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CASE REPORT

Miguel Martorell · Ana Pérez-Vallés
Jose Angel García-García · Consuelo Calabuig
Luis Aguilella

Angiolymphoid hyperplasia with eosinophilia involving the cubital nerve

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Abstract A tumor involving cubital nerve was resected and studied; it was classified as an angiolymphoid hyperplasia with eosinophilia (ALHE). Immunohistochemical and molecular study was done both to confirm the reactive nature of the process and rule out the presence of clonal T or B cell rearrangement. This lesion has been designated as epitheloid hemangioma [Coindre (1994) Ann Pathol 14:426]. Typically, ALHE occurs in the skin and the subcutaneous tissue, and extracutaneous involvement is rare. No cases of ALHE affecting a nerve have been described, but a case of Kimura's disease, the lesions of which have repeatedly been confused with ALHE, has been reported involving median nerve.

Keywords Angiolymphoid hyperplasia with eosinophilia · Kimura's disease · Nerve

Introduction

Angiolymphoid hyperplasia with eosinophilia (ALHE) is an uncommon benign inflammatory vascular lesion of unknown etiology. Patients develop nodules in the skin and the subcutaneous tissue of the head and neck [11] with a predilection for the retroauricular area [30]. Lymphadenopathy and blood eosinophilia are uncommon [7]. The disease has a slight predominance in women, with a peak incidence in the third decade [12, 17]. ALHE share many clinical and histopathological features with Kimura's disease and these lesions had repeatedly been confused, but several reports indicate that significant differences exist and separate these entities. In this report we describe a case of ALHE affecting and entrapping the motor branch of the cubital nerve in a 34-year-old non-Oriental man presenting pain and paresthesias in his left hand. This case with such unusual location highlights the fact that clinicians, and also pathologists, should be aware of this entity.

M. Martorell (✉) · A. Pérez-Vallés · J. A. García-García
C. Calabuig
Department of Pathology, Hospital General Universitario,
Avda Tres Cruces s/n, 46014 Valencia, Spain
e-mail: miguel-martorell@uv.es

L. Aguilella
Department of Traumatholgy, Hospital de la Ribera,
Alcira, Valencia, Spain

Case report

A 34-year-old man, a right-handed, professional tailor and amateur guitar player, without pathological antecedents and no history of trauma, presented with a 1-year history of pain in the cubital side and paresthesias in the fourth and fifth finger of the left hand.

These symptoms had increased during the last month. Previous electrophysiological study had been normal. There was no external deformity. Palpation of the left cubital nerve at the Guyon's canal was extremely painful, with positive Tinel-Hofmann sign at this level. There was motor weakness but sensitivity was conserved. Magnetic resonance imaging showed a lesion involving the cubital nerve that was interpreted as a ganglion. A blood test was normal with no peripheral eosinophilia and no elevation in serum IgE level. HIV1 and 2, hepatitis profiles and Epstein-Barr virus serologies were negative. Axillar and cervical exploration revealed no enlarged lymph nodes. The patient underwent surgery with the finding of a firm fusiform tan brown tumor surrounding and entrapping the motor fascicles of the cubital nerve. The tumor was resected together with the motor branch of the cubital nerve and a sural nerve graft was done. The sensory branch was left intact. Surgical resection was followed by treatment with non-steroidal anti-inflammatory drugs.

Throughout the 2-year follow-up period, the patient's condition has been satisfactory, with good functional recuperation and no tumoral recurrences. He continues working and playing guitar.

