Editorial Manager(tm) for The American Journal of Dermatopathology
Manuscript Draft

Manuscript Number: AJD-D-10-00314R1

Title: An infrequent case of neoplasm with fibroepithelioma of Pinkus and hidradenomatous features arising at the umbilicus: a rare finding

Article Type: Letter to the Editor

Keywords: basal cell carcinoma; eccrine differentiation; fibroepithelioma of Pinkus; Sister Mary Joseph's nodule; umbilical tumor.

Corresponding Author: Po-Yuan Wu, M.D.

Corresponding Author's Institution:

First Author: Tzu-Chun Lin, M.D.

Order of Authors: Tzu-Chun Lin, M.D.;Tsong-Liang Lee, M.D.;Tze-Yi Lin, Ph.D.;Po-Yuan Wu, M.D.

Manuscript Region of Origin: TAIWAN

Dear editors and reviewers:

We acknowledge that our manuscript has been reviewed. We agree that this is an important area that requires more detailed revisions. I am detailing the changes I have made in response to the reviewers' comments point-by-point.

Reviewer #1:

- Comment 1: The authors describe an unusual case. I do agree that it has follicular differentiation, in addition to probable both eccrine and apocrine differentiation (it's somewhat difficult to assess from the photos). Based on the histological description and figures, and clinical photo, it appears malignant. I am not convinced of its classification and it may be better to call it "Neoplasm with fibroepithelioma of Pinkus and hidradenomatous features", although I do agree that it is difficult to accurately classify it.
  Response to Comment 1: We agree with the referee that this is an important point and a very good suggestion. We revised the manuscript title and context according to the referee's suggestions. Thank for this comment very much.

In accordance with the referees' wishes, we have made changes and supplements in the revised manuscript. We thank the referees and Editorial Office for these comments.
Sincerely,

Po-Yuan Wu, MD
Department of Dermatology
China Medical University Hospital
2 Yude Road, Taichung 40447, Taiwan

The American Journal of Dermatopathology

Authorship Responsibility, Financial Disclosure, and Copyright Transfer

Manuscript title: An infrequent case of fibroepithelioma of Pinkus with eccrine differentiation, including all accompanying digital supplementary content, if any (the "Work") Arising at the umbilicus: a rare finding

Corresponding Author: Po-Yuan Wu

Mailing Address and Telephone/Fax Numbers: 2 Yude Road, Taichung 404, Taiwan
Tel: +886 (4) [illegible] ext. [illegible] Fax: +886 (4) [illegible]

Each author must read and sign the following statements; if necessary, photocopy this document and distribute to coauthors for their original ink signatures. Completed forms should be submitted to the Editorial Office with the Work or returned to: **Omar P. Sangueza, M.D., Department of Pathology, 2nd. Floor, Watlington Hall, Wake Forest University-Baptist Medical Center, Medical Center Boulevard, Winston-Salem, NC 27157-1072. Email:** [illegible]

CONDITIONS OF SUBMISSION

RETAINED RIGHTS: Except for copyright, other proprietary rights related to the Work (e.g., patent or other rights to any process or procedure) shall be retained by the authors. To reproduce any text, figures, tables, or illustrations from this Work in future works of their own, the authors must obtain written permission from Lippincott Williams & Wilkins (LWW); such permission cannot be unreasonably withheld by LWW.

ORIGINALITY: Each author warrants that his or her submission to the Work is original and that he or she has full power to enter into this agreement. Neither this Work nor a similar work has been published nor shall be submitted for publication elsewhere while under consideration by this Publication.

AUTHORSHIP RESPONSIBILITY: Each author warrants that he or she has participated sufficiently in the intellectual content, the analysis of data, if applicable, and the writing of the Work to take public responsibility for it. Each has reviewed the final version of the Work, believes it represents valid work, and approves it for publication. Moreover, should the editors of the Publication request the data upon which the work is based, they shall produce it.

