

### Spontaneous remission of giant cell arteritis: possible association with a preceding acute respiratory infection and seropositivity to *Chlamydia pneumoniae* antibodies

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#### ABSTRACT

Recent epidemiological or immunopathological studies demonstrate the possible association between giant cell arteritis and infectious agents including *Chlamydia pneumoniae*. A 62-year-old Japanese man with type 1 diabetes mellitus developed biopsy-proven giant cell arteritis after acute upper respiratory infection. Serological examination indicated concurrent re-infection with *C. pneumoniae*. Clinical manifestations of the vasculitis subsided within a month without any immunosuppressive therapy, and no relapse was observed for the following 12 months. The natural history of this disease is unclear and spontaneous remission is rarely reported. The self-limiting nature of the infection could contribute to this phenomenon.

Keywords: giant cell arteritis, *Chlamydia pneumoniae*, spontaneous remission

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#### INTRODUCTION

Temporal arteritis or giant cell arteritis (GCA), is a systemic vasculitis that affects medium- or large-sized arteries. Some advances have been made regarding the understanding of the pathogenesis of vasculitis in recent years; vascular dendritic cells play a critical role by monitoring the tissue environment for danger signals such as infectious agents or products of tissue degeneration.<sup>1</sup> Although there is no direct evidence, many observations suggest a link between infections and the development of vasculitis.<sup>2</sup> Consequently, an International Chapel Hill Consensus Conference held in 2012 added the new category, “vasculitis-associated with probable cause” including vasculitis associated with infectious agents such as hepatitis B virus, hepatitis C virus, or syphilis.<sup>3</sup> However, the pathogenesis of the condition, especially the trigger of the onset, is unclear. Additionally, since virtually all patients are treated with corticosteroids, the natural history of the vasculitis is unclear.<sup>4</sup>

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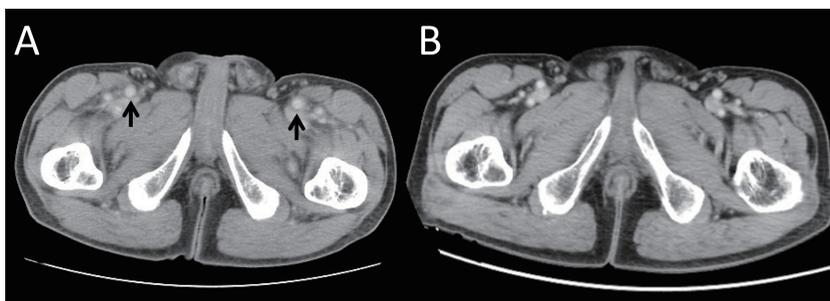
We, herein, present a case of GCA with spontaneous remission. An antecedent upper respiratory infection and elevated antibodies against *Chlamydia pneumoniae* during the acute phase of the vasculitis suggested that *C. pneumoniae* re-infection contributed to the development and spontaneous remission of the vasculitis.

## CASE PRESENTATION

A 62-year-old man with a medical history of type 1 diabetes mellitus requiring insulin therapy, with a last recorded hemoglobin A1c level of 8.3%, was admitted with fever for 7 days. Four months before admission, painful erythematous papules developed on the left side of his face and he was diagnosed with a herpes zoster infection involving the mandibular division of the trigeminal nerve. The patient was treated with antiviral therapy, leading to the rapid improvement of the skin lesion. Of note, he had presented to the outpatient department 3 weeks prior to the admission, with a few days of high-grade fever and accompanying malaise, nasal congestion, mild sore throat, and pruritic rash over the truncus, all of which resolved within 5 days. After the first episode of fever, there was a 1-week defervescence period. Subsequently, he developed fever again, leading to hospitalization for further evaluation. He experienced a body weight loss of 6 kg (10% of the body weight) during the 3 weeks. Headache, jaw or arm claudication, and visual symptoms were absent.

