Dig Dis Sci (2012) 57:496–502
DOI 10.1007/s10620-011-1874-9

ORIGINAL ARTICLE

Clinicopathologic Features and Treatment Outcomes in Cronkhite–Canada Syndrome: Support for Autoimmunity

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Received: 17 May 2011 / Accepted: 12 August 2011 / Published online: 1 September 2011

Abstract
Background and Aims Cronkhite–Canada syndrome (CCS) is a noninherited condition, associated with high morbidity, and characterized by gastrointestinal hamartomatous polyposis, alopecia, onychodystrophy, hyperpigmentation, and diarrhea. All features may respond to immunosuppressive therapy, but little is known about the etiology. An autoimmune origin has been suggested but not proved. From a retrospectively selected cohort, we evaluated clinicopathologic features, including immunostaining for IgG4 (an antibody associated with autoimmunity), and therapeutic outcomes in a cohort of CCS patients to provide further insights into this disease.
Methods Cases included 14 consecutive CCS patients seen at the Mayo Clinic on whom tissue and follow-up were available. All histology was reviewed by an expert gastrointestinal pathologist. Immunostaining for IgG4 was performed on 42 polyps from CCS cases and on control tissues, including 46 histologically similar hamartomas [from juvenile polyposis syndrome (JPS)] and 20 normal mucosae (six stomach, three small bowel, and 11 colon). Clinical features and treatment outcomes were descriptive.
Results All CCS cases had both upper and lower gastrointestinal polyps; most had typical dermatologic features of alopecia, hyperpigmentation, and onychodystrophy; and most had evidence of protein-losing enteropathy. Ten patients (71%) had adenomatous polyps and 2 (14%) had colorectal cancer. IgG4 immunostaining was positive (>5 cells/HPF) in 52% of CCS polyps compared to 12% of JPS polyps ($P = 0.001$); IgG4 staining was negative in all other control tissues. Of 11 CCS patients treated with oral corticosteroids, 91% achieved remission. Relapse was common with steroid tapering. Five patients who initially responded to corticosteroids were maintained in remission on azathioprine (2 mg/kg/day) with no relapse after a median of 4.5 years.
Conclusions Immunostaining for the autoimmune-related IgG4 antibody is significantly increased in CCS polyps compared to disease and normal control tissues. Furthermore, immunosuppression by corticosteroids or long-term azathioprine may eradicate or lessen manifestations of CCS. These histologic findings and treatment responses are consistent with an autoimmune mechanism underlying CCS.

Keywords Cronkhite–Canada syndrome · Juvenile polyposis syndrome · Autoimmunity · Colorectal cancer risk · Treatment response

Abbreviations

CCS	Cronkhite–Canada syndrome
JPS	Juvenile polyposis syndrome
AIP	Autoimmune pancreatitis

Introduction

The Cronkhite–Canada syndrome (CCS) was first described in 1955 as a rare noninherited disorder manifested by

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diffuse gastrointestinal polyposis with associated ectodermal changes, including alopecia, hyperpigmentation, and onychodystrophy [1]. The potentially devastating clinical features of this entity have been described elsewhere in detail [1–8]. The polypoid lesions are nonneoplastic hamartomas with cystic dilation and typical glandular changes similar to those seen in either sporadic juvenile polyps or those associated with juvenile polyposis syndrome (JPS) [9]. In comparison, JPS is an inherited condition associated with mutations in the MADH4 and BMPR1A genes [10]. JPS is associated with an increased risk of gastrointestinal cancer but lacks the ectodermal changes typical of CCS and JPS polyps do not regress with steroid treatment [10, 11]. Compared to JPS, CCS polyps tend to be less pedunculated when seen endoscopically and may show enhanced edema in the lamina propria when evaluated histologically [12]. A critical diagnostic point is that the nonpolypoid mucosa of CCS is histologically abnormal (edema, dilated crypts), while the mucosa between JPS polyps is normal. Despite these differences, CCS and JPS can occasionally be confused both clinically and histologically. Therefore, additional objective criteria to distinguish these two conditions would be useful.

Little is known about the pathophysiology of the CCS, although it appears to be an inflammatory condition and treatment with immunosuppressing anti-inflammatory regimens often leads to complete clinical response and polyp regression [5, 7, 13–15]. Immunologic dysfunction has been suggested as an etiology raising the possibility of an autoimmune basis [16].

