CASE 1 (Cronkhite-Canada syndrome - gastrointestinal polyposis for late starters)

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Discussion

Both gastric and duodenal biopsies reveal mucosa with a partly polypoid appearance. Numerous tortuous and cystically dilated glands / crypts are present in both specimens, which also show lamina propria expansion by oedema and a diffuse mixed inflammatory cell infiltrate. Some biopsies do not appear obviously polypoid but reveal similar glandular / crypt and lamina propria changes. No fundic gland component or dysplasia is present.

Differential diagnosis

The presence of multiple gastric polyps with hyperplastic, cystic and inflammatory features in an adult raises numerous diagnostic possibilities. Close correlation with the endoscopic findings (distribution and appearance of the polyps), clinical features and histology of uninvolved mucosa is of great importance when rendering a final diagnosis.

Hyperplastic polyps most often affect the antrum and are frequently multiple, but are seldom so numerous as to diffusely involve the stomach (gastric hyperplastic polyposis). The intervening mucosa usually demonstrates evidence of chronic gastritis, but no architectural distortion, prominent mucosal oedema, associated small bowel polyps or systemic manifestations are present.[1] Histologic overlap exists with *gastritis cystica polyposa* which encompasses polypoid gastric lesions with hyperplastic mucosal features and deeper lying misplaced glands / epithelium, most frequently seen in the vicinity of prior gastric surgery.

Fundic gland polyps are usually multiple, small, limited to the fundus / corpus, comprise cystically dilated fundic glands with abundant parietal and chief cells, and are not associated

with abnormalities of the intervening mucosa. These polyps may occur in a syndromic setting (familial adenomatous polyposis and its attenuated variants, as well as the recently described gastric adenocarcinoma and proximal polyposis of the stomach/GAPPS).[2,3]

Menetrier's disease may result in decidedly polypoid gastric mucosa and is associated with significant clinical disturbances including diarrhoea, protein-losing enteropathy and peripheral oedema. The hyperplastic foveolar pathology in this disorder is virtually always limited to the proximal stomach and not accompanied by a significant degree of muosal oedema, pronounced inflammation or abnormalities of the grossly spared antral mucosa.

Multiple gastric polyps with hyperplastic features may be seen in numerous rare gastrointestinal (GI) polyposis disorders, including *Peutz-Jeghers*, *generalized juvenile polyposis*, the *PTEN/hamartoma tumour (Cowden and Bannayan-Riley-Ruvalcaba)*, as well as *Cronkhite-Canada syndromes.* The presence of polypoid mucosa in both gastric and duodenal specimens from this patient points to a polyposis syndrome. Although some microscopic differences do exist between polyps in these diseases (e.g. the extensive arborizing smooth muscle of Peutz-Jeghers polyps), their reliable distinction is not possible on histologic grounds alone.[4] These disorders are, however, readily distinguished by their different extragastrointestinal (EGI) manifestations, age at presentation and histology of the intervening mucosa. Notably, *Cronkhite-Canada syndrome (CCS)* is the only one of these diseases which is non-hereditary (presents in late adulthood), has characteristic associated ectodermal abnormalities and demonstrates lamina propria oedema, inflammation and architectural disorder of the macroscopically spared mucosa.[5]

<u>Additional findings in this patient</u>

Upper endoscopy showed the nodular and polypoid mucosa to involve the distal stomach and the entire visualized duodenum. Lower endoscopy revealed a normal large bowel mucosa but for six descending / sigmoid colon polyps, which were removed. These demonstrated a predominantly conventional adenoma histology, but patchy cystic crypt dilation and focal serrated features were identified in some polyps. On specific enquiry, it was ascertained that the patient had consulted a dermatologist one year previously complaining of alopecia and nail pitting. She had also seen a dietician very recently due to an unexplained metallic taste in

her mouth. On examination she was found to have numerous hyperpigmented patches on her upper trunk.

Final diagnosis

Cronkhite-Canada syndrome involving the stomach and duodenum (but sparing the colorectum), with multiple colonic adenomas.

