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Case Report

A Case Report of Cronkhite-Canada Syndrome Complicated by Membranous Nephropathy

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Cronkhite-Canada syndrome · Polyposis syndrome · Membranous nephropathy · Proteinuria · Rituximab

Abstract
Cronkhite-Canada syndrome (CCS) is a very rare disorder with less than 500 reported cases. It is characterized by extensive gastrointestinal polyposis and ectodermal anomalies including alopecia, cutaneous hyperpigmentation, and onychodystrophy. Only 3 cases of associated kidney disease (membranous nephropathy [MN]) have been reported. A 71-year-old male with CCS was referred for further evaluation of proteinuria. The patient initially presented with abdominal discomfort, weight loss, dysgeusia, skin hyperpigmentation, alopecia, and dystrophic nails. Endoscopic evaluation showed widespread gastrointestinal nodular inflammation and polyps. Histopathology was consistent with CCS. Initial treatment was with prednisone, azathioprine, and ranitidine. He had moderate clinical improvement but developed nephrotic-range proteinuria. Renal biopsy showed MN, and cyclosporine was started. The patient had significant improvement in his CCS manifestations; however, his proteinuria and renal function worsened. Rituximab was added to his regimen of cyclosporine and azathioprine, which resulted in remission of his MN, marked improvement in his polyposis, and near resolution of his cutaneous symptoms. This case represents a unique presentation of CCS associated with MN treated with rituximab. The excellent clinical response observed for both CCS and MN advocates consideration of this treatment, especially for refractory disease.

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Introduction

Cronkhite-Canada syndrome (CCS) is a very rare, noninherited disease that involves widespread hamartomatous gastrointestinal polyposis and variable abnormalities of ectodermal tissues including alopecia, cutaneous hyperpigmentation, and onychodystrophy [1]. Other prominent symptoms include weight loss, protein-losing enteropathy, diarrhea, abdominal pain, nausea and vomiting, dysgeusia, and atrophic tongue [2]. Although the literature reveals a number of gastrointestinal and malignant complications, only a few cases of associated nephropathy (membranous) have been reported [3, 4]. The suspected etiology of CCS is autoimmune, and corticosteroids are the mainstay of treatment. Steroid-resistant CCS is rarely reported, and in cases of refractory CCS, cyclosporine, azathioprine, and infliximab have been used with some success. Herein is summarized the case of a patient with CCS who developed membranous nephropathy (MN) and had remission of both conditions with rituximab. After careful review of the literature, this represents only the fourth reported case of CCS associated with nephropathy and the first case of CCS treated with rituximab.

Case Report

A 71-year-old male with a past medical history significant for calcium pyrophosphate deposition disease presented with dysgeusia, abdominal discomfort, and weight loss. He had developed dysgeusia and tongue changes followed by nail changes and hair loss, and subsequent anorexia with a 45-pound weight loss. He had no family history of autoimmune disease, colonic polyps or malignancy. Examination showed alopecia, geographic tongue, onychodystrophy, and hyperpigmentation on bilateral arms. Laboratory studies within normal limits included complete blood count, electrolytes, creatinine (0.7 mg/dL), urinalysis, liver function tests, albumin, folate, vitamin B_{12}, zinc, vitamin D, copper, selenium, vitamin E, celiac antibodies, erythrocyte sedimentation rate, antinuclear antibody, extractable nuclear antigen panel, serum protein electrophoresis, and free light chains. Prealbumin was 15.9 mg/dL (18–36). Three months prior to presentation, a colonoscopy performed for evaluation of rectal bleeding at an outside facility revealed diverticulosis, an anal fissure, and a small tubulovillous adenoma in the rectum. Upper endoscopy was also performed showing erythema, congestive gastropathy, gastric polyps, and nodular, diffusely polypoid appearing small bowel with fissuring and scalloping. Biopsies of the polypoid excrescences and the mucosa throughout showed severely edematous, atrophic stroma with glandular loss and dilated/cystic glands, and inflammation with mononuclear and eosinophil infiltrate. Immunohistochemical stain was negative for Helicobacter organisms. Video capsule endoscopy revealed nodular mucosa throughout the small bowel and denuded intestinal villi.

