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Angiolymphoid hyperplasia with eosinophilia of the nail unit

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Abstract

Angiolymphoid hyperplasia with eosinophilia (ALHE) is a distinctive lymphocyte rich vasoformative proliferation comprising epithelioid-appearing endothelial cells with partially canalized capillary vessels in a lymphohistiocytic and eosinophil rich environment. ALHE presents clinically as single or multiple pink-brown dome-shaped papules or nodules, most commonly on the ear and peri-auricular area, followed by the face, and scalp. ALHE involving the subungual unit is rare with only 5 previously reported cases and all involved the underlying bone. The authors describe a case of a painful subungual nodule of the left 1st fingernail in a 48-year-old woman. An excisional biopsy was performed confirming a diagnosis of ALHE. There was no bone involvement and immediately following excision of the tumor, there was complete resolution of her symptoms. Our patient's presentation expands upon the clinical and histopathological spectrum of subungual ALHE.

Keywords: nail disorders, benign tumors

Introduction

ALHE was first described in 1969 by Wells and Whimster [1]. The authors characterized the histopathological features of 9 patients with persistent subcutaneous nodules involving the head and neck showing a characteristic and reproducible histology. In all cases there were proliferating vessels lined by plump hobnailed-appearing endothelial cells with an accompanying lymphocyte rich infiltrate including germinal centers and many eosinophils, hence manifesting a significant degree of morphologic overlap with Kimura disease. The latter differs by virtue of the deeper-seated nature of

the inflammatory cell infiltrate with involvement of deep soft tissue and muscle and a lesser proliferative vascular component [1].

In 1984, Olsen and Helwig further characterized the clinical and histological findings of ALHE in a study of 116 patients. Clinically, patients presented with light pink-to-red-brown dome-shaped papules or subcutaneous nodules with a mean duration of 13 months. Peripheral blood eosinophilia and lymphadenopathy occurred in 20% and 19% of patients respectively [2].

In a systematic review of ALHE, which included 416 studies and 908 patients, the mean age at presentation was 37.6 years (range 0.7-91), with 53.4% of patients presenting with a solitary lesion and 46.6% with multiple lesions. The analysis showed near sex parity [3], conflicting with some smaller studies showing male or female sex predominance [2, 4-6]. The most common sites were the ear and peri-auricular area (36.3%), followed by the face (28.2%), and scalp (17.3%), but cases in other anatomic locations of the skin, including the extremities and genitalia were also reported. Pruritus was reported by 36.8% of patients, whereas 25.3% described bleeding (25.3%) or pain (20.2%). In 15.4% of patients, ALHE was asymptomatic.

There are rare reports of ALHE in the nail unit [7-10]. We report a case of ALHE involving the nail apparatus in a 48-year-old woman and review the literature as it pertains to subungual ALHE. Because of the rarity of ALHE in this location, the clinical impression would invariably encompass alternative and more common diagnostic considerations such as a pyogenic granuloma, glomus tumor, digital mucous cyst, or amelanotic melanoma [11].



Figure 1. Left first fingernail with 0.5-centimeter smooth pink-brown translucent, tender nodule protruding through the proximal nail plate. A superficial longitudinal groove extends from the nodule to the hyponychium.

Case Synopsis

A healthy 48-year-old woman was referred for evaluation of her left first fingernail. She noticed a longitudinal groove in her nail approximately 3 months prior to presentation, but experienced no pain or cold sensitivity. One week preceding her visit, her nail began to peel near the cuticle and a painful red mass emerged, with some drainage. She was right handed, worked in finance and regularly played billiards. Her past medical and family medical history was unremarkable.

The physical examination was significant for a 0.5-centimeter smooth pink-brown translucent, tender nodule protruding through the proximal left first fingernail plate. A superficial longitudinal groove extended from the nodule to the hyponychium. The proximal and lateral nail folds were unremarkable (Figure 1). Evaluation of the other fingernails and toenails were non-contributory. She had no lymphadenopathy. The proximal nail fold was incised and reflected to fully expose the tumor, which was excised.

The biopsy specimen was processed routinely and sent for histological examination.

The biopsy showed a proliferation of venules and small arteries lined by plump endothelial cells exhibiting distinct cytoplasmic vacuolization. The vessels walls demonstrated myxomatous expansion. There was a lymphocytic and eosinophil rich inflammatory background (Figure 2). A CD68 stain highlighted the distinctive epithelioid-appearing endothelium and the background macrophages (Figure 3). The vessels were also highlighted by CD31. A diagnosis was made of ALHE.

