A Case of Cronkhite-Canada Syndrome and a Review of Gastrointestinal Polyposis Syndromes

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Case Report

A 78-year-old Chinese man presented with weight loss, diarrhea, and an altered sense of taste for the past 6 months. The patient had a history of prostate and cecal cancers, for which he had undergone a right hemicolecction in 1988. At that time, 2 of 18 lymph nodes were positive. Since then, the patient has been undergoing periodic surveillance colonoscopies, and hyperplastic polyps have occasionally been identified and removed. In 2000 and 2003, his colonoscopies had normal findings. In 2007, a colonoscopy revealed a normal anastomosis and a large inflammatory polyp 60 cm within the descending colon.

On physical examination, the patient did not appear cachectic, and his abdomen was soft, nontender, and nondistended. He had hemoccult-positive stool. Of note, he had hyperpigmentation of both hands, alopecia, and atrophic nail changes (Figure 1). His carcinoembryonic antigen level was 3.3 ng/mL, his hemoglobin level was 14.4 g/dL, and his albumin level was 3.4 g/dL.

The patient underwent an upper endoscopy and colonoscopy to further investigate his condition. The upper endoscopy revealed a carpet of predominantly sessile polyps coating the gastric body, antrum, and duodenum (Figure 2). Multiple new polyps were found in the patient’s remaining colon and rectum (Figures 3 and 4). Pathologic review of all specimens demonstrated multiple benign, juvenile-like polyps with cystically dilated and distorted hyperplastic glands; marked stromal edema; and a mixture of inflammatory cells, including eosinophils. In addition, there was a small adenoma in the...
antrum, a small tubular adenoma in the rectum, and a microscopic focus of moderate-to-severe dysplasia in the duodenum. Results of a gastric CLO test were negative, and no Helicobacter organisms were seen in gastric or duodenal specimens.

The patient underwent a small bowel follow-through, which revealed multiple jejunal and ileal polyps (Figure 5). A computed tomography scan of the abdomen and pelvis with intravenous contrast had unremarkable findings. The patient’s prostate-specific antigen level was 3.3 ng/mL, his erythrocyte sedimentation rate was 2 mm/hr, and his serum gastrin level was 406 pg/mL; in addition, testing for antinuclear antibody was negative. Genetic testing of peripheral blood revealed no adenomatous polyposis coli or MutY human homologue germline mutations. Subsequent upper enteroscopy, colonoscopy, and biopsies of duodenal, jejunal, and colonic polyps were performed after the patient was placed on proton pump inhibitor therapy. The findings of these procedures were similar to those from the first set of procedures, although the atypia in the duodenal polyp specimens had regressed.

**Discussion**

A number of syndromes exhibit polyposis of the gastrointestinal tract. Our patient is an unusual case, as he had both upper and lower gastrointestinal polyposis with anatomic distributions and unique histopathologies that were consistent with the rare Cronkhite-Canada syndrome (CSS).

Our patient had widespread non-neoplastic polyposis throughout the stomach, small intestine, and colon. The pathology of these polyps was very similar to that of juvenile-type polyps, but it was unique in that the stroma showed striking edema and eosinophilic inflammation. The diagnosis of this patient (as with any case of CCS) involves a clinicopathologic correlation of endoscopic, pathologic, and cutaneous features. Patients may have dysgeusia and diarrhea and may be positive for antinuclear antibo-
Approximately 400 cases of CCS have been reported worldwide, mainly from Japan. The characteristic pathology of CCS polyps, which was seen in our patient, consists of cystic gland dilation and elongation with variable hyperplasia, stromal edema, and eosinophilic inflammation (Figure 6). Adenomatous polyps may occasionally develop. CCS patients also have an increased risk of gastric and predominantly left-sided colon cancers.

The 5-year mortality rate for CCS has been reported to be 55%. Complications include gastrointestinal bleeding, intussusception, rectal prolapse, portal vein thrombosis, membranous glomerulonephritis, and protein-losing enteropathy. Forty-one percent of patients also have adenomas, including serrated adenomas, which are precursor lesions to colorectal cancer; they are associated with a 15% increased risk of cancer development. The most common sites for malignancy are the sigmoid colon and rectum, although our patient had prior right-sided colon cancer. Gastric cancer has been reported in 32 Japanese patients with CCS. These gastric cancers were usually large in size, well differentiated, and generally limited to the submucosa.