Cronkhite-Canada syndrome - the whole nine yards…

Introduction and epidemiology

Cronkhite-Canada syndrome (CCS) is a rare non-hereditary GI polyposis syndrome associated with ectodermal abnormalities and a high mortality.[6] The syndrome was first documented in two female patients in 1955 by Leonard Cronkhite Jr and Wilma Canada.[7] Over 400 cases have been reported worldwide since,[8] the majority in patients of Asian or European decent.[9] Approximately 75% of cases on record are from Japan.[10] The mean age at presentation is 59 years, but >80% of patients are over 50.[11] A slight male predominance exists (male:female ratio = 3:2).[9] Paediatric cases have been documented, but are extremely rare.[12]

Etiology and pathogenesis

Although the etiology of CCS is still uncertain, no convincing familial predisposition exists.[13] Various etiologies have been suggested, with autoimmunity favoured by many authors.[6,13-15] The latter etiopathogenesis is supported by CCS cases demonstrating elevated serum IgG4 and antinuclear antibodies, polyp infiltration by IgG4 plasma cells, as well as an association with hypothyroidism and other autoimmune diseases (including systemic lupus erythematosus, rheumatoid arthritis and scleroderma).[13,16] Ultrastructural study of 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 gland/crypt dilation and architectural distortion.[17]

Clinical findings

The commonest GI-related symptoms in CCS are diarrhoea, weight loss, abdominal pain, anorexia, haematochezia, nausea/vomiting and dysgeusia.[11] Protein-losing enteropathy with hypoproteinaemia and marked peripheral oedema, glossitis, xerostomia and weakness have also been reported.[8,11] Paraesthesias, seizures and tetany may occur and are likely secondary to electrolyte disturbances.[11]

Although primarily a GI polyposis syndrome, CCS is associated with numerous EGI manifestations. Ectodermal abnormalities are present in virtually all cases and include alopecia (scalp and body), nail dystrophy (thinning, splitting and separation from the nail bed) as well as skin hyperpigmentation.[7,11,18] The latter usually involves the extremities, face, neck, palms and soles; the buccal mucosa may also be affected. The lesions are characterised by light to dark brown macules, although vitiligo may occur. Other manifestations include anosmia, cataracts, thrombosis, hypothyroidism and cardiac failure.[8,11,19] 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.[7,11]

Pathology

The polyposis in CCS is diffuse and may involve any part of the GI tract, except for the oesophagus.[9] Selective sparing of the small intestine or colorectum may occur.[5]

CCS polyps are typically sessile with cystic to somewhat translucent features,usually varying in size from a few millimeters to 1,5 cm. Their endoscopic appearance has been described as “polyps upon polyps”, “rambling” and likened to a hydatidiform mole.[19] Gastric mucosal thickening may lead to giant rugal folds, particularly along the greater curvature.[11] Histologically, the mucosal polyps have an expanded oedematous lamina propria containing abundant mononuclear inflammatory cells and tortuous, dilated / cystic glands / crypts.[20,21] Microabscesses, erosions, crowded glands, scattered smooth muscle cells,[5] as well as prominent eosinophil,[22] mast cell[9] and IgG4 plasma cell[14] infiltration may be seen.

Of cardinal diagnostic importance is that the intervening non-polypoid (macroscopically spared) mucosa is characterised by similar histologic findings (lamina propria oedema, inflammatory cell infiltration and gland / crypt dilation).

Although biopsy of EGI lesions is seldom performed due to the characteristic clinico-pathologic features of CCS, previous studies of skin lesions have demonstrated increased epidermal melanin (with or without increased melanocytes), pigmentary incontinence, hyperkeratosis and non-specific perivascular inflammation.[23,24]

Differential diagnosis – see above

Risk for GI Malignancy

CCS polyps are considered hamartomatous (non-neoplastic) and their malignant potential remains controversial. Gastrointestinal carcinomas, including those of the stomach [25,26] and colorectum [27-31] have been documented in 15-25% of CCS patients at diagnosis.[32,33] Adenomatous change has also been reported, sometimes in close proximity to CCS polyps and carcinoma.[28,34] The association of CCS with serrated adenomas and colorectal adenocarcinoma has raised the possibility of a serrated adenoma-carcinoma sequence in these patients.[31] Reliable evaluation of GI malignancy risk in CCS is, however, hampered by the rarity of the syndrome and the fact that synchronous neoplasia may be coincidental due to the relatively advanced age of most patients.

Therapy and outcome

CCS is a rare disease and evaluation of therapeutic regimens has been problematic. Numerous treatment approaches, including aggressive nutritional support, antibiotics, histamine receptor antagonists, immune suppression (corticosteroids, azathioprine) and surgery - usually in different combinations - have had variable success.[6,9,35] Corticosteroids remain the mainstay of medical therapy. [33]

Overall outcome remains poor despite therapy. Although the data are dated, 5 year disease-related mortality is cited as 55%[10] and is most frequently due to GI haemorrhage, infection, malnutrition, fluid/electrolyte imbalance, coagulation abnormalities or congestive heart failure.[11]

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