DISCLAIMER: Each author warrants that this Work shall not violate any trademark registrations nor the right of privacy of any person, contains no libelous, obscene, or other unlawful matter, and does not infringe upon the statutory or common law copyright or any other right of any person or party. If excerpts (e.g., text, figures, tables, illustrations, or audio/video files) from copyrighted works are included, a written release will be secured by the authors prior to submission, and credit to the original publication will be properly acknowledged. Each author further warrants that he or she has obtained, prior to submission, valid written releases from all patients whose names, likenesses, or other protected health information are submitted as part of the Work. Should the Editor or LWW request copies of such written releases, authors shall provide them in a timely manner.

PREPRINTS: Upon acceptance of the article for publication, each author warrants that he/she will promptly remove any prior versions of this Work (normally a preprint) that may have been posted to an electronic server.
of such a release.

TRANSFER OF COPYRIGHT

AUTHORS' OWN WORK: In consideration of LWW's publication of the Work, the authors hereby transfer, assign, and otherwise convey all copyright ownership worldwide, in all languages, and in all forms of media now or hereafter known, including electronic media such as CD-ROM, Internet, and Intranet, to LWW. If LWW should decide for any reason not to publish an author's submission to the Work, LWW shall give prompt notice of its decision to the corresponding author, this agreement shall terminate, and neither the author nor LWW shall be under any further liability or obligation. Each author grants LWW the rights to use his or her name and biographical data (including professional affiliation) in the Work and in its or the Publication's promotion.

WORK MADE FOR HIRE: If this Work or any element thereof has been commissioned by another person or organization, or if it has been written as part of the duties of an employee, an authorized representative of the commissioning organization or employer must also sign this form stating his or her title in the organization.

GOVERNMENT EMPLOYEES: If the Work or a portion of it has been created in the course of any author's employment by the United States Government, check the "Government" box at the end of this form. A work prepared by a government employee as part of his or her official duties is called a "work of the U.S. Government" and is not subject to copyright. If it is not prepared as part of the employee's official duties, it may be subject to copyright.

FINANCIAL DISCLOSURE: Each author warrants that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted Work, except as disclosed on a separate attachment. All funding sources supporting the Work and all institutional or corporate affiliations of the authors are acknowledged in a footnote in the Work.

INSTITUTIONAL REVIEW BOARD/ANIMAL CARE COMMITTEE APPROVAL: Each author warrants that his or her institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

AUTHOR(S) POSTING OF ARTICLES TO AN INSTITUTIONAL REPOSITORY

The American Journal of Dermatopathology will permit the author(s) to deposit for display a "post-print" (the final manuscript after peer-review and acceptance for publication but prior to the publisher's copyediting, design, formatting, and other services) 12 months after publication of the final article on his/her personal web site, university's institutional repository or employer's intranet, subject to the following:

Copyright Transfer Form p2

Click here to download high resolution image

- You may only deposit the post-print.
- You may not update the post-print text or replace it with a proof or with the final published version.
- You may not include the post-print or any other version of the article in any commercial site or in any repository owned or operated by any third party. For authors of articles based on research funded by NIH, Wellcome Trust, HHMI, or other funding agency, see below for the services that LWW will provide on your behalf to comply with "Public Access Policy" guidelines.
- You may not display the post-print until twelve months after publication of the final article.
- You must attach the following notice to the post-print: "This is a non-final version of an article published in final form in (provide complete journal citation)".
- You shall provide a link in the post-print to *The American Journal of Dermatopathology*'s website.

"PUBLIC ACCESS POLICY" FUNDING DISCLOSURE

Please disclose below if you have received funding for research on which your article is based from any of the following organizations:

- ☐ National Institutes of Health (NIH)
- ☐ Wellcome Trust
- ☐ Howard Hughes Medical Institute (HHMI)
- ☐ Other: Please List ____________________________

COMPLIANCE WITH NIH AND OTHER RESEARCH FUNDING AGENCY ACCESSIBILITY REQUIREMENTS

A number of research funding agencies now require or request authors to submit the post-print (the article after peer review and acceptance but not the final published article) to a repository that is accessible online by all without charge. Within medical research, three funding agencies in particular have announced such policies:

• The U.S. National Institutes of Health (NIH) requires authors to deposit post-prints based on NIH-funded research in its repository PubMed Central (PMC) within twelve months after publication of the final article in the journal.

