

Treatment Effects Can Mimic Recurrent Extramammary Paget Disease in Perianal Skin

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- **Definition**

primary extramammary Paget disease (EMPD) is a rare apocrine-type adenocarcinoma that develops in skin with **numerous apocrine glands**, such as axillary, vulvar, and perianal sites.

While this neoplasm often remains limited to the epidermis (carcinoma in situ), it has the potential for extensive lateral **spread, invasion**, and even **metastasis** to regional lymph nodes.

- **ICD-O code** 8542/3

- **Epidemiology**

1% of all neoplasms in the anogenital area

White postmenopausal women

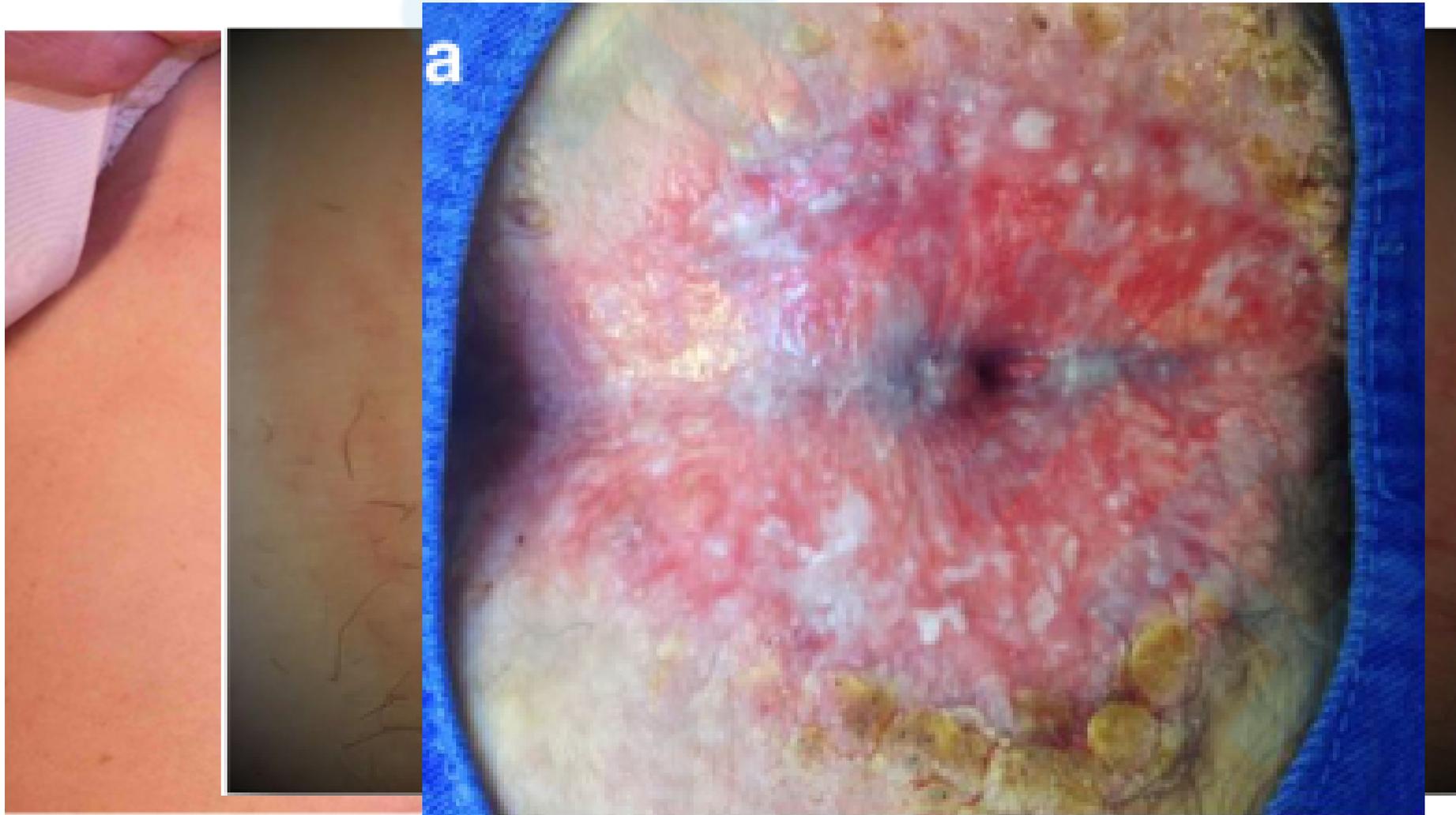
median age of about 70-75 years

- **Etiology**

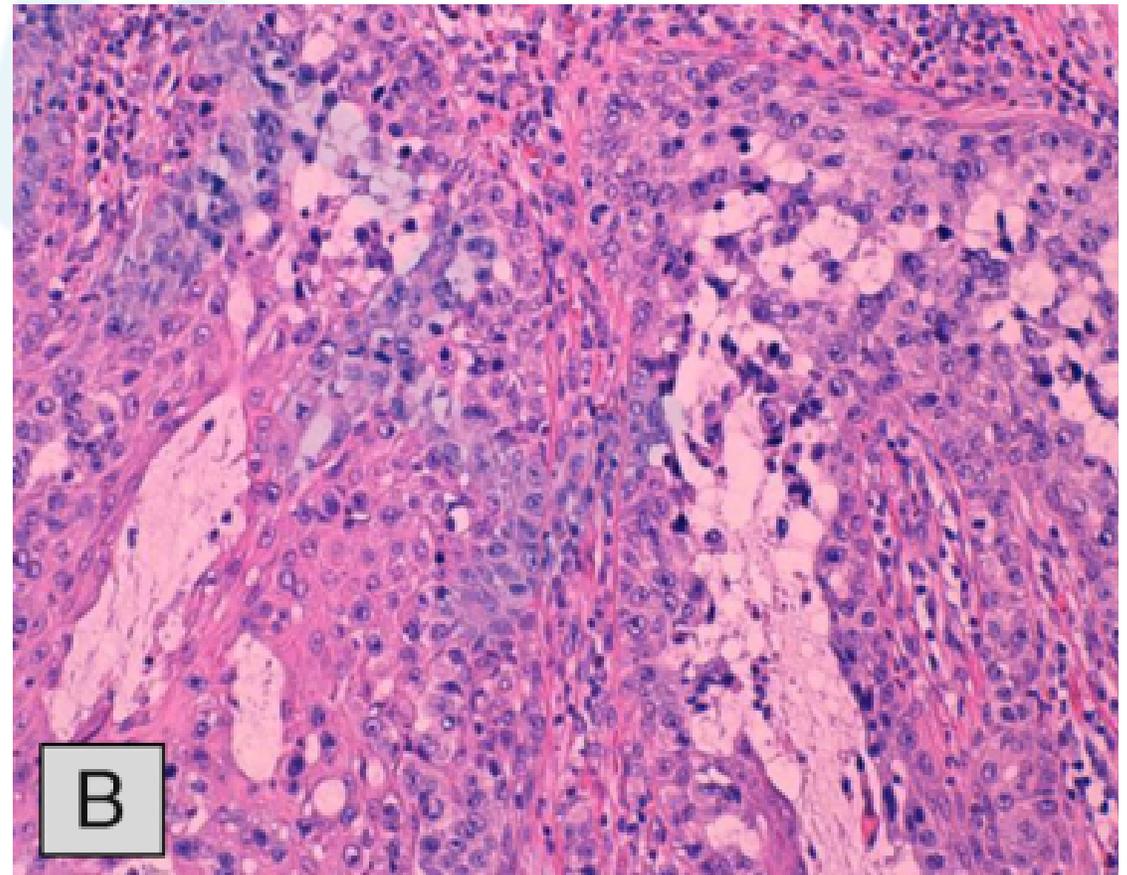
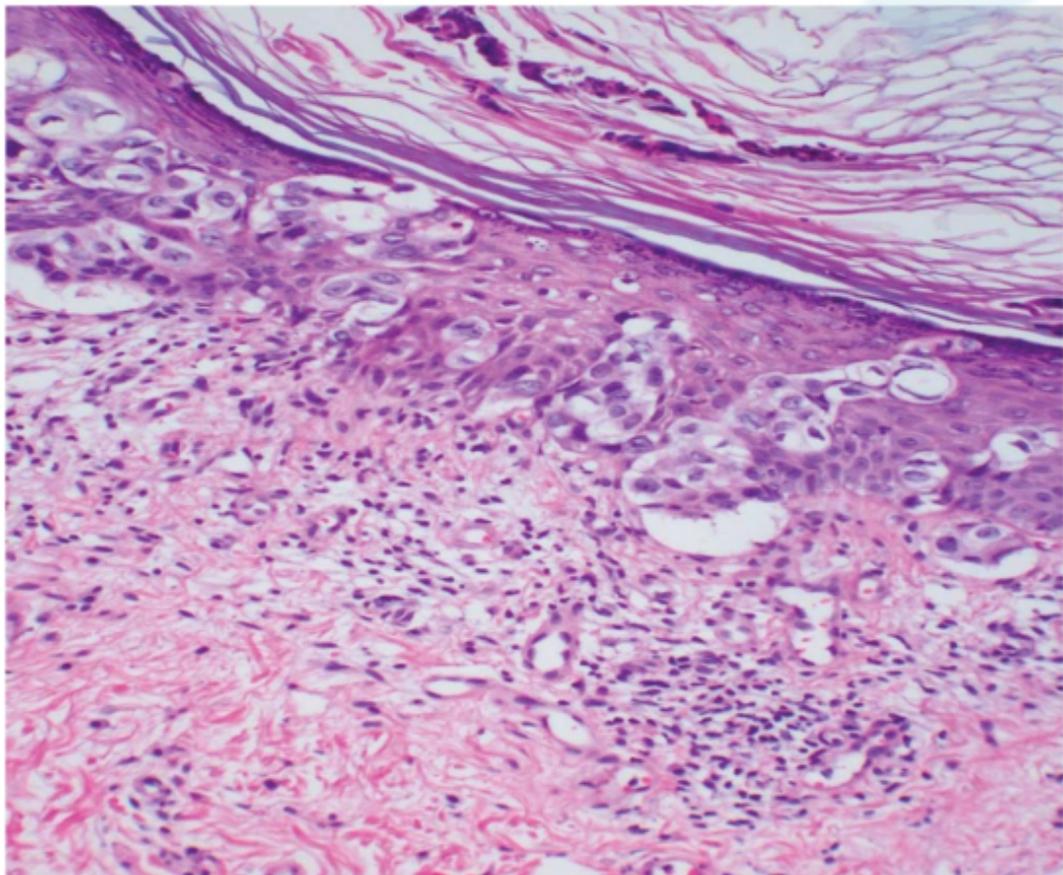
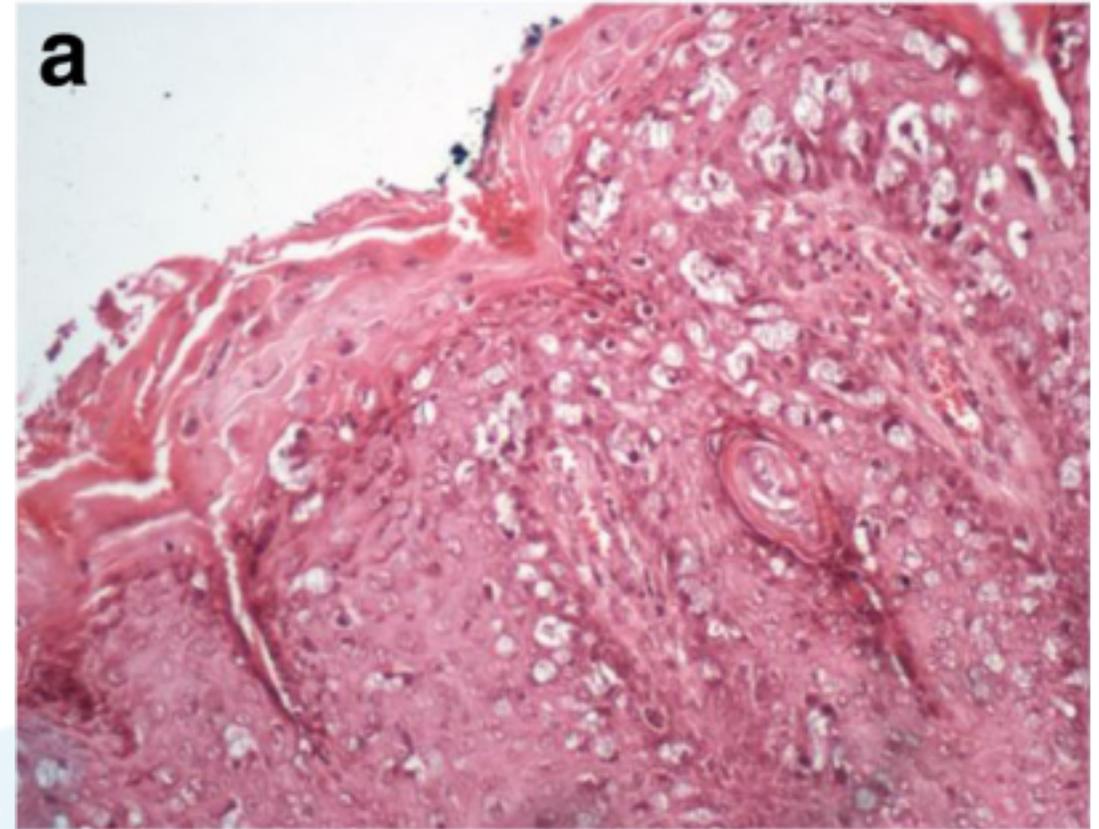
Primary EMPD: unknown

