Journal of Clinical and Translational Pathology **2024** vol. 4(4) | 178–183
DOI: 10.14218/JCTP.2024.00033

Case Report

Paget's Disease of the Esophagus Recurred Coexisting with Small Cell Carcinoma: A Case Report and Literature Review

Zhaoyang Yang[1], Bin Wang[2], Liang Yang[3], Xuemin Xue[1], Jiacong Wei[1] and Liyan Xue[1*]

[1]Department of Pathology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [2]Department of Pathology, The Fourth Central Hospital of Baoding City/The People's Hospital of Tangxian County, Baoding, Hebei, China; [3]Department of Endoscopy, The Fourth Central Hospital of Baoding City/The People's Hospital of Tangxian County, Baoding, Hebei, China

Received: August 06, 2024 | **Revised:** September 23, 2024 | **Accepted:** September 25, 2024 | **Published online:** October 30, 2024

Abstract

Paget's disease of the esophagus is extremely rare, with few cases reported. In this report, we describe a case of recurrent esophageal Paget's disease coexisting with small cell carcinoma. A 63-year-old man presented with the chief complaint of a rediscovered early esophageal cancer. Endoscopic examination revealed two separate superficial flat tumors in the upper and mid esophagus. Endoscopic submucosal dissection was performed, diagnosing diffuse Paget's disease (5.5 × 3.5 cm) and a small focus on intramucosal squamous cell carcinoma, respectively. Paget's cells were also found in the distal and right margins of the first specimen of endoscopic submucosal dissection. Immunohistochemical analysis showed that Paget's disease diffusely expressed cytokeratin 7 (CK7), CK18, and mucin 6 (MUC6), and focally expressed CD56 and chromogranin A, but not CK5/6, p63, p40, MUC5AC, MUC2, or synaptophysin. A complete absence of p53 and Rb1 was observed in Paget's disease. However, overexpression of p53 and retention of Rb1 were seen in squamous cell carcinoma. Approximately 27 months later, a prominent tumor was found at the same location as the previous Paget's disease. Subsequently, radical surgery was performed, and the final pathological evaluation revealed esophageal small cell carcinoma coexisting with Paget's disease. Moreover, both p53 and Rb1 were completely absent in both Paget's disease and the small cell carcinoma. This suggests that esophageal Paget's disease may dedifferentiate and develop into small cell carcinoma. In conclusion, esophageal Paget's disease can co-occur with invasive carcinomas, including small cell carcinoma, and should be completely resected endoscopically, with close follow-up.

Citation of this article: Yang Z, Wang B, Yang L, Xue X, Wei J, Xue L. Paget's Disease of the Esophagus Recurred Coexisting with Small Cell Carcinoma: A Case Report and Literature Review. J Clin Transl Pathol 2024;4(4):178–183. doi: 10.14218/JCTP.2024.00033.

Keywords: Esophagus; Paget's disease; Squamous cell carcinoma; Small cell carcinoma.

***Correspondence to:** Liyan Xue, Department of Pathology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China. ORCID: https://orcid.org/0000-0001-5185-0126. Tel: +86-10-87787514, E-mail: xuely@cicams.ac.cn

Introduction

Paget's disease is generally considered an intraepidermal proliferation of malignant glandular epithelial cells on a non-glandular epithelial surface. It is classified into mammary Paget's disease and extramammary Paget's disease (EMPD). EMPD typically occurs in areas of the skin with apocrine glands, with the most common sites being the vulva, followed by the perianal region, scrotum, penis, and armpit.[1] Paget's disease of the esophagus is extremely rare, with few cases reported.[2–9] In 1968, Yates and Koss reported the first case of esophageal Paget's disease with invasive esophageal squamous cell carcinoma (ESCC); however, the so-called Paget's cells in this case did not demonstrate any evidence of glandular differentiation.[2] To define esophageal Paget's disease, Matsukuma *et al*.[4] proposed that Paget's cells should colonize the epithelium far from the underlying carcinoma and exhibit evidence of glandular differentiation, which can be demonstrated by positive expression of cytokeratin 7 (CK7), carcinoembryonic antigen (CEA), or mucin. Most cases of esophageal Paget's disease have been associated with invasive adenocarcinoma.[2,3,9,10] Additionally, pagetoid squamous cell carcinoma *in situ* and pagetoid ESCC have also been reported.[11–15]

Small cell carcinoma of the esophagus (SCCE), a rare tumor with aggressive behavior and poor prognosis, can occur alongside ESCC, adenocarcinoma, or precursor lesions, such as high-grade squamous dysplasia (HGSD) or Barrett's esophagus with dysplasia.[16] However, SCCE coexisting with Paget's disease has never been reported. In this report, we describe a unique case of esophageal Paget's disease with ESCC in combination with SCCE.

