

Cronkhite–Canada syndrome six decades on: the many faces of an enigmatic disease

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ABSTRACT

Cronkhite–Canada syndrome is a rare gastro-enterocolopathy of uncertain aetiology first described almost 60 years ago. It is characterised by diffuse gastrointestinal polyposis sparing only the oesophagus, ectodermal abnormalities and an unpredictable but often fatal clinical course. The disease may demonstrate extremely diverse clinical and endoscopic features, which often leads to a delay in diagnosis. A high index of suspicion and recognition of the characteristic histological findings frequently facilitate a correct diagnosis, but the distribution of the gastrointestinal pathology and its microscopic features may be atypical. The pathologist thus requires a thorough knowledge of both the typical and many atypical faces of this disease, for which various documented therapies often still prove ineffective. Close correlation with clinical findings, including any pertinent ectodermal abnormalities, and careful examination of biopsies derived from polypoid and endoscopically spared mucosa will ensure a timely and correct diagnosis in patients with this enigmatic syndrome.

INTRODUCTION AND EPIDEMIOLOGY

In 1955, Leonard Cronkhite Jr and Wilma Canada reported an unusual, hitherto undocumented disorder characterised by gastrointestinal (GI) polyposis and unique ectodermal abnormalities.¹ Their two female patients both died within 8 months of diagnosis. Eleven years later, Jarnum and Jensen coined the eponym Cronkhite–Canada syndrome (CCS) for this rare and peculiar non-hereditary disease and added protein-losing enteropathy, electrolyte disturbances and non-adenomatous cystic polyps to the growing spectrum of its clinical manifestations.²

To date over 500 cases of CCS have been reported worldwide,^{3–5} significantly broadening our understanding of the diverse clinical and histological manifestations of this disorder. Most cases on record are single case reports or small series, the majority in patients of Asian or European descent.⁶ The preponderance of documented cases stem from Japan, including the largest series in the international literature of 180 patients.⁷ The syndrome manifests in middle to late adulthood: the mean age at presentation is 59 years but >80% of patients are over 50 at the time of diagnosis.⁸ The extremely rare paediatric cases reported actually have features of infantile juvenile polyposis.^{9–11} CCS shows a slight male predominance with a male:female ratio=3:2⁶ and has an estimated incidence of one per million (in a Japanese study).⁷

At present, no algorithm or specific criteria exist for the diagnosis of CCS. The presence of diffuse

GI polyposis, characteristic histology in both endoscopically abnormal and spared mucosa as well as relevant supporting clinical findings, including typical ectodermal changes, are the current cornerstones of diagnosis.¹² Although most patients with CCS demonstrate these cardinal features at presentation,¹³ not all the manifestations may be evident or typical.

AETIOPATHOGENESIS

The precise aetiology of CCS remains uncertain, but no convincing familial predisposition exists and to date no germline mutations have been associated with this disorder.^{14 15} Various aetiologies have been proposed, but many recent studies favour an autoimmune process characterised by immune dysregulation.^{13 14 16 17} An autoimmune aetiopathogenesis is supported by the demonstration of antinuclear antibodies,¹⁸ an association with hypothyroidism,^{8 19} and other autoimmune diseases (including systemic lupus erythematosus, rheumatoid arthritis and scleroderma),^{14 20–22} elevated serum IgG4 levels and polyp infiltration by IgG4 plasma cells.^{13 16} Additionally, some GI histological features in CCS patients demonstrate overlap with those documented in conditions associated with impaired regulatory T-cell function.^{23–25} A potential autoimmune aetiology is further supported by the well-documented clinical response to steroid and azathioprine therapies.^{13 26} Ultrastructural study of intestinal polyps has revealed crypt epithelial damage as the likely initiating morphologic abnormality, leading to mucin leakage into the lamina propria with resultant oedema, inflammation, crypt obstruction, secondary crypt dilation and architectural distortion.²⁷

CLINICAL FEATURES

The commonest GI-related symptoms in CCS are diarrhoea, weight loss, abdominal pain, anorexia, haematochaezia, nausea, vomiting and hypo-/dysgeusia.^{3 8 28} Protein-losing enteropathy with hypoproteinaemia and marked peripheral oedema, glossitis, xerostomia and anaemia have also been reported and are ascribed to malabsorption.^{1 3 8} Paraesthesias, seizures and tetany may occur secondary to electrolyte disturbances (including those of calcium, potassium and magnesium).⁸ GI endoscopic findings are usually striking and are discussed below under macroscopic pathology.

