Epithelioid Haemangioma (Angiolymphoid Hyperplasia with Eosinophilia subtype) involving the vermillion of the lower lip

L Robinson: BChD, PDD (Maxillofacial Radiology), PDD (Forensic Odontology). Department of Oral Pathology and Oral Biology, School of Dentistry, Faculty of Health Sciences, University of Pretoria.
ORCID Number: 0000-0002-0549-7824
CS Lebaka: B Dent Ther, BDS, PGDipOdont (Oral Surgery), MChD, FC MFOS. Department of Maxillofacial and Oral Surgery, School of Dentistry, Faculty of Health Sciences, University of Pretoria.
ORCID Number: 0000-0001-7518-0585
WFP van Heerden: BChD, MChD, FC Path (SA) Oral Path, PhD, DSc. Department of Oral Pathology and Oral Biology, School of Dentistry, Faculty of Health Sciences, University of Pretoria.
ORCID Number: 0000-0003-2494-667X

Corresponding author: Willie FP van Heerden
Department of Oral Pathology and Oral Biology, University of Pretoria, South Africa. Tel: +27 012 319 2320, Fax: +27 012 321 2225.
Email: willie.vanheerden@up.ac.za

Declarations:
Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Conflict of Interest: The authors declare that they have no conflict of interest.
Ethics approval: This study was approved by the University of Pretoria, Faculty of Health Sciences Research Ethics Committee (Reference no.: 478/2020).

Abstract

Epithelioid vascular tumours include benign epithelioid haemangioma and epithelioid angiomatous nodule, low grade malignant epithelioid haemangioendothelioma and high grade epithelioid angiosarcoma. These tumours share epithelioid cell morphologies and intracytoplasmic vacuoles, with distinction based on differing architectural and nuclear features. This report highlights a case of epithelioid haemangioma, angiolymphoid hyperplasia with eosinophilia (ALHE) subtype, involving the vermillion of the lower lip in an elderly female patient. The clinical and histological features, differential diagnosis, aetiopathogenesis, molecular basis and treatment options are discussed as part of a comprehensive review of this rare entity.

Introduction

The family of epithelioid vascular tumours encompasses a wide histologic and behavioural spectrum, including benign epithelioid haemangioma and epithelioid angiomatous nodule, low grade malignant epithelioid haemangioendothelioma and high grade epithelioid angiosarcoma.[1-2] These tumours share features of plump, polygonal cells with abundant eosinophilic cytoplasm and occasional intracytoplasmic vacuoles. However, their architectural and nuclear features differ, allowing for ease of distinction in most cases.[1] Epithelioid haemangioma is a benign vascular tumour of uncertain pathogenesis most commonly affecting patients in their third to fifth decades of life with a propensity for the head and neck region.[2-11] Many other terms have been used in literature to describe this lesion, emphasising the confusion that exists regarding this unusual condition.[4,12-13] Distinguishing EH from other malignant epithelioid vascular tumours is paramount due to differences in their management and clinical outcome.[2] This report highlights a case of epithelioid haemangioma, angiolymphoid hyperplasia with eosinophilia (ALHE) subtype, involving the vermillion of the lower lip in an elderly female patient.

Case Report

A 75-year-old female patient presented to the Department of Oral and Maxillofacial Surgery at the Pretoria Oral and Dental Hospital (Pretoria, South Africa) with a three-week history of a nodular mass involving the right vermilion of the lower lip (Figure 1). The patient's medical history was unremarkable. Furthermore, the patient denied any previous trauma to the region. On examination, the mass was firm on palpation with a broad base and areas of overlying skin ulceration. At this stage the clinical suspicion was that of a squamous cell carcinoma, pyogenic granuloma or Kaposi sarcoma. An incision biopsy was performed and submitted for histological

assessment. During the surgical procedure, the mass bled excessively, indicative of a vascular lesion.

Pathological Findings

The specimen consisted of three soft tissue fragments, the largest measuring 10x7x5mm and the smallest measuring 5x4x3mm.

