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What is the next step for gastric atypical epithelium on histological findings of endoscopic forceps biopsy?

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ABSTRACT

Background: Gastric atypical epithelium on endoscopic biopsy is borderline lesions between benign and malignant. Definitive management of this lesion remains debatable.
Aims: We aimed to analyze the final histological diagnosis for atypical epithelium on endoscopic biopsy and to examine the discrepancy rate between the final histological diagnosis and the initial endoscopic assessment.
Methods: This retrospective study finally enrolled 24 cases proven atypical epithelium on initial histology of an endoscopic biopsy. Of 24 cases, endoscopic submucosal dissection ($n = 22$), operation ($n = 1$) and follow-up biopsy without endoscopic submucosal dissection ($n = 1$) were performed.
Results: Of the 24 cases, early gastric cancer ($n = 15$, 62%) and adenoma ($n = 7$, 30%) lesions were finally diagnosed in 22 cases. Age, sex, endoscopic results and number of biopsy did not significantly influence the result of final outcome. Between the initial endoscopic assessment and the final histological diagnosis, 12 cases (50%) showed a concordant diagnosis, but eight (33%) and four cases (17%) showed upgraded and downgraded diagnoses, respectively.
Conclusions: Of atypical epithelium cases, the rate of malignant and premalignant lesions was 92% and it was difficult to distinguish between malignant and benign lesions using the initial endoscopic findings. Therefore, endoscopic submucosal dissection can be considered in patients with atypical epithelium on endoscopic biopsy.

1. Introduction

Gastric cancer is the most prevalent cancer in Korea. Screening endoscopy to identify cancer and/or precancerous lesion is important. Gastric epithelial dysplasia is an important lesion, because it is thought to be a precursor lesion of gastric adenocarcinoma [1–6]. Endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) is widely performed to treat gastric adenomas and early gastric cancer (EGC).

Gastric adenocarcinoma may coexist with cyto-architectural alterations of the adjacent glands showing a degree of (de-)differentiation somewhere between that of the native mucosa and that of the concomitant cancer. For such phenotypical alterations, the Western literature proposed the definition of dysplasia, while Japanese authors adopted the definition of borderline lesions, atypical epithelium or group 3 lesions [7,8]. Atypical gastric epithelium on forceps biopsy specimens is often observed. Frequently, the pathologist is unable to determine if the lesion represents neoplastic or non-neoplastic cells. Atypical epithelium is often found when biopsy materials are inadequate or develop cellular architectural distortion and/or nuclear atypia during the endoscopic biopsy procedure [9]. When gastric atypical epithelium is found, the second biopsy is recommended, but treatment guidelines for gastric atypical epithelium are not established because their malignancy potential is unclear. Typically, four to six forceps biopsy specimens are taken from a lesion suspicious of malignancy. However, if the lesion is resectable by ESD or EMR, only one to two pieces of biopsy sample are taken to decrease fibrosis and ulcers following the biopsy. Several studies have reported that forceps biopsy sampling is insufficient to confirm a definitive diagnosis, and that EMR is a superior histological diagnostic and staging modality [10–12].

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Table 1
Characteristics of the enrolled patients with atypical epithelium.

Variable	Final outcome				Total ($n = 24$)
	EGC ($n = 15$)	Adenoma ($n = 7$)	Gastritis ($n = 2$)	*P* value	
Mean age (years)	66.20 ± 8.98	60.00 ± 5.54	60.50 ± 14.85	0.219	63.92 ± 8.70
Sex				0.600	
Male (%)	11 (73%)	5 (71%)	1 (50%)		17 (71%)
Endoscopic size				0.716	
<10 mm	5 (33%)	2 (29%)	1 (50%)		8 (33%)
10 mm ≤ 20 mm	6 (40%)	4 (57%)	1 (50%)		11 (46%)
≥20 mm	4 (27%)	1 (14%)	0		5 (21%)
Endoscopic finding				0.126	
Elevated	4 (27%)	2 (29%)	2 (100%)		8 (33%)
Flat	3 (20%)	2 (29%)	0		5 (21%)
Depressed	8 (53%)	3 (43%)	0		11 (46%)
Endoscopic location				0.109	
Antrum	13 (87%)	4 (57%)	0		17 (70%)
Angle	0	1 (14%)	2 (100%)		3 (13%)
Body	2 (13%)	2 (29%)	0		4 (17%)
Number of biopsies[a]				0.948	
<2	7 (47%)	3 (43%)	1 (50%)		11 (46%)
≥2	8 (53%)	4 (57%)	1 (50%)		13 (54%)
H. pylori infection				0.722	
Positive	6 (40%)	4 (57%)	0		10 (42%)
Negative	9 (60%)	3 (43%)	2 (100%)		14 (58%)

EGC, early gastric cancer.