Although CCS is primarily a GI mucosal disorder, it is associated with numerous characteristic extra-gastrointestinal (EGI) abnormalities. Ectodermal manifestations are present in virtually all cases and include alopecia (of the scalp and body), nail dystrophy (thinning, splitting, separation from the nail

bed and shedding) as well as skin hyperpigmentation.^{1 8 29–31} The latter may be diffuse or localised and usually involves the extremities (particularly the hands, and sometimes the palms and soles), face and neck; the labial and buccal mucosa may also be affected.^{1 8 32} The lesions are characterised by light to dark brown macules, although rarely vitiligo may occur.³³ Other manifestations include anosmia,³⁴ cataracts,^{8 35 36} thrombosis and coagulation disorders,^{8 20} cardiac failure,⁸ peripheral neuropathy,^{28 37} vestibular disturbances,^{28 38} recurrent acute pancreatitis³⁹ and psychiatric disorders.⁴⁰ The EGI findings most often follow the GI manifestations by weeks to months, but may be present at diagnosis or even precede the GI pathology by a number of years.^{1 8}

PATHOLOGY

The polyposis in CCS is typically diffuse and involves the entire GI tract, except the oesophagus.^{6 8} Two case reports cite oesophageal ‘prominences’ or isolated polyps, but these were

never histologically substantiated.^{2 41} Occasionally, selective sparing of the stomach, small intestine (particularly the jejunum and proximal ileum) or colorectum may occur.^{1 8 27 42–44}

On endoscopy and macroscopy, CCS GI polyps are typically broad based and sessile with cystic to somewhat translucent features, varying in size from a few millimetres to 1.5 cm in diameter. Their endoscopic appearance has been described as polyps upon polyps, rambling and likened to a hydatidiform mole (figure 1A,B).³⁴ Uncommonly, an elongated or villiform morphology may be seen. Sometimes diffuse mucosal thickening rather than obviously polypoid change is present. This most often occurs in the upper GI tract, may represent an early active stage of the disease and can lead to giant duodenal and gastric rugal folds (particularly along the greater curvature).^{8 45} An endoscopically flat or even atrophic intestinal mucosa has also been described.^{46–49} Medical therapy is often associated with attenuation of the polyps, resulting in a nodular mucosa with a cobblestone appearance (figure 2).

