Review Article

Adenosquamous carcinoma of the esophagus: A literature review

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ABSTRACT

Adenosquamous carcinoma (ASC) of the esophagus is an uncommon type of esophageal cancer that contains both adenocarcinoma and squamous cell carcinoma elements. Data on this biologically unique type of cancer are limited and mainly stem from case reports and small case series. We performed an audit of the available literature and synthesized a review on the epidemiology, pathogenesis, histopathology, clinical manifestations, diagnosis, treatment and prognosis of ASCs. Adenosquamous carcinoma of the esophagus is a rare type of esophageal cancer. Histological examination is necessary to confirm the diagnosis of ASC and patients usually receive multimodal treatment. Patient outcomes are not well defined and further research could help us better understand the pathophysiology and unique needs of patients with this rare malignancy.

Key words: adenosquamous carcinoma, esophageal cancer, esophageal carcinoma, esophageal tumor, esophageal malignancy

INTRODUCTION

Esophageal cancer is the 8th most common type of cancer worldwide and the 6th leading cause of cancer-related deaths. The two major histological types of esophageal cancer are Squamous Cell Carcinoma (SCC) and Adenocarcinoma (AC). There are significant geographic variations in the incidence rates of esophageal cancer and its histological types. SCC is the most prevalent esophageal cancer worldwide, while AC occurs more frequently in Western countries.[1,2] One of the less common variants of esophageal cancer is Adenosquamous Carcinoma (ASC), which is comprised by both SCC and AC elements. Literature on ASC is scare and mostly consists of small case series.[3–7] Only recently did larger case series emerge.[8,9] The purpose of this review is to summarize the existing data on epidemiology, pathogenesis, histopathology, clinical characteristics, diagnosis and staging of ASC, as well as treatment and prognosis.

DEFINITION AND CLASSIFICATION

The first description of ASC was in 1947, in a case report by McPeak *et al.*, where it was characterized as adenoacanthoma.[10] ASC was also referred to as the Mucoepidermoid Carcinoma of the Esophagus (MECE) and those entities were initially considered as one in literature.[11] Originally, in the Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus (GCPSCE) by the Japanese Society for Esophageal Disease (JSED), ASC was classified in "other malignancies" and distinguished from adenoacanthoma. Later in the 8th GCPSCE [1992], JSED classified ASC as "adenosquamous carcinoma" and MECE was classified to the subclass type of "adenosquamous carcinoma". Finally, in the 9th GCPSCE [1999], MECE was completely distinguished from ASC. In addition to JSED, the World Health Organization (WHO) distinguished ASC from MECE, in the 1990 WHO Classification of Tumors of the Esophagus.[3]

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Based on the aforementioned classification systems, there are two ways to define ASC. According to the Japan Esophageal Society (JES), in order for an esophageal tumor to be characterized as ASC, the SCC component and AC component need to be identified under microscopic examination, with each accounting for at least 20% of the tumor.[12] On the other hand, the WHO Classification of Digestive Tumors states that ASC is any esophageal lesion containing a significant SCC component intermingled with tubular AC elements, with no special reference to the ratio of these two components.[13]

EPIDEMIOLOGY

ASC is a rare type of esophageal cancer. In patient series from both Asia[3–7] and the US,[8,9] the reported incidence rates range between 0.37%[5] and 1%.[3,7,9] The age and gender distribution is also consistent throughout the literature. ASC mostly presents in people older than 40 years, with incidence peaking around the 7th decade of life. Men are more frequently affected than women, with male-to-female ratios ranging from 4:1[8] to 8:1.[4]

PATHOGENESIS

The origin of ASC is not clear yet and various theories regarding the histogenesis of these tumors have been suggested. Several authors have studied ASC in the setting of Barrett's Esophagus.[11,14–17] Pascal *et al.* suggested that ASC arises from esophageal gland cells or ductal cells. Because epithelium and submucosal glands are all derived from the foregut during embryogenesis, the AC component has the potential to transform into SCC.[11] In addition, Van Rees et. al. proposed a tumor progression pathway in which Barrett's epithelium, after losing heterozygosity at chromosome arm 9p, exhibits further loss of heterozygosity at several other chromosomal loci and a missense mutation in the p53 gene. From there, a malignant cell can develop into either SCC or AC. If an additional shift at chromosomal arm 16q occurs, AC can develop.[15] In contrast, some authors believe that ASC arises from the mucosa, where it begins originally as SCC and glandular differentiation occurs later within the tumor.[6,7,18–20] Last but not least, a collision concept has been proposed, in which ASC comes from two individual stem cells that simultaneously and independently undergo malignant transformation.[21,22]

HISTOPATHOLOGY

ASC has various macroscopic tumor types, such as ulcerative, medullary, intraluminal, polypoid and sclerotic, and upon macroscopic inspection, it is indistinguishable from SCC.[5,6] Microscopically, it is characterized by an AC and a SCC component that either have a clear boundary or exhibit a gradual transition between them. This is a main point of differentiation with Mucoepidermoid Carcinoma of the Esophagus (MECE), where the mixture of squamous cells and mucus secreting cells is homologous and intermediate cells can be observed.[6,23,24] The SCC element contains pathologic findings such as keratin pearl formation, zonal differentiation towards the center of the tumor nests and intercellular bridges, while the AC element is characterized by the presence of tubular and/or glandular structures and, occasionally, by mucus production.[6,7] Finally, both Chen and Yachida found that the squamous cell component dominates in the mucosa and the AC component is mainly found in the deeper parts of the tumor.[6,7]

