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Angiolymphoid hyperplasia with eosinophilia associated with arteriovenous malformation: a clinicopathological correlation with angiography and serial estimation of serum levels of renin, eosinophil cationic protein and interleukin 5

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Summary We present a case of angiolymphoid hyperplasia with eosinophilia (ALHE) affecting the auricular area of a 31-year-old man, which clinically mimicked arteriovenous malformation (AVM). The histology and laboratory data distinctively revealed ALHE, while angiography demonstrated typical findings of AVM. Although several reports have hitherto mentioned the relationship between ALHE and AVM, the aetiology of the disease remains unknown. During the 3 years treatment course, we performed angiography several times to assess the efficacy of the treatments and compared the clinical and pathological findings, based on the hypothesis that AVM might be a cause of ALHE. This study showed first, that the clinicopathological findings of ALHE correlated with the extent of AVM shown by angiography, so that AVM could be a primary cause of ALHE. Secondly, systemic corticosteroids and local irradiation therapy produced only a temporary effect on the inflammatory changes of ALHE; therefore, surgical resection is recommended as a curative treatment. Thirdly, the patient's serum levels of renin, eosinophil cationic protein and interleukin 5 corresponded closely with the clinical course of ALHE.

Key words: angiography, angiolymphoid hyperplasia with eosinophilia, arteriovenous malformation, eosinophilic cationic protein, interleukin 5, renin

Angiolymphoid hyperplasia with eosinophilia (ALHE) is a rare disorder which clinically manifests in young adults with solitary or multiple dermal nodules on the head and neck region. Histopathologically, it is characterized by vascular proliferation and inflammatory infiltrates. The vascular component consists of irregularly shaped aberrant vessels lined by swollen or vacuolated endothelial cells that protrude into the lumen, showing a 'hob-nailed' appearance. The inflammatory infiltrates are composed of eosinophils, lymphocytes and histiocytes. The aetiology of the disease is unknown, and it is still controversial as to whether it is a neoplasia or an inflammatory process.

Case report

A 31-year-old man had noticed a swelling of his left auricle in 1987, which had gradually increased in size and spread to the left temporal region to form reddish macules. He neglected the lesion until the lesion became itchy and bled easily after scratching. His first visit to us was in September 1992. No episode of trauma was known. He had a history of bronchial asthma. His family history was unremarkable.

The erythematous swelling on his left auricle was elastic and hard on palpation, with an irregular surface and local heat. Arterial pulsation was prominent over the entire lesion. Besides the auricular lesion, an elevated, reddish and papular lesion was seen on his temple (Fig. 1a). The left cervical and postauricular lymph nodes were swollen. He had mild pruritus over the whole body. Laboratory tests showed eosinophilia ($1{\cdot}00\times10^9$/L, 15% of white blood cells (WBC), normal: $0{\cdot}06–0{\cdot}8\times10^9$/L) and a high serum IgE level (612 U/mL, normal: < 350 U/mL). Digital subtraction angiography (Fig. 1b) demonstrated typical findings of arteriovenous malformation (AVM) with feeding arteries (arrow), nidus, early venous filling and late-phase pooling of contrast medium.

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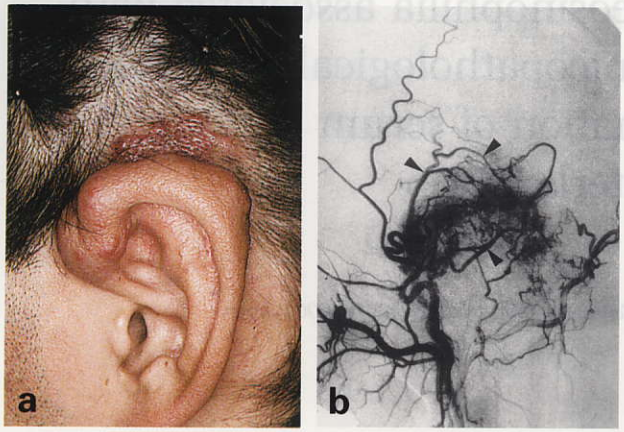

Figure 1. (a) An erythematous pulsatile swelling of the auricle is seen, with an elevated, reddish and papular lesion on the left temporal site. Angiography (b) showed abnormal vascular stains with feeding arteries (arrowed), compatible with arteriovenous malformation.

