Case report

Association of hereditary spherocytosis with familial adenomatous polyposis in a pedigree: a new syndrome or coincidence?

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No association of familial adenomatous polyposis (FAP) and hereditary spherocytosis (HS) has been reported, both of which are inherited in an autosomal dominant manner. We present the first reported case of FAP with spherocytosis and construct the family pedigree. In the patient’s pedigree, both FAP and spherocytosis were inherited in an autosomal dominant trait. In the 34-year-old Japanese proband’s leukocytes, we found no abnormal chromosomal band, and a germline mutation of the APC gene was not detected. All possible genes reported to be linked to HS were located far from chromosome 5q on which the APC gene is located. Although it is unknown if erythrocyte membrane disorder is an additional phenotype of FAP, to the best of our knowledge, this is the first documentation of FAP associated with spherocytosis.

Key words: familial adenomatous polyposis, hereditary spherocytosis, APC gene

Introduction

The autosomal dominant pattern of inheritance has been firmly established for familial adenomatous polyposis (FAP), characterized by hundreds to thousands of colorectal adenomas that usually emerge during the second and third decade of life and which harbor a high risk of malignant transformation. Nishio et al. and Kinzler et al. found the responsible APC gene on chromosome 5q21. Hereditary spherocytosis (HS) also is inherited as an autosomal dominant trait, and several responsible genes have been linked to the erythrocyte membrane. Clinical features include hemolytic anemia, jaundice, splenomegaly, and microspherocytosis. Red blood cells do not survive osmotic stress and are easily destroyed during microcirculation in the spleen. We report here data on a patient with HS who developed FAP, as did her mother. When we constructed the family pedigree, we discovered that the patient’s mother and uncle were affected by HS. Although we could not determine if the appearance of spherocytosis in the setting of FAP is a coincidence, these association is indubitably very interesting and unusual. To our knowledge, this is the first such case to be reported in the literature.

Case report

The proband (individual III-2 in Fig. 1) is a 34-year-old Japanese woman with HS, causing hemolytic anemia and cholecystolithiasis, first diagnosed at age 16 years. She underwent splenectomy and cholecystectomy at age 24 years. She also was diagnosed as having colorectal polyposis with advanced cecal cancer (Dukes B) at age 34 years old, and total proctocolectomy with ileal J-pouch anal anastomosis were done. The resected colorectum had several hundred adenomatous polyps. Duodenal adenomatous polyposis, occult osteoma in the mandible, unerupted teeth, and hypertrophy of the retinal pigment epithelium were also evident. The proband’s blood samples were sent for molecular genetic examination. There was no obvious abnormality in the chromosomal band, determined by a differential staining method (G banding). Germline mutation of the APC gene was screened using a protein truncation test, but no truncated protein band was evident.

The patient’s mother (II-2) was diagnosed as having colonic polyposis at age 55 years, at which time partial colectomy revealed approximately 30 adenomatous
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polyps in the resected specimen; 1 of these polyps exceeded 5 cm in diameter and proved to be a tubulovillous adenocarcinoma with lymph node metastasis. Next, a semiannual endoscopic examination revealed numerous remnant colorectal polyps, several of which (about 10 polyps per endoscopy) were removed by hot biopsy forceps or use of a polypectomy snare, and all were histologically tubular to tubulovillous adenomas. HS was diagnosed at age 42 years, and she underwent cholecystectomy against cholecystolithiasis. Splenectomy was not done, and even today hemolytic anemia and hemolytic jaundice remain.

One of her siblings (II-3) who had rheumatoid arthritis died of unknown causes. Another sibling (II-4), whose father was the younger brother of the proband’s maternal grandfather, had spherocytosis, and he underwent splenectomy and cholecystectomy. Neither individual II-3 nor II-4 was known to have been examined for the presence of colonic polypsis, nor were the proband’s two first cousins (III-3, III-4). The proband’s maternal grandmother (I-7) had neither colonic polypsis nor spherocytosis. The proband’s maternal grand- father (I-3) and his younger brother (I-4) died at ages 32 and 30 years, respectively, details of which are unknown. The proband’s paternal family history is negative for colonic polypsis or spherocytosis, and the parents are not consanguineous.

Discussion

In our present state of knowledge, referring to MEDLINE for stored documents, no association of FAP and HS has been reported. Although we could not determine if the appearance of spherocytosis in the setting of FAP is merely an occasional finding, such an occurrence in the kindred reinforces the likelihood of a meaningful association.

The precise functions of the \(\text{APC}\) gene product have not been elaborated so far. However, various experimental studies suggest that the \(\text{APC}\) protein is involved in cell adhesion, transcriptional regulation, and cytoskeleton organization through its interaction with \(\beta\)-catenin and tubulin.\(^{11-14}\) One of the most intriguing findings was the identification of correlations between the site of mutation in the \(\text{APC}\) coding region and clinical disease features, including extracolonic manifestations.\(^{15-18}\) Moreover, recent evidence suggests that relating the location of mutations to the phenotypic disease expression could be helpful in surgical decision making.\(^{19,20}\) We detected no mutation of the proband’s germ-line \(\text{APC}\) gene, using a protein truncation test for screening, first described by Roest et al.\(^9\) and applied to \(\text{APC}\) screening by Powell et al.\(^10\) The causative \(\text{APC}\) germline mutation across which reported mutations are scattered\(^{21}\) has not been identified in one-third to one-fourth of the FAP patients using the protein truncation test, even combined with several molecular approaches.\(^{10,22-24}\) This result may reflect the sensitivity and strength of the mutation detection technique used, the presence of causative gene alterations influencing \(\text{APC}\) expression outside the coding sequence, or the possibility of genetic heterogeneity in FAP. The mutational hot spots should be subjected to direct DNA sequence analysis in attempts to identify missense mutations that might have escaped detection by the protein truncation test. If no causative mutation could be identified, the complete coding region and all splice sites of the \(\text{APC}\) gene should be sequenced.

As for responsible genes against HS, we speculate that the responsible gene for HS may be located near the \(\text{APC}\) gene on chromosome 5q. However, all reported genes linked to the erythrocyte membrane, such as SLC4A1, erythrocyte membrane protein band 3 located on chromosome 17q12–q21; ANK1, ankyrin 1 on 8p21.1–p11.2; SPTA1, alpha-spectrin on 1q21; EPB42, erythrocyte membrane protein band 4.2 on 15q15–q21;