Familial Barrett's Esophagus Associated With Adenocarcinoma

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A family with six cases of Barrett's esophagus over three generations is described. The Barrett's esophagus affected only males, and there were three associated adenocarcinomas. The mechanism of inheritance is compatible with an autosomal dominant pattern with nearly complete penetrance. Other case reports in the literature are compared with this familial case of Barrett's esophagus with associated adenocarcinomas.

Barrett's esophagus is a clinical condition in which the squamous mucosa of the esophagus is replaced by columnar epithelium. The metaplastic change can result from a congenital abnormality but is usually the result of chronic gastroesophageal reflux. The average age of diagnosis is the fifth decade,[1–4] with cases rarely seen before age 20.[1] This pattern is more consistent with an acquired cause. However, several case reports of a familial association have suggested that hereditary factors may contribute to the pathogenesis. In addition, Barrett's esophagus is associated with the development of adenocarcinoma of the esophagus.[2–6] Here we report the aggregation of Barrett's esophagus through three generations of a family with three associated esophageal adenocarcinomas.

Case Report

The proband, (IV-3, age 67; Figure 1) a cigarette smoker, who had a lifelong history of reflux symptoms, presented with a 3-month history of dysphagia and a 30-lb weight loss. Endoscopic evaluation revealed a diffuse infiltrating carcinoma from the midesophagus to the gastroesophageal junction. Biopsies confirmed adenocarcinoma and the histopathology from the resected esophagus showed typical columnar lined Barrett's epithelium in addition to the adenocarcinoma. The proband died about 1 year later from metastatic disease.

It was apparent from reviewing the family history of the proband that reflux symptoms were quite common. The proband's great grandfather (I-1, age mid-80s) had severe reflux symptoms and, in fact, died from malnutrition related to dysphagia. The proband's grandfather (II-1, age mid-80s) had lifelong heartburn relieved with antacids and died from a myocardial infarction. The proband's father (III-2) died at age 89 from metastatic esophageal cancer. Review of the surgical specimen from esophagectomy showed an adenocarcinoma with surrounding Barrett's epithelium.

We have studied the three siblings of patient IV-3. Sister (IV-2; age 66) was found to have some vague abdominal complaints. An Esophagogastroduodenoscopy (EGD) showed only a hiatal hernia, but no indication of Barrett's esophagus or esophagitis. She had three sons (V-2, age 41; V-3, age 32; V-4, age 35), only one of whom had heartburn. None have been endoscoped.

Endoscopy was performed on the brother (IV-4; age 66) of the proband. He had esophagitis with typical Barrett's epithelium extending several centimeters into the lower esophagus. Biopsies from an irregular appearing patch of mucosa showed severe dysplasia. He underwent esophagogastrectomy and the surgical specimen showed frankly invasive adenocarcinoma. The patient (IV-4) is alive and well 4 years after surgery. Endoscopy was subsequently performed on the four children of patient IV-4. One daughter (V-7, age 27) was asymptomatic and had a normal EGD. Another daughter (V-5, age 38) had symptoms of reflux, and the EGD showed some antral erosions but no esophagitis or Barrett's esophagus. A son (V-6, age 35) had characteristic reflux symptoms relieved with antacids. His EGD showed severe distal esophagitis with Barrett's epithelium in the lower esophagus. The other son (V-8, age 25) also had typical reflux symptoms. EGD revealed moderate antritis, but a normal esophagus.

The probands second brother (IV-5, age 60), who is a cigarette smoker, also had typical reflux symptoms. Endoscopic evaluation revealed Barrett's epithelium extending into the distal esophagus. Biopsies confirmed the clinical diagnosis. However, there was no evidence of dysplasia. His son (V-10, age 36) also a cigarette smoker with reflux symptoms, had changes of early Barrett's esophagus documented endoscopically. One daughter (V-9, age 38) also had some dyspeptic symptoms. The EGD showed gastritis with esophagitis, but no Barrett's esophagus. Another daughter (V-12, age 40) who was asymptomatic has not been endoscoped. A third daughter (V-11, age 34) has reflux symptoms, but no EGD has been done. Extension of the family history revealed several cousins (IV-1, age 72; V-1 and V-13, both mid-30s) with reflux symptoms. Pa-

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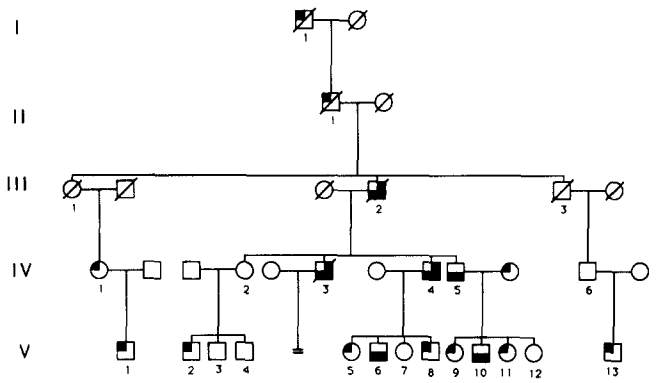

Figure 1. Pedigree of Barrett's Esophagus Family. Solid quadrant indicates affected status: lower half, Barrett's esophagus; upper left quadrant, acid peptic disease; upper-right quadrant, adenocarcinoma. Deceased individuals indicated by diagonal line.

tient V-13 has a benign esophageal stricture that responded to dilatation at a local hospital.

