Cowden syndrome revealed by gestrointestinal and mucocutaneous manifestations. A case report from Morocco

Le syndrome de Cowden révélé par des manifestations gastro-intestinales et cutanéomuqueuses. *Une observation marocaine*

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Résumé

Le syndrome de Cowden, l'un des nombreux syndromes des hamartomes multiples, est une maladie génétique rare, caractérisée par des lésions hyperplasiques et des hamartomes répartis dans tout le corps. Ce syndrome prédispose à la survenue de différents cancers dans de nombreux tissus, mais en particulier le sein, la thyroïde et l'endomètre. Nous rapportons un nouveau cas de syndrome de Cowden chez un patient de 33 ans qui a été diagnostiqué grâce aux données de l'endoscopie gastro-intestinale, et les manifestations cutanéo-muqueuses ont permis de confirmer le diagnostic.

Mots-clés: syndrome de Cowden, papillomatose orale, kératose acrale, polypes gastro-intestinaux, polypes œsophagiens.

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Summary

Cowden syndrome, one of the several hamartoma syndromes, is a rare genetic condition characterized by hyperplastic lesions and hamartomas distributed in the whole body. It is a cancer predisposition syndrome with an increased risk of developing malignancy in many tissues but especially breast, thyroid and endometrium. We reported a case of Cowden's syndrome in a 33-year-old male patient who was diagnosed based on the characteristic findings at gastrointestinal endoscopy, and current mucocutaneous manifestations confirmed the diagnosis.

Keywords: Cowden syndrome, oral papillomatosis, acral keratosis, gastrointestinal polyps, esophageal polyposis.

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Introduction

Cowden syndrome (CS), or multiple hamartomatous syndrome, is an autosomal dominant disorder characterized by hyperplastic lesions and hamartomas distributed on the whole body (1-2). It is a cancer predisposition syndrome with an increased risk of developing malignancy in many tissues but especially breast, thyroid and endometrium (3). We, here, report a new Moroccan case of Cowden's disease diagnosed based on the characteristic findings at gastrointestinal endoscopy.

Case report

A 30-year-old male patient was admitted to our department in September of 2014 for chronic recurrent rectal bleeding with melena, without other symptoms associated. Clinical history revealed a previous surgery for mass on the right leg in 2006 (probably an angioma?), he had no family history of malignancy or genetic disorders.

Physical examination revealed macrocephaly (figure 1), a lipoma of right inguinal fold, puncture pigmented macules at the elbows, knees, palmoplantar, and perianal, evolving since childhood evoking lentigines, a number of keratotic papules on the dorsum of the hands and feet (figure 2). Intraoral examination found a gingival hypertrophy and hyperemia, with fleshy papules on the gums, buccal mucosa and tongue (figure 3). His thyroid was not palpable. Anorectal examination revealed multiple rectal polyps without obvious bleeding hemorrhoids or anal fissure, abdominal examination was normal without organomagaly, palpable mass, rigidity or pain.

Upper gastrointestinal endoscopy and colonoscopy showed the presence of whitish polypoid lesions in the esophagus, histologically these showed glycogenic acanthosis. There were multiple diminutive polyps of the duodenal and gastric mucosa, multiple diminutive polyps between 6 and 10 mm in the last ileal loop, transverse colon, left colon and rectum (figure 4), histologically it was lipomas, inflammatory and hyperplastic polyps.

Cervical ultrasound found out a normal sized thyroid with a several nodules (at least 6 right and 4 left), thyroid nodule cytopuncture showed no malignancy signs. Otherwise, no abnormal findings were found both at computed tomography scan of the abdomen and at abdominal ultrasonography.

The evolution was marked by the spontaneous cessation of rectal bleeding, a oral iron supplementation was prescribed, and since then, the patient continue to have periodic transdisciplinary follow-up including an annual endoscopic monitoring.

Discussion

CS is a rare genetic condition, with estimated one case in every 200,000 to 250,000 people (1). The causes remain unclear, but mutation in the PTEN gene (phosphatase and tensin homolog gene, a tumor suppressor gene) has been strongly considered, the mutations are typically point mutations or smaller deletions or insertions. The mutation detection rate in patients fulfilling the diagnostic criteria has been reported to 80% (4). Mutation in PTEN determines the loss of tissue cell proliferation control, resulting in diverse hamartomatous growth and neoplasia development (5-6). Germline mutations in the PTEN gene are associated with a number of clinically distinct syndromes other than CS (7-8). These include Bannayan-Riley-Ruvalcaba syndrome (BRRS), proteus syndrome, proteus like syndrome. BRRS has been shown to be allelic to CS, with approximately 60% of patients with a clinical diagnosis of BRRS having PTEN mutations, leading to the hypothesis that CS and BRRS should be considered as one condition, and that the increased cancer risks in CS should also apply to BRRS patients (9).

