Virchows Archiv
https://doi.org/10.1007/s00428-024-03788-7

ORIGINAL ARTICLE

Esophageal squamous cell carcinoma with pagetoid spread: a clinicopathologic study

Tiffany R. Miller[1,2,3] · Xuchen Zhang[4] · Huaibin M. Ko[5] · Stephen M. Lagana[5] · Namrata Setia[6] · Lindsay Yassan[6] · Maria Westerhoff[7] · Vikram Deshpande[3,8] · Jason L. Hornick[1,3] · Mark S. Redston[1,3] · Lei Zhao[1,3]

Received: 12 January 2024 / Revised: 11 March 2024 / Accepted: 13 March 2024

Abstract

Pagetoid spread in esophageal squamous epithelium associated with underlying esophageal adenocarcinoma (EAC) has been well studied. Case reports describing pagetoid spread of esophageal squamous cell carcinomas (ESCC) also exist in the literature. The latter, however, has not been systematically studied. In this study, we report seven cases of pagetoid spread associated with ESCC. The clinical, morphologic, and immunophenotypic profiles of pagetoid spread in the context of ESCC and EAC are compared. Cases of pagetoid spread of ESCC were identified through computerized search of pathology archives at five institutions. Additional cases were identified through manual review of surgical resection cases of treatment naive ESCC in Mass General Brigham (MGB) pathology archive. Clinical history was collected via chart review. Immunohistochemistry for CK7, CK20, CDX2, p53, p63, and p40 was performed on selected cases. A computerized search of pathology archives of five institutions revealed only two cases. A manual review of 76 resected untreated ESCC revealed five additional cases with unequivocal pagetoid spread of ESCC, indicating the condition was not uncommon but rarely reported. Patient age ranged from 54 to 78 years (median, 65). There were six women and one man. One case had in situ disease, five had pT1 (1 pT1a and 4 pT1b), and one had pT3 disease. One of the patients with pT1 tumor had a positive lymph node, while the remaining six patients were all N0. Four tumors were in the proximal to mid esophagus, and three in the distal esophagus. Patient survival ranged from 25 months to more than 288 months. The pagetoid tumor cells demonstrated enlarged, hyperchromatic nuclei with variable amounts of eosinophilic cytoplasm. The cytoplasm was often condensed to the perinuclear area, creating peripheral clearing. By immunohistochemistry, the pagetoid cells were positive for p40 (6/6) and p63 (7/7) and negative for CDX2 (7/7). The tumor cells showed mutant-type staining for p53 in five of seven cases. One of the patients had pagetoid tumor cells at the resection margin and subsequently had recurrent disease 2 years later. All other patients had negative resection margins and did not have local recurrence. Four cases of pagetoid spread in the context of EAC were used as a comparison group. Previously published studies were also analyzed. These tumors were all located in the distal esophagus or gastroesophageal junction. All cases were associated with underlying invasive EAC. Pagetoid spread associated with EAC often had cytoplasmic vacuoles or mucin. They were more frequently positive for CK7 than pagetoid ESCC ($p = 0.01$). Both ESCC and EAC may give rise to pagetoid spread of tumor cells within surface squamous epithelium. Pagetoid spread from ESCC and EAC have overlapping morphologic features. P40 and p63 immunostains can facilitate the distinction between ESCC and EAC. P53 immunostain can aid in confirmation of malignancy. Understanding their overlapping pathologic features will help pathologists avoid pitfalls and diagnose these lesions correctly on biopsy specimens.

Keywords Squamous cell carcinoma · Extra-mammary paget disease · Pagetoid · Squamous cell carcinoma in situ

Introduction

Extramammary Paget disease (EMPD) of the esophagus is rare and includes two forms: primary and secondary. Primary Paget disease is challenging to diagnose, and there are only a handful of potential cases reported in the literature [1–4]. Secondary Paget disease is caused by intra-epithelial spreading of malignant cells from an underlying internal malignancy. It is often phrased as "pagetoid spread" in pathology reports. The most common and better understood neoplasm that demonstrates intra-epithelial spread is esophageal adenocarcinoma (EAC). Abraham et al. [5]

