We describe a confusing case of GATA3-positive adnexal adenocarcinoma with a potential pitfall of leading to a misdiagnosis of urothelial carcinoma. A 62-year-old male presented with a subcutaneous nodule on the right lower abdomen around a scar from surgery for urothelial carcinoma in the right urinary tract, which had been resected 8 years previously. Histologically, atypical cells possessing ample cytoplasm and partial intracytoplasmic lumens were densely grouped in the subcutaneous expansive nodule and bilateral inguinal lymph nodes dissected. Decapitation secretion could not be seen. Neoplastic cells were positive for CK7, GATA3, and GCDFP15, and negative for CK5/6, CK20, p63, PAX8, HER-2, and uroplakin-II. Neoplastic cells in the urothelium and the metastasized lung were positive for CK7, CK5/6, and GATA3, and negative for CK20, p63, GCDFP15, and TTF-1. A variable level of GATA3 expression in malignant tumors with apocrine and eccrine differentiation should be recognized by dermatologists. (Ann Dermatol 32(5) 417～421, 2020)

Keywords
Adnexal, Carcinoma, GATA3, GCDFP15, Urothelial

INTRODUCTION
Malignant tumors with apocrine and eccrine differentiation (MTAEs) constitute a heterogeneous group of neoplasms. Some MTAEDs are considered the malignant counterpart of well-recognized benign tumors of similar derivation; those MTAEDs include porocarcinoma, malignant spiradenoma, malignant cylindroma, hidradenocarcinoma, and malignant mixed tumor. Other MTAEDs are morphologically analogous to carcinomas that are not of skin origin, which include mucinous carcinoma, endocrine mucin-producing sweat gland carcinoma (EMPSGC), adenoid cystic carcinoma, and signet-ring cell/histiocytoid carcinoma. The rest of the group includes microcystic adnexal carcinoma, digital papillary adenocarcinoma, apocrine carcinoma (AC), squamous eccrine ductal carcinoma, syringocystadenocarcinoma papilliferum, secretory carcinoma, and cribriform carcinoma. Adnexal adenocarcinoma not otherwise specified (NOS) is a primary carcinoma of the skin with ductal/glandular differentiation but lacking specific histological features that would allow further classification. Extramammary Paget’s disease (EMPD) is reported to be a site-specific malignant tumor probably with apocrine differentiation.

CASE REPORT
A 54-year-old Japanese male suffered from urothelial carcinoma (UC) of the right urothelium, which was completely excised. Three years later, a metastasis to the lower lobe...
of the right lung arose, and was treated by resection and chemotherapy. At the age of 62 years, the patient presented with a subcutaneous nodule around the surgical scar on the right lower abdomen, measuring 20 mm in diameter (Fig. 1A). One year after we performed an excisional biopsy, we performed a lymph node dissection (LND) of the rightinguinal lymph node (LN), which was swollen. The next year, a LND of the swollen left inguinal LN (Fig. 1B) was performed. A hematoxylin and eosin (H&E)-stained specimen of the nodule from the right lower abdomen demonstrated an expansive nodule from the dermis to the subcutis, not involving the epidermis (Fig. 2A). The neoplastic cells possessed oval nuclei and ample eosinophilic cytoplasm, and were densely grouped (Fig. 2B). Clear cells were mixed in part (Fig. 2B). Although decapitation secretion could not be seen, intracytoplasmic lumens were partially detected (Fig. 2C). Cell atypia was severe, with some giant cells and occasional atypical mitoses (Fig. 2D). In some areas, there was a significant deposit of pale-staining mucin in the stroma. The histologic findings of the dissected bilateral inguinal LNs were completely the same as those of the right lower abdomen. An H&E-stained specimen of the right urinary tract showed a nodule radially proliferating from the urothelial epithelium (Fig. 2E). The neoplastic cells possessed oval nuclei and ample eosinophilic cytoplasm, and were densely grouped (Fig. 2F). There were no intracytoplasmic lumens. Cell atypia was severe, with occasional atypical mitoses. Mucin deposition was not significant in the stroma. The neoplastic cells of the resected specimen in the lower lobe of the right lung were the same as those of the urothelium. Neoplastic cells in the subcutis and LNs were positive for CK7, GATA-bind-
Table 1. Summary of published data of immunohistochemical staining results of GATA3 in malignant tumors with apocrine and eccrine differentiation

