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Primary anorectal mammary-like adenocarcinoma: a potential diagnostic pitfall with conventional colorectal adenocarcinoma

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Abstract
Anogenital mammary-like glands (AGMLGs) are present in the anogenital region that bear striking morphologic and protein-expression similarities to mammary glands in the breast. AGMLGs can give rise to both benign and malignant lesions which mimic primary breast lesions. Herein, we report two mammary-type adenocarcinomas arising from AGMLGs, including one in the previously unreported site of the rectum. Recognition of mammary-type adenocarcinoma in the rectal and anogenital regions is crucial as clinical management options may differ compared to conventional colorectal adenocarcinomas.

Keywords Mammary-like adenocarcinoma, Rectum, Breast cancer, Anogenital mammary like adenocarcinoma

Introduction

The presence of mammary-like glands in the anogenital region has been recognized since the 1870s [1, 2]. Anogenital mammary-like glands (AGMLGs) are known to give rise to both benign and malignant lesions mimicking those arising in the breast [2, 3]. There have been several reported cases of mammary-type carcinomas arising from AGMLGs in the vulva and perianal region [1, 2, 4–8]. These tumors are rare and were presumed to be arising from the caudal end of embryologic milk line existing from axilla to the groin region [9]. Some studies postulate that the milk line may be a myth and that mammary ridges in humans are confined to the axillary-pectoral region [1, 8]. Instead, AGMLGs may be derived from the normal eccrine glands present in the region [2, 3]. Regardless of the origin of AGMLGs, lesions arising from these glands show striking similarities to breast proper.

We hereby report two cases of mammary-type adenocarcinoma arising from AGMLGs, one of them arising in a hitherto unreported site of rectum. Recognition of these lesions is critical as morphological characteristics and clinical management might be distinctive compared to conventional colorectal adenocarcinomas.

Case 1

An 85-year-old-woman with a previous history of T2N0M0 colon cancer (treated with right hemicolectomy 15 years prior) presented to the emergency department with rectal bleeding and was found to have an anal mass.

An MRI pelvis showed a 3.5×3.0 cm left perirectal mass and enlarged local lymph nodes. The mass involved the internal anal sphincter and likely portions of the external sphincter. A chest CT showed no breast mass as well as no metastases.

Colonoscopy showed the left anal mass and an additional smaller anterior right anal mass. Both lesions were

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biopsied. The small right anal mass was consistent with an early melanocytic nevus (images not shown). The left anal mass biopsy showed a subepithelial tumor composed of sheets and nests of large cells, with abundant eosinophilic granular cytoplasm. The cell borders were distinct. The nuclei were enlarged with prominent nucleoli (Fig. 1A-B). Occasional mitoses were also seen. No significant inflammatory cell infiltrate or glandular differentiation were noted. The overlying squamous epithelium was free of tumor involvement. Immunohistochemical stains showed positivity for cytokeratin-AE1/AE3, cytokeratin 7, GATA3 (Fig. 1C), GCDFP-15 (Fig. 1D), TRPS1, androgen receptor, estrogen receptor (ER; rare; Fig. 1E) and progesterone receptor (PR; rare; Fig. 1F). The carcinoma cells were negative for S-100 protein, cytokeratin 20, TTF-1, p63, Melan-A/Mart-1, vimentin, Desmin, HMB45, SMA, and CDX-2. Tumor cells showed intact nuclear expression for MMR immunostains (MLH1, MSH2, MSH6 and PMS2). HER2 immunostain showed complete and intense membranous staining, consistent with a 3+pattern. The histomorphology was consistent with an apocrine carcinoma and a diagnostic consideration of anogenital mammary-like adenocarcinoma, skin adnexal carcinoma or metastatic breast cancer was raised. Repeat biopsies demonstrated metastatic disease in the left inguinal lymph node.