Discussion

Barrett's esophagus is a metaplastic columnar lined esophageal epithelium. The most common theory of pathogenesis is that chronic reflux of gastric contents leads to a continual reparative process and metaplastic change. There have been several case reports of familial Barrett's that point toward a possible genetic predisposition.[1,7-9] Additional evidence for possible genetic factors contributing to this condition include its rarity in the black population[2] and the male predominance (men to women ratio is 5.5:1).[10]

Here we report a familial cluster of Barrett's esophagus together with an association of Barrett's esophagus with reflux symptoms and esophageal adenocarcinoma. The diagnosis in this family of Barrett's esophagus in two men in their mid-30s suggests an earlier age of onset in individuals who may be genetically predisposed to the syndrome than in sporadic cases. This is also consistent with some of the other reports of familial Barrett's esophagus that also suggested earlier ages of onset.[1,7] Such data must be viewed cautiously because of the lack of systematic screening for Barrett's esophagus in the general population.

The appearance of Barrett's esophagus in this family is consistent with an autosomal dominant pattern of inheritance. The inheritance of phenotypic symptoms, such as acid peptic disease, without the tissue changes of Barrett's esophagus is not as clear. Penetrance of the Barrett's esophagus phenotype in this family is complete or nearly complete because all individuals with unequivocal Barrett's esophagus had a parent with symptoms. The data suggest that the Barrett's esophagus phenotype may show some sex-modified differences in this family. In the three generations for which the physical data is most complete, only men show unequivocal Barrett's esophagus, the associated reflux symptoms, and adenocarcinoma. Several women show acid peptic disease but none show esophageal tissue changes characteristic of Barrett's esophagus. Previous reports on familial clustering of Barrett's esophagus were consistent with autosomal dominant inheritance and would rule out unusual sex-associated modes of inheritance, such as Y linkage, because of the presence of affected female individuals.[7-9] Only four other cases of familial Barrett's esophagus have been reported. The most extensive of the previous case reports by Crabb et al.,[7] indicated autosomal dominant inheritance for the reflux disease, but an uncertain inheritance for the Barrett's esophagus. It was diagnosed in a father, one son, and two daughters leaving four siblings unaffected. A second case report describes one father and two sons with Barrett's esophagus.[1] The remaining reports are of two elderly female twins[8] and two sisters who presented with Barrett's esophagus at age 66.[9] Clearly, these are isolated case reports of familial Barrett's esophagus that all could be consistent with an autosomal dominant pattern of inheritance with incomplete penetrance. The frequency of familial Barrett's esophagus appears very small but may increase substantially as endoscopy is more commonly used to investigate patients with reflux symptoms.

Given a small number of isolated reports of familial clustering of Barrett's esophagus, the presence of genetic factors predisposing to the onset of the syndrome, nevertheless seems clear. They are consistent with a pattern of autosomal dominance. However this familial pattern does not necessarily prove a genetic basis for Barrett's esophagus. Additional familial studies with inclusion of gene linkage information will provide further insight into the pathogenesis of Barrett's esophagus.

The mechanism by which familial Barrett's esophagus occurs is uncertain. It is possible that environmental effects, (i.e., diet, alcohol, or cigarettes) could be factors effecting the development of Barrett's esophagus. However, in this family it seems unlikely that diet and alcohol are important. None of the affected individuals in any of three different generations were heavy drinkers. Cigarette smoking might be an aggravating factor. Three of the five individuals with Barrett's esophagus were smokers, although one (IV-3) had ceased smoking 10 years before the onset of his esophageal carcinoma. The two others who developed Barrett's esophagus were nonsmokers. Other possible explanations include an inherited defect in the intrinsic antireflux mecha-

nisms associated with an esophageal motility disorder with poor clearance of acid, decreased lower esophageal sphincter pressure, or abnormal gastric motility. Another possibility is a defect in mucosal protective mechanisms. A final possibility is abnormal gastric contents, which in some way predispose to metaplastic changes. None of these has been investigated in the family reported here.

The high occurrence of esophageal adenocarcinoma could also be genetically determined. Whether an increased risk of cancer is directly caused by the same genetic factors predisposing to Barrett's esophagus is not clear.[3] The risk of adenocarcinoma for nonfamilial Barrett's esophagus approaches 10%.[11] Clearly the risk in this family with a father and two of three sons developing adenocarcinoma specifically associated with Barrett's esophagus is much higher than normal. The metaplastic response with continual inflammation could lead to chromosomal rearrangements. In a study of nonfamilial Barrett's esophagus, 9 of 10 cytogenetic analyses showed a structural abnormality.[12] Perhaps a chromosomal rearrangement superimposed on a previously susceptible genotype is in some way oncogenic. It may have been a trigger for uncontrolled cell proliferation. Whatever the mechanism, this family certainly represents a situation of an increased risk of adenocarcinoma arising from Barrett's esophagus.

This case history emphasizes the occurrence of familial Barrett's esophagus and its association with increased risk of adenocarcinoma of the esophagus. Given this association, we would recommend endoscopy for the symptomatic relatives of patients with this condition as well as close surveillance of those with proven familial Barrett's esophagus. In addition, because early onset of symptoms seems associated with the familial form of Barrett's esophagus, data on other family members should be gathered from younger patients with documented Barrett's esophagus.

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