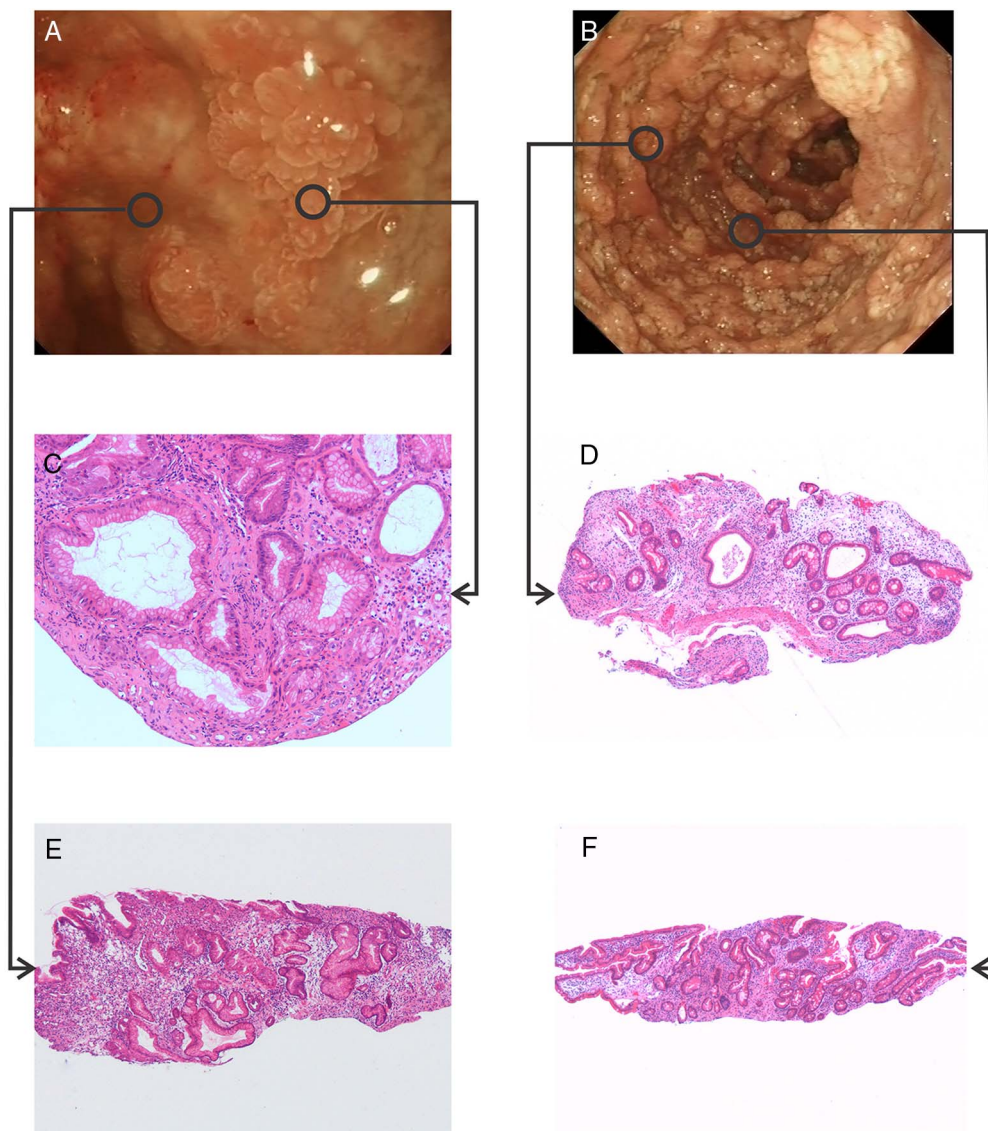


Figure 1 Typical endoscopic characteristics of Cronkhite–Canada syndrome polyps, demonstrating (A) hydatidiform mole-like features in the stomach and (B) a sessile, polyp-on-polyp appearance in the duodenum. Typical histology of polypoid mucosa in the (C) stomach and (D) duodenum reveals obvious architectural distortion and gland/crypt dilation, with an expanded, oedematous and inflammatory stroma. The endoscopically spared (E) gastric and (F) duodenal mucosa reveals similar but more subtle histological abnormalities, with partial duodenal villous atrophy.

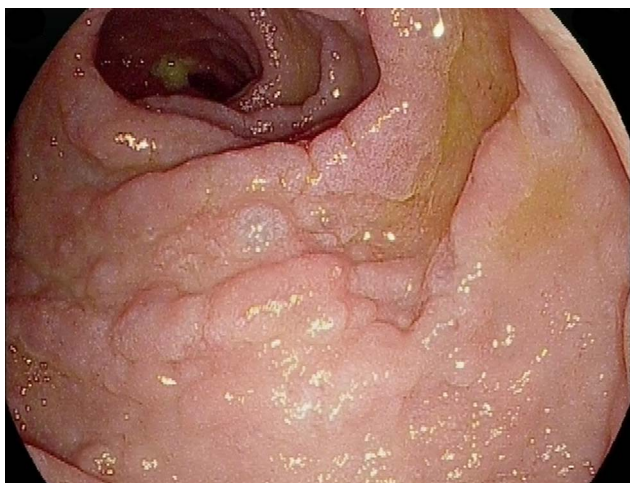


Figure 2 Atypical endoscopic features in a Cronkhite–Canada syndrome patient on azathioprine: attenuation of gastric polyps leading to a cobblestone mucosa.