Few data are available to support the hypothesized autoimmune nature of this disorder other than the clinical signs of CCS often respond to immune-modulating therapy. Recently, inflammatory markers for other gastrointestinal autoimmune inflammatory disorders, namely, immunoglobulin G4 (IgG4)-associated systemic disease, have been studied. IgG4-associated systemic disease may present with the involvement of many organ systems, alone or in combination, including the pancreas (autoimmune pancreatitis, AIP), bile ducts (IgG4-associated sclerosing cholangitis), retroperitoneum (retroperitoneal fibrosis), salivary glands (sialoadenitis), and major duodenal papilla (papillitis) [17–19]. In AIP, the pancreatic manifestation of IgG4-associated systemic disease, high serum IgG4 concentrations, and tissue infiltration by IgG4-positive plasma cells provide a means of distinguishing inflammation from other conditions, such as cancer [20, 21]. IgG4 immunostaining of biopsy specimens has been reported to identify the presence of corticosteroid-responsive inflammatory conditions [22]. Furthermore, IgG4 antibodies to various food antigens have been reported and implicated in the pathogenesis of food hypersensitivity; IgG4 antibody-guided exclusion diets may improve symptoms in patients with irritable bowel syndrome [23–25].

Although neoplastic (or malignant) transformation has not been convincingly linked to CCS, many recent reports describe the development of adenomas and carcinomas in affected patients [26–37]. Serrated adenomas have also been described [38]. CCS can occur with a paucity of gastrointestinal polyps [39] and has also been documented after hemicolectomy for colorectal cancer [40].

In this retrospective CCS case series, we sought to document the clinical features, evaluate polyp histology for clues to the underlying pathophysiology, and describe the response to both steroids and the steroid-sparing agent azathioprine.

Materials and Methods

The investigation was approved by the Mayo Clinic Institutional Review Board and Biospecimen Subcommittee of the Mayo Rochester Research Committee.

Subjects

Cronkhite–Canada Syndrome

Patients were identified through a Mayo Clinic registry; the query dates were from January 1955 to December 2009. Clinical variables were abstracted from the medical records. For CCS, the inclusion criteria required that the patients have at least three documented signs of the disease, including ectodermal changes, malabsorption, and diffuse polyposis with a pathological diagnosis of typical CCS inflammatory polyps. Patients were excluded if they failed to meet these criteria or if there was further documented evidence of a family history of a typical polyposis syndrome or additional testing suggesting another etiology. A total of 14 patients met the criteria for CCS, including eight males and six females. The available information regarding possible pancreatic involvement was retrieved from medical records, including cross-sectional imaging, serum pancreatic enzymes, the presence of steatorrhea, and the need for pancreatic supplementation.

Controls

The primary control group was juvenile polyposis syndrome (JPS). The inclusion criteria required that the patients met clinical criteria for the syndrome and that they had been evaluated by a physician and/or geneticist trained

in the disorder. Patients were excluded if they failed to meet these criteria. A total of seven patients with JPS were selected. Additional controls included normal tissue from resection specimens, including the colon ($n = 11$), stomach ($n = 6$), and small bowel ($n = 3$).

Tissue Microarray Construction

Available tissues were obtained in paraffin-embedded blocks from the pathology archive. For CCS, there were a total of 42 separate tissues from 13 patients (36 polyps and six nonpolypoid colonic epithelium samples). For JPS, a total of 49 tissues were available from seven patients (46 polyps and three samples of normal colonic epithelium). For the remaining controls, one specimen was utilized from each patient based on the diagnosis. All tissues from CCS and JPS patients were reviewed by a pathologist blinded to the original diagnosis (S.S.); the diagnosis was confirmed as compatible with juvenile inflammatory or inflammatory polyps, consistent with all of the original diagnoses. A similar protocol was employed for the controls. A fresh section stained with hematoxylin and eosin (H & E) was cut from each block and three representative areas were designated by dotting the stained section with a permanent marker. Individual donor blocks were overlaid with the corresponding H & E slide and the areas for tissue microarray sampling were marked. Using instrumentation developed at the Mayo Clinic, three cylindrical cores of 0.6 mm in their greatest dimension were removed from each donor paraffin block and transferred to pre-molded recipient paraffin blocks at defined array positions. Recipient paraffin blocks contained holes of appropriate dimensions in a grid pattern, maximally 12 holes wide by 18 holes in length, allowing for 216 tissue cores per block. This construction design permitted multiple blocks with identical array patterns to be constructed simultaneously, serially sectioned at 5 microns, placed on charged glass slides, and stored at 4°C.

