Envoi SPECIALIST PATHOLOGISTS *inside insights*

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Cowden syndrome

Cowden syndrome is a rare inherited multiple hamartoma syndrome with a reported, but likely underestimated, prevalence of 1 in 200,000. Affected individuals usually have macrocephaly and develop benign mucocutaneous lesions (trichilemmomas, papillomatous papules and acral keratosis) by early adulthood.

The clinical diagnosis of Cowden syndrome is complex and based on diagnostic criteria divided into 3 categories (pathognomonic, major and minor). Gastrointestinal manifestations are common and can be suggestive of Cowden syndrome in a patient with other manifestations of the disease.

Genetics: Autosomal dominant inheritance. Up to 85% of cases are caused by mutations in the PTEN gene on chromosome 10 or its promoter. Mutation of the gene and altered protein product leads to unchecked cellular proliferation.

Gastrointestinal tract manifestations: More recent studies suggest that 75-95% of patients with Cowden syndrome will have gastrointestinal manifestations. These can include:

- Oesophageal glycogenic acanthosis, which often presents as small white lesions endoscopically
- Multiple hamartomatous polyps of the GI tract
  - Small sessile hamartomatous polyps of the large bowel frequently containing adipose tissue and lymphoid follicles (Fig. 1)
  - Ganglioneuroma (Fig. 2), lipoma, and fibrolipoma of the large bowel
  - Inflammatory/hyperplastic polyps of the stomach
- Increased risk of adenomas in the large bowel

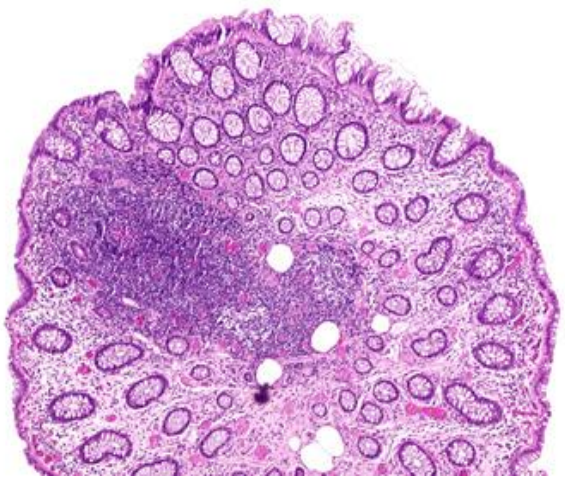

Fig. 1 Hamartomatous polyp

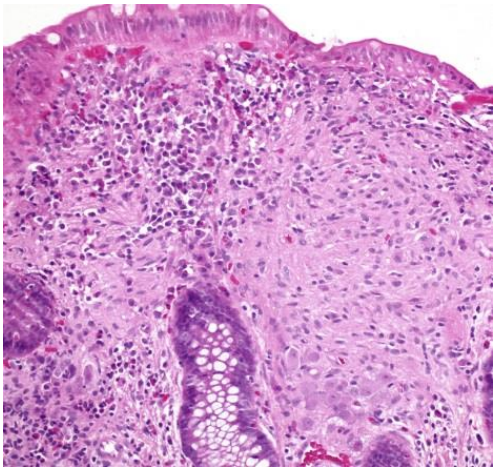

Fig. 2 Ganglioneuroma

Malignant risk: It is important to recognise Cowden syndrome due to the high lifetime risk of tumours of the breast (85%), thyroid and kidney (35%), endometrium (28%) and colon (9%).

Differential diagnosis with other hamartomatous syndromes of the GI tract:

- Peutz-Jeghers syndrome (STK11 mutation): Large polyps in the small bowel with typical histology and often presenting with clinical complications, mucocutaneous pigmentation around the mouth, non-specific inflammatory/hyperplastic polyps of the stomach and hamartomatous polyps of the large bowel; 39% risk of CRC

- Juvenile polyposis syndrome (SMAD4 or BMPR1A mutation): Large pedunculated colonic polyps causing bleeding, non-specific inflammatory/hyperplastic polyps of the stomach, can be diagnosed in adults; 40% risk of CRC.

When to suspect Cowden syndrome and what to do about it:

Gastroenterologists can suspect Cowden syndrome in a patient with:

- multiple small colonic polyps classified as hamartomas, ganglioneuromas or fibrolipoma
- association with glycogenic acanthosis of the oesophagus
- association with benign mucocutaneaous lesions (trichilemmomas, papillomas)
- personal or familial context - macrocephaly, previous history of cancers of the breast, endometrium or thyroid

If Cowden syndrome suspected, the patient should be referred to genetic counselling for clinical diagnosis and genetic testing (PTEN mutation).

Further reading:

Cleveland Clinic Online scoring system for Cowden syndrome
http://www.lerner.ccf.org/gmi/ccscore/
Eng C. Will the real Cowden syndrome please stand up: revised diagnostic criteria. *J Med Genet* 2000; **37**:828–30.
Syngal S, Brand RE, Church JM, *et al.* ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. *Am J Gastroenterol* 2015; **110**:223–62.
Tan M-H, Mester JL, Ngeow J, *et al.* Lifetime cancer risks in individuals with germline PTEN mutations. *Clin Cancer Res* 2012; **18**:400–7.