The patient had no personal history of breast cancer or concern for breast mass. An abdominoperineal resection was deferred due to the patient's age. Radiation therapy and concurrent capecitabine were recommended. The option of endocrine therapy was discussed. The patient opted to pursue treatment locally and was lost to follow up.

Case 2

A 51-year-old woman presented with constipation and progressive, severe epigastric pain with radiation to the right upper and right lower quadrants. A CT scan of the abdomen and pelvis showed a small amount of pelvic free fluid and matted bowel loops. A colonoscopy showed a tight stricture at the rectosigmoid junction that could not be passed. An upper endoscopy was unremarkable. An MRI showed an infiltrative tumor in the rectum at and slightly above the anterior peritoneal reflection.

Biopsies of the rectosigmoid stricture revealed tumor cells infiltrating and expanding the lamina propria of the colonic mucosa. Tumor cells were arranged in solid nests as well as single files and individual cells. Individual tumor cells were large with abundant eosinophilic cytoplasm with some cytoplasmic clearing, giving an appearance of a signet ring cell carcinoma. Many of the cells displayed variably indented and crescent shaped nuclei and prominent nucleoli (Fig. 2A-C). The overlying epithelium was intact and precursor lesion, i.e. rectal adenoma, was absent. The unusual morphology prompted us to perform a broad range of immunohistochemical stains. Upon staining with breast specific markers, the cells showed positivity for GATA-3 (Fig. 2D), cytokeratin 7 (Fig. 2E), ER (Fig. 2F), and significant attenuation of e-cadherin. The tumor cells were negative for cytokeratin 20 (Fig. 2G), PR, and CDX-2 (Fig. 2H). MMR immunostains (MLH1, MSH2, MSH6 and PMS2) performed showed intact nuclear expression, while HER2 immunostain was negative (score 0). The differential diagnosis thus included a metastatic breast carcinoma or an aberrantly expressing primary adenocarcinoma of the rectum. The patient was then evaluated for breast imaging. MRI and mammogram of the breast showed no suspicious lesions. A PET-CT showed an enlarged right axillary lymph node; however, an ultrasound-guided biopsy showed reactive lymph node without evidence of malignancy. Myriad genetics MyRisk hereditary cancer testing was negative for clinically significant mutations. A variant of uncertain significant (VUS) was identified in *SMAD4* (c.997G>A; p.Val333Ile).

Considering negative breast specific imaging, the patient was presumed to have a primary rectal tumor and after undergoing total neoadjuvant therapy (FOLFOX+radiation), she underwent low anterior resection for the aforementioned carcinoma.

The resection specimen was examined to show ill-defined indurated areas; however, no gross mass or ulceration was appreciated (Fig. 3A-B). Histopathological examination revealed residual invasive adenocarcinoma, with similar morphological features to the prior biopsy, and with partial treatment effect (Fig. 3C-D). The tumor cells were singly scattered throughout the wall of the rectum. As opposed to sheet-like growth pattern seen in the biopsy sample, the resection showed more singly scattered tumor cells with hyperchromatic and focally eccentric nuclei. Also seen was involvement of one out of seventeen lymph nodes (Fig. 3E). No precursor adenomatous epithelium was seen in the overlying rectal mucosa. Similar to the biopsy, the tumor cells again showed positivity for cytokeratin 7, GATA3 (Fig. 3F), GCDFP-15 (Fig. 3G) and ER (Fig. 3H).

The patient subsequently received breast-specific adjuvant ovarian suppression treatment utilizing leuprolide acetate in combination with aromatase inhibitor therapy of anastrozole. She had no evidence of metastatic or recurrent cancer at her 12 month follow up and remained on adjuvant hormone therapy. At the time of this manuscript preparation, the patient had no evidence of breast cancer by physical and imaging examinations.

