EPOS™ Electronic Presentation Online System

ESR European Society of Radiology

Recognizing Cowden Syndrome; radiological findings to look for

Poster No.:	C-2457
Congress:	ECR 2019
Type:	Educational Exhibit
Authors:	M. Gredilla[1], M. LETURIA ETXEBERRIA[2], A. Serdio[3], J. Elejondo Oddo[4], E. Pardo Zudaire[5]; [1]DONOSTIA/ES, [2]San Sebastian, Gipuzkoa/ES, [3]Donostia - San Sebastián/ES, [4]San Sebastián/ES, [5]San sebastian/ES
Keywords:	CNS, Thyroid / Parathyroids, Gastrointestinal tract, MR-Diffusion/ Perfusion, Ultrasound, CT-Colonography, Diagnostic procedure, Connective tissue disorders, Cancer
DOI:	10.26044/ecr2019/C-2457

Learning objectives

- To review the most common radiological findings on Cowden Syndrome.

Background

Cowden Syndrome is an autosomal dominant disorder. It belongs to a group linked to germline mutations in the Phosphate and Tensin homolog tumour suppressor gene (PTEN) that includes basically three disorders: the Cowden Syndrome, the Bannayan-Ruvalcaba Syndrome and the Proteus-like Syndrome. Given the common genetic aetiology of the aforementioned syndromes, they are grouped under the term PTEN hamartoma tumour syndromes (PTHS).

Amongst these three syndromes, Cowden Syndrome, is the prototype, the most well-known and better characterised one. It was described for the first time in 1962 by Doctors Macey Dennis and Kenneth M. Lloyd, and diagnostic criteria were depicted for the first time by the International Consortium of Cowden in 1995. Criteria continue to evolve and change at the same time that new research and investigations define Cowden Syndromes ´ clinical spectre.

Previous studies estimate an incidence of 1 case per 200,000 people, although this number is thought to be underestimated. This inherited syndrome has no gender predilection, but some manifestations are more likely to appear in males; thyroid cancer, while others will appear more frequently in females; breast cancer.

It is a multisystem disease with increased risk for malignancies (breast, thyroid, kidney, and endometrium), as well as benign hamartomatous overgrowth of several tissues (skin, mucosae, colon, thyroid…).

Among the benign lesions we can find various mucocutaneous changes that are considered to be pathognomonic of Cowden Syndrome, including trichilemmomas and other facial papules, acral keratosis and oral papilloma. Other benign findings include lipomas, colonic polyps and thyroiditis.

Patients have traditionally been considered at a higher risk for developing breast and thyroid tumours, both benign and malignant.

Other associated features, such as Lhermitte-Duclos disease, are less frequent diseases, but it is important for both clinicians and radiologists to be acquaintance with them, since they could be signals that lead to Cowden Syndrome diagnosis.

Molecular genetics:

The spectrum of mutations of the germline detected in these syndromes expands along the PTEN gene codification sequence; gene that is found in 10q 23.3 chromosome.

PTEN gene is a tumour suppressor gene involved in many different cell signalling pathways, such as the PI2K/AKT/mTOR pathways. Mutations in PTEN tumour suppressor gene therefore causes, a dysregulation of the AKT pathways, which subsequently leads to a decrease in the apoptosis and an increase of cellular growth.

In the last decade, it has become obvious that some individuals with Cowden Syndrome do not present with PTEN germline mutations, but rather show mutations in other susceptible genes in the PTEN germline, or in other germlines. Moreover, unfortunately, the attempts to establish a clear correlation between the clinical phenotypic variations and the genotype have been unsuccessful, and due to high risk of cancer development, patients with PTHS must be offered a special management, independent of the type of mutation.

For this reason, molecular genetic testing can be offered to these patients to assess this mutation, nevertheless, the consensus diagnostic criteria should always be used. These criteria are listed in Table 1. (Fig. 1)

Diagnosis will be established when encountering:

Diagnosis:

• # 3 major criteria: including macrocephaly, Lhermitte-Duclos and gastrointestinal hamartomas

• 2 major y 3 minor criteria

Family diagnosis (one family member already diagnosed):

• Any major criteria with or without minor criterion

• One major and one minor criterion

• 3 minor criteria

Criteria highlighted in bold are nowadays considered pathognomonic of Cowden Syndrome.