Histological evaluation showed several tissue fragments with a papillomatous architectural pattern. These fragments were surfaced by hyperplastic stratified squamous epithelium with areas of surface hyperkeratosis (Figure 2). The lamina propria contained a vascular proliferation of predominantly capillary-sized blood vessels with interspersed larger vessels. These larger vessels were lined by plump, polygonal endothelial cells with abundant eosinophilic cytoplasm and occasional hobnailing into the lumina (Figure 3A). The surrounding stroma consisted of a dense mixed chronic inflammatory cell infiltrate with scattered eosinophils throughout (Figure 3B). In addition, several indistinct lymphoid follicles were noted within the inflammatory infiltrate. There were no features of cytological atypia, mitoses or a frankly malignant neoplastic process in the sections examined.

PAS and Grocott-Gomori histochemical stains failed to highlight any fungal elements. CD31 (Figures 4A) and ERG (Figures 4B) immunohistochemical stains highlighted the vascular proliferation within the lamina propria. An HHV-8 immunohistochemical stain for Kaposi sarcoma was negative.

In conclusion, the histological features and immunohistochemical staining pattern were in keeping with an epithelioid haemangioma, angiolymphoid hyperplasia with eosinophilia (ALHE) subtype. A subsequent full blood count (FBC) was performed, whereby the eosinophil count was within the normal range.

Discussion

The term angiolymphoid hyperplasia with eosinophilia (ALHE) was first coined by Wells and Whimster in 1969.[14] Their initial description pertained to a neoplasm characterised by a florid proliferation of blood vessels lined by plump endothelial cells, admixed with a dense inflammatory cell infiltrate of lymphocytes, eosinophils and mast cells.[14] However, due to uncertainty regarding the nature of this entity, the term epithelioid haemangioma (EH) was first proposed by Weiss and Enzinger in 1982. They believed the lesion was truly neoplastic and therefore wanted to clearly separate the entity from epithelioid haemangioendothelioma, a malignant vascular tumour. Since then EH has been reported under a plethora of terms, including angiolymphoid hyperplasia with eosinophilia, atypical or pseudopyogenic granuloma, inflammatory angiomatous nodule, popular angioplasia, inflammatory arteriovenous haemangioma and intravenous atypical vascular proliferation.[4,12-13,15] In many instances EH has been grouped with histologically similar lesions such as Kimura disease, under the umbrella term "angiolymphoid hyperplasia with eosinophilia".[4,8,15]

EH most commonly presents in mid-adult life as single or multiple erythematous/hyperpigmented dome-shaped papules or nodules with an average size of 1cm.[3-4,7,12-13,16-17] When multiple, they tend to be grouped, often coalescing, raising concern for a malignant process.[3,15,18] EH frequently involves the head and neck region, penis and the extremities, especially the arms and hands.[4-5,9,11,17] A study of 58 cases by Huang et al[18], found that sites of involvement included the extremities (48%), head and neck region (34%), trunk (13%), and penis (3%). In the head and neck region, any site may be affected including the maxillary bones, salivary glands, muscles and skin.[9,13] Oral lesions are rare, with only 28 cases of oral EH described in literature.[19] The most common oral sites include the lips, followed by the buccal mucosa and tongue.[12-13] Patients present over a wide range of ages, with a peak in the third to fifth decades of life.[4,9-10,17] Several reports indicate a predilection for women, although some have reported a male preponderance.[4,9,11,13,15,17] EHs usually present without associated symptoms.[4,17,20] Although, owing to their vascularity, tenderness, pulsation or bleeding (spontaneously or after minor trauma), may occur in some patients.[3-4,17,20] While peripheral blood eosinophilia and regional lymphadenopathy may be present in 5-20% of patients, IgE levels are not elevated.[4,6,9,17]