Secondary EMPD: from an underlying carcinoma originating from the lower gastrointestinal tract or urinary tract.

- **Clinical features:** a pruritic patch of erythematous, scaling skin



- **Histological characteristics:**
Singly dispersed and clustered large, mucin-containing cells with eccentric, often hyperchromatic, nuclei are characteristic. These Paget cells may be present at all levels in the epidermis (deep epidermis and adnexal structures)



- **Clinical differential diagnosis:** an infectious or inflammatory dermatitis.
- **The histopathologic differential diagnosis:** malignant melanoma, squamous cell carcinoma, and secondary involvement of perianal skin by adenocarcinoma.
- **Primary treatment:**
 1. Local excision with skin grafting
 2. Follow-up surveillance with biopsy sampling
 3. Adjuvant topical chemotherapy or radiotherapy

- Once a patient has an established diagnosis of extramammary Paget disease, distinction between **recurrent** Paget disease and **therapy-induced** cytologic abnormalities becomes more important, as the former will result in additional therapy.
- The author have received serial biopsy sample to describe the morphologic changes that can be seen in perianal skin samples from patients with longstanding primary perianal Paget disease in an effort to **illustrate pitfalls for under-diagnosis and over-diagnosis of this rare malignancy.**

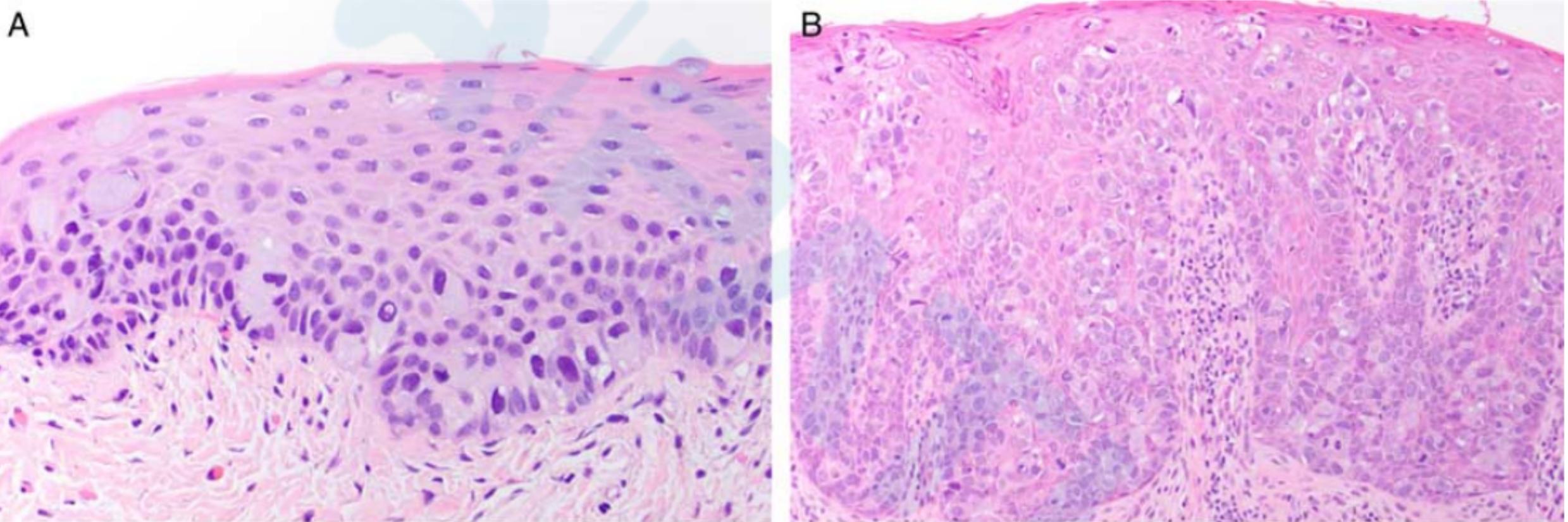
METHODS

- Weill Cornell Medicine.
- Surveillance biopsy samples
- Clinical information: age, sex, clinical symptoms, surgical findings, and type of therapy
- Immunohistochemistry: CK7, S100, p63, syn, mucicarmin