Patient information

A 63-year-old man presented to the Cancer Hospital of the Chinese Academy of Medical Sciences for assessment, with a chief complaint of a relapse of early esophageal cancer for half a month. The patient underwent a local early gastrointestinal cancer screening in April 2015. The gastroscopy examination revealed a rough, congestive, and erosive lesion of the esophagus located at the six to ten o'clock position, between 24 cm and 25 cm from the incisors. Following the diagnosis of HGSD from a pathological biopsy, endoscopic mucosal resection was performed. The pathological results

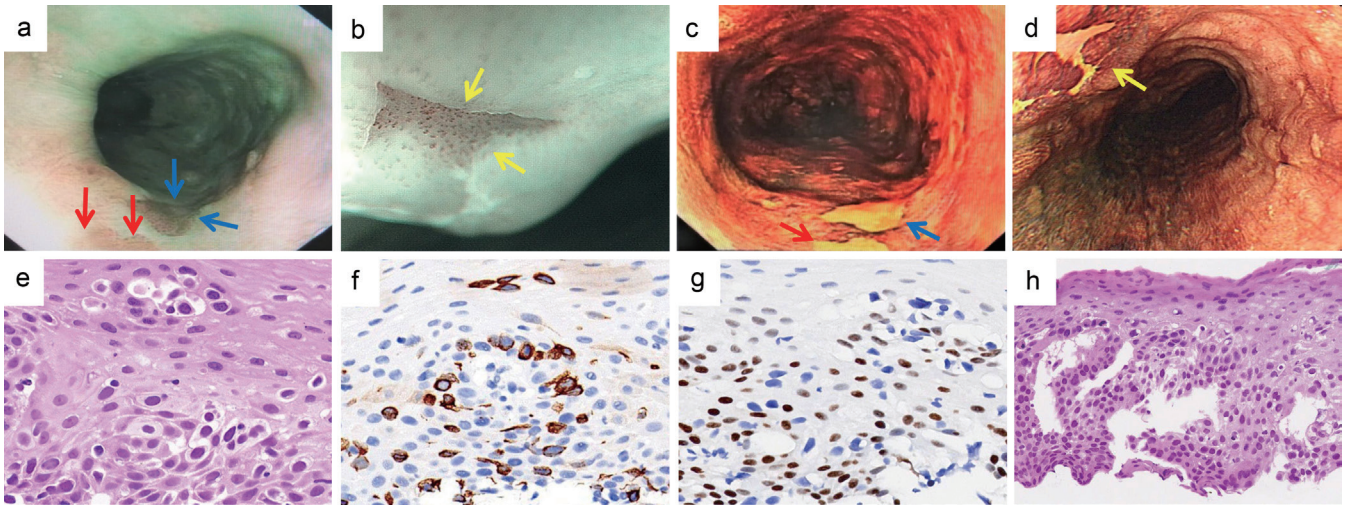

Fig. 1. Endoscopic and pathological findings of the esophagus. Narrow Band Imaging revealed three dark brown areas: one scar-like change area (a, red arrowheads) and two superficial flat tumors (a, blue arrowheads and b, yellow arrowheads). These areas were all positive for iodine staining (c and d). Biopsies of the first tumor showed atypical cells involving the lower half of the epithelium (e), which were positive for CK7 (f) and negative for p40 (g). Biopsies of the second tumor showed squamous dysplasia involving the lower half of the epithelium (h). Magnification: e–g: 400×; h: 200×. CK7, cytokeratin 7.

indicated multifocal HGSD, with foci extending into the submucosa. Lesions were also noted in the lateral margin, while the vertical margin was negative. Since then, the patient has undergone regular follow-up endoscopies at the Fourth Central Hospital of Baoding City. By February 2016, HGSD was found to be recurring. The patient was subsequently referred to the Cancer Hospital of the Chinese Academy of Medical Sciences for further treatment.

Clinical findings and therapeutic intervention

Gastrointestinal endoscopy demonstrated the following: (1) a scar-like change region (Fig. 1a, red arrowheads) in the esophagus at the three to eleven o'clock position between 20 and 24 cm from the incisors, with slightly rough mucosa; (2) two superficial flat tumors in the esophagus, located at the eight to twelve o'clock position between 21 and 29 cm (the first tumor, Fig. 1a, blue arrowheads) and at the nine to twelve o'clock position between 27 and 29 cm (the second tumor, Fig. 1b, yellow arrowheads). These abnormal areas were all positive for iodine staining (Fig. 1c and d). Biopsies of the two tumors were performed, with a diagnosis of low-grade squamous dysplasia (Fig. 1e and h, respectively). Considering the endoscopic appearance, the biopsy results, and the patient's medical history, endoscopic submucosal dissection (ESD) was performed in April 2016.

