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Angiolymphoid hyperplasia with eosinophilia: A potential mimic of Kimura's disease

Laila Wahyuningsih[1], Maria Fransiska Pudjohartono[2], Hanggoro Tri Rinonce*[2]

[1]Salatiga City Hospital, Central Java, Indonesia
[2]Department of Anatomical Pathology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/ Dr. Sardjito Hospital, Yogyakarta, Indonesia

Case Report

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***Corresponding author:**
hanggoro_rinonce@ugm.ac.id

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ABSTRACT

Angiolymphoid hyperplasia with eosinophilia (ALHE) is a rare reactive angio-proliferative lesion. ALHE was initially classified as the late stage of Kimura's disease (KD), although studies later showed that they were two separate clinical entities. Diagnosing ALHE remains a clinical challenge. Here, we report a case of ALHE in a young man and review current literature with an emphasis on how to distinguish ALHE particularly from KD. A 26-year-old man presented with a subcutaneous nodule in right infra-auricular area. Recurrence had occurred after three surgical excisions. Neither enlargement of salivary glands nor lymph nodes were found. Hematological examinations and renal function were normal. The mass was removed surgically. Microscopic examination showed proliferation of vascular channels with accompanying mixed inflammatory infiltrate consisting of lymphocytes, plasma cells, and eosinophils. Based on clinical data and histopathological examination, the patient was diagnosed with ALHE. Several clinical features differ between ALHE and KD, such as gender predilection, hypereosinophilia, IgE levels, and renal involvement. However, clinical features can overlap, so definitive diagnosis relies on histopathological examination. The most important hallmark of ALHE is vascular proliferation with epithelioid endothelial cells. Distinguishing ALHE from KD is important due to the lack of systemic manifestations in ALHE. However, ALHE can be easily mistaken for other diseases due to its rarity. Careful microscopic examination is very important to distinguish ALHE from KD and other mimicking lesions.

Hiperplasia angiolimfoid dengan eosinofilia (HALE) merupakan lesi angioproliferatif reaktif yang jarang ditemukan. Lesi ini biasanya muncul sebagai nodul subkutan di regio kepala leher. Dahulu HALE dan penyakit Kimura (PK) diklasifikasikan sebagai penyakit yang sama, tetapi penelitian terbaru menunjukkan bahwa keduanya merupakan dua penyakit berbeda. Penegakan diagnosis HALE menantang secara klinis, terutama dalam hal membedakannya dengan PK. Kami melaporkan kasus HALE pada seorang laki-laki muda. Telaah pustaka juga dilakukan dengan menitikberatkan cara membedakan HALE terutama dengan PK. Seorang pria 26 tahun datang ke rumah sakit karena nodul subkutan di daerah infra-aurikula kanan. Penderita telah menjalani tiga kali eksisi bedah, tetapi lesi muncul kembali. Pemeriksaan darah dan fungsi ginjal dalam batas normal. Benjolan dieksisi dan secara mikroskopik menunjukkan proliferasi pembuluh darah dengan sebukan sel radang campuran yang terdiri atas limfosit, sel plasma, dan eosinofil. Berdasarkan data klinis

dan histopatologik, pasien didiagnosis menderita HALE. Beberapa ciri klinis dapat mengarahkan ke diagnosis HALE atau PK, seperti jenis kelamin, hipereosinofilia, kadar IgE, dan keterlibatan ginjal, namun gambaran klinis keduanya dapat tumpang tindih. Oleh karena itu, penegakan diagnosis pasti HALE kadang bergantung kepada pemeriksaan histopatologis dengan ditemukannya gambaran khas berupa proliferasi pembuluh darah dengan sel endotel epitelioid. Pembedaan HALE dengan penyakit Kimura sangat penting karena HALE tidak berkaitan dengan manifestasi sistemik seperti yang terjadi pada PK. Namun, karena HALE jarang dijumpai, kesalahan diagnosis mungkin terjadi. Pemeriksaan mikroskopik yang teliti sangat diperlukan untuk menyingkirkan PK dan lesi serupa lainnya.

INTRODUCTION

Angiolymphoid hyperplasia with eosinophilia (ALHE) is a rare benign vasoproliferative disorder characterized by pink to red-brown dome-shaped papules or nodules over the head and neck region.[1] Although most commonly found on the head or neck, it has also been reported on the other body sites such as extremities, mucosal surfaces, and internal organs.[2] The disease is most prevalent in young to middle-aged adults with no gender preference.[3] No study has established precisely the incidence of this disease, but a systematic review in 2016 found 908 cumulative cases reported worldwide.[1] To our knowledge, only one case has been reported from Indonesia.[4]

Wells and Whimster first described ALHE as a late stage of Kimura's disease (KD) in 1969.[4,5] However, in the 1980s, it was demonstrated that these two diseases are two separate entities with distinct clinical and histological features.[6] There are several diseases which share similar features with ALHE, including several variants of hemangioma, Kaposi's sarcoma, and vascular hamartomas. However, as befits its historic origins, KD is the closest diagnosis which is most often confused with ALHE.

