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Case Report

Common carotid arteritis and polymyalgia with *Mycoplasma pneumoniae* infection☆

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ABSTRACT

A few pediatric cases with brain vasculitis most frequently affecting the middle cerebral artery have been reported in association with *Mycoplasma pneumoniae* infection, but involvement of the common carotid artery (CCA) before the bifurcation has not been reported to date. We report herein a case of 10-year-old boy with common carotid arteritis and polymyalgia associated with *Mycoplasma pneumoniae* infection. His fever and cough began 2 weeks before, and his right upper and lower extremity pains began 2 days before admission. He had initially been treated with clarithromycin followed by tosufloxacin, but his symptoms persisted. His *M. pneumonia*–specific antibody titer was high on admission (1:10240 by particle agglutination method) and the gene of *M. pneumoniae* was detected in a throat swab specimen by the loop-mediated isothermal amplification method with initial high levels of serum interleukin-8, tumor necrosis factor-α, and interleukin-18 along with elevated blood levels of complements. On the 5th day of hospitalization, vascular echograms of the extremities and neck showed increasing intima-media thickness of bilateral CCAs without stenosis and/or thrombosis and T2-weighted with lipid suppression magnetic resonance imaging of the neck showed high signal intensity of bilateral CCA walls. Coagulation studies were unremarkable and no autoantibodies were detected as far as tested. He was successfully treated by intravenous administration of prednisolone and was stable without any neurological sequelae 17 months after the onset without medication. His particle agglutination titer decreased to 1:5120, and serum interleukin-8, tumor necrosis factor-α, interleukin-18, and complement levels returned to normal.

1. Introduction

Despite the fact that brain vascular occlusive disease and arteritis are very rare in children, not a few such cases have been reported in association with *Mycoplasma (M.) pneumoniae* infection [1–4]. The middle cerebral artery is the most frequently affected, followed by the internal carotid artery. However, to the best of our knowledge, involvement of the common carotid artery before the bifurcation has not been reported. Here we report a case of common carotid arteritis that occurred in a 10-year-old boy. Vasculitis caused by complement activation as a result of cytokine production such as interleukin (IL)-8 [5], IL-18 [6], and tumor necrosis factor (TNF)-α [7] in association with *M. pneumoniae* infection can be considered the pathogenesis [1,2].

2. Case report

A 10-year-old boy was transferred from another hospital with fever, cough, and walking disability due to right upper and lower extremity pains in May 2016. His past history was unremarkable, and his growth and development were normal. His fever and cough began 2 weeks before, and the pains began 2 days before admission to our hospital. He had been treated with clarithromycin for 3 days followed by tosufloxacin for 10 days by a general physician, but his symptoms persisted. His younger brother had been diagnosed with *M. pneumoniae* pneumonia 16 days earlier and successfully treated by clarithromycin for 7 days with an uneventful course.

Abbreviations: CCA, common carotid artery; IL, interleukin; TNF, tumor necrosis factor; FDP, fibrinogen degradation products; MRI, magnetic resonance imaging.

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On admission, he appeared ill, with a temperature of 39.5 °C, pulse rate of 100 beats/min, blood pressure of 102/69 mmHg, and a respiratory rate of 20 beats/min. Physical examination was unremarkable except for the spontaneous pains of the right upper and lower extremities without redness or swelling of any joint. No abnormal neurological findings were present. His pulse was palpable on bilateral radial arteries. Admission laboratory data showed a white blood cell count of 12,600 cells/μL (neutrophils 73%, lymphocytes 18%), hemoglobin 12.7 g/dL, and a platelet count of 45.6×10^4/μL. C-reactive protein was 17.4 mg/dL. Hypertransaminasemia was not seen (ALT 19 U/L, AST 18 U/L) and blood levels of creatine phosphokinase (37 U/L) and aldolase (5.7 IU/L) were within normal range. The blood level of immunoglobulin G was 1682 mg/dL, with increased complement levels (CH_{50} > 60.0 U/mL, C3 188 mg/dL, C4 40 mg/dL). Prothrombin time was 67.5% of a reference, activated partial thrombin time was 70.4% of a reference, and fibrinogen degradation products (FDP)-D-dimer was 2.4 μg/mL (reference <1.0 μg/mL). Chest X-ray showed a slight infiltration in the right lower lung field. Ultrasound examination of the heart and abdomen was unremarkable.

The following data were obtained later in the course. His *M. pneumoniae* antibody titer by the particle agglutination method was very high (1:10,240, reference <1:40) on the 2nd day of hospitalization, and the gene of *M. pneumoniae* was detected in a throat swab specimen by the loop-mediated isothermal amplification method (Loopamp Mycoplasma P Detection kit, Eiken Chemical, Tokyo, Japan) on the 3rd day of hospitalization. Routine bacterial cultures including blood culture yielded no pathogenic bacteria and viral cultures could not be performed. There was no recognizable epidemic of a certain viral disease at that time. Serum antibodies for *Yersinia pseudotuberculosis* and *Orientia tsutsugamushi* were negative. Blood PCR results for *Rickettsia japonica* and *Coxiella burnetti* were negative, and a blood EB virus load measured by quantitative PCR was the same level when compared with those from antibody-positive healthy children. Autoantibodies including anti-nuclear antibody, rheumatoid factor, *anti*-citrullinated peptide antibody, anti-phospholipid (cardiolipin) antibody, and anti-neutrophil cytoplasmic antibody were negative. Immune complexes were undetectable. Elevated serum levels of IL-8 (38.8 pg/mL, reference <2.0 pg/mL, R & D Systems, Minneapolis, MN, USA), TNF-α (7.7 pg/mL, reference <1.8 pg/mL, R & D Systems), and IL-18 (408.2 pg/mL, reference <260.0 pg/mL, MBL, Nagoya, Japan) were detected by the commercial ELISA kits mentioned above on the 4th day of hospitalization.

The patient was started on intravenous administration of minocycline (4 mg/kg/day) at admission on a tentative diagnosis of *M. pneumoniae* infection because his younger brother had suffered from *M. pneumoniae* pneumonia. The patient's hospital course was complicated by a continuous fever and extremity pains accompanied later by bilateral neck pains. On the 5th day of hospitalization, vascular echograms of the extremities and neck which were performed as part of thorough investigations for fever origin and cause of pains showed increasing intima-media thickness of bilateral common carotid arteries (CCAs) without stenosis and/or thrombosis (maximum IMT: right CCA 1.7 mm and left CCA 1.4 mm, reference <1.1 mm), and T2-weighted with lipid suppression magnetic resonance imaging (MRI) of the neck performed on the same day showed high signal intensity of bilateral CCA walls (Fig. 1A, B). Intravenous administration of prednisolone (1 mg/kg/day) was given instead of