 6: Ultrasonography with color Doppler showing multiple nodules in the lobes of the thyroid

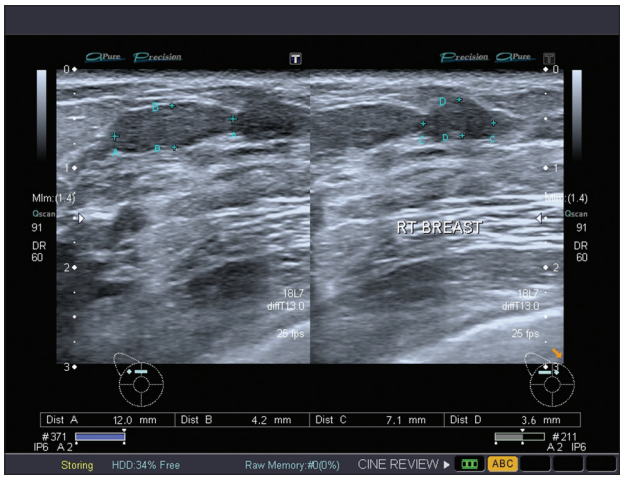

Figure 7a: Ultrasonography showing oval hypoechoic areas in the breast with smaller adjacent similar areas suggestive of multiple fibroadenomas

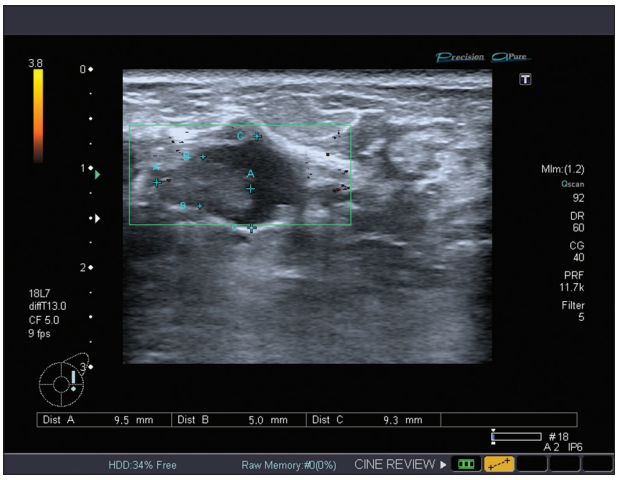

Figure 7b: Ultrasonography showing cystic area with nodular solid component in the left breast suggestive of an intracystic mass

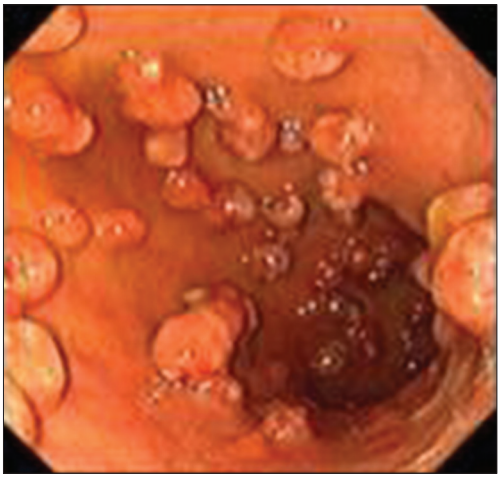

Figure 8: Multiple polypoid lesions having smooth overlying mucosa seen randomly distributed throughout the stomach and duodenum on upper GI endoscopy

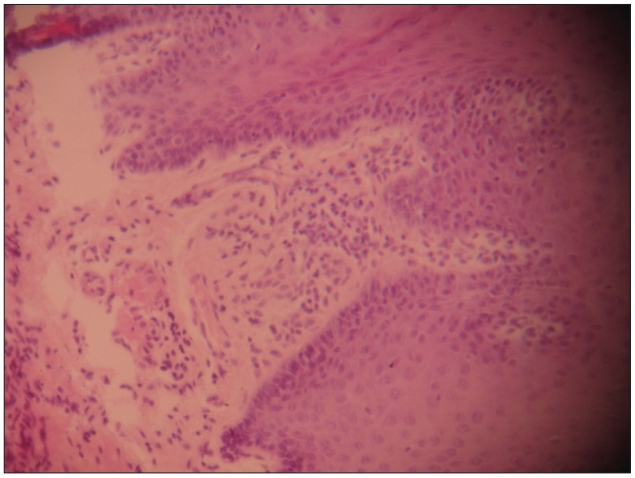

Figure 9: Histopathology from papillomatous lesions on tongue and lower lip showed epithelial hyperplasia

gland. The FNAC from the thyroid gland yielded blood mixed aspirate and showed occasional groups of follicular epithelial cells in the background of abundant colloid giving impression of multiple colloid nodules in the thyroid gland.

