Abdom Imaging 20:291–298 (1995)

Abdominal Imaging

Update

Barrett's esophagus and esophageal adenocarcinoma: the scope of the problem

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Since its original description by Barrett in 1950 [1], Barrett's esophagus has been recognized as a premalignant condition in which the normal squamous epithelium in the esophagus has been replaced by a columnar epithelial lining due to chronic gastroesophageal reflux and reflux esophagitis. Recent data suggest that this condition is more common than previously recognized. Many investigators advocate periodic surveillance of patients with known Barrett's esophagus to detect precancerous or early cancerous changes before the development of overt carcinoma. However, many questions remain about Barrett's esophagus as well as the risk of malignant transformation and the benefits of surveillance in these patients. The purpose of this article is to provide a current overview of the epidemiologic, clinical, radiologic, and pathologic aspects of Barrett's esophagus and esophageal adenocarcinoma.

Definition and Histologic Features of Barrett's Esophagus

Barrett's esophagus is a metaplastic process in which the squamocolumnar mucosal junction is located above the proximal border of the lower esophageal sphincter [2, 3]. This columnar epithelial lining may extend proximally as a continuous sheet, finger-like projections, or islands of columnar epithelium separated by residual areas of normal squamous epithelium [2]. Barrett's esophagus is often confined to the distal third of the esophagus, but it may extend as far proximally as the aortic arch.

Barrett's esophagus can be diagnosed at endoscopy by typical changes in the color and texture of the epithelium, as Barrett's mucosa usually has a velvety, pinkish-red appearance in contrast to the flat, relatively pale appearance of the esophageal squamous epithelium. Although biopsy specimens are required for a definitive diagnosis, endoscopy is reported to have a sensitivity of greater than 90% in diagnosing Barrett's esophagus solely on the basis of the endoscopic appearance [4, 5].

Barrett's esophagus can be diagnosed histologically by the presence of glandular epithelium 3 cm or more above the lower esophageal sphincter and/or intestinal metaplasia even if such epithelium is located less than 3 cm above the sphincter. Occasionally, ciliated epithelium may be present in the upper thoracic esophagus as an embryonic remnant of columnar epithelium, also known as the "inlet patch"; this ciliated epithelium should not be considered Barrett's mucosa. The glandular mucosa found in Barrett's esophagus usually consists of gastric fovealar-type epithelium with or without intestinal metaplasia (Fig. 1) [6, 7]. This intestinal metaplasia is manifested histologically by goblet cells with acidic mucin and, in some cases, enterocyte differentiation with brush border formation. Although well-formed goblet cells are not always present, these cells are still considered to have undergone intestinal metaplasia when they produce acidic mucin.

Epidemiology of Barrett's Esophagus

In the past, it was argued that Barrett's esophagus is a congenital condition caused by abnormal embryologic development with incomplete squamous re-epithelialization of the columnar-lined fetal esophagus [8]. However, embryonic columnar mucosa in the esophagus is ciliated, it does not contain glandular tissue, and it does not resemble any of the three types of columnar mucosa that comprise Barrett's esophagus. Furthermore, Barrett's mucosa is virtually never found in neonates at autopsy [9]. Thus, most investigators no longer accept the theory that Barrett's esophagus is a congenital abnormality.

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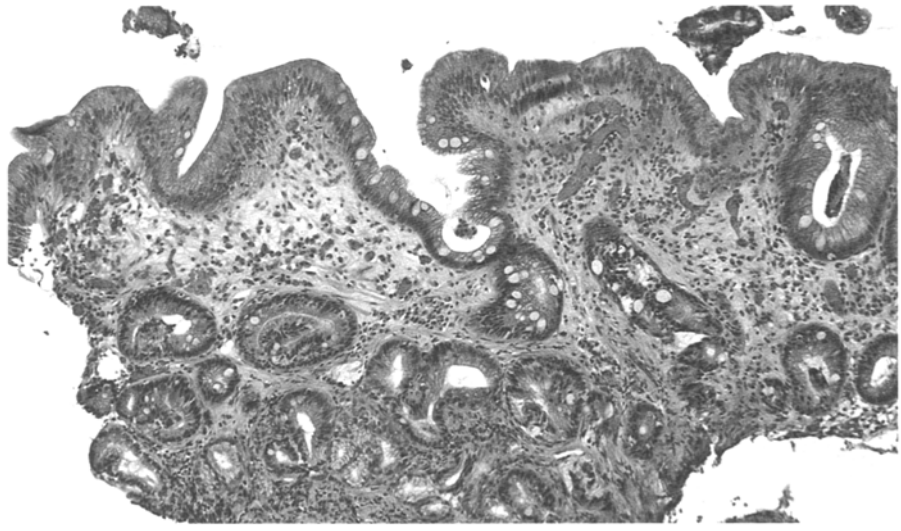

Fig. 1. Histologic section shows typical changes of Barrett's mucosa with glandular epithelium and intestinal metaplasia (H & E, original magnification ×200).

