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Case Report

Esophageal invasive acantholytic anaplastic Paget's disease: report of a unique case

Dong-Liang Lin[1*], Jie Liu[3*], Zhen Yang[1], Yu-Jun Li[1], Ji-Gang Wang[1], Jiao Wang[4], Li Ding[2]

Departments of [1]Pathology, [2]YIWU, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, China; [3]Department of Gastroenterology, Yantai YEDA Hospital, Yantai City, Shandong, China; [4]Department of Pathology, People's Hospital of Rizhao, Rizhao, Shandong, China. [*]Equal contributors and co-first authors.

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Abstract: Paget's disease (PD) is an intraepithelial growth of neoplastic cells showing glandular differentiation. Primary esophageal PD is extremely rare, with only 14 cases reported to date. We report a case of esophageal PD in a 63-year-old man presenting with progressive dysphagia. On gross examination, the esophageal mucosa had a slightly mottled appearance and felt slightly thickened and indurated. Microscopically, the atypical tumor cells were mostly located in middle to basal cell layers of the squamous epithelium. Some tumor cells were difficult to be distinguished from normal squamous epithelium. Some regions of the lesion showed full-thickness cellular atypia with mitotic figures, and some tumor cells invaded through the basement membrane into the lamina propria, mimicking a squamous cell carcinoma. Acantholytic regions were prominent in the epithelium, and some gland-like clefts were formed. One recurrent laryngeal nerve lymph node showed metastatic foci. Immunohistochemically, tumor cells were positive for cytokeratin (CK) 7, CK8/18, carcinoembryonic antigen (CEA) and Her-2, but negative for CK5/6, p63, S-100 protein and HMB45, yielding the diagnosis of PD. This is the first case report of esophageal invasive Paget's disease (invPD) and the first case report of esophageal acantholytic anaplastic Paget's disease (AAPD).

Keywords: Paget's disease, esophagus, carcinoma, diagnosis, pathology

Introduction

PD is an intraepithelial growth of neoplastic cells showing glandular differentiation by mucin histochemistry and/or immunohistochemical staining. It was first described in 1874 by Sir James Paget. After its initial description in the areolar skin, PD has been described in many other extramammary locations. The most common site of extramammary Paget's disease (EMPD) is the vulva (accounting for 65% of EMPD), followed by the perianal region, male genitalia, and the apocrine gland-rich skin of the axilla [1, 2]. More rarely, EMPD occurs in areas of the skin that are normally devoid of apocrine sweat glands such as the back, arms, knees and digits [1]. There have also been case reports of EMPD in pure mucous membrane sites including the cervix [3], bronchus [4], and oral mucosa [5]. Esophageal PD is extremely rare. The first esophageal PD was reported in Japanese literature in 1988 [6]. To our knowledge, there have been only 14 cases of PD involving the esophagus in PubMed [6-12].

InvPD can occur in mammary and extramammary areas. Among the 14 reported esophageal PDs, none was invasive. AAPD, a rare and less-known variant of PD, which was originally named by Rayne and Santa Cruz [13], is characterized by anaplastic tumor cells, full-thickness atypia of the epithelium, and acantholysis. Herein, we report an additional esophageal PD, and this is the first case of esophageal invPD and the first case of esophageal AAPD.

Case summary

Clinical summary

A 63-year-old Chinese man was admitted to the Affiliated Hospital of Qingdao University, with the complaint of progressive dysphagia of 6 months duration. He did not have any underlying diseases and had maintained good health. Endoscopic examination performed in another hospital showed stiffness and roughness of the distal esophageal wall. Mucosal erosion was detected in some regions of the lesion. The pa-