Extended author information available on the last page of the article

Published online: 26 April 2024

reported that after screening all endoscopic biopsies, endoscopic mucosal resection and surgical resections in a 13-year timespan (from 1994 to 2007), no primary Paget disease of the esophagus was identified. Instead, all cases containing Paget cells (5 cases) represented secondary extension from underlying invasive adenocarcinoma. It was also the authors' anecdotal experience that pagetoid tumor cells encountered in esophageal biopsies are almost always from an underlying adenocarcinoma. We recently encountered a case of pagetoid spread of esophageal squamous cell carcinoma (ESCC), which shares morphologic resemblance to that of EAC. In this report, we set out to determine the prevalence of pagetoid spread of ESCC and the immunohistochemical profile of these tumor cells as they may be mistaken as EAC or other entities and can be a pitfall of misdiagnosis.

Table 1 Clinicopathologic characteristics of patients with Paget cells associated with esophageal squamous cell carcinoma

Case	Age at diagnosis (yr)	Gender	Tumor T stage (AJCC 8th)	Tumor N stage (AJCC 8th)	Location of the tumor	Survival (months)
1	60	Female	T1b	N0	Distal	36*[&]
2	68	Female	Tis	N0	Distal	170
3	54	Female	T3	N1	Distal	25
4	56	Male	T1b	N1	Proximal/mid	288*
5	78	Female	T1a	N0	Proximal/mid	53
6	65	Female	T1b	N0	Proximal/mid	112*
7	68	Female	T1b	N0	Proximal/mid	78*

*Patient alive at last follow-up

[&]With recurrence

Table 2 Summary of immunophenotypic profile of pagetoid tumor cells associated with esophageal squamous cell carcinoma

Case	CK7	CK20	CDX2	P40	P63	P53	CK5
1	Focal positive	Negative	Negative	Positive	Positive	Mutant type	Weakly positive
2	N/A	N/A	Negative	Positive	Positive	Mutant type	N/A
3	Negative	Positive	Negative	Positive	Positive	Mutant type	Negative
4	Negative	Negative	Negative	Positive	Positive	Equivocal	Weakly positive
5	Negative	Negative	Negative	Positive	Positive	Mutant type	Weakly positive
6	Negative	Negative	Negative	Positive	Positive	Wild type	Negative
7	Negative	Negative	Negative	Positive	Positive	Mutant type	Weakly positive

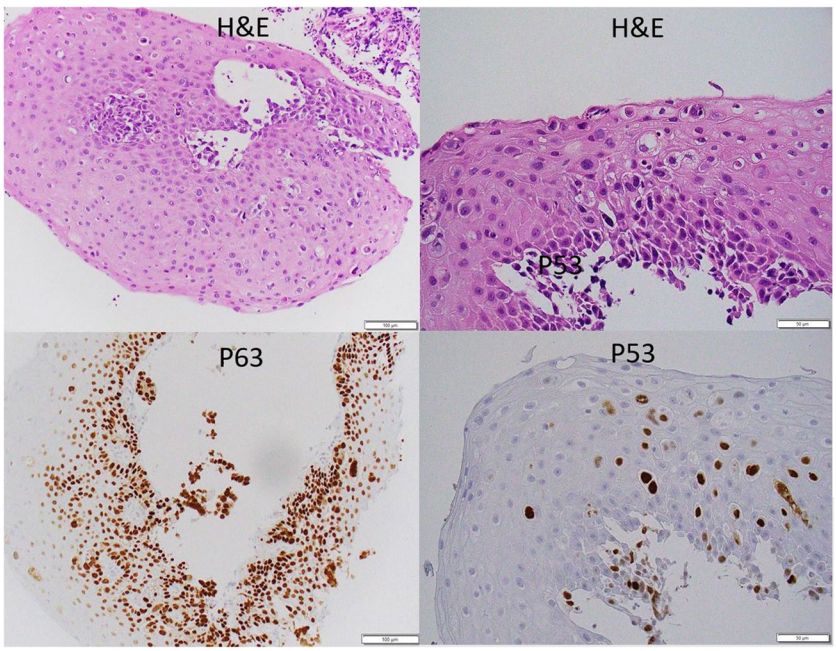

Fig. 1 Case 1 shows pagetoid spread of esophageal squamous cell carcinoma (×200 magnification upper left, ×400 magnification upper right), and P63 (lower left) and P53 (lower right) immunostains