Barrett's esophagus is currently thought to be an acquired condition with progressive columnar metaplasia of the distal esophagus due to long-standing gastroesophageal reflux and reflux esophagitis [2, 3, 10–13]. It has been postulated that chronic gastroesophageal reflux causes repeated mucosal damage and ulceration, so that the normal squamous epithelium is eventually denuded and replaced by a metaplastic columnar epithelial lining. This theory is supported by studies on laboratory animals showing that reflux of acid into the esophagus leads to replacement of squamous epithelium by a more acid-resistant columnar epithelium [9, 14, 15]. However, Barrett's esophagus has also been documented after total gastrectomy and esophagojejunostomy [16, 17], so this condition may be caused not only by refluxed acid but also by refluxed biliary and pancreatic secretions in the esophagus.

Although Barrett's esophagus appears to be acquired, an association with sex and race suggests an underlying genetic predisposition for developing this condition. In various studies, the ratio of men to women with Barrett's esophagus has ranged from 2:1 to 9:1 [18–20], and the ratio of Caucasians to Blacks has ranged from 7:1 to 10:1 [19, 21]. Caucasian men therefore appear to be at greater risk for developing Barrett's esophagus than other groups. However, cigarette smoking and alcohol have also been implicated as risk factors for this condition [21–24]. Thus, it remains unclear whether Caucasian men are more likely to develop Barrett's esophagus because of genetic or environmental factors.

Other investigators have also implicated genetic factors in the development of Barrett's esophagus. In one study, six cases of Barrett's esophagus were documented in a single family over three generations, suggesting a familial basis for this disease [25].

Prevalence and Incidence of Barrett's Esophagus

In evaluating the frequency of Barrett's esophagus, it is important to understand the concepts of prevalence and incidence. The prevalence of Barrett's esophagus refers to the number of cases that are present in the population at a given *point* in time. In contrast, the incidence of Barrett's esophagus refers to the number of new cases that develop over a given *length* of time. The prevalence of Barrett's esophagus in patients with reflux esophagitis has ranged from 8 to 20%, with an average prevalence of about 10% [18, 22, 26, 27]. However, prevalence data may exaggerate the risk of Barrett's esophagus, as patients with reflux symptoms who undergo endoscopy are more likely to have significant reflux disease that those who do not seek medical attention.

Unlike prevalence data, incidence data tend to underestimate the actual number of new cases of Barrett's esophagus, as patients who are asymptomatic do not seek medical attention. In a recent study, Cameron et al. [28] found that the number of cases of Barrett's esophagus at autopsy was about 20 times greater than the number of cases at endoscopy. The findings in this study suggest that the vast majority of cases of Barrett's esophagus remain undiagnosed because of the absence of esophageal symptoms. Although the incidence of Barrett's esophagus does appear to be increasing, it is uncertain how much of this apparent increase is related to greater use of endoscopy and/or greater awareness of this condition.

Relationship to Adenocarcinoma

Awareness of Barrett's esophagus is important because it is a premalignant condition associated with an in-

creased risk of developing esophageal adenocarcinoma (i.e., Barrett's carcinoma). The sequence of events leading to the development of malignancy has been the subject of considerable interest. It is widely believed that adenocarcinoma evolves through a sequence of progressively severe epithelial dysplasia in preexisting areas of columnar metaplasia [2, 3, 7, 22, 29–31]. Dysplastic changes are classified histologically either as low grade or high grade; this grading of dysplasia has important therapeutic implications (see below). Low-grade dysplasia is characterized by nuclei that are confined to the base of the epithelial cells, whereas high-grade dysplasia is characterized by an increased ratio of nuclear-to-cytoplasmic area, nuclear hyperchromaticity, cellular crowding, and an increase in mitotic figures (Fig. 2) [2]. This dysplastic epithelium may then progress to carcinoma in situ or invasive carcinoma.

