Review

Squamous intraepithelial neoplasia of the esophagus: past, present, and future

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With regard to the esophagus, the term “squamous dysplasia” has been used in European countries, the United States, and China, while its use is controversial in Japan. Recently, “low-grade intraepithelial neoplasia” and “high-grade intraepithelial neoplasia” have been used as inclusive terms for dysplasia and carcinoma in situ in the World Health Organization classification. Endoscopically, it is often difficult to identify squamous intraepithelial neoplasia by conventional endoscopy, but application of iodine is useful for the diagnosis of such a lesion. In addition, new types of endoscopic techniques, including magnifying endoscopy, narrow-band imaging (NBI), and endocytoscopy are helpful to detect squamous intraepithelial neoplasia. NBI is very useful for identifying the intrapapillary capillary loop pattern. Regarding the pathological criteria of squamous dysplasia and squamous cell carcinoma, the views of Japanese and Western pathologists have differed significantly. Before the term “intraepithelial neoplasia” was introduced, severe dysplasia as diagnosed by Western pathologists was in fact the same as squamous cell carcinoma in situ or noninvasive carcinoma as diagnosed by Japanese pathologists. This problem has been solved by the introduction of the Vienna classification; however, there are still some issues that need to be resolved. One of them is the presence of basal layer type squamous cell carcinoma in situ, which is often underdiagnosed as low-grade intraepithelial neoplasia by Western pathologists. Endoscopic treatments such as endoscopic mucosal resection and endoscopic submucosal dissection have recently become possible choices for squamous intraepithelial neoplasia; however, these techniques are not in widespread use in the West. We believe that a consensus meeting between Japanese and Western pathologists as well as endoscopists should be held promptly to reach a common ground for the nomenclature.

Key words: esophageal squamous intraepithelial neoplasia, squamous cell carcinoma in situ (CIS), endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), narrow-band imaging (NBI)

Introduction

Of the esophageal cancers, squamous cell carcinoma is the most common carcinoma in Japan. However, in the United States, esophageal squamous cell carcinoma is relatively uncommon, with the incidence of adenocarcinoma being higher and rapidly increasing. Adenocarcinomas of the esophagus usually arise in the setting of Barrett’s esophagus. Therefore, dysplasia in the esophagus, even in English gastrointestinal textbooks, usually refers to glandular dysplasia, especially in Barrett’s esophagus, and not squamous dysplasia. Even when searching for articles on esophageal dysplasia, we found that most papers deal with glandular dysplasia in relation to adenocarcinoma derived from Barrett’s esophagus. Thus, squamous dysplasia of the esophagus is very rare in the English literature, and most articles are contributed from China or Japan. In 2000, the World Health Organization (WHO) classification introduced the term “intraepithelial neoplasia” for the esophagus. Since then, many articles have been using the term “intraepithelial neoplasia” rather than dysplasia or carcinoma in situ (CIS). In this review article, we specifically focus on and review squamous dysplasia, not glandular dysplasia. Then, we focus on the squamous intraepithelial neoplasia, including the difference in the clinical and pathological diagnoses between Japan and the West. In addition, the tenth Japanese edition of the Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus (Second English edition is now available from Kanehara, Tokyo) as well as the
Definition and concept of dysplasia and intraepithelial neoplasia

The term “dysplasia” literally means disordered growth or abnormality of development. However, the pathological definition of dysplasia is alteration in size, shape, and organization of adult cells, which means that it can include pleomorphic cells with hyperchromatic nuclei and mitotic figures. In the field of pathology, the term “dysplasia” is used in relation to some organs such as the uterine cervix and the urinary bladder to indicate a precancerous lesion, while different terminology has been used for the same condition in other organs: for example, “atypical hyperplasia” in the endometrium, “atypical ductal hyperplasia” in the breast, and “prostatic intraepithelial neoplasia” in the prostate. With regard to the esophagus, the term “dysplasia,” especially for the squamous epithelium, has been used in European countries and in the United States as well as in China to mean a precancerous lesion, while different terminology has been used for the same condition in other organs: for example, “atypical hyperplasia” in the endometrium, “atypical ductal hyperplasia” in the breast, and “prostatic intraepithelial neoplasia” in the prostate. With regard to the esophagus, the term “dysplasia,” especially for the squamous epithelium, has been used in European countries and in the United States as well as in China to mean a precancerous lesion, while it is controversial to use it that way in Japan. Therefore, the concept of esophageal dysplasia of the squamous epithelium still remains to be debated.