CLINICAL PRESENTATION

ASC has the same clinical manifestations with SCC and AC. Studies have shown dysphagia to be the most common presenting symptom of ASC, followed by retrosternal or upper abdominal pain and weight loss.[3,5,6,9,25]

There are discordant reports throughout the literature regarding the location distribution of ASC. In some studies, ASC mainly presented in the middle esophagus,[3,6,7] which is the area where SCC is most commonly found.[25] In contrast, others reported the distal esophagus as being more frequently affected,[4,8,9] thus resembling the distribution pattern of AC.[25]

DIAGNOSIS

Even though esophagogastroduodenoscopy (EGD) with endoscopic biopsy is important in the preoperative diagnosis of esophageal cancer; when it comes to ASC, it has been shown to have low diagnostic accuracy. Large series have reported a misdiagnosis rate of 61.1%–100%, and in most cases, that diagnosis was SCC. Only when resection specimens from surgery were examined, the tumors were found to be ASC.[4–7] A reason for this discrepancy could be the fact that, in most tumors, the SCC component is located in the mucosa, while the AC component is mainly found in deeper areas of the tumor, where getting specimen from is not always possible.

STAGING

Throughout literature, the AJCC/UICC TNM staging system[26] has been utilized in the staging of ASC. The predominant stage at the time of diagnosis differed between the studies.[3–5,7,9] In the same way, the data regarding the distribution of patients in different pT and pN stages are contradicting.[3–8] When it comes to Tumor Grade, several

studies showed that ASC are more commonly higher grade tumors (poorly differentiated or undifferentiated) than lower grade.[3,5,9] Finally, Yendamuri *et al.*[9] found that ASC is at more advanced stages and higher grade when diagnosed, in comparison with AC and SCC.

TREATMENT

The role of surgery and other therapeutic measures on the treatment of ASC are yet unclear. Current literature is limited to patient treatment allocation statistics and observational data regarding prognosis. The two largest patient series to date have found that approximately 33–37% of patients with ASC underwent surgical removal of the tumor. When compared with the other histological types, ASC and AC had comparable resection rates and both were more frequently resected than SCC. These studies also reported that approximately 55% received the Radiation Therapy, the same as in AC, but lower than SCC. Evans *et al.* also showed that 60% of ASC patients received Chemotherapy, a rate similar to the other histological types. A major limitation of those studies is that they do not specify if those non-surgical modalities are neo-adjuvant or adjuvant.[8,9]

The treatment of esophageal cancer is multimodal. Surgical resection is the cornerstone of treatment for locally advanced SCC and AC. No approach has been found to be superior over others in regard to survival and the choice of surgical technique mainly depends on the tumor location and the preference of the surgeon. In addition, lymph node dissection and adequate lymph node sampling are important parts of surgery, although the extent of lymphadenectomy (two-field *vs.* three-field lymphadenectomy) is still a matter of debate.[1] Provided that the tumor is resectable and not misdiagnosed as another type, it would be safe to assume that the principles mentioned for SCC and AC are applicable to ASC.

What is more, non-surgical therapeutic measures, such as radiotherapy and chemotherapy, play a significant part in the treatment of esophageal cancer. The combination and timing of those treatments are matters of great complexity. Nevertheless, it seems that neoadjuvant therapy, either chemoradiotherapy or chemotherapy, offers a significant survival advantage over surgery alone in both major histological types.[25] As a result, the adoption of neoadjuvant modalities seems like the reasonable choice when it comes to ASC. Finally, since the role of adjuvant therapy differs between SCC and AC, no logical conclusion for the use in ASC can be drawn.

PROGNOSIS

Current literature is conflicting when it comes to the prognosis of ASC. The reported Median Survival Time (MST) is 9.6–44.4 months[3,5,6,8] and 5-year Overall Survival (OS) rates reported were as low as 12.8%[8] and as high as 63.6%.[7]

Although the relationship between various clinicopathological features of ASC and prognosis has been examined by most authors, no consensus has been reached yet on what the prognostic factors of ASC are. In univariate analyses, each author found a different set of variables that significantly affected survival.[3–6,9] In multivariate analyses, Ni *et al.* and Zhang *et al.* reported lymph node metastasis to be the only independent prognostic factor for ASC, while Chen *et al.* found that only adjuvant radiotherapy independently affected survival. Finally, in a study by Sun *et al.*, the independent prognostic factors were tumor length, perineural invasion and the type of surgical resection.[3–6]

When the survival of ASC was compared with AC and SCC, the results were also contradicting. The largest patient series was by Evans *et al.* , where ASC was found to have the same Median Survival Time (MST) with SCC and lower than AC. In the same study, the Overall Survival of ASC was lower than SCC and AC.[8] In contrast, Chen *et al.* reported that ASC has lower MST and OS than SCC.[6] Finally, Yachida *et al.* shows that the OS for ASC is better than AC and SCC, but this finding can be attributed to the smaller size and lower stage of the ASC tumors in their study.[7]

CONCLUSION

In conclusion, adenosquamous carcinoma is a rare type of esophageal tumor that is challenging to diagnose prior to surgery. Potential solutions to maximize diagnostic accuracy could be deeper biopsies, that obtain a greater tissue sample, and stricter implementation of the JES and WHO diagnostic criteria. Patients with these tumors may benefit from a multidisciplinary treatment approach. However, definitive conclusions regarding pathogenesis, biological behavior, treatment and prognosis have yet to be reached. Therefore, future studies providing more granular data are required.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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