Cowden’s syndrome affecting the mouth, gastrointestinal, and central nervous system: A case report and review of the literature

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Cowden’s syndrome (CS) is a rare genodermatosis, of autosomal dominant inheritance and variable phenotype, principally characterized by the formation of hamartomas in various organs, including skin, thyroid, breast, brain, and gastrointestinal tract and by the increased risk for the development of malignancy. The present report details the features of a very rare presentation of Cowden’s syndrome affecting not only the mouth and gastrointestinal mucosa but also the central nervous system. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;99:569-72)

Cowden’s syndrome (CS) is a rare genodermatosis, of autosomal dominant inheritance and variable phenotype, principally characterized clinically by multiple hamartomas of ectodermic, mesodermic, or endodermic origin.1 Although the majority of the associated tumors are benign, the prevalence of malignancy, particularly breast and thyroid carcinomas, in affected patients is greater than in the general population.2 The present report details the features of a very rare presentation of a 38-year-old male patient with Cowden’s syndrome affecting not only the mouth and gastrointestinal mucosa but also the central nervous system.

CASE HISTORY

A 38-year-old male was referred to the Hospital das Clínicas, Recife, Brazil, complaining of multiple swellings of the mouth that had progressively increased in size and number over the previous 20 years. The patient was single and unemployed, had no siblings, and denied any use of tobacco or alcohol. The only notable feature of his previous medical history was an ankle surgery for unknown reasons. Extraoral examination revealed a single fibrous nodule of approximately 1.5 cm in diameter, on the skin of the forehead. Intraorally there were multiple, confluent, and asymptomatic papules on the upper and lower labial mucosa and ventral surface of the tongue and gingiva (Fig 1). Based upon the clinical features, particularly the presence of multiple mucocutaneous nodules, a working diagnosis of Cowden’s syndrome was made. A series of additional investigations were undertaken to establish the definitive diagnosis and search for other manifestations of this disease and more importantly search for possible associated malignancy.

Laboratory investigation was divided into 4 steps. First, renal biochemistry and liver function tests were normal as was a full blood cell count. Serum levels of relevant thyroid hormones (T3, T4, and TSH) were within the normal limits. There was no clinical evidence of goiter, but ultrasound scan of the thyroid gland revealed echoing nodules of approximately 0.3 cm on the right lobe. Subsequent histopathologic examination of a fine needle biopsy revealed features of Hashimoto’s thyroiditis. Also, histopathologic examination of an oral nodule revealed features of fibroepithelial polyp (Fig 2), although immunohistochemistry of the tissue revealed the presence of human papilloma virus (HPV) within the epithelium.

Secondly, plain radiography and computerized tomography of the thorax, laryngotraceacoscopy, and ultrasonic scan of the breast did not reveal any pathologies. Thirdly, endoscopy of the upper gastrointestinal tract revealed esophageal polyps, hiatus hernia, and severe erosive esophagitis (Fig 3). Colonoscopy revealed polyps in the rectum, transverse and ascending colon, and caecum (Fig 4). Histological examination of the polyps revealed these to be hyperplastic and adenomatous.

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Finally, contrast magnetic resonance image (MRI) of the brain revealed an image suggestive of a cavernous angioma (Fig 5) of the left frontal lobe. Based on the clinical and laboratory findings the patient was diagnosed as a carrier of Cowden’s syndrome.

DISCUSSION

Cowden’s syndrome was first described by Lloyd and Dennis in 1963 referring to their patient Rachael Cowden, who died of breast carcinoma. Weary and coworkers reported a further 5 patients in 1972 and suggested the name multiple hamartoma syndrome (MHS). There have now been about 200 further documented cases, the number of reports increasing owing to the
greater awareness of this disorder. CS is probably more common than previously suggested, owing to its variable phenotype and dominant autosomal penetration. However, to our knowledge, there has been no report of a patient diagnosed with CS associated with a cavernous angioma.