Histologically, EH presents as a circumscribed proliferation of blood vessels of varying sizes lined by plump endothelial cells.[3-4,7-8] The background stroma often appears fibromyxoid.[8] The endothelial cells are mostly cuboidal, with occasional "hobnailing" or a "tombstone"

appearance related to cytoplasmic vacuoles causing protrusion into the lumina.[1,4,7-8] These endothelial cells have a characteristic epithelioid appearance with ample eosinophilic cytoplasm.[1,3,7-8] In some examples, medium-sized arteries show fragmentation of the smooth muscle cells in their medial layer.[6,15] Others may show poorly canalised vessels, giving the lesion a deceptively solid appearance.[1,11] Ultrastructural features are generally shared with normal endothelium, although some differences do exist. An accumulation of cytofilaments may be in part responsible for the epithelioid appearance of the endothelial cells. Adjacent cells are often separated by rather large gaps, and organelles are generally more abundant in these cells.[7,11] Inflammation is the second defining feature, characterised by lymphocytes, plasma cells, mast cells and varying amounts of eosinophils adjacent to the vascular proliferation.[4,9,16] The lymphocytes may form distinct follicles with or without germinal centers, particularly in long-standing lesions.[4,7] In a large series by Fetsch and Weiss[11] approximately half of the 96 EHs examined were associated with prominent lymphoid follicles and damaged medium-sized vessels. Importantly, both the endothelial and inflammatory cells are bland and mitoses are rare, if present at all.[4,12] Depending on the age of the lesion, the vascular or inflammatory component may predominate.[4] In the early stages, the vascular component predominates, whereas in the late stages of the disease lymphocytes become more prominent.[4,11] Neither a prominent lymphoid infiltrate nor the presence of eosinophils is required for the diagnosis, and the inflammatory component may be completely absent.[1] To better understand recent genetic findings, EH can be subclassified into three subtypes according to histomorphology: (1) the "conventional" subtype; (2) the "angiolymphoid hyperplasia with eosinophilia" subtype containing lymphoid follicles and eosinophils; and (3) the "cellular subtype" which exhibits greater than 50% solid tumour growth.[8,18]

Due to its diverse histomorphology the diagnosis of EH may be challenging, being confused with both inflammatory conditions and malignant vascular tumours.[18] EH is often accompanied by an exuberant inflammatory infiltrate that may obscure its vascular component, mimicking a lymphoproliferative disorder, especially when the lesion arises in an atypical location.[1,5] The key in diagnosing EH relies on the recognition of its distinctive vascular component.[5] In the past, EH and Kimura disease were thought to be the same entity.[4] Kimura disease usually presents with a large subcutaneous mass with a strong predilection for young Asian males. In addition, it is an immune-mediated process often seen in association with lymphadenopathy, peripheral eosinophilia and raised IgE levels.[4,7,15] Histologically, Kimura disease shows features of a reactive inflammatory process, including lymphoid follicles, marked eosinophilic infiltrate, dense fibrosis and proliferating high endothelial venules. In contrast to EH, the endothelium in

Kimura disease does not appear epithelioid, nor does it contain intracytoplasmic vacuoles. These histological features are replicated in the involved lymph nodes, a feature not seen in EH.[1,4,7] Another consideration is the so-called epithelioid angiomatous nodule, which is regarded as a benign vascular proliferation. This entity is distinguished from EH on architectural grounds, presenting as a single exophytic nodule composed of epithelioid endothelial cells arranged in sheets.[1,7] Despite their similar terminology, epithelioid haemangioendothelioma (EHE) and epithelioid angiosarcoma rarely arises in the differential diagnosis for EH. However, the cellular subtype of EH, composed of large solid components, or EH with atypical histologic features, displaying cytological atypia and necrosis, may be challenging to distinguish from malignant epithelioid vascular tumours.[1,4,7,18] EHE is composed of cords and strands of epithelioid endothelial cells, with glassy, pale pink cytoplasm embedded in a chondromyxoid or hyalinised matrix.[1,7,18] Importantly, most EHEs lack prominent vasoformative areas and an inflammatory infiltrate.[1,4,18] Around 85% of EHEs harbor a characteristic t(1;3) translocation resulting in a WWTR1-CAMTA1 gene fusion. Antibodies directed against CAMTA1 can be used via immunohistochemistry to detect the fusion protein with 85% sensitivity and near 100% specificity within the differential diagnosis of epithelioid vascular tumours.[8] In rare instances epithelioid angiosarcoma may show deceptively bland cytology, however most cases show significant cytological atypia and mitotic activity, features not seen in EH.[1,4,7,18]