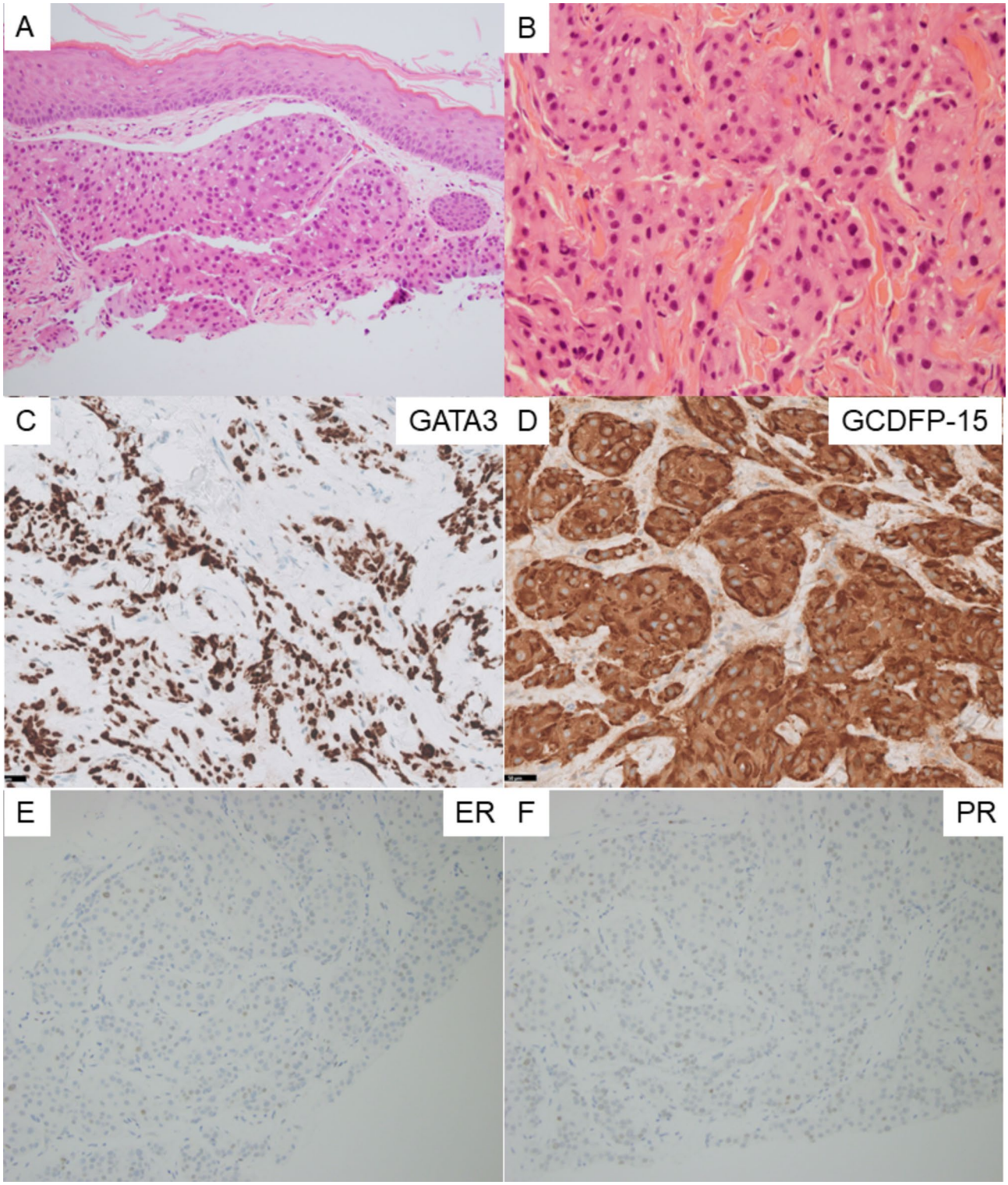

Fig. 1 Case#1, Apocrine carcinoma of the anus. H&E sections showed sheets and nests of tumor cells underlying the uninvolved squamous mucosa (**A**) higher power image of tumor cells with enlarged nuclei, conspicuous nucleoli and abundant eosinophilic cytoplasm (**B**). Immunohistochemical stains showed that the tumor was positive for GATA3 (**C**) and GCDFP-15 (**D**), with rare positivity for estrogen receptor (**E**) and progesterone receptor (**F**)