Microscopic and immunohistochemical findings

The first ESD specimen from 2016 contained the first tumor and part of the scar-like change region. Microscopic examination revealed atypical cells present in the epithelium, as well as in the mucosal and submucosal ducts and glands (Fig. 2a). These cells were large and round or oval, containing mild acidophilic cytoplasm. The nuclei were also large and round or oval, with rough chromatin. These atypical cells appeared singly or in clusters (Fig. 2b), primarily confined to the lower part of the epithelium, and were focally penetrating all layers. The ducts and submucosal glands were expanded and filled with atypical cells, exhibiting a cribriform or solid pattern resembling that of breast ductal carcinoma *in situ* (Fig. 2c). However, basement membrane invasion was not observed, as basal cells were retained, as shown by CK5/6, p63, and p40 immunohistochemistry. The area of distribution of atypical cells measured 5.5 × 3.5 cm. Atypical cells were found in the distal and right margins of the resection, while the proximal, left, and vertical margins were negative. These atypical cells were positive for CK7 (Fig. 2d), CK18, and mucin 6 (MUC6) (Fig. 2e), with foci positive for CD56 (Fig. 2f) and chromogranin A (CgA) (Fig. 2g). They were negative for CK5/6, p63, p40 (Fig. 2h), MUC5AC, MUC2, and Syn. Additionally, there was a complete absence of p53 (Fig. 2i and j) and retinoblastoma protein 1 (Rb1) (Fig. 2k and l) in the atypical cells. The Ki-67 proliferation index was 60%. The final pathological diagnosis was esophageal Paget's disease. The distribution of the Paget's cells, the involved submucosal glands, and the scar are illustrated in Figure 3. A biopsy of this tumor was reviewed, revealing atypical cells with mild acidophilic cytoplasm and poor adhesion distributed singly or in clusters in the middle and lower parts of the squamous epithelium. These cells were positive for CK7 (Fig. 1f) and negative for p40 (Fig. 1g). Therefore, the biopsy specimen should be diagnosed as Paget's disease instead of squamous dysplasia.

The second ESD specimen from 2016 showed moderately differentiated ESCC invading the lamina propria mucosae, surrounded by continuous squamous dysplasia. The lateral and vertical margins of the resection were free of tumor cells. Immunohistochemically, both the squamous cell carcinoma and squamous dysplasia were positive for CK5/6, p63, and p40 and negative for CK7. Overexpression of p53 and retained Rb1 were observed in the ESCC.

Follow-up and outcomes

Afterward, the patient did not receive additional treatments, such as radical surgery, radiotherapy, or chemotherapy. The patient did not undergo an endoscopic examination until October 2018, when an obvious tumor with a rough, hyperemic, and erosive surface was found in the upper esophagus. Radical surgery for esophageal cancer was performed at a local hospital, and the pathological results revealed SCCE coexisting with Paget's disease. The SCCE measured 2.3 × 1.5 × 1.2 cm and had infiltrated the muscularis propria. Metastatic