The aetiopathogenesis of EH is currently incompletely understood. Several hypotheses have been put forth, including reactive, neoplastic or infectious processes. None of which have been proven conclusive.[3-4,7-8,13,17] The fact that 10% of lesions occur following trauma, are symmetrically arranged around a vessel with mural damage, and are associated with an inflammatory response has led to the conclusion by some that they are reactive.[7,11] Some authors believe that they represent an unusual manifestation of hypersensitivity to a variety of agents.[12-13,16] An immunoglobulin E reticulated pattern has been observed in cases of EH, consistent with an atopic reaction. Other authors propose that EH is a benign vascular tumour responding to elevated serum estrogen, because of the presence of estrogen receptors in the lesion.[12-13] The characteristic inflammatory infiltrate is a key component of the lesion, with its aetiological role needing further clarification.[4] The vascular proliferation may be in part due to the endothelial response to stimuli produced by the accompanying inflammatory cells. EH has also been associated with various lymphoproliferative conditions, supporting the hypothesis by some authors that the lesion represents a monoclonal T-cell process. There have been reported

cases of EH in which T-cell receptor gene (TCR) rearrangement and monoclonality have been detected.[4,20]

A neoplastic origin of EH is further supported by the recently reported recurrent cytogenetic abnormalities involving the FOS gene. The Fos gene family consists of 4 members: FOS, FOSB, FOSL1 and FOSL2.[3,18] These FOS proteins have been implicated as regulators of cell proliferation, differentiation, and transformation, as well as tumour invasion, distant metastasis and angiogenesis.[2-3,18] A FOSB rearrangement with diagnostic value was first identified in pseudomyogenic haemangioendothelioma (PHE). In PHE, the recurrent t(7;19) fusion gene SERPINE1-FOSB is associated with FOSB upregulation, with immunohistochemistry showing a constant strong and diffuse FOSB staining pattern in these tumours.[2-3] Initial reports found that about 20% of cellular EHs cases harbor ZFP36-FOSB or WWTR1-FOSB rearrangements.[1-3,8,18] FISH analysis subsequently found recurrent FOS rearrangements with a range of fusion partners in nearly one-third of all EHs, regardless of site or histologic variant.[1,3,18] A systematic study by Huang et al[18] found recurrent FOS gene rearrangements in 29% (17/58 cases), spanning a diverse anatomic location. However, in this study the incidence of FOS alterations was unevenly distributed, with EH of the head and neck region showing the lowest incidence of rearrangements.[18] Another study detected FOS rearrangements in 5 of 11 examined cases of EH of bone, including two with novel FOS-MBLN1 or FOS-lincRNA fusions, and two with unidentified fusion partners.[21] No FOS gene rearrangements have been detected by FISH in the ALHE subtype, suggesting a different pathogenesis.[1,18]

Despite the genetic heterogeneity, strong and diffuse nuclear FOSB immunohistochemical (IHC) staining is more than 95% specific for EH. Sensitivity of FOSB IHC is problematic, with several studies showing varied results.[8] A study by Hung *et al*[22] found diffuse nuclear positivity for FOSB in half the cases of EH, including all 6 cases of the ALHE subtype. In their series of 15 cases, Ortins-Pina *et al*[3] found constant strong and diffuse FOSB nuclear positivity in the tumour cells of the ALHE subtype. This difference in FOSB IHC sensitivity could be explained in terms of the different morphological subtypes, with 75% sensitivity for the conventional subtype, 100% sensitivity for the ALHE subtype, and only 10% sensitivity for the cellular subtype.[8] Considering the results of FISH studies, the consistent strong FOSB IHC staining pattern in the ALHE subtype raises questions regarding which mechanism drives FOSB protein overexpression.[1,18] A likely explanation is that FOSB upregulation in the ALHE subtype may be driven by a translocation-independent mechanism. FOSB overexpression may result from epigenetic modifications or point changes, both of which would not be detected by FISH

analysis. Alternatively, other unknown genetic events may lead to proliferative pathways that drive FOSB expression in the ALHE subtype.[18] Regardless of the underlying mechanisms, FOSB nuclear positivity helps differentiate EH from malignant epithelioid vascular tumours.[3]