CSS therapies have included corticosteroids for treatment of protein-losing enteropathy, weight loss, and diarrhea; nonsteroidal anti-inflammatory drugs for suppression of polyps; and proton pump inhibitors for suppression of acid. Our patient was treated with sulindac (150 mg twice daily), pantoprazole sodium (Protonix, Wyeth), and prednisone. He also received endoscopic surveillance.

Other polyposis syndromes involve different segments of the gastrointestinal tract (Table 1). These polyps can be classified as hamartomatous, adenomatous, or hyperplastic in nature. Hamartomas are lesions that result from disorderly proliferation of normally occurring tissue with varying degrees of hyperplasia, inflammation, and fibrosis. CCS is considered to be a hamartomatous polyposis syndrome. The distribution and pathology of polyps in CCS patients are distinct. CCS is differentiated from other hamartomatous polyposis syndromes by its widespread polyp distribution in the stomach, small bowel, and colon. Peutz-Jeghers syndrome involves hamartomatous lesions throughout the gastrointestinal tract, mainly in the jejunum, followed by the colon, and then the stomach. In addition, these patients often have associated extraintestinal manifestations, such as pigmented macules in the skin and mouth. Symptom onset usually occurs prior to 30 years of age. Juvenile polyposis syndrome develops before 10 years of age and is characterized by hamartomatous polyps with an inflammatory component; these polyps are usually found in the colon and, to a much lesser degree, in the stomach and small intestine.

Adenomatous polyposis syndromes are characterized by inheritance of an abnormal autosomal dominant gene that results in multiple colorectal adenomatous polyps. Familial adenomatous polyposis (FAP) usually involves the colon and rectum and, to a much lesser extent, the stomach and small bowel. In FAP patients, the risk of adenomas progressing to colon cancer approaches 100% by the time these patients are 50 years of age.
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Age of symptom onset</th>
<th>Transmission</th>
<th>Distribution of polyps</th>
<th>Histology</th>
<th>Extraintestinal manifestations</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplastic polyposis syndrome</td>
<td>&gt;40 years</td>
<td>Familial clusters</td>
<td>0% 0% 100%</td>
<td>Hyperplastic polyps, sessile serrated adenomas</td>
<td>None</td>
<td>Colon cancer (mostly right-sided)</td>
</tr>
<tr>
<td>Cronkhite-Canada syndrome</td>
<td>50–60 years</td>
<td>Sporadic</td>
<td>100% 50% 100%</td>
<td>Hamartomatous polyps (juvenile type) exhibiting glandular hyperplasia, cystic dilation, mucosal edema, and eosinophilic inflammation</td>
<td>Alopecia, dermal hyperpigmentation, onychodystrophy, diarrhea, protein-losing enteropathy, dysgeusia</td>
<td>Cachexia, colon cancer (mostly left-sided)</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>10–30 years</td>
<td>Autosomal dominant</td>
<td>25% 64–96% 25–35%</td>
<td>Hamartomas in the stomach and small bowel, adenomatous polyps in the colon</td>
<td>Mucocutaneous melanosis (mostly in the lips and buccal mucosa)</td>
<td>Colon, gastric, pancreatic, breast, and/or gynecologic cancers</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>15–20 years</td>
<td>Autosomal dominant</td>
<td>10–30% 10% 100%</td>
<td>Adenomas</td>
<td>Hypertrophy of retinal pigment epithelium, brain tumors (Turcot syndrome), epidermoid cysts, mandibular osteomas, desmoids, thyroid tumors (Gardner syndrome)</td>
<td>Colon, duodenal, and/or thyroid cancers</td>
</tr>
<tr>
<td>Juvenile polyposis syndrome</td>
<td>&lt;10 years</td>
<td>Autosomal dominant</td>
<td>14% &lt;10% 100%</td>
<td>Hamartomas with an inflammatory component, usually solitary in nature, and commonly found in the rectum. Adenomas and hyperplastic polyps are less common.</td>
<td>Rectal bleeding, protein-losing enteropathy, intussusception</td>
<td>Colon and/or gastric cancers</td>
</tr>
<tr>
<td>Cowden syndrome</td>
<td>9–20 years</td>
<td>Autosomal dominant</td>
<td>20% 20% 30%</td>
<td>Hamartomas</td>
<td>Facial trichilemmomas, macrocephaly, mucocutaneous lesions, acral keratoses, thyroid disease, breast disease</td>
<td>Breast, thyroid, reproductive organ, and/or colon cancers</td>
</tr>
</tbody>
</table>