Immunohistochemistry

The IgG4 antibody (Zymed) was used. Immunohistochemical staining was performed using the En Vision+ system (Dako Corporation, Carpinteria, CA). Slides were heated in a 60°C oven for 1 h. Sections were deparaffinized in three changes of xylene, then rehydrated by exposure to an ethanol gradient and placed in preheated (98°C) 1 mM ethylenediamine tetraacetic acid retrieval buffer (pH 8.0) for 30 min. Slides were cooled in retrieval buffer for 5 min, rinsed in running tap water, and placed in Dako wash buffer (10× Tris-buffered saline with Tween 20) for autostaining. After heat-inactivated epitope retrieval, the slides were placed on the Dako Autostainer to be stained at room temperature for 30 min, as per antibody and detection specifications. The primary antibody was omitted in negative controls. In addition, the tissue arrays were stained with nonspecific rabbit immunoglobulin G (IgG) and mouse IgG_1, and the slides were reviewed by one of our senior experimental pathologists, who confirmed the lack of staining using these controls.

The IgG4 slides were graded by T.C.S., who was blind to all conditions; slides were scored using a 0–4+ scale, as follows: 0 = no staining (no epithelia available), 1 =0–5 cells/HPF, 2 = 6–10 cells/HPF, 3 = 11–30 cells/HPF, and 4 ≥30 cells/HPF. The final score was averaged for each set. The results were considered to be positive when a score of 2 or higher was achieved.

Statistical Analysis

A Chi-square test was used to analyze the data obtained by immunohistochemistry. Analyses were performed using JMP 5.1 Statistical Discovery Software (SAS Institute Inc., Cary, NC).

Results

Clinical Features: Cronkhite–Canada Syndrome

The patient demographics and clinical variables are summarized in Table 1. Most patients exhibited the majority of the cardinal manifestations of the syndrome, including gastrointestinal polyposis, skin hyperpigmentation, alopecia, and onychodystrophy. Laboratory evaluation revealed indirect evidence of malabsorption with hypoproteinemia. Serum albumin was low in all patients, with a range of 1.8–3.5 g/dl (normal >3.5 g/dl), suggesting protein-losing enteropathy. Quantitative stool fat was elevated in three patients (11, 23, and 96 g/24 h [normal 2–7 g/24 h]) and was normal in two patients. Anatomical locations of the polyps are reported in Table 1. The polyps occurred throughout the gastrointestinal tract, except for characteristic sparing of the esophagus. Five patients underwent surgical colectomy for the management of disease complications.

In regards to pancreatic evaluation, only 8 of 14 patients had radiographic imaging performed and all revealed normal pancreas parenchyma and duct with no biliary abnormalities. Serum amylase was measured and normal in five patients. Malabsorption was nearly universally seen in CCS based on the indirect measurements of serum albumin and total protein, and further analysis concluded that the process was temporally associated with polyposis and mucosal inflammation, and decreased with steroid treatment.

Table 1 Demographic and clinical variables in Cronkhite–Canada syndrome

Demographics	
Gender	Male 8; female 6
Age at diagnosis, median (quartiles)	66 (51.75)
Clinical presentation	
Alopecia	93%
Onycholysis	86%
Protein-losing enteropathy	93%
Hyperpigmentation	71%
Diarrhea	86%
Abdominal pain	79%
Hypogeusia	64%
Edema	57%
Hematochezia/melena	64%
Polyp anatomical location	
Esophagus	0%
Stomach	100%
Duodenum	100%
Small bowel	71%
Colon and rectum*	100%

Total of 14 patients

* 13 patients had available colonoscopy data

Ten patients had adenomatous polyps removed by colonoscopic polypectomy (mean of 1.7 polyps per patient); one of these had two synchronous adenomatous polyps removed >5 years prior to the diagnosis of CCS, and the other nine had adenomas and CCS discovered concurrently. No adenoma had high-grade dysplasia. No serrated adenomas were identified. Two patients were diagnosed with stage I–II colorectal adenocarcinoma; neither patient had a history of adenomatous polyps and both had the cancer diagnosed concurrently with CCS.