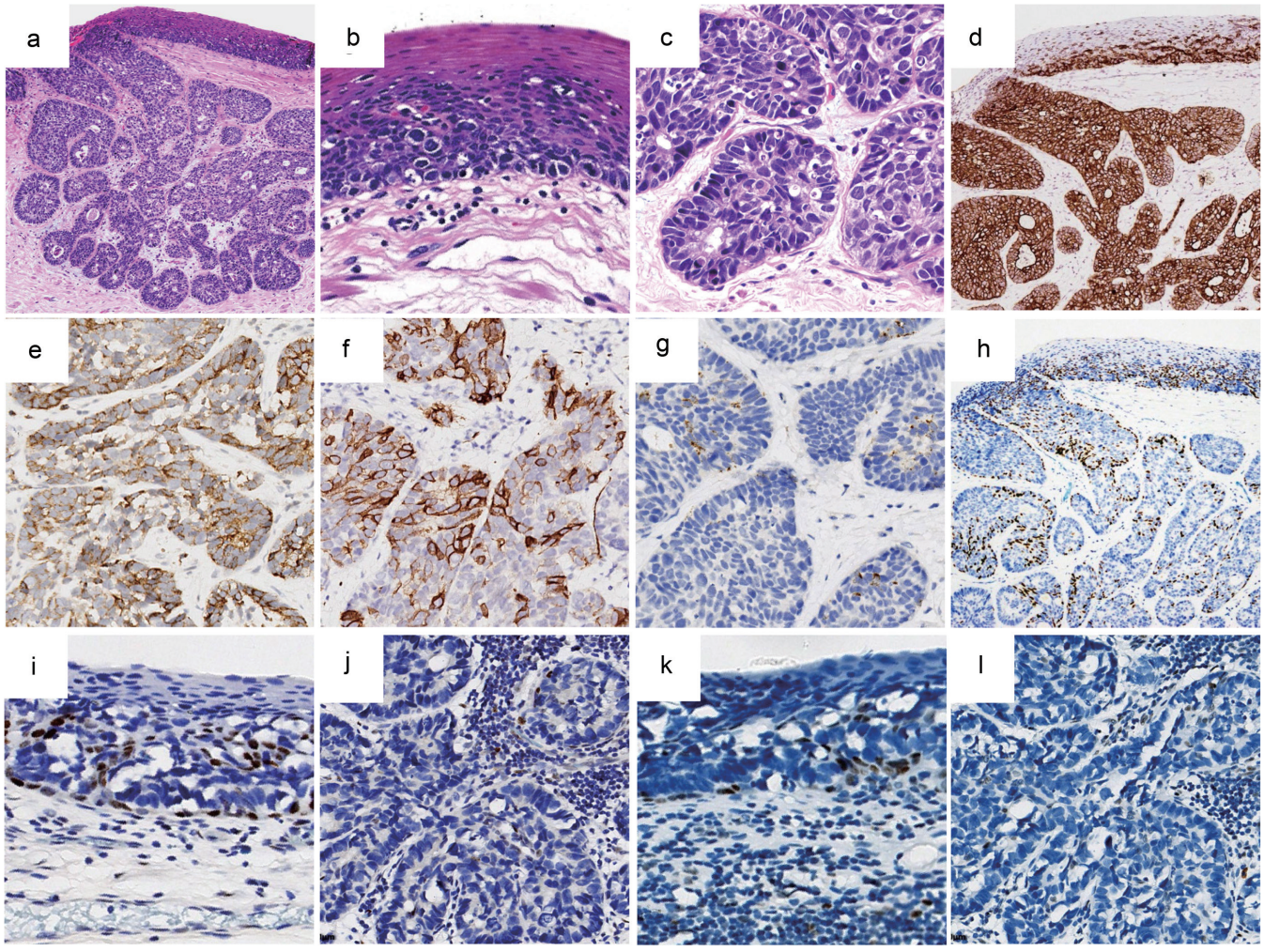

Fig. 2. Pathological findings of esophageal Paget's disease. (a–c): Atypical cells were observed in the superficial epithelium. The ducts and submucosal glands were expanded, also filled with atypical cells, exhibiting a cribriform or solid pattern. Atypical cells were diffusely positive for CK7 (d) and MUC6 (e), and focally positive for CD56 (f) and CgA (g). p40 (h) was negative in atypical cells but positive in normal basal cells. Complete absence of p53 (i and j) and loss of Rb1 (k and l) were observed in atypical cells within the superficial epithelium, ducts, and submucosal glands. Magnification: a, h: 40×; b, i, k: 400×; c–g, j, l: 200×. CgA, chromogranin A; CK7, cytokeratin 7; MUC6, mucin 6.

small cell carcinoma was confirmed in two out of 28 regional lymph nodes, and the stage was pT2N1MX.

Microscopic findings revealed two distinct components in the tumor in 2018. Paget's cells were visible in the squamous epithelium (Fig. 4a and b), and small cell carcinoma invaded the outer longitudinal muscle layer (Fig. 4a and e). Paget's cells were positive for CD56 staining and negative for p40. Small cell carcinoma was positive for CD56, CgA, and Syn, and negative for p40. The Ki-67 index was 80%. Furthermore, p53 and Rb1 were absent in both Paget's cells (Fig. 4c and d, respectively) and small cell carcinoma (Fig. 4f and g, respectively).

Approximately three months after surgery, the patient deceased from complications of distant metastases (lung and brain).

Discussion

Esophageal Paget's disease is a very rare neoplasm. Most cases of esophageal Paget's disease are associated with invasive adenocarcinoma.[2,3,9,10] The striking feature of the esophageal Paget's disease described here is the successive concomitant occurrence of squamous cell carcinoma and small cell carcinoma. As far as we know, this is the first reported case.

Esophageal Paget's disease is characterized by the invasion of the epidermis by Paget's cells, which are malignant glandular epithelial cells with enlarged, pleomorphic, and hyperchromatic nuclei, discernible but not prominent nucleoli, and abundant pale, clear cytoplasm.[3,4,7] The difference in this case is that the tumor cells contained abundant mild acidophilic cytoplasm and large nuclei with rough chromatin, similar to the tumor cells of ESCC. This explains why it was misdiagnosed as low-grade squamous dysplasia on biopsy. In histology, the main differential diagnoses of esophageal Paget's disease include pagetoid squamous cell carcinoma *in situ* and pagetoid ESCC. Immunohistochemistry plays an important role in the diagnosis of Paget's disease. By definition, Paget's cells express markers of glandular differentiation, such as CK7, CEA, and mucin. Previously, we thought CK7 was a specific and sensitive index of EMPD, with sensitivity as high as 100%.[17] However, both pagetoid squamous