The prevalence of high-grade dysplasia in patients with Barrett's carcinoma has ranged from 68 to 100% [2, 22, 32]. Dysplasia may occur within all histologic types of Barrett's mucosa, but it is more likely to occur within areas of intestinal metaplasia [3, 20, 22, 30–32]. Studies have also shown a marked association between intestinal metaplasia and esophageal adenocarcinoma [22, 33]. Although the reason for this association is unclear, patients with Barrett's esophagus who have a high concentration of intestinal metaplasia should be considered to be at greatest risk for developing adenocarcinoma.

The risk of malignant degeneration in Barrett's esophagus can also be assessed by prevalence and incidence data. The prevalence of esophageal adenocarcinoma in patients with Barrett's esophagus has ranged from 2 to 46%, with an average prevalence of about 10% [2, 18, 22, 27, 30, 32, 34–36]. Prevalence data may exaggerate the risk of cancer, as many patients with Barrett's esophagus remain asymptomatic until the development of a superimposed adenocarcinoma. Incidence data therefore may provide more realistic estimates of the risk of malignant transformation in Barrett's mucosa. However, incidence data can only be obtained by long-term prospective studies of large numbers of patients with Barrett's esophagus who previously have been shown to be free of esophageal adenocarcinoma. Although patient follow-up has been limited, several such studies have found that the risk of developing adenocarcinoma in patients with Barrett's esophagus is about 30–40 times greater than that in the general population [37, 38].

Recent data suggest that the incidence of adenocarcinoma in Barrett's esophagus has increased more rapidly than that of any other form of esophageal cancer in this country during the past two decades [39–42]. Currently, Barrett's carcinomas are thought to comprise 30–50% of all esophageal cancers [41–43]. Unlike squamous cell carcinomas, these tumors often involve the gastric cardia and fundus. In fact, the apparent increase in the frequency of esophageal adenocarcinomas may be partly related to earlier confusion regarding the origin of adenocarcinomas at the gastroesophageal junction. In the past, these tumors were almost always classified as primary gastric carcinomas invading the distal esophagus. However, up to 50% of tumors at the gastroesophageal junction are now thought to represent Barrett's carcinomas invading the stomach [44, 45]. Whether or not the tumors arise in Barrett's esophagus or in the gastric fundus, they have similar features in terms of the degree of differentiation, depth of invasion, and overall prognosis.

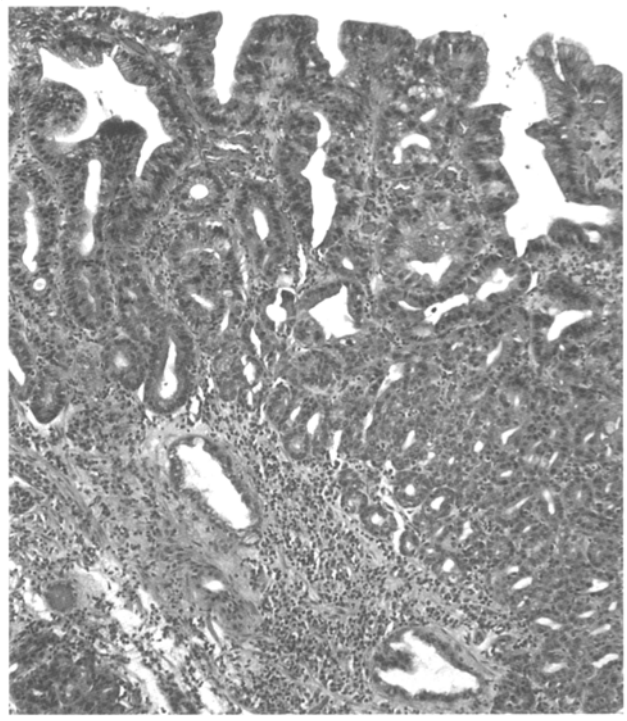

Fig. 2. Histologic section shows high-grade dysplasia in Barrett's mucosa, manifested by nuclear hyperchromaticity and high nuclear-to-cytoplasmic ratio (H & E, original magnification ×400).