The genetic and molecular aspects of CS have been investigated. Mutation of the PTEN/MMAC1 gene, a tumor suppressor gene located in the chromosome 10q 22-23 and responsible for the malignancy of the breast and thyroid, is observed in CS.5 The mutations of the gene PTEN identified in families and patients with SC could be the cause for the tendency of the disordered proliferation of tissue thus producing the formation of hamartomas.6

CS is clinically characterised by multiple hamartous lesions and neoplasias of the skin, mucosa, breast, thyroid gland, and gastrointestinal tract,7,8 with mucocutaneous features being the most common characteristic findings.9 Because the development of associated malignancy may take several years, these mucocutaneous lesions may serve as important clinical markers in identifying patients at high risk of malignancy of the breast and thyroid.10-12 Table I summarizes the main findings of CS.

Before 1996, little was known about the molecular etiology of the inherited hamartoma syndromes, including CS. For purposes of localizing the CS gene, the International Cowden Consortium proposed a set of operational diagnostic criteria to ascertain CS families and to assign affected status within families (Table II).13

Once the diagnosis of Cowden syndrome is made, these patients have to be considered as high risk 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. Women should also carry out monthly selfexamination. Some authors have recommended prophylactic bilateral mastectomy, particularly in women with extensive fibrocystic breast disease or breast carcinoma.14,15 Considering reports of breast carcinoma in male patients16 a prophylactic bilateral mastectomy in men with CS may also be advocated.

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. 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.

The facial papules may cause a considerable cosmetic problem. They can be treated physically by CO2-laser ablation or surgical removal or chemically by topical 5-fluorouracil. Cnudde et al17 observed good cosmetic

<table>
<thead>
<tr>
<th>Location</th>
<th>Abnormality</th>
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<tbody>
<tr>
<td>Mucocutaneous</td>
<td>Multiple facial truqueomomas, oral papillomas, actinic keratosis lymphomas, vitiligo</td>
</tr>
<tr>
<td>Thyroid gland</td>
<td>Goitre, adenomas, adenocarcinomas, thyroiditis, hyper and hypothyroidism, cysts of thyroglossal duct</td>
</tr>
<tr>
<td>Breast</td>
<td>Fibrocystic disease, carcinoma, intraductal Papilloma, atypical ductal hyperplasia</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>Polips of various types, including adenomatous, hamartomatous, lipomatous, lymphomatous, hyperplastic, and diverticulum of the colon</td>
</tr>
<tr>
<td>Central nervous System</td>
<td>Ganglionic neurons, neurofibromas, intracranial hypertension, Hydrocephalous, dysfunction of cerebella and cranial nerves, Subarachnoid haemorrhage, meningioma</td>
</tr>
<tr>
<td>Genito-urinary</td>
<td>Female- irregular periods, ovarian cysts, leiomyomas, teratomas, Uterine fibroma, adenocarcinoma of the urethra, cervix and Kidney, vaginal cysts</td>
</tr>
<tr>
<td></td>
<td>Male- hydrocele, varicoccele, hypoplastic testicles</td>
</tr>
<tr>
<td>Skeletal</td>
<td>Increased cranium size, kyphosis, kyphoscoliosis, pectus</td>
</tr>
<tr>
<td></td>
<td>Excavatum, large hands and feet, syndactily, mandibular and Maxilar hypoplasia</td>
</tr>
<tr>
<td>Visual</td>
<td>Hypertelorism, congenital vascular abnormalities, glaucoma, myopia</td>
</tr>
<tr>
<td>Cardio-vascular</td>
<td>Hypertension, prolapse of mitral valve, aortic insufficiency</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Polips of the larynx, pulmonary cysts, bilateral pulmonary lipomatosis</td>
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Fig 5. Probable cavernous angioma of the left frontal lobe.
results for all mucocutaneous lesions during a systemic therapy with acitretine 0.75 mg/kg/day. The effect of systemic retinoids is of course transient, with reappearance of the lesions after interruption of the therapy. Retinoid acid analogs have been shown to decrease growth fraction and to induce differentiation and apoptosis in organotypic cultures of ovarian carcinoma. 18 Newly appearing headaches should arouse suspicion for Lhermitte-Duclos disease and should be examined by MRI of the brain. 19 A thorough family history and an appropriate screening of family members is important to detect further CS cases as early as possible. 20,22

The present report thus detailed the features of a patient who initially presented with oral swellings and was subsequently found to have Cowden’s syndrome.

REFERENCES

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