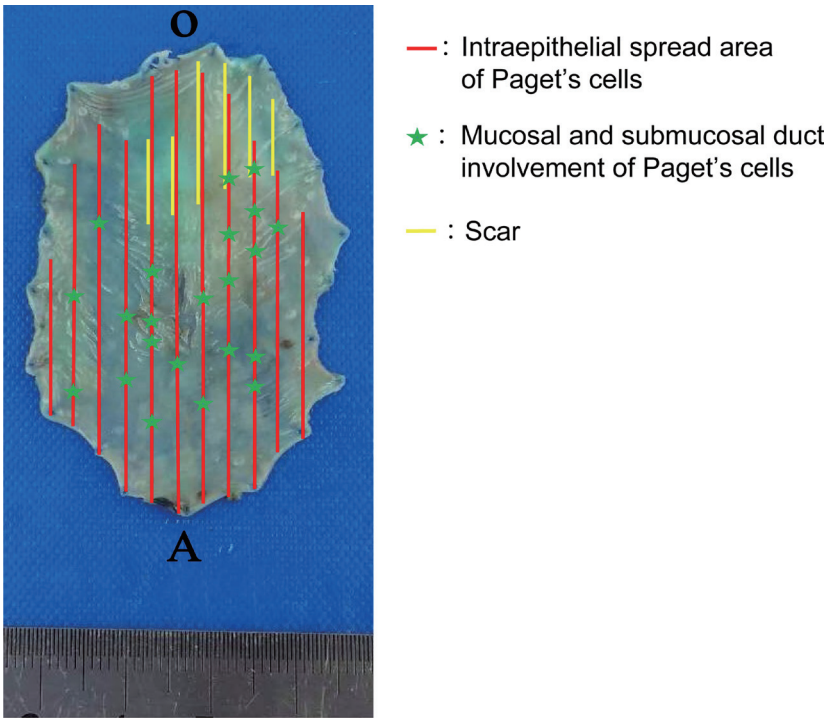

Fig. 3. Mapping of the distribution of Paget's cells and scar. The red line indicates the intraepithelial spread of Paget's cells. Green stars denote mucosal and submucosal duct involvement of Paget's cells. The yellow line represents the scar.

cell carcinoma *in situ* and pagetoid ESCC can exhibit CK7 positivity, providing further evidence of a shared histogenesis with divergent differentiation.[14,15] The distinction can be better made by employing more specific lineage markers, particularly p40 or p63, to provide support for squamous differentiation in pagetoid squamous cell carcinoma *in situ* and pagetoid ESCC.

