—Case Reports—

Cutaneous Vasculitis in Cogan's Syndrome: A Report of Two Cases Associated with Chlamydia Infection

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Cogan's syndrome (CS) is defined by the combination of hearing loss, vertigo, and ocular inflammation of uncertain cause, and can be associated with variable vessel vasculitis. Vasculitic manifestations may include arteritis (affecting large, medium or small arteries), aortitis, and aortic and mitral valvulitis. Cutaneous manifestations including erythema, papules, subcutaneous nodules, and purpura sometimes occur; however, to date, only six cases have been histologically confirmed to have genuine vasculitis. Here, we report two cases of CS, one of which involved a patient who developed the typical symptoms of Takayasu arteritis and purpuric lesions in the legs, with histologic findings consistent with small vessel vaculitis in the dermis. The second case involved a patient who developed subcutaneous nodules in the legs and the axilla, and histologic findings revealed a necrotizing vasculitis of the small arteries in the interlobular area. Both cases were successfully treated with systemic steroid therapy. Based on the clinical features and the examination data, there is a possibility that a *Chlamydia trachomatis* infection played a pivotal role in the pathogenesis of those vasculitides. (J Nippon Med Sch 2018; 85: 172–177)

Key words: Cogan's syndrome, small vessel vasculitis, cutaneous polyarteritis nodosa, *Chlamydia trachomatis*, heat shock protein

Introduction

Cogan's syndrome (CS) is a systemic inflammatory disease of unknown origin that presents with a combination of inner ear disease, including sensorineural hearing loss and vestibular dysfunction, and inflammatory ocular lesions, including interstitial keratitis, uveitis, and episcleritis[1]. CS is associated with various types of vasculitis in 13–27% of patients[2–4], including arteritis (affecting large, medium or small arteries), aortitis, aortic aneurysms, and aortic and mitral valvulitis[2–4]. The aorta and its branches are affected in approximately 10% of patients with CS[2]. CS with vasculitic lesions in the aorta and its branches can resemble the symptoms of Takayasu arteritis[5]. Conversely, medium vessel vasculitis, such as polyarteritis nodosa (PAN)[6–10], and small vessel vasculitis[8,11–13] were much less commonly reported because it is highly likely that the autopsies carried out in those cases failed to reveal them.

Various skin manifestations, including urticaria, erythema, purpura, papules, vesicles, pustules, abscesses, and subcutaneous nodules have been reported in 6-19% of CS cases[2–4,10]. However, to date, cutaneous vasculitis has been histologically confirmed in only six cases reported in the English literature, including four cases of systemic PAN[7–10,13] and two cases of small vessel vasculitis[11,13].

Here we describe two cases of CS with cutaneous vasculitis, one with small vessel vasculitis and the other with small vessel arteritis mimicking cutaneous PAN. On the basis of the clinical features and high antibody titers of *Chlamydia trachomatis* (*C. trachomatis*), we discuss the relationship between heat shock proteins (Hsps), produced following chronic Chlamydia infection and the development of vasculitis.

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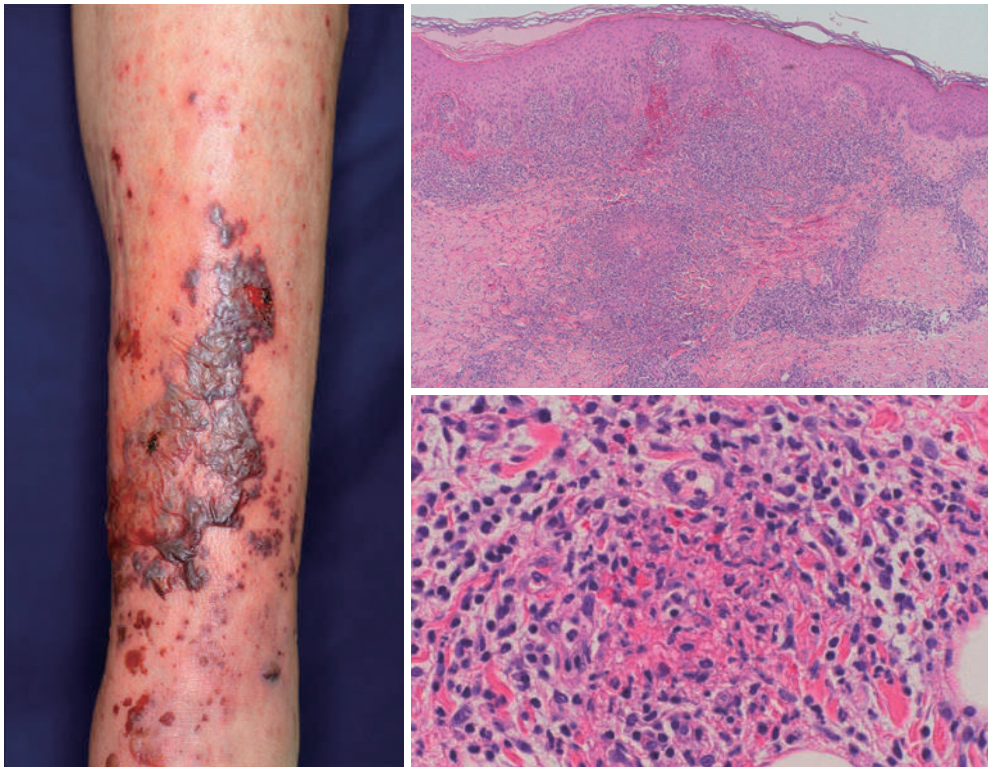

