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Letter to the Editor

How to recognize Cowden syndrome: A novel PTEN mutation description

Comment reconnaître un syndrome de Cowden : à propos d'une nouvelle mutation du gène PTEN

Keywords: Cowden syndrome; PTEN; Multinodular goiter; Hamartomatous tumour; PTEN hamartoma tumour syndrome

Cowden syndrome (CS) is an autosomal dominant disorder associated with an inherited predisposition to cancer, characterized by the appearance of hyperplastic hamartomas, tumours or lesions affecting multiple organs [1]. Neoplastic lesions predominantly involve the skin, mucous membranes, thyroid, breast, colon and endometrium, and may affect the central nervous system in the form of gangliocytoma and vascular malformations [2].

A twenty year old Belgian woman (1 m 60, 65 kg) presented with a multinodular goiter associated with cervical discomfort. Physical examination revealed multiple nevi. An atypical melanocytoma was resected in 2011. The patient repeatedly consulted for gingival hypertrophy extending from the anterior portion of the palate (Fig. 1). The woman was not currently taking any medications, and the family history was unremarkable. Her thyroid function was normal. No intellectual disability was noticed. A thyroid ultrasound confirmed a 29 mL goitre with a marked development of the right lobe, which was cold at scintigraphy. Echographic score of this lesion was TRADS 4B. Fine-needle aspiration cytology of this cold nodule was consistent with atypical follicular lesions. The risk of malignancy was estimated at 20–30% (Bethesda III). After total thyroidectomy, pathological studies confirmed the existence of a right 6.3 cm thyroid adenoma.

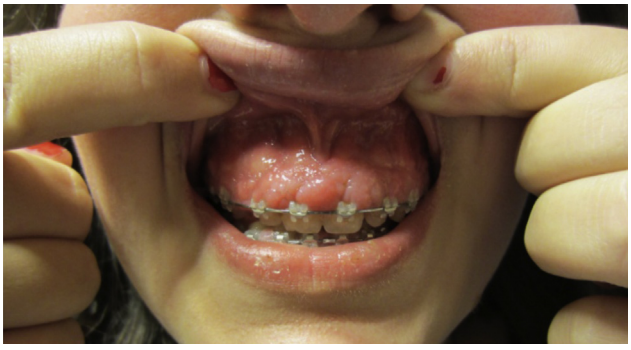

Fig. 1. Upper hamartomatous gingival lesions.

The occurrence of a thyroid adenoma with mucocutaneous lesions in a young patient suggested a syndromic association. In addition to hamartomatous lesions in the gums and the anterior portion of the palate (Fig. 1), further clinical examination revealed a papillomatous nodule on the little finger of the right hand and a macrocephaly of 60 cm (>97 percentile). Cowden syndrome was then suspected. Genetic analysis confirmed a heterozygous germinal mutation c.445C> T (p.Gln149 *) in the *PTEN* gene (*phosphatase and tensinhomolog*). This mutation was not present in her mother. Her father, who was asymptomatic, refused genetic exploration. Significantly, psychological support and a programme of early screening and oncological follow-up were designed for our patient.

Cowden syndrome, which is a form of PTEN hamartoma tumour syndrome (PHTS), is a rare genetic syndrome caused by a mutation of the PTEN tumour suppressor gene. PHTS is inherited in an autosomal dominant manner [1–3]. Affected individuals have a predisposition to developing benign and malignant lesions as a consequence of a disruption of the signaling pathways involved in cell growth and survival (Table 1) [3,4].

Dennis and Lloyd described the syndrome in 1963 in a 20-year-old patient named Rachel Cowden [1], who was first diagnosed with thyroid, breast and oral mucosa lesions. The PTEN gene, identified in 1997 [2–4], is a tumour suppressor gene located on chromosome 10q 23, comprising nine exons and coding for a protein of 403 amino acids [2]. The phosphatase activity of PTEN targets the phosphatidylinositol (3,4,5)-triphosphate (PIP3), thus opposing the action of PI3 K (Phosphoinositide 3-kinase). By reducing the rate of PIP3, PTEN is a negative regulator of the PI3K-Akt and mTOR pathways, which are involved in cell growth and survival, progress through the cell cycle, apoptosis and the signaling pathway of insulin. Consequently, in normal conditions, PTEN blocks the cell in G1, induces apoptosis and reduces sensitivity to insulin [3–5]. The PTEN mutation

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Table 1
Clinical manifestations in Cowden syndrome [3–10].

