

Title:

Giant pilomatrical tumor with broad epidermal components: An example of histological diversity and a potential diagnostic pitfall of tumors with pilomatrical differentiation

Running title:

Pilomatrical tumors with epidermal components

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24 **Conflict of interest:**

25 None declared

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28 **Abstract (197 words):**

29 The diagnosis of pilomatricoma, the most common matrical tumor, is generally
30 straightforward; however, it exhibits diverse histology associated with various morphological
31 stages and several clinical variants, and matrical differentiation can occur in various
32 neoplastic diseases. A 56-year-old male was admitted to our hospital to resect an 11.0 cm skin
33 tumor on his right shoulder. Due to its large size and surface irregularities, including multiple
34 erosions and ulcers, cutaneous malignancies were clinically suspected. Histologically, the
35 tumor formed numerous nodules with marked matrical differentiation in the superficial to
36 deep dermis. Although the tumor was macroscopically asymmetrical and irregular, each
37 nodule was microscopically round-shaped and consisted of basaloid cells without marked
38 atypia, atypical mitoses, or lymphovascular invasion. Immunohistochemically, the tumor
39 cells were positive for beta-catenin, LEF-1, and PHLDA-1, consistent with their pilomatrical
40 differentiation. We diagnosed the case as a giant pilomatrical tumor with uncertain malignant
41 potential, considering its “contradictory” features, namely, the worrisome histoarchitecture,
42 such as the asymmetrical silhouette, but bland-looking cytological appearance. Unlike typical
43 pilomatrical tumors, this tumor contained numerous epidermal components with features
44 similar to those of the dermal components, resulting in a unique macroscopic and histological
45 appearance. Our case broadens the known histological diversity of pilomatrical tumors.

46

47 **Keywords:**

48 1) Pilomatricoma, 2) Pilomatrical carcinoma, 3) Basal cell carcinoma, 4) Beta-catenin, 5)

49 LEF-1

50

51

52 **Main text (1148 words)**

53 **Introduction**

54 Matrical (or shadow cell) differentiation, in which a cell keratinizes into a so-called shadow
55 cell with distinct cell borders, an eosinophilic cytoplasm, and a space where the nucleus was
56 once located, is a typical feature of pilomatricoma, a common and benign adnexal tumor. In
57 most cases, the diagnosis is straightforward; however, its histology is diverse associated with
58 various morphological stages and several clinical variants¹⁻⁶, including a giant form.
59 Moreover, matrical differentiation can occur in various neoplastic diseases other than
60 pilomatricoma, including non-cutaneous tumors⁷⁻¹¹. Here, we present a case of giant
61 pilomatrical tumor with uncertain malignant potential, exhibiting broad epidermal
62 components, which, to our knowledge, has not been well recognized.

63

64 **Case report**

65 A 56-year-old male consulted a physician regarding a large skin tumor with erosion on his
66 right shoulder, extending toward the axilla (Figure 1). He had first noticed the tumor three to
67 four years earlier, when it was approximately 3 to 4 cm in size. It had subsequently expanded
68 particularly rapidly after bruising appeared at the tumor site. Approximately two years earlier,
69 the tumor had spontaneously disintegrated, but later recurred. He underwent a punch biopsy
70 on the tumor, and a malignant appendageal tumor was suspected. He was hospitalized at our

institution for further investigation and surgical removal of the tumor. Image analysis revealed enlargement of the cervical lymph nodes with abnormal uptake on ¹⁸F-fluorodeoxyglucose-positron emission tomography (FDG-PET), and a metastatic tumor was suspected. No lesions suggesting distant metastasis were evident. The tumor was subsequently resected with dissection of the cervical lymph nodes.

The resected specimen was 21.0 cm × 11.0 cm × 7.5 cm and contained a large tumor measuring 11.0 cm × 10.0 cm × 7.5 cm on its superior end. The tumor was yellow to whitish, asymmetrical, and poorly circumscribed on the cut section, and formed irregular nodules from the epidermis to the deep dermis, exhibiting a partly wedge-shaped distribution (Figure 2).