The patient was diagnosed with CCS given his typical clinical history and exam, and consistent biopsy findings. The diagnosis of CCS is reviewed in the discussion section. He was treated with prednisone 40 mg daily, ranitidine, and fexofenadine, and referred to medical nutrition. Azathioprine was initiated 3 months later, and steroids were tapered to 5 mg daily. He had some ectodermal recovery with hair growth and nail improvement. Antegrade double balloon enteroscopy showed multiple sessile gastric polyps and nodular/polypoid mucosa throughout the small bowel with some return of villi and resolution of metaplasia on random mucosal biopsies. As is typical of CCS, the polyps showed no characteristic architectural or cytological features, but consisted of expanded edematous lamina propria with scattered inflammatory cells (chiefly mononuclear and eosinophils), with absent villi, regenerative

changes without dysplasia and focal positivity (>40 per high-power field) for IgG4 plasma cell immunohistochemical staining (Fig. 1). The clinical response to immunosuppressive therapy further substantiated the initial CCS diagnosis.

One year after presentation, the patient developed proteinuria (grade 1 on urinalysis) and subsequent 24-h urine collection showed 1,610 mg protein. His medications at that time included prednisone 5 mg daily, azathioprine 75 mg daily, ranitidine, fexofenadine, and allopurinol (because of an interim diagnosis of gout). He denied the use of nonsteroidal anti-inflammatory medications. Total protein, albumin, hepatitis panel, human immunodeficiency virus, lipids, and urine protein electrophoresis were normal. He was monitored with serial laboratories including urinalysis and 24-h urine protein collection. He developed overt hypothyroidism requiring treatment and had worsening CCS symptoms requiring increased prednisone dose. His proteinuria progressed to nephrotic range (4.4 g on 24-h urine collection). Renal biopsy showed membranous glomerulonephritis (Fig. 2). Cyclosporine, losartan, and torsemide were added to his regimen of prednisone and azathioprine.

With the initiation of cyclosporine and tapering off prednisone his CCS symptoms improved dramatically (e.g., substantial weight gain, new nail growth, growth of hair and eyebrows, return of taste, and resolution of geographic tongue). His proteinuria, however, was relatively stable, possibly exaggerated by his weight gain. Surveillance esophagogastroduodenoscopy showed multiple subcentimeter gastric sessile polyps and nodular/polypoid duodenal mucosa with ongoing mucosal changes including edema and crypt distortion. Colonoscopy showed greater than 25 larger polyps and innumerous 1- to 5-mm colonic and rectal polyps. Pathology of biopsied polyps showed background changes compatible with CCS (lamina propria edema and glandular hyperplasia and disarray) as well as fragments of tubular adenoma in the majority of the biopsies. Given the extensive nature of his polyposis, total colectomy was discussed, but close monitoring was pursued while observing for treatment effect. Genetic testing for other polyposis syndromes was negative.

His proteinuria did not resolve and eventually worsened coincident with declining glomerular filtration rate. A second renal biopsy was completed which did not show any superimposed process. Rituximab 1,000 mg i.v. was administered times two (days 1 and 15) along with prophylactic antimicrobials in addition to his regimen of cyclosporine and azathioprine (continued given good CCS symptom response). Rituximab resulted in a striking remission of his MN, and azathioprine was stopped. A substantial decrease in polyp burden and mucosal normalization was seen on a subsequent colonoscopy. Cycle two of rituximab was given 6 months later and repeat colonoscopy showed only 2 small polyps consistent with benign tissue and no other abnormalities of the entire colon. He has since been maintained for over 2 years with sustained remission of MN (urine protein absent) and CCS symptoms, and near resolutions of gastrointestinal pathology on cyclosporine (maintaining goal trough levels of 75–125 ng/mL) and rituximab 1,000 mg every 12 months.

Discussion

CCS is a relatively new syndrome, first described in 1955 and later coined in 1966 [5, 6]. CCS is extremely uncommon with only 450 reported cases and an estimated incidence of 1 per million in one of the largest case series from Japan [2, 7]. CCS can develop in all ethnic groups, but the majority of cases are reported from Japan [1, 7]. There is a minor male to female predominance and onset is in the fifth to sixth decades [2, 8]. Hypogeusia has been described as the dominant initial symptom, typically followed by gastrointestinal symptoms and ensuing

ectodermal changes [1, 7]. Malabsorption relating to gastrointestinal polyposis may induce the ectodermal findings. However, alopecia, skin hyperpigmentation and dystrophic nails can less commonly proceed the diarrhea [7]. Furthermore, the hair and nail changes may not improve with restored nutrition [9].