• The Howard Hughes Medical Institute (HHMI) requires as a condition of research grants, deposit in PMC, but in its case within six months after publication of the final article.

• The Wellcome Trust requires, as a condition of research grants, deposit in UK PubMed Central within six months after publication of the final article.

As a service to our authors, LWW will identify to National Library of Medicine (NLM) articles that require deposit. This Copyright Transfer Agreement provides the mechanism for identifying such articles. LWW will transmit the post-print of an article based on research funded in whole or in part by one or more of these three agencies to Pub Med Central.

Upon NIH request, it remains the legal responsibility of the author(s) to confirm with NIH the provenance of their manuscript for purposes of deposit.

Author(s) will not deposit their articles themselves.

Author(s) will not alter the post-print already transmitted to NIH.

Author(s) will not authorize the display of the post-print prior to:

(a) 12 months following publication of the final article, in the case of NIH.

(b) 6 months following publication of the final article, in the case of Wellcome Trust and HHMI.

Tzu-Chun Lin | Tzu-Chun Lin | 2010.10.14
Signature | Printed Name | Date
☑ Author's Own Work ☐ Work for Hire ☐ Government ☐ Financial Disclosure Attached

Tsung-Liang Lee | Tsung-Liang Lee | 2010-10-03
Signature | Printed Name | Date
☑ Author's Own Work ☐ Work for Hire ☐ Government ☐ Financial Disclosure Attached

Tze-Yi Lin | Tze-Yi Lin | 2010-10-03
Signature | Printed Name | Date
☑ Author's Own Work ☐ Work for Hire ☐ Government ☐ Financial Disclosure Attached

Po-Yuan Wu | Po-Yuan Wu | 2010.10.13
Signature | Printed Name | Date
☑ Author's Own Work ☐ Work for Hire ☐ Government ☐ Financial Disclosure Attached

Title page:

Title: An infrequent case of neoplasm with fibroepithelioma of Pinkus and hidradenomatous features arising at the umbilicus: a rare finding

Tzu-Chun Lin, MD; Tsong-Liang Lee, MD; Tze-Yi Lin, MD, PhD; Po-Yuan Wu, MD

Affiliations:

Tzu-Chun Lin, MD; Tsong-Liang Lee, MD; Po-Yuan Wu, MD

Department of Dermatology, China Medical University Hospital, Taichung, Taiwan

Tze-Yi Lin, MD, PhD

Department of Pathology, China Medical University Hospital, Taichung, Taiwan

Correspondence to: Po-Yuan Wu, Department of Dermatology, China Medical University/Hospital, 2 Yude Road, Taichung 404, Taiwan

Tel: +886(0)422052121 ext. 4497, Fax: +886(0)422064561

E-mail: wu.poyuan@gmail.com

Funding sources: None.

Conflicts of interest: The authors report no conflict of interest.

Key words: basal cell carcinoma, eccrine differentiation, fibroepithelioma of Pinkus, Sister Mary Joseph's nodule, umbilical tumor

To the Editors:

Fibroepithelioma of Pinkus (FEP) has been generally considered to be an unusual variant of basal cell carcinoma (BCC). However, some authors elucidated that FEP more closely resembles trichoblastoma than BCC due to the contrast between FEP and BCC with respect to site of occurrence, gender difference, relationship to sun damage, histopathologic features, and immunohistochemical studies.[1] After reviewing the literature, there were five reported cases of BCCs arising from the umbilicus identified, four females and one male, ranging from 27 to 76 years of age,[2-5] none of which are FEP variants. Clinical manifestations varied from a BCC associated with pre-existing intradermal nevus,[3] superficial BCC[4] and sprouting from previous laparoscopy scar after a latent period of 21 years.[5] We report a rare case of neoplasm with fibroepithelioma of Pinkus and hidradenomatous features presenting on the umbilicus.