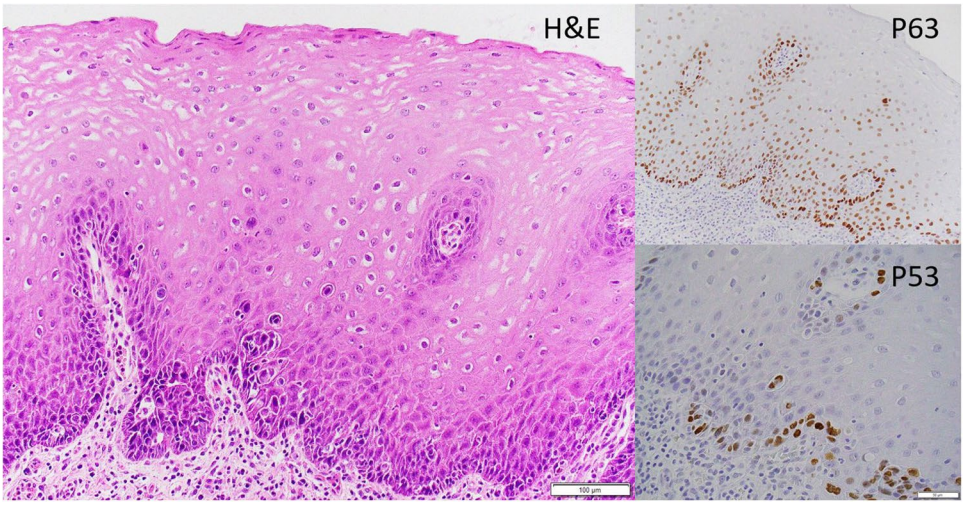

Fig. 2 Case 7 shows pagetoid spread of esophageal squamous cell carcinoma (×200 magnification left), and P63 (upper right) and P53 (lower right) immunostains

Methods

Two approaches were used to determine the prevalence of pagetoid spread of squamous cell carcinoma. First, a systematic search of pathology archives using the phrases "pagetoid" (or "Paget") and "squamous cell carcinoma" and "esophagus" was performed at five participating institutions. To establish a control group, a systematic search using the phrases "pagetoid" (or "Paget") and "adenocarcinoma" and "esophagus" was also performed. For all search hits, clinical history was collected through electronic chart review. Histologic slides were retrieved and reviewed. Due to the paucity of search hits, a manual review of 76 surgical resections of treatment naive squamous cell carcinoma was performed.

Paraffin-embedded tissue of selected blocks was retrieved, and immunohistochemistry for p53 (1:500; DAKO), CK7 (1:1000; DAKO), CK20 (1:50; DAKO), CDX2 (1:150; BioGenex), p40 (1:250; BioCare), and p63 (1:150; BioCare) was performed.

Chi-square was used for statistical analysis. A p value (two-tailed) less than 0.05 was considered statistically significant.

The study was approved by the institutional review board (IRB) of participating institutions.

Results

Prevalence and clinical characteristics of pagetoid spread of squamous cell carcinoma

A systematic search of pathology archives from 2010 to 2020 at five institutions revealed two documented cases of pagetoid spread of ESCC (case 1 and 2, Table 1 and 2, Fig. 1, and Supplemental Fig. 1) (case 2 previously published [6] but now with additional follow-up data). Four cases of pagetoid spread of underlying esophageal adenocarcinoma (EAC) were identified using a similar approach during the same time period.

A systematic review of 76 resected untreated ESCC from MGB pathology archives revealed five additional cases (case 3–7) (Fig. 2 and Supplemental Fig. 1) with unequivocal pagetoid spread of ESCC, indicating that the condition was not uncommon, but was rarely documented.

Patient age ranged from 54 to 78 years (median, 65). There were six women and one man. One case had in situ disease, five had pT1 (1 pT1a and 4 pT1b), and one had pT3 disease. One of the patients with pT1 tumor had a positive lymph node, whereas the remaining six patients were all N0. Four tumors were in the proximal to mid esophagus and three in the distal esophagus. Patient survival months ranged from 25 months to more than 288 months. One of the patients had pagetoid tumor cells at the resection margin and subsequently had recurrent disease 2 years later. All other patients had negative resection margins and did not have local recurrence.

