Observation of Angiolymphoid Hyperplasia with Eosinophilia (ALHE) at Three Arterial Sites and Its Association with Membranous Nephropathy

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Abstract

We herein report a case involving the systemic presentation of angiolymphoid hyperplasia with eosinophilia (ALHE) in association with membranous nephropathy (MN). A 34-year-old Japanese man presented with leg edema and bilateral temporal nodules. He had a history of Buerger’s disease and recurrent coronary stenosis. A renal biopsy performed to assess nephrotic syndrome revealed MN. Furthermore, a temporal nodule was excised, and ALHE was diagnosed. We reevaluated the coronary and posterior tibial artery specimens obtained in his twenties and presumed that these lesions were also vascular tumors arising from ALHE. The association of ALHE and MN is quite rare.

Key words: angiolymphoid hyperplasia with eosinophilia (ALHE), membranous nephropathy (MN), Kimura’s disease, type 2 helper T cells (Th2)

(DOI: 10.2169/internalmedicine.54.4031)

Introduction

Angiolymphoid hyperplasia with eosinophilia (ALHE) is a rare disease that presents as subcutaneous vascular nodules within the head and neck region (1). Although several hypotheses explaining the etiology of ALHE have been proposed, including vascular malformation, viral infection and certain reactive lesions, the exact etiology remains unknown (2-4). The histological features of ALHE include an increased number of small vessels exhibiting epithelioid endothelial cell proliferation with eosinophil and lymphocytic infiltration. The most important differential diagnosis is Kimura’s disease (Table 1, made by the authors based on references 2, 4-7). Although Kimura’s disease is often accompanied by membranous nephropathy (MN), this association is rare for ALHE (8-10). In this report, we describe a very rare case of ALHE in which the patient presented with three vascular lesions accompanied by MN.

Case Report

A 34-year-old Japanese man was admitted to our hospital for the treatment of nephrotic syndrome. He showed bilateral temporal painless and pulsatile nodules measuring approximately 5 mm in width and 25 mm in length (Fig. 1). A systemic itchy skin rash and severe leg edema were also observed.

Titanium bolts had been implanted in the patient’s left shoulder as a result of recurrent dislocation of the joint at 23 years of age. One year later, he was diagnosed as having Buerger’s disease with eosinophilia. At 25 years of age, he developed acute myocardial infarction (AMI), and an intracoronary stainless steel stent was placed. Because remarkable eosinophilic infiltration was observed in the endothelium of the affected coronary artery, the lesion was sus-
Table 1. Angiolympohydric Hyperplasia with Eosinophilia (ALHE) versus Kimura Disease.

<table>
<thead>
<tr>
<th></th>
<th>ALHE</th>
<th>Kimura disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), gender</td>
<td>20-50, F &gt; M</td>
<td>10-30, M &gt; F</td>
</tr>
<tr>
<td>Symptoms and signs</td>
<td>Painless superficial nodules</td>
<td>Tender soft tissue masses</td>
</tr>
<tr>
<td>Swelling of lymph nodes</td>
<td>Unknown</td>
<td>Characteristic</td>
</tr>
<tr>
<td>Vessel or lymphoid tissue involvement</td>
<td>Usually small vessels, but medium artery involvement, including temporal artery, is possible</td>
<td>Usually small vessels and lymph nodes, but can surround larger vessels in deep tissue</td>
</tr>
<tr>
<td>Systemic manifestations</td>
<td>Eosinophilia may be present</td>
<td>Eosinophilia and IgE elevation usually present; nephrotic syndrome may occur</td>
</tr>
<tr>
<td>Lymphoeosinophilic infiltration</td>
<td>not seen</td>
<td>Lymphoeosinophilic infiltration is remarkable; granulomas or giant cells</td>
</tr>
<tr>
<td>Proliferation of endothelial cells</td>
<td>Characteristic</td>
<td>Not characteristic</td>
</tr>
<tr>
<td>Epithelioid endothelial cells</td>
<td>Characteristic; endothelial changes include epithelioid morphology, hob nailing, and vacuolation</td>
<td>Not characteristic</td>
</tr>
<tr>
<td>Perivascular extension</td>
<td>Forming clusters of small vessels around arteries and veins</td>
<td>Forming perivascular lymphoid follicles</td>
</tr>
<tr>
<td>Coronary lesions</td>
<td>Previously unreported; in our case, the endothelium showed remarkable eosinophilic infiltration</td>
<td>Coronary spasm reported</td>
</tr>
<tr>
<td>Arteries of lower limbs</td>
<td>Previously unreported; in our case, stenosis of arteries of the limbs was present</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Figure 1. Left temporal nodule. The region is surrounded by an orange broken line.

pected to have arisen from vasculitic, rather than atherosclerotic, changes. At 26 years of age, he developed in-stent restenosis at the distal site of the #1 stent with remarkable systemic eosinophilia, and the titanium bolts in his left shoulder were removed due to a suspected metal allergy. At 27 years of age, intracoronary stents made of stainless steel were placed in positions #1 and #2 to treat recurrent AMI.