Materials and methods

Tumor tissues obtained at surgery were fixed in 10% formalin and embedded in paraffin. Sections were stained with hematoxylin-eosin. Special stains for bacteria, fungi, and mycobacterium were done. Immunohistochemical analysis was performed on paraffin sections, with antibodies against CD20 (L26), CD3, CD43, CD45 (LCA), CD68, S100 protein, vimentin, CD31, CD34, cytokeratin (AE1-AE3), p53, bcl-2, cyclin D1 and Ki67. All the antibodies used were from Dako Corporation (Glostrup, Denmark). Molecular study to detect clonally rearranged T cell receptor (TCR) and

immunoglobulin heavy chain (IgH) genes was performed on genomic DNA isolated from paraffin sections by standard protocols [30]. Polymerase chain reaction (PCR) was done with consensus primers for the variable (V) and joining (J) regions of TCR-γ chain genes by mean of PCR fluorescent product analysis [24], by fast single-strand conformation polymorphism using an ALFexpress DNA sequencer (recommended operating procedure by Amersham Biosciences, Buckinghamshire, England) [31]. IgH gene rearrangement was done according to Diss et al. [10].

Results

Light microscopy

The tumor consisted of a vascular proliferation (Fig. 1) together with a lymphoid and eosinophilic infiltrate entrapping nerve fibers. Vessels showed prominent endothelial cells

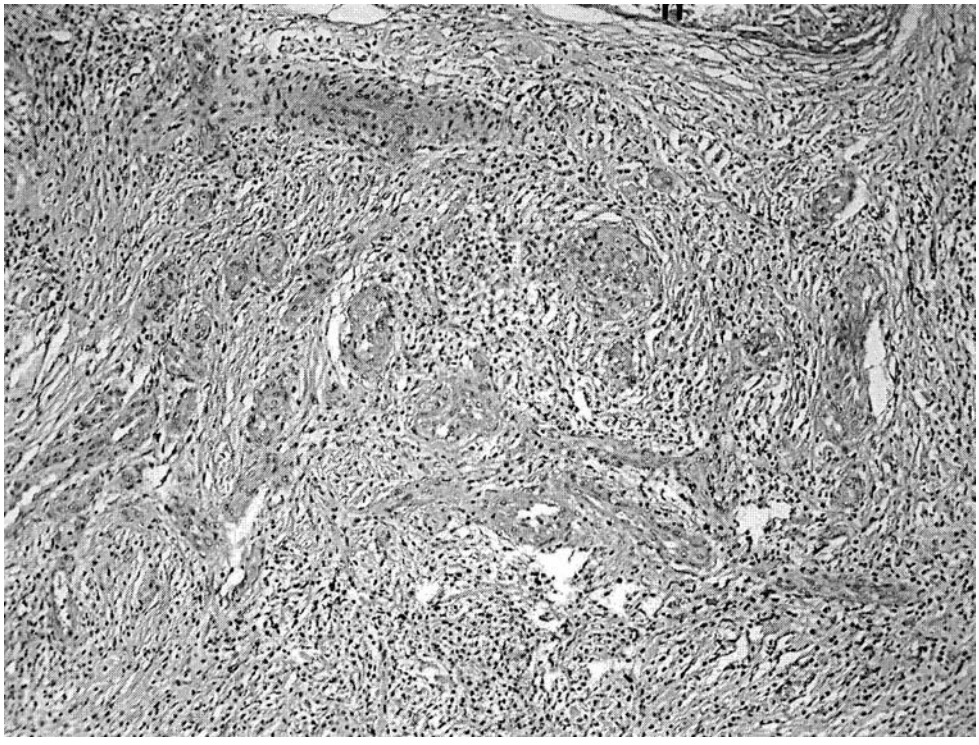

Fig. 1 Vascular proliferation surrounding nerve fibers (*n*). Hematoxylin and eosin (*HE*), ×100