The most affected tissues in CS are skin, mucous membranes (such as oral and gastrointestinal mucosa), thyroid, breast, and endometrium, all tissues composed by cells with high ability of proliferation (2).

Diagnosis is based mainly on clinical criteria, more recently in the United States the National Comprehensive Cancer Network (NCCN) have published CS testing criteria based on pathognomonic criteria, and major and minor diagnostic criteria (3) depicted in the table 1. Our patient presented acral keratoses, oral papillomatosis (pathognomic criteria), macrocephaly (major criteria), gastrointestinal hamartomas, thyroid nodules, and lipomas (minor criteria).

Although hamartomas can develop in almost all organs, they predominantly occur in the skin and gastrointestinal system in CS. Skin disease is present in 90% to 100 % of patients (4) and the characteristic mucocutaneous lesions usually start to appear during the second and third decades of life (5). Oral papillomatosis is an important clinical manifestation for diagnosis and is usually located in the buccal and gingival mucosa, acral keratosis, another common

finding, presents as flesh-colored hyperkeratotic papules with a central depression resembling flat warts on the dorsal surfaces of the hands and feet (2), this two lesions are present in the case reported herein.

The gastrointestinal system is involved in 95% of patients with CS, polyps are multiple, usually smaller than 5 mm, and distributed throughout the colon, the most common type of polyp is hamartomatous, these are usually juvenile polyps, other reported polyp types include ganglioneuromas, adenomatous, and inflammatory polyps, and less commonly leiomyomatous, lipomatous, and lymphoid polyps (6). Esophageal polyposis found in 85.7% of Cowden's disease patients, it shows histopathologically glycogenic acanthosis (7), and it has been suggested that diffuse oesophageal lesions composed of glycogenic acanthosis combined with other benign gastrointestinal polyposis should be considered pathognomonic of CS and used as diagnostic criteria (8). In our case we did not recognize the mucocutaneous manifestations at the first examination, the patient also did not recognize them, it was the endoscopic and pathological gastrointestinal findings which lead us to a tentative diagnosis of CS, what drove us to a very careful clinical examination including mucocutaneous review.

The main complication of CS is the high prevalence of breast, thyroid, and endometrium neoplasias, and contributes greatly to morbidity if not detected early. Three studies to date have examined risks for malignancy, the largest one identified greatly increased lifetime risks for breast (85.2%), thyroid (35.2%), renal (33.6%), and endometrial cancers (28.2%) and slightly elevated risks for colorectal cancers (9%) and melanoma (6%) (9). Therefore, CS carriers should be periodically followed-up so as to make it possible to diagnose malignant tumors as early as possible, allowing less invasive treatment approaches. Guidelines from the National Comprehensive Cancer Network (NCCN) are listed in table 2.

Most of the gastrointestinal polyps found with this syndrome are non-adenomatous and possess little malignant potential, but, it is important to recognise that these lesions may be a marker for existing or potential internal malignancy. An increased risk of colon cancer is now reported and surveillance with colonoscopy is indicated. It is recommended that if a patient remains asymptomatic, the first colonoscopy occurs at age 35 or 10 years younger than the earliest colorectal cancer diagnosis in a first-degree relative with future surveillance intervals determined by the number and type of polyps seen on previous scoping. The authors recommend colonoscopy every 1-2 years if multiple polyps and/or adenomatous polyps are present or every 3-5 years if either sparse, nonadenomatous polyps or no polyps are present. At this time prophylactic colectomy is not considered unless a patient has several adenomas seen on subsequent scopes, and there is such a large number of other polyps that the surgeon is concerned that adenomas may be missed among the field of hamartomatous, hyperplastic, and other polyp types (9-10).

PTEN is a tumor-suppressor gene that maps to 10q22-23. It encodes a dual-function phosphatase whose substrate is phosphatidylinositol, which is a phospholipid in the phosphatidylinositol 3-kinase pathway that shares homology with the adhesion molecules tensin and auxilin. Using both protein and lipid substrates, it regulates cell cycling, cellular growth, proliferation, and angiogenesis.

Future treatment options to help control the increased cancer risk of patients with CS may focus on inhibition of the Phosphatidylinositol 3-kinase-AKT-mammalian target of rapamycin (PI3K-Akt-mTOR) pathway which is increased in patients with CS and restoration of the normal PTEN-associated molecular pathways (4).