Images for this section:

MAJOR CRITERIA	MINOR CRITERIA
Breast cancer	Colon cancer
Endometrial cancer (epithelial)	Autism espectrum disorder
Thyroid cancer (follicular)	Lipomas (≥3)
Gastrointestinal hamartomas	Esophageal glycogenic acanthosis (≥3)
Lhermitte-Duclos disease (adult)	Mental retardation (IQ ≤ 75)
Macrocephaly (≥97 percentile)	Renal cell carcinoma
Macular pigmentation of the glans penis	Testicular lipomatosis
• **Multiple trichilemmomas (≥3)** • **Acral keratoses (≥3)** • **Mucocutaneous neuromas (≥3)** • **Multiple oral papillomas (≥3) or biopsy proven or dermatologist diagnosed**	Thyroid cancer: papillary (follicular variant)
	Thyroid lesions: adenoma, multinodular goiter
	Vascular anomalies (intracranial venous anomalies)

Diagnosis in an individual:

- **≥ 3 or more major criteria**: macrocephaly, Lhermitte-Duclos or gastrointestinal hamartomas must be included
- **2 major and 3 minor criteria**

Diagnosis in a family where one individual is already diagnosed:

- **2 major criteria with or without minor criteria**
- **1 major and 2 minor**
- **3 minor criteria**

(Fig. 1): **Diagnostic criteria**

Fig. 1

Findings and procedure details

We now describe the most common features and pathologies related to Cowden Syndrome, and a variety of radiological findings we should look for when this syndrome is suspected.

1. Mucocutaneous manifestations:

Mucosae and skin features are present in around 90-100% of patients with Cowden Syndrome and are many times the initial finding. They begin to appear generally around the second decade of life, in earlier stages than the life-threatening malignancies.

The most common lesions are the facial papules, with predilection for the perioral area and oral mucosa, acral keratosis, mucocutaneous neuromas, penile pigmentation and trichilemmomas. The latter, are defined as benign cutaneous hamartomas of the sheath of the hair follicle. The presence of three or more trichilemmomas is considered pathognomonic.

2. Breast cancer:

Breast cancer is considered a major criterion, with an estimated lifetime risk for its development of 25-50%, although i is thtought to be underestimated, and some further researches suggest an accumulate risk as high as 81-85%. It is important to emphasise that breast cancer has been reported to be the most frequent malignancy related to Cowden Syndrome, and therefore should always be taken into consideration.

It tends to develop in younger patients than sporadic caner, with an average age of 38-46 years. Ductal origin accounts for the majority of these cancers and they usually show an aggressive behaviour, with multifocal and bilateral lesions.

Encountering an aggressive, multifocal, bilateral breast cancer, in a young woman, should raise the suspicion of a possible underlying associated genetic disease, such as Cowden Syndrome.

Men who present PTEN mutations can also present with breast cancer, although, a clear increase in the risk has not been established.

There is not enough evidence to establish an increase in the incidence of benign breast conditions, such as fibroadenomas, nipple or areolar malformations or proliferative fibrocystic diseases.

3. Thyroid:

The thyroid is one of the major organs affected in Cowden Syndrome.

Benign anomalies are present in 50-70% of the patients with Cowden Syndrome, being adenomas, multinodular goitre and Hashimoto thyroiditis the most frequent ones.

Regarding malignancy, thyroid cancer is the second most common Cowden Syndrome associated cancer, appearing exclusively as follicular and papillary carcinomas; overrepresented entities in these patients.

Benign anomalies and papillary thyroid cancer are included in the minor diagnostic criteria, whereas follicular thyroid cancer is considered a major one.

4. Soft-tissue hamartomas:

Hamartomas are benign tumour-like malformations, considered a developmental error, made up of an abnormal mixture of tissues with mature characteristics and no atypia, mitosis nor necrosis. They are composed of adipose, fibro dense and/or myxoid and anomalous vascular tissues. Hamartomas related to Cowden Syndrome have an average age of appearance of 15 years.

The muscle is the most frequent site of appearance, followed by fascia, subcutaneous fat, dermis and rarely bone. They can be found in any body part, in decreasing order: lower limbs, upper limbs, trunk and head and neck.

5. Genitourinary variations:

Testicular lipomatosis is a rare benign condition of the testes, characterised by the appearance of hyperechoic lesion on the ultrasound, with no posterior shadow and no vascularity on colour Doppler.

As for malignant lesions, renal cell carcinoma has been described, with a lifetime estimated risk of 14-34%. Histological tests have demonstrated these carcinomas to

be either papillary or chromophobe. While bilateral diseased has been described, no metastatic disease has been reported.

Endometrium carcinoma is another kind of cancer that women with Cowden Syndrome may suffer from, with an underestimated lifetime risk that current reports suggest as high as 28%.

6. Gastrointestinal:

Several gastric, duodenal, colonic and rectal polyps may be found, with a high prevalence and frequency. Histologically most of them will be hamartomatous or inflammatory.