In the dermis, the tumor microscopically consisted of numerous nests composed of immature basaloid cells exhibiting matrical differentiation, accompanying calcification and foreign body reactions to the shadow cells (Figure 3). Each of the matrical cells had scant cytoplasm, a vesicular nucleus, and a prominent nucleolus (Figure 3). Although mitoses were readily apparent (Figure 3), no atypical mitoses or lymphovascular invasion were noted. Subcutaneous invasion was not evident, and coagulative necrosis was not seen.

The epidermis covering the dermal lesions had a papillary appearance and multifocally consisted of tumor cells, with exophytic matrical differentiation (Figure 4). Epidermal tumor cells often formed nests showing downward growth, with or without cystic

changes (Figure 4), but some cells or nests did not show such apparent features and were continuous with the surrounding apparently non-neoplastic keratinocytes (Figures 5). No tumor components exhibited features reminiscent of basal cell carcinoma (BCC) or other cutaneous neoplasms such as actinic keratosis, Bowen's disease, (conventional) squamous cell carcinoma (SCC), or trichoblastoma. The dissected lymph nodes revealed follicular hyperplasia without metastasis.

Immunohistochemically, both epidermal and dermal components were positive for beta-catenin (nuclei and cytoplasms), LEF-1, p40, and PHLDA-1 (Figure 3-5). The tumor was focally (10%) positive for EMA, and almost negative for ADRP, BerEP4 (Figure 3-5), CK7, and perilipin. The Ki-67 labeling index varied among the nests, ranging from approximately 10 to 50% (Figure 3-5). Considering all of these findings together, we reached a diagnosis of giant pilomatrical tumor with uncertain malignant potential, exhibiting epidermal components (see Discussion).

Discussion

Pilomatricoma is benign and the most common matrical tumor. The tumor is believed to arise from hair follicle matrix cells and consequently occurs typically as a dermal tumor⁶. Considering that pilomatricoma is generally symmetrical and well circumscribed, the irregular shape of the tumor in our case was unusual, and pilomatrical carcinoma was first

considered. Despite the irregular distribution, however, each tumor nest was microscopically round-shaped and did not exhibit clear subcutaneous invasion. Further, the tumor cells lacked the marked atypia, atypical mitoses, and lymphovascular invasion that are typical of pilomatrical carcinoma¹². Lymph node metastasis was not observed, and tumor recurrence or metastasis has not been evident. Also, considering the long history of this patient's tumor, including the bruising and self-destruction, it is possible that the tumor was originally well demarcated but became asymmetrical in response to external stimuli.

Considering the macroscopic and histological features combining worrisome features (e.g., large size, ulceration, asymmetrical silhouette) and conventional pilomatricoma-like features (e.g., round-shaped nest, lack of significant cytological atypia, atypical mitoses, and lymphovascular invasion), we think this case should be diagnosed as “a giant pilomatricoma with uncertain malignant potential.” Careful follow-up is needed to monitor its malignant potential.

Our case presented another matter of debate as a pilomatrical tumor, due to the numerous epidermal components. Consistent with its putative origins, pilomatricoma can be continuous with the hair infundibula during the early stage, often accompanied by cystic formation¹. One clinical variant, perforating pilomatricoma, can also attach to the surrounding epidermis²⁻⁵. Pilomatrical carcinoma also generally presents as a subepidermal nodule¹². However, the epidermal components observed in our case appear difficult to explain

as findings related to either early-stage development or perforation because the tumor had a relatively long history of more than three years, and the tumor nests were occasionally located in the relatively flat epidermis, with gradual connections to the surrounding keratinocytes.

Skin tumors other than pilomatricoma and matrical carcinoma can exhibit matrical differentiation, and BCC or Bowen's disease with matrical differentiation^{9,10} should also be considered as differential diagnoses because these tumors can contain epidermal components. We did not observe any features suggesting these tumors, however, such as tumor nests with peripheral palisading and mucin deposition in BCC, or dyskeratotic and/or multinucleated cells in Bowen's disease. Immunohistochemical analysis did not support these possibilities either.