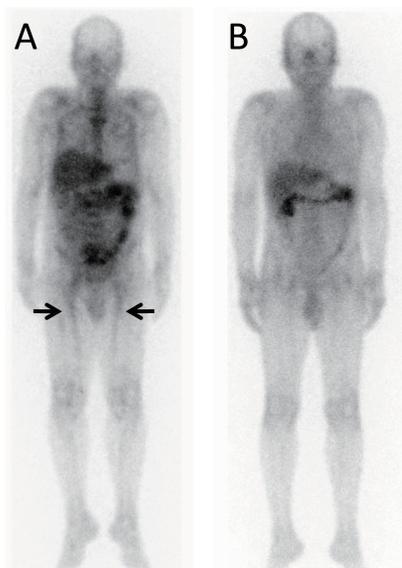
On admission, the patient was relatively well with a blood pressure of 122/70 mmHg, temperature of 38.3°C, and pulse of 97 beats per minute. Physical examination revealed normal findings on oral, cardiovascular, lung, and abdominal examination. Digital cyanosis, ulceration, or peripheral adenopathy were absent. The bilateral temporal arteries were easily palpable and non-tender. On ophthalmic examination, there were no signs of ischemic optic neuropathy. Chest radiography demonstrated no remarkable findings. A laboratory test showed the following: normal results on liver and kidney function; hemoglobin level, 10.2 g/dL; white blood cell, 8720/ $\mu$ L with neutrophil predominance; platelet count,  $44.5 \times 10^9$ /L; erythrocyte sedimentation rate (ESR), 71 mm/hour; C-reactive protein, 13.5 mg/dL; and glucose level, 447 mg/dL. His hemoglobin A1c level had worsened to 10.3% from the previous measurement. Immunological examination showed normal complement levels and negativity for rheumatoid factor, antinuclear antibody, PR3-ANCA, MPO-ANCA, and cryoglobulin. Immunoglobulin (Ig) G, A, M, and E levels were 922 mg/dL, 594 mg/dL, 44 mg/dL, and 396 IU/mL, respectively. Serum IgG4 level was 85 mg/dL (reference 4–108 mg/dL). Urine analysis results were within normal limits except for a strongly positive glucosuria. The procalcitonin level was 0.15 ng/mL, and two sets each of blood and urine culture were negative. Contrast-enhanced computed tomography showed arterial wall thickening and elevated density of the surrounding tissue in the bilateral femoral arteries and arteries in the abdominal wall (Fig. 1). Despite these findings, a definite diagnosis could not be made in the first week of admission.

By day 10 of admission, the origin of the persistent fever could still not be determined. At the time, the patient experienced myalgia in the legs. Pressure pain was noted along the bilateral cervical, femoral, and popliteal arteries. In addition, we also recognized tenderness located longitudinally from the epigastric region to the umbilical region, which was possibly the tenderness of the abdominal aorta. Otherwise, morning stiffness and pain in the neck, torso, hand, and shoulders were absent. Subsequently, a gallium scan showed an abnormal accumulation in the bilateral femoral arteries (Fig. 2), and a temporal artery biopsy revealed the infiltration of inflammatory cells in the arterial wall (Fig. 3). Giant cells were not detected in the specimen. The old-age onset, elevated ESR without another cause, and positive temporal artery biopsy met



**Fig. 1 Vascular inflammation on computed tomography**

(A) Contrast-enhanced computed tomography on the second hospital day demonstrating the thickening of the bilateral femoral arteries and their branches. (B) These findings disappeared after the spontaneous remission of the vasculitis. The imaging was obtained on day 14.



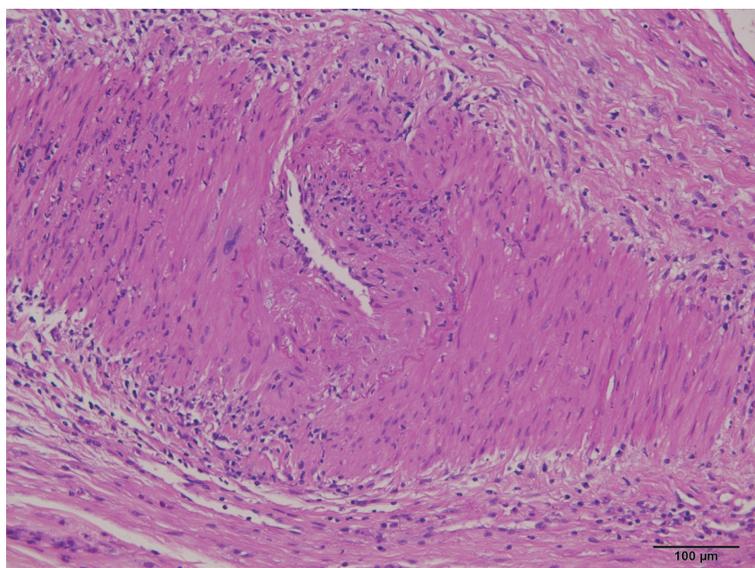
**Fig. 2 Vascular inflammation on Gallium scintigraphy**

(A) Gallium scintigraphy, which was performed on day 9, showing increased uptake in the bilateral femoral arteries in the acute phase of GCA. (B) These findings disappeared in the follow-up study after 14 months of admission.