Glycogenic acanthosis of the oesophagus is a common benign thickening of the oesophageal squamous epithelium. Prevalence related to Cowden Syndrome is unknown, but it must always be taken into consideration when encountering it together with hamartomatous polyps, as both findings are highly suggestive of Cowden Syndrome.

A recent increase in the lifetime risk for developing colorectal cancer has been described, with no exact prevalence been reported. They are thought to arise from pre-existing hamartomatous and adenomatous polyps.

7. Neurologic:

Macrocephaly is a frequent characteristic seen in children with Cowden Syndrome. Besides, these patients may present associated peculiar facial characteristics (ojival palate, aquiline nose, mandible or maxillary hypoplasia), mental and developmental retardation and autism spectrum disorders, which would support diagnosis.

Lhermitte-Duclos disease of the adult or dysplastic gangliocytoma of the cerebellum is a rare but benign and slow-growing cerebellar hamartomatous tumour with unique pathological features. It is considered a pathognomonic feature of Cowden Syndrome occurring in 3rd and 4rd decades of life with no definitive gender preference. It can produce progressive mass effect of the posterior fossa, causing headaches, nausea, vomits, cerebellar ataxia, obstructive hydrocephalus, papilledema and cranial nerve palsies.

Neuroimaging evaluation will show the following features:

On CT it will appear as a nonspecific hypo-attenuating posterior fossa mass and sometimes occipital bone thinning, suggesting chronicity.

MR will show a single and unilateral, non-enhancing cerebellar mass with a striated, thickened and enlarged folia pattern. These striated bands of folia will appear iso- or hypo-intense at T1 and iso- or hiper-intense at T2 weighed images. "Corduroy or tiger-striped" terms are used to describe this characteristic appearance. Normally it does not cause perilesional oedema and intra-lesion calcifications are rare. Vascular proliferation will appear as enhancement areas after contrast administration. Diffusion-weighted sequences will show diffusion restriction, appearing hyper-intense and hypo-intense in diffusion and ADC maps respectively.

Differential diagnosis includes several and varied entities such as subacute cerebellar infarction, cerebellitis, ganglioglioma, meningeal metastasis or granulomatous disease. Regarding the treatment, conservative treatment is preferred in asymptomatic patients, with surgical resection been performed in symptomatic ones.

A relation has been established between other tumours; meningioma; and malformations; cavernous and venous angioma, and Cowden Syndrome, although it is difficult to estimate their real frequency.

Follow-up:

A coordinated multidisciplinary follow-up of these patients is recommended, and surveillance for early cancer detection is critical:

- Thyroid: annual US

- Mucocutaneous manifestations: annual dermatologic revision

- Gastrointestinal: colonoscopy every 5 years starting at age 35

- Genitourinary: Kidney US every 1 or 2 years starting at age 40

- Breast: annual mammography or MR starting at age 30 to 35 or 5 to 10 years before a family´s earliest breast cancer diagnosis

- Endometrium: annual transvaginal US and blind suction endometrial biopsies

- Lhermitte-Duclos of the adult: no surveillance guidelines have been established

Following, we exhibit two different cases of two patients diagnosed with Cowden Syndrome in our hospital:

Patient 1:

It is a 38 year old female with personal history of macrocephaly and multinodular goitre. In the dermatologic exam and colonoscopy she manifested trichilemmomas and colonic hamartomatous polyps respectively, both histologically confirmed. Regarding neurologic findings, she was diagnosed with Lhermitte-Duclos disease of the adult (Fig. 2) (Fig. 3). Genetic and molecular testing was performed identifying PTEN gene mutation.

Patient 2:

It is a 56 year old male who underwent a complete thyroidectomy because of a papillary cancer. He exhibited multiple mucocutaneous papilloma and gastrointestinal polyps (Fig. 4) that were biopsied and proven to be hamartomatous. He also presented multiple renal cell carcinoma, biopsy confirmed to be chromophobe (Fig. 5), PTEN hamartoma of soft-tissue (Fig. 6), pulmonary hamartomas (Fig. 7), pancreatic lipomas (Fig. 8). Genetic and molecular testing for PTEN gene mutation assessment turned out to be negative, however, this patient was diagnosed with Cowden Syndrome following the diagnostic criteria.