Polyps involve the stomach, intestines and colon, but spare the esophagus. Polyp features are typical to those of benign juvenile or hamartomatous polyps with cystic dilated and distorted glands, submucosal edema especially in the lamina propria, and mild inflammatory cell infiltrate including eosinophils [2, 9]. Approximately half of patients have some nonneoplastic adenomatous changes, either tubular or serrated [2, 9, 10]. The gastrointestinal mucosa is also significantly altered, especially in the small bowel [2, 9]. This entails edema, distortion of crypt architecture, villous atrophy, nodulations, atrophic or hyperplastic changes, and mixed inflammatory infiltrate. CCS diagnosis is based on endoscopic findings of gastrointestinal polyposis with appropriate histology and compatible history and physical exam [1]. It is usually not difficult to distinguish from other polyposis syndromes as each has a characteristic presentation.

The disease is sporadic, and the etiology is not well elucidated, but an autoimmune cause is suspected [1, 8]. Cases have been associated with elevated autoimmune markers including antinuclear antibodies and IgG4 [8]. IgG4 plasma cell infiltration on gastrointestinal biopsies and clinical improvement with immunosuppressive therapy particularly support an autoimmune etiology [3, 8]. Moreover, the syndrome is associated with other autoimmune conditions [1]. The present case supports an autoimmune etiology given associated MN and hypothyroidism and marked response to immunosuppressive therapy.

Complications include gastrointestinal bleeding, protein-losing enteropathy, malnutrition, vitamin deficiencies, intussusception, and prolapse [9]. The incidence of gastric and colorectal cancer in patients with CCS is around 15% [2]. Multiple reports document a transition from hamartomatous polyps to adenomatous polyps with dysplasia [9]. Malignancy may also arise from the abnormal gastrointestinal mucosa [10]. Optimal screening is not defined due to the rarity of CCS, but regular to annual endoscopic surveillance is suggested depending on the degree of polyposis [2].

Spontaneous regression occurs in 5–10% [2]. The treatment of CCS is unclear, largely due to its scarcity. Treatments have included nutritional support, antihistamines, acid suppression, antibiotics, glucocorticoids, immunosuppressive medications, and surgery with mixed success [8, 11]. Treatment often involves a combination of the aforementioned therapies. Steroids are felt to be the core of medical treatment, but relapse is not uncommon with tapering. No regimen has been shown to be consistently effective and the optimal duration of therapy is unclear [2]. Azathioprine and calcineurin inhibitors have been effective in maintaining remission in some cases after steroid taper [8, 12]. Combination therapy with azathioprine and cyclosporine has been used in steroid-resistant cases [13]. There are three recent case reports using anti-tumor necrosis factor antibody therapy with success [14, 15]. Overall, reports of steroid-sparing therapies in CCS are sparse.

Cyclosporine in the present case evoked a response superior to azathioprine, approaching remission of his symptoms. This is the first report of using rituximab for treatment of CCS and shows that rituximab can effectively induce remission, most importantly with near resolution of the patients' colonic polyposis, sparing him from colectomy.

Rituximab, interestingly, also induced complete and sustained remission in the patient's associated MN. MN is the sole known renal complication associated with CCS and is described in only 3 prior cases [3, 4]. One case of MN responded well to prednisone [3], while another achieved remission with cyclosporine although later relapsed [4]. Our case demonstrates that

rituximab should be considered for resistant MN especially given the profound effect on the patient's CCS.

The diagnosis of CCS should be considered in patients with gastrointestinal symptoms and polyposis, and ectodermal irregularities. It is a rare, but progressive disease with poor prognosis marked by 5-year mortality rates as high as 55%, largely secondary to associated complications [2, 4]. We described an unusual complication of MN and an excellent CCS treatment outcome. Cyclosporine showed a superior therapeutic effect over azathioprine and rituximab resulted in near resolution of colonic polyps and mucosal changes. The management of CCS is unclear. This case adds vital knowledge to help establish a therapeutic strategy for steroid-resistant CCS. Such immunosuppressive regimens may more effectively treat symptoms and polyposis, and lead to a favorable prognosis.

Statement of Ethics

The present study adhered to the Declaration of Helsinki, and the patient gave consent for the details of his case to be published.

Disclosure Statement

The authors declare no competing financial interests. The authors also declare that they have no conflicts of interest.