Data from Rosai J14; Mills SE, et al15; Kumar V, et al16; Brunicardi FC, et al17; Chandrasoma P18; Townsend CM Jr, et al19; and Margulis A.20
Hyperplastic polyps are often found in the rectum and are considered to be the most common type of nonmalignant colonic polyp. Hyperplastic polyposis syndrome is a specific entity in which hyperplastic polyps are found in abundance throughout the colon in the absence of gastric or small bowel involvement. Diagnostic criteria for hyperplastic polyposis syndrome include: 5 or more hyperplastic polyps proximal to the sigmoid colon, 2 of which are larger than 1 cm; any number of hyperplastic polyps proximal to the sigmoid colon in a patient who has a first-degree relative with hyperplastic polyposis; or, more than 30 hyperplastic polyps throughout the colon.15,19 This syndrome has a male predominance and is more common in patients over 40 years of age. Usually, the polyps are large, flat, and found along haustral folds. Polyps located in the proximal colon are usually sessile, serrated adenomas, which lead to an increased risk of right-sided colon cancer.19,20 CCS polyps have been described and interpreted as hyperplastic in appearance, but they are most appropriately characterized as hamartomatous and are distinct from hyperplastic polyps.

When encountering an unusual number or distribution of polyps during an endoscopy, clinicians can find it helpful to examine the entire gastrointestinal tract for additional involvement and to scrutinize the histopathology of the polyps. Recognition of extraintestinal manifestations also facilitates accurate identification of polyposis syndromes.

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References


Review

Cronkhite-Canada Syndrome: An Acquired Condition of Gastrointestinal Polyposis and Dermatologic Abnormalities

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Cronkhite-Canada syndrome (CCS) is a noninherited condition associated with high morbidity and characterized by gastrointestinal hamartomatous polyposis,
alopecia, onychodystrophy, hyperpigmentation, and diarrhea. Seshadri and colleagues present a typical case of CSS and provide a succinct review of the syndrome’s diagnosis and management.1

The case report by Seshadri and colleagues describes an elderly Asian man who presented with weight loss, diarrhea, dysgeusia, and the dermatologic triad of hyperpigmentation, alopecia, and dystrophic nails.1 Subsequent endoscopic and radiologic evaluation revealed sessile polyps in the stomach, small bowel, and colon. Histopathologic review of biopsies obtained from these polyps showed cystically dilated and distorted glands with inflammatory infiltration and edematous changes of the lamina propria; these findings are consistent with juvenile or inflammatory polyps. Based on clinical features, endoscopic and radiologic findings, and histopathology, a diagnosis of CCS was correctly made.

Despite being first described over 50 years ago, CCS has an obscure etiopathogenesis.2 Given increased immunoglobulin (Ig)G4 mononuclear cell staining in CCS polyps, an autoimmune mechanism may be involved.3 CCS can develop in all ethnic groups, and symptomatic disease onset occurs at a mean age of 59 years. Diarrhea and dysgeusia are the most common initial symptoms, with the dermatologic symptoms of alopecia, hyperpigmentation, and onychodystrophy often occurring later.4 Most CCS patients exhibit all of the cardinal manifestations of the syndrome.3 Polyps in CCS patients can develop throughout the gastrointestinal tract (except for the esophagus) and are non-neoplastic hamartomas.3,4 Nevertheless, there is concern that CCS polyps may possess malignant potential, as evidenced by the dysplastic intestinal changes noted by Seshadri and coworkers and by reports of gastric, colon, and rectal cancers in patients with CCS.1,5-11