The patient healed well after the procedure, with no evidence of recurrence 1 month after surgery. A complete blood count was within normal limits with 1.4% eosinophils (normal range 0.0-5.0%). X-rays of the hands and feet were completely normal.

Case Discussion

We describe a 48-year-old woman with ALHE involving the left first fingernail. The clinical

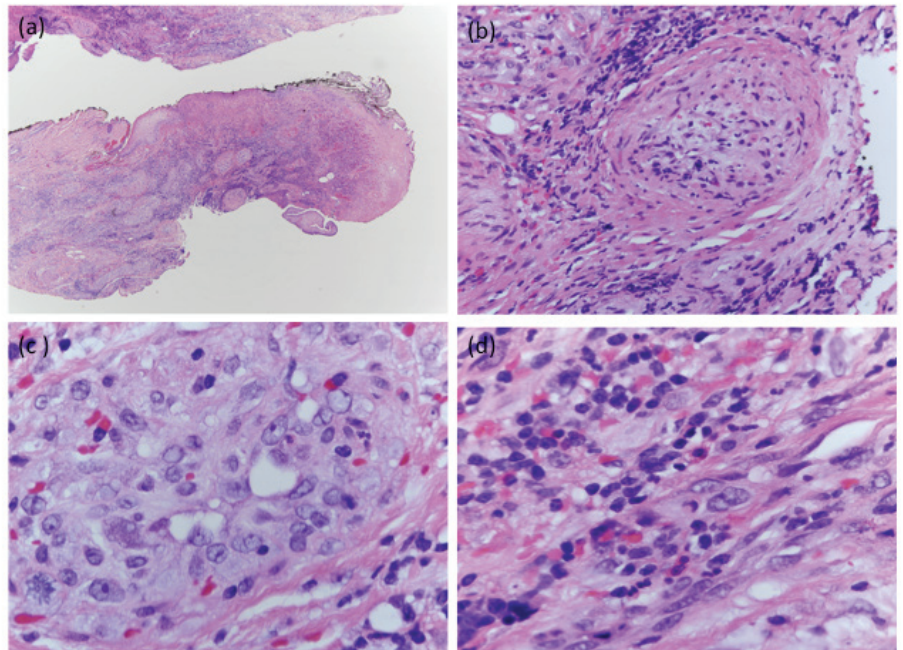


Figure 2. a) The biopsy shows a polypoid exophytic vascular lesion associated with ulceration. There are venules and muscular arteries in a highly inflammatory lymphocyte-rich background (H&E, 20x). b) Many of the larger smooth muscle containing arteries exhibit luminal obliteration due to intimal and medial wall myxomatous expansion, accompanied by endothelial cell and smooth muscle hyperplasia (H&E, 40x). c) One of the hallmarks is prominent vacuolation of the endothelial cell cytoplasm (H&E, 100x). d) The background inflammatory cell infiltrate is predominated by lymphocytes and eosinophils (H&E, 100x).

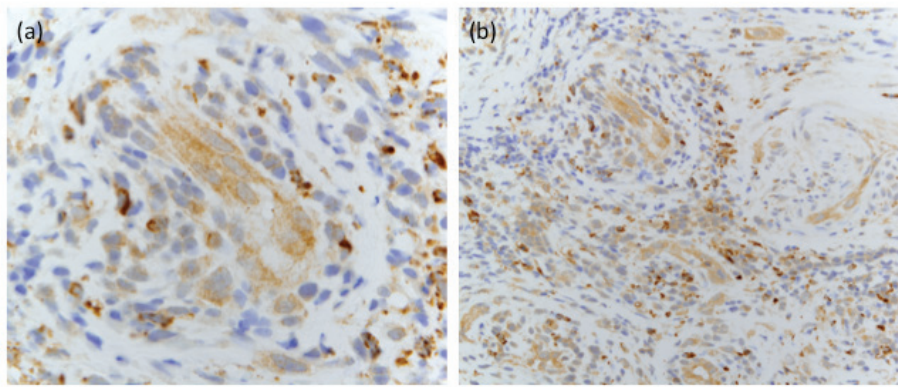


Figure 3. Immunohistochemical stains. a) The endothelial cells show prominent staining for CD68 (40x). b) There is striking immunoreactivity to KP1, highlighting a number of perivascular macrophages in addition to endothelial cells (40x).