The pathogenesis of esophageal Paget's disease is contro-

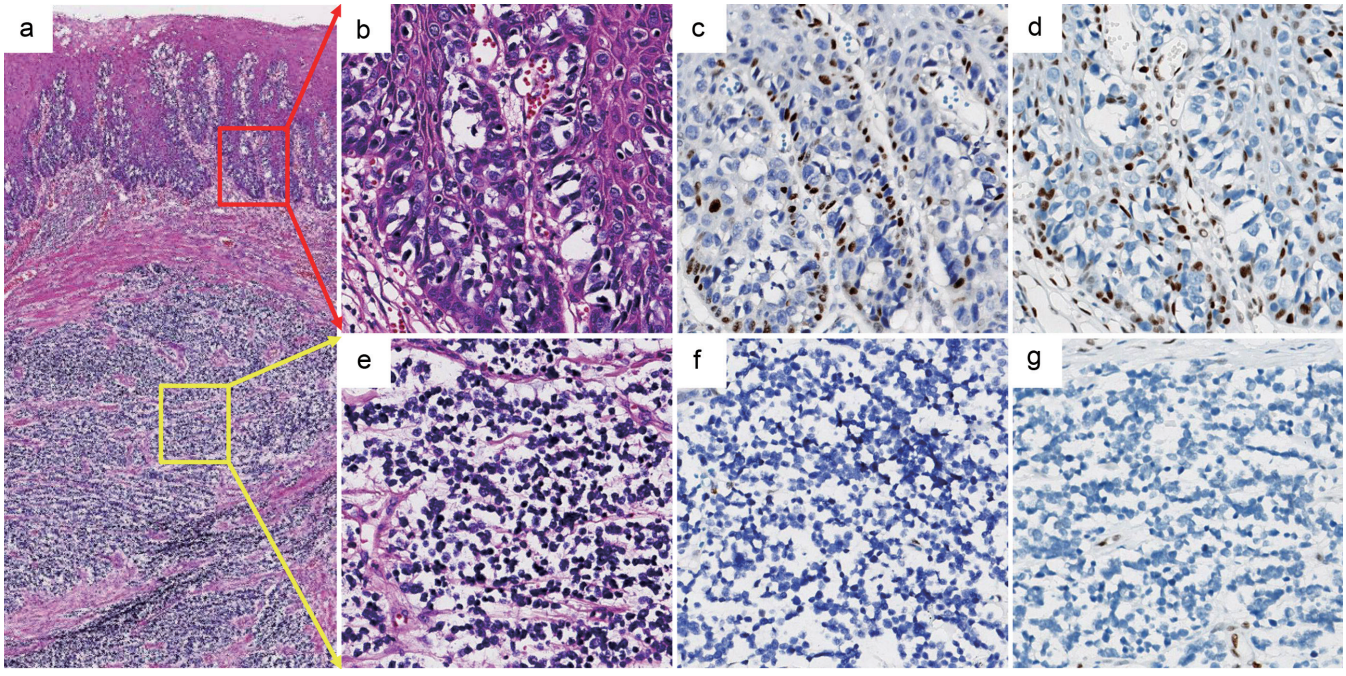

Fig. 4. Pathological findings of esophageal Paget's disease and small cell carcinoma. Paget's disease was observed in the lower part of the esophageal epithelium (a and b). Small cell carcinoma was seen in the esophageal wall (a and e). Complete absence of p53 and loss of Rb1 were observed in Paget's cells (c and d, respectively) and small cell carcinoma (f and g, respectively). Magnification: a: 20×; b–g: 200×.

versial. Here, we have summarized three potential origins of Paget's cells in the esophagus based on a review of the literature.[10] Firstly, Paget's cells may originate from pluripotent stem cells within the epithelium. Secondly, they may be derived from the duct cells or the submucosal glands in the epithelium. Thirdly, Paget's disease may result from the direct epithelial spreading of an invasive carcinoma. Esophageal Paget's disease is classified into two types: primary disease, which develops as an intraepithelial neoplasm, and secondary disease, which develops from the epidermotropic spread of cancer cells from an internal malignancy, as described by Abraham *et al*.[10] In primary disease, Paget's cells infiltrate a wide range of mucosa, concomitant with the malignant transformation of esophageal mucosal ducts or submucosal glands.[4,6] Mucosal involvement in secondary Paget's disease is relatively limited.[2,10] In this case, the first specimen in 2016 exhibited extensive involvement of Paget's cells within the ducts and submucosal glands. Therefore, the diagnosis of this case was established as primary Paget's disease.

Involvement of mucosal ducts or submucosal glands is notable in primary esophageal Paget's disease. Some scholars believe that duct and submucosal gland involvement is the downward extension of Paget's disease.[4,6] However, others speculate that the involvement of esophageal glands or ducts may be one of the pathways for the upward migration and lateral spread of Paget cells.[2] The esophagus contains epithelial ducts and submucosal glands, which are similar to the duct-lobular system structure of the breast. It is now considered that most mammary Paget's disease is an extension of ductal carcinoma *in situ* from the underlying ducts.[18] This hypothesis may also be applicable to esophageal Paget's disease. Previous studies have reported that dysplasia and cancerization can also develop within the esophageal ducts and submucosal glands.[19–21] Therefore, we concluded that ductal dysplasia and gland carcinomatosis were also present in this case. Studies have shown that TP53 mutation is one of the significantly mutated genes in SCCE, dysplastic Barrett's esophagus, esophageal adenocarcinoma (EAC), and ESCC.[22,23] The RB1 disruption rate in SCCE is reported to be as high as 98%,[23] significantly higher than that in ESCC and EAC.[24,25] In terms of genomic alterations, transcriptomic features, and molecular subtyping, SCCE is highly similar to small cell lung carcinoma (SCLC).[23] Studies have demonstrated that TP53 and RB1 are the most commonly mutated genes in combined SCLC, with high concordance rates of TP53 and RB1 aberrations between SCLC and other components.[26,27] In addition, the most accepted hypothesis suggests that gastric mixed neuroendocrine-non-neuroendocrine neoplasms derive from a single precursor cell (an overlapping mutational spectrum of the two cell varieties), but the process of neuroendocrine differentiation occurs in a non-neuroendocrine phenotype as a result of the accumulation of genetic abnormalities.[28] In our case, the loss of p53 and Rb1 expression (suggesting TP53 mutation and RB1 disruption) occurred in both Paget's disease and SCCE. Therefore, we hypothesized that Paget's disease and small cell carcinoma in this case may originate from the same precursor cell. In the presence of persistent pathogenic factors, the residual Paget cells undergo neuroendocrine differentiation and eventually develop into small cell carcinoma.