Table 3 Comparison of immunophenotypic profile of pagetoid tumor cells associated with esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) in a previously published study

		Paget cells in ESCC (positive/total)	Paget cells in EAC (positive/total)	p value
CK7		1/6	7/7	0.0121
CK20		1/6	5/7	0.156
P53	Mutant type	5/7	3/7	0.554
	Null type	0/7	1/7	
	Wild type	1/7	3/7	

Table 4 Case reports of Paget disease of the esophagus

Reference	Diagnosis (primary vs. secondary)	Underlying neoplasm	Patient's age	Patient's gender	Number of patients	Gross or endoscopic findings	Immunohistochemistry	Note	Outcome
Li et al. [15]	Predominantly secondary	EAC (8 cases, including one in situ); SCC (2 cases, both in situ)		7 M, 3 F	10	All invasive EAC located at the GEJ or distal esophagus, while the in situ EAC and ESCC predominantly involved the mid esophagus. Invasive EAC often presented as mass lesions (6/7, 88%), while in situ ESCCs and EAC were flat and described as "nodularity," "thinned out," "narrowing," or just "abnormality"	All invasive EAC were positive for CK7 and CAM5.2, with variable expression of CDX2 (5/7, 68%), GATA3 (3/7, 37.5%), CEA (4/7, 57%), and CK20 (1/7, 14%). Intracytoplasmic mucin was identified in 6 of 7 (86%) cases. EACs were completely negative for p63, GCDFP-15, and SOX10. Both in situ ESCC were positive for p40 and lacked intracytoplasmic mucin, one also positive for CK7	In situ ESCCs and in situ EAC were interpreted as primary Paget disease	Four patients, all with invasive EAC, died of disease at a median follow-up of 10 months, while the others were alive at the time of reporting
Yada et al. [16]	Secondary	SCC (invasive)	74	M	1	Circumferential ring-shaped scars mid to lower esophagus, 1 cm red flat elevated lesion at the lower esophagus (which is the invasive SCC)	Pos: p53, CK7, GCDFP15, Alcian blue, PAS-D. Neg: CK5/6, CK20, HMB45, Melan A	Presumed secondary given invasive SCC poorly diff, with submucosal invasion	NA
Chen et al. [9]	Secondary	SCC (in situ)	89	F	1	Multiple clean base ulcers spanning 4 cm in the proximal esophagus	Pos: p40, CK7, p53 mutant. Neg: CK20, GATA3, CDX2, TTF1, SOX10. Kreyberg stain negative for mucin		NA

Table 4 (continued)

Reference	Diagnosis (primary vs. secondary)	Underlying neoplasm	Patient's age	Patient's gender	Number of patients	Gross or endoscopic findings	Immunohistochemistry	Note	Outcome
White et al. [17]	Secondary	Hypopharyngeal carcinoma T1 (most c/w poorly differentiated adenocarcinoma)	63	M	1	Diffusely abnormal Lugol's iodine test	Pos: CK7, EMA, patchy BerEP4, patchy p16. Neg: p63, CK20, CK5, CEA, Bcl-2, S100, PSA, TTF-1, CDX2. Alcian blue PAS positive for mucin	Paget cells immunostaining pattern identical to hypopharyngeal cancer; initial resection of the hypopharyngeal primary had positive margin for Paget cells; subsequent esophagectomy revealed diffuse pagetoid spread with no invasion	NA
Lin et al. [1]	Likely primary	NA	63	M	1	Slightly mottled appearance, thickened, and indurated	Pos: CK7, CK8/18, CEA, Her-2, Ki67. Neg: CK5/6, p63, S100, HMB45, GCDFP-15. Alcian blue, PAS-D, and mucicarmine were negative for mucin	Focal invasion into lamina propria	Chemo (docetaxel and cisplatin), 21 months with no recurrence or mets
Sano et al. [18]	Likely secondary	SCC in situ	81	F		Mild elevated granular lesion, slightly depressed irregular mucosa, in distal esophagus	Pos: CK7, patchy CK20, P53 mutant. Neg: p63, S100, HMB-45,CK5, MUC2, MUC5AC, HIK1083. Focal pos for PAS Alcian blue	SCC in situ arising in squamous metaplasia and reserve cell hyperplasia in the gastric mucosa of GEJ	Surgery only, 2 years and 8 months with no recurrence of Paget
Mori et al. [2]	Primary	NA	53	M	1	Whole circumference ring-shaped scarring, suggestive of eosinophilic esophagitis, without erosive of ulcerative lesions	Pos: "mucins," CK18, E-Cad, PAS (partially positive)	No primary lesion, diffuse Paget cells with focally invading mucosal and submucosal ducts	Diagnosed on a large bloc specimen obtained by EMR-c; outcome NA