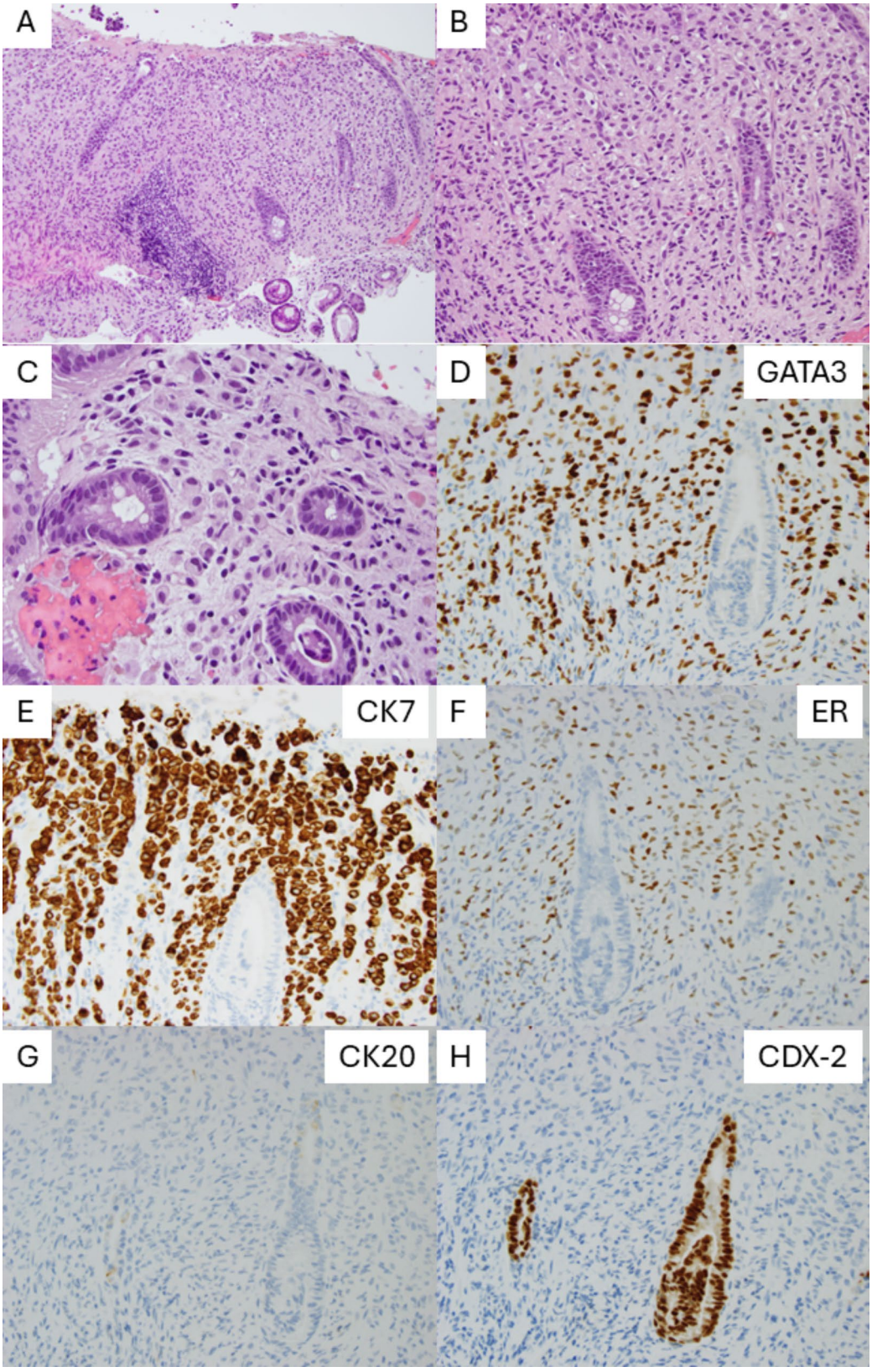

Fig. 2 Case#2, biopsy. H&E sections showed tumor cells within the lamina propria surrounding colonic crypts (**A**-**B**) higher power image of carcinoma cells with enlarged, slightly indented, eccentric nuclei with eosinophilic cytoplasm (**C**). Immunohistochemical stains showed that the tumor was positive for GATA3 (**D**), cytokeratin 7 (**E**), and estrogen receptor (**F**), while negative for cytokeratin 20 (**G**), and CDX-2 (**H**)