Fig. 1 Skin manifestations and histopathological findings in case 1
(a): The skin manifestations included edematous erythema, purpura, papules, bloody vesicles/bullae, and erosions of various sizes on the lower legs.
(b): Histopathological findings of a purpuric skin lesion indicated perivascular neutrophilic and lymphocytic infiltration in the whole dermis (magnification, ×4; hematoxylin and eosin staining).
(c): Leukocytoclastic vasculitis of small vessels was observed in the middle and deep dermis (magnification, ×20; hematoxylin and eosin staining).

Case Reports

Case 1

A 44-year-old woman developed pain in multiple joints, fever, shortness of breath, right cervical pain, and generalized fatigue. A number of irregularly-shaped purpura, 5 mm in diameter, in addition to edematous erythema and papules, developed in a scattered distribution in both lower legs over the course of 1 week. Within 2 weeks, the patient was admitted to our hospital for possible Takayasu arteritis, based on physical examination findings including a diastolic murmur at the cardiac base, and systolic bruits over both subclavicular areas. During the first examination, brachial blood pressures were 80/50 and 96/57 mmHg in the left and right arms, respectively, and her pulse rate was 64 beats/min. No abnormal physical findings were noted in the abdomen or joints. However, bloody blisters of various sizes gradually appeared on the lower legs due to self-scratching (**Fig. 1a**).

A skin biopsy of a purpuric lesion with bloody blisters was performed. Histopathological examination indicated perivascular infiltration by a large number of neutrophilic and lymphocytic cells in the full-thickness of the dermis, and evidence of leukocytoclastic vasculitis in the small vessels of the middle and deep dermis (**Fig. 1b-c**).

The patient had no family history of or significant risk factors (e.g. old age, smoking, hypertension, hyperlipidemia) for cardiovascular disease. She had a history of tinnitus, vertigo, and the acute onset of bilateral sensorineural hearing loss 2 years previously. She had also experienced recurrent redness of the eyes despite being treated with a topical steroid 1 year prior.

The laboratory test results were as follows: white blood cell count, 15,810/mm^3 (neutrophil count, 14,230/mm^3); hemoglobin level, 10.7 g / dL ; platelet count, 443,000/mm^3; erythrocyte sedimentation rate, >120 mm/h; C-reactive protein (CRP) level, 22.69 mg/dL (normal < 0.3 mg/dL); partial thromboplastin time (PTT), 14.7 s (normal <13.0); prothrombin time-international normalized ratio (PT-INR), 1.29 (0.90−1.13); and D-dimer level,