Association of IgG4 Expression with CCS

From 13 patients with CCS, 42 polyps revealed positive staining with 0–5 cells/HPF in 20, 6–10 cells/HPF in 8, 11–30 cells/HPF in 8, and >30 cells/HPF in 6. From seven patients with JPS, 49 polyps revealed 0–5 cells/HPF in 43, 6–10 cells/HPF in 3, and 11–30 cells/HPF in 3; there were no occurrences of staining with >30 cells/HPF in this group. Figure 1 shows the significantly higher ($P = 0.001$) staining in CCS as compared to JPS. IgG4 expression was not associated with histopathologic severity, disease severity, neoplasia, relapse, or response to steroid medication in CCS polyps. Table 2 shows IgG4 within individual polyps taken from the same endoscopy. All normal controls were negative. Figure 2 shows representative photomicrographs of the IgG4 staining.

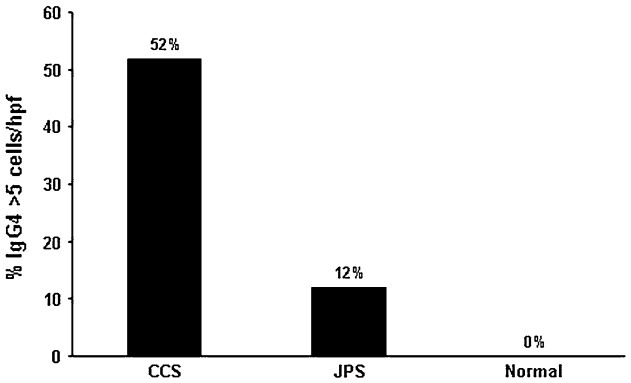

Fig. 1 IgG4 positivity (>5 cells/HPF) for Cronkhite–Canada syndrome (CCS), Juvenile polyposis syndrome (JPS), and normal controls

Table 2 IgG4 staining in hamartomatous polyps from patients with Cronkhite–Canada syndrome

Case, year	Polyps (*n*)	0–5 cells/HPF (*n*)	6–10 cells/HPF (*n*)	>10 cells/HPF (*n*)
1, 2004	C10	6	3	1
2, 1981	C1			1
2, 1982	SB1	1		
3, 1998	C3, SB1	2	1	1
3, 2004	C1, SB4	3	1	1
4, 2000	SB4			4
5, 2003	C3, A1*	3		1
6, 1995	G1	1		
7, 1997	C1, G1		1	1
8, 1999	C1	1		
8, 2000	C1, G1		1	1
9, 2000	C1, G1	1		1
10, 2000	C1			1
11, 2005	C1		1	
12, 2007	C1, SB1	1		1
13, 2008	C1		1	

C colon polyp, *A* colon adenocarcinoma, *G* gastric, *SB* small bowel polyp

* Adenocarcinoma of the colon in case 5 was negative for IgG4 staining

Treatment Response in CCS

Long-term follow-up data were available in 12 of the 14 CCS patients. Conservative therapy in the form of parenteral nutrition and antibiotics was attempted in one patient with little symptomatic improvement after 3 months, although the weight and albumin levels increased. Another patient was commenced on zinc supplementation (zinc acetate 50 mg orally once daily) with complete symptomatic response after 6 months but with persistent