No definitive treatment exists for EH. Skin lesions are usually treated with complete excision, but recurrences are common.[4,6,16] One-third of cases that are incompletely excised do recur, typically along the course of the affected vessel.[4,20] Mohs micrographic surgery with excision of abnormal vessels at the base may be effective in reducing recurrences. Intralesional injections with corticosteroids, interferon alfa-2a and cytotoxic agents have been used successfully, with spontaneous remission within months to years.[16-17] Other options include diathermy, cryotherapy, radiotherapy and laser treatments.[16,20] Complete excision is the treatment of choice for oral lesions, with limited incidence of recurrences.[12-13] The lesion has a chronic and benign biological course with no reports of malignant transformation.[4,13]

References

1. Hornick JL. Practical Soft Tissue Pathology: A Diagnostic Approach. 2nd ed. Philadelphia, PA: Elsevier; 2019.

2. Antonescu CR, Chen HW, Zhang L, Sung YS, Panicek D, Agaram NP, et al. ZFP36-FOSB fusion defines a subset of epithelioid hemangioma with atypical features. Genes Chromosomes Cancer. 2014; 53(11):951-9.

3. Ortins-Pina A, Llamas-Velasco M, Turpin S, Soares-de-Almeida L, Filipe P, Kutzner H. FOSB immunoreactivity in endothelia of epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia). J Cutan Pathol. 2018; 45(6):395-402.

4. Guo R, Gavino AC. Angiolymphoid hyperplasia with eosinophilia. Arch Pathol Lab Med. 2015; 139(5):683-6.

5. Cham E, Smoller BR, Lorber DA, Victor TA, Cibull TL. Epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia) arising on the extremities. J Cutan Pathol. 2010; 37(10):1045-52.

6. Sanchez-Orgaz M, Insausti-Garcia A, Gregorio LY, Duralde AA, Romero-Martin R. Epithelioid hemangioma of the orbit or angiolymphoid hyperplasia with eosinophilia. Ophthalmic Plast Reconstr Surg. 2014; 30(3):e70-2.

7. Goldblum JR, Folpe AL, Weiss SW. Enzinger and Weiss's Soft Tissue Tumors. 7th ed. Philadelphia, PA: Elsevier; 2020.

8. Papke DJ, Jr., Hornick JL. What is new in endothelial neoplasia? Virchows Archiv : an international journal of pathology. 2020; 476(1):17-28.

9. Thompson LD. Angiolymphoid hyperplasia with eosinophilia. Ear Nose Throat J. 2015; 94(10-11):443-4.

10. Ciaramicolo N, Custodio M, de Sousa S, Naclerio-Homem MG. Rare lesion, unusual location, uncommon presentation: a case of angiolymphoid hyperplasia with eosinophilia. Br J Oral Maxillofac Surg. 2019; 57(5):479-80.

11. Fetsch JF, Weiss SW. Observations concerning the pathogenesis of epithelioid hemangioma (angiolymphoid hyperplasia). Mod Pathol. 1991; 4(4):449-55.

12. Mariatos G, Gorgoulis VG, Laskaris G, Kittas C. Epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia) in the oral mucosa. A case report and review of the literature. Oral Oncol. 1999; 35(4):435-8.

13. Tenorio JR, Gonzaga AKG, Goncalves PGP, de Oliveira DHIP, Queiroz LMG. Hiperplasia angiolinfoide com eosinofilia: Um caso raro em cavidade oral. Jornal Vascular Brasileiro. 2016; 15(4):317-21.