	Nature of lesions	Prevalence/risk
Mucocutaneous lesions	Hamartomas, facial trichilemmomas (hair follicle benign tumors), Papillomatous lesions, acral keratosis, lipomas, fibromas, neuromas	99–100%
Thyroid disease	Multinodular goiter, lymphocytic (Hashimoto) thyroiditis, adenomas, thyroid cancer	Benign thyroid abnormalities: 68% Risk of thyroid cancer 3–35%
Gastrointestinal manifestations	Esophageal glycogen acanthosis, gastro intestinal tract polyps (histologic spectrum is diverse), Colorectal cancer. . .	Gastric and duodenal polyps: 66 –100% Colonic polyps: 93%. 18% risk of colorectal cancer by the age of 60
Breast disease	Benign breast disease: ductal hyperplasia, intraductal papillomatosis, adenosis, lobular atrophy, fibroadenomas, fibrocystic change, and densely fibrotic hyalinized nodules Breast cancer	Benign breast disease: 50% The lifetime risk of breast cancer for affected female patients: 25 to 50% (recent reports indicate a cumulative risk as high as 80% Malignant breast disorders risk: 25–50%
Genitourinary lesions	Uterine fibroids, endometrial carcinoma, testicular lipomatosis, renal cell carcinoma, genitourinary malformation	Endometrial carcinoma: 13–28% Renal cell carcinoma: 2–5%
Neurologic disease	Macrocephaly, Lhermitte-Duclos disease (defined as presence of a cerebellar dysplastic gangliocytoma), vascular malformations, tumors, mental retardation (IQ = 75)	Lhermitte-Duclos disease: 6–32% Macrocephaly 21–38% (recent reports indicate a prevalence as high as 80% [9], vascular malformations: 30% [9], Mental retardation: 12–20%
Immune dysregulation	Defects in T and B cell homeostasis, autoimmunity, intestinal lymphoid hyperplasia, thymus hyperplasia, and thymoma as well as T-cell lymphoma	Unknown

This table is not exhaustive, only the most commonly encountered events are listed.

c.445C > T (p.Gln149*) has only been described as a somatic mutation. However, to the best of our knowledge, this mutation has not been described at the germline level, as occurred with our patient. This mutation leads to a truncated protein (and/or to the premature destruction of the mRNA by non-sense-mediated decay), which finally leads to haploinsufficiency. It is estimated that 76% of PTEN germinal mutations lead to haploinsufficiency [2,5]. Because there was no CS family history in our case, there is a strong suspicion that this mutation occurred de novo. Notably, our patient experienced a weight gain and had difficulty losing weight, which could be attributed to a haploinsufficiency of the PTEN gene. Indeed, such patients, similar to our case, show an increase in insulin sensitivity [4,5] an increase in adipogenesis and a high obesity risk [5] because of altered PTEN metabolic pathways.

Currently, an increased neoplastic risk is supported because of the numerous discoveries regarding the clinical consequences of PTEN gene mutations (Table 1). However, no genotype/phenotype correlations have yet been described. In our patient, the diagnosis of CS was conditioned by a strong clinical suspicion but was, however, not strictly based on the classical diagnostic criteria [3,6]. Operational diagnostic criteria were formulated to select families and affected individuals for purposes of identifying the specific mutated gene. Recently, Pilarski et al. revised the diagnostic criteria leading to the "PTEN hamartoma tumor syndrome" [7]. Nevertheless, these new criteria are much debated and need to be validated in large cohorts. Differential diagnosis and a carefully clinico-biological discussion are thus recommended [7,8]. Early diagnosis of Cowden syndrome is mandatory because surveillance and screening of the different malignancies are likely to improve the life expectancy of these

Table 2
Cowden syndrome management.

Women	Men and women
Breast self-exam training and education beginning at age 18	Annual physical exam starting at age 18 years old or 5 years before the youngest age of diagnosis of a component cancer in the family, with particular attention to breast and thyroid exam
Clinical breast exam every 6–12 months beginning at age 25 or 5–10 years before the earliest known breast cancer in the family	Annual thyroid ultrasound starting at age 18 years
Annual mammography and breast MRI[a] with contrast beginning at age 30–35 or 5–10 years before the earliest known breast cancer in the family	Colonoscopy every 5 years beginning age 35 or earlier based on family colon cancer history
Education regarding endometrial cancer and prompt response to symptoms consistent with endometrial cancer	Consider annual dermatologic exam
Discussion of options of risk-reducing mastectomy and hysterectomy	Education regarding the signs and symptoms of cancer
Reproductive options: advice regarding options for prenatal diagnosis and assisted reproduction, including pre implantation genetic diagnosis	

Adapted from National Comprehensive Cancer Network, version 1, 2012.
In addition to these recommendations, several other screening tests not endorsed by the NCCN could also be considered [10]: (a) annual urinalysis with cytology to screen for renal cell cancer beginning at the age of 35 years; (b) some authors recommend an intensive renal imaging based surveillance regimen using twice yearly ultrasound. Renal CT or MRI beginning five years before the earliest onset of a renal cancer in the family [7,10].

[a] Mammography is an irradiant method that can be debated in young women, whereas breast MRI is the preferred choice in this population, but still it can have false negatives. In particular, microcalcifications are not detected with this method.

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patients. Some screening recommendations for CS are listed in Table 2.

Research is currently being conducted to target the genetic pathways affected by the loss of the effects of PTEN. Several therapeutic targets of PTEN, including mTOR inhibitors and other modulators of the PTEN transcript, are under study [8].

This case highlights the importance of the extreme care of clinicians regarding the clinical context of a common pathology such as a goiter, particularly in young patients. Multiple skin lesions such as hamartoma in association with breast, uterine, colon and/or kidney neoplasia must raise the suspicion of Cowden syndrome [6–10].

Disclosure of interest

The authors declare that they have no competing interest.

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