A 67-year-old female presented with a progressively enlarging, asymmetric, variegated erythematous, dark brownish to bluish mass over the umbilicus in the recent 3 months (Fig. 1). The nodule was fixed, nontender, but erosion developed in some areas of the lesion. There was no previous history of overexposure to sunlight, or environmental carcinogens such as arsenic and chemical agents. Elsewhere, she did not have any burn scars, chronic skin ulcers or any remarkable pre-existing skin lesions. A wide-excision surgery was performed and, during the procedure, there was no fistula or any connection with the underlying soft tissue of abdomen.

Histopathologically, there were distinctive foci of thin, branching, anastamosing strands of basaloid cells connecting with the overlying epidermis, which were surrounded by fibromyxoid stroma in the upper dermis. The presence of peripheral palisading, trabecular pattern of basaloid cells and focal clefts between tumor and adjacent stroma are diagnostic of FEP (Fig. 2A, B). In addition, some scattered areas of classical nodulocystic BCC were also present (Fig. 2C). Elsewhere, other distinct tumor differentiation was noted as patchy atypical basaloid cells arranged in glandulocystic pattern with conspicuous mucin contents favoring hidradenomatous differentiation (Fig. 3A, B). This distinct differentiation preserved the characteristics of peripheral palisading and myxoid stroma (Fig. 3C). According to the clinical presentations and histopathological findings, a neoplasm with FEP and hidradenomatous features is considered.

The anatomy of umbilicus is complex. It serves as a conduit between the developing embryo and the placenta when the fetus develops. It is important to distinguish the nature of umbilical tumors, whether benign or malignant components, including the primary or metastatic neoplasms. Benign tumors make up around 57% of all the umbilical tumors.[2] In the majority of benign umbilical tumors, it included cutaneous endometriosis, congenital polyps (enteromas, adenomas, and omphalomesenteric duct remnants), benign nevi, and papillomas.[6] Endometriosis was the most common benign umbilical tumor during the previous study.[2] Primary malignant neoplasm is extremely rare as compared with metastatic ones, occupying 20% of all the malignant umbilical tumors. The most common primary malignancy included adenocarcinomas and myosarcomas arising from remnants of the omphalomesenteric duct or urachus, malignant melanomas, BCCs, and squamous cell carcinomas.[6] Metastatic tumors, so-called Sister Mary Joseph's nodule (SMJN), which account for approximately 80% of the umbilical malignancies,[6] have traditionally been considered a sign of ominous prognosis. Underlying primary malignancies that may give rise to clinical presentation of SMJN are, in order of frequency, gastrointestinal (52%), gynaecologic (28%), gastric (23%) and ovarian (16%) cancer.[7] The survival rate is around 10~11 months on average.[8] Therefore, a low threshold for performing biopsy for atypical umbilical lesions in appearance should be advocated.

FEP, first described in 1953, has now been generally recognized as an unusual variant of BCC.[9] However, FEP, in contrast to conventional BCCs that commonly located on sun-exposure area and particularly on the head and neck, has the overwhelming predilection on the trunk with fewer cases presenting on the more sun-exposure area.[10] FEP has a predilection for females and is found mainly in individuals over 50 years of age, whereas BCCs are more common in males.[1] Thereby, some authors elucidated that FEP more closely resembles trichoblastoma than BCC due to the contrast between FEP and BCC with respect to site of occurrence, gender difference, relationship to sun damage, histopathologic features, and immunohistochemical studies.[1] To our knowledge, FEP arising at the umbilicus is an exceedingly infrequent case.