GCA, giant cell arteritis

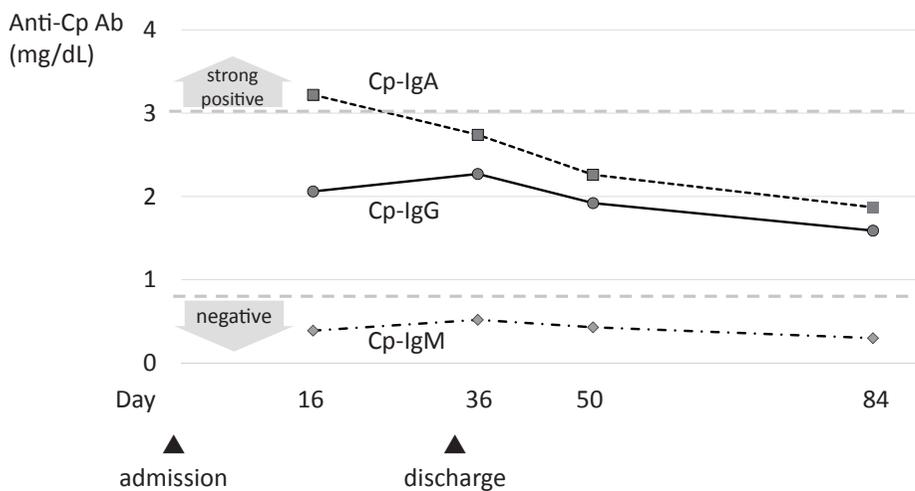
the American College of Rheumatology (ACR) criteria for GCA. In addition to the pathological evidence of vasculitis, there were no clinical symptoms or findings which suggested other large-vessel vasculitis. Consequently, we made the clinical diagnosis of GCA.

Since the patient had an antecedent acute respiratory infection, we investigated infectious agents as the precipitants of the vasculitis; serological tests for human immunodeficiency virus, hepatitis B virus, hepatitis C virus, and syphilis were negative. IgM antibody tests for parvovirus B19, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, and varicella zoster virus (VZV) were also all negative. A serological test for *Mycoplasma pneumoniae* was not performed. The



**Fig. 3 Pathological findings of the temporal artery biopsy specimen**

Inflammatory cells infiltrated the muscular layer of the artery. Giant cells were not detected.



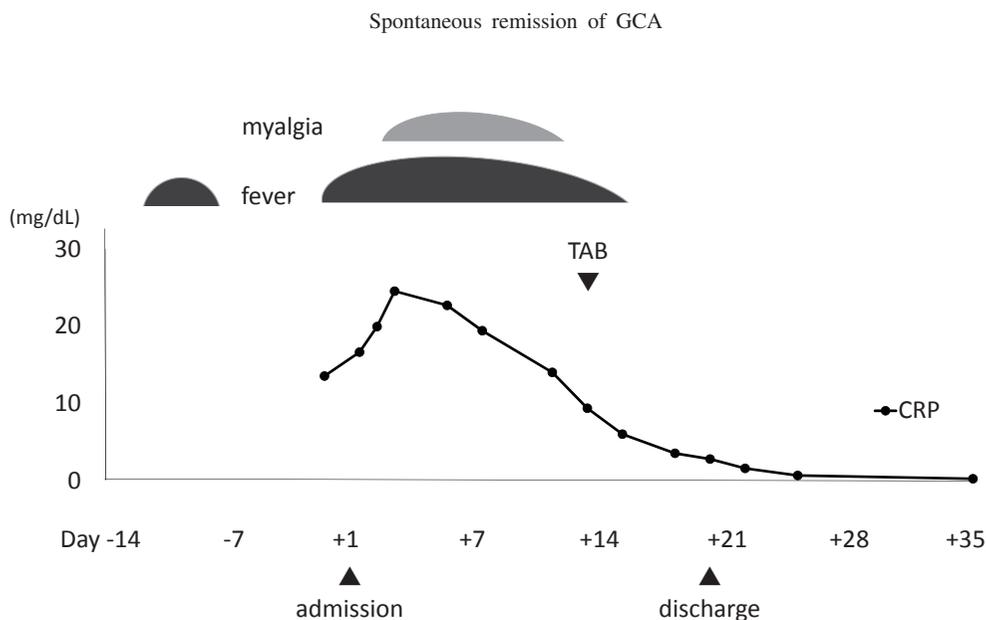
**Fig. 4 Longitudinal change of the serological tests**

Antibodies against *Chlamydia pneumoniae* during follow-up are indicated.