We report a rare case of ALHE in a 26-year-old male patient who was treated with complete excision. We also reviewed the current literature with an emphasis on how to distinguish ALHE from other similar diseases, particularly KD.

CASE DESCRIPTION

A 26-year-old male patient was admitted to the hospital with the chief complaint of a recurrent right infraauricular mass. The mass had been excised three times but continued to recur. Clinical examination revealed a skin-colored mass on the right infraauricular region, measuring 5.2 cm at its greatest diameter and pushing the auricula cranially. The mass was tender to palpation. Cervical radiographic examination showed soft tissue swelling and an inhomogenous opacity in the right infraauricular region. Laboratory examinations, including hematological counts and renal function, were within normal limits. The mass was surgically excised and sent for histopathological examination.

Gross examination showed a skin tumor tissue, measuring 5.2 x 3.3 x 2 cm. The mass had a spotted brown-to-tan cut surface and rubbery consistency. Microscopically, the lesion consisted of numerous blood vessels lined by epithelioid endothelial cells. The vascular proliferation was surrounded by inflammatory infiltrates consisted of lymphocytes, plasma cells, and eosinophils (Fig. 1A and B). Immunohistochemical staining for cluster of differentiation 31 (CD31) was positive in the atypical endothelial cells (Fig. 1C). Based on clinical and histopathological findings, the diagnosis of ALHE was determined.

All data were reported from existing clinical findings and diagnostic test results in medical record, and no identifiable information was included in the report. The patient had given his consent preoperatively to the usage of the tissue samples for future study purposes. For those reasons, the Medical and Health Research Ethics Committee of Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta exempted the protocol for review (KE/FK/0952/EC/2021).

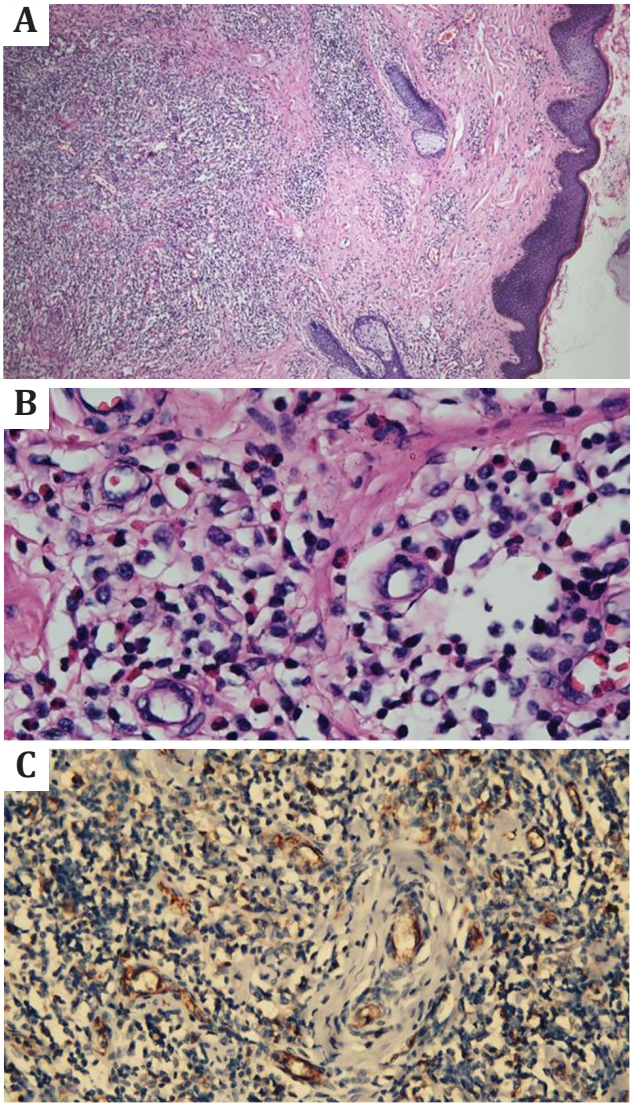

Figure 1. Microscopic examination at low power magnification showed (A) vascular proliferation with rich inflammatory infiltrates in dermis [hematoxylin and eosin (HE) stain, 40x]. Higher magnification showed (B) the epithelioid endothelial cells lining the blood vessels and copious infiltrating eosinophils (HE, 400x). CD31 immunostaining showed (C) strong CD31 expression in the cytoplasm of the epithelioid endothelial cells.

DISCUSSION

Due to its rarity, ALHE can be easily mistaken for other diseases, especially KD. These two diseases may seem very similar but have significantly different systemic associations and prognoses. Thus, distinguishing ALHE and KD is important for determining the treatment and follow-up for the patient. Table 1 compares the clinical and histopathological features of these two diseases.