Because of the increased risk of developing adenocarcinoma in Barrett's esophagus and because advanced adenocarcinomas have the same poor prognosis as squamous cell carcinomas [22, 35, 46], many investigators advocate periodic endoscopic surveillance of patients with known Barrett's esophagus at yearly intervals to detect dysplastic or carcinomatous changes at the earliest possible stage. Although it is impossible to predict with certainty which cases of Barrett's esophagus will undergo malignant transformation, about one-third of patients with severe dysplasia develop adenocarcinoma within 5 years [31]. Detection of dysplasia in Barrett's mucosa and quantification of its histologic grade therefore permits identification of a subgroup of patients with

Barrett's esophagus who require aggressive follow-up and treatment because of a higher risk of developing esophageal adenocarcinoma.

Although endoscopic surveillance has been widely advocated for patients with Barrett's esophagus, it is unclear what measures should be taken when endoscopy reveals dysplasia. The presence of high-grade dysplasia or carcinoma in situ probably warrants an immediate esophagectomy, but it is uncertain how often low-grade dysplasia progresses to invasive carcinoma. There also is controversy as to whether endoscopic surveillance of patients with Barrett's esophagus is a cost-effective approach for detecting early adenocarcinomas [37, 47–49]. In fact, some asymptomatic patients who undergo surveillance are found to have advanced, unresectable adenocarcinomas at endoscopy, so this approach does not necessarily improve patient survival. Thus, many questions remain about the role of endoscopic surveillance and its ultimate value in these patients.

Attention also has recently been focused on the role of DNA flow cytometry and cellular genetic analysis to identify patients who are at increased risk for the development of esophageal adenocarcinoma. Some investigators have shown that aneuploidy is related to genomic instability with genetic mutations and neoplastic transformation [30, 50]. In one study, the findings on DNA flow cytometry directly correlated with the presence of high-grade dysplasia or invasive carcinoma on endoscopic biopsy specimens from the esophagus [50]. Thus, DNA flow cytometry may provide another diagnostic tool for surveillance of patients with known Barrett's esophagus.

Clinical Aspects

Barrett's esophagus may occur in adults of all ages, but the prevalence of this disease increases with age [2, 12]. Patients may present with reflux-related symptoms (e.g., heartburn, substernal chest pain, and regurgitation) or low-grade upper gastrointestinal bleeding due to underlying reflux esophagitis, or they may present with dysphagia due to the development of peptic strictures [51, 52]. However, many patients with Barrett's esophagus are asymptomatic. It has been postulated that the metaplastic columnar epithelium in Barrett's esophagus is less susceptible to inflammation and ulceration than the normal squamous epithelium, so patients with Barrett's esophagus are less likely to have continuing reflux symptoms than other patients with gastroesophageal reflux disease [28, 53].

The development of esophageal adenocarcinoma in Barrett's esophagus may be manifested clinically by dysphagia, weight loss, and/or upper gastrointestinal bleeding. The clinical presentation may therefore be indistinguishable from that of patients with reflux esophagitis or benign peptic strictures. However, recent onset of dysphagia in a patient with known Barrett's esophagus should raise clinical concern about the possibility of a superimposed adenocarcinoma.

In symptomatic patients with Barrett's esophagus, treatment is generally aimed at controlling the underlying gastroesophageal reflux disease to prevent the development of complications such as esophagitis, ulcers, or strictures and halt the progression of columnar metaplasia. These patients may therefore be treated medically with antisecretory agents (e.g., H2-receptor antagonists or proton-pump inhibitors) or surgically with antireflux procedures to decrease esophageal exposure to refluxed peptic acid [2, 3, 54]. Some investigators have found that regression of Barrett's mucosa may occur after successful medical treatment, antireflux procedures, or even laser ablation [55–57]. However, apparent regression of columnar mucosa could result from endoscopic sampling errors, so that Barrett's esophagus may be a life-long condition even after successful treatment of the patient's underlying reflux disease.

Radiologic Aspects

Barrett's Esophagus

The classic radiologic features of Barrett's esophagus consist of a midesophageal stricture or ulcer, often associated with a hiatal hernia and/or gastroesophageal reflux (Fig. 3) [58–60]. For reasons that are unclear, these high strictures or ulcers tend to be located in the proximal zone of columnar metaplasia near the squamocolumnar junction [59]. The strictures may appear as ring-like constrictions or, less commonly, as smooth, tapered areas of narrowing in the midesophagus [58]. Some patients with early strictures in the midesophagus may have focal puckering, flattening, and/or pleating of the esophageal wall associated with only minimal loss of distensibility, so the radiographic findings can be quite subtle [61]. Barrett's ulcers typically appear as relatively deep ulcer craters within the columnar mucosa at a considerable distance from the gastroesophageal junction. Because these findings are unusual in uncomplicated reflux esophagitis, the presence of a high esophageal stricture or ulcer, particularly if associated with a hiatal hernia and/or gastroesophageal reflux, should be strongly suggestive of Barrett's esophagus. However, studies have found that strictures are actually more common in the distal esophagus and that most cases do not fit the classic description of a high stricture or ulcer [62–64].