Anti-Cp Ab: Anti-*Chlamydia pneumoniae* antibody, Cp: *Chlamydia pneumoniae*

only significant finding was increased IgG and IgA levels for *C. pneumoniae* without increased IgM, suggesting a current re-infection with the microorganism. These antibodies continuously declined during follow-up (Fig. 4).

C-reactive protein level peaked on day 4 of admission and there were apparent signs of the spontaneous resolution of the systemic symptoms and fever (Fig. 5). Erythrocyte sedimentation



**Fig. 5 Clinical course**

The development of vasculitis was preceded by several days of fever accompanied by nasal congestion, mild sore throat, and pruritic rash. The patient subsequently achieved remission from biopsy-proven GCA without any immunosuppressive or antimicrobial therapy.

CRP: C-reactive protein, TAB: temporal artery biopsy

rate (ESR) reached a maximum on day 14. Given these findings, it seemed reasonable to monitor without therapy pending any worsening of the symptoms or signs of vasculitis. Thereafter, the symptoms gradually resolved without any immunosuppressive therapy or antimicrobials; the fever was absent and the myalgia and tenderness along the arteries diminished by the third week of admission. He was subsequently discharged without any residual symptoms.

In the subsequent follow-up visit as an outpatient, C-reactive protein level and ESR had normalized after 5 weeks and 4 months from admission, respectively. One year after admission, the patient still maintained a complete remission of the vasculitis.

## DISCUSSION

This was a case of GCA with a clinical course of spontaneous remission, in which acute respiratory infection with *C. pneumoniae* could have contributed to the development of vasculitis.

Various infectious agents have been proposed as potential triggers of GCA.<sup>5</sup> An epidemiological study showed that a marked increase of newly diagnosed GCA was observed when *C. pneumoniae* had become endemic in a certain area in Denmark.<sup>6</sup> Other studies also showed the relationship between the risk for GCA onset and the number of infections.<sup>7,8</sup> Thus, there is increasing evidence suggesting the involvement of infectious agents in the pathogenesis of GCA.

*C. pneumoniae* is a major pathogen causing upper and lower respiratory infections that are often mild and self-limiting. It is also an important microorganism investigated as a trigger of GCA.<sup>9</sup> The development of GCA possibly induced by *C. pneumoniae* was first described in 1997: a 54-year-old woman suddenly developed GCA following a 1-day history of respiratory symptoms accompanied with serological evidence of *C. pneumoniae* infection.<sup>10</sup> In addition to these case reports, Wagner et al reported that *C. pneumoniae* was detected in temporal artery

biopsy specimens via immunohistochemical staining or PCR in 8 of 9 GCA patients.<sup>11</sup> Moreover, this study demonstrated the distribution of the microorganism in the infiltrating dendritic cells of the arterial wall, strongly suggesting its etiological role.

Molecular mimicry and the common pathway of the activation of Toll-like receptors (TLRs) are the potential mechanisms through which chlamydial infection induces vascular inflammation in GCA patients. *C. pneumoniae* is known to be associated with the development of various autoimmune diseases and molecular mimicry is the putative mechanism.<sup>12,13</sup> However, no cross-reactivity between *C. pneumoniae* and the human arterial component have been reported in the past. Conversely, there is a common pathway of the immune responses between vasculitis and chlamydial infection, that is, the activation of particular kinds of TLRs. TLRs are regarded as receptors which perform pattern recognition of the molecules that are contained by exogenous or endogenous antigens and do not require the shared epitope. The receptors, especially TLR 2 and 4, induce the recruitment of monocytes and the induction of inflammation of the arterial wall and play an important role in the pathogenesis of vascular inflammation in GCA patients.<sup>14</sup> TLR 2 and 4 are also reported to play vital roles in the recognition of *C. pneumoniae*.<sup>15-17</sup> Furthermore, the previous study indicated that the administration of some TLR ligands could induce a marked increase of mature dendritic cells and vascular inflammation.<sup>18</sup> Despite the lack of direct evidence that the shared epitope is present between the microorganism and arterial component or that *C. pneumoniae* induces the activation of TLRs in GCA patients, it is possible that chlamydial infection induces vasculitis in patients with predisposing factors.