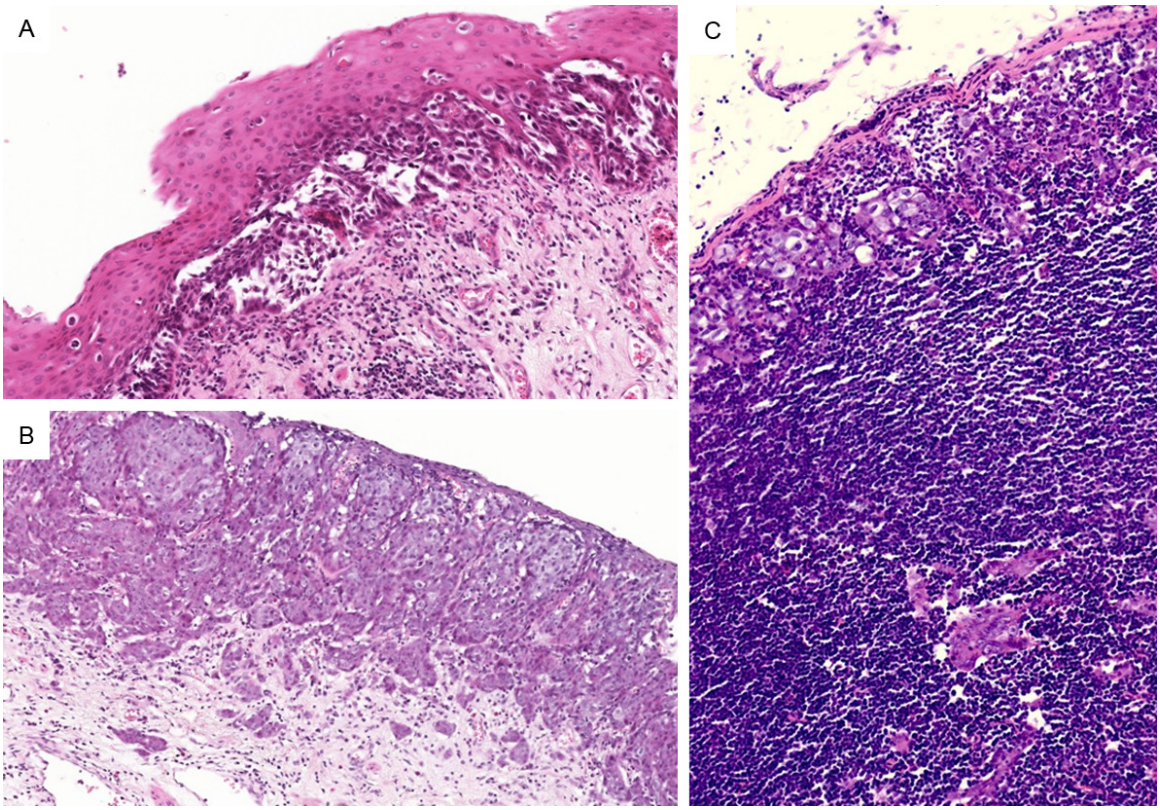

Figure 1. Pathologic results of the primary tumor and the metastatic foci. A. Atypical cells were mostly located in middle to basal cell layers of the squamous epithelium and acantholytic regions (gland-like clefts) were prominent in the epithelium; B. Paget's cells invading through the basement membrane into the lamina propria; C. Metastatic foci in recurrent laryngeal nerve lymph node.

thologic diagnosis based on endoscopy suggested esophageal squamous cell carcinoma. Thereafter, the patient underwent esophagectomy.

Materials and methods

The resected esophageal specimen was fixed in 10% formalin. Routine histologic examination was performed after paraffin embedding and staining with hematoxylin-eosin, alcian blue, mucicarmine and periodic acid-Schiff with diastase (PAS-D). Immunohistochemical analysis was performed on paraffin-embedded sections using the following primary antibodies: CK7, CK8/18, CEA, CK5/6, p63, S100 protein, Ki67, Her-2, gross cystic disease fluid protein-15 (GCDFP-15) and HMB45.

Pathologic findings

On gross examination, there was no palpable tumor mass or ulcer on the esophageal mucosa. However, the mucosa had a slightly mottled appearance and felt slightly thickened and indurated. Mucosal erosion was detected in some regions of the lesion. The extent of the lesion was about 6.2 cm, and the distance from the lesion to the dentate line was about 5.0 cm.

Microscopically, the mucosa was slightly thickened. Atypical cells were mostly located in middle to basal cell layers of the squamous epithelium (**Figure 1A**). Acantholytic regions were prominent in the epithelium, and some gland-like clefts were formed (**Figure 1A**). In some areas, it was difficult to distinguish the tumor cells from normal squamous epithelium. Some regions of the lesion showed full-thickness cellular atypia with mitotic figures, similar to squamous cell carcinoma in situ. Three foci of invasion consisted of isolated or small clusters of Paget's cells invading through the basement membrane into the lamina propria were detected (**Figure 1B**). The tumor cells were large and contained rich basophilic cytoplasm. A small number of tumor cells had clear or pale-stain-

ing cytoplasm, which is the characteristic of Paget's cells. The nucleus of the tumor cells was large and the nucleolus was prominent. The cytologic features of the invading cells in the lamina propria were identical to those of intraepithelial tumor cells. Moreover, some mucosal and submucosal ducts showed luminal stenosis and some tumor cells existed in the ducts. Forty lymph nodes were identified. One recurrent laryngeal nerve lymph node showed metastatic foci with features identical to the esophageal lesion (**Figure 1C**). The surgical margin was free of tumor cells.