Our case was thus not consistent with the histology of any previously reported matrical tumors. Considering two previous reports of a superficial variant of pilomatricoma^{13,14}, we eventually concluded that our case could be a giant pilomatrical tumor with both epidermal and dermal components. When we reviewed all of the other pilomatricoma cases in our archives from 2011 to 2020 (n = 87), we found that one case contained an epidermal component, although the findings were less marked than those observed in the present case (Figure 6). Because this finding can confer a unique macroscopic and microscopic appearance for a pilomatrical tumor, either benign or malignant, we believe

that this phenomenon should be recognized as an example of the histological diversity of pilomatrical tumors to prevent misdiagnosis. We speculate that these epidermal components developed as the tumor cells merged with the surrounding non-neoplastic epidermis through repetitive erosion and ulcer formation, followed by regeneration. Alternatively, the tumor might have partly arose in the epidermis, similar to the previously described superficial pilomatricoma variant ^{13,14}.

Overall, our case extends the range of the histological variations reported in pilomatrical tumors. We believe that this unusual phenomenon should be recognized so as to prevent misdiagnosis, including other cutaneous malignancies exhibiting pilomatrical differentiation.

Acknowledgments

We sincerely appreciate Keisuke Goto for his valuable advice relating to the diagnosis and histogenesis of this case.

163 **Figure legends**

164 **Figure 1. Macroscopic characteristics of the tumor.**

165 A large skin tumor on the patient's right shoulder was observed, with a reddish color, erosions,
166 and ulcers, extending toward the axilla.

167

168 **Figure 2. Macroscopic characteristics of the resected tumor.**

169 The resected specimen was 21.0 cm × 11.0 cm × 7.5 cm and contained a large verrucous
170 tumor sized 11.0 cm × 10.0 cm × 7.5 cm on the superior surface. The tumor exhibited a
171 partially wedge-shaped distribution from the epidermis to the deep dermis. The tumor was
172 yellow to whitish, asymmetrical, and poorly circumscribed.

173

174 **Figure 3. Microscopic findings of the dermal components of the tumor**

175 In the dermis, the tumor consisted of numerous nests composed of immature basaloid cells
176 exhibiting matrical differentiation (a-b). Despite the irregular distribution, each tumor nest
177 was microscopically round-shaped (b). The matrical cells had scant cytoplasm, vesicular
178 nuclei, and prominent nucleoli. Mitoses were readily apparent (arrow) but lacked marked
179 atypia and atypical mitoses (c). Calcification and foreign body reactions to keratinous
180 materials from the shadow cells were also noted (d). Immunohistochemically, the tumor cells
181 were positive for beta-catenin (nucleus and cytoplasm), LEF-1, PHLDA-1, and p40. They

were negative for BerEP4. The Ki-67 labeling index was approximately 20%. (a-d: H&E section, e-j: immunohistochemistry [e: beta-catenin, f: LEF-1, g: PHLDA1, h: p40, i: BerEP4, j: Ki-67]).

Figure 4. Microscopic findings of the epidermal components of the tumor

The epidermis covering the dermal lesions exhibited a papillary appearance and multiple tumor nests with exophytic matrical differentiation (a-b). The tumor cells were immunohistochemically positive for beta-catenin (nucleus and cytoplasm), LEF-1, p40, and PHLDA-1. They were almost negative for BerEP4. The Ki-67 labeling index was approximately 25% (c-f). (a-b: H&E section, c-h: immunohistochemistry [c: beta-catenin, d: LEF-1, e: PHLDA1, f: p40, g: BerEP4, h: Ki-67]).

Figure 5. Microscopic findings of the epidermal components of the tumor.

Some superficial tumor cells/nests were continuous with the surrounding and apparently non-neoplastic keratinocytes (a, e, g, h). The tumor cells were immunohistochemically positive for beta-catenin (nucleus and cytoplasm) and LEF-1, and negative for BerEP4. The Ki-67 labeling index was approximately 25% (c-f). (a-d: H&E section, e-h: immunohistochemistry [e: beta-catenin, f: LEF-1, g: BerEP4, h: Ki-67]).

