Cronkhite-Canada Syndrome Hamartomatous Polyps Are Infiltrated with IgG4 Plasma Cells

Douglas L. Riegert-Johnson^a Neal Osborn^a Thomas Smyrk^b Lisa A. Boardman^a

^aDivision of Gastroenterology and ^bDepartment of Pathology, Mayo Clinic, Rochester, Minn., USA

Dear Sir,

IgG4-related autoimmune disease (IRAD) is a recently described multisystem disorder characterized by IgG4 plasma cell infiltration with manifestations including autoimmune pancreatitis, sclerosing cholangitis and retroperitoneal fibrosis [1]. Cronkhite-Canada syndrome

(CCS) is a rare autoimmune disorder characterized by hamartomatous intestinal polyps, protein-losing enteropathy and eczematous changes [2]. To investigate if CCS is a manifestation of IRAD we examined hamartomatous CCS intestinal polyps for IgG4 plasma cell infiltration using

both sporadic and syndromic juvenile hamartomatous intestinal polyps and normal tissue as controls.

IgG4 staining (Zymed, San Francisco, Calif., USA) was performed using routine immunohistochemical techniques. Slides were scored as described by Kamisawa et

Fig. 1. IgG4 immunohistochemistry with hematoxylin counterstain of a CCS-associated hamartomatous intestinal polyp showing marked IgG4 plasma cell infiltration (arrow).

Table 1. IgG4 plasma cell infiltration in hamartomatous intestinal polyps from different groups and normal colonic and small bowel mucosa

Group	Polyps or tissue samples	Degree of IgG4 plasma cell infiltration	
		none	mild, moderate or marked
CCS (n = 7)	29	16 (55)	13 (45)
SJP (n = 8)	49	43 (88)	6 (12)
Sporadic JP (n = 3)	3	2 (67)	1 (33)
Normal colonic (n = 11) and small bowel (n = 3) mucosa	14	14 (100)	0 (0)

Figures in parentheses are percentages. SJP = Syndromic juvenile polyposis; JP = juvenile polyp.

al. [1]: none 0–5 cells/high-power field (HPF), mild 6–10 cells/HPF, moderate 11–29 cells/HPF and marked >30 cells/HPF.

CCS polyps were significantly more likely to be infiltrated with IgG4 plasma cells than syndromic juvenile polyps (Fisher's exact test $p < 0.01$) or normal tissue (Fisher's exact test $p < 0.01$; table 1, fig. 1). Six of the 7 CCS patients studied had at least 1 polyp with moderate to marked IgG4 plasma cell infiltration. In the combined cohort of CCS and syndromic juvenile polyposis patients, the presence of at least 1 polyp with moderate or marked IgG4 plasma cell infiltration had a sensitivity of 0.85 and a specificity of 0.66 for the diagnosis of CCS. In CCS patients, the degree of IgG4 plasma cell infiltration was not associated with histopathological severity, disease severity, neoplasia, relapse or response to steroid medication. Serum IgG4 values were not available. One of 3 sporadic juvenile polyps was infiltrated

with IgG4 plasma cells. As only a small number of sporadic juvenile polyps were studied, only limited conclusions can be drawn regarding IgG4 plasma cell infiltration in this group.

These findings support the hypothesis that CCS is an intestinal manifestation of IRAD. To date there have been no other reports of intestinal manifestations of IRAD. An argument against CCS being associated with IRAD is that no CCS patient had another IRAD-related disorder. This is in contrast to the prototypical IRAD disorder, autoimmune pancreatitis, where 90% of patients have 2 or more IRAD-related disorders [3].

The pathophysiology of CCS is unknown, although genetic factors do not appear to play a strong role as no more than 1 case of CCS has ever been reported in a single family [2]. Regardless of whether the IgG4 plasma cell infiltration of CCS polyps reported here is linked to IRAD,

this finding is the first clue to the pathophysiology of CCS. In addition, IgG4 staining of hamartomatous intestinal polyps could be clinically useful when more information is needed to exclude or include the diagnosis of CCS.

References

- 1 Kamisawa T, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K, Okamoto A, Egawa N, Nakajima H: A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003;38:982–984.
- 2 Ward EM, Wolfsen HC: The non-inherited gastrointestinal polyposis syndromes. *Aliment Pharmacol Ther* 2002;16:333–342.
- 3 Hamano H, Arakura N, Muraki T, Ozaki Y, Kiyosawa K, Kawa S: Prevalence and distribution of extrapancreatic lesions complicating autoimmune pancreatitis. *J Gastroenterol* 2006;41:1197–1205.