RESULTS

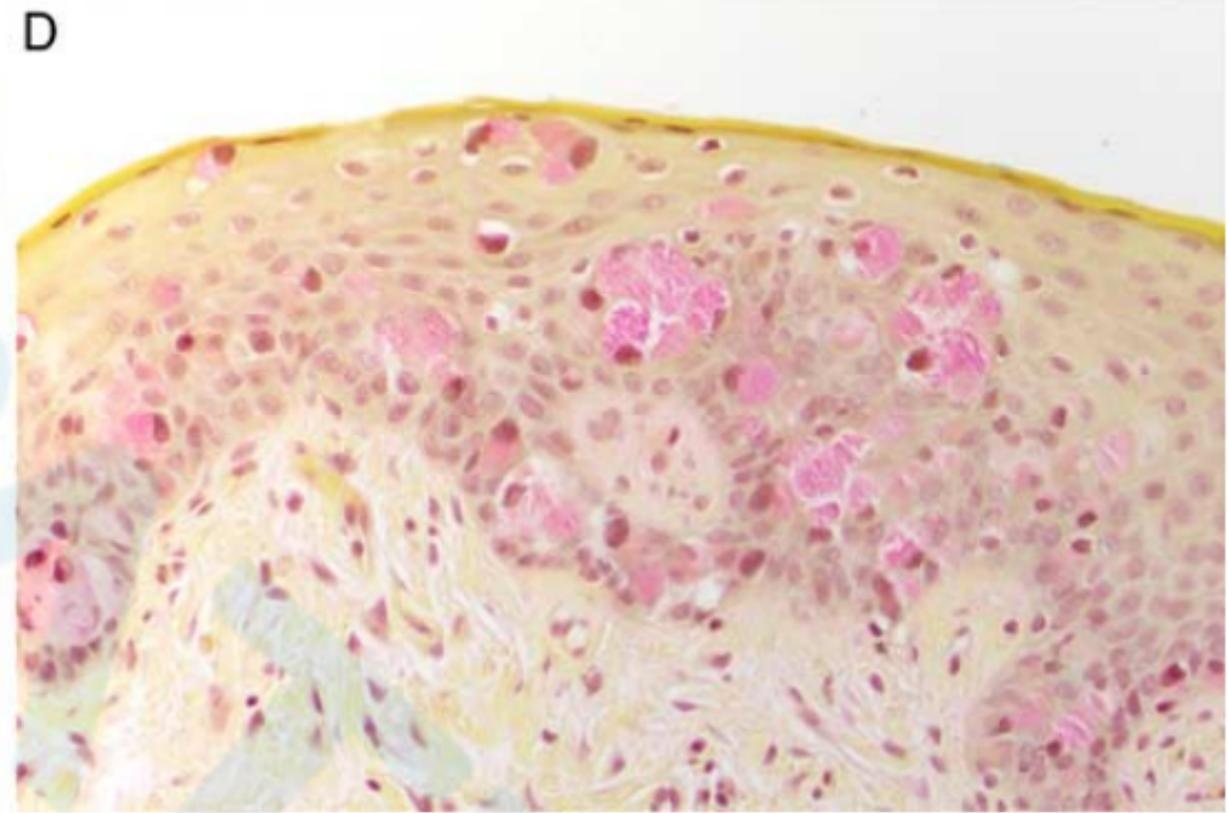
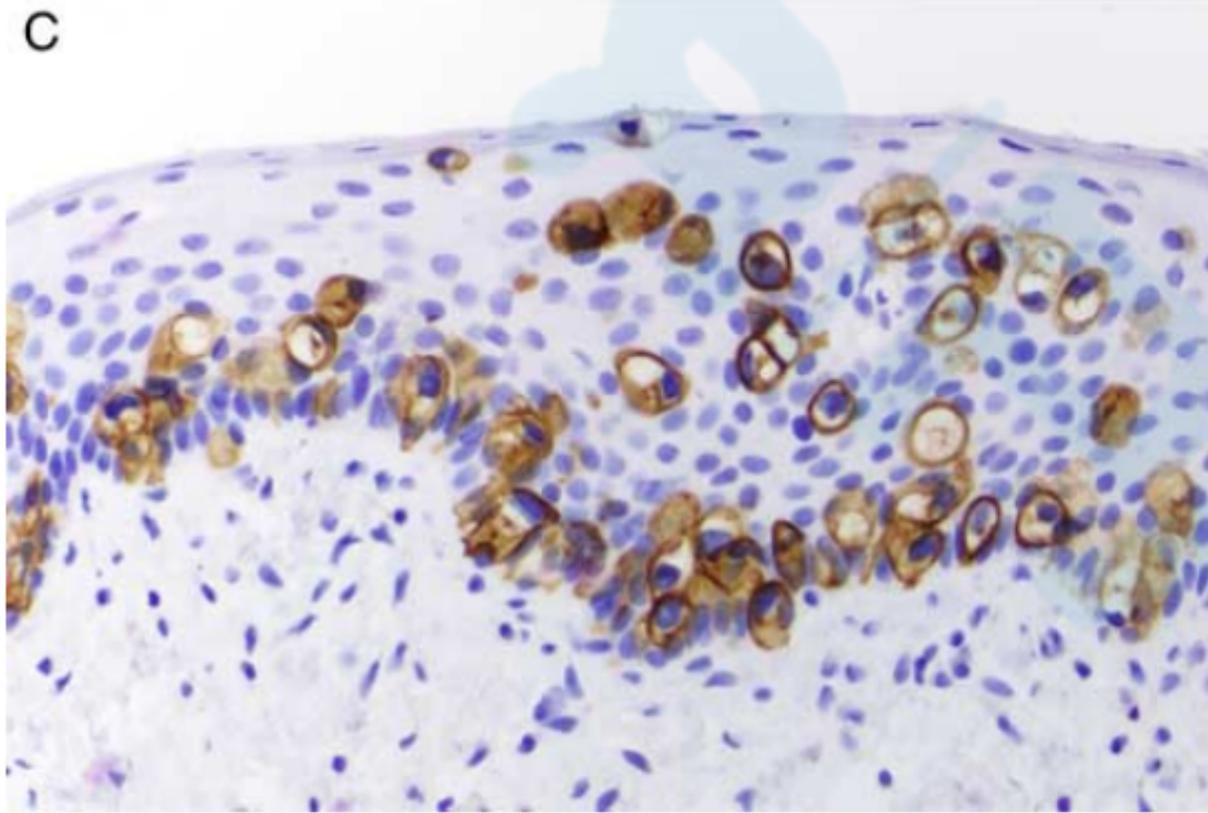
- Surveillance biopsy samples: 39 time points from 3 patients with perianal Paget disease
- 412 posttreatment tissue samples
- The average age: 65 years (60—71 y).

RESULTS



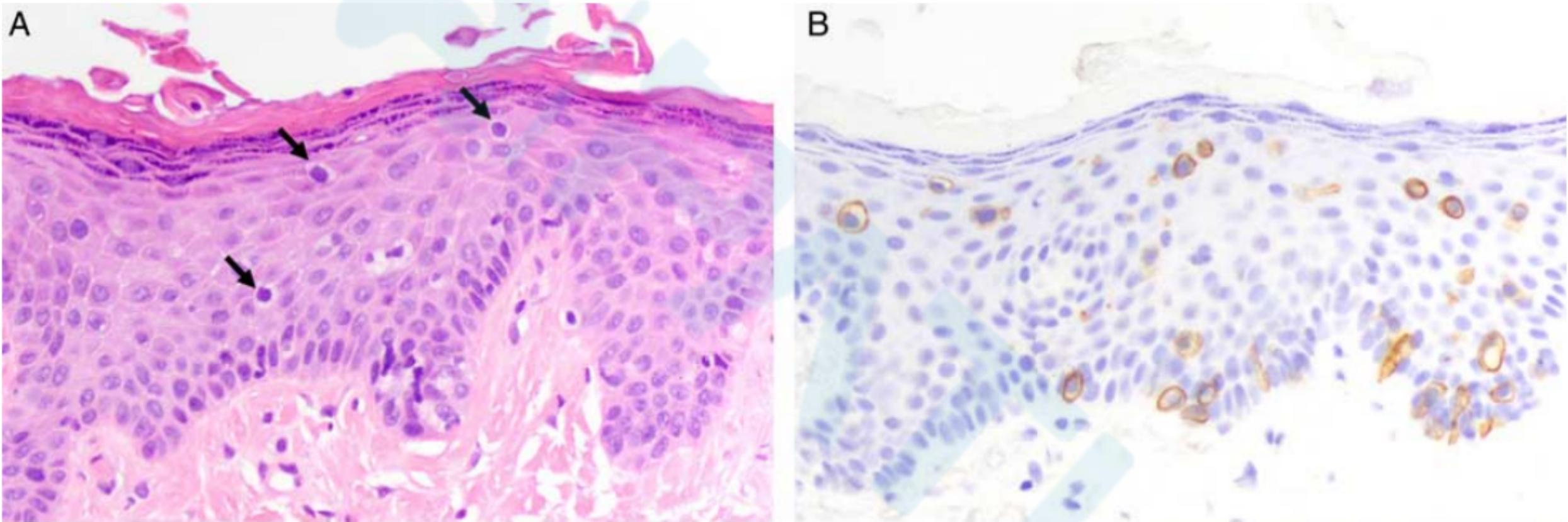
Perianal Paget cells contain voluminous, slightly basophilic mucinous cytoplasm and large, eccentric nuclei with dense chromatin and small nucleoli (A, B). Neoplastic cells are dispersed singly and in clusters throughout the epithelium, but are concentrated in the deeper epithelium.