Several clinical features can help distinguish ALHE and KD. ALHE is evenly distributed between male and female patients, although some studies report a slight female predilection.[7] In comparison, KD has a strong predominance for male patients, with a male/female ratio of approximately 3:1. Although both commonly manifest as subcutaneous nodules around the head and neck, KD is often accompanied by enlargement of salivary glands and/or regional lymph nodes.[8]

Table 1. Clinical and histopathological features comparison of ALHE and KD

	ALHE	KD
Clinical features		
Gender	No gender preference or slightly higher in females	Male predominance (male/female ratio = 3:1)
Local involvement	Rare	Enlarged salivary glands and/or regional lymph nodes
Laboratory tests	Normal blood counts and IgE levels	Hypereosinophilia and elevated IgE
Systemic associations	Rare	Renal involvement in 10-60%
Histopathological features		
Dominant feature	Proliferation of epithelioid endothelial cells, "hobnail" or "cobblestone" appearance	Lymphoid follicle hyperplasia, moderate proliferation
Endothelial cells	Epithelioid/histiocytoid endothelial cells with atypia and prominent vacuoles	Moderate proliferation, flat endothelial cells
Fibrosis	Uncommon	Common

ALHE and KD also differ in laboratory examination results. Despite the name of the disease, ALHE patients rarely exhibit eosinophilia. Meanwhile, eosinophilia is found in over 80% of KD patients, with eosinophils comprising 10-50% of leukocytes.[9] Elevated immunoglobulin E (IgE) levels is common in KD but seldom found in ALHE cases. One limitation of this case is that the IgE level was not measured. The excessive IgE can deposit in renal glomeruli, causing renal dysfunction in KD. ALHE is rarely associated with any systemic involvement.

Although these clinical differences can be suggestive, definitive diagnosis and differentiation of ALHE and KD rely on histopathological examination.[10] The most prominent finding in ALHE is vascular proliferation with plump endothelial cells, which are called epithelioid endothelial cells.[3] The epithelioid endothelial cells often have rounded or polygonal nuclei with cytoplasmic vacuoles. The small blood vessels lined with the prominent epithelioid endothelial cells are said to have a "hobnail" or "cobblestone" appearance.[11] The atypical endothelial cells are also surrounded by other inflammatory cells, including lymphocytes, mastocytes, and eosinophils. Lymphoid follicles can also be present, albeit not abundantly. In contrast, KD is dominated by lymphoid follicular hyperplasia with infiltration of eosinophils and mast cells.[9] The follicles are often hyperplastic with enlarged germinal centers. The follicular hyperplasia is accompanied by vascular hyperplasia and fibrosis. Although vascular proliferation is present, the endothelial cells are usually still flat and do not show vacuolization. KD lesions lack the hallmark epithelioid cells of ALHE.

Besides KD, common differential diagnoses for ALHE include other vascular lesions, such as epithelioid hemangioendothelioma, hemangioma, pyogenic granuloma, Kaposi's sarcoma, and angiomyomatous hamartoma.[4] Epithelioid hemangioendothelioma also shows epithelioid cells, but they rarely form vessels and are usually scattered in a myxohyaline stroma.[12] Epithelioid hemangioendothelioma also has a different location predilection, more commonly appearing in the bone, liver, or lungs. Other differential diagnoses do not have the epithelioid endothelial cells characteristics of ALHE.

Immunohistochemistry using endothelium markers (such as CD31, CD34, and factor VIII) is occasionally used in diagnosing ALHE.[13] These markers are less helpful in distinguishing

ALHE and KD, as they would be positive in both ALHE and KD. However, the staining will help delineate the shape of the endothelial cells, making visualization of the atypical epithelioid endothelial cells easier. Staining the tumor cells with endothelial markers can also help exclude non-endothelial diseases.

ALHE tends to have an indolent clinical course and the majority of cases regress spontaneously. Small lesions can be observed for 3-6 months to await spontaneous regression.[14] Persistent or recurrent lesions are most commonly treated by surgical removal, although the masses recur in about 40% of cases.[15] Other therapeutic options include laser therapy, radiofrequency ablation, cryotherapy, tacrolimus, corticosteroids, and beta-blockers.[16,17]

CONCLUSION

ALHE is an uncommon proliferative disorder of blood vessels which is often confused with KD. Clinical features can help direct suspicion to ALHE or KD, but definitive diagnosis relies on histopathological examination. The most important hallmark of ALHE is the presence of vascular proliferation with plump epithelioid endothelial cells. As opposed to Kimura's Disease, ALHE is not associated with systemic manifestations. Thus, correct diagnosis of this condition can help reassure the patient and direct the choice of treatment.

CONFLICT OF INTEREST

Authors declare that they do not have any conflicts of interest.

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