14. Wells GC, Whimster IW. Subcutaneous angiolymphoid hyperplasia with eosinophilia. Br J Dermatol. 1969; 81(1):1-14.
15. Antony FC, Miller JA, Calonje E, Belli A, Burnand K, Mortimer PS. Epithelioid haemangioma in association with a deep arteriovenous malformation. Clin Exp Dermatol. 2005; 30(3):238-40.
16. Chitrapu P, Patel M, Readinger A, Menter A. Angiolymphoid hyperplasia with eosinophilia. Proc (Bayl Univ Med Cent). 2014; 27(4):336-7.
17. Ozkan BT, Eroglu CN, Cigerim L, Gunhan O. Angiolymphoid hyperplasia with eosinophilia in the angle region of the mandible. J Oral Maxillofac Pathol. 2015; 19(1):108.
18. Huang SC, Zhang L, Sung YS, Chen CL, Krausz T, Dickson BC, et al. Frequent FOS Gene Rearrangements in Epithelioid Hemangioma: A Molecular Study of 58 Cases With Morphologic Reappraisal. Am J Surg Pathol. 2015; 39(10):1313-21.
19. Suzuki H, Hatamochi A, Horie M, Suzuki T, Yamazaki S. A case of angiolymphoid hyperplasia with eosinophilia (ALHE) of the upper lip. J Dermatol. 2005; 32(12):991-5.
20. Santosa C, Wardhana M, Saputra H. Angiolymphoid hyperplasia with eosinophilia with clinical pictures of keratoacanthoma: A rare case report. Clin Case Rep. 2019; 7(1):189-92.
21. van IDG, de Jong D, Romagosa C, Picci P, Benassi MS, Gambarotti M, et al. Fusion events lead to truncation of FOS in epithelioid hemangioma of bone. Genes Chromosomes Cancer. 2015; 54(9):565-74.
22. Hung YP, Fletcher CD, Hornick JL. FOSB is a Useful Diagnostic Marker for Pseudomyogenic Hemangioendothelioma. Am J Surg Pathol. 2017; 41(5):596-606.

Figure legends

Figure 1. Initial clinical presentation. Nodular mass with surface ulceration involving the right vermilion of the lower lip.

Figure 2. A low-power hematoxylin and eosin (H&E)-stained section showing a papillomatous tissue fragment surfaced by hyperplastic stratified squamous epithelium (original magnification x 10).

Figure 3. High-power H&E-stained sections showing (A) the capillary-sized vascular proliferation within the lamina propria with a larger vessel showing endothelial cell hobnailing into the lumen (original magnification x 40) and (B) the stromal mixed chronic inflammatory cell infiltrate with scattered eosinophils (original magnification x 100).

Figure 4. (A) CD31 and (B) ERG immunohistochemical stains highlighting the vascular proliferation of varying sizes within the lamina propria (original magnification x 40).

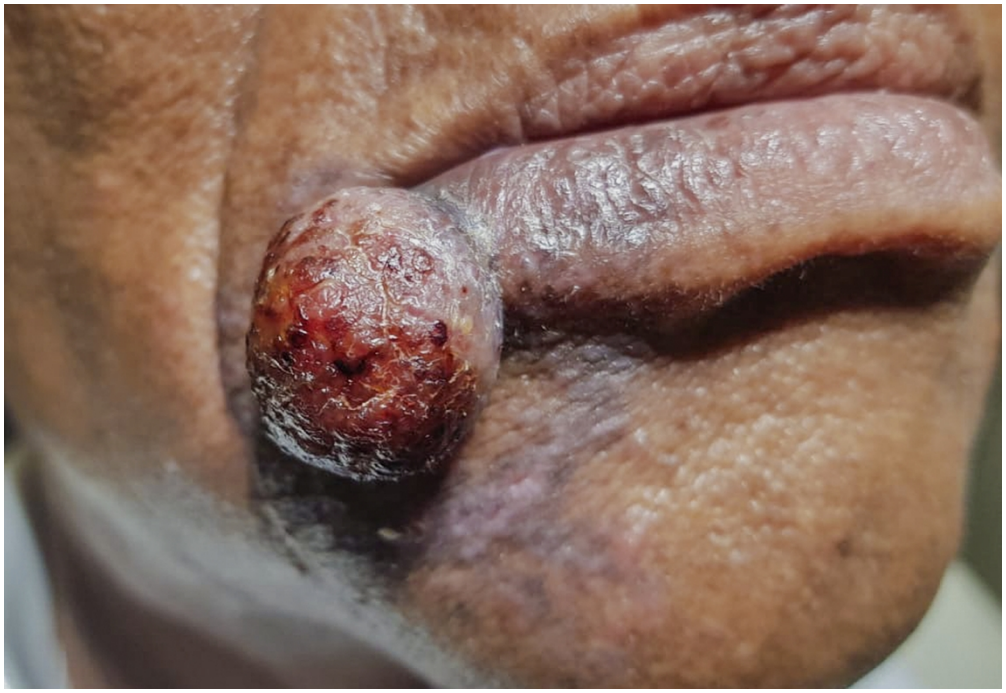

Figure 1. Initial clinical presentation. Nodular mass with surface ulceration involving the right vermilion of the lower lip.