A reticular mucosal pattern has also been described as a relatively specific sign of Barrett's esophagus, particularly if located adjacent to a stricture (Fig. 4) [65]. This reticular pattern is characterized radiographically

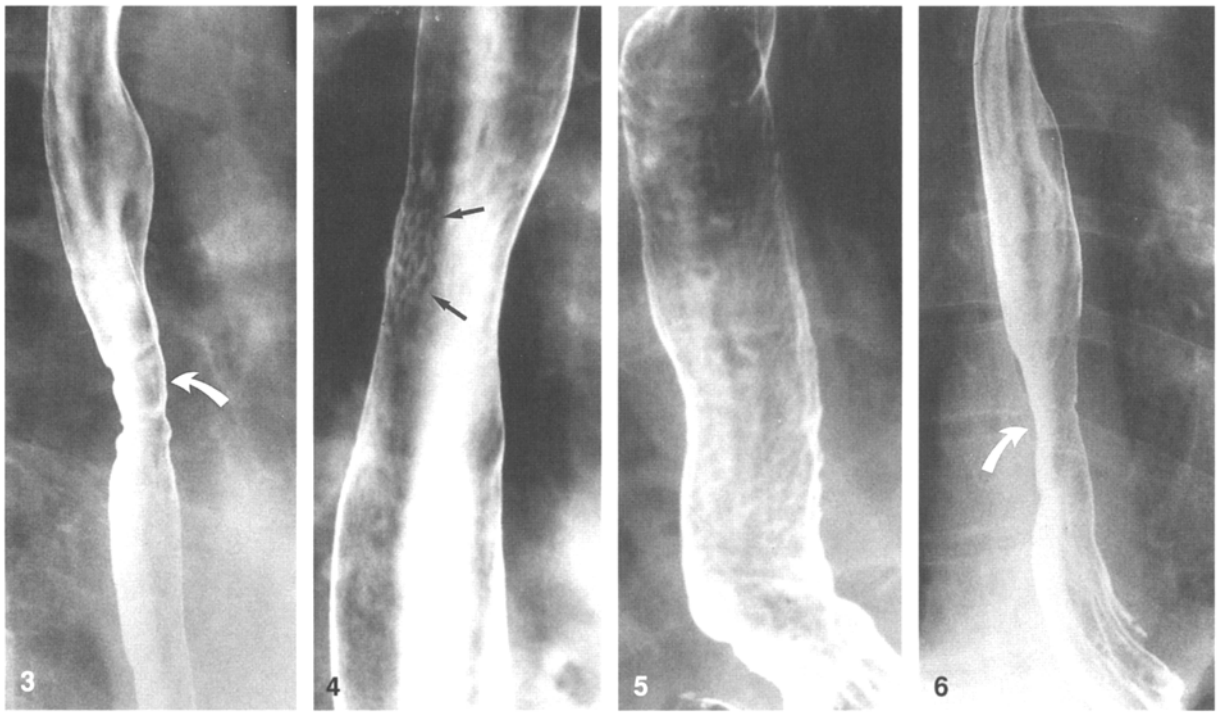

Fig. 3. Barrett's esophagus with a high stricture. A short stricture (*arrow*) is seen in the midesophagus. This patient also had a hiatal hernia and gastroesophageal reflux (reproduced with permission [68]).

Fig. 4. Barrett's esophagus with a reticular mucosal pattern. A mild stricture is present in the midesophagus, with a distinctive reticular pattern (*arrows*) abutting the stricture.

Fig. 5. Barrett's esophagus with reflux esophagitis. There is nodularity of the mucosa in the distal third of the esophagus due to edema and inflammation.

