An Association Between Ulcerative Colitis and Atopic Dermatitis, Diseases of Impaired Superficial Barriers

To the Editor:

Atopic dermatitis (AD) and inflammatory bowel disease (IBD) are disorders in which mucocutaneous barrier dysfunction and immunologic phenomena play a role in pathogenesis (Ogawa and Yoshiike, 1993; Taieb, 1999). It has been suggested that these two conditions may coexist with greater than expected frequency (Pugh *et al*, 1979), but data are scarce. Between 1992 and 2003, a total of 47,862 adult AD patients ages 18–62 y (25,512 males, 22,350 females; 39,450 out-patients, 7412 in-patients) were evaluated and treated for AD at Tosashimizu Hospital and its 11 satellite clinics throughout Japan. Patients were selected only for suspicion or previous diagnosis of AD, and each diagnosis of AD by Hanifin and Rajka criteria was confirmed by one or more of our staff dermatologists. AD severity was assessed as described in Table I. All of the AD patients were consecutively evaluated by questionnaire for evidence of IBD (macroscopic blood in stool, chronic abdominal pain, chronic diarrhea, or previous diagnosis of ulcerative colitis (UC) or Crohn's disease (CD)). Patients with chronic pain and diarrhea were tested for fecal occult blood. Those testing positive, as well as patients with a history of blood in stool or previous diagnosis of UC or CD for whom inadequate documentation was available, were asked to undergo colonoscopy and biopsy. As controls, 600 patients with other skin disorders (352 patients with contact dermatitis, 173 patients with cutaneous dermatophyte infection, and 75 patients with psoriasis vulgaris; ages 20–53 y, equal male:female ratio) were similarly screened. Informed consent was obtained from each subject.

Out of the 47,862 consecutive AD patients, 452 underwent colonoscopy and biopsy. A diagnosis of UC was confirmed in 112 and a diagnosis of CD was confirmed in 6 (prevalence of 0.234% and 0.012%, respectively). In addition, 15 of the AD patients with clinical criteria for IBD, and four with a prior incompletely documented diagnosis of UC or CD refused colonoscopy and were therefore not included among the patients with a diagnosis of UC or CD. Among the 600 control patients, 11 underwent colonoscopy and biopsy. No cases of UC or CD were identified.

The estimated prevalence of UC and CD reported in Japan in the annual report of the Japanese Ministry of Health (2002, latest figures available) was 49,000 and 16,000 cases, respectively. The Japanese population in 2002 was approximately 127.4 million. The estimated frequency of UC in the Japanese population is thus 0.038%, and that of CD is 0.013%. UC is thus estimated to be more frequent in adult AD patients than in the Japanese population with an odds ratio of 6.1 [5.1–7.3, 95% confidence interval], whereas CD was not more prevalent in the AD patients than in the Japanese population (odds ratio 1.0 [0.45–2.2]). There was no correlation between the severity of AD and the prevalence of associated UC or CD (Table I).

These results suggest an association between AD and UC. The AD patients came from all parts of Japan and showed a wide range of skin disease activity, and the increased association of UC was found irrespective of AD disease activity. These three factors substantially reduce the likelihood that the apparent association with UC is an artifact of patient selection (Conn *et al*, 1979). There was no increased frequency of CD in the AD patients, although the age distributions of UC and CD in Japan are almost the same (Yoshida and Murata, 1990). This finding reduces the likelihood that the apparent association with UC is an artifact of the surveillance methods or criteria for diagnosis. The absence of UC or CD in the control patients, despite the known association of IBD with psorasis (Brophy *et al*, 2001), also suggests absence of bias in surveillance or observation, although the number of control subjects is relatively small. An estimated 30%–45% of CD patients in Japan do not show colonic involvement (Yao *et al*, 2000), and our surveillance method thus might have somewhat underestimated the prevalence of CD in the AD patients. Even if the odds ratio for CD in the AD patients increased to 1.5 (nine cases instead of six), however, it would still be significantly lower than the UC odds ratio at $p < 0.0001$.

The prevalence of CD in Japan that we calculated agrees well with other recent estimates (Yao *et al*, 2000), whereas recent published data on UC prevalence are not available. The prevalence rates of UC and CD that we calculated for 2002 are each approximately 2.1-fold higher than those reported in a 1991 survey (Morita *et al*, 1995), a fold increase closely matching that reported for CD between 1991 and 1998 (Yao *et al*, 2000). Overall, the observations and calculations in our study seem sufficiently free of sources of potential bias and error to support the provisional conclusion of a significantly increased prevalence of UC in the AD patients.

Both AD and UC are characterized by inflammation in the superficial layers of mucocutaneous tissue, in contrast to CD, in which the lesions are deep and often transmural. Asthma and allergic rhinitis, which are often associated with AD (Umeki, 1994), are also diseases affecting superficial

Abbreviations: AD, atopic dermatitis; CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis

Table I. Lack of correlation between AD severity and associated IBD

	AD disease activity					AD *versus* all patients	
Patients	**Mild**	**Moderate**	**Severe**	**Extra-severe**	**Total**	χ^2	**p**
AD (all)	4748	19,862	21,567	1685	47,862		
AD with UC	14	40	52	6	112	2.7	0.4
AD with CD	1	2	3	0	6	0.6	0.9

Severity was assessed by modified AD score (Niwa *et al*, 2003): extra-severe $\geqslant$220, severe 170–219, moderate 120–169, mild $\leqslant$119. Score = Ia $\times$ 1 + IIa $\times$ 2 + IIIa $\times$ 3, where Ia is the percentage of body surface area with mild lesions (erythema or papules), IIa is the percentage with moderate lesions (elevated erythema, papules, or scratch marks), and IIIa is the percentage with severe lesions (lichenification or prurigo nodularis).
AD, atopic dermatitis; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease.

mucosal layers. Therefore, AD seems to be the disease of the impaired superficial barriers of whole body. The inflammatory infiltrate in these disorders, like AD, characteristically shows a TH2 pattern (Taieb, 1999). The cytokine pattern found in UC mucosa has usually been characterized primarily as TH2, in contrast to the TH1 pattern seen in CD (Inoue *et al*, 1999; Sawa *et al*, 2003). Although AD, UC, allergic rhinitis, and bronchial asthma all have important immunologic components, no one specific antigen is thought to be responsible for any of these disorders. Rather, antigen specific immune responses are more likely to result from impairment of barrier function that is a more primary part of the pathogenesis of these disorders.

Genome-wide scans have identified loci with linkage to IBD (Wild and Rioux, 2004) and other loci with suggestive linkage to AD (Bowcock and Cookson, 2004). Although no direct genetic linkage between the two disorders has been identified, a haplotype on chromosome 5q31 that contains a cluster of atopy-related genes including interleukin (IL)-4 and IL-13 is strongly linked to CD and probably also to UC (Giallourakis *et al*, 2003), and shows linkage to serum IgE levels in AD families (Cookson *et al*, 2001).

In summary, our large 11 y prospective study suggests an association between AD and UC, and recent data from several sources suggest potential sharing of TH2 cytokine-related pathways in the pathogenesis of these two disorders of barrier dysfunction. This intriguing association merits its further investigation.

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