Histology showed irregularly shaped blood vessels proliferating mainly in the dermis (Fig. 2a), with an infiltrate of numerous eosinophils, lymphocytes and histiocytes in the dermal stroma. A high power view (Fig. 2b) revealed the aberrant vessels lined by plump endothelial cells, some of which protruded into the vascular lumen with cytoplasmic vacuoles. These immature endothelial cells were stained by factor VIII. No lymphoid follicle could be found throughout the histological specimen. Clinically and pathologically, we diagnosed this lesion as ALHE associated with AVM.

Initial treatment with irradiation (electron beam: 2 Gy daily to a total of 46 Gy) and oral prednisolone, 20 mg daily, reduced the lesion to half its initial size with clearance of the lymphadenopathy. The eosinophilia also improved ($0{\cdot}13\times10^9$/L, 1·9% WBC). However, 3 weeks after that, the swelling of the lesion and lymphadenopathy recurred together with an increase of peripheral eosinophils ($0{\cdot}54\times10^9$/L, 9·8% WBC). The local injection of triamcinolone acetonide, 20 mg over 2 weeks, merely produced a temporary remission. Angiography in 1994 (Fig. 3a,b) showed the persistent AVM. Finally, we resected the lesion with 1 cm of healthy margin at the periosteal level and covered the defect with a skin graft. In comparison with the first biopsy, the surgical specimen (Fig. 4a,b) showed less inflammatory infiltrate and more fibrotic changes, and a similar proliferation of abnormal blood vessels. Postoperatively, the peripheral eosinophil count and serum IgE level had decreased together.

In November 1995, 1½ years after surgery, a small prurigo-like nodule reappeared in the grafted skin on the postauricular region. It was purplish, firm, excoriated on the top, and 15×10 mm in size (Fig. 5a). Arterial pulsation was prominent in the nodule. The number of peripheral eosinophils rose again ($0{\cdot}43\times10^9$/L, 8·5% WBC). Angiography (Fig. 5b) showed the reappearance of a tiny AVM (see arrow). The histology of this nodule revealed the same findings as those of the primary lesion in 1993. We resected the recurrent lesion again including 3 cm of healthy

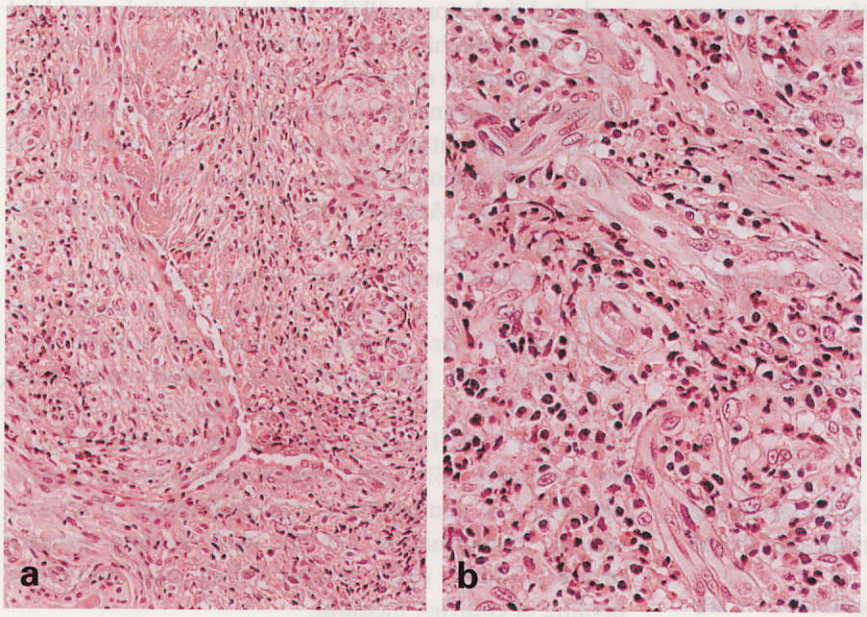

Figure 2. Biopsy specimen: Proliferation of irregularly shaped blood vessels in the dermis with numerous infiltrates of eosinophils, lymphocytes and histiocytes. High power view revealed the aberrant vessels lined by plump endothelial cells, some of which protruded into the vascular lumen showing hob-nailed appearance. [(a), haematoxylin and eosin, original magnification ×200. The proliferation of small abnormal vessels with oedematous endothelial cells were prominent. (b) haematoxylin and eosin, original magnification ×400].