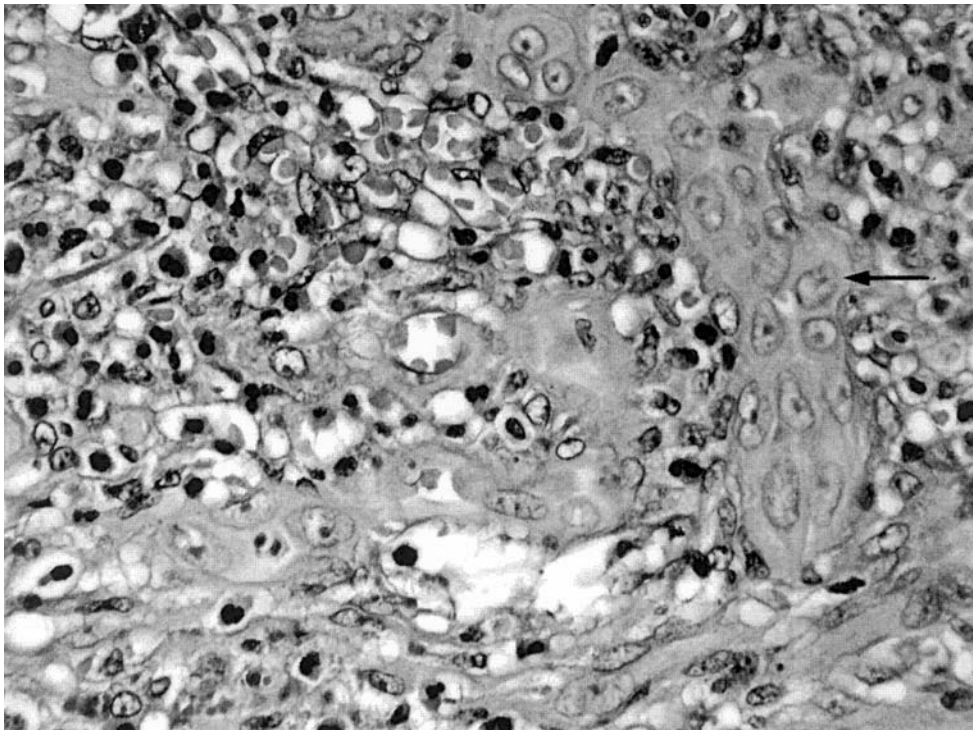

Fig. 2 Vessels with prominent endothelial cells (*arrow*). HE, ×200

Fig. 3 Lymphoid infiltrate surrounding nerve fibers (*n*). There are a lot of follicles (*f*) with prominent germinal centers. HE, ×100

(Fig. 2) often with plump or "hobnail" appearance, eosinophilic cytoplasm and round nuclei with granular chromatin. No mitosis or nuclear atypia was seen in the vascular component. The lymphoid infiltrate (Fig. 3) showed both a diffuse and nodular pattern, with formation of follicles with prominent germinal centers. There were also a lot of eosinophils and an infarction area with secondary ischemic necrosis. Surgical margins presented no lesions.

Immunohistochemistry

CD20 highlighted the follicle center B cells; CD3 and CD43 demonstrated numerous interfollicular T cells. Nerve fibers and reticular cells were positive for S-100 protein. CD34 and CD31 stained the vessels and also did vimentin. Endothelial cells were positive for p53. Positive staining with Ki67 was seen in follicle center B cells (>50%), but endothelial cells of proliferative vessels showed weak staining (<5%). Additional stains for bcl-2, cyclin D1, CD 68 and cytokeratin were negative. Stains for bacteria, fungi, and mycobacterium were negative.

Molecular study

No clonal rearrangement of IgH and TCR-γ genes was detected in the sample (Fig. 4).

Discussion

ALHE is a rare but distinctive vascular lesion that typically occurs in the skin and the subcutaneous tissue. Extracutaneous involvement is rare, but ALHE has also been described less frequently in other sites, including oral mucosa [25], tongue [28], parapharyngeal space [4], and breast [27], as well as in hand [16] and the upper extremities [3, 32], within skeletal muscle [5] or involving or arising from large vessels [26]. No cases of ALHE affecting a nerve have been described, but a case of Kimura's disease involving median nerve has been reported [23].

ALHE was originally described by Wells and Whimster in 1969 [34], and has been known with a lot of synonyms including Kimura's disease, first described in China in 1937 [20] and later by Kimura and coworkers in 1948 [21]. Since then, considerable confusion exists in the literature due to the usage of the two terms as synonyms. Rosai et al [29] were the first to distinguish the two entities as separate diseases, and this has been supported by subsequent authors [6, 19, 22, 33].