RESULTS



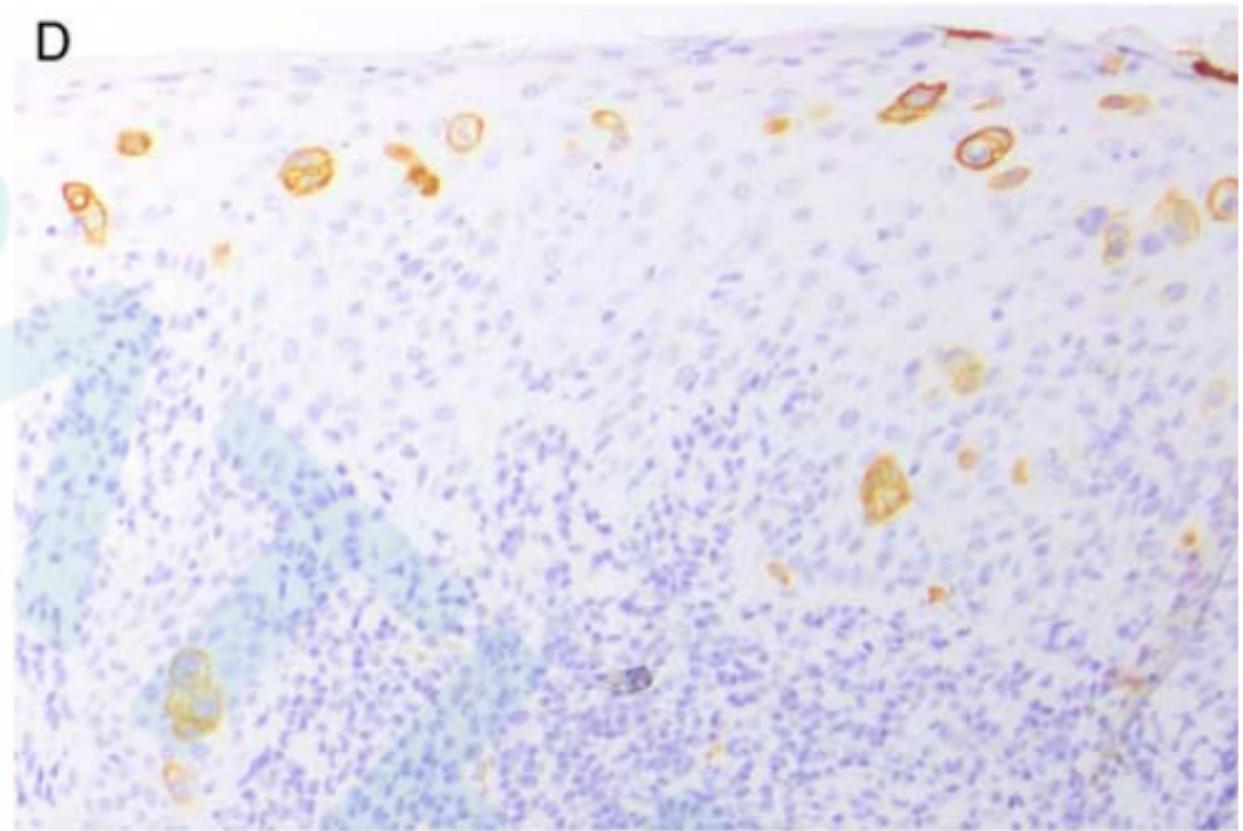
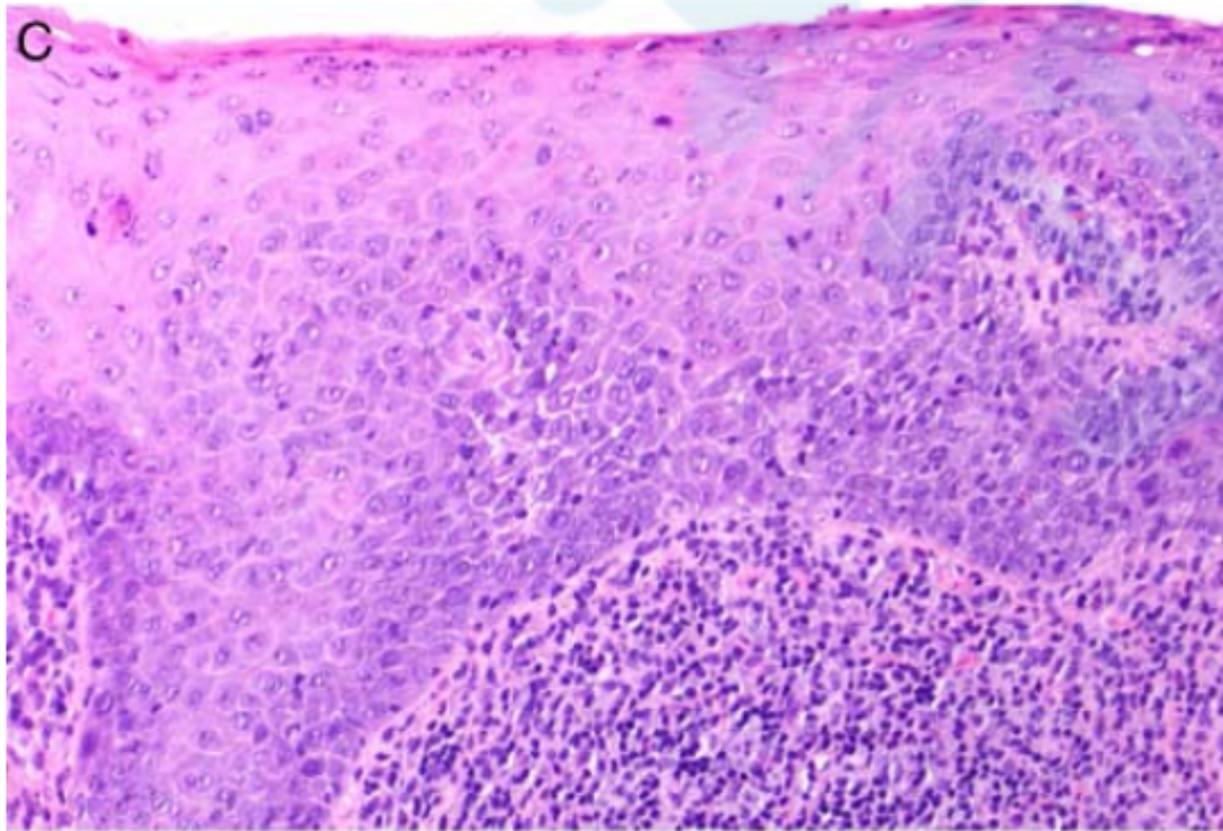
They universally show strong membranous CK7 staining, as well as fainter staining of the cytoplasm (C). A mucicarmine stain highlights the mucinous nature of the cytoplasm (D).

RESULTS



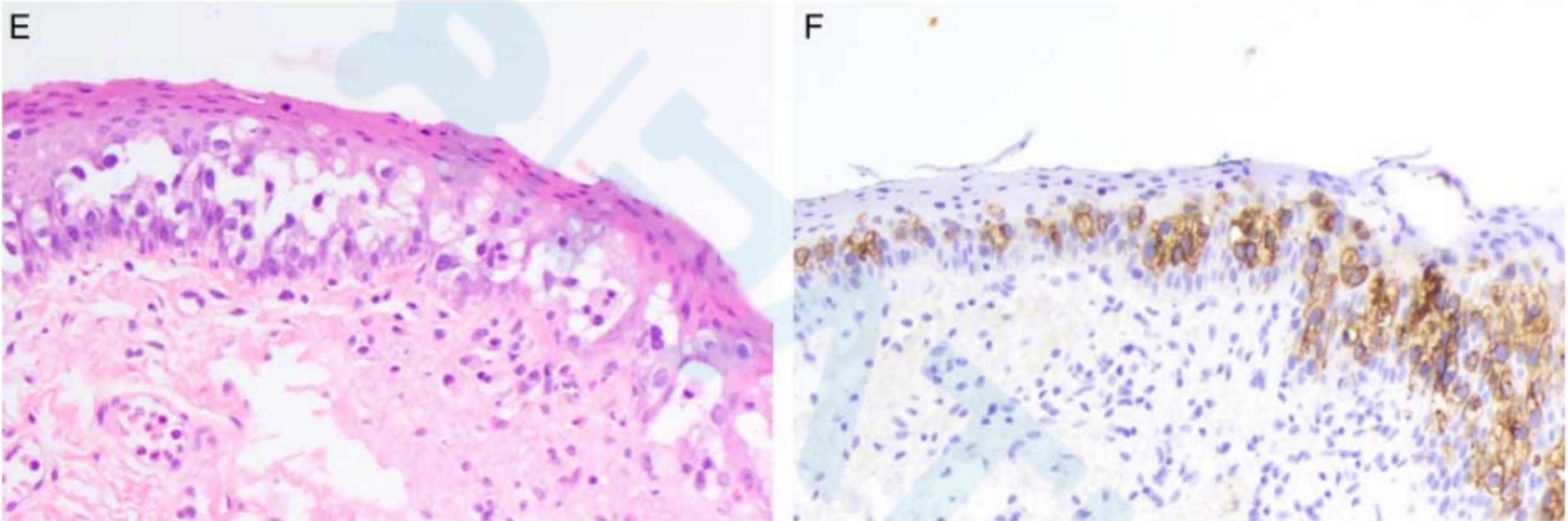
Paget cells in skin treated with topical 5-fluorouracil were often similar in size to adjacent keratinocytes because of a decrease in amount of cytoplasm and nuclear size (A, black arrows). Nuclear hyperchromasia was helpful in identifying the lesional cells. The Paget cells were uniformly positive for membranous CK7 immunohistochemistry.

RESULTS



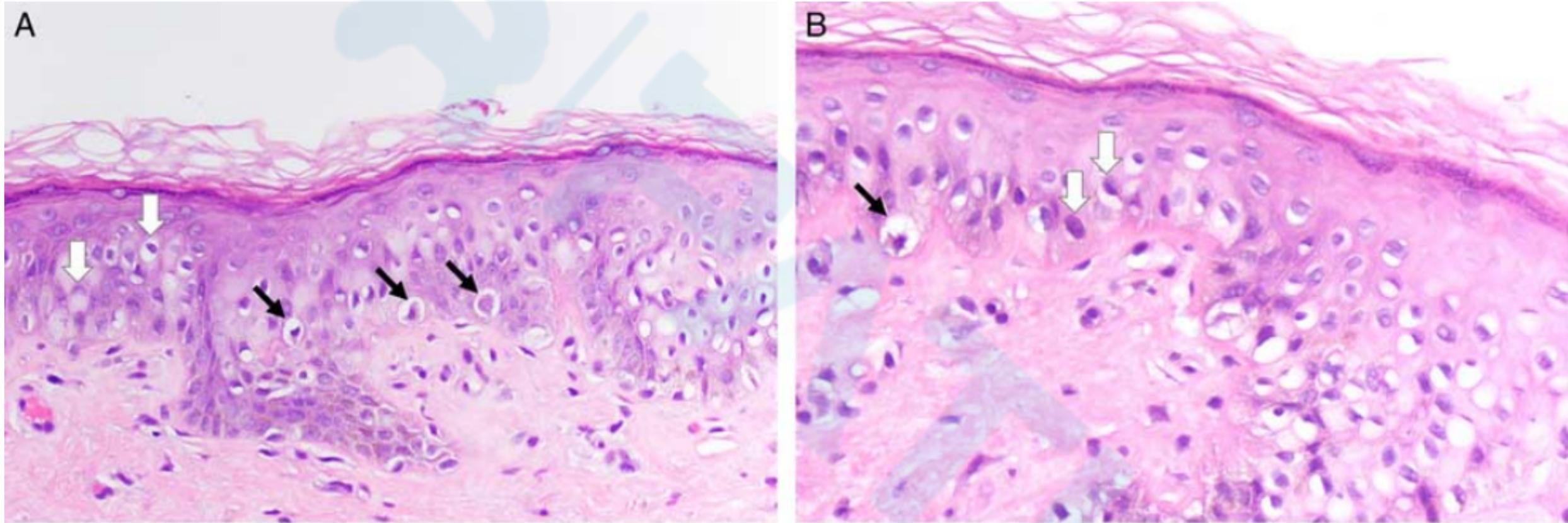
Paget cells could also be masked by inflammation. The Paget cells were uniformly positive for membranous CK7 immunohistochemistry.