presentation suggested a differential diagnosis of pyogenic granuloma, Kaposi sarcoma, glomus tumor, and amelanotic melanoma. However, histopathologic analysis of the subungual biopsy was diagnostic for ALHE. In our case there was both the distinctive epithelioid quality of the endothelial cells including intracytoplasmic vacuolation along with significant reactive eosinophil enriched lymphoid hyperplasia characteristic of ALHE. However the morphologic spectrum of ALHE encompasses cases in which the dominant morphology is one reflective of the vascular component unaccompanied by significant inflammation, warranting the alternative appellations of epithelioid hemangioma and histiocytoid hemangioma. It was in 1982 when Dr. Juan Rosai first proposed that ALHE was part of the morphologic spectrum of histiocytoid hemangioma [12]. While in 1985, Shrigley and co-workers were the first to apply the term epithelioid hemangioma to similar lesions [13]. In more recent years the preferred designations have emerged as ALHE and epithelioid hemangioma although for many years all three terms were used interchangeably [14].

ALHE involving the subungual region has been reported only 5 previous times in the literature (**Table 1**), [7-10, 15-17]. The mean age of presentation was 44.5 years of age (range 31-69 years of age, SD: 13.9 years), which is similar to the reported mean age of onset of 37.6 years reported for cutaneous ALHE [3]. There is no clear sex predominance or associated comorbidities as seen with cutaneous cases [3]. The mean duration prior to presentation for nail ALHE is 6 months (range 1 week-2 years). Based on our data, subungual ALHE is diagnosed much earlier than

cutaneous ALHE (mean duration nail ALHE 6 months versus cutaneous ALHE 13 months), [2]. The fingernails are affected in the majority of cases, with only one case affecting a toenail [15]. Of the 6 nail cases, half affected only one digit and half involved multiple digits, which is roughly consistent with the cases of ALHE not involving the nail apparatus [3]. Other nail changes associated with ALHE are non-specific and rather protean in their presentation, comprising longitudinal nail ridges, onycholysis, paronychia, and periungual erythema.

In those cases showing a nodular distortion of the nail, as noted in our patient, tenderness is noted in most cases (67%) and pain in the interphalangeal joints is often reported. Subungual ALHE differs from cutaneous ALHE, in that osteolytic bone changes are present in the majority of cases. Therefore, X-ray and/or MRI should be ordered when subungual ALHE is suspected, to assess the presence and extent of bone involvement.

ALHE has characteristic histopathological features, which are common to both cutaneous and subungual tumors. The endothelial cells have a plump proplastic hobnailed appearance with cytoplasmic vacuolation accounting for its alternative designation as epithelioid hemangioma. The vessel wall may show myxomatous alteration of the wall. An exuberant lymphocytic and eosinophilic infiltrate is oftentimes present although not in every case. Endothelial cells of ALHE exhibit low alkaline phosphatase levels and high levels of acid phosphatase, in addition to nicotinamide-adenine dinucleotide content opposite to that observed in normal endothelial cells and similar to histiocytes, likely accounting for its distinctive CD68 positive phenotypic profile. The endothelial cells do not express other histiocyte specific markers such as CD14 and CD163 while retaining other endothelial cell specific markers including factor VIII and CD34.

The etiology of ALHE has not been elucidated, but it is believed to involve reactive hyperplasia and/or benign neoplasia [2, 18]. However, an atopic diathesis including peripheral blood eosinophilia and high

Table 1: Review of Cases Involving the Subungual Unit.