According to these reports, differential diagnosis between Kimura's disease and ALHE can be established clinically and histopathologically. Clinically, Kimura's disease is more common in Oriental young men, who present a tumoral-like nodule and lymphadenopathy. ALHE usually follows a benign indolent course and, in contrast to Kimura's disease, the presence of peripheral eosinophilia, elevated serum IgE levels and proteinuria are rare, although a nephrotic syndrome has been described associated to ALHE [2]. Recurrences are common.

Histopathologically the two diseases have common findings but they have also some differences. In Kimura's disease, there are well-formed lymphoid follicles and marked eosinophil infiltration, but epitheloid or histiocytoid endothelial changes are not as prominent as those observed in ALHE. ALHE is characterized by epitheloid endothelial cell changes, and the presence of lymphoid follicles is rare.

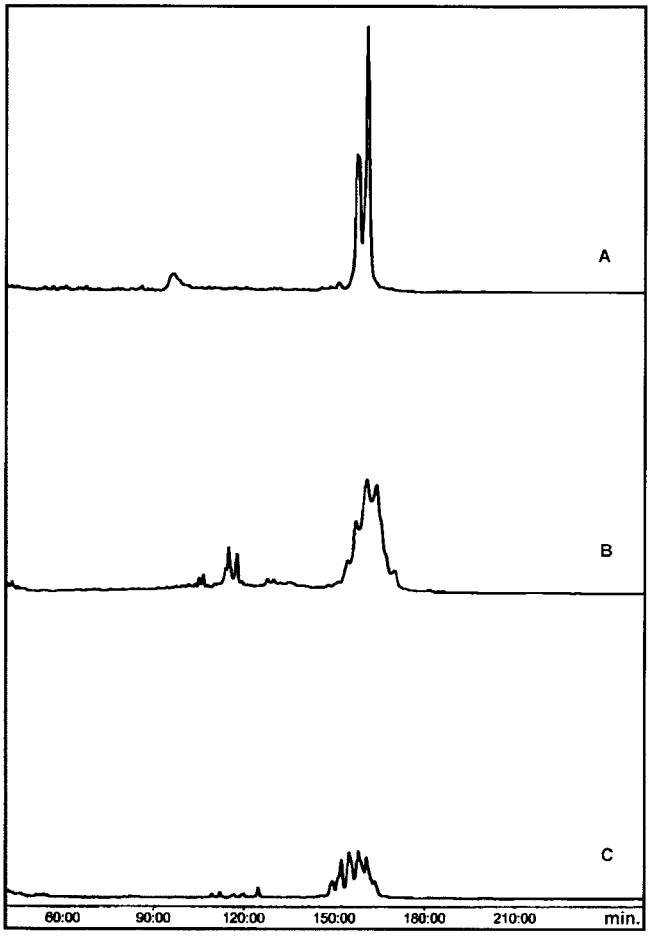

Fig. 4 Fast single-strand conformation polymorphism profiles from ALFwin Fragment Analyzer 1.00. **A** Jurkat cell line (monoclonal control). **B** Peripheral blood cells from a normal donor (polyclonal control). **C** Angiolymphoid hyperplasia with eosinophilia

There is of course a morphological spectrum among ALHE lesions. Cases of ALHE showing characteristics of Kimura's disease [8] or cases with intermingled features of these two entities [32] have been reported.

The cause and pathogenesis of ALHE is unclear, with the opinions varying between a benign vascular neoplasm [12, 29] to a reactive inflammatory lesion [1]. Some authors had proposed that ALHE involves immunological factors [13] and other reports propose a possible viral etiology, with involvement of HHV-8 in some cases of ALHE [14].

Complete surgical excision is considered to be the treatment of choice, although other therapeutic options have been probed with little success [11].