Immunohistochemically, tumor cells showed immunoactivity for CK7, CK8/18, CEA, Ki67, and Her-2 (**Figure 2A-D**), and were negative for S-100 protein, HMB45, CK5/6, p63, and GCDFP-15 (**Figure 2E** and **2F**). However, all mucin stains (including alcian blue, mucicarmine and PAS-D) were negative (**Figure 2G**). The metastatic foci in the lymph node showed identical immunophenotype to the esophageal lesion (**Figure 2H**).

Discussion

PD, a tumor usually described as an intraepithelial lesion, has been described in many other extramammary locations. The most common location of EMPD is the vulva (accounting for 65% of EMPD) [2]. Primary esophageal PD is extremely rare. To date, only 14 cases have been reported [6-12]. In general, PD had an underlying carcinoma [2], nonetheless PD can also exist independently without underlying carcinoma [14, 15], especially in vulval PD [2]. Thus, EMPD can be classified into primary type and secondary type based on the presence or absence of associated malignancies [2]. It is generally believed that secondary PD originates from the underlying carcinoma, but primary EMPD originates from pluripotent stem cells which can differentiate into Paget's cells. The pathologic specimen of the present case underwent complete pathology dissection, and underlying carcinoma was not observed in histologic sections. Of the 14 cases of reported esophageal PD, most are secondary cases [6, 8-11]. Including the present case, 3 cases should be considered as esophageal primary PD [7, 12].

In some PD cases, Paget's cells can invade through the basement membrane into the superficial dermis, which was defined as invPD [16, 17]. InvPD can occur in both mammary and extramammary cases [16, 17]. Invasion of Paget's cells into the lamina propria was detected in the present case, making it the first case of esophageal invPD reported. InvPD of the vulva has a higher recurrence rate and mortality rate [17]. Moreover, lymph node metastasis was identified in our case. Therefore, aggressive postoperative treatment and close follow-up is necessary for this patient.

Histologically, AAPD is characterized by full-thickness atypia of the epithelium, fissurations (acantholysis), prominent mitotic figures, and lacks nesting architectures in classic PD. Some researchers believe that AAPD is a rare subtype of PD [13, 18]. Unlike classic PD, most AAPD were negative by mucin stain [13]. Our case has all the above mentioned features. Invasive AAPD has not been reported in the literature, and this is the first invasive case. Squamous cell carcinoma should be regarded as one of the main histologic differential diagnoses because of the full-thickness atypia of the epithelium and invasion of tumor cells. The present patient was initially misdiagnosed with a squamous cell carcinoma due to the similarities between the two. Moreover, the Paget's cells showed immunoactivity for CK7, CK8/18, CEA and Her-2, but were negative for CK5/6 and p63, which can distinguish AAPD from squamous cell carcinoma. In addition, melanoma should also be regarded as a histologic differential diagnosis. Positive cytokeratin staining and lack of melanocytic marker (S-100 protein and HMB45) expression can contribute to an accurate diagnosis.

In conclusion, we report a rare case of esophageal PD, and this is the first case of esophageal invPD and the first case of esophageal AAPD. The accurate diagnosis was a challenge both for clinicians and for pathologists. The patient underwent chemotherapy with docetaxel and cisplatin, and has been followed up for 21 months with no recurrence or metastasis.