RESULTS



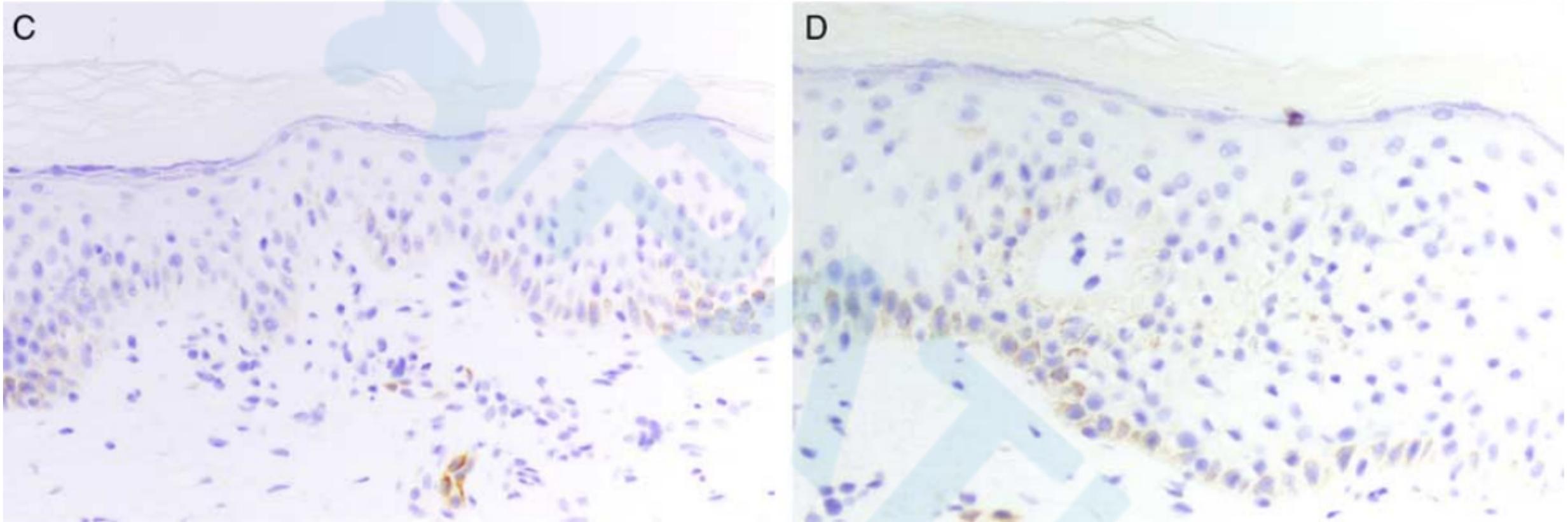
Paget cells could also be masked by epithelial vacuolization (E). The Paget cells were uniformly positive for membranous CK7 immunohistochemistry.

RESULTS



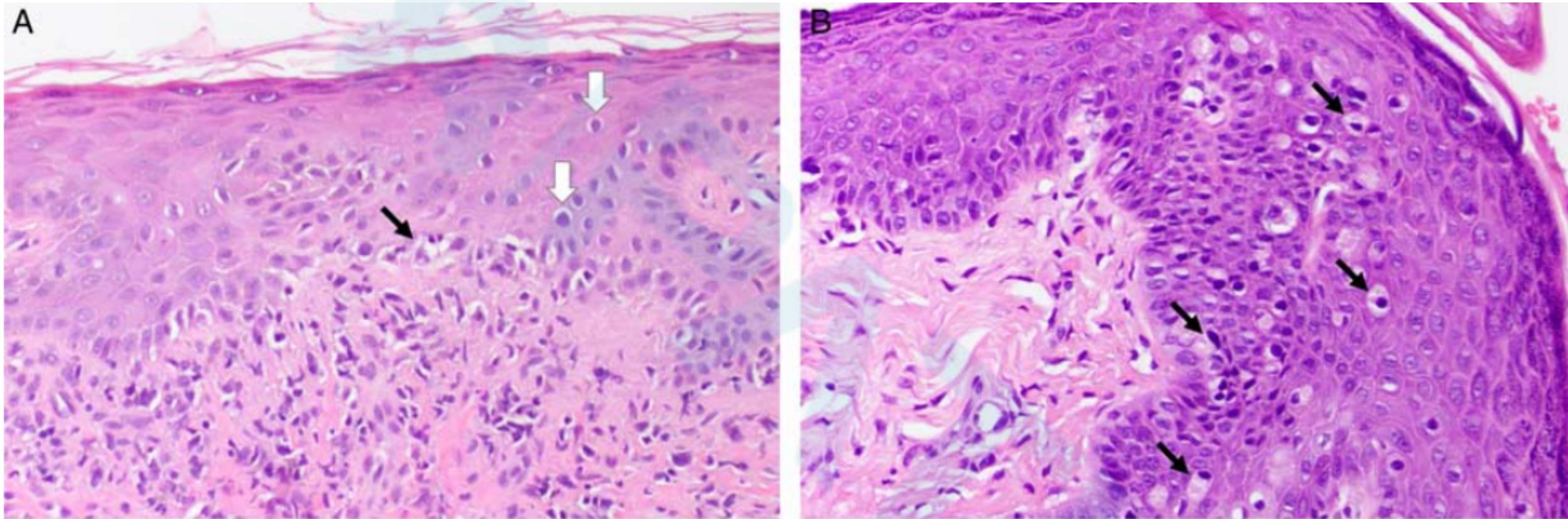
Epithelial vacuolization was also seen in surveillance biopsy samples from skin grafts, and a subset of cells in the basal layer had enlarged nuclei, eosinophilic cytoplasm, and peripheral cytoplasmic clearing (A, B, black arrows). Still other cells demonstrated nuclear hyperchromasia and indeterminate cytoplasm (A, B, white arrows).

RESULTS



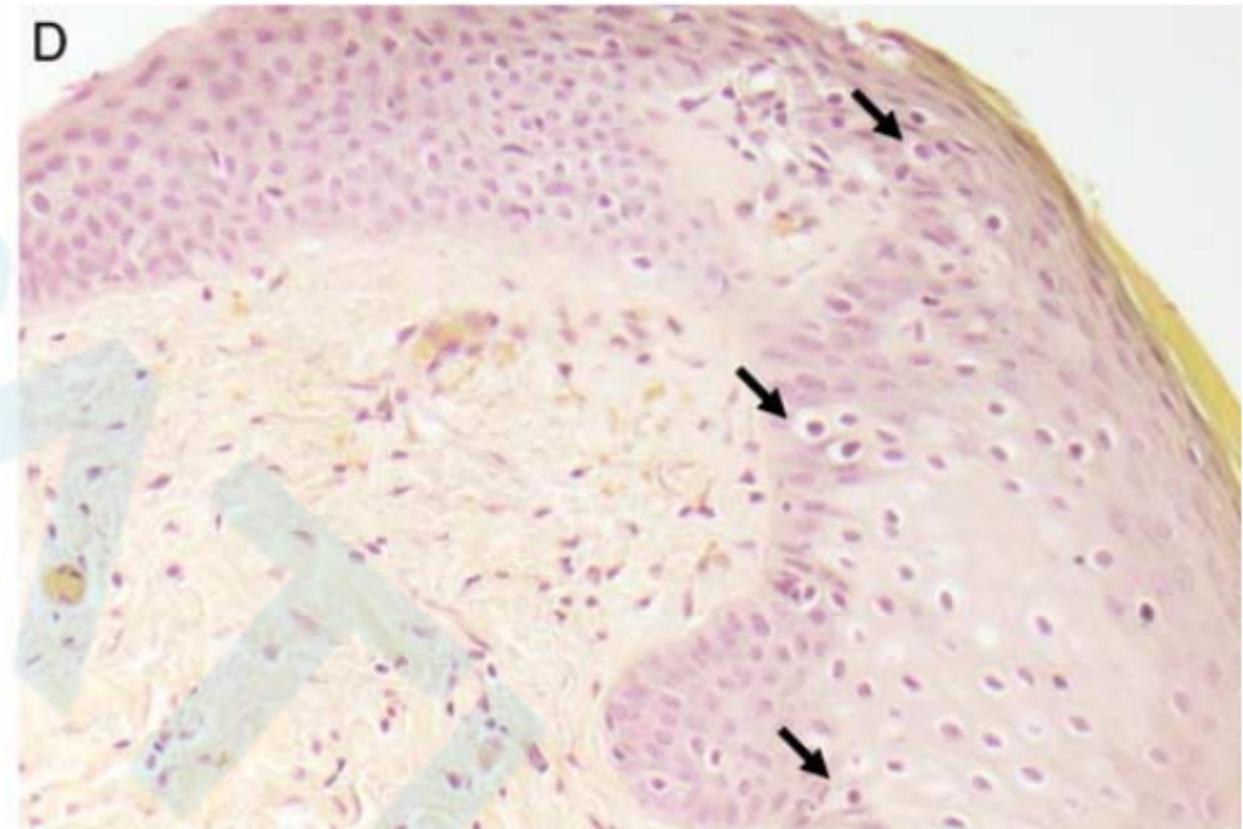
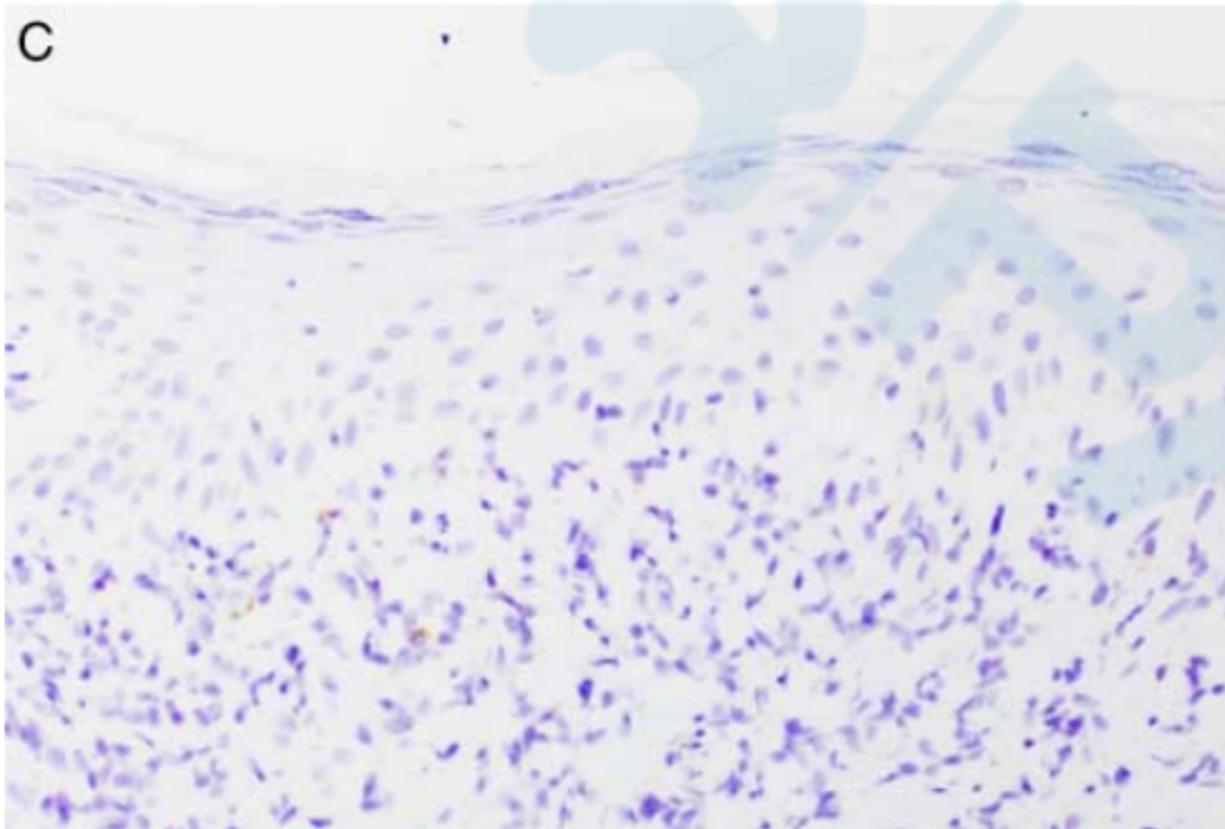
CK7 immunohistochemistry was negative in these tissue samples (C, D).