Images for this section:

MAJOR CRITERIA	MINOR CRITERIA
Breast cancer	Colon cancer
Endometrial cancer (epithelial)	Autism espectrum disorder
Thyroid cancer (follicular)	Lipomas (≥3)
Gastrointestinal hamartomas	Esophageal glycogenic acanthosis (≥3)
Lhermitte-Duclos disease (adult)	Mental retardation (IQ ≤ 75)
Macrocephaly (≥97 percentile)	Renal cell carcinoma
Macular pigmentation of the glans penis	Testicular lipomatosis
• **Multiple trichilemmomas (≥3)** • **Acral keratoses (≥3)** • **Mucocutaneous neuromas (≥3)** • **Multiple oral papillomas (≥3) or biopsy proven or dermatologist diagnosed**	Thyroid cancer: papillary (follicular variant)
	Thyroid lesions: adenoma, multinodular goiter
	Vascular anomalies (intracranial venous anomalies)

Diagnosis in an individual:

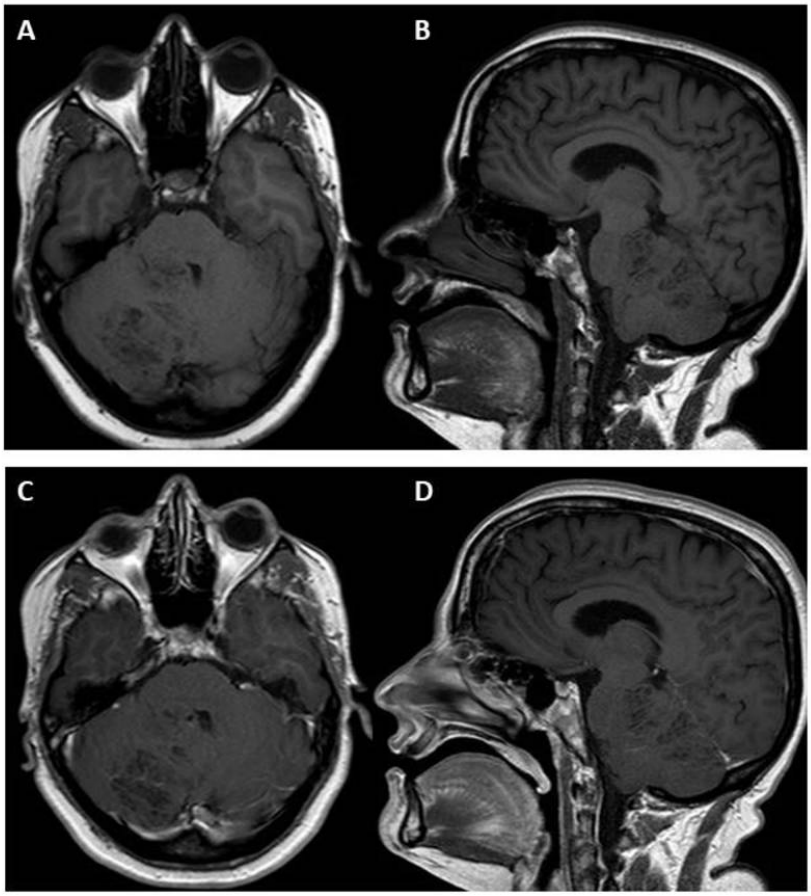
- **≥ 3 or more major criteria**: macrocephaly, Lhermitte-Duclos or gastrointestinal hamartomas must be included
- **2 major and 3 minor criteria**

Diagnosis in a family where one individual is already diagnosed:

- **2 major criteria with or without minor criteria**
- **1 major and 2 minor**
- **3 minor criteria**