201 **Figure 6. Microscopic findings of the epidermal components of pilomatricoma in a**
202 **reference case**

203 Focally, the neoplastic cells merged with the surrounding non-neoplastic epidermis (a–b:
204 H&E section, c–d: immunohistochemistry [c: beta-catenin, d; LEF-1]).

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Figure 1



Figure 2



Figure 3

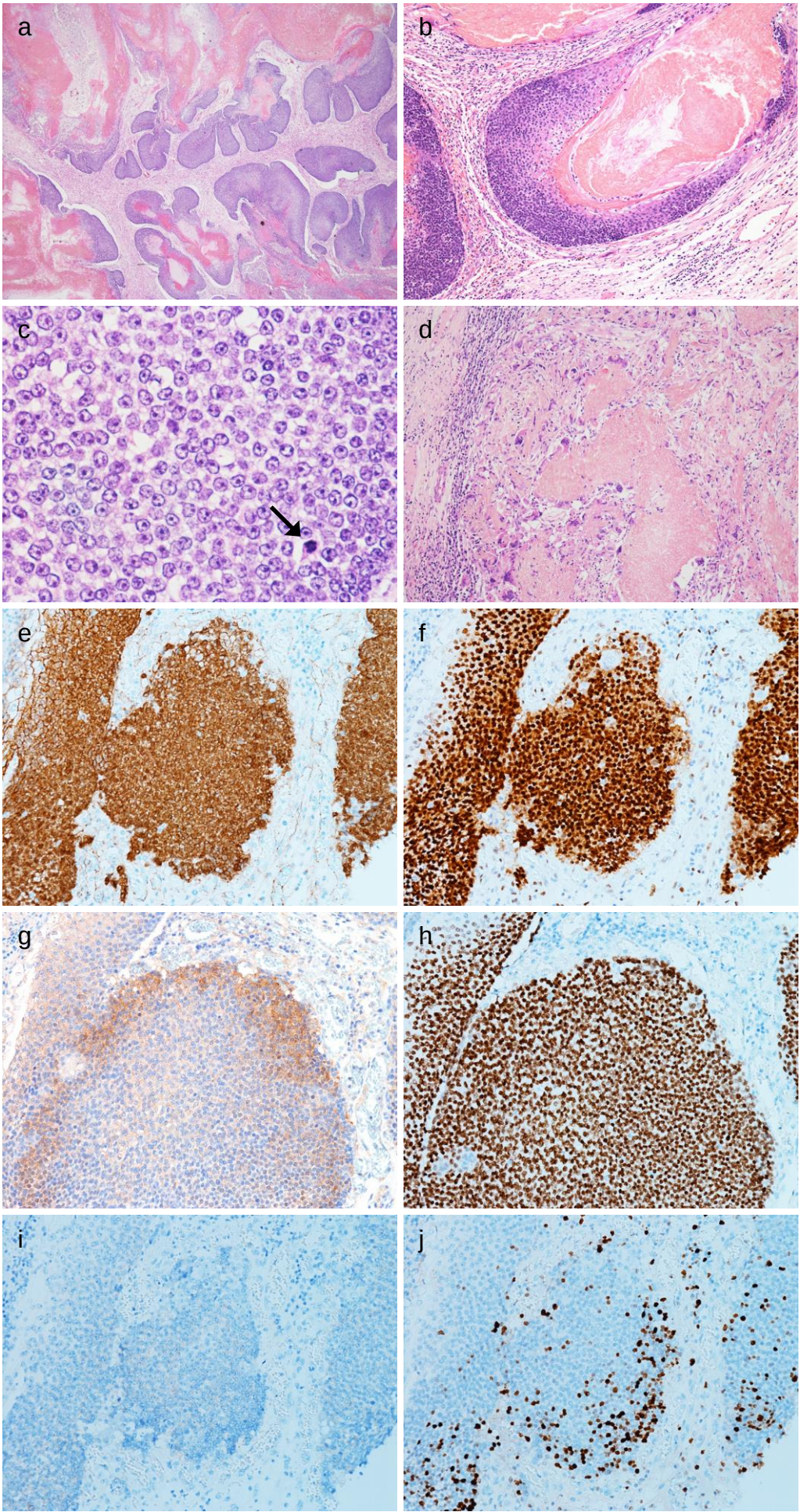


Figure 4

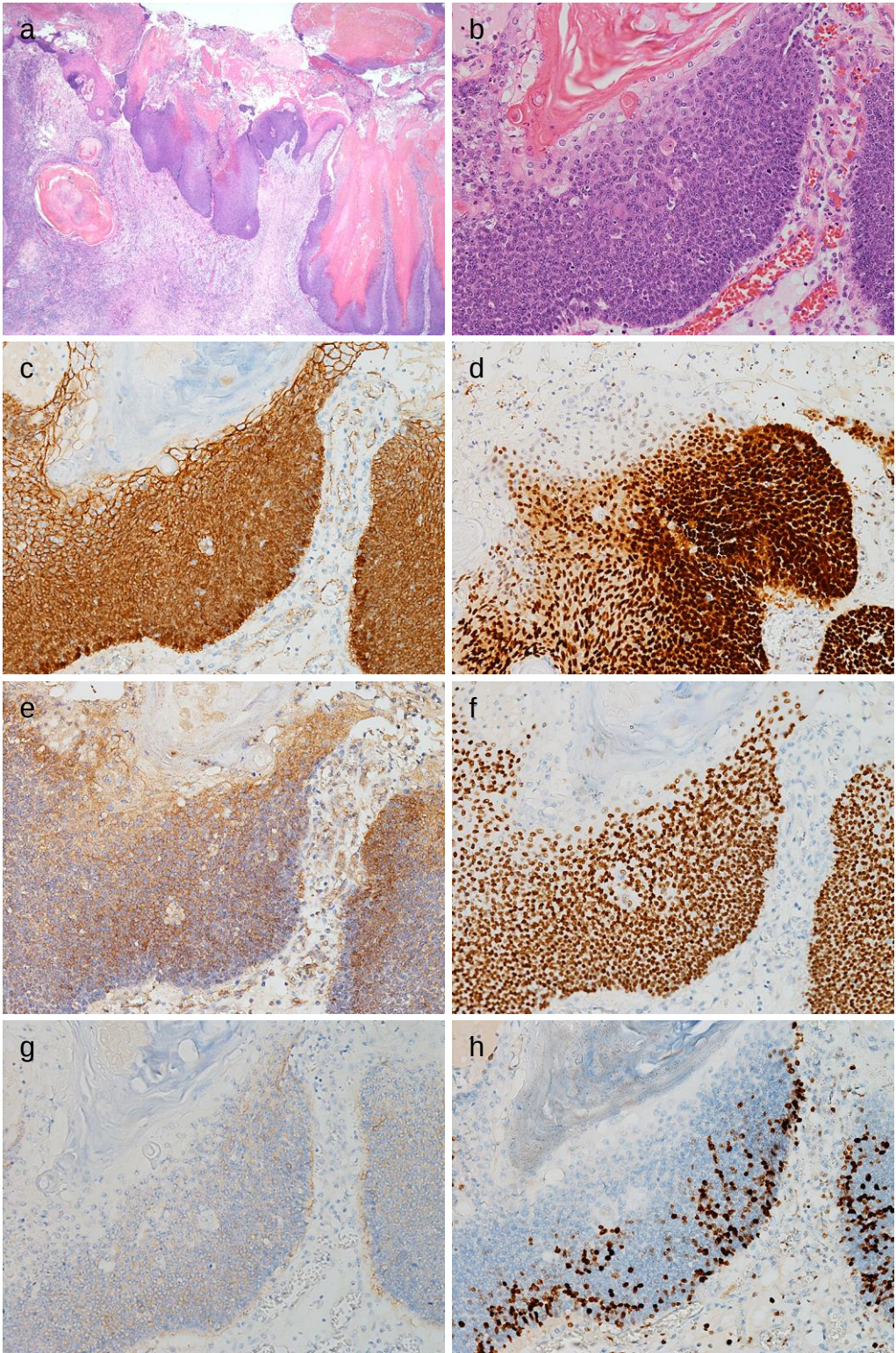


Figure 5

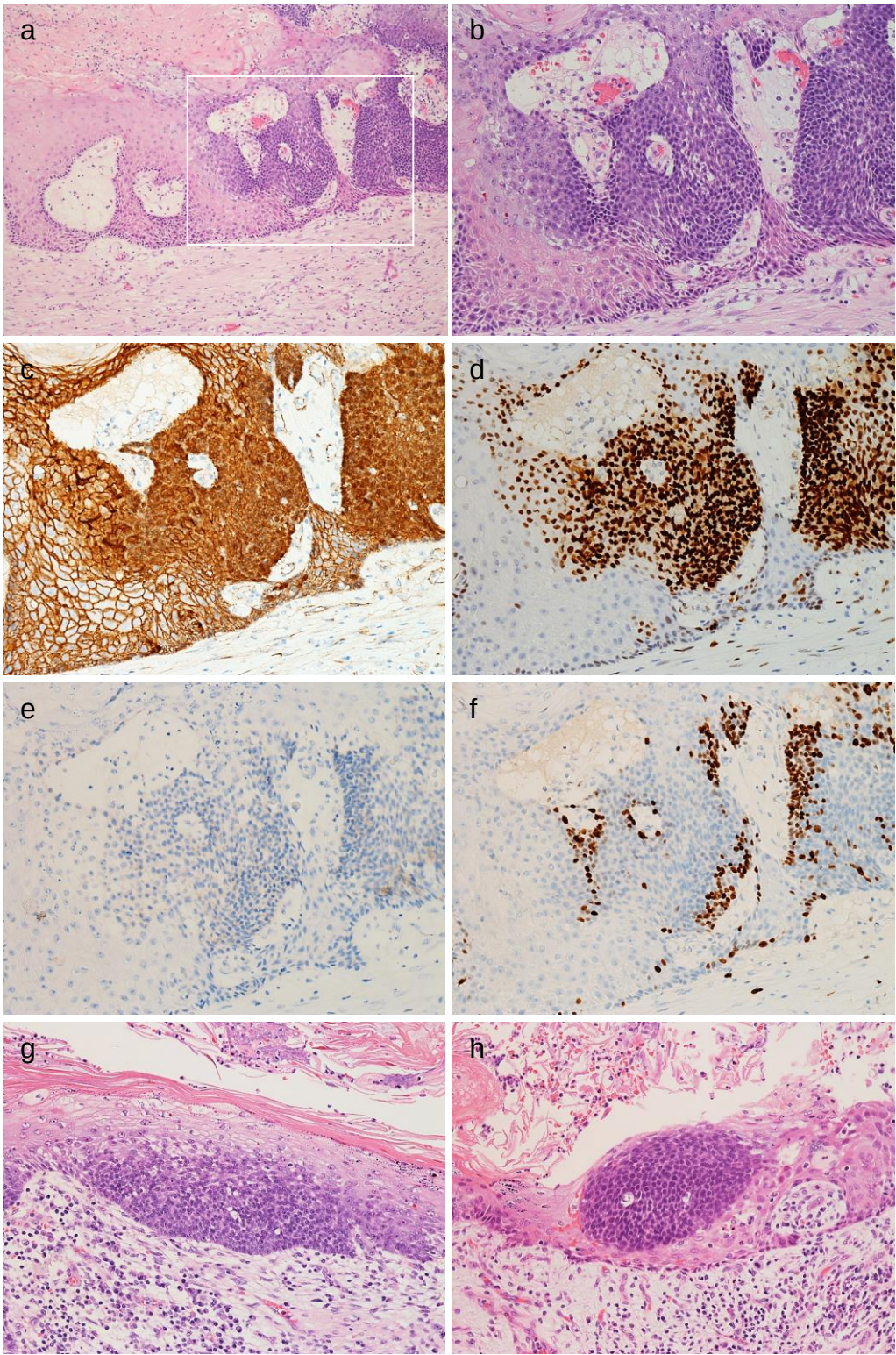


Figure 6