On histology, CCS polyps have a hamartomatous appearance. They typically reveal an expanded oedematous lamina propria, contain a scant predominantly mononuclear inflammatory cell infiltrate and have tortuous, dilated to cystic glands/foveolae or crypts (figure 1C,D).^{50 51} The latter may contain inspissated mucin and granular material.² Specialised oxyntic, chief, Paneth and endocrine cells are typically scant or absent.⁴⁹ Abundant neutrophils, microabscesses, erosions and non-caseating granulomas have been documented in some cases and may potentially cause confusion with chronic inflammatory bowel disease.^{8 44 50} Scant scattered smooth muscle cells and prominent mast cell and IgG4 plasma cell infiltration can also be seen.^{6 16 44} Eosinophil infiltration may be so pronounced as to mimic eosinophilic gastroenteritis.⁴⁸ Some polyps may have a decidedly paucicellular stroma and submucosal epithelial invagination has been documented.^{44 52} In the upper GI tract, villous atrophy, crypt shrinkage or withering and epithelial apoptosis are sometimes conspicuous.²³ Of cardinal diagnostic importance, and in contradistinction to other GI polyposis syndromes, is the finding of lamina propria oedema and (usually

mild) inflammatory cell infiltration, as well as gland/crypt dilation and distortion in the intervening endoscopically/macrosopically spared non-polypoid mucosa (figure 1E,F).

Typical and atypical GI endoscopic and histological features of CCS are summarised in table 1.

Although biopsy of EGI lesions is seldom performed due to the characteristic clinicopathological features of CCS, previous studies of pigmented skin lesions have demonstrated increased epidermal melanin (with or without increased melanocytes), pigmentary incontinence, hyperkeratosis and non-specific perivascular inflammation.^{53 54} The alopecia has been associated with diffuse anagen–telogen conversion,⁵⁵ as well as follicular unit loss, miniaturisation and dermal glycosaminoglycan deposition.⁵⁶

DIFFERENTIAL DIAGNOSIS

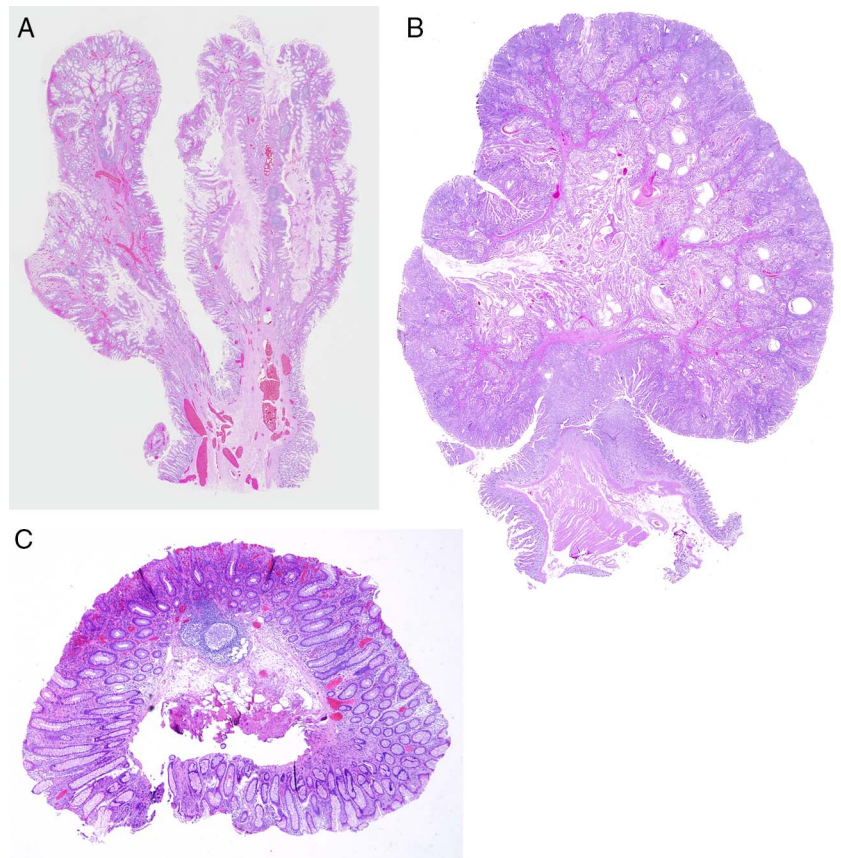
The histopathologist may be confronted with endoscopic biopsy material in three different clinical scenarios.