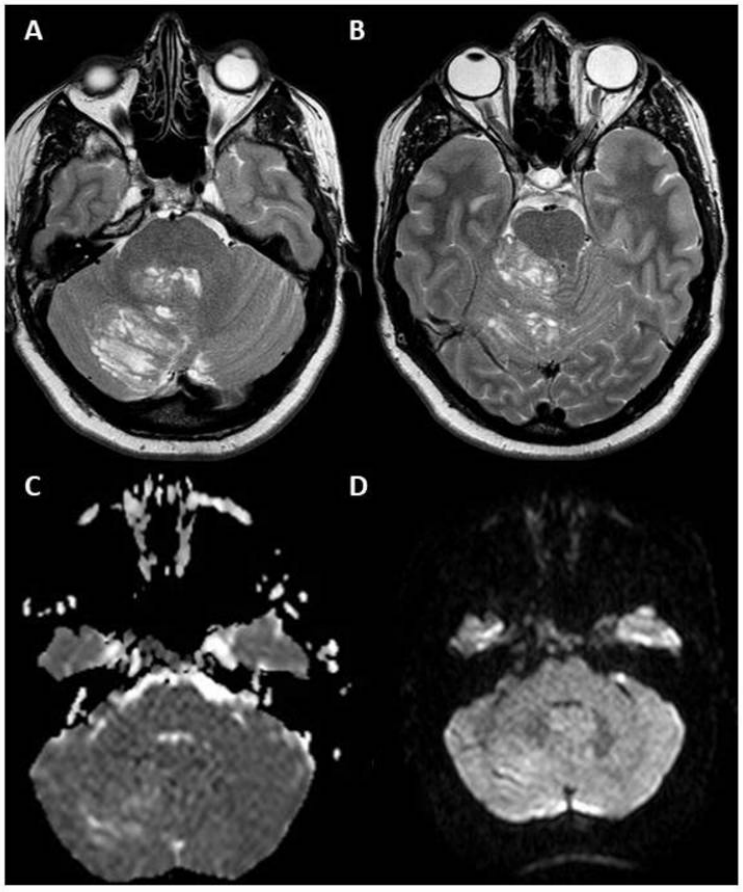
(Fig. 1): **Diagnostic criteria**

Fig. 1



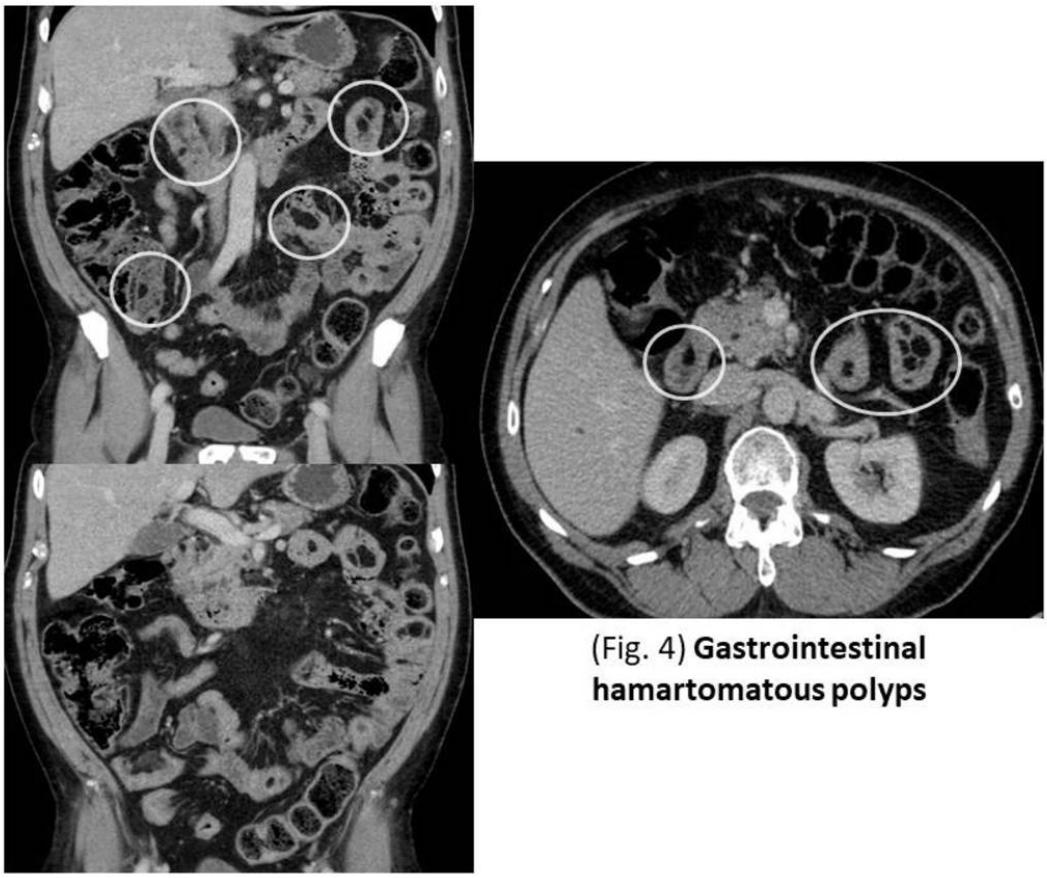
(Fig. 2) **Lhermitte-Duclos disease of the adult.** Figures A and B: **T1W axial and sagittal**: Right cerebellar mass: prominent hypo /isointense striations Figures C and D**: T1W axial and sagittal after**: gadolinium: No enhacement nor perilesional edema