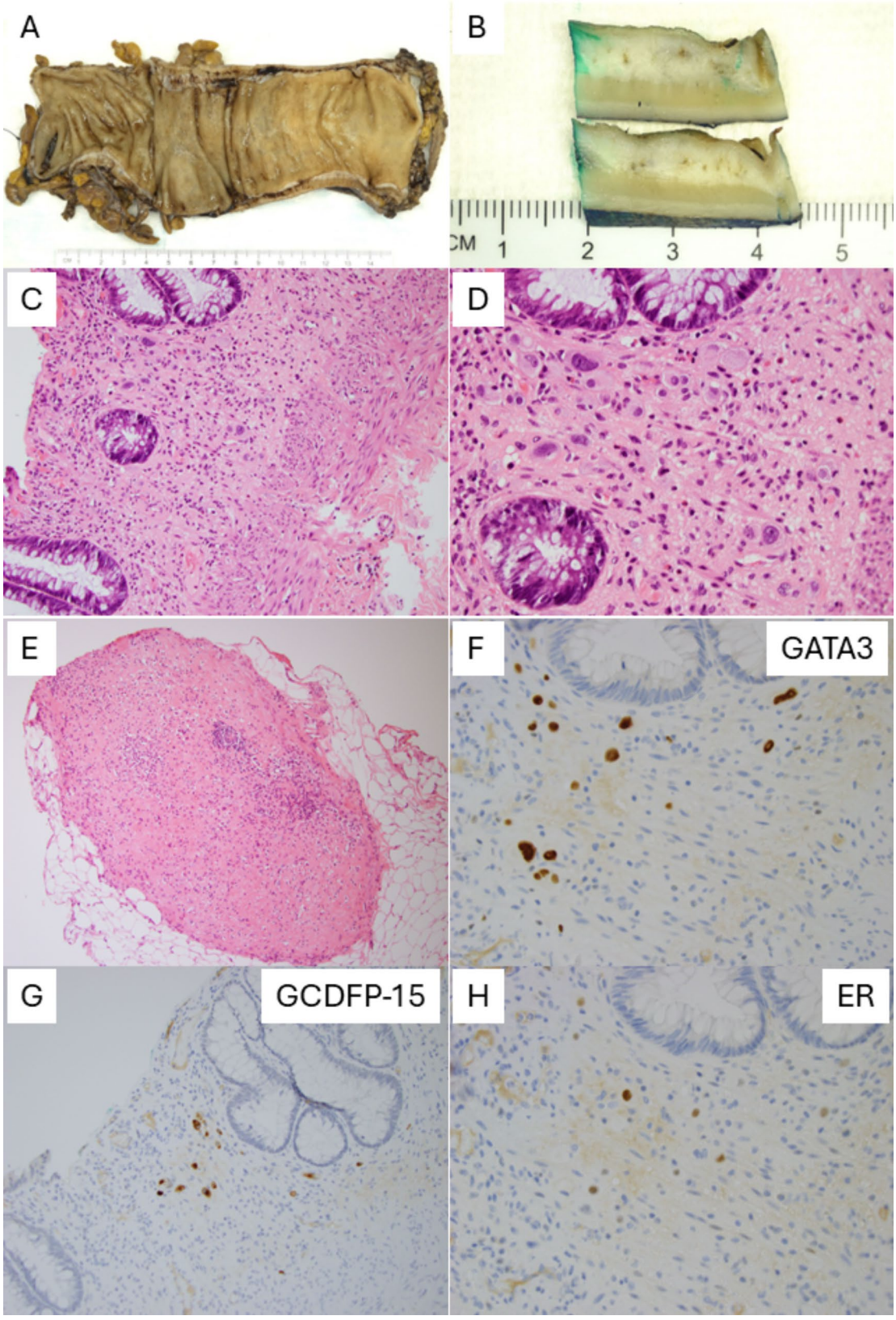

Fig. 3 Case#2, post-neoadjuvant therapy low anterior resection. Gross photographs showed no obvious residual tumor invading the colorectal mucosa (**A**) and a thickening of the colorectal wall (**B**). H&E sections from the rectum showed residual singly scattered tumor cells with pleomorphic, eccentric nuclei and abundant eosinophilic cytoplasm around colonic crypts (**C**-**D**). There was a regional lymph node metastasis (**E**). Immunohistochemical stains on the rectal tumor highlighted tumor cells positive for GATA3 (**F**), GCDFP-15 (**G**), and estrogen receptor (**H**)

Discussion

We report two cases of mammary-like adenocarcinoma in the anorectal region, one of which could be easily mistaken for a signet ring cell type of conventional colorectal adenocarcinoma (case#2). The source of mammary-like adenocarcinoma is presumed to be in AGMLG, that have been well documented in both male and female patients as early as the 1870s [1, 2]. AGMLGs are more prevalent in the vulvar region of female patients but have been found in association with the anus, perineum and penis [1].

These glands can give rise to both benign and malignant lesions that appear histologically identical to lesions occurring in the breast [2–4, 10]. The AGMLG are usually discovered only incidentally upon microscopic review, unless forming a mass lesion [2]. There is a wide morphological spectrum of lesions likened to mammary gland proper arising from AGMLG, including fibroadenoma, lactating adenoma, hidradenoma papilliferum, hidradenocarcinoma papilliferum, phyllodes tumor, sclerosing adenosis, pseudoangiomatous stromal hyperplasia, atypical ductal hyperplasia, columnar cell changes, as well as malignancies [2, 3, 11]. While both of our cases showed presence of malignancies, we did not identify benign counterparts of mammary-like glands in our cases, despite one case being extensively sampled for histological evaluation upon low anterior resection. Although one cannot rule out sampling issues, it is possible that the benign mammary-like glands were completely overridden by the tumor.