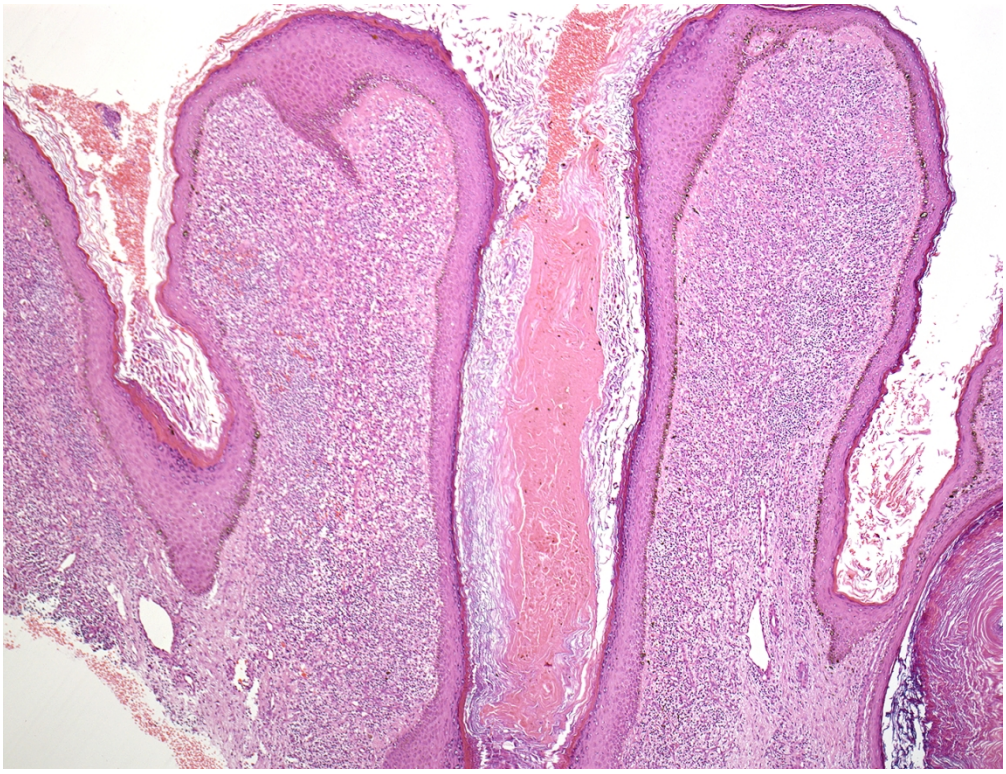

Figure 2. A low-power hematoxylin and eosin (H&E)-stained section showing a papillomatous tissue fragment surfaced by hyperplastic stratified squamous epithelium (original magnification x 10).