Fig. 2



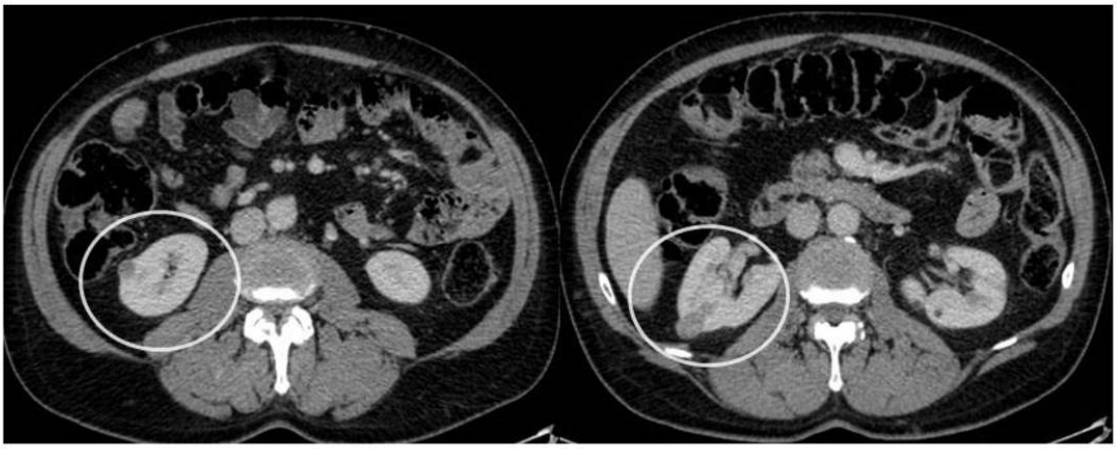
(Fig. 3) **Lhermitte-Duclos disease of the adult**. Figures A and B: **T2W axial**: Mass effect over 4th ventricle. Alternate hiper/isointense bands ("tiger stripes" appearance) Figures C and **D:DWI sequences and ADC map**: No restriction