FEP with eccrine differentiation, i.e. hidradenomatous growth pattern in this case, is interesting. From previous study, the histological pattern of FEP perhaps suppose to be a consequence of the spreading of the basaloid cells along the pre-existing eccrine ducts.[11] The recent concept postulates that duct-like structure of FEP originates from the intraepidermal eccrine duct with CK1 and CK10, and proliferates to spread in the dermis with CK16 and CK17.[12] In our patient, FEP with hidradenomatous growth pattern supports the concept that duct-like structure of FEP is mainly originated from the intraepidermal eccrine duct and we proposed this duct-like structure is pluripotent and possess capacity in differentiation into sweat glandular structures when spreading into the dermis.

In conclusion, based on a clinical and histopathological point of view, we present a rare case of umbilical FEP. It is important when physicians in face of an umbilical tumor, the distinction between benign and possible malignant nature should be carefully evaluated. The characteristic hidradenomatous features in this case highlight the rational explanation that the duct-like structures of FEP may originate from the intraepidermal eccrine duct and have the pleuripotent capacity to differentiate toward sweat glandular structures.

REFERENCES

1. Bowen AR, LeBoit PE. Fibroepithelioma of pinkus is a fenestrated trichoblastoma. *Am J Dermatopathol*. 2005;27:149-54.
2. Steck WD, Helwig EB. Tumors of the umbilicus. *Cancer.* 1965;18:907-15.
3. Walker SL, Banerjee P, Marsden RA. Basal cell carcinoma arising at the umbilicus. *Clin Exp Dermatol.* 2001;26:458-9.
4. Etter L, Cook JL. Basal cell carcinoma of the umbilicus: a case report and literature review. *Cutis*. 2003;71:123-6.
5. Durrani AJ, Miller RJ, Davies M. Basal cell carcinoma arising in a laparoscopic port site scar at the umbilicus. *Plast Reconstr Surg*. 2005;116:348-50.
6. Meine JG, Bailin PL. Primary melanoma of the umbilicus: report of a case and review of the relevant anatomy. *Dermatol Surg.* 2003;29:405-7.
7. Galvañ VG. Sister Mary Joseph's nodule. *Ann Intern Med.* 1998;128:410.
8. Powell FC, Cooper AJ, Massa MC et al. Sister Mary Joseph's nodule: a clinical and histologic study. *J Am Acad Dermatol*. 1984;10:610-5.
9. Pinkus H. Premalignant fibroepithelial tumors of skin. *AMA Arch Derm Syphilol.* 1953;67:598-615.
10. Bowen AR, LeBoit PE. Fibroepithelioma of pinkus is a fenestrated trichoblastoma. *Am J Dermatopathol*. 2005; 27: 149-54.
11. Stern JB, Haupt HM, Smith RR. Fibroepithelioma of Pinkus. Eccrine duct spread of basal cell carcinoma. *Am J Dermatopathol.* 1994;16:585-7.
12. Kurokawa I, Yokoyama T, Nishimura K et al. Pinkus tumor may originate from intraepidermal eccrine ducts and proliferate in the dermis. Oncol Rep. 2007;17:49-54.

Figure 1. A progressively enlarging, dark erythematous with focal blotchy mass over the umbilicus.

Figure 2. (A) Low power view: it shows a majority of Fibroepithelioma of Pinkus (FEP) connecting with the overlying epidermis, and another part of distinct hidradenomatous features presenting at the bottom. (haematoxylin and eosin [H&E] × 20). (B) Distinctive foci of branching, anastamosing strands of basaloid cells, indicative of FEP (H&E × 100). (C) Nodulocystic classical basal cell carcinoma (H&E × 100).

Figure 3. (A) Another part of hidradnomatous nodule with tubular and cystic structures. (H&E × 20). (B) Basaloid cells arranged in glandulocystic pattern with conspicuous mucin contents indicative of hidradenomatous features (H&E × 100). (C)The hidradenomatous features preserved the characteristics of peripheral palisading and myxoid stroma (H&E × 100).