Dysplasia of the squamous epithelium was defined as precancerous lesions with both architectural and cytological abnormalities by the earlier WHO classification of esophageal tumors. Dysplasia was traditionally classified as mild, moderate, or severe; however, most pathologists prefer to use low-grade and high-grade dysplasia because of the poor interobserver agreement with a three-tier classification. With the increasing grade of dysplasia, atypical cells involve and replace the entire thickness of the squamous epithelium, but the lesion remains confined to the epithelium. This is referred to as CIS, and no evidence of maturation is observed at the surface of the epithelium. Lymph node metastases are not found in CIS. Once the atypical cells invade the lamina propria, the lesion becomes known as invasive carcinoma.

Looking back at the history of the term “squamous dysplasia” in Japan, there are two famous round-table talks published in the Japanese literature in 1996 and 2007, called Stomach and Intestine. In both round-table talks, active discussions were conducted. Although no definite conclusion was reached on the definition/existence of dysplasia, it is clear that most pathologists who attended these discussions did not use the term “squamous dysplasia” except on very rare occasions. In addition, some pathologists deny the existence of squamous dysplasia in the esophagus as a precancerous lesion, and they classify esophageal atypical squamous epithelium into nonneoplastic atypical epithelium and noninvasive carcinoma. The former lesion includes reactive immature epithelium seen in esophagitis, erosion, ulcers, or hyperplasia, and the latter is divided into low-grade carcinoma and high-grade carcinoma.

Thus, most gastrointestinal pathologists in Japan would regard the photographs of high-grade dysplasia, sometimes even low-grade dysplasia, published in recent gastrointestinal pathology textbooks as noninvasive squamous cell carcinoma. This topic is discussed later in the section of pathological findings of squamous intraepithelial neoplasia.

In the recent WHO classification, “intraepithelial neoplasia” has been used as an inclusive term for dysplasia and CIS. High-grade intraepithelial neoplasia is used for severe dysplasia and CIS, since they may have the same clinical implications. The term “esophageal intraepithelial neoplasia” is used in some textbooks.

Clinical findings of squamous intraepithelial neoplasia

Generally, patients with squamous intraepithelial neoplasia present no symptoms. Squamous intraepithelial neoplasia of the esophagus may be frequently encountered in biopsy specimens in China and Japan, whereas in the United States and European countries it is more commonly observed in resected specimens of esophageal squamous cell carcinoma. Squamous intraepithelial neoplasia can be present adjacent to squamous cell carcinoma. Dysplasia is found in 60%–90% of the resected cases of squamous cell carcinoma of the esophagus. About 30% of autopsy cases of squamous cell carcinoma of the esophagus are said to reveal squamous dysplasia in varying degrees, including mild, moderate, and severe. According to follow-up studies of Chinese patients with squamous dysplasia, squamous cell carcinoma develops through a progression of dysplastic lesions; in other words, squamous dysplasia plays a role in the genesis of squamous cell carcinoma of the esophagus. Furthermore, DNA methylation was recently found to contribute to the progression of intraepithelial neoplasia to carcinoma.

It is very difficult to detect squamous intraepithelial neoplasia of the esophagus by esophagography, and it is frequently difficult to identify intraepithelial neoplasia by conventional endoscopy. Generally, squamous intraepithelial neoplasia is composed of flat lesions with poor quality color variation, or focal red areas, nodules,