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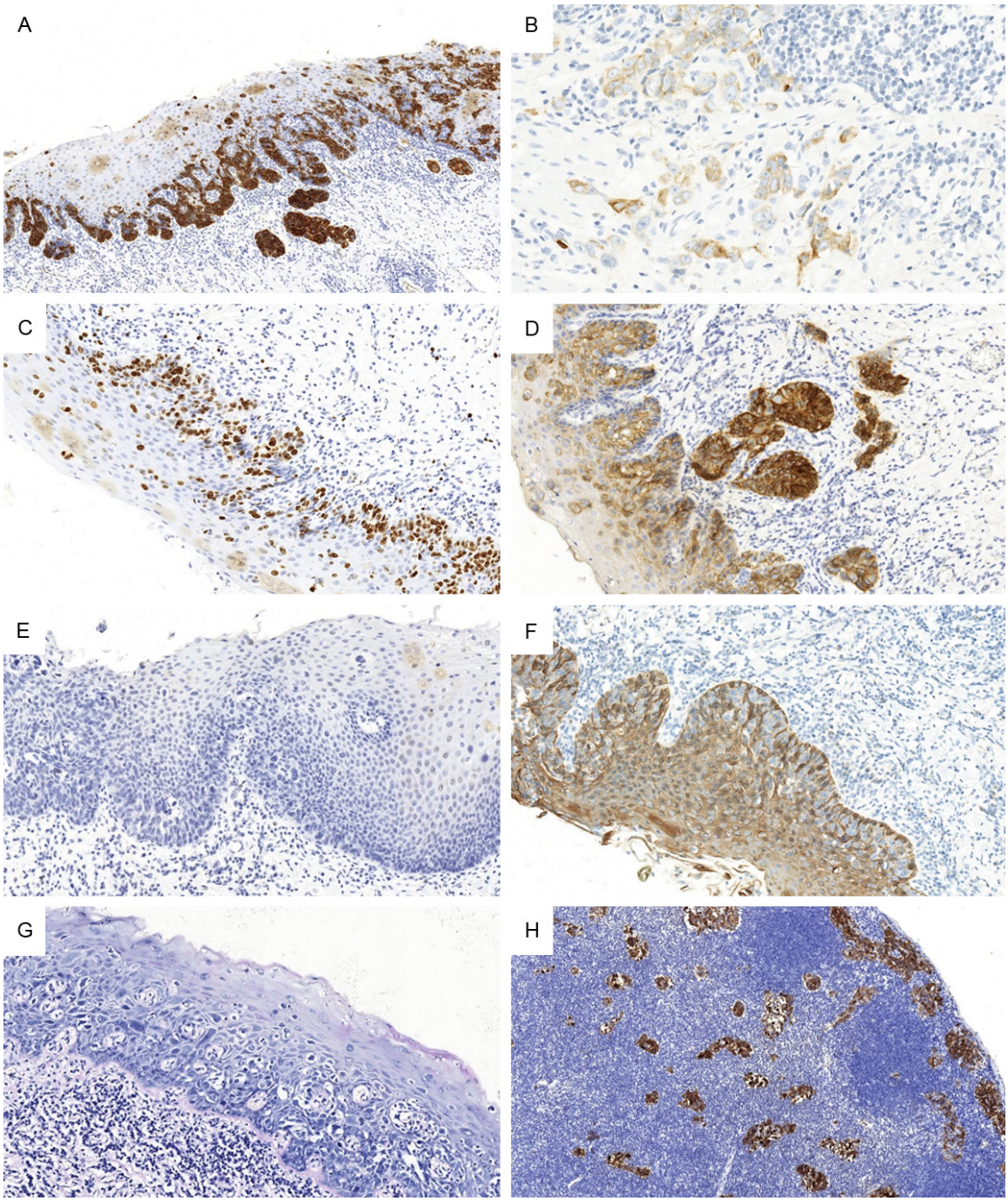

Figure 2. Immunohistochemical and mucin staining of the lesion. A. The tumor cells (noting the intraepithelial tumor cells and the invasive tumor foci) were highlighted by CK7; B. The tumor cells were positive for CEA; C. The tumor cells were highlighted by Ki67; D. The tumor cells were positive for Her-2; E. The tumor cells were negative for HMB45; F. CK5/6 negative tumor cells forming a distinct blank zone in the squamous epithelium; G. PAS-D was negative; H. The metastatic foci in the lymph node showed immunoactivity for CK7.

Liu collected patient's data and did the follow-up, completed the manuscript with Zhen Yang and Jiao Wang. Ji-Gang Wang and Li Ding provided clinical support and carried out guidance and supervision for the work. All authors read and approved the final manuscript.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Li Ding, Department of YIWU, The Affiliated Hospital of Qingdao

University, 16 Jiangsu Road, Qingdao 266003, Shandong, China. E-mail: dingli831010@sina.com

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