A differential diagnostic consideration in these cases is of tumor origin from the eccrine sweat glands. Although breast tissue is considered modified eccrine gland, we could rule out adnexal spread in our cases from (1) no topographic connection to perianal skin, especially case#2 and (2) consistent expression of hormonal markers. There are no criteria established to make a diagnosis of mammary-like adenocarcinoma, however a keen eye on the morphological features and a low threshold to perform breast-specific and hormonal immunohistochemical stains might uncover more such cases.

We observed two distinctive malignancies in the anus and rectum showing immunohistochemical marker profiles similar to breast cancer proper. The first case is of an anal apocrine carcinoma. Although apocrine carcinomas in the colorectal regions are unheard of, apocrine carcinomas of the breast are well-described in the literature [12, 13]. The second case is unique as the histomorphology of the tumor cells might prompt a diagnosis of a poorly differentiated carcinoma with signet ring cell features from a gastrointestinal pathologist lens; although with the knowledge of strong GATA-3 and hormone expression, along with attenuation of e-cadherin, a morphological definition of pleomorphic lobular carcinoma seems more appropriate. Previous studies have shown that invasive carcinomas in the AGMLG can take morphologic appearance analogous to breast counterparts [2]. Invasive ductal, invasive lobular and tubulolobular carcinomas have been described. While not seen in our cases, extramammary Paget's disease has also been reported in AGMLGs [14].