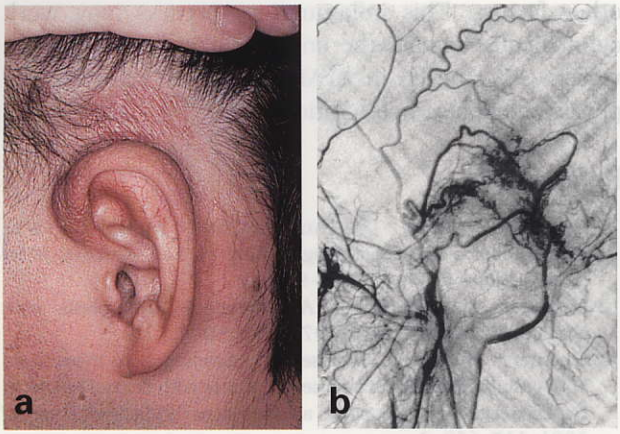

Figure 3. Although the size of the lesion had been reduced by irradiation and corticosteroid therapy (a), the persistent abnormal vascular stains were still found on angiography (b).

margin. The peripheral eosinophils decreased again to $0{\cdot}19 \times 10^9$/L, 4·8% WBC, after the second surgery, and he has been without recurrence since then.

The serum renin, eosinophil cationic protein (ECP) and interleukin (IL)-5 level were measured before and after the second surgery. Initially, all were higher than the physiological range (renin 37·3 pg/mL, normal:17·9–24·7, ECP 40·9 g/L, normal: < 15·7, IL-5 21·3 pg/mL, normal: < 8), but all decreased after the operation (renin 11·1 pg/mL, ECP 26·3 g/L, IL-5 < 15·6 pg/mL). There was no remarkable rise during the year after the second surgery (renin 11·3 pg/mL, ECP 22·6 g/L in April 1996, IL-5 < 5·0 pg/mL in December 1996).

Discussion

In 1985, Olsen and Helwig[1] found histological evidence of arteriovenous (AV) shunts in 42% of 116 cases of ALHE, and referred to the associated AVM as a possible cause of ALHE. Other authors also reported cases associated with arteritis,[2,3] thrombus[1–4] and AVM,[1,3–14] mentioning the causal relationship of arterial lesions to ALHE. Our patient also had AVM in combination with ALHE.

Simultaneous improvement of the clinical appearance, histology and laboratory tests was achieved after steroids and irradiation therapy. This result explains that those treatments were efficacious against the inflammatory reaction of ALHE. However, the remission was merely temporary. The failure of conservative treatment was due to the coexistence of the AVM. Generally speaking, curative treatment of ordinary AVM is accomplished by wide resection of the haemangioma together with ligation of the feeding and draining vessels. Consequently, treatment for ALHE associated with AVM is not satisfactory without radical surgery. Our experience suggests that insufficient treatment resulted in the reproliferation of the remaining vascular components of AVM. Moreover, the AVM and ALHE were synchronized in their recurrence. We believe that AVM promotes an inflammatory reaction of ALHE.

Fernandez *et al.*[14] discovered renin-containing cells histopathologically in his six cases of ALHE and suggested renin might be a pathogenic agent for ALHE, mentioning the association with AVM. Stimulation of