Fig. 6. Barrett's esophagus with a distal stricture. A smooth, tapered peptic stricture (*arrow*) is seen in the distal esophagus (reproduced with permission [68]).

by innumerable tiny, barium-filled grooves or crevices, often resembling the areae gastricae pattern found on double-contrast studies of the stomach. There is usually an adjacent stricture in the middle or, less commonly, distal third of the esophagus, with the reticular pattern extending distally a short but variable distance from the stricture [65]. Occasionally, however, a reticular or villous pattern of the mucosa may be observed as the only morphologic abnormality in Barrett's esophagus without evidence of strictures [66]. Although this distinctive reticular pattern should be highly suggestive of Barrett's esophagus, it is found in only 5–30% of patients [60, 63–65, 67]. Thus, most cases of Barrett's esophagus will be missed on double-contrast esophagography if a reticular pattern of the mucosa is used as the primary radiologic criterion for diagnosing this condition.

Because Barrett's esophagus develops as the sequela of long-standing gastroesophageal reflux disease, these patients often have radiologic evidence of hiatal hernias, gastroesophageal reflux, reflux esophagitis (Fig. 5), and/or peptic strictures (Fig. 6) [59, 60, 62–65, 67]. However, these findings may also be present in patients with uncomplicated reflux disease. As a result, inclusion of these findings as criteria for Barrett's esophagus increases the sensitivity of the radiologic examination but decreases its specificity, so that many patients would be referred unnecessarily for endoscopy and biopsy [67]. Thus, radiographic findings that are relatively specific for Barrett's esophagus are not sensitive, and those findings that are sensitive are not specific. Many investigators therefore believe that esophagography has limited value as a screening examination for Barrett's esophagus and that endoscopy and biopsy are required to diagnose this condition.

Recently, however, Gilchrist et al. [68] performed a blinded retrospective study of 200 patients who had both double-contrast esophagrams and endoscopy because of reflux symptoms. The patients were classified into high-, moderate-, and low-risk groups for Barrett's esophagus on the basis of the radiographic findings. Patients who were classified as at high risk for Barrett's esophagus because of a high stricture or ulcer or a reticular mucosal pattern were almost always found to have this condition, so endoscopy and biopsy should be performed in this group for a definitive diagnosis. About 15% of patients who were classified as at moderate risk for Barrett's esophagus because of a distal peptic stricture and/or reflux esophagitis were found to have this

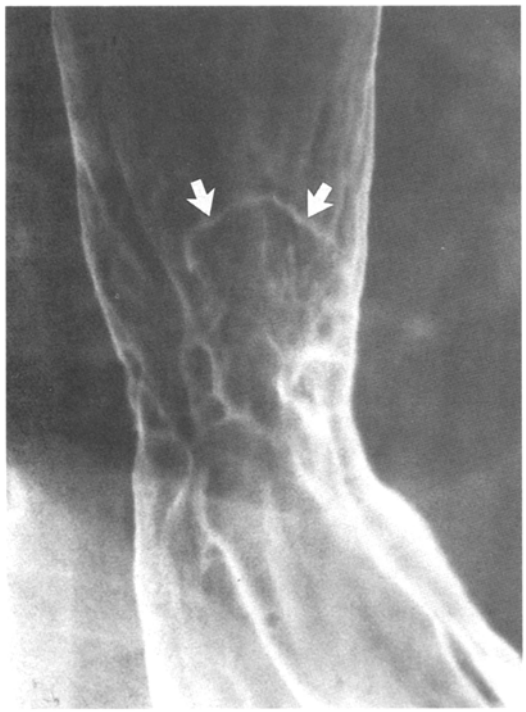

Fig. 7. Early adenocarcinoma arising in Barrett's esophagus. A plaque-like lesion (*arrows*) is seen in the distal esophagus above a hiatal hernia. Also note how the tumor causes nodularity of the adjacent mucosa.