In summary, we reported a case of Cowden's syndrome diagnosed based on the characteristic findings at gastrointestinal endoscopy. Gastroenterologists should consider the diagnosis in any patient with esophageal

glycogenic acanthosis and multiple polypoid lesions of the gastrointestinal tract.

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Figure 1. Frontal aspect of the patient showing macrocephaly

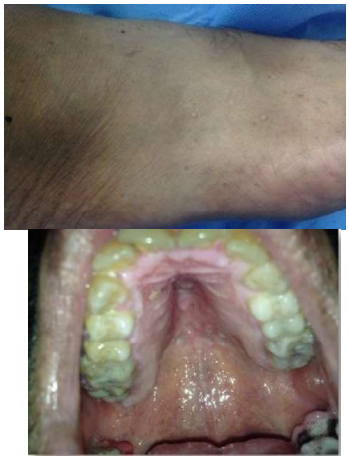


Figure 2. Plantar keratotic papules

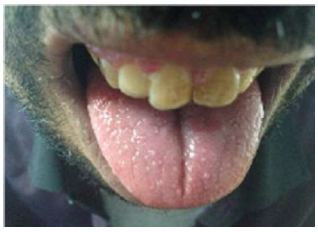
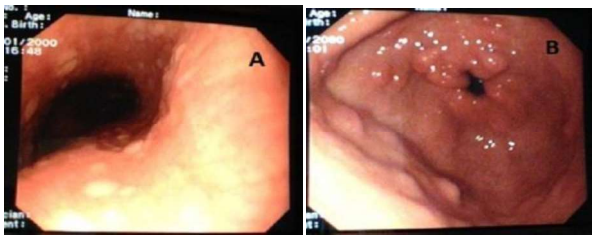


Figure 3. Oral mucosal papillomatosis



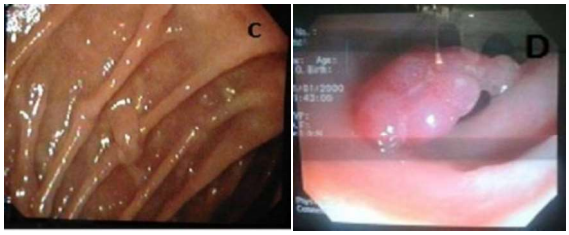


Figure 4. A: olypoid lesions in the esophagus: Glycogen acanthosis
B, C, D: Upper gastrointestinal endoscopy and colonoscopy showing whitish polypoid lesions

Table 1. Cowden Syndrome Clinical Diagnostic Criteria

Pathognomonic Criteria
Mucocutaneous lesions alone if
• There are six or more facial papules of three or more must be trichilemmomas or
• Cutaneous facial papules and oral mucosal papillomatosis or
• Oral mucosal papillomatosis and acral keratosis or
• Palmoplantar keratosis, six or more
Major Criteria—Two criteria (one of which must be macrocephaly or Lhemitte–Duclos disease
Breast carcinoma
Thyroid carcinoma (nonmedullary), especially follicular thyroid carcinoma
Macrocephaly
Lhermitte–Daclos disease
Endometrial carcinoma
Minor criteria—Four criteria
Other thyroid lesions
Mental retardation
Gastrointestinal hamartomas
Fibrocystic disease of the breast
Lipomas
Fibromas
Genitourinary malformations or carcinoma
Or One major criterion and three minor criteria may also indicate diagnosis of CS

Table 2. Management program for men and woman with CS from the National comprehensive Cancer Network (1)

Woman
• Breast awareness starting at age 18 years • Clinical breast exam, every 6–12 month, starting at age 25 y or 5–10 y before the earliest known breast cancer in the family • Annual mammography and breast MRI screening starting at age 30–35 y or individualized based on earliest age of onset in family • For endometrial cancer screening, encourage patient education and prompt response to symptoms and participation in a clinical trial to determine the effectiveness or necessity of screening modalities • Discuss risk-reducing mastectomy and hysterectomy and counsel regarding degree of protection, extent of cancer risk and reconstruction options • Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy and/or hysterectomy
Men and Woman
• Annual comprehensive physical exam starting at age 18 y or 5 y before the youngest age of diagnosis of a

component cancer in the family (whichever comes first), with particular attention to breast and thyroid exam
• Annual thyroid starting at age 18 y or 5-10 y before the earliest known thyroid cancer in the family, whichever is earlier
• Colonoscopy, starting at age 35 y, then every 5 y or more frequently if patient is symptomatic or polyps found
• Consider renal ultrasound starting at age 40 y, then every 1-2 y
• Dermatological management may be indicated for some patients
• Consider psychomotor assessment in children at diagnosis and brain MRI if there are symptoms
• Education regarding the signs and symptoms of cancer