The survival rate of esophageal Paget's disease is unknown, and treatment strategies have not been standardized due to its rarity. ESD is an effective treatment for superficial esophageal neoplasms. It may also be a good choice for esophageal Paget's disease if all horizontal and vertical margins are free of tumor cells. However, it is challenging to attain negative surgical margins due to the tendency for Paget's disease to be irregular, dispersed, and potentially widespread throughout the epidermis. Thus, we propose regular and short-term follow-up examinations upon the revealing of Paget's disease with clear resection margins, and either adjuvant radiotherapy or extensive surgical intervention for long-term survival in cases with positive resection margins.

Conclusions

Esophageal Paget's disease can co-occur with invasive carcinoma, including small cell carcinoma, and should be completely resected endoscopically with close follow-up.

Acknowledgments

None.

Funding

There is no financial support to declare.

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Supervising the literature search and writing the majority of the paper (ZYY), providing the case reported, guiding and editing throughout the writing process (LYX), evaluating the histopathological images, and preparing the figures (ZYY, BW, LY, XMX, JCW). All authors have read and approved the final manuscript.

Ethical statement

This study was performed following the Helsinki Declaration as revised in 2013. The protocol was approved by the Ethics Committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (reference number 21/103-2774). Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

Data sharing statement

As a case report, all data generated or analyzed are included in this article.

References

[1] Shah RR, Shah K, Wilson BN, Tchack M, Busam KJ, Moy A, *et al*. Extramammary Paget disease. Part I. epidemiology, pathogenesis, clinical features, and diagnosis. J Am Acad Dermatol 2024;91(3):409–418. doi:10.1016/j.jaad.2023.07.1051, PMID:38704032.
[2] Haleem A, Kfoury H, Al Juboury M, Al Husseini H. Paget's disease of the oesophagus associated with mucous gland carcinoma of the lower oesophagus. Histopathology 2003;42(1):61–65. doi:10.1046/j.1365-2559.2003.01514.x, PMID:12493026.
[3] Karakök M, Aydin A, Sari I, Koruk M, Savaş MC, Kadayifçi A. Paget's disease of the esophagus. Dis Esophagus 2002;15(4):334–335. doi:10.1046/j.1442-2050.2002.00266.x, PMID:12472483.
[4] Matsukuma S, Aida S, Shima S, Tamai S. Paget's disease of the esophagus. A case report with review of the literature. Am J Surg Pathol 1995;19(8):948–955. doi:10.1097/00000478-199508000-00011, PMID:7611542.
[5] Mori H, Ayaki M, Kobara H, Goda Y, Nishiyama N, Masaki T. Rare Primary Esophageal Paget's Disease Diagnosed on a Large Bloc Specimen Obtained by Endoscopic Mucosal Resection. J Gastrointestin Liver Dis 2017;26(4):417–420. doi:10.15403/jgld.2014.1121.264.pag, PMID:29253058.
[6] Nonomura A, Kimura A, Mizukami Y, Matsubara F, Yagi M. Paget's disease of the esophagus. J Clin Gastroenterol 1993;16(2):130–135. doi:10.1097/00004836-199303000-00010, PMID:8385166.