In the first, a patient who has undergone endoscopy is found to have diffuse GI polyposis and the polyps reveal a hamartomatous histology. In such cases, the chief diagnostic consideration is one of the rare hereditary hamartomatous GI polyposes. The polyps of *juvenile polyposis* histologically most closely mimic CCS polyps. In the colorectum and small bowel, the presence of pedunculation and atypical polyp morphology including multi-lobation and villiform features, prominent epithelial overgrowth and associated ganglioneuromatous components all point to juvenile polyposis (figure 3A).^{44 57 58} Polyps of the *Peutz-Jeghers syndrome* are differentiated by their extensive arborising smooth muscle core and pedunculation, frequent small bowel predominance and sometimes prominent and deep epithelial misplacement (figure 3B).⁵⁹ GI polyposis is found in 60–85% of *Cowden syndrome* patients.^{60 61} In the colorectum, these polyps are differentiated from CCS polyps by their frequent distal location, small size (usually <0.5 cm), dome-shaped appearance, minimal crypt dilation and surrounding non-oedematous and pauci-inflammatory, often concentric fibrous stroma (figure 3C).^{62 63} The presence of oesophageal glycogenic acanthosis is a further distinguishing feature of Cowden syndrome.⁶⁰ It should be noted, however, that in the stomach all of the preceding syndromic polyps may have a similar histological appearance.^{44 64} At this site, all tend to be sessile (especially if

Table 1 Gastrointestinal (GI) endoscopic and histological features of Cronkhite–Canada syndrome

Typical	Atypical
<i>Endoscopy</i>	
Diffuse involvement of entire GI tract, excluding the oesophagus	Selective sparing of the stomach, small intestine or colorectum
Multiple distinct sessile polyps, with rambling or polyp-on-polyp appearance	<ul style="list-style-type: none"> ▶ Elongated or villiform polyps ▶ Polyp attenuation with cobblestone or nodular mucosa (particularly after medical therapy) ▶ Diffuse thickening of the mucosa (particularly upper GI tract) with hypertrophic rugae and duodenal folds ▶ Mucosal atrophy
<i>Polyp histology</i>	
Architectural distortion and cystic dilation of mucosal glands/crypts	<ul style="list-style-type: none"> ▶ Submucosal gland/crypt invagination ▶ Glandular/crypt atrophy with epithelial attenuation ▶ Prominent epithelial apoptosis
Diffuse expansion of lamina propria by oedema and scant predominantly mononuclear inflammatory cell infiltrate	<ul style="list-style-type: none"> ▶ Prominence of specific inflammatory cell type ▶ Neutrophils, sometimes with microabscesses (mimicking ulcerative colitis) ▶ Eosinophils (mimicking eosinophilic gastroenteritis) ▶ Mast cells ▶ IgG4 plasma cells ▶ Paucicellular stroma

Figure 3 Cardinal histological differential diagnoses of Cronkhite–Canada syndrome. (A) Juvenile polyp demonstrating a villiform architecture and obvious pedunculation, the latter a reliable distinguishing feature of syndromic colonic juvenile polyps. (B) Intestinal Peutz–Jeghers polyp with characteristic arborising smooth muscle core. (C) Small dome-shaped polyp in Cowden’s disease showing a rather unremarkable appearance; diagnosis requires a high index of suspicion in a patient with multiple non-specific appearing polyps.