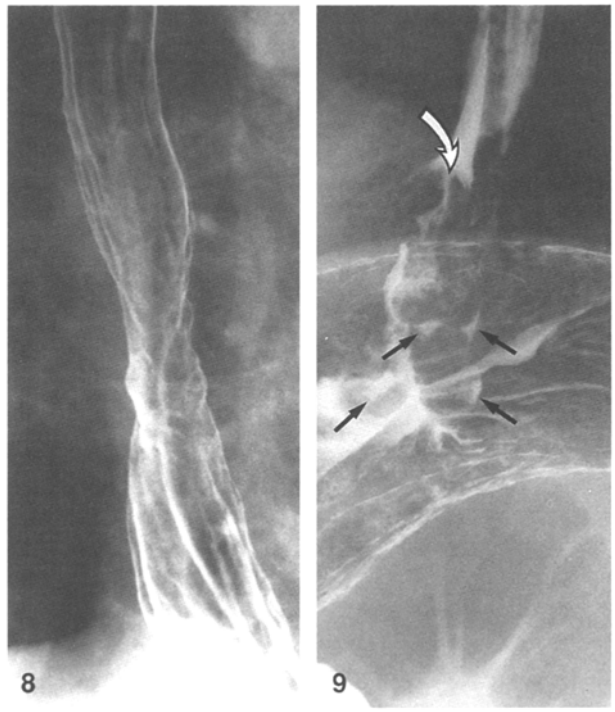

Fig. 8. Advanced adenocarcinoma arising in Barrett's esophagus. Irregular narrowing is present in the distal esophagus due to an infiltrating carcinoma.

Fig. 9. Barrett's carcinoma invading the stomach. A double-contrast view of the fundus shows obliteration of the normal anatomic landmarks at the cardia with irregular areas of ulceration (*straight arrows*). Also note how the tumor involves the distal esophagus (*curved arrow*) (reproduced with permission [44]).

condition, so clinical judgment should be used regarding the decision for endoscopy in this group based on the severity of reflux symptoms, age, and overall health of the patient. Finally, fewer than 1% of patients who were classified as at low risk for Barrett's esophagus because of the absence of esophagitis or strictures were found to have this condition, so the risk of Barrett's esophagus is low enough in this group that endoscopy does not appear to be warranted. Patients who have a normal esophagram or a hiatal hernia and/or gastroesophageal reflux without morphologic evidence of reflux disease can therefore be treated empirically for their reflux symptoms without need for endoscopic evaluation. Thus, double-contrast esophagography is a useful screening examination for Barrett's esophagus in patients with reflux symptoms, as it allows these individuals to be separated into high-, moderate-, and low-risk groups for Barrett's esophagus to determine the relative need for endoscopy and biopsy [68].

Esophageal Adenocarcinoma

Most early adenocarcinomas in Barrett's esophagus reported in the radiologic literature have been discovered fortuitously during radiologic evaluation of patients with reflux symptoms. However, barium studies are sometimes performed on patients with known Barrett's esophagus. In such cases, the radiographs should be scrutinized carefully for signs of early adenocarcinoma. These tumors may appear as plaque-like lesions (Fig. 7) or as flat, sessile polyps [69]. In patients with peptic strictures, the earliest manifestation of a developing adenocarcinoma may be a localized area of flattening or stiffening in one wall of the stricture. Other patients may have superficial spreading cancers with diffuse nodularity of the mucosa but no focal lesion [69]. Rarely, early cancers may be manifested by relatively large polypoid masses that are indistinguishable radiographically from advanced adenocarcinomas [69].

Advanced Barrett's carcinomas usually appear on barium studies as infiltrating (Fig. 8), polypoid, ulcerated, or, less frequently, varicoid lesions [44, 45]. These tumors therefore have the same radiologic features as squamous cell carcinomas. However, squamous cell carcinomas tend to be located in the upper or midesophagus, whereas adenocarcinomas tend to be located in the distal esophagus. Thus, the histologic nature of the tumor can often be predicted on the basis of its location in the esophagus.

When adenocarcinomas are located in the distal esophagus, they often involve the gastric cardia or fundus [7, 44, 45]. Gastric involvement may be manifested radiographically by a polypoid or ulcerated fundal mass. In other patients, these tumors may cause obliteration of the normal anatomic landmarks at the cardia and irregular areas of ulceration without a discrete mass (Fig. 9) [44]. The findings can be quite subtle, so that optimal double-contrast views of the gastric cardia are required to demonstrate these lesions.

Conclusion

Barrett's esophagus is probably a more common condition than previously recognized. Although the classic radiologic findings of Barrett's esophagus are present in only a small percentage of patients, this condition should be suspected whenever reflux esophagitis or peptic strictures are demonstrated on double-contrast esophagography. Recent literature also suggests that Barrett's carcinomas comprise up to 50% of all esophageal cancers. Because of the increased risk of developing adenocarcinoma in Barrett's esophagus, endoscopic surveillance has been advocated to detect dysplastic or carcinomatous changes at the earliest possible stage. When barium studies are performed on patients with known Barrett's esophagus, the radiographs should be carefully evaluated for signs of early adenocarcinoma, so these patients can be referred for appropriate management prior to the development of advanced, unresectable tumors.

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