Table 4 (continued)

Reference	Diagnosis (primary vs. secondary)	Underlying neoplasm	Patient's age	Patient's gender	Number of patients	Gross or endoscopic findings	Immunohistochemistry	Note	Outcome
Abraham et al. [5]	Secondary	EAC	36–87 (mean 62.4)	7 M, 1 F	8	No lateral spreading	Pos: PAS-D (7/7), mucicarmine (6/7), P53 abnormal (5/7), CK7 (7/7), CK20 (5/7), E-Cad reduced (4/7)		NA
Haleem et al. [19]	Secondary	Submucosal gland carcinoma	74	F	1	Ulcerated tumor at GEJ extending into cardia	Pos: CK7, CAM5.2, BerEP4, CEA. Neg: CK20, CEA, LCA, S100, chromogranin		
Ishihara et al. [2]	Secondary	SCC in situ	70	M	1	Thickened wall involving most of the esophagus	Pos: keratin. Neg: PAS-D, CK14, CEA	Diffuse SCC in situ, focal submucosal and mucosal invasion	Diagnosed at autopsy
Karakok et al. [20]	Secondary	EAC	72	M	1	Mucosal irregularities of distal esophagus, cardia, and proximal fundus	Pos: Alcian blue, mucicarmine, PAS, EMA, CEA. Neg: S100, HMB45, Masson-Fontana		NA
Suarez et al. [21]	Secondary	SCC	59	M	1	NA	Neg: CEA, PAS Alcian blue		
Chu et al. [9]	Secondary	SCC in situ	68	F	1	Sharply demarcated, tan-colored, circumferential depressed, erythematous mucosa with friability and congestion in the mid and lower esophagus, no ulcer, or mass, 45 cm^2 in area	Pos: overexpressed p53, CAM5.2, AE1/3 (weak), PCNA. Neg: CEA, GCDFP-15, HER2, EMA, Alcian blue, PAS	No invasion noted	Surgery only, 3 years and 5 months with no recurrence of Paget

Table 4 (continued)

Reference	Diagnosis (primary vs. secondary)	Underlying neoplasm	Patient's age	Patient's gender	Number of patients	Gross or endoscopic findings	Immunohistochemistry	Note	Outcome
Matsukuma et al. [4]	Primary	NA	59	M	1	Wide irregular surface in the upper to middle esophagus, no elevated or ulcerated lesions	Pos: PAS, Alcian blue, EMA, AE1, CEA (focal), SC (focal). Neg: NSE, S100	Upper to mid esophagus extensively infiltrated, with minimal submucosal invasion. Invasive cells were neg for PAS, and Alcian blue	Surgery and adjuvant radiation, patient expired 5–6 months later
Nonomura et al. [3]	Primary	NA	60	M	1	Mucosa diffusely indurated with irregular reticulated erosions in the upper- middle esophagus, no mass or ulcer	Pos: EMA, CEA. Neg: PAS, Alcian blue, mucicarmine, S100, NSE, melanin, SC	Extensive intraepithelial growth of cancer cells with no glandular or squamous diff, multifocally invading mucosal and submucosal ducts, no invasion	Surgery and adjuvant radiation, 3 years and 2 months with no recurrence of Paget
Norihisa et al. [22]	Secondary	Adenosquamous	68	M	1	middle portion	Pos: "mucin" by histochemistry	Both adenocarcinoma and epidermoid carcinoma components	Expired 6 months later

Histopathologic features

The seven cases that were included in the study all demonstrated individual or small clusters of malignant tumor cells spreading within esophageal squamous epithelium, without direct connection with the main tumor. The involved epithelium was often adjacent to (within 1 cm) or overlying the main tumor, except for cases 1 and 2. In case 1, the recurrent disease presented as intraepithelial spreading only and was extensive by endoscopic examination (more than 5 cm in length). For case 2, the disease was in situ only and spanned 9 cm in total. The pagetoid tumor cells demonstrated enlarged, hyperchromatic nuclei with variable amounts of eosinophilic cytoplasm. The cytoplasm was often condensed to the perinuclear area, creating peripheral clearing. By immunohistochemistry, the pagetoid cells were positive for p40 (6/6) and p63 (7/7) and negative for CDX2 (7/7). One of six cases showed CK7 positivity while another case showed CK20 positivity. The tumor cells showed mutant-type staining for p53 in five of seven cases (Table 2).