At 28 years of age, the patient began to receive oral prednisolone therapy (30 mg/day) based on his hypersensitive reaction to stainless steel. This diagnosis was made according to a positive skin patch test for a stainless steel stent. After the start of treatment with prednisolone, the eosinophil count decreased rapidly, and the dose of prednisolone was tapered off six months later. Soon after the withdrawal of steroids, restenosis occurred in #1 and #2, and an intracoronary stent was again placed at site #1. Coronary vasospasms were noted on coronary angiography. At 29 years of age, bypass surgery was performed due to complete obstruction of the right coronary artery. During the perioperative period, intestinal obstruction was detected on four occasions. No signs or history of asthma were observed.

On admission, the patient’s blood pressure was 134/77 mmHg, and his medications included diltiazem hydrochloride, isosorbide mononitrate, antiplatelet drugs and antihistaminic agents. He had smoked 30 cigarettes/day for four years and subsequently stopped smoking after receiving the diagnosis of Buerger’s disease. He had allergies to shellfish and house dust; however, there was no family history of allergic or kidney diseases.

Laboratory data showed nephrotic syndrome with hypereosinophilia and an elevated serum IgE level, with the following data (Table 2): white blood cell count (WBC) =8.2×10^3/μL (eosinophils: 23.0%); hemoglobin (Hb) =15.7 g/dL; platelet (Plt) count =27.6×10^4/μL; erythrocyte sedimentation rate =34 mm/1 hour; serum total protein =4.5 g/dL; albumin =1.7 g/dL; serum creatinine =1.03 mg/dL, blood urea nitrogen =15 mg/dL; uric acid =7.4 mg/dL; C-reactive protein =0.4 mg/dL; C3 =128 mg/dL; C4 =35 mg/dL; CH50 =54.6 U/mL; IgE =11,713 mg/dL; soluble interleukin 2 receptor...
Table 2. Laboratory Data on Admission.

<table>
<thead>
<tr>
<th>Complete blood count</th>
<th>Serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 8.2×10^3 /μL</td>
<td>C3 128 mg/dL</td>
</tr>
<tr>
<td>eosinophils 23.0 %</td>
<td>C4 35 mg/dL</td>
</tr>
<tr>
<td>Hb 15.7 g/dL</td>
<td>CH50 54.6 U/mL</td>
</tr>
<tr>
<td>Pt 27.6×10^9 /μL</td>
<td>IgG 423 mg/dL</td>
</tr>
<tr>
<td>ESR 34 mm/l hour</td>
<td>IgG4 16.0 mg/dL</td>
</tr>
<tr>
<td>T-bil 0.3 mg/dL</td>
<td>IgA 245 mg/dL</td>
</tr>
<tr>
<td>AST 33 IU/L</td>
<td>IgE-RIST 11,713 IU/mL</td>
</tr>
<tr>
<td>ALT 27 IU/L</td>
<td>RF &lt;20 IU/mL</td>
</tr>
<tr>
<td>ALP 367 IU/L</td>
<td>ANA (-)</td>
</tr>
<tr>
<td>LDH 186 IU/L</td>
<td>Anti-dsDNA Ab (-)</td>
</tr>
<tr>
<td>TP 4.5 g/dL</td>
<td>MPO-ANCA &lt;10 EU</td>
</tr>
<tr>
<td>Alb 1.7 g/dL</td>
<td>PR3-ANCA &lt;10 EU</td>
</tr>
<tr>
<td>BUN 15 mg/dL</td>
<td>Cryoglobulin (-)</td>
</tr>
<tr>
<td>Cr 1.03 mg/dL</td>
<td>sIL2-R 824 U/mL</td>
</tr>
<tr>
<td>cGFR 68.3 mL/min/1.73 m²</td>
<td>Protein 6.0 g/gCr</td>
</tr>
<tr>
<td>UA 7.4 mg/dL</td>
<td>NAG 22.0 IU/L</td>
</tr>
<tr>
<td>Na 140 mEq/L</td>
<td>β2-MG 208 µg/L</td>
</tr>
<tr>
<td>K 4.4 mEq/L</td>
<td>UA 11,713 µg/dL</td>
</tr>
<tr>
<td>Cl 107 mEq/L</td>
<td>RBC 5-9 /HPF</td>
</tr>
<tr>
<td>CRP 0.4 mg/dL</td>
<td>WBC 0-4 /HPF</td>
</tr>
</tbody>
</table>


(sIL-2R) =824 U/mL. No other markers of collagen disease, including antinuclear antibodies, anti-double-stranded DNA antibodies, antineutrophil cytoplasmic antibodies or cryoglobulin, were detected. A urinalysis showed a protein level of 6.0 g/gCr, with 5-9 red blood cells (RBCs)/high-power field, 1-5 granular casts per each whole field, an N-acetyl-β-D-glucosaminidase (NAG) level of 22.0 IU/L, and a β2-microglobulin level of 208 µg/L. An examination for parasite eggs was negative, as was a drug lymphocyte-stimulation test (DLST) for oral medicines taken by the patient on admission. The FIP1L1/PDGFRα fusion gene was not detected on the bone marrow biopsy, and gallium-67 scintigraphy showed integration in the left axillary lymph nodes.