Fig. 3



(Fig. 4) **Gastrointestinal hamartomatous polyps**

Fig. 4



(Fig. 5) **Multiple renal cell carcinoma**

Fig. 5

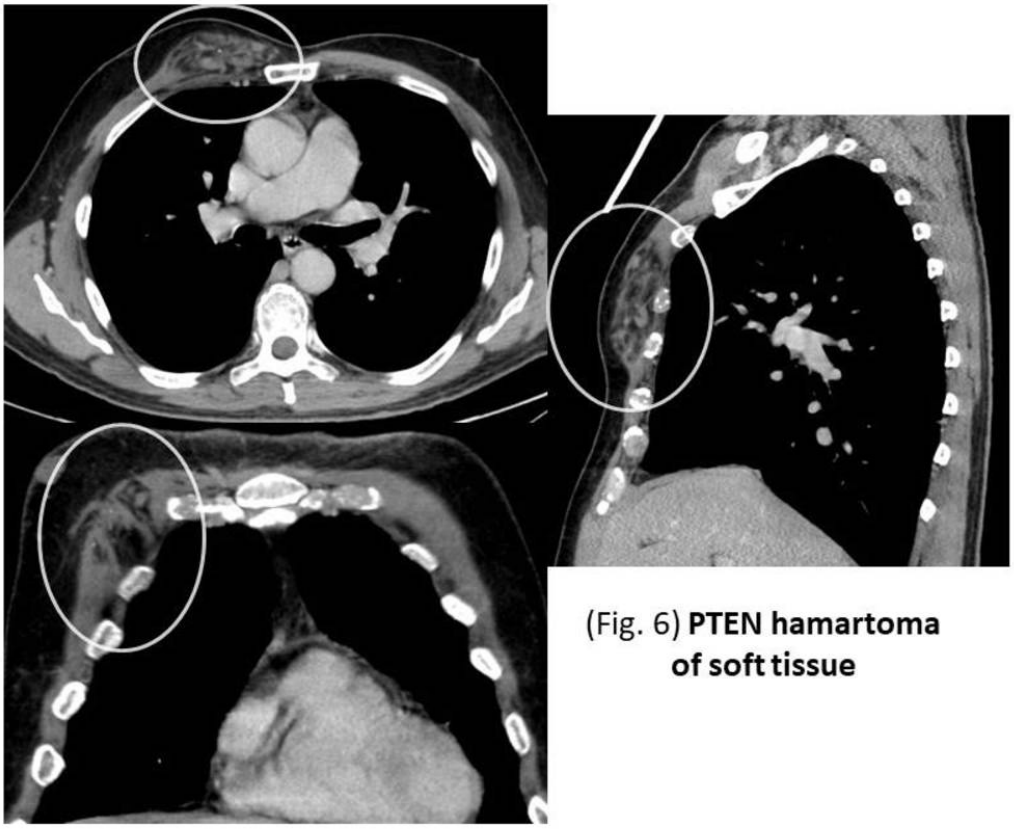
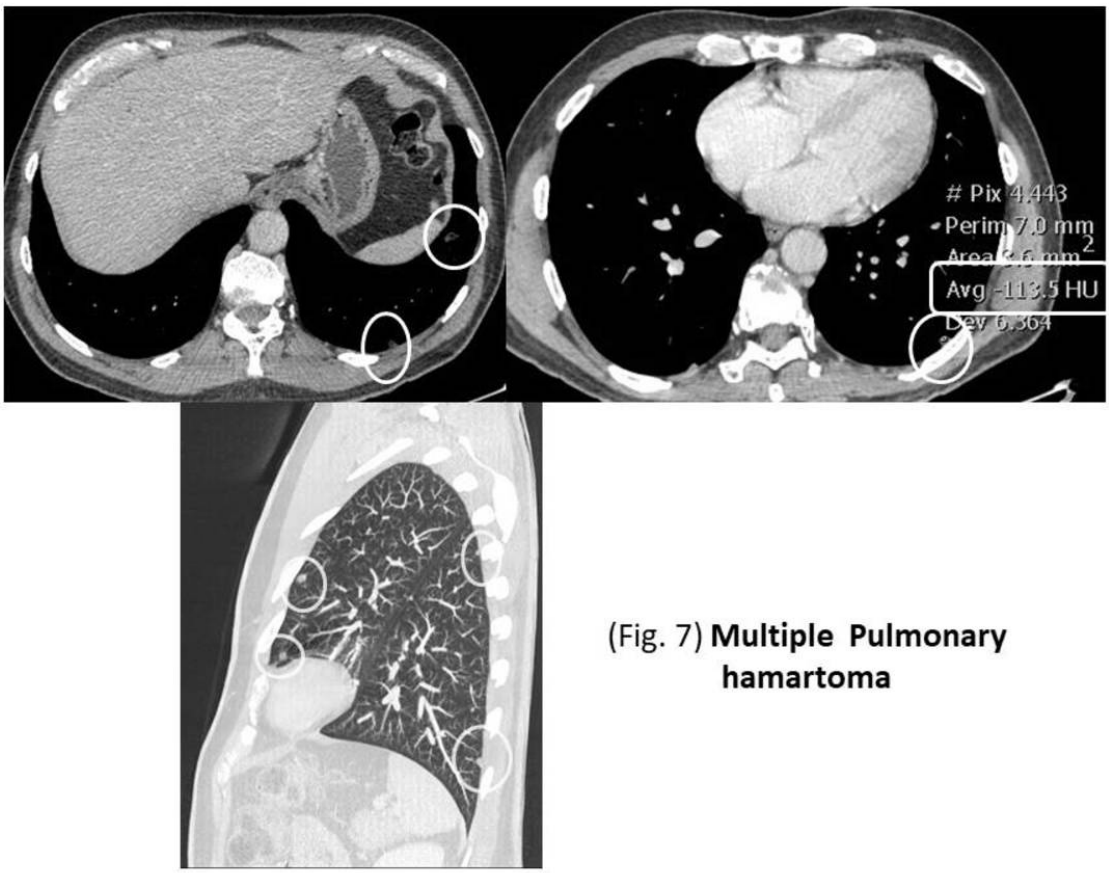
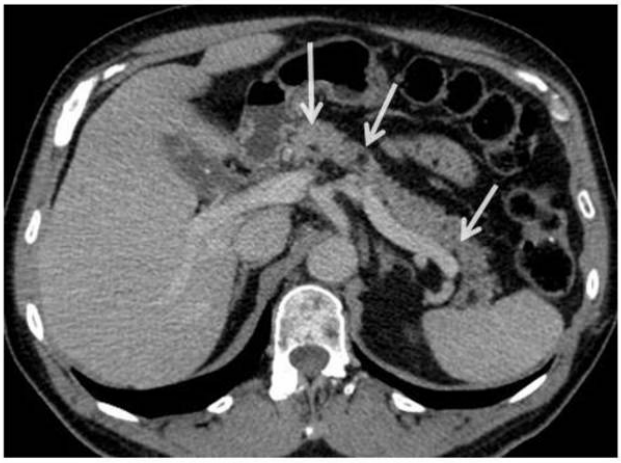


Fig. 6



(Fig. 7) **Multiple Pulmonary hamartoma**

Fig. 7



(Fig. 8) **Pancreatic lipomas**

Fig. 8

Conclusion

Cowden Syndrome is likely to be an underdiagnosed condition, but its identification is of vital importance due to its cancer development predisposition.

Some of the features that have been described in Cowden Syndrome, and that are characteristic of this disorder, can also be found in the general population with relative frequency, which makes clarifying the real prevalence of the syndrome difficult.