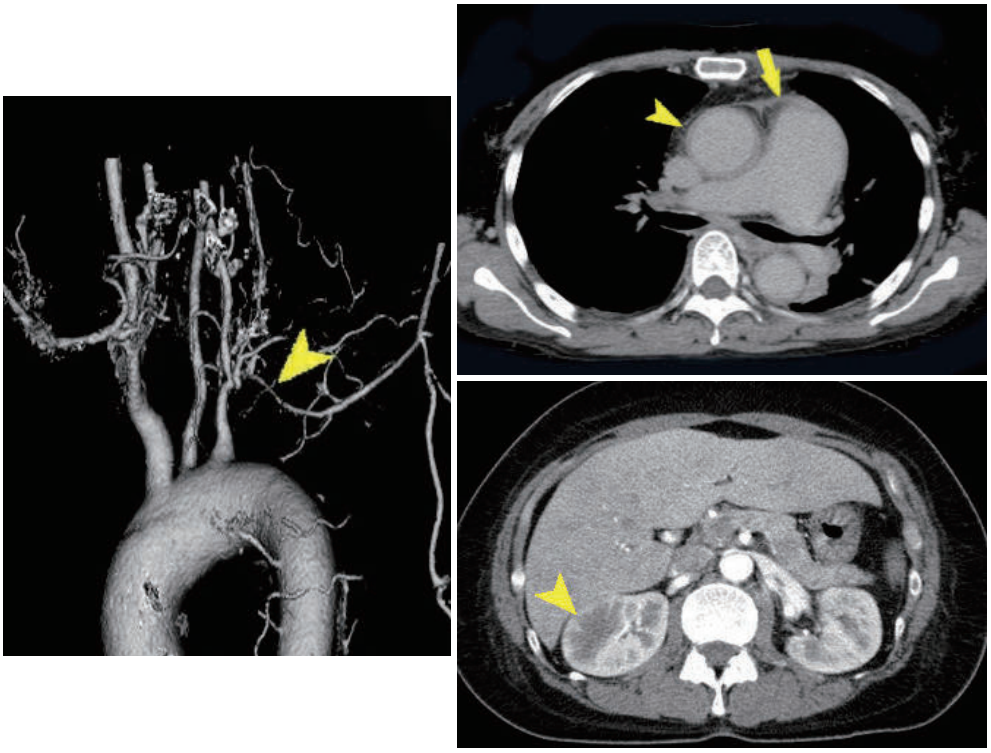

Fig. 2 Imaging studies in case 1
(a): A three-dimensional computed tomography angiogram showed left subclavian artery stenosis (**arrowhead**).
(b): A computed tomography scan showed thickened walls of the thoracic ascending aortic artery (**arrowhead**) and pulmonary artery (**arrow**).
(c): Computed tomography revealed hepatomegaly and infarction of the right kidney (**arrowhead**).

4.2 mcg/mL (normal <1.0). Immunological tests were negative for the rheumatoid factor, anti-nuclear antibody (ANA) using immunofluorescence, and anti-neutrophil cytoplasmic antibody (ANCA). Serologic immunoglobulin (Ig) titers, IgA, and IgG antibodies were 4.45 and 7.97, respectively, for *C. trachomatis* using an enzyme-linked immunosorbent assay (ELISA), normal <0.9. The serologic test result for syphilis was negative. Histocompatibility testing indicated positive results for HLA-B52 and HLA-DR B1*15, which have been proven to be associated with Takayasu arteritis and a variety of other autoimmune diseases[14,15].

A three-dimensional computed tomography (CT) angiogram showed left subclavian artery stenosis (**Fig. 2a**), thickened thoracic aortic walls, and renal artery stenosis. Furthermore, the CT scan showed evidence of thickened walls of the thoracic ascending aorta and pulmonary artery (**Fig. 2b**), splenomegaly, hepatomegaly, and infarctions of both kidneys (**Fig. 2c**). Pure-tone audiometry, performed 2 years before admission, indicated a 20-dB and 20-40-dB loss in the left and right ears, respectively.

Atypical CS was diagnosed on the basis of the definition introduced by Haynes[15], and we considered that CS was accompanied by Takayasu arteritis as well as small vessel vasculitis in the skin. The patient was treated with prednisolone (0.5 mg/kg/day) for 7 weeks, after which her inflammatory indices, systemic joint pain, abnormal blood pressure, and skin manifestations had normalized.

Case 2

A 27-year-old woman developed acute onset headache, transient systemic musculoskeletal and joint pain, high fever, eye redness, and pain in her right hypochondrium. She received cephem antibiotics intravenously for 29 days after admission. The fever and pain in her right hypochondrium improved slightly, but remained persistent. Subsequently, she was treated with minocycline hydrochloride (200 mg/day) intravenously based on a diagnosis of *C.trachomatis*-induced perihepatitis, as indicated by the clinical features and positive serological tests for *C. trachomatis*. The pain in her right hypochondrium and fever improved within 24 hours of the initiation of the treatment. Minocycline hydrochloride was continued for