As demonstrated in the report by Seshadri and colleagues, CCS is a clinicopathologic diagnosis based on features of malabsorption in the setting of characteristic clinical, endoscopic, radiologic, and histologic findings.1 Although CCS often has characteristic features, the differential diagnosis includes a number of polypoid syndromes, including familial adenomatous polyposis, Peutz-Jeghers syndrome, Cowden disease, and juvenile polyposis. Usually, it is not difficult to distinguish CCS from these polypoid syndromes, as each exhibits its own characteristic clinicopathologic features.12 However, the endoscopic and histologic features of CCS polyps and juvenile polyps overlap and may appear identical.13 A useful distinction between these two types of polyps is that the mucosa among CCS polyps is histologically abnormal, revealing edema, congestion, and inflammation of the lamina propria; in contrast, the mucosa among juvenile polyps is histologically normal.13 In addition, IgG4 plasma cell infiltration occurs in CCS polyps, and IgG4 staining of hamartomatous intestinal polyps may provide additional information when evaluating polyposis syndromes.3,14 The considerable overlap among the endoscopic and histologic features of CCS polyps and polyps in other polyposis syndromes makes CCS a clinicopathologic diagnosis that cannot be made solely based on polyp histology.

The question of whether polyps in CCS patients possess malignant potential is controversial. As seen in the report by Seshadri and colleagues, the risk of colorectal neoplasia appears to be increased in CCS patients.1 There are case reports suggesting that both typical and serrated adenomatous polyp pathways may be involved, and the overall risk of colorectal cancer has been suggested to be as high as 25%.6,11,15 In the largest single-center case series conducted in CCS patients to date, the incidence of colorectal neoplasia within the follow-up period was high (adenomas, 71%; cancer, 14%).13 It is unknown whether the duration and/or extent of polyp formation accelerate the risk of neoplasia in CCS patients. One possibility is that the chronic generalized mucosal inflammation in CCS may increase neoplastic transformation similar to the inflammation-induced mutagenesis of idiopathic inflammatory bowel disease.

The risk of colorectal cancer may warrant aggressive screening in CCS patients. It may be extremely difficult—in fact, nearly impossible—to endoscopically detect background malignant polyps or concurrent adenocarcinoma, given the myriad of inflammatory-type polyps in CCS patients.16 A recommended solution to this dilemma is to perform a repeat endoscopy after successful treatment, as treatment causes remission of most CCS polyps that respond to therapy, at which time otherwise obscured adenomas or cancer may be revealed.

Given the rarity of CCS, there are no evidence-based therapies, and no systematic investigations of medical or surgical interventions have been conducted to guide management. Numerous treatments have been attempted in CCS patients, with varying degrees of success. These treatments include hyperalimentation, corticosteroids, H2-receptor antagonists, antibiotics, acid suppression, cromolyn sodium, anabolic steroids, surgery, and combinations of these therapies.17 Corticosteroids are considered the mainstay of medical treatment for CCS. The typical steroid treatment regimen is 40 mg of prednisone for
1 week, with a 5-mg decrease every week until the patient is tapered off. In one study, a symptomatic response was seen within 3 months in 10 of 11 CCS patients treated with this regimen. However, relapse of symptoms is common during the taper of corticosteroids; therefore, a steroid-sparing strategy has been employed with the immunomodulatory agent azathioprine in the previously mentioned study. Five CCS patients who responded to corticosteroid treatment were placed on immunomodulatory therapy in the form of azathioprine (2 mg/kg/day); these patients achieved maintenance of clinical remission and no relapse after approximately 5 years of follow-up.

Summary

The report by Seshadri and colleagues describes a patient diagnosed with the rare gastrointestinal polyposis syndrome of CCS based on a combination of clinical, endoscopic, and pathologic findings. The diagnosis of CCS should be considered in patients with gastrointestinal hamartomatous polyps, diarrhea, and the dermatologic triad of alopecia, hyperpigmentation, and onychodystrophy. Malignant transformation of CCS polyps may occur, and the risk of colorectal cancer may warrant aggressive screening in CCS patients. Immunosuppression with corticosteroids or long-term azathioprine therapy may eradicate or lessen manifestations of CCS.

References