Case Reference		Verret et al. [7]	Dannaker et al. [8]	Tosti et al. [9]	Conill et al. [10]	Tsubio et al. [15]	Halteh et al.
Age/Race/Sex		40 year old/ Unknown/ Woman	31 year- old/ Mexican-Ameri- can/Man	47 year-old/Un- known/Man	32 year- old/Cau- casian/ Woman	69 Year old/Japa- nese/Woman	48 year old/ Caucasian/ Woman
Pertinent History	Medical	None	Plaque psoriasis	Liver cirrhosis secondary to Hepatitis C, Esophageal varices	Last months of pregnancy	History of tuberculosis of the lung and bronchiectasis at age 9	None
Duration of tumor prior to presentation		2 years	4 months	10 days	Unknown	2 months	1 week
Nail Examination (PE) & Nail symptoms (Sx)	Physical	<u>PE:</u> Right second and third fingernails with onycholysis. <u>Sx:</u> Tender	<u>PE:</u> Left second, fourth and fifth fingernails with onycholysis, longitudinal splitting, periungual erythema, paronychia changes, and purulent discharge. <u>Sx:</u> Unknown	<u>PE:</u> Proximal right third fingernail with 0.5 cm bright red vegetating nodule with superficial erosions. Proximal nail fold with mild erythema and swelling. <u>Sx:</u> Tender	<u>PE:</u> Right second and third fingernails with onycholysis, longitudinal ridging, and periungual erythema. Erythematous nodule at distal tip of right second digit. <u>Sx:</u> Unknown	<u>PE:</u> Right third distal toenail with 0.1 cm well-circumscribed, bright red nodule, with irregular surface, and periungual erythema. <u>Sx:</u> Tender	<u>PE:</u> Left first fingernail longitudinal groove and 0.5-centimeter smooth pink-brown, translucent, nodule protruding through the proximal plate. <u>Sx:</u> Tender
Other Skin Involvement		Unknown	Ipsilateral Firm, tender red/brown papules on thenar eminence, and flexor surface of wrist.	Ipsilateral 0.1 -0.3 cm angiomatous nodules on the lateral aspect of the third distal digit.	Ipsilateral firm, red-brown papules and nodules on forearm and hand.	None	None
History of trauma to involved nail		Yes (unknown type of injury)	Yes (crush injury to left hand 6 months prior)	Yes (mild compressive trauma one month prior)	Unknown	No	No

Case Reference	Verret et al. [7]	Dannaker et al. [8]	Tosti et al. [9]	Conill et al. [10]	Tsubio et al. [15]	Halteh et al.
Bone Imaging	X-ray: Lytic bone lesion of the right third phalange at the level of the second metacarpophalangeal joint.	X-ray: Acro-osteolytic bony changes most evident in the left second and fifth fingers Bone Scan: Diffuse involvement of left hand with greatest uptake in the distal area of fourth and fifth fingertips.	X-ray: Right third and fourth digits with minimal bone erosions. MRI: right third digit with marked high-intensity signaling on volar aspect.	X-ray: Lytic bone lesions of the right second and third distal phalanges.	X-ray: Osteolytic lesion of the right third distal toe.	X-rays of bilateral hands and feet: normal.
Laboratory Tests	Normal CBC with differential.	Normal CBC with differential.	Labs consistent with cirrhosis. Peripheral eosinophilia (10.6 x 10ml).	Normal CBC with differential.	Peripheral Eosinophilia (18.9%).	Normal CBC with differential.
Immunohistochemistry	Perl's Prussian blue Stain: -	Factor VIII-related antigen, nicotinamidene, alkaline phosphatase: + S100, lysozyme, IgA, IgM, IgG, C3: -	Factor VIII-related antigen, vimentin, anti-CD20, CD3, CD45RO, CD45RA: + S-100, CD68: -	Not Performed	Factor-VIII-related antigen, lysozyme: + α1-antikimotrypsin, S-100: -	CD68, KP1: +
Treatment	Radiation Therapy	Radiation Therapy	Surgical Excision	Radiation Therapy	Surgical Excision	Surgical Excision
Recurrence	None (2 years)	None (12 months)	Unknown	None (9 years)	None (6 months)	None (1 month)

IgE levels have been described in some patients. Its localization to sites of tetanus vaccination in 3 separate cases suggests an unusual immunologic response to antigen. In our patient a clear-cut trigger could not be isolated and no history of atopy.

With cutaneous ALHE, recurrences after treatment are common, but the lowest recurrence rates are seen after excision (40.8%, n=262), pulsed dye laser (50.0%, n=18), carbon-dioxide laser (54.6%, n=11), and radiotherapy (60.0%, n=30). The mean time to recurrence of lesions after treatment with excision was 4.2 ± 0.6 years; multiple lesions and pain were both associated with higher rates of recurrence [3]. Only surgical excision [9, 15], and radiation therapy [8, 10] have been used to treat ALHE of the subungual region and no recurrences have reported thus far.

Since the recurrence probability for cutaneous ALHE is highest in the first 5 years [3], all patients with ALHE should be followed for at least 5 years.

This patient with subungual ALHE emphasizes the need for high clinical suspicion and biopsy in patients with a tender nodule in the subungual region with associated onychodystrophy. Bone imaging should be performed since osteolytic changes are common. Although there are a limited number of cases of subungual ALHE, evidence from the cutaneous ALHE literature suggests that surgical excision, laser treatment, and radiation therapy have the lowest recurrence rates. Patients should be followed for at least 5 years following treatment, to recognize early recurrences and prevent permanent nail dystrophy.

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