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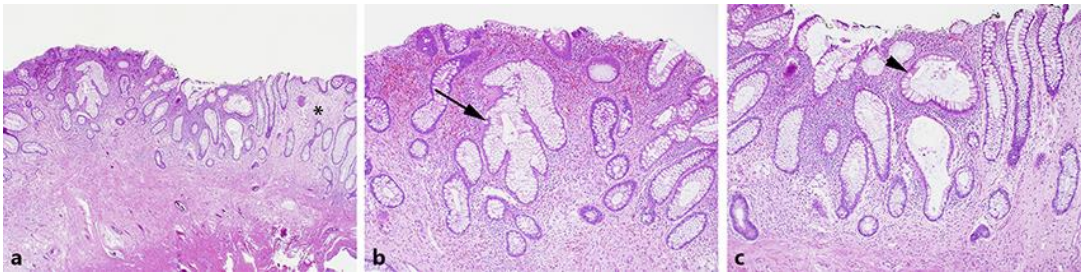

Fig. 1. Histology of colon polyp biopsies. Features of Cronkhite-Canada syndrome include an expanded lamina propria (asterisk) as well as a mild lymphoid infiltrate (**a**, H&E, ×40). Glands show excessive branching (**b**, arrow, H&E, ×100) and dilation with mucous filling (**c**, arrowhead, H&E, ×100).

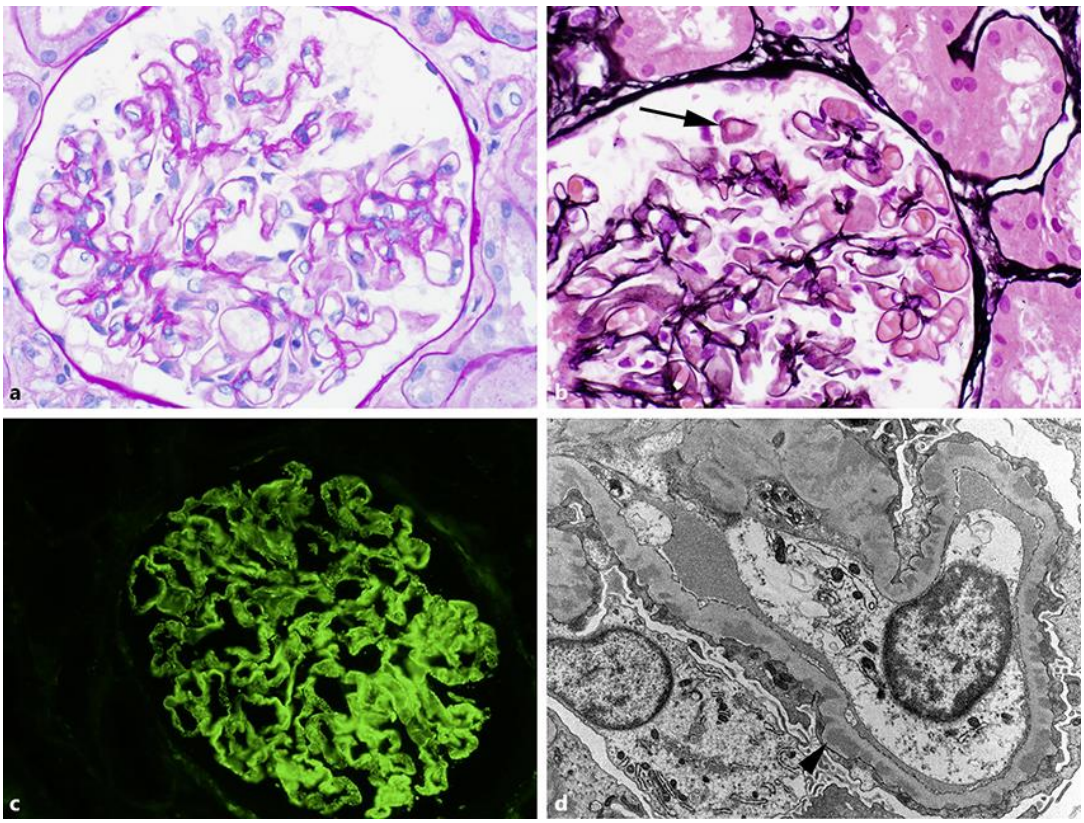

Fig. 2. **a** Pathology of membranous nephropathy. The glomerular basement membranes show subtle thickening and remodeling (periodic acid-Schiff, ×600). **b** Focal spikes are noted (arrow), especially when sectioned tangentially (Jones silver stain, ×600). **c** Immunofluorescence studies show strong granular peripheral capillary loop reactivity for IgG, C3, kappa, and lambda (IgG, ×400). **d** Subepithelial immune complex deposits are present diffusely on electron microscopy studies (arrowhead, ×12,000).