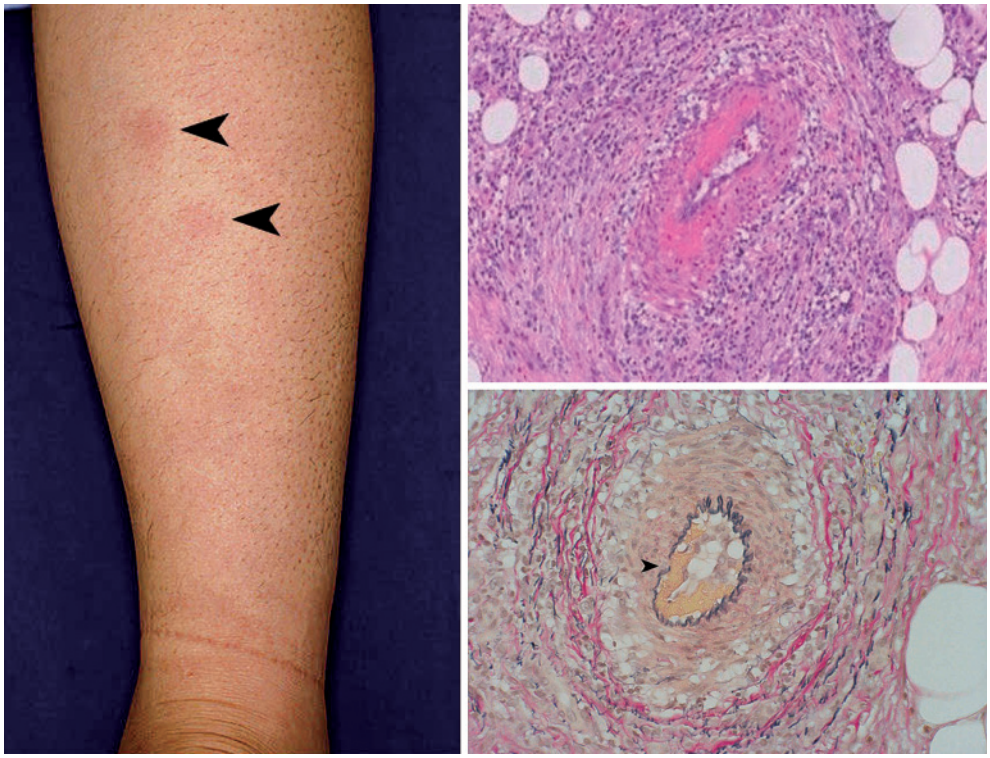

Fig. 3 Skin manifestations and histopathological findings in case 2
(a): Salmon-pink, painful subcutaneous nodules (diameter, 2 cm) (**arrowheads**) were seen on the ventral side of the right lower leg.
(b): Histological findings indicated fibrinoid necrotizing vasculitis of a small artery in the interlobular area (magnification, ×20; hematoxylin and eosin staining).

an additional 10 days. However, after 3.5 weeks, she rapidly developed progressive hearing loss and tinnitus, as well as several salmon-pink, tender subcutaneous nodules located in her right axilla and on her right lower leg (**Fig. 3a**).

Histological results of a subcutaneous nodule biopsy of her right lower leg indicated necrotizing vasculitis of a small artery in the interlobular area (**Fig. 3b**).

The laboratory test results were as follows: red blood cell count, $4.16\times10^6/mm^3$; white blood cell count, $10{,}450/mm^3$ (neutrophil count, $9{,}300/mm^3$); platelet count, $402{,}000/mm^3$; CRP level, 18.64 mg/dL; glutamic-oxaloacetic transaminase, 132 IU/L; glutamic-pyruvic transaminase, 102 IU/L; PTT, 14.1 s; PT-INR, 1.30; D-dimer level, 2.2 mcg/mL. The serologic test result for syphilis was negative. However, the IgG and IgA antibody titers for *C. trachomatis* were 3.52 and 0.9, respectively. Immunological test results, including ANA and ANCA, were negative.

A systemic CT scan showed no apparent arterial stenosis or vascular disease in other organs. On the basis of the aforementioned findings, we diagnosed the patient with atypical CS, and we considered that the CS was accompanied by cutaneous PAN-like small arteritis.

Prednisolone (1.2 mg/kg/day) was administered because of progressive bilateral sensorineural hearing loss and an increased CRP level. The dose was tapered down to 0.2 mg/kg/day after 2 weeks. The bilateral sensorineural hearing loss eventually resolved, and the subcutaneous nodules completely disappeared. Subsequently, she was transferred to another hospital for further treatment.