The Ultrasonography examination of breast showed multiple nodular cystic areas bilaterally suggestive of fibroadenomas which were confirmed by FNAC and miscroscopy while a cystic area with nodular solid component eccentrically originating from the walls occupying more than 50% of the cystic lumen was seen at a single area in the left breast which was suggestive of intracystic complex mass [Figure 7a and b]. Ultrasonography of the left palm showed 12 mm × 9 mm sized mildly hypoechoic lobulated nodule with internal arterial and venous vascular channels suggestive of arterio-venous malformation.

The digestive endoscopy of the stomach and the duodenum revealed multiple polypoid lesions having smooth overlying mucosa. Some of them were hyperplasic; some were sessile while others were adenomatous, fibroid like. These were randomly distributed throughout the stomach and duodenum, mostly measuring less than 1 cm in diameter [Figure 8].

Histopathology from the sections taken from the lower lip and tongue revealed hyperkeratinized stratified squamous hyperplastic epithelium with no inflammatory evidence in the connective tissue suggestive of epithelial hyperplasia [Figure 9].

Multidisciplinary approach was followed and various opinions were taken from gynecologists, gastroenterologist, general surgeon and oral pathologist. Patient is under regular follow-up and care.

Discussion

CS is clinically characterized by multiple hamartomas and neoplasias of the skin, mucosa, breast, thyroid gland, and

gastrointestinal tract with mucocutaneous features being the most common characteristic findings.[5] Because the development of associated malignancy may take several years, these mucocutaneous lesions may serve as an important clinical markers in identifying patients at high-risk of malignancy of the breast and thyroid.[5,6] The syndrome is usually diagnosed between ages of 13 and 64 with average being 22 years with a slight female predilection.[3]

Mutation of the Phosphatase and tensin homolog/Mutated in multiple advanced cancer gene, a tumor suppressor gene located in the chromosome 10q 22-23 has been documented to be responsible for the malignancy of the breast and thyroid in these patients. The mutations of the gene PTEN identified in families and patients with CS could be the cause for the tendency of the disordered proliferation of tissue thus producing the formation of hamartomas.[5]

CS consortium has proposed operational criteria for the diagnosis of CS.[3,5] Our case report fulfilled the pathognomonic and the minor criteria and can be placed under diagnostic criteria one [Table 1].[5,7]

Oral signs are remarkable in this syndrome as were with the present case and thus dentist is usually the first professional to encounter this disease. Oral lesions vary in severity from patient to patient and are usually in the form of small, symptomless papules with smooth whitish surface affecting the gingiva, dorsal surface of the tongue and buccal mucosa.[4] These lesions often coalesce into confluent sheets, which are described as having cobblestone appearance.[8] In our case, lower lip, tongue as well as buccal mucosa showed presence of multiple small papules which were smooth and were around 1-3 mm in diameter. Histopathologically they showed epithelial hyperplasia.

Cutaneous lesions are present in the form of trichilemmomas, acral keratosis and palmoplantar keratosis.[3,4,6] The present case also showed a thick keratotic plaque involving the left thumb. Less frequently noted lesions include lipomas, neuromas and hemangiomas. Our patient also showed a lobulated nodule on the left palm with internal arterial and venous vascular channels suggesting an arterio-venous malformation on ultrasonographic examination, which is a rare finding.

In women, fibrocystic disease of the breast and fibrodenomas are frequently observed. Unfortunately, breast cancer occurs with a relatively high frequency (25-50%) in these patients.[3,4] The present case showed multiple fibroadenomas involving both right and left breast, which were also confirmed on the FNAC.

Digestive endoscopy is important for the confirmation of this disease. The presence of polyps in the gastrointestinal tract has been documented in one third of the patients. Intestinal polyps may be of a diverse nature: Inflammatory, hamartomatous (in this disease) or neoplasic (adenomas) and are commonly found in the esophagus, stomach, intestine, and anus.[1-3,5,6] Our case showed presence of multiple polypoid lesions having varied forms in the stomach and duodenum.

