Cowden Syndrome: a novel PTEN mutation description and how to recognize a Not-So-Rare Hereditary Cancer Syndrome.

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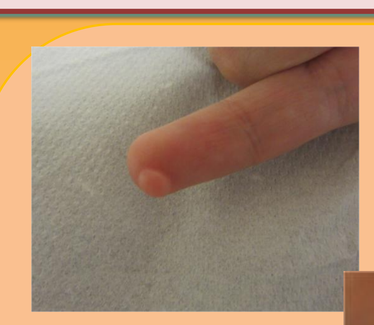
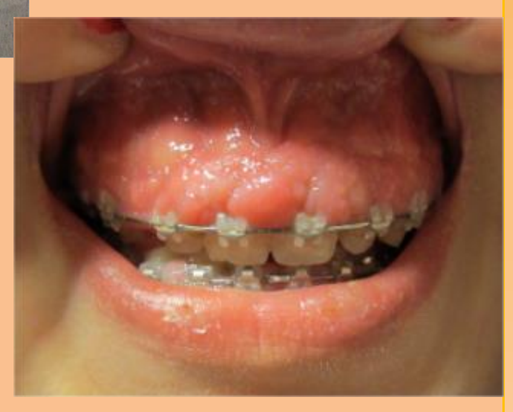
Introduction: The PTEN hamartoma tumor syndrome (PHTS) includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome. Cowden syndrome is a genodermatosis of autosomal dominant transmission, characterized by an increase in cell proliferation of the endodermal, mesodermal and ectodermal tissues with hereditary predisposition to develop benign and malignant tumors in different organs. Breast, kidney, thyroid and endometrium cancers are the most prevalent in this syndrome.

Case Report:
2011: 17 years old woman presents with:
-Epidermal nodule and multiple hamartomas at the level of gums and anterior 1/3 of the palate.
-Multiple nevi with an atypical melanocytoma resected in 2011.
- Acral keratosis at the end of the fifth finger of the right hand.
2013: multinodular goiter with a dominant 6 cm nodule.
- cytopunction found a follicular lesion with an atypical cytology with Hurtle cells. After thyroidectomy, confirmation of a thyroid adenoma.
Family history is not contributive



Acral keratosis



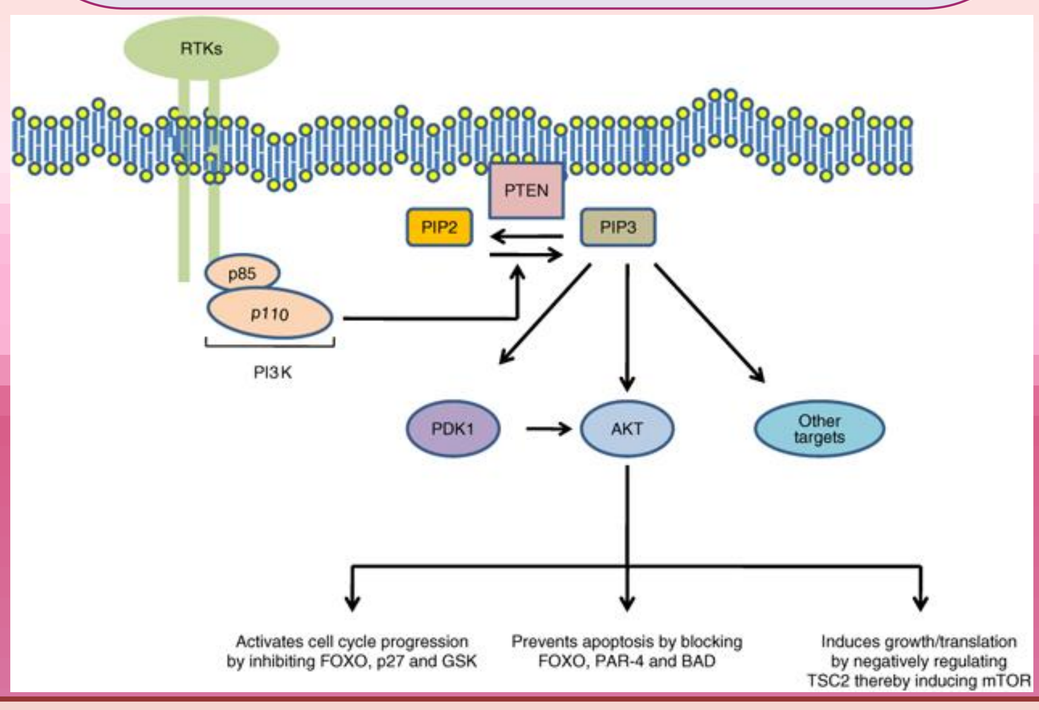
gingival hamartomas

Table 1: Cowden Syndrome Diagnostic Criteria (National Comprehensive Cancer Network 2008)

Pathognomonic critera	• Lhermitte-Duclos disease (LDD) – adult
	• Mucocutanous lesions:
	  • Trichilemmomas, facial
	  • **Acral keratoses**
	  • **Papillomatous lesions**

Major criteria	• Breast Cancer • Thyroid Cancer (papillary or follicular) • Macrocephaly (=97%ile) • Endometrial cancer
Minor criteria	• Other structural thyroid lesions (e.g., adenoma, **multinodular goiter**) • Mental retardation (i.e., IQ = 75) • Gastrointestinal hamartomas • Fibrocystic disease of the breast • Lipomas • Fibromas • Genitourinary tumours (e.g., uterine fibroids, renal cell carcinoma) or • Genitourinary structural malformations • Uterine fibroids
Operational diagnosis in an Individual	Any of the following: 1. Mucocutanous lesions alone if: (a) There are six or more facial papules, of which three or more must be trichilemmoma, or (b) Cutaneous facial papules and oral mucosal papillomatosis, or **(c) Oral mucosal papillomatosis and acral keratoses**, or (d) Palmoplantar keratoses, six or more 2. Two or more major criteria, but onemust include macrocephaly or LDD; or 3. One Major and three minor criteria; or 4. Four minor criteria.

Genetics : Cowden syndrome was suspected based on highlighted diagnostic criteria. *PTEN* gene analysis revealed the heterozygous c.445C>T mutation. This previously undescribed mutation was predicted to result in truncated (p.Gln149*) and inactive protein, and/or instability of mRNA, destroyed by non sense mediated decay. This mutation was not found in the father and mother is unavailable for analysis.



Discussion: First case of germinal mutation c.445C > T (p.Gln149*). The frequency of neomutations is not known but for some authors it may account for 44% of cases. Up to now, more than 100 mutations in the PTEN gene have been described at the germ level . However, no genotype/phenotype correlation has been demonstrated.
It is important for clinicians to recognize these patients and refer them for cancer genetics consultation. The lifetime risk for thyroid cancer (usually follicular, rarely papillary, but never medullary thyroid cancer) is approximately 35%, so thyroid surgery is recommended when thyroid nodular pathology is present. Early diagnosis of this syndrome in a young may allow the implementation of specific screening and treatment strategies.

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