Four cases of pagetoid spread in the context of EAC were used as a comparison group. These tumors were all located in the distal esophagus or GE junction. All cases were associated with underlying invasive EAC. Pagetoid spread associated with EAC often had cytoplasmic vacuoles or mucin. The tumor cells were positive for CK7 and MOC31 (in one case with available immunohistochemical study) and negative for CK5, p40, and/or p63 (in three cases with available immunohistochemical study).

A comprehensive immunophenotypic profile of pagetoid cells in the setting of EAC has been reported previously (Table 3) [5]. Pagetoid tumor cells in EAC were more commonly CK7 positive ($p=0.0121$). They also showed a higher frequency of CK20 positivity, although the difference did not reach statistical significance ($p=0.156$). P53 expression patterns were abnormal in most Paget cells in ESCC (6 of 7) and were often observed in EAC as well (4 of 7).

Discussion

In this study, we identified seven cases of pagetoid spread of ESCC, including one case of in situ disease only and six cases of invasive disease. It is worth noting that a systematic search of electronic pathology archives at five institutions only revealed two cases, although a manual review of 76 cases of resected ESCC revealed five additional cases (6.5%). This suggests that pagetoid spread of ESCC is not uncommon but is not generally reported. The pagetoid tumor cells were all within 1 cm from the main tumor, but this could be due to sampling, as mucosa away from the main tumor is often not extensively sampled.

ESCC can involve the epithelium through two main mechanisms: intraepithelial neoplasia or lateral/intraepithelial spread. Squamous intraepithelial neoplasia represents an in situ neoplasm confined to the epithelial layer without involvement of deeper layers of the esophageal wall. In contrast, lateral spread or intraepithelial spread of ESCC represents a unique form of tumor invasion. Tumor cells exhibiting lateral spread travel horizontally along the surface epithelium or ducts of submucosal glands, without breaching the basement membrane [7].

Lateral spread or intraepithelial spread has been classified into three subtypes [8]: "total layer type" (the entire epithelium is replaced by tumor cells), "basal layer type" (only basal half of the epithelium is replaced by tumor cells), and mixed type (showing a combination of both patterns).

Pagetoid spread reported in this study refers to individual or small clusters of tumor cells spread discontinuously along the epithelium. This would be another unique subtype of "intraepithelial spread."

The pagetoid tumor cells associated with ESCC show a high degree of morphologic similarities with those of EAC. They demonstrate enlarged, hyperchromatic nuclei with variable amounts of eosinophilic cytoplasm. The presence of cytoplasmic clearing in some of the cases may mimic mucin vacuoles. By immunohistochemistry, pagetoid SCC is p40 and p63 positive, but they can be CK7 or CK20 in rare examples, which may lead to misdiagnosis of EAC. P53 often shows an abnormal staining pattern in pagetoid tumor cells. Although it is not useful in distinguishing between SCC or EAC, it can be helpful to confirm the neoplastic nature of these cells.

The prognostic value of pagetoid spread of ESCC is unclear. In the study, survival ranged from 25 months to more than 288 months. There are too few reported cases to evaluate whether this feature correlates with long-term survival since it likely poses difficulty for endoscopic evaluation and histologic diagnosis.

Like Bowen's disease of the skin, pagetoid spread of in situ ESCC can occur and has been reported in the literature [6, 9] (Table 4). We also identified a case from systematic review of computerized archives in this series. All reported cases (3 from literature and 1 reported here) were from female patients, and the disease involved proximal esophagus in one patient, and the mid and lower esophagus in two.