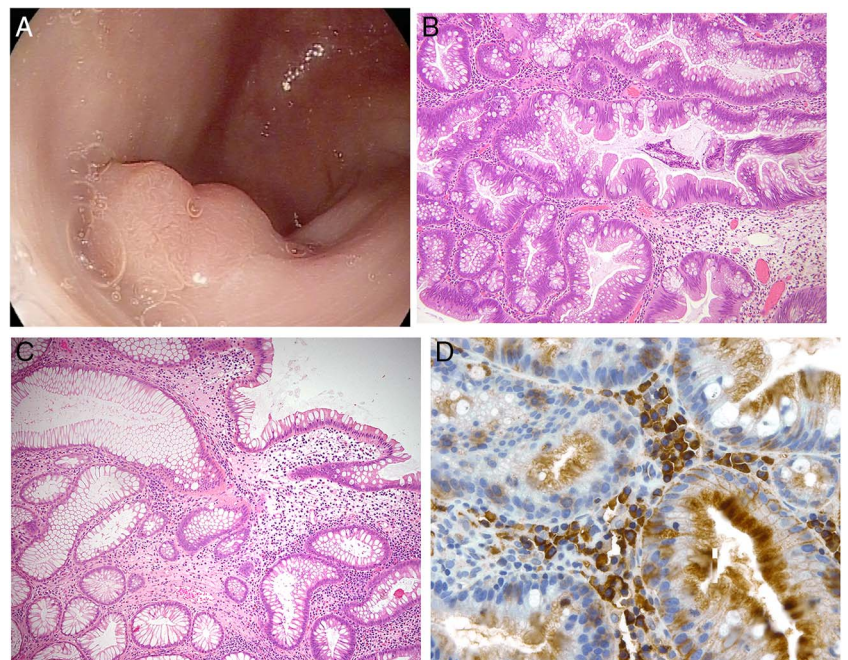


<1 cm in size), Peutz–Jeghers polyps often lack a prominent smooth muscle core and frequently only the superficial part of the polyps is sampled on endoscopic biopsy, making reliable differentiation impossible.^{64–68}

The second, less common scenario entails a patient who presents with atypical endoscopic features that do not suggest GI polyposis. This most often occurs in the upper GI tract, where a diffusely thickened or atrophic rather than polypoid mucosa is

seen.⁴⁶ An *infiltrative neoplastic process* (especially lymphoma or diffusely invasive/linitis plastica-like carcinoma) or *infectious pathology* may be suspected on clinical grounds.²³ Careful evaluation of endoscopic biopsy material, however, will readily exclude neoplasia and confirm the characteristic architectural distortion and lamina propria changes of CCS. Stains for infectious microorganisms and close correlation with microbiological studies further help exclude an infectious

Figure 4 Atypical findings in Cronkhite–Canada syndrome (CCS). (A) Selective colorectal sparing, with one of six colon polyps demonstrated on endoscopy. (B) Polyp histology demonstrating features of a traditional serrated adenoma (TSA). (C) Adjacent endoscopically spared mucosa showing characteristic microscopic changes associated with CCS. (D) TSA stromal infiltration by IgG4-positive plasma cells, a finding of uncertain pathogenetic significance.



process. The true nature of the pathology in such cases may easily escape both clinician and histopathologist unless a high index of suspicion is maintained and careful attention is paid to the clinical features.

In the third, least common scenario, biopsy material is received from a patient who has undergone only upper endoscopy or who has selective sparing of the lower GI tract on panendoscopy. In such a case, the possibility of multiple sporadic gastric polyps may enter the differential diagnosis. *Gastric hyperplastic polyps* are frequently multiple and may have some microscopic features resembling CCS polyps. The former polyps most often affect the antrum, however, and are seldom so numerous as to diffusely involve the stomach. Although the intervening mucosa often demonstrates a *Helicobacter*-associated chronic gastritis, no architectural distortion nor obvious mucosal oedema is present.⁶⁹ *Sporadic diffuse gastric polyposis*, a recently described entity of uncertain aetiology, is characterised by multiple hyperplastic polyps limited to the stomach but is distinguished by the intimately associated adenomatous lesions.⁷⁰ *Fundic gland polyps* are usually sporadic and multiple, although they may also occur in a syndromic setting (familial adenomatous polyposis and Zollinger–Ellison syndrome).^{71–74} These polyps are, however, small, limited to the fundus/corpus and comprise cystic glands with abundant parietal and chief cells, without associated abnormalities of the intervening mucosa. *Menetrier's disease* may result in polypoid gastric mucosa and, like CCS, is associated with systemic clinical disturbances including diarrhoea, protein-losing enteropathy and peripheral oedema. The hyperplastic pathology in this disorder, however, is virtually always limited to the foveolar compartment of the proximal stomach, is not accompanied by pronounced mucosal oedema nor inflammation and demonstrates an endoscopically and histologically unremarkable antral mucosa.⁷⁵ Importantly, similar duodenal involvement is not seen in any of the preceding disorders and should indicate an alternative diagnosis of a GI polyposis syndrome.

In all three of the above scenarios, careful correlation with the family history (which sometimes may be negative in hereditary polyposis syndromes with a *de novo* mutation), clinical presentation (including patient age and any EGI manifestations), as well as endoscopic distribution and characteristics of polypoid or irregular mucosa will assist the pathologist in making the correct diagnosis. Furthermore, the gastroenterologist should be urged to submit biopsies of intervening, endoscopically spared/non-polypoid mucosa in order to help confirm the microscopic diagnosis of CCS.