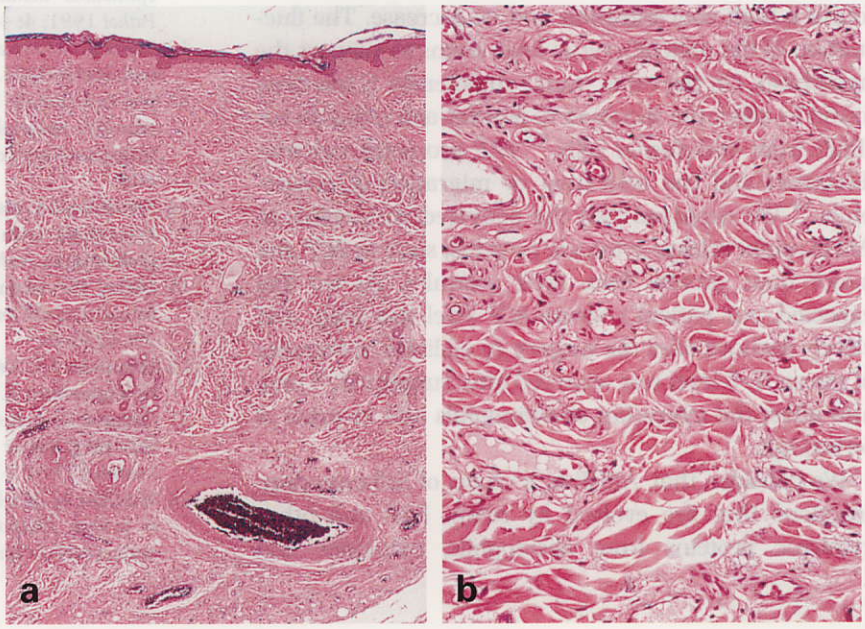

Figure 4. The histology of the resected specimen (a,b) revealed a decrease of inflammatory infiltrates, while the proliferation of small abnormal vessels were still noted [haematoxylin and eosin; (a), original magnification ×40; (b) original magnification ×200].

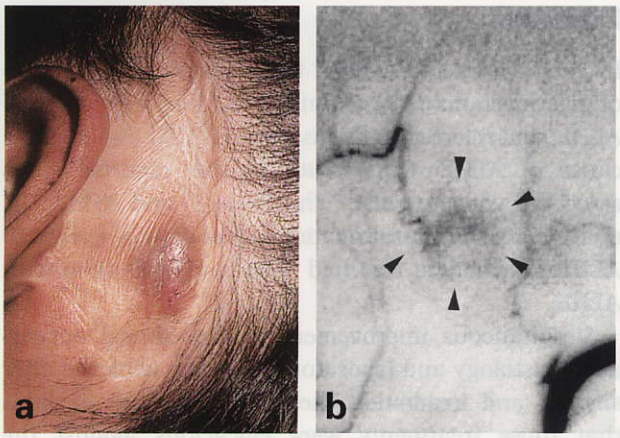

Figure 5. Recurrence at 1·5 years after the first excision. A prurigo-like nodule newly appeared in the grafted skin (a). Angiography (b) detected tiny abnormal vascular stains (arrowed) with a feeder in the arterial phase.

the renin–angiotensin cascade by renal ischaemia, or by the formation of a renal AV has been verified.[15] The capacity to synthesize renin has been found in many organs beside the kidney. They[14] considered that renin in ALHE might be induced by an associated AVM, similarly to the kidney. Angiotensin II, a product of renin, has been found to stimulate new vessel formation.[16] They[14] suggested that renin, through angiotensin II, contributes to the proliferation of endothelial cells in ALHE, and stimulates the evolution of a collateral circulation to compensate local ischaemia in AVM. Following these hypotheses, we measured our patient's serum renin level before and after the surgery, and found a high concentration and its decrease. The fluctuation of the patient's renin level seems to support the hypothesis. On the other hand, angiotensin II has been found to affect the secretion of platelet-activating factor (PAF) from endothelial cells.[17] PAF promotes vascular dilatation and the activation or migration of eosinophils.[18] We supposed that the activated eosinophils in ALHE might release cytotoxic proteins, such as ECP and major basic protein from their granules. As we had expected, our patient's serum ECP level was high, and clearly declined after the surgery. In addition, a decrease of serum IL-5 level was observed after surgery. IL-5 may also affect the migration of eosinophils and increase of serum IgE.

We consider that ALHE is a chain of inflammatory reactions that are evolved by renin, ECP and other cytotoxic proteins from eosinophils, cytokines and other factors. This inflammatory process may work cytotoxically against the endothelial cells of aberrant vessels (AV shunts) in AVM in order to reinstate the physiological blood circulation.

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