Figure 1

Click here to download high resolution image

Figure 2

Click here to download high resolution image

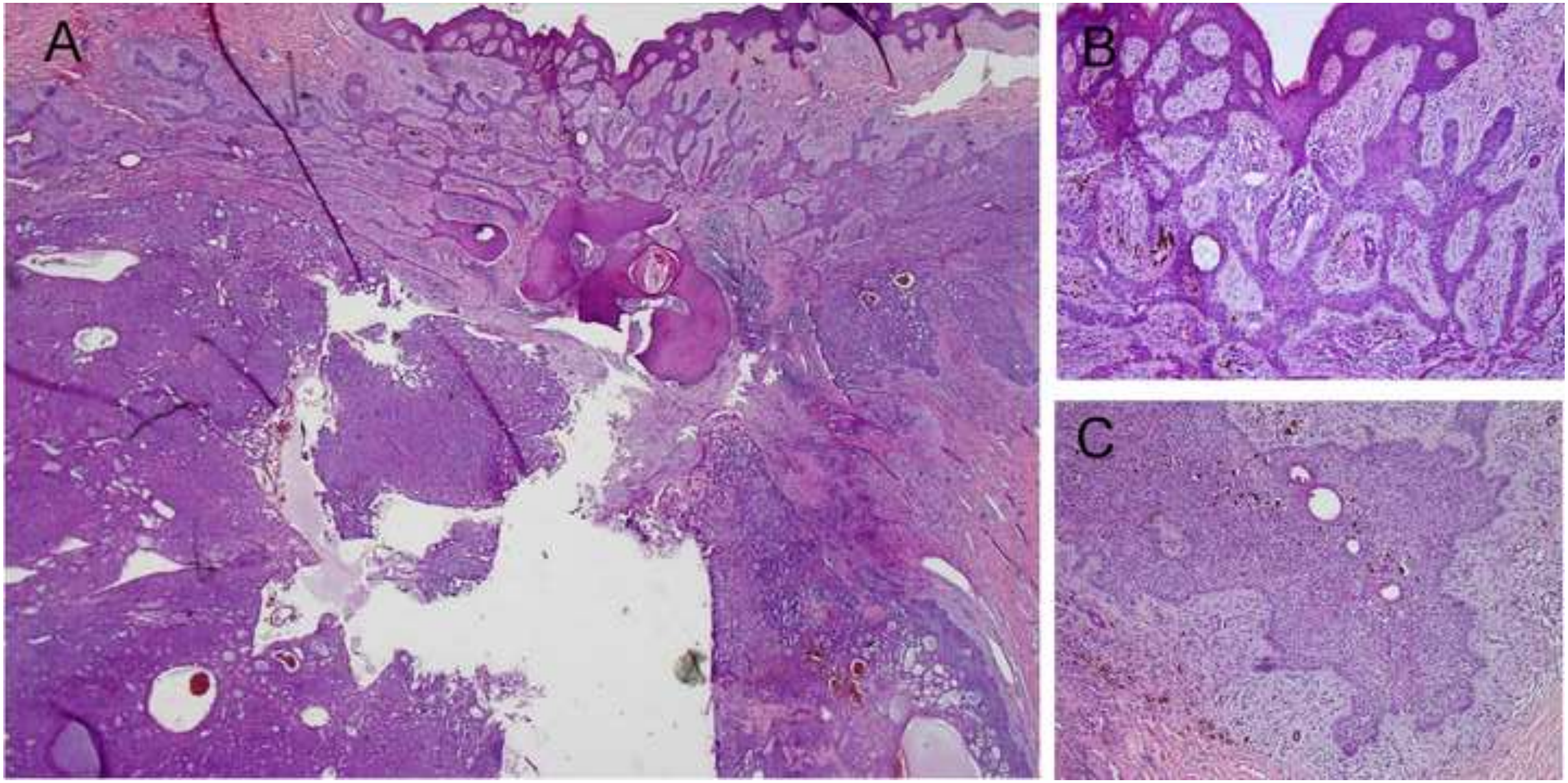

Figure 3

Click here to download high resolution image