A kidney biopsy was performed to histologically assess nephrotic syndrome. Twenty-six glomeruli were observed on light microscopy. No glomeruli exhibited global or segmental sclerosis, crescent formation or adhesion to Bowman’s capsule; however, segmental thickening of glomerular tufts was occasionally observed on light microscopy of periodic acid-Schiff (PAS)-stained sections (Fig. 2a). In contrast, spike formation was not found in periodic acid-methenamine-silver (PAM)-stained sections (Fig. 2b), and the vessels were unremarkable. Tubulointerstitial changes, including tubular atrophy, interstitial fibrosis and inflammatory cell infiltration, were minimal. The glomeruli showed granular 2+ capillary wall staining for IgG (Fig. 2c) and C3 (Fig. 2d) and ± capillary wall staining for IgA, IgM, C1q and fibrinogen. Additionally, immunofluorescence staining for IgG subclasses revealed granular 2+ capillary wall staining for IgG4 (Fig. 2e), while electron microscopy disclosed diffuse subepithelial electron-dense deposits (Fig. 2f). Based on these findings, the patient was diagnosed with Stage 1 MN. No eosinophil infiltration was present in the renal biopsy specimens.

According to a histological examination of an excised left temporal nodule, the main vascular lumen was severely narrowed and surrounded by characteristic neovascularization composed of hob-nailing and plump endothelial cells (Fig. 3a, b). A centroclinal endothelium and the proliferation of epithelioid endothelial cells with remarkable eosinophil infiltration were identified. Furthermore, the examination showed thickening of the wall in the left superficial temporal artery, a remarkable increase in the number of small blood vessels (Fig. 3c, d), significant eosinophil infiltration (Fig. 3e) and prominent proliferation of CD31+ cells (a marker of endothelial cells, Fig. 3f). These characteristic findings led to a diagnosis of ALHE.

A biopsy of the left axillary lymph node showed noteworthy eosinophil infiltration and accumulation with lymphocyte proliferation. Consequently, the tumors was diagnosed as a lesion of reactive lymphadenitis with eosinophilia.

Soon after the initiation of oral prednisolone therapy (40 mg/day), the eosinophilia disappeared and the serum IgE level subsequently decreased. Moreover, the urinary protein level decreased to less than 1 g/gCr within two weeks of the
start of prednisolone therapy, and the right temporal residual nodules totally disappeared by three months after the start of treatment.

Discussion

ALHE and Kimura’s disease are conditions that affect the head and neck regions and tend to recur despite treatment, sharing several histopathological features (Table 1) (2, 4–7). Nevertheless, the two diseases have important differences. For example, medium-size arteries, such as the temporal arteries, are involved in cases of ALHE, whereas only small vessels and lymph nodes are affected in Kimura’s disease. Although both ALHE and Kimura’s disease show remarkable tissue lymphoepithelial infiltration, the proliferation of endothelial cells, existence of epithelioid endothelial cells and proliferation of capillaries around vessels are characteristics of ALHE.

We hypothesized that the coronary artery stenosis and Buerger’s disease observed in the present case were caused

Figure 2. Histological findings of the kidneys (a-f). a: Light microscopy of a sample obtained from a renal biopsy [periodic acid-Schiff (PAS) staining, ×400]. Segmental thickening of glomerular tufts was occasionally observed. b: Light microscopy of a sample obtained from a renal biopsy [periodic acid-methenamine-silver (PAM) staining, ×400]. No spike formation was detected in the stained section. c: Immunofluorescence staining for IgG showed glomerular granular 2+ capillary wall staining. d: Immunofluorescence staining for C3 showed glomerular granular 2+ capillary wall staining. e: Immunofluorescence staining for IgG4 showed glomerular granular 2+ capillary wall staining. f: Diffuse subepithelial electron-dense deposits were observed on electron microscopy.
by ALHE and thus reexamined the histology of the involved
vessels in samples obtained in the patient’s youth. These
vessels were preserved at Japanese Red Cross Kyoto Daini
Hospital. Consequently, endothelial proliferation with re-
m Markable neovascularization in the adventitia with promi-
nent proliferation of CD34+ cells (endothelial cells); how-
ever, eosinophil infiltration was not remarkable in this tis-
sue. The similarities of the histological changes in these ar-
teries suggest that Buerger’s disease and the recurring steno-
sis of the coronary arteries may also have been vascular dis-
orders associated with ALHE. To our knowledge, this is the
first case in which vessel involvement in the setting of
ALHE has been shown to include the superficial as well as
systemic deep vessels.