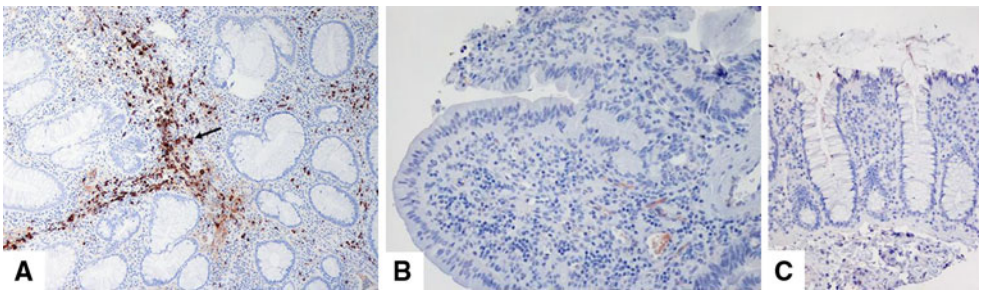

Fig. 2 Immunohistochemistry staining of IgG4. **a** Cronkhite–Canada syndrome (CCS) polyp showing >80 cells/HPF staining positive (*arrow*). **b** Juvenile polyposis syndrome (JPS) polyp showing the absence of staining. **c** Normal colon showing the absence of staining

endoscopic abnormalities. Eleven patients were treated with varying doses of steroids in a tapered regimen. The typical steroid treatment regimen was 40 mg of prednisone for 1 week, with a decrease by 5 mg every week until 20 mg a day, and then decrease by 2.5 mg every 2 weeks until it was tapered off. Symptomatic response to this regimen within 3 months was seen in 10 of 11 patients (8 of 10 had complete response and 2 of 10 had >50% response). One patient failed to respond to steroid therapy and was treated with serial endoscopic photocoagulation of gastric polyps. The available endoscopic follow-up in 11 patients showed complete polyp regression in five patients within 3 months of steroid therapy. Ten of 14 patients were treated with the combination of antihistamines and acid-suppressing medications in addition to steroids. Five of the 11 patients who responded to corticosteroid treatment were placed on immunomodulatory therapy in the form of azathioprine (2 mg/kg/day), with the maintenance of clinical remission and no relapse after 4.5 years of follow-up. Clinical remission was based on the absence of diarrhea and integumentary manifestations of CCS, maintenance of weight, and normal serum albumin.

One patient underwent partial colectomy and duodenotomy with subsequent colostomy in an attempt to remove polyp burden after relapsing upon steroid withdrawal; no further details were available. Another patient required subtotal colectomy with ileorectostomy for the treatment of refractory colonic polyposis and the repeated finding of tubular adenomas with low-grade dysplasia. After surgery, the patient has been in complete clinical remission after 2 years of follow-up. Two patients underwent laparoscopic-assisted total colectomy for complications of disease, namely, intussusceptions; both patients were subsequently placed on azathioprine with subsequent complete clinical response.

Discussion

This study examined key questions involving the clinical, pathologic, and treatment aspects of CCS. Because the syndrome is extremely rare, most of the available data comes from case reports and pooled analyses. This is the largest single-center series reported on CCS. As a result, several conclusions can be drawn concerning this disease. First, the infiltration of CCS polyps with IgG4 plasma cells supports an autoimmune process. Second, corticosteroids are effective in inducing remission in CCS. And, third, azathioprine is useful for maintaining disease remission.

Within this cohort of CCS patients, the characteristic clinical manifestations were present. Diffuse polyposis throughout the gastrointestinal tract with esophageal sparing and ectodermal abnormalities (alopecia, onychodystrophy, and skin hyperpigmentation) were seen in most patients. The laboratory findings in this study suggest that malabsorption with hypoalbuminemia is nearly universal, and all such manifestations typically responded to immunosuppressive therapy.

This study provides clues to the etiopathology of CCS by evaluating IgG4 mononuclear cell staining. The significant level of IgG4 in steroid-responsive polypoid tissue suggests autoimmunity. IgG4 is the least common of the Ig subclasses and cannot bind complement and, therefore, does not activate the classic pathway of complement [41]. High serum and tissue levels of this immunoglobulin are seen in only a few conditions, such as AIP, atopic dermatitis, parasitic disease, and pemphigus vulgaris [20]. Recent data also support the hypothesis that IgG4 tissue infiltration may be an organ-specific manifestation of an autoimmune process called IgG4-related systemic disease [17]. It is unknown whether CCS is associated with AIP or other conditions. In this study, there were no significant pancreatic abnormalities or other organ involvement suggesting IgG4-related systemic disease based on the limited available laboratory and radiographic data. CCS has been associated with autoimmune phenomena such as membranous glomerulonephritis [42]; this association was noted in the current study as well. However, the observation of increased IgG4 staining in CCS does not prove that this disorder is autoimmune.