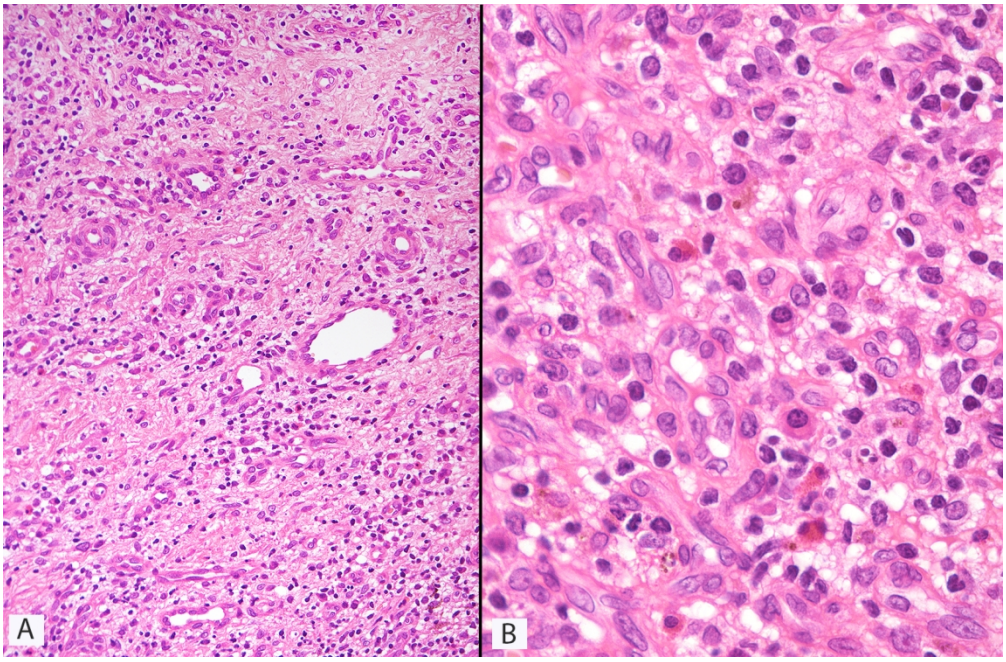

Figure 3. High-power H&E-stained sections showing (A) the capillary-sized vascular proliferation within the lamina propria with a larger vessel showing endothelial cell hobnailing into the lumen (original magnification x 40) and (B) the stromal mixed chronic inflammatory cell infiltrate with scattered eosinophils (original magnification x 100).

140x91mm (300 x 300 DPI)

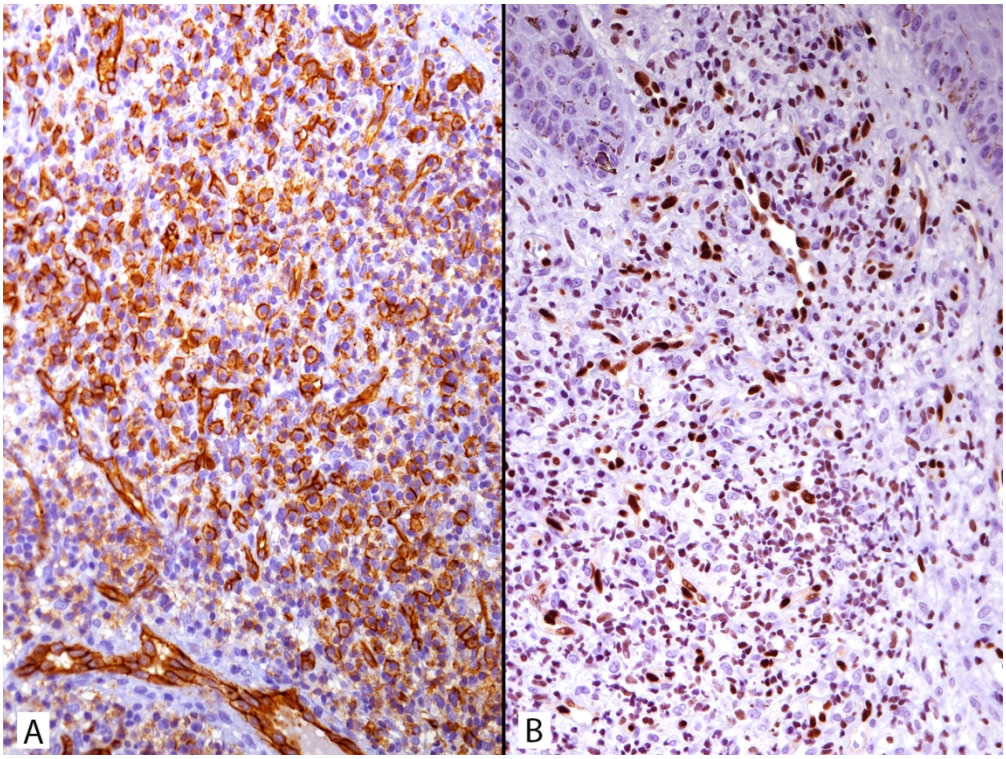

Figure 4. (A) CD31 and (B) ERG immunohistochemical stains highlighting the vascular proliferation of varying sizes within the lamina propria (original magnification x 40).

119x90mm (300 x 300 DPI)