Primary Paget disease is exceedingly rare, with only four possible cases reported in the literature [1–4]. EMPD (both primary and secondary forms) more commonly involves skin or mucosa with apocrine gland, such as the genital skin, axillae, and anus [10, 11]. Primary EMPD is an intraepithelial tumor that possibly arises from the epidermis or apocrine glands. Primary EMPD can occasionally become invasive and/or metastasize. It is postulated that the precursor cells may be a pluripotent progenitor epidermal cell or adnexal cell. By definition, primary Paget cells are of glandular origin; they are CK7 positive and CK20 negative, with expression of gross

cystic disease fluid protein (GCDFP-15). HER2, overexpressed in 70–100% of mammary Paget disease, shows significant variability in EMPD [12]. The esophagus contains submucosal glands, not unlike the perianal gland of the anus. It is reasonable to speculate that the secondary Paget cells likely spread to the epithelium through the submucosal gland ducts, whereas primary Paget disease arises from the intraepithelial portion of the submucosal gland. All four reported primary Paget disease of the esophagus presented as non-mass forming mucosal lesions, with two demonstrating ring-like scarring similar to eosinophilic esophagitis.

In addition to primary Paget disease of the esophagus and pagetoid spread of EAC, the differential diagnoses of pagetoid spread of ESCC mainly include amelanotic mucosal melanoma, Langerhans cell histiocytosis [13], and mycosis fungoides [14], which can potentially be mistaken for EMPD at other anatomic sites, but are exceedingly rare.

While acknowledging the limitations imposed by the study's small size, primarily due to the lower incidence of ESCC in North America, it is important to note that pagetoid spread of ESCC can be easily mistaken for pagetoid spread of EAC, a more prevalent type of esophageal cancer in this region. Therefore, recognizing this lesion will assist pathologists in avoiding a diagnostic pitfall.

In summary, both ESCC and EAC may give rise to pagetoid spread of tumor cells within the surface squamous epithelium. Pagetoid spread from ESCC and EAC has overlapping histologic features. P40 and p63 immunostains can facilitate the distinction between ESCC and EAC. P53 immunostain can aid in the confirmation of malignancy. Understanding their overlapping pathologic features will help pathologists avoid pitfalls and diagnose these lesions correctly on biopsy specimens.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00428-024-03788-7.

Author contribution TRM and LZ designed the study. TRM, XZ, HMK, SL, NS, LY, MW, VD, JLH, MSR, and LZ collected the data. TRM and LZ analyzed the data. TRM and LZ drafted the manuscript. TRM, XZ, HMK, NS, MW, JLH, and LZ revised the manuscript.

Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest TRM, XZ, HMK, SL, NS, LY, MW, MSR, and LZ have no relevant disclosures. VD serves on the Scientific advisory boards of Incyte and Viela and receives research support from Advanced Cell Diagnostic and Agios. JLH is a consultant to Aadi Bioscience, TRACON Pharmaceuticals, Adaptimmune, and Leica Biosystems.

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Authors and Affiliations

Tiffany R. Miller[1,2,3] · Xuchen Zhang[4] · Huaibin M. Ko[5] · Stephen M. Lagana[5] · Namrata Setia[6] · Lindsay Yassan[6] · Maria Westerhoff[7] · Vikram Deshpande[3,8] · Jason L. Hornick[1,3] · Mark S. Redston[1,3] · Lei Zhao[1,3]

✉ Lei Zhao
lzhao19@bwh.harvard.edu

Tiffany R. Miller
TRMILLER@BWH.HARVARD.EDU

Xuchen Zhang
xuchen.zhang@yale.edu

Huaibin M. Ko
hmk2102@cumc.columbia.edu

Stephen M. Lagana
sml2179@cumc.columbia.edu

Namrata Setia
Namrata.Setia@uchicagomedicine.org

Lindsay Yassan
lyassan@bsd.uchicago.edu

Maria Westerhoff
mwesterh@med.umich.edu

Vikram Deshpande
vdeshpan@bidmc.harvard.edu

Jason L. Hornick
jhornick@bwh.harvard.edu

Mark S. Redston
mredston@mgb.org

[1] Department of Pathology, Brigham and Women's Hospital, 75 Francis Street, Boston, MA, USA

[2] Department of Dermatology, Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, USA

[3] Harvard Medical School, Boston, USA

[4] Department of Pathology, Yale University School of Medicine, New Haven, USA

[5] Department of Pathology, Columbia University, New York, NY, USA

[6] Department of Pathology, University of Chicago, Chicago, USA

[7] Department of Pathology, University of Michigan, Ann Arbor, USA

[8] Department of Pathology, Beth Israel Deaconess Medical Center, Boston, USA