Despite the clinical and genetic differences, CCS and JPS have enough histopathologic similarities that it can be

difficult to microscopically distinguish between these hamartomatous entities [12]. Our direct comparison between CCS and JPS hamartomatous polyps showed significantly higher numbers of IgG4-positive plasma cells in CCS. As in AIP and IgG4-associated cholangitis, a tissue analysis of IgG4 staining may help in differentiating these varying types of juvenile polyps. The serum levels of IgG4 were not evaluated in this study; future data would be valuable in this regard.

The question of whether the hamartomas in CCS possess malignant potential has been controversial. However, colorectal neoplasia risk appears to be increased in CCS. There are case reports to suggest that both typical adenomatous and serrated polyp pathways may be involved, and the overall risk of colorectal cancer has been suggested to be as high as 20–25% [26, 28–30, 38]. In this series, the incidence of colorectal neoplasia, both adenomas (71%) and cancer (14%), was high within the period of follow-up. Whether the duration and/or extent of polyp formation accelerate the risk for neoplasia in CCS is unknown. It is possible 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 for colorectal cancer may warrant aggressive screening in the CCS patient. Surveillance may be possible (or practical) only after the diffuse inflammatory polyposes has responded to steroid therapy, which then reveals the otherwise buried adenomas or cancer, and surveillance frequency is empiric at this time.

Corticosteroids appear to effectively induce remission in most patients with CCS. Because corticosteroids have many adverse side effects, they should be tapered and discontinued when a complete response has been achieved. However, relapse of symptoms is common on the tapering of corticosteroids; therefore, a steroid-sparing strategy is rational and supported by our findings. In this cohort, corticosteroids were used for induction and as a bridge to allow time for the immunomodulatory agent, azathioprine, to take effect. Surgery may be indicated for the treatment of bowel complications and rarely for removing the polyp burden in attempts to control malnutrition and/or untoward effects.

The response of CCS to steroids was similar to that observed with other autoimmune gastrointestinal conditions. For example, the pancreatic manifestation of IgG4-associated systemic disease responds dramatically to steroid treatment. In a large multicenter study from Japan, corticosteroids were 98% effective in inducing remission in the initial presentation of AIP [43]. In fact, corticosteroids are so effective against AIP that a rapid response to corticosteroid treatment helps substantiate the diagnosis of AIP in selected patients [44]. As we observed with our CCS patients, disease relapse is common in AIP on steroid tapering, with many patients requiring maintenance treatment [45]. As in both CCS and AIP, the extraintestinal organs involved in IgG4-associated systemic disease also have a good response to steroids [17].

This study has several limitations. First, the actual significance of IgG4 tissue infiltration as a specific manifestation of an autoimmune process remains speculative; IgG4-positive cells in polyps may only be a reactive change. Second, given the small number of patients, no firm conclusions can be made in regards to colorectal cancer risk in CCS. Third, it is a case series, so a uniform approach to these patients in regards to diagnosis and treatment cannot be fully assessed.

In summary, this case series of patients with CCS has allowed the description and confirmation of several features of CCS. The IgG4 infiltration of CCS polyps suggests the possibility of an autoimmune inflammatory process. This study supports the use of corticosteroids to induce remission and is the first study to show that the use of azathioprine can effectively maintain remission in CCS.

Conflict of interest No conflicts of interest exist.