RESULTS



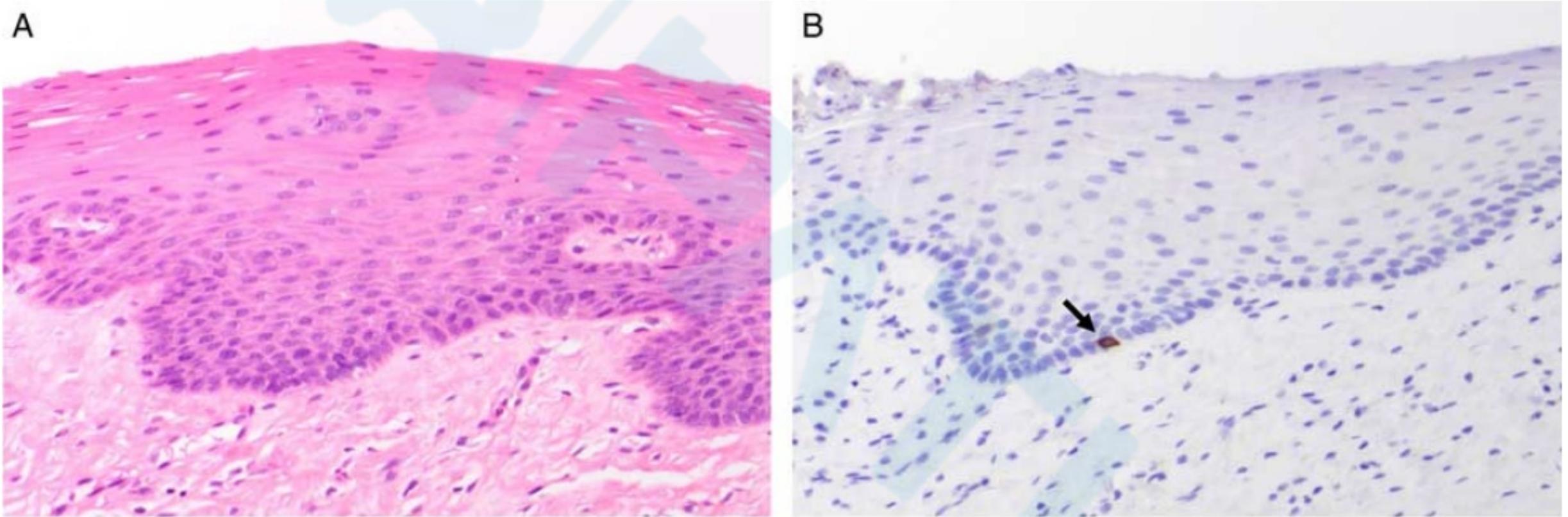
Epithelial cell changes in skin treated with 5-fluorouracil could be severe, and disorganization of the basal cell layer was commonly seen in conjunction with vacuolated change (A, black arrow). Nuclear hyperchromasia with indeterminate cytoplasm was similar to that seen in treated skin with Paget disease (A, white arrows; compare with Fig. 2A). In other biopsy samples, singly dispersed atypical cells with indeterminate cytoplasm were present throughout the epithelium (B, black arrows).

RESULTS



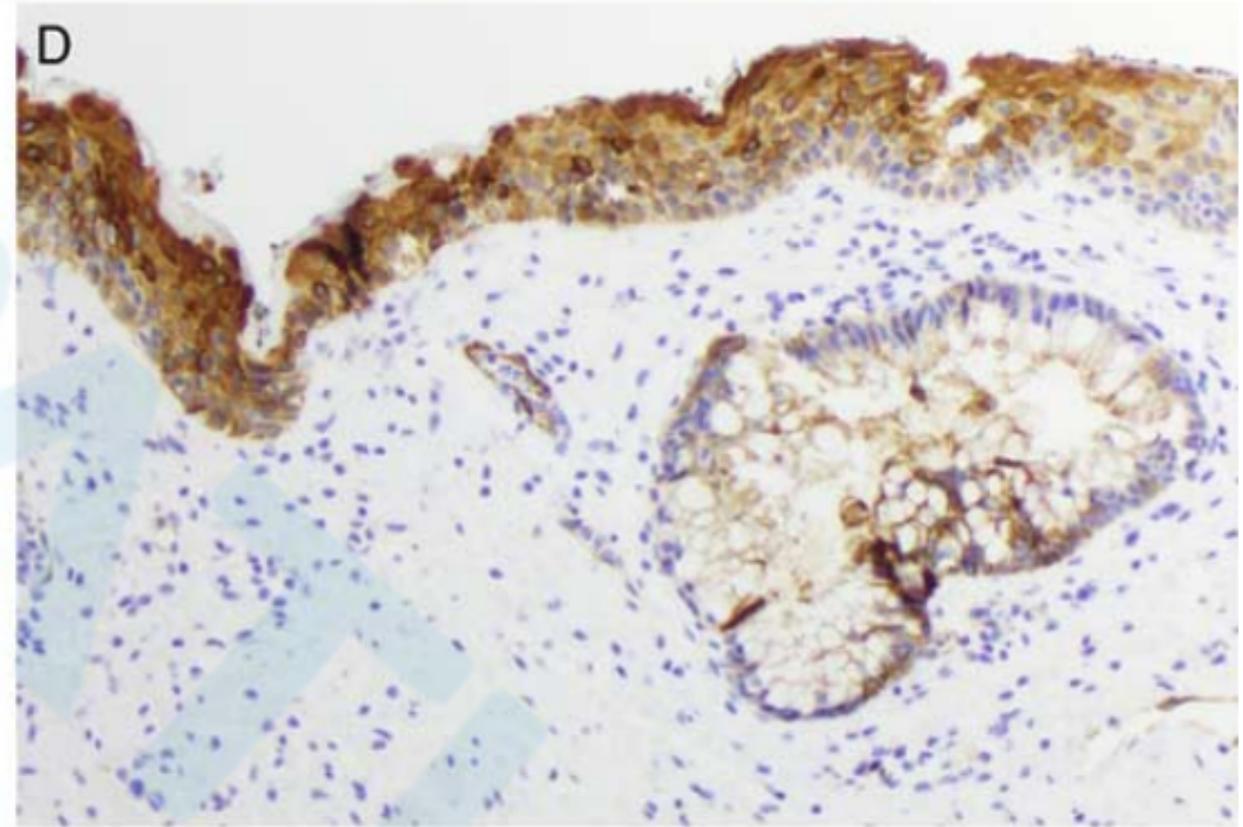
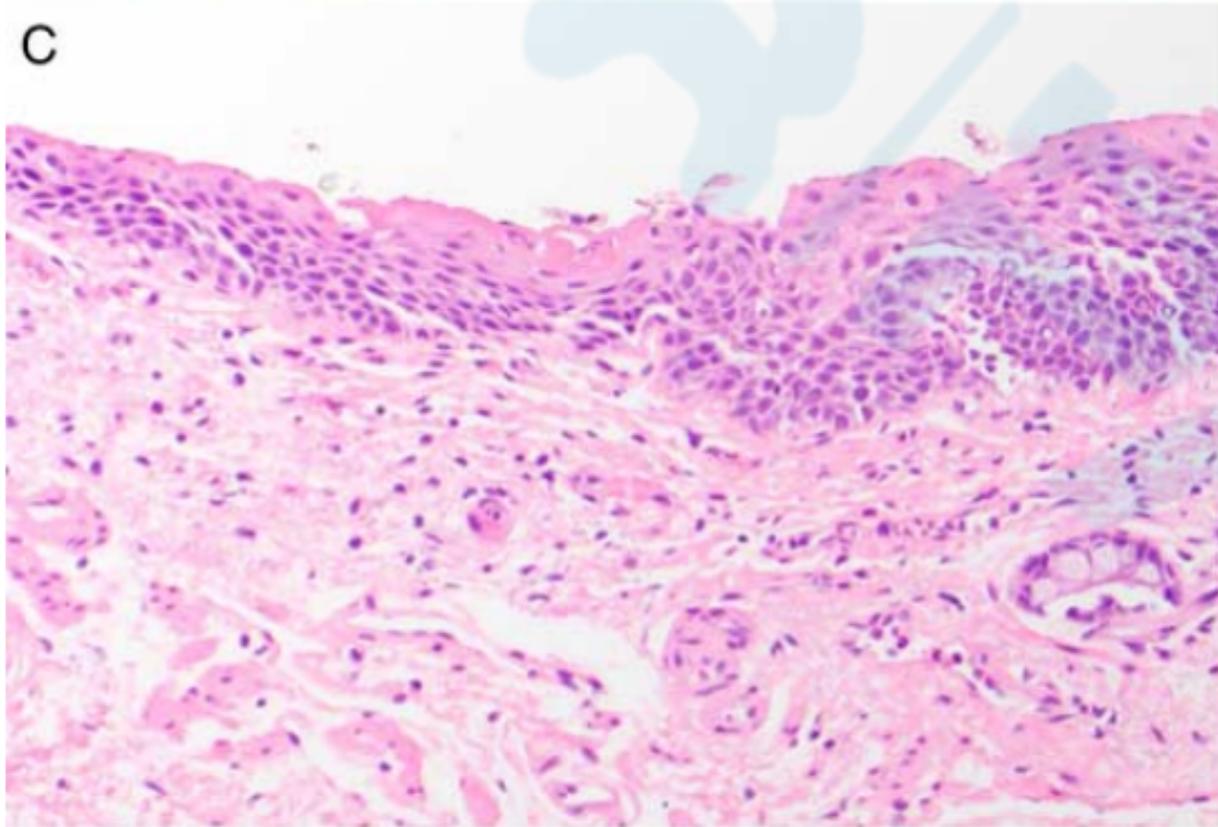
Immunohistochemistry for CK7 and mucin stains were negative in these atypical cells (C–D). Black arrows in (D) are pointing out the same atypical cells with black arrows in (B).