[7] Sano A, Sakurai S, Komine C, Tabe Y, Saito K, Fukasawa T, *et al*. Paget's disease derived in situ from reserve cell hyperplasia, squamous metaplasia, and squamous cell carcinoma of the esophagogastric junction: a case report. Surg Case Rep 2018;4(1):81. doi:10.1186/s40792-018-0489-1, PMID:30046968.
[8] Yada S, Sasaki S, Tokuno K, Yamashita Y, Sakaida I. Gastrointestinal: Extramammary Paget disease of the esophagus. J Gastroenterol Hepatol 2022;37(3):419. doi:10.1111/jgh.15665, PMID:34474506.
[9] Liu X, Zhang D, Liao X. Paget cells of the esophagus: A clinicopathologic and immunohistochemical study of 10 cases. Pathol Res Pract 2023;242:154345. doi:10.1016/j.prp.2023.154345, PMID:36708601.
[10] Abraham SC, Wang H, Wang KK, Wu TT. Paget cells in the esophagus: assessment of their histopathologic features and near-universal association with underlying esophageal adenocarcinoma. Am J Surg Pathol 2008;32(7):1068–1074. doi:10.1097/PAS.0b013e318160c579, PMID:18496141.
[11] Norihisa Y, Kakudo K, Tsutsumi Y, Makuuchi H, Sugihara T, Mitomi T. Paget's extension of esophageal carcinoma. Immunohistochemical and mucin histochemical evidence of Paget's cells in the esophageal mucosa. Acta Pathol Jpn 1988;38(5):651–658. doi:10.1111/j.1440-1827.1988.tb02337.x, PMID:2850706.
[12] Chu P, Stagias J, West AB, Traube M. Diffuse pagetoid squamous cell carcinoma in situ of the esophagus: a case report. Cancer 1997;79(10):1865–1870. PMID:9149010.
[13] Suárez Vilela D, Izquierdo García F, Alonso Orcajo N. [Squamous carcinoma of the esophagus with extensive pagetoid dissemination]. Gastroenterol Hepatol 1997;20(7):360–362. PMID:9377235.
[14] Chen IY, Bartell N, Ettel MG. Diffuse Pagetoid Squamous Cell Carcinoma in Situ of the Esophagus: A Rare Case Report and Review of Literature. Int J Surg Pathol 2022;30(3):326–330. doi:10.1177/10668969211046814, PMID:34633887.
[15] Miller TR, Zhang X, Ko HM, Lagana SM, Setia N, Yassan L, *et al*. Esophageal squamous cell carcinoma with pagetoid spread: a clinicopathologic study. Virchows Arch 2024. doi:10.1007/s00428-024-03788-7, PMID:38671319.
[16] Mastracci L, Rindi G, Grillo F, Solcia E, Campora M, Fassan M, *et al*. Neuroendocrine neoplasms of the esophagus and stomach. Pathologica 2021;113(1):5–11. doi:10.32074/1591-951X-229, PMID:33686305.
[17] Ohnishi T, Watanabe S. The use of cytokeratins 7 and 20 in the diagnosis of primary and secondary extramammary Paget's disease. Br J Dermatol 2000;142(2):243–247. doi:10.1046/j.1365-2133.2000.03291.x, PMID:10730755.
[18] WHO Classification of Tumours Editorial Board. Breast tumours. 5th edition. Lyon (France): International Agency for Research on Cancer; 2019.
[19] Fabre A, Tansey DK, Dave U, Wright M, Teare JP, Rosin DR, *et al*. Adenocarcinoma in situ arising from the submucosal oesophageal mucous glands. Eur J Gastroenterol Hepatol 2003;15(9):1047–1049. doi:10.1097/00042737-200309000-00018, PMID:12923381.
[20] Endoh Y, Miyawaki M, Tamura G, Watanabe H, Motoyama T. Esophageal adenocarcinoma that probably originated in the esophageal gland duct: a case report. Pathol Int 1999;49(2):156–159. doi:10.1046/j.1440-1827.1999.00838.x, PMID:10355970.
[21] Gangarosa L, Halter S, Mertz H. Dysplastic gastroesophageal junction nodules—a precursor to junctional adenocarcinoma. Am J Gastroenterol 1999;94(3):835–838. doi:10.1111/j.1572-0241.1999.00955.x, PMID:10086675.
[22] The Cancer Genome Atlas Research Network. Integrated genomic characterization of oesophageal carcinoma. Nature 2017;541(7636):169–175. doi:10.1038/nature20805, PMID:28052061.
[23] Li R, Yang Z, Shao F, Cheng H, Wen Y, Sun S, *et al*. Multi-omics profiling of primary small cell carcinoma of the esophagus reveals RB1 disruption and additional molecular subtypes. Nat Commun 2021;12(1):3785. doi:10.1038/s41467-021-24043-6, PMID:34145257.
[24] Gao YB, Chen ZL, Li JG, Hu XD, Shi XJ, Sun ZM, *et al*. Genetic landscape of esophageal squamous cell carcinoma. Nat Genet 2014;46(10):1097–1102. doi:10.1038/ng.3076, PMID:25151357.
[25] Salem ME, Puccini A, Xiu J, Raghavan D, Lenz HJ, Korn WM, *et al*. Comparative Molecular Analyses of Esophageal Squamous Cell Carcinoma, Esophageal Adenocarcinoma, and Gastric Adenocarcinoma. Oncologist 2018;23(11):1319–1327. doi:10.1634/theoncologist.2018-0143, PMID:29866946.
[26] Jimbo N, Ohbayashi C, Fujii T, Takeda M, Mitsui S, Tanaka Y, *et al*. The expression of YAP1 and other transcription factors contributes to lineage plasticity in combined small cell lung carcinoma. J Pathol Clin Res 2024;10(5):e70001. doi:10.1002/2056-4538.70001, PMID:39283755.
[27] Zhang J, Zhang L, Luo J, Ge T, Fan P, Sun L, *et al*. Comprehensive genomic profiling of combined small cell lung cancer. Transl Lung Cancer Res 2021;10(2):636–650. doi:10.21037/tlcr-20-1099, PMID:33718010.
[28] Liu L, Li Q, Liu W, Qiu Z, Wu Z, Yu D, *et al*. Gastric mixed neuroendocrine non-neuroendocrine neoplasms. Front Oncol 2024;14:1335760. doi:10.3389/fonc.2024.1335760, PMID:38655135.