We consider this case to be ALHE because prominent endothelial cell changes were seen in the histological study. The question is to discriminate between a benign vascular tumor arising in the nerve or a reactive vascular proliferation involving nerve fibers. Immunohistochemically, the growing fraction of the endothelial cells determined using Ki67 is low (<5%). The occasional p53 positivity of the endothelial cells together with negativity for cell-cycle markers such as bcl-2 or cyclin D1 would support the argument in the literature that such tumors are non-neoplastic lesions [3, 15]. The present case showed a polyclonal immunostaining of the lymphoid infiltrate. The detection of clonally rearranged TCR by some authors [18] suggests that ALHE or a subset of ALHE cases may represent a T cell lymphoproliferative disorder of a benign or low-grade malignant nature. In the case reported, we failed to detect a clonal TCR rearrangement, a fact that supports the reactive nature of the process.

References

1. Akosa AB, Ali MH, Khoo CT, Evans DM (1990) Angiolymphoid hyperplasia with eosinophilia associated with tetanus toxoid vaccination. Histopathology 16:589–593
2. Altman DA, Griner JM, Lowe L (1995) Angiolymphoid hyperplasia with eosinophilia and nephrotic syndrome. Cutis 56:334–336
3. Arnold M, Geilen CC, Coupland SE, Krengel S, Dippel E, Sproder J, Goerdt S, Orfanos CE (1999) Unilateral angiolymphoid hyperplasia with eosinophilia involving the left arm and hand. J Cutan Pathol 26:436–440
4. Backhouse SS, Shone GR, Douglas-Jones AG (1998) Angiolymphoid hyperplasia with eosinophilia of the parapharyngeal space. J Laryngol Otol 112:802–804
5. Buchanan R, Sworn MJ, Mousley JM (1980) Angiolymphoid hyperplasia with eosinophilia involving skeletal muscle. Histopathology 42:197–204
6. Chan JK, Hui PK, Ng CS, Yuen NW, Kung IT, Gwi E (1989) Epitheloid haemangioma (angiolymphoid hyperplasia with eosinophilia) and Kimura's disease in Chinese. Histopathology 15:557–574
7. Chun S, Ji HG (1992) Kimura's disease and angiolymphoid hyperplasia with eosinophilia: clinical and histopathological differences. J Am Acad Dermatol 27:954–958
8. Chung TS, Kim DK, Yoon MS, Yang WI (2000) Angiolymphoid hyperplasia with eosinophilia showing characteristics of Kimura's disease. J Dermatol 27:27–30
9. Coindre JM (1994) Histologic classification of soft tissue tumors (WHO, 1994). Ann Pathol 14:426–427
10. Diss TC, Huaizheng P, Wotherspoon AC, Isaacson PG, Pan L (1993) Detection of monoclonality in low grade B-cell lymphoma using the polymerase chain reaction is dependent on primer selection and lymphoma type. J Pathol 169:291–295
11. Don DM, Ishiyama A, Johnstone AK, Fu YS, Abemayor E (1996) Angiolymphoid hyperplasia with eosinophilia and vascular tumors of the head and neck. Am J Otolaryngol 17:240–245
12. Enzinger FM, Weiss SW (1995) Angiolymphoid hyperplasia with eosinophilia. In: Enzinger FM, Weiss SW (eds) Soft tissue tumours, 3rd edn. Mosby, St. Louis, pp 593–598
13. Grimwood R, Swinehart JM, Aeling JL (1979) Angiolymphoid hyperplasia with eosinophilia. Arch Dermatol 115:205–207
14. Gyulai R, Kemeny L, Adam E, Nagy F, Dobozy A (1996) HHV8 DNA in angiolymphoid hyperplasia of the skin. Lancet 347:1837
15. Helander SD, Peters MS, Kuo TT, Su WP (1995) Kimura's disease and angiolymphoid hyperplasia with eosinophils: new observations from immunohistochemical studies of lymphocyte markers, endothelial antigens and granulocyte proteins. J Cutan Pathol 22:319–326
16. Imbing FD Jr, Viegas SF, Sanchez RL (1996) Multiple angiolymphoid hyperplasia with eosinophilia of the hand: report of a case and review of the literature. Cutis 58:345–348
17. Ingrams DR, Stafford ND, Creagh TM (1995) Angiolymphoid hyperplasia with eosinophilia. J Laryngol Otol 109:262–264