RESULTS



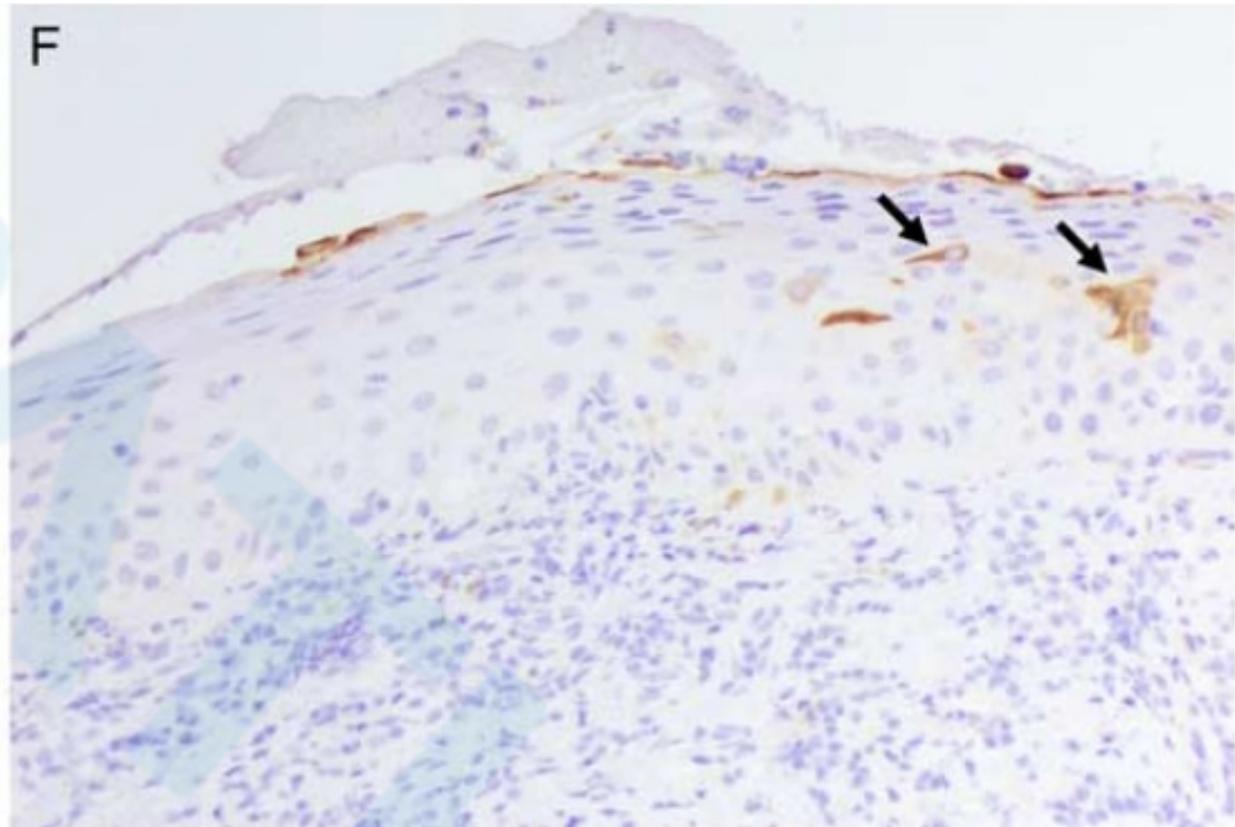
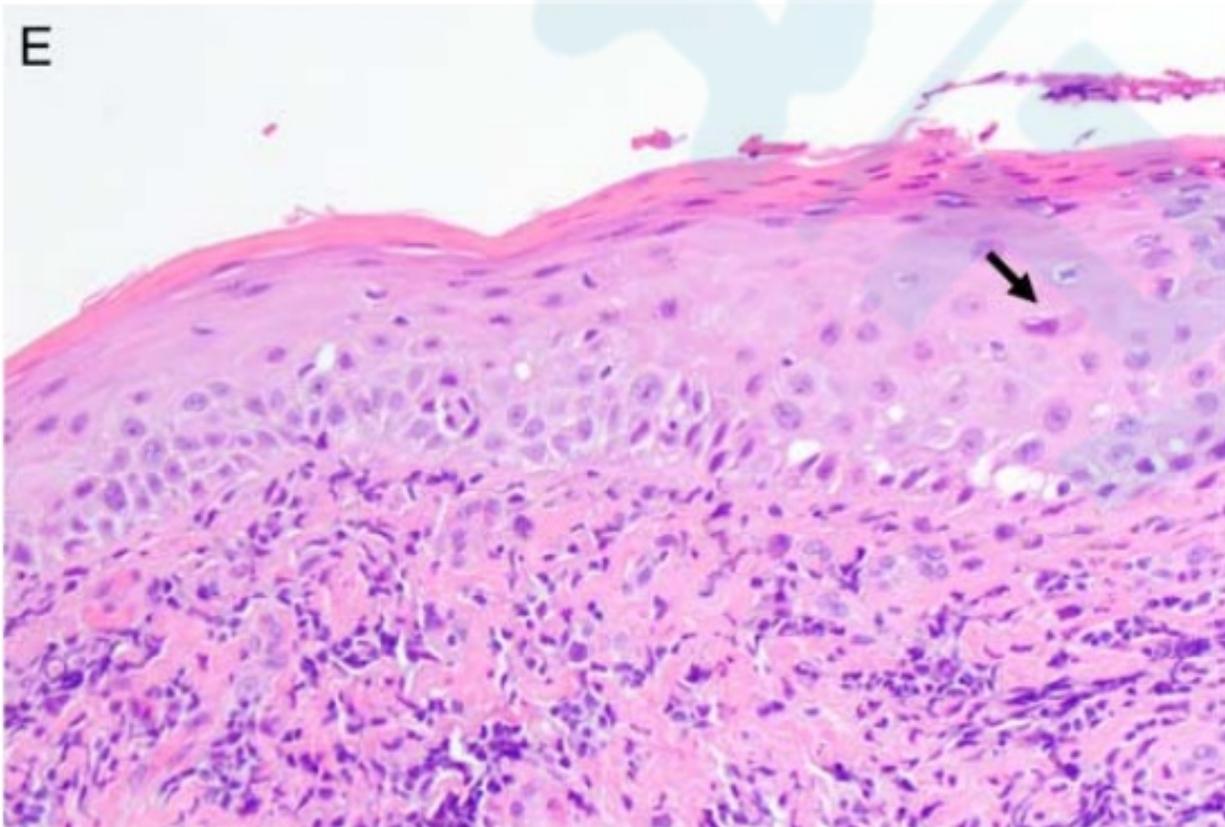
Merkel cells are difficult to appreciate in hematoxylin and eosin–stained sections (A), but show strong cytoplasmic CK7 staining (B, black arrow).