Discussion

The two patients described herein were diagnosed with atypical CS according to the definition introduced by Haynes[15], and the CS was accompanied by different types of vasculitis over the disease course. In case 1, the imaging analysis of the subclavian and pulmonary arteries showed that the CS had developed into Takayasu arteritis, and the histological examination of a purpuric skin lesion in the lower leg showed leukocytoclastic vasculitis of small vessels in the dermis. In case 2, the histology of a subcutaneous nodule in the lower leg showed necrotizing vasculitis of a small artery in the interlobular area. A detailed analysis revealed no abnormalities in the inter-

nal organs, which confirmed cutaneous PAN-like small arteritis.

Various skin lesions, including urticaria, erythema, purpura, papules, vesicles, pustules, abscesses, and subcutaneous nodules have been reported in 6-19% cases of CS[2–4,10]. However, cutaneous vasculitis has been confirmed in only six cases to our knowledge to date, partly because definite findings of vasculitis could not always be detected in the histology. Skin biopsies were not performed in the majority of the cases, and the diagnosis of vasculitis in the previous reports was made based on clinical grounds alone, although histology is essential for the correct understanding of the vasculitis of CS. Thus, our two cases deserve thorough examination.

It is significant that the laboratory results revealed elevated IgG and/or IgA antibody titers of *C. trachomatis* in both patients'sera, and minocycline hydrochloride substantially improved the perihepatitis, which was probably caused by *C. trachomatis* in case 2. Haynes et al[15] found that among their 13 patients with CS, 9 and 4 patients had significant titers of serum IgG and IgM antibodies to *C. trachomatis*, respectively. Hammer et al[16] also reported very high titers of serum IgA as well as IgG antibodies to *C. trachomatis*. Furthermore, a large number of additional cases of CS with high titers of IgG, IgM, or IgA antibodies to *Chlamydia* species have been reported[11,17–20] although some cases did not show any evidence of Chlamydia infection[5–9,12]. Thus Chlamydia infection has been considered to be a possible cause of CS, in addition to many other causative diseases including autoimmune arthritis, systemic lupus erythematosus, Takayasu arteritis, Still's disease, multiple sclerosis, atherosclerosis, vasculitis, diabetes mellitus, and thyroiditis[20–23].

The details of causative immunological mechanisms have been introduced in conjunction with persistent Chlamydia infection and Hsps as described; Hsps are highly conserved proteins present in practically all prokaryotic and eukaryotic organisms. Owing to the high amino acid and structural homology of Hsps among different species, microbial Hsps secreted in the process of infection can be an obvious target for an immune response[21,24,25]. Capello et al[21] has suggested that *C. trachomatis* Hsp 60 (Ct-Hsp 60) is synthesized during *C. trachomatis* infection and is released into the blood stream. Consequently, immune cells will produce anti-Ct-Hsp 60 antibodies that recognize the Hsps antigens on the surface of stressed cells (endothelium, myocardiocytes, Beta-cells, and other tissue cells), which can ultimately result in cell lysis and organ destruction[21,26,27]. Likewise, immune complexes composed of anti-Ct-Hsp 60 antibodies and Ct-Hsp 60 antigens may form deposits in anatomical locations like the glomerular basal membrane, which causes glomerulonephritis[21]. Besides these humoral immune responses, Ct-Hsp 60 derived antigens may promote a Hsp 60 specific T-cell response, followed by tissue destruction, through cytotoxic reactions[24,28,29].

Recently, Bonaguri[30] has reported that serum anti-human Hsp 70 (anti-hHsp 70) antibody is significantly high in 92.9% of patients with typical CS and its titer can be a serological marker for diagnosing CS. Anti-hHsp 70 antibody is likely to erroneously recognize Ct-Hsp 60 derived antigens because of the structural mimicry between hHsp 70 and Ct-Hsp 60[21,31]. This finding would indicate that there is some correlation in the pathogenesis of CS and Ct-Hsps.

We hypothesize that a coordinated interaction between Chlamydia infection and Hsps contributes to the pathogenesis of CS, especially with respect to the development of the vascular symptoms of CS. In the present cases, the humoral and cytotoxic reactions may have been involved in the development of small vessel vasculitis and small arteritis in the skin, respectively, although further confirmation is needed.

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Conflict of Interest: The authors declare no conflict of interest.

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