Abnormalities of thyroid are present in approximately 60% of the cases manifested as goiter, benign adenomas but follicular adenocarcinomas may develop.[3,4] The present case showed presence of multinodular goiter which was confirmed on the Tc-99 m-Pertechnetate thyroid scintigraphy and thyroid ultrasonography.

Skeletal abnormalities also have been rarely reported in the CS that includes bone cysts, thoracic khyphosis as well as one reported case of osteosarcoma.[3,9,10] Genitourinary manifestations

Table 1: International cowden consortium operational diagnostic criteria 2000[5,7]

Pathognomic criteria
Mucocutaneous lesions
Trichilemmomas, fascial acral keratosis
Papillomatous papules
Major criteria
Breast carcinoma
Thyroid carcinoma (non-Meddulary), especially follicular thyroid carcinoma
Macrocephaly (megalencephaly) (≥95th centile)
LDD
Endometrial carcinoma
Minor criteria
Other thyroid lesions (e.g. adenoma or multinodular goitre)
Mental retardation (Iq≤75)
GI hamartomas
Fibromas
Genitourinary tumors (e.g. renal cell carcinoma, uterine fibroids) or malformation
Operational diagnosis in a person
Mucocutaneous lesions alone if:
There are six or more facial papules, of which three or more must be trichilemmoma or Cutaneous facial papules and oral mucosal papilomatosis or Oral mucosal papilomatosis and acral keratoses or Palmoplantar keratosis, six or more
Two major criteria but one must include macrocephaly or LDD
One major and three minor criteria
Four minor criteria
Operational diagnosis in a family where one person is diagnostic for cowden syndrome
The pathognomic criteria
Any one major criterion with or without minor criteria
Two minor criteria

LDD: Lhermitte-duclos disease

like ovarian cysts, leiomyomas, Adenocarcinomas of cervix and benign urethral polyps can also be present. Similarly involvement of reproductive system has also been reported in the form of ovarian cysts, fibroids, uterus adenocarcinomas, cervical carcinomas and benign vaginal and vulvar lesions.[6] Lhermitte disease is currently considered as a part of CD, caused by hamartomatous growth of the cerebellum.[3,6] These features were however not present in our case.

Differential diagnosis of this condition includes bannayan riley ruvalcuba syndrome (which shows multiple subcutaneous lipomas, macrocephaly and hemangiomas), proteus syndrome (which includes skin overgrowth and atypical bone development accompanied by tumors over half the body), tuberous sclerosis (having multi-system genetic disease that causes non-malignant tumors to grow in the brain and on other vital organs such as kidneys, heart, eyes, lungs, and skin), fragile X syndrome (characterized by elongated face, large or protruding ears, and larger testes (macroorchidism), Heck's disease (which shows white to pinkish papules that occur diffusely in the oral cavity), Darier's disease (keratosis follicularis or dyskeratosis follicularis) and juvenile polyposis syndrome (characterized by multiple polyps in the gastrointestinal tract with an increased risk of adenocarcinomas).[3,11]

The patients suffering from CS have to be considered as high-risk patients for developing of malignancies. Women with CS have a 30% to 50% risk for breast cancer. Therefore, mammography is suggested to be performed twice a year and professional physical examination quarterly.[5,12]

Functional thyroid examinations and thyroid scanning should be performed as baseline diagnostic examinations. In case of anomalies, fine needle aspiration or surgical biopsies are indicated as were done in the present case. In addition, complete blood cell count, liver and renal function test, urine analysis, and chest radiography belong to the baseline diagnostic examinations and are repeated as needed.[5]

Newly appearing headaches should arouse suspicion for Lhermitte-Duclos disease and should be examined by MRI of the brain. A thorough family history and an appropriate screening of family members is important to detect further CS cases as early as possible.[1,5,12]

Treatment in such patients is complicated by high-risk of development of cancers of various organ systems. Therefore, prophylactic mastectomy should be considered. The mucocutaneous lesions can be treated with Carbon dioxide laser ablation, surgical removal, electrosurgery, cryosurgery, interferon-2-alpha and 5-fluorouracil. The prognosis is dependent on the frequent follow-up and timely treatment owing to the high-risk of cancer development.[3,5]

Conclusion

The present case report signifies the responsibility of the oral physician in the early diagnosis of this progressive pathological syndrome as it leaves its footmark in the oral cavity as an early sign. This case also highlights the important muco-cutaneous and systemic manifestations of the syndrome including arterio-venous malformations, which are rare.

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