18. Kemps W, Haeffner AC, Zepter K, Sander CA, Flaig MJ, Mueller B, Panizzon RG, Hardmeier T, Adams V, Burg G (2002) Angiolymphoid hyperplasia with eosinophilia: evidence for a T-cell lymphoproliferative origin. Hum Pathol 33:1023–1029
19. Kim BH, Sithian N, Gucolo, GF (1975) Subcutaneous angiolymphoid hyperplasia (Kimura's disease). Report of a case. Arch Surg 110:1246–1248
20. Kim HT, Szeto C (1937) Eosinophilic hyperplastic lymphogranuloma, comparison with Mikulicz's disease. Chin Med J 23:699–700
21. Kimura T, Yoshimura S, Ishikaura E (1948) Unusual granulation combined with hyperplastic changes of lymphatic tissue. Trans Soc Pathol Jpn 37:179–180
22. Kuo TT, Shih LY, Chan HL (1988) Kimura's disease. Involvement of regional lymph nodes and distinction from angiolymphoid hyperplasia with eosinophilia. Am J Surg Pathol 12: 843–854
23. Lee YS, Ang HK, Ooi LLPJ (1995) Kimura's disease involving the median nerve: a case report. Ann Acad Med Singapore 24:462–464
24. Lukowsky A, Richter S, Dijkstal K, Sterry W, Muche M (2002) A T-cell receptor γ polymerase chain reaction assay using capillary electrophoresis for the diagnosis of cutaneous T-cell lymphomas. Diagn Mol Pathol 11:59–66
25. Mariatos G, Gorgoulis VG, Laskaris G, Kittas C (1999) Epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia) in the oral mucosa. A case report and review of the literature. Oral Oncol 35:435–438
26. Morton K, Robertson AJ, Hadden W (1987) Angiolymphoid hyperplasia with eosinophilia: report of a case arising from the radial artery. Histopathology 11:963–969
27. Nair M, Aron M, Sharma MC (2000) Angiolymphoid hyperplasia with eosinophilia (epitheloid hemangioma) of the breast: report of a case. Surg Today 30:747–749
28. Park Y, Chung J, Cho CG (2002) Angiolymphoid hyperplasia with eosinophilia of the tongue: report of a case and review of the literature. Oral Oncol 38:103–106
29. Rosai J, Gold J, Landy R (1979) The histiocytoid hemangiomas. A unifying concept embracing several previous described entities of skin, soft tissue, large vessels, bone and heart. Hum Pathol 10:707–730
30. Sambrook J, Fritsch EF, Maniatis T (1989) Molecular cloning: a laboratory manual, 2nd edn. Cold Spring Harbor Laboratory Press, Cold Spring Harbor
31. Signoretti S, Murphy M, Cangi MG, Puddu P, Kadin ME, Loda M (1999) Detection of clonal T-cell receptor γ gene rearrangements in paraffin-embedded tissue by polymerase chain reaction and nonradioactive single-strand conformational polymorphism analysis. Am J Pathol 154:67–75
32. Toth E, Orosz Z, Rahoty P (2000) Angiolymphoid hyperplasia with eosinophilia: report of a lesion mimicking soft tissue tumor of extremely long duration. Pathol Res Pract 196:99–101
33. Urabe A, Tsuneyoshi M, Enjoji M (1987) Epithelioid hemangioma versus Kimura's disease. A comparative clinicopathologic study. Am J Surg Pathol 11:758–766
34. Wells GC, Whimster IW (1969) Subcutaneous angiolymphoid hyperplasia with eosinophilia. Br J Dermatol 81:1–14