Cronkhite-Canada Syndrome

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Cronkhite-Canada syndrome (CCS) is a rare sporadically occurring non-familial syndrome. It was first reported in 1955 by Leonard Wolsey Cronkhite Jr., an American internist and Wilma Jeanne Canada, an American radiologist, as a new distinct clinical entity diagnosed in 2 women [1]. Since then, several case reports and few small series have been published. Large studies evaluating pathogenesis and medical treatment do not exist because of the rareness of this syndrome. The distribution of the disease varies significantly around the world, while about 75% of the cases are diagnosed in Japan [2]. The etiology, pathogenesis, clinical course, prognosis and optimal treatment are yet to be determined. There is no evidence to suggest a genetic, environmental or specific infectious origin or a reason for its being largely confined to Japan.

Comparing this syndrome to other similar genetic gastrointestinal polyposis syndromes that are associated with dermatologic symptoms and malabsorption is of a special interest. There is significant phenotypic overlap between the features of CCS, juvenile polyposis (JPS) and Peutz-Jegher syndrome (PJS), and in particular in the morphology of intestinal hamartomatous polyps [3, 4].

CCS usually manifests in the sixth decade. It is characterized by the presence of non-adenomatous juvenile type or hamartomatous polyps that occur throughout the gastrointestinal (GI) tract excluding the esophagus [5].

The polyps are a part of a generalized GI mucosal disturbance that results in malabsorption and protein losing enteropathy. The vast majority of affected individuals manifest with alopecia, skin pigmentation and alterations in the nail beds. These ectodermal features and the various clinical courses [6] are probably a consequence of malab-

sorption and a profound malnutrition. Like all the hereditary polyposis syndromes, subjects with CCS are also prone to develop cancer. Among all patients with CCS 50 (13%) cases were associated with gastrointestinal cancer, including 31 (8%) cases with colon cancer (usually in the rectosigmoid area) and 19 cases (5%) with gastric cancer [7]. Of particular interest is that males were significantly more prone to cancer genesis than females (27 out of 31).

JPS presents during the first or second decades in life, and feature a similar phenotype like CCS. In both syndromes the presented symptoms are very much alike: diarrhea, bleeding and malnutrition. Polyps develop throughout the entire GI tract and there is an increased risk for GI malignancies. Cancers appear to arise from adenomatous components present in some juvenile polyps [8]. JPS is inherited as a rare autosomal-dominant disease, yet significant numbers of cases are sporadic with no previous familial history.

PJS is another similar syndrome. It is an autosomal-dominant disorder characterized by the presence of numerous hamartomatous polyps throughout the entire GI tract (mostly in the small bowel) along with mucocutaneous melanin pigmentation spots that appear most commonly on the lips and buccal mucosa. Many organs are prone to cancer in these patients, and the small bowel in particular.

Is it possible that JPS and/or PJS are a form of CCS or vice versa? Both JPS and PJS are examples of syndromes with a genetic predisposition that may vary from 'high' to 'low' penetrance, and between 'familial' and 'sporadic' cases [4]. The genes that are associated with predisposition to these syndromes have been recently identified.

Two genes are known to be associated with JPS: *MADH4* (previously known as *SMAD4*) and *BMPRIA* genes; PJS is associated with mutations in the *LKB1* gene. Should molecular genetic examinations for these mutations be performed in the setting of CCS? As already mentioned, a considerable number of reports of CCS cases associate the syndrome with gastrointestinal tumors, but the underlying mechanism is unknown. It remained to be seen if the tumors arise as a part of the CCS, or that they represent sporadic carcinomas.

In the January 2004 issue of this journal, Yashiro et al. [7] described a case of CCS associated with colon cancer. They suggested that the precursor lesion in this patient is serrated adenoma. The authors were able to obtain tissues from 25 of the 31 CCS cases associated with colon cancer. In a retrospective reexamination of these cases serrated adenoma were found in 10 (40%). As a comparison, the incidence of serrated adenomas was estimated to occur in about 1% of all general polyps. Hence, it was suggested that in CCS, significant numbers of hyperplastic polyps are in fact serrated adenoma, and can serve as the precursor lesion for colon cancer in this setting. Additionally, genetic analysis of seven polyps (including 3 serrated adenomas) and the cancer lesion in one patient was performed: microsatellite instability and overexpression of the p53 protein were found in the serrated adenomas and the adenocarcinoma, but not in the hyperplastic polyps. None of the lesions showed loss of heterozygosity of other genes that are known to be mutated in CRC, sug-

gesting that these tumors may belong to the RER mutator phenotype. Unfortunately, tests for the aforementioned mutations in JPS and PJS were not performed.

In this issue of *Digestion*, Blonski et al. [6] describe a case of CCS with dysgeusia as the presenting symptom. Indeed, Goto [9] found that dysgeusia is an important part in the clinical picture of CCS, in the majority of the cases. The hypogeusia is related to zinc deficiency, and restoring zinc to normal level is an important aspect in the management of these patients. While discussing the case, Blonski et al. [6] introduce a thorough review of the literature concerning this rare and intriguing syndrome. In particular they summarized the unique clinical approach based on the patients' symptoms. They also present different attitudes for surveillance in this setting [10–15], although at present, no formal guidelines exist. In particular when there are many polyps; the clinical dilemma is which and how many polyps should be resected each time. Yashiro et al. [7] also address this issue. They examined histologically 18 (of 73) polyps ranging in size from 10 to 20 mm (in 1 subject). Nine of the 18 polyps were serrated adenomas. Based on this data the possibility of a serrated adenoma-carcinoma sequence was suggested.

CCS is a rare nonhereditary polyposis syndrome. The two papers that were published during the last year shed new light on the diagnosis and clinical approach to this disease. It suggests that the serrated adenoma-carcinoma may underline the multi-step carcinogenesis process, and that this syndrome may overlap with PJS and JPS.

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