References

1. Cronkhite L, Canada W. Generalized gastrointestinal polyposis: An unusual syndrome of polyposis, pigmentation, alopecia, and onychotrophia. *N Engl J Med*. 1955;252:1011–1015.
2. Bacher T, Schonekas H, Steurer KT, Wunsch PH. The Cronkhite-Canada Syndrome. A rare differential diagnosis of generalized gastrointestinal polyposis. *Dtsch Med Wochenschr*. 1997;122:676–681.
3. Burnell RH. Cronkhite-Canada syndrome. *Med J Aust*. 1976;1:347–348.
4. Cotterill JA, Hughes JP, Day JL, Paulley JW, Turk E. The Cronkhite-Canada syndrome. *Postgrad Med J*. 1973;49:268–273.
5. Daniel ES, Ludwig SL, Lewin KJ, Ruprecht RM, Rajacich GM, Schwabe AD. The Cronkhite-Canada syndrome. An analysis of clinical and pathologic features and therapy in 55 patients. *Medicine*. 1982;61:293–309.
6. Freeman K, Anthony PP, Miller DS, Warin AP. Cronkhite-Canada syndrome. *J R Soc Med*. 1984;77:4–5.
7. Goto A. Cronkhite-Canada syndrome: Epidemiological study of 110 cases reported in Japan. *Nihon Geka Hokan*. 1995;64:3–14.
8. Nishiki M, Takasugi S, Kanao M, Okumichi T, Tamura T, Ezaki H. Cronkhite-Canada syndrome. A case report and analytical review of 37 other cases reported in Japan. *Hiroshima J Med Sci*. 1984;33:607–614.
9. Lipper S, Kahn LB. Superficial cystic gastritis with alopecia. A forme fruste of the Cronkhite-Canada syndrome. *Arch Pathol Lab Med*. 1977;101:432–436.
10. Boardman L. Hereditable colon cancer syndromes: Recognition and prevention management. *Gastroenterol Clin North Am*. 2002;31:1107–1131.
11. Schreibman I, Baker M, Amos C, McGarrity T. The hamartomatous polyposis syndromes: A clinical and molecular review. *Am J Gastroenterol*. 2005;100:476–490.