| Tumor                                      | Reference no. | GATA positive | Total   | Notice                  |
|--------------------------------------------|---------------|---------------|---------|-------------------------|
| Eccrine carcinoma                          | 2             | 5/14 (35.7)   | 18/33 (54.5) | -                       |
|                                            | 8             | 13/19 (68.4)  |         |                         |
| Eccrine porocarcinoma                      | 2             | 10/23 (43.5)  | 10/24 (41.7) | -                       |
|                                            | 7             | 0/1 (0)       |         |                         |
| Hidradenocarcinoma                         | 2             | 6/12 (50.0)   | 6/12 (50.0) | Described as ‘predominantly eccrine’ |
| Mucinous carcinoma                         | 2             | 3/3 (100)     | 5/5 (100) | -                       |
|                                            | 7             | 2/2 (100)     |         |                         |
| Endocrine mucin-producing sweat gland carcinoma | 9          | 2/2 (100)     | 2/2 (100) | -                       |
| Adenoid cystic carcinoma                   | 2             | 2/10 (20.0)   | 2/11 (18.2) | -                       |
|                                            | 7             | 0/1 (0)       |         |                         |
| Apocrine cribriform carcinoma              | 10            | 0/14 (0)      | 0/14 (0) | -                       |
| Microcystic adnexal carcinoma              | 2             | 5/12 (41.7)   | 7/15 (46.7) | Described as ‘predominantly apocrine’ in reference 2 |
|                                            | 7             | 2/3 (66.7)    |         |                         |
| Malignant spiradenoma                      | 2             | 1/1 (100)     | 1/1 (100) | Described as ‘predominantly apocrine’ |
| Malignant chondroid syringoma              | 2             | 3/4 (75.0)    | 3/4 (75.0) | Described as ‘predominantly apocrine’ |
| Aggressive digital adenocarcinoma          | 2             | 4/7 (57.1)    | 4/7 (57.1) | Described as ‘predominantly apocrine’ |
| Apocrine carcinoma                         | 2             | 13/14 (92.9)  | 17/18 (94.4) | -                       |
|                                            | 7             | 1/1 (100)     |         |                         |
|                                            | 8             | 2/2 (100)     |         |                         |
| Present                                    |               | 1/1 (100)     |         |                         |
| Primary genital extramammary              | 2             | 8/8 (100)     | 91/91 (100) | -                       |
| Paget’s disease                            | 5             | 11/11 (100)   |         |                         |
|                                            | 6             | 72/72 (100)   |         |                         |

Values are presented as number (%). -: not available.

DISCUSSION

GATA3 is a member of the GATA family of zinc finger nuclear transcription factors that bind to G-A-T-A nucleotide sequences within the promotor regions of target genes. GATA3 is involved in the normal development of a variety of tissues and cell types. GATA3 target gene promoters are involved in epidermal differentiation, and in the skin barrier function, as well as in the differentiation of the mammary glands and the urothelial tract and the regulation of T-cell differentiation.

In 2007, Higgins et al. found that GATA3 was a sensitive diagnostic marker for UC. Since then, there has been growing evidence that GATA3 could serve mainly as a sensitive diagnostic marker for breast carcinoma (BC) and UC. GATA3 target gene promoters are involved in epidermal differentiation, and in the skin barrier function, as well as in the differentiation of the mammary glands and the urothelial tract and the regulation of T-cell differentiation.
a potential pitfall leading to a misdiagnosis of UC with pagetoid spread\textsuperscript{11}. A high level of GATA3 expression was demonstrated in normal apocrine glands\textsuperscript{4,13}, whereas eccrine glands were negative for GATA3\textsuperscript{13}. Among MTAEDs, 55\% of cases were reported to be positive for GATA3\textsuperscript{2,14}. EMPSCG had GATA3 expression\textsuperscript{15} similar to mucinous carcinoma\textsuperscript{2,13}. Microcystic adnexal carcinoma was reported to be positive for GATA3 in 47\% of cases\textsuperscript{2,13}. Whereas positive staining for GATA3 was reported in 94\% cases of AC\textsuperscript{2,13,14}, no expression was observed in apocrine cribriform carcinoma\textsuperscript{16}. Because the classification and the GATA3 sensitivity in MTAEDs are not well established, further study of a larger number of cases is needed.

GCDFP15 is reported to be of cutaneous or mammary origin\textsuperscript{11,12}. In the present case, the diagnosis of GATA3-positive adnexal adenocarcinoma was also confirmed by the positive staining of GCDFP15. In retrospect, GATA3 expression could have been a potential pitfall leading to a misdiagnosis of UC in this case. Whereas GATA3 is specific for BC and UC to some degree, both GCDFP15 and uroplakin-II should be used in conjunction to avoid a misdiagnosis in confusing cases\textsuperscript{12}.

We have described a confusing case of GATA3-positive adnexal adenocarcinoma with a potential pitfall of leading to a misdiagnosis of UC. Whereas GATA3 is sensitive for BC and UC to some degree, it is also expressed in MTAEDs. A variable level of GATA3 expression in MTAEDs should be recognized by dermatologists.

**CONFLICTS OF INTEREST**

The authors have nothing to disclose.

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**DATA SHARING STATEMENT**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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