RESULTS



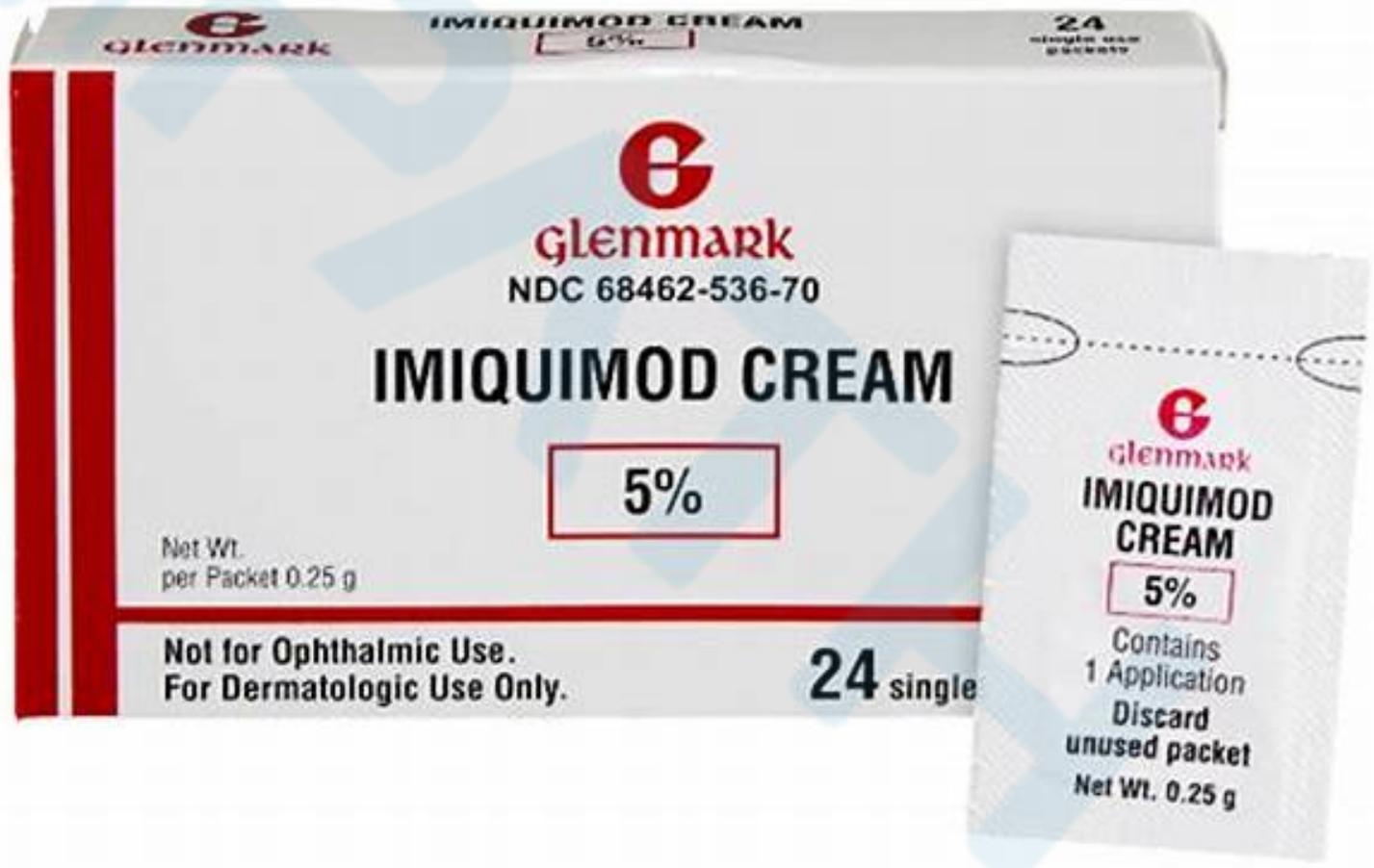
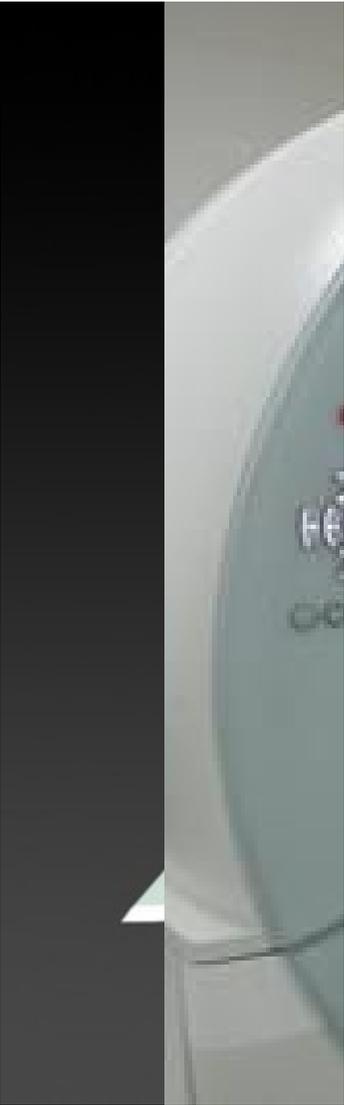
Transitional epithelium at the anorectal junction (C) also shows strong CK7 positivity (D).

RESULTS



Occasional benign keratinocytes (arrow) can show CK7 staining, but the reaction is cytoplasmic rather than the membranous pattern seen in Paget disease (E, F).

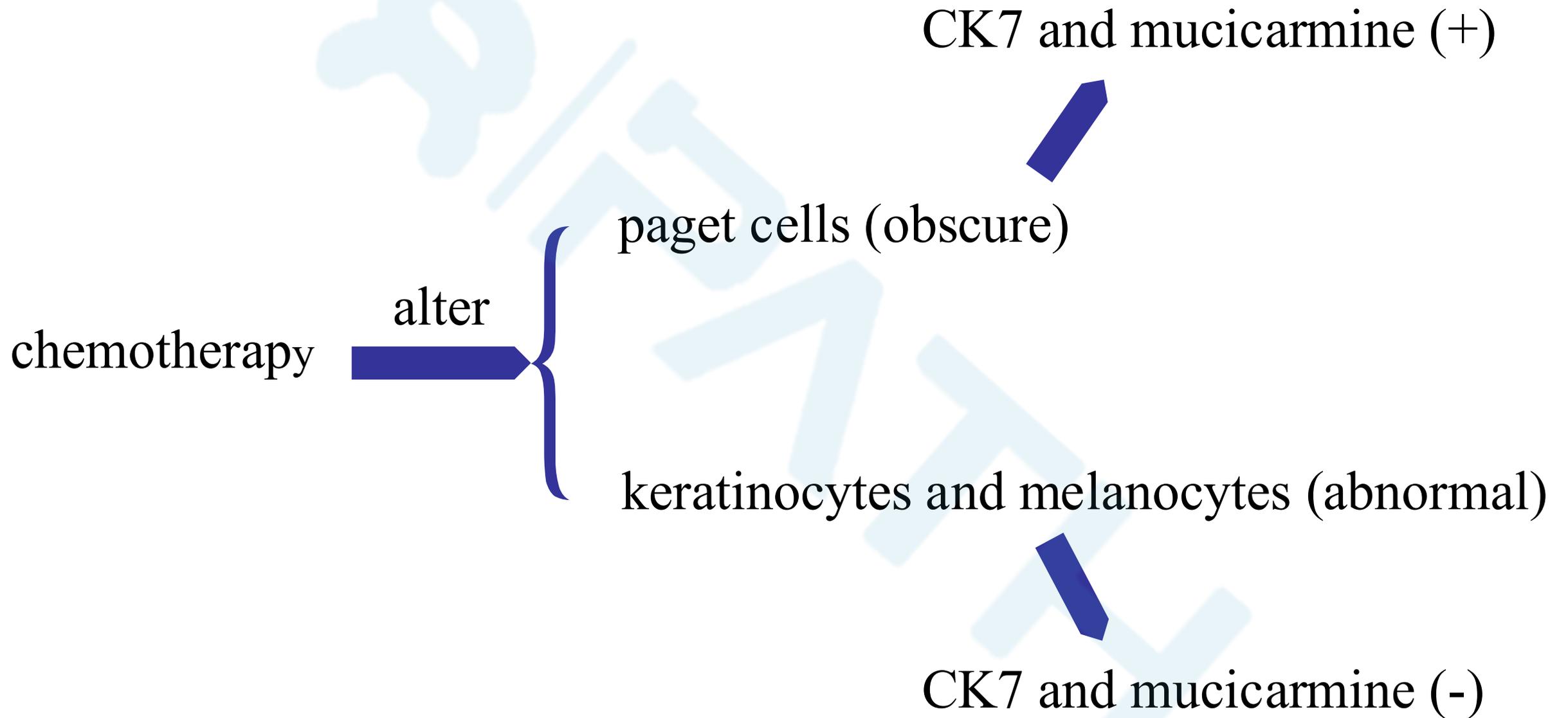
DISCUSSION



DISCUSSION

- Paget cells: GCDFP, CEA, and mucicarmine(+), CK20 or CDX2(-)
- The histologic differential diagnosis : secondary extramammary Paget disease, malignant melanoma, and squamous cell carcinoma in situ.
- These tumors can be distinguished using a panel of immunohistochemical markers: CK7, GCDFP, CK20, CDX2, S100, CK 5/6, p63

DISCUSSION



- There are no data describing its effects when chronically applied to **grafted skin**.
- In our experience, perianal skin grafts frequently display scattered degenerated keratinocytes, melanocytes, and Merkel cells which, can **simulate neoplasia**.
- It is worth noting that **cytoplasmic staining for CK7** can be seen in Merkel cells, adnexal epithelia, and benign keratinocytes.
- As a result, we regularly resort to **CK7 immunohistochemistry** to evaluate biopsy samples from patients with established perianal Paget disease and occasional atypical intraepithelial cells.

THANK YOU