We mus always consider the possibility of Cowden-Syndrome when encountering with multi-organ tumours, searching for other manifestations, especially the characteristic mucocutaneous conditions; thrichilemmomas.

Genetic molecular tests may be offered and performed to try to assess for the typical genetic mutations, however, the agreed diagnostic criteria must always be used and fulfilled for a proper diagnosis, as evidence for genetic testing criteria is limited.

Radiologists play an important role in the detection, diagnosis and monitoring of some of the characteristic features of this syndrome, and therefore, should be able to recognise them and know when to look for them.

Even though the study of this disease is complex, more studies, preferably multi-centric and prospective ones, are needed for its better characterisation and understanding.

References

1. Juan de Dios García Díaz; Síndrome de Cowden; Grupo de trabajo sobre cáncer en síndrome genéticos pilomalformativos (GT-CSGP); Orphanet February 2012

2. Katherine H. Fiala, Christopher G. Staples, Richard P. Vinson, Lester F. Libow, William D. James; Cowden Disease (Multiple Hamartoma Syndrome); Medscape 24 June 2016

3. JNCI: Journal of the National Cancer Institute, Volume 106, edition 6, 1 June 2014

4. Kurek KC, Howard E, et al; The American Journal of Surgical Pathology; PTEN hamartoma of soft tissue: a distinctive lesion in PTEN syndromes; May 2012; 36 (5): 671-687

5. Peter P. Stanich, Noralane M. Lindor; PTEN hamartoma tumor syndrome, including Cowden syndrome; 11 January 2018

6. Joanne Ngeow, Kaitlin Sesock, Charis Eng; Clinical Implications for Germline PTEN Spectrum Disorders; Endocrinology and Metabolism Clinics of North America; volume 46, edition 2: 503-517; June 2017

7. Jessica Mester, Charis Eng; Cowden Syndrome: Recognizing and Managing a Not-So-Rare Hereditary Cancer Syndrome; Journal of Surgical Oncology; 2015; 111:125-130

8. Pilarski R., Burt R., Kohlman W., Pho L., Shannon KM., Swisher E.; Cowden Syndrome and the PTEN hamartoma syndrome: systematic review and revised diagnostic criteria; JNCI: Journal of the National Cancer Institute, volume 105, edition 21; 1607-16, 6 de November de 2013

9. Mirinae Seo, MD, Nariya Cho, MD, Hye Shin Ahn, MD, and Hyeong-Gon Moon, MD; Cowden Syndrome Presenting Breast Cancer: Imaging and Clinical Features; Korean J. Radio. Volume 15, edition 5; 586-590 September-October 2014

10. Fuyo Kimura, Ai Ueda, Eiichi Sato, Jiro Akimoto, Hiroshi Kaise, Kimito Yamada, Mari Hosonaga, Yuko Kawai, Saeko Teaoka, Miki Okazaki, and Takashi Ishikawa; Hereditary Breast Cancer Associated with Cowden Syndrome-Related PREN Mutation with Lhermitte-Duclos Disease; Surgical Case Reports 3:83; July 2017

11. Anna Raymond and Michael Esson; Cowden Syndrome: Mucocutaneous Lesions as Precursors of Internal Malignancy; April 2014

12. Romeo Patini, Edoardo Staderini, and Patrizia Gallenzi; Multidisciplinary Surgical Management of Cowden Syndrome: Report of a Case; volume 8 (4); 472-474; October 2016

13. Wanfeng Yu, Ying Ni, Motoyasu Saji, Matthew D. Ringel, Ritika Jaini, and Charis Eng; Cowden Syndrome-Associated Germline Succinate Dehydrogenase Complex Subunit D (SDHD) Variants Cause PTEN-Mediated Down-Regulation of Autophagy in Thyroid Cancer Cells; Human Molecular Genetics, Volume 26, Issue 7, Pages 1365-1375; April 2017

14. Joe B. Woodhouse, Brett Delahunt, Sharon F. English, Hamish H. Fraser, and Martin M. Ferguson; Testicular Lipomatosis in Cowden´s Syndrome; Modern Pathology; Volume 18; Pages 1151-1156; May 2005

15. Sapna Syngal , MD, MPH, FACG, Randall E. Brand , MD, FACG, James M. Church, MD, FACG, Francis M. Giardiello, MD 8, Heather L. Hampel, MS, CGC, and Randall W. Burt , MD, FACG; ACG Clinical Guideline: Genetic Testing and Management of Hereditary Gastrointestinal Cancer Syndromes; Am J Gastroenterol; 110:223-262; February 2015