In this case, the patient’s systemic symptoms developed
after the implantation of metals, including titanium bolts and
stainless steel stents, in his youth. However, the causal rela-
tionship between the use of metallic implants and ALHE is
unknown. We investigated the existence of metals, such as
nickel, chromium and iron, within the subepithelial electron-
dense deposits using electron microscopy of the kidneys, al-
though no such metals were detected (data not shown). Fur-
thermore, we did not find any case reports showing that
stainless steel stents can cause MN and ALHE or that MN
may occur accompanied by a systemic metal allergy.

To our knowledge, only two cases of ALHE affecting the
temporal artery accompanied by renal disease have been re-
ported to date; the present case is the third such case (Ta-
ble 3) (7, 10, 11).

The pathogenesis of ALHE with nephrotic syndrome is
not fully understood. In patients with ALHE, the upregu-
lated expression of IL-4, IL-5 and IL-13 mRNA (12-15) as

Figure 3. Histological findings of the left temporal nodule (a-f). a, b: Narrowing of the vascular lu-
men (black arrow) and new small blood vessels with the proliferation of so-called hob-nailing and
plump endothelial cells (black arrowhead). c, d: Thickening of the vascular wall (star) and narrowing
of the lumen of the temporal artery (black arrow). A remarkable increase in the number of small
blood vessels was noted (black broken arrow). e: Infiltration of eosinophils in the arterial wall (aster-
isk). f: Proliferation of CD31+ cells in the arterial wall (brown lines and dots, white arrows). [a, Hema-
toxylin and Eosin (H&E) staining, original magnification: ×40; b, d and e, H&E staining, original
magnification: ×100; c, H&E staining, original magnification: ×20; f, CD31 staining, original magnifi-
cation: ×40].
The predominant immune response may be the underlying pathogenesis involving three arterial sites in association with MN. A Th2-induced by activating B cells (19). IgE synthesis associated with the pathogenesis of MN in—

increased the production of IL-5 and IL-4. IL-5 then in-

mannous nephropathy, NS: nephrotic syndrome, Common findings: common pathological findings in respective cases (such as the proliferation of capillaries around vessels and epithelioid endothelial cells with eosinophilic infiltration, remarkable thickened intima, the obstruction of vessels, and the lack of the disruption of the internal elastic lamina)

well as marked proliferation of activated CD4+ T cells in the peripheral blood, lymph nodes and skin lesions have been reported (16-19). Therefore, the immune response mediated by type 2 helper T cells (Th2) is likely involved in the pathogenesis of ALHE. On the other hand, the involvement of predominant Th2 immune responses in the development of MN has been widely reported (20). Hence, the predominant Th2 immune response in the current patient may connect MN with ALHE. We hypothesize that the metallic implants triggered the activation of Th2, which subsequently increased the production of IL-5 and IL-4. IL-5 then induced the differentiation, proliferation, chemotaxis and activation of eosinophils, which was related to the pathogenesis of ALHE, while IL-4 was responsible for the induction of IgE synthesis associated with the pathogenesis of MN induced by activating B cells (19).

In summary, we herein presented a rare case of ALHE involving three arterial sites in association with MN. A Th2-predominant immune response may be the underlying patho-

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

We thank Ms. Toshie Fujiwara for providing expert secretarial assistance.

References


Table 3. ALHE Including Lesions of Temporal Arteries (TA) and Renal Complications.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (y), Gender, Presenting Symptoms</th>
<th>Laboratory data, Complication</th>
<th>TA Pathology</th>
<th>Treatment, Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>44, M, pulsating, painless, in right temporal region</td>
<td>NS (low-grade mesangial proliferative glomerulonephritis)</td>
<td>Common findings, periarterial lymphoid follicles, eosinophilic abscesses</td>
<td>Steroid, remission and recurrence of NS</td>
</tr>
<tr>
<td>11</td>
<td>48, F, bitemporal region</td>
<td>Eosinophilia, MN</td>
<td>Common findings, Focal disappearance of endothelial cells</td>
<td>Steroid</td>
</tr>
<tr>
<td>Our case</td>
<td>34, M, pulsating, painless, bitemporal region</td>
<td>Eosinophilia, IgE elevation, MN</td>
<td>Common findings</td>
<td>Steroid, Remission of NS and disappearance of the TA lesions</td>
</tr>
</tbody>
</table>


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