RISK FOR GI AND OTHER NEOPLASMS

CCS polyps are considered non-neoplastic and their malignant potential is controversial. Carcinomas of the colorectum (most often distal) and stomach have been documented in 15–25% of patients with CCS at diagnosis and may be multiple.^{5 26 76–92} Additionally, up to 40% of patients with CCS have been found to harbour colorectal adenomas and adenomatous change is sometimes seen in close proximity to CCS polyps and carcinoma.^{12 79 82 86 93–95} The association of CCS with serrated adenomas and colorectal adenocarcinoma has raised the possibility of a serrated adenoma–carcinoma sequence in these patients (figure 4A–D).^{5 78} Reliable evaluation of GI malignancy risk in CCS is hampered by the rarity of the syndrome and the fact that synchronous neoplasia may be coincidental due to the relatively advanced age of many patients with CCS. The overall risk of colorectal neoplasia does appear to be increased, however, and may be secondary to the generalised chronic mucosal inflammation characteristic of CCS.²⁶

Isolated CCS cases with EGI neoplasms have also been reported, but this association appears to be fortuitous. The latter have included giant cell tumour of bone,⁹⁶ cholangiocarcinoma,⁹⁷ lung carcinoma (with metachronous oesophageal carcinoma),⁹¹ multiple myeloma⁹⁸ and myelodysplastic syndrome.⁹⁹

THERAPY AND OUTCOME

CCS is a rare disease, which has made systematic evaluation of therapeutic regimens problematic. Numerous treatment approaches, including aggressive nutritional support,^{14 100 101} antibiotics,^{8 42} histamine receptor antagonists,¹⁴ cromolyn sodium,¹⁴ immune suppression (corticosteroids, azathioprine and cyclosporine),^{13 20 102 103} and surgery^{89 104 105}—often in different combinations—have had variable success.^{4 6 100 102 106} Apart from nutritional support, corticosteroids are currently recommended as the mainstay of medical treatment,²⁶ with azathioprine used for its steroid-sparing effect.¹³ Endoscopic mucosal resection has successfully been used to remove adenomatous polyps and early carcinomas.^{87 107}

CCS has an extremely variable clinical course, ranging from fulminant cases to those with initial remission of GI as well as systemic manifestations (occurring spontaneously or after therapy).^{42 92 103 106 108–113} Less than 5% of patients have a complete remission, however, and overall outcome remains poor.¹¹⁴ The variable clinical course and differing response to therapy has raised the question of whether CCS does not, in fact, represent more than one disease entity.⁴⁵ Although much of the data are dated, 5-year disease-related mortality is cited as 55% and is most frequently due to GI haemorrhage, infection, malnutrition, fluid/electrolyte imbalance, coagulation abnormalities or congestive heart failure.^{8 28}

CONCLUSION

Although CCS was first documented almost six decades ago, there is still much to learn about this disorder, particularly regarding its aetiopathogenesis and evidence-based efficacious treatment. The protean nature of the syndrome's clinical presentations, endoscopic findings and histological features may confound clinician and pathologist alike. The histopathologist thus needs to be well versed in the many different faces of this disease. Effective communication between clinician and pathologist, adequate sampling of endoscopically abnormal and spared mucosa and a thorough knowledge of both typical and atypical features of this peculiar disease remain pivotal in rendering a timely and correct diagnosis of CCS.

Take home messages

- ▶ Cronkhite-Canada syndrome (CCS) is a peculiar acquired idiopathic gastro-entero-colopathy associated with characteristic ectodermal abnormalities.
- ▶ As CCS is rare and has extremely diverse clinical and pathological features, the histopathologist needs to be aware of the disorder's many faces and maintain a high index of suspicion in order to correctly diagnose this syndrome.
- ▶ CCS shows characteristic microscopic changes in endoscopically polypoid and spared mucosa, thus biopsies of both abnormal and normal appearing mucosa should be submitted for analysis by the clinician.
- ▶ Treatment of CCS remains problematic and the majority of patients have a poor outcome.

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