In our study, both tumors were positive for markers associated with breast origin (such as GCDFP-15 and GATA3) and cytokeratin 7. Case#1 showed rare positivity for ER, while case#2 showed stronger ER positivity. One of the tumors showed patchy positivity for PR, while the other case did not show any PR expression. Our findings align with prior reports of AGMLG lesions [2, 3, 6]. Similar to primary breast carcinoma, AGMLG lesions have been reported to express markers associated with breast origin such as GATA3 [3, 15]. Also consistent with primary breast carcinoma, AGMLG lesions are typically positive for cytokeratin 7, negative for cytokeratin 20 and show variable expression for ER and PR [2, 3, 6].

The mutational landscape of lesions arising from AGMLGs is similar to that of primary breast lesions. The *PI3K-AKT* pathway is commonly mutated in these tumors, similar to breast proper [16–18]. Several studies, using targeted sequencing approaches, have shown that cases of hidradenoma papilliferum, which is analogous to intraductal papilloma of the breast, harbor frequent *PIK3CA* mutations [16–18], similar to intraductal papilloma. *AKT* and *BRAF* V600E mutations have also been reported in hidradenoma papilliferum, similar to intraductal papilloma. Similarly, *AKT1*, *MET*, *ABL1*, and *TP53* mutations are noted in AGMLG fibroadenomas and phyllodes tumors, which again is similar to those found in the breast lesion counterparts [16]. Taken together, these studies suggest that AGMLG lesions are molecularly similar to analogous lesions in the breast; however, more studies on malignancies of the AGMLGs are necessary to understand and compare them to mammary proper carcinomas.

Herein, we report two cases of mammary-like adenocarcinomas, one of which was located in a novel and previously undescribed site of rectum. We propose that these two adenocarcinomas originated from the AGMLGs. The occurrence of tumor in case#2 in the more proximal rectal region raises a hypothesis that AGMLGs could have a wider distribution than previously reported. While theoretically these two cases could represent metastatic primary breast carcinoma to the rectum and the anus, we think this is very unlikely as neither patient has a primary breast lesion evaluated by multiple modalities, significant metastatic disease to other sites before the anal/rectal malignancy diagnosis or on follow up studies longer than 12 months (for case #2). Thus, we hypothesize that these two carcinomas are mammary-like and of

AGMLG origin. This hypothesis is further strengthened by the observations that AGMLG-associated tumors are rarely accompanied by synchronous or metachronous breast cancers [16]. We advocate liberal usage of immunohistochemical stains such as GATA3, ER, PR and AR if the morphological features are not classic for a colorectal adenocarcinoma but resemble breast carcinoma. This approach will help unravel distinctive carcinomas that might best be treated with breast-specific regime.

To the best of our knowledge, this is the first report of mammary-like adenocarcinoma arising in the AGMLGs of the rectum. This is an important diagnostic consideration to be aware of given the strikingly different morphology of this entity from other primary adenocarcinomas of the rectum. The mammary-like adenocarcinoma of the AGMLGs are biologically similar to breast cancer impacting their treatment managements. Further studies are necessary to exploit the possibilities of whether such tumors respond to therapies specifically targeted for breast cancers. Prognosis of these tumors also might differ from conventional colorectal adenocarcinomas, but concrete data are lacking.

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Author contributions
P.N., X.L., and M.L.A. wrote and reviewed the manuscript. M.L.A. prepared the figures.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Washington University in St. Louis Institutional Review Board (IRB # 202010108).

Consent for publication
The IRB approved waiver of consent for this retrospective evaluation of archival material.

Competing interests
The authors declare no competing interests.

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