The changes in the anti-*C. pneumoniae* antibody titer in the current case could be interpreted in different ways. First, it could reflect a preceding infection. Since the first measurement of the antibody titer was 1 month after the infection episode, the level could have declined during the recovery phase. This agrees with the findings in previous studies, that infection episodes could trigger the development of vasculitis. Second, arterial inflammation could have given rise to immune responses against *C. pneumoniae* that resided in the arterial wall. This hypothesis is consistent with the findings that *C. pneumoniae* infection persists in the artery and leads to atherosclerosis or ischemic heart disease. When vascular inflammation develops, the antigenicity of the microorganism is induced, resulting in the activation of the immune reactions against *Chlamydia*. Third, the infection may not have been involved in the development of the vasculitis. We could not confirm experimentally that *C. pneumoniae* induced the arterial inflammation. We also measured IgG and IgA antibodies against *Chlamydia trachomatis* at the same time as a control, and these levels were within normal limits. This suggests that systematic inflammatory reactions with high IgA levels were less likely to influence specific antibodies levels.

Since immunosuppressive therapy is initiated immediately after the diagnosis of GCA as recommended in current guidelines,<sup>19,20</sup> the natural history of the vasculitis is not well known. In 1932, Horton et al reported the pathologic features and clinical manifestations of two patients with GCA as a new clinical entity, where they documented the clinical course with an acute inflammatory phase and subsequent spontaneous remission.<sup>21</sup> In another earlier report demonstrating the efficacy of corticosteroid in GCA, the authors referred to the natural course of the disease as follows: "temporal arteritis, with the exception of ocular manifestations, is a self-limited and benign condition."<sup>22</sup> However, in the period after the introduction of corticosteroid therapy, only a few cases of biopsy-proven GCA with spontaneous remission were described. Nevertheless, in one study reporting the spontaneous remission of GCA, only partial remission had been observed in some cases, or normalization of the inflammatory markers was not described in other patients.<sup>23</sup> Another study reported spontaneous remission and no relapse for 10 years in a male patient that presented with acute phase GCA for several months.<sup>24</sup> Thus, spontaneous remission is rare in GCA.

The spontaneous remission of an autoimmune disease might depend on its pathogenesis; the virus or bacteria that causes acute infection could trigger immunological abnormalities; thereafter, autoimmune responses would be modified after eliminating the inciting microorganisms, resulting in spontaneous remission of the autoimmune disease in a few cases. Recently, the association of VZV infection with the development of vasculitis in the central nervous system, known as VZV vasculopathy, or GCA was reported in some studies.<sup>25,26</sup> These patients are typically treated with antiviral therapy for 2 weeks and corticosteroid for several days, after which patients usually achieve complete remission.<sup>25</sup> In addition to the inciting cause, genetic factors and age-related defects in the regulatory control of immune responses appear to have a major pathogenic function, and a diversity of such factors might work in the resolution of the inflammation.<sup>27,28</sup> Furthermore, a case study demonstrated that antibiotic therapy against chlamydial infection led to improvement of GCA.<sup>29</sup> Regarding the regulation of autoimmune reaction triggered by chlamydial infection, the case report suggests the importance of reducing the microorganism's burden or the rapid resolution of the initial immune responses of the host. Moreover, during the acute phase of chlamydial infection, the suppressive activity of regulatory T cell is decreased; thereafter, the activity recovers as the initial inflammation abates.<sup>30</sup> In a small proportion of patients, the recovery of regulatory T-cell activity might result in the suppression of the aberrant immune reaction in the arterial wall via unknown mechanisms.

## CONCLUSION

This report described the development of GCA that could be associated with a preceding episode of acute respiratory infection, possibly due to *C. pneumoniae*. The limitation of this report is that the evidence of infection was based only on serological tests. Spontaneous remission without immunosuppressive therapy was documented. Since some GCA patients are intolerant to immunosuppressive therapy or have an extremely high risk of opportunistic infections, our observation raises questions regarding the strategy in current guidelines that recommend the immediate initiation of high-dose corticosteroids and prolonged therapy in all patients with suspected GCA.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest in association with the present study.

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