12. Burke AP, Sobin LH. The pathology of Cronkhite-Canada polyps. A comparison to juvenile polyposis. *Am J Surg Pathol*. 1989;13:940–946.
13. Chadalavada R, Brown DK, Walker AN, Sedghi S. Cronkhite-Canada syndrome: Sustained remission after corticosteroid treatment. *Am J Gastroenterol*. 2003;98:1444–1446.
14. Doyle T, Jarvis R. Reversal of changes in Cronkhite-Canada syndrome. *Australas Radiol*. 1984;28:19–22.
15. Goto A. Cronkhite-Canada syndrome: Observations about treatment, course and prognosis of 123 cases reported in Japan. *Nihon Geka Hokan*. 1988;57:427–433.
16. Lin HJ, Tsai YT, Lee SD, et al. The Cronkhite-Canada syndrome with a focus on immunity and infection, report of a case. *J Clin Gastroenterol*. 1987;9:560–570.
17. Takahashi H, Yamamoto M, Suzuki C, et al. The birthday of a new syndrome: IgG4-related diseases constitute a clinical entity. *Autoimmun Rev*. 2010;9:591–594.
18. Nishimori I, Otsuki M. Autoimmune pancreatitis and IgG4-associated sclerosing cholangitis. *Best Pract Res Clin Gastroenterol*. 2009;23:11–23.
19. Kim M-W, Moon S-H, Kamisawa T. Major duodenal papilla in autoimmune pancreatitis. *Dig Surg*. 2010;27:110–114.
20. Hamano H, Kawa S, Horiuchi A, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med*. 2001;344:732–738.
21. Moon S-H, Kim M-H, Park DH, et al. Is a 2-week steroid trial after initial negative investigation for malignancy useful in differentiating autoimmune pancreatitis from pancreatic cancer? A prospective outcome study. *Gut*. 2008;57:1704–1712.
22. Hamano H, Kawa S, Uehara T, et al. Immunoglobulin G4-related lymphoplasmocytic sclerosing cholangitis that mimics infiltrating hilar cholangiocarcinoma: Part of a spectrum of autoimmune pancreatitis? *Gastrointest Endosc*. 2005;62:152–157.
23. Awazuhara H, Kawai H, Maruchi N. Major allergens in soybean and clinical significance of IgG4 antibodies investigated by IgE- and IgG4-immunoblotting with sera from soybean-sensitive patients. *Clin Exp Allergy*. 1997;27:325–332.
24. el Rafei A, Peters SM, Harris N, Bellanti JA. Diagnostic value of IgG4 measurements in patients with food allergy. *Ann Allergy*. 1989;62:94–99.
25. Zar S, Mincher L, Benson MJ, Kumar D. Food-specific IgG4 antibody-guided exclusion diet improves symptoms and rectal compliance in irritable bowel syndrome. *Scand J Gastroenterol*. 2005;40:800–807.
26. Nagata J, Kijima H, Hasumi K, Suzuki T, Shirai T, Mine T. Adenocarcinoma and multiple adenomas of the large intestine, associated with Cronkhite-Canada syndrome. *Dig Liver Dis*. 2003;35:434–438.
27. Nonomura A, Ohta G, Ibata T, Shinozaki K, Nishino T. Cronkhite-Canada syndrome associated with sigmoid cancer case report and review of 54 cases with the syndrome. *Acta Pathol Jpn*. 1980;30:825–845.
28. Katayama Y, Kimura M, Konn M. Cronkhite-Canada syndrome associated with a rectal cancer and adenomatous changes in colonic polyps. *Am J Surg Pathol*. 1985;9:65–71.
29. Malhotra R, Sheffield A. Cronkhite-Canada syndrome associated with colon carcinoma and adenomatous changes in C–C polyps. *Am J Gastroenterol*. 1988;83:772–776.
30. Jain A, Nanda S, Chakraborty P, et al. Cronkhite-Canada syndrome with adenomatous and carcinomatous transformation of colonic polyp. *Indian J Gastroenterol*. 2003;22:189–190.
31. Kaneko Y, Kato H, Tachimori Y, et al. Triple carcinomas in Cronkhite-Canada syndrome. *Jpn J Clin Oncol*. 1991;21:194–202.
32. Murai N, Fukuzaki T, Nakamura T, et al. Cronkhite-Canada syndrome associated with colon cancer: Report of a case. *Surg Today*. 1993;23:825–829.
33. Watanabe T, Kudo M, Shirane H, et al. Cronkhite-Canada syndrome associated with triple gastric cancers: A case report. *Gastrointest Endosc*. 1999;50:688–691.
34. Yamaguchi K, Ogata Y, Akagi Y, et al. Cronkhite-Canada syndrome associated with advanced rectal cancer treated by a subtotal colectomy: Report of a case. *Surg Today*. 2001;31:521–526.
35. Zugel NP, Hehl JA, Jechart G, Tannapfel A, Wienbeck M, Witte J. Colorectal carcinoma in Cronkhite-Canada syndrome. *Z Gastroenterol*. 2001;39:365–367.
36. Radha Krishna Y, Ghoshal UC, Pandey R, et al. Cronkhite-Canada syndrome with Adenomatous polyposis. *J Postgrad Med*. 2008;54:144–146.
37. Nakatsubo N, Wakasa R, Kiyosaki K, et al. Cronkhite-Canada syndrome associated with carcinoma of the sigmoid colon: Report of a Case. *Jpn J Surg*. 1997;27:345–348.
38. Yashiro M, Kobayashi H, Kubo N, Nishiguchi Y, Wakasa K, Hirakawa K. Cronkhite-Canada syndrome containing colon cancer and serrated adenoma lesions. *Digestion*. 2004;69:57–62.
39. Misra SP, Misra V, Dwivedi M, Singh PA, Gupta SC. Cronkhite–Canada syndrome without colonic polyps. *Endoscopy*. 1997;29:333.
40. Naitoh H, Eimoto T, Kamachi H. An autopsy case of Cronkhite-Canada syndrome developing after hemicolectomy for colonic cancer. *Gan No Rinsho*. 1986;32:1619–1624.
41. van der Zee JS, van Swieten P, Aalberse RC. Inhibition of complement activation by IgG4 antibodies. *Clin Exp Immunol*. 1986;64:415–422.
42. Takeuchi Y, Yoshikawa M, Tsukamoto N, et al. Cronkhite-Canada syndrome with colon cancer, portal vein thrombosis, high titer of antinuclear antibodies, and membranous glomerulonephritis. *J Gastroenterol*. 2003;38:791–795.
43. Kamisawa T, Shimosegawa T, Okazaki K, et al. Standard steroid treatment for autoimmune pancreatitis. *Gut*. 2009;58:1504–1507.
44. Chari ST, Smyrk TC, Levy MJ, et al. Diagnosis of autoimmune pancreatitis: The Mayo Clinic experience. *Clin Gastroenterol Hepatol*. 2006;4:1010–1016.
45. Pannala R, Chari ST. Corticosteroid treatment for autoimmune pancreatitis. *Gut*. 2009;58:1438–1439.