[a] In the six cases of 13 cases with number of biopsy ≥ 2, the atypical epithelium was detected in one part of the obtained forceps biopsy specimens (in the respect cases, one of two specimens, one of three, two of four, three of five, two of three, two of four). Finally, EGC was diagnosed in 4 cases and adenoma in 2 cases.

The aim of this study was to analyze the final histological diagnosis for atypical epithelium on endoscopic forceps biopsy and to examine the discrepancy rate between the final histological diagnosis and the initial endoscopic diagnosis.

2. Patients and methods

2.1. Patients

The study involved 27 patients with atypical epithelium that were histologically proven based on forceps biopsy specimens using esophagogastroduodenoscopy (EGD) between April 2008 and September 2010 at Digestive Disease Center, Konkuk University Medical Center, retrospectively. Of these cases, three were excluded due to follow-up loss. During the same period, gastric cancer and gastric adenoma were proven based on forceps biopsy in 775 cases and 317 cases. Gastric atypical epithelium on endoscopic forceps biopsy specimens were defined as atypical changes interpreted as questionable dysplasia with a detailed description. Atypical epithelium with reactive and regenerative gastric epithelium was excluded because reactivity is resolved when infection or inflammation improves, and the lesion is considered benign. The cases in which the distinction between regenerative and dysplastic epithelium was not clear were labelled atypia. The institutional review board of Konkuk University Medical Center approved this study.

2.2. Endoscopic and histopathologic evaluations

Diagnostic endoscopy was performed with a single-channel endoscope (GIF-Q260J; Olympus Co, Tokyo, Japan). ESD was performed with a water jet endoscope (GIF-H260Z; Olympus) with a transparent hood attached to the top, according to a standardized protocol after obtaining informed consent. The procedure was performed using the following methods: (1) marking using a flex knife, (2) lifting by submucosal injection of a mixed glycerol solution, (3) precutting using a flex knife and an insulated tipped electrosurgical (IT-2) knife, (4) submuosal dissection and cutting using an IT-2 knife, (5) hemostasis using coagrasper and (6) fixation (Fig. 1). We reviewed the endoscopic images in relation to lesion size (mm), location and type (elevated, flat or depressed).

Three pathologists including one gastrointestinal pathologic specialist (HS Han) were involved in the histological diagnosis in this study. Histological diagnoses were based on the World Health Organization classification of pathology and genetics of tumours of the digestive system [13]. Especially, atypical epithelium was at the base of the definition of borderline of Japanese classification [8]. According to the Japanese Society Histologic Classification, Group 3 lesion was defined into the borderline lesions between benign (non-neoplastic) and malignant lesions. This group includes lesion that are difficult to diagnose as either benign (non-neoplastic) or malignant in terms of cellular and structural atypia. In specimens suspicious of atypical epithelium, the final histological diagnosis was reported when a consensus was reached among all pathologists. Of our cases, eight cases were decided as atypical epithelium by consent of three specialized pathologists at the Pathologic Departmental Collegial Session. Fig. 2 shows the histology characteristics of atypical epithelium on initial forceps biopsy specimens.

The presence of *H. pylori* infection was determined by both histology (Giemsa stain) and a rapid urease test (CLO test; Delta West, Australia, manufactured by Korea Green Cross Medical Science, Eumseong, Korea); the subjects were judged to be *H. pylori*-positive only when both tests were positive.

There were classified into three categories according to agreement between the forceps biopsy and the final histological diagnosis from ESD (or an operation). A concordant diagnosis was reached when the biopsy and final histological diagnosis was the same. An upgraded diagnosis occurred when the final histological diagnosis showed histology with more malignant potential. A downgraded diagnosis was defined when the final histological diagnosis showed histology with less malignant potential.

2.3. Statistical analysis

Statistical analysis was performed using the chi-square test to compare discrete variables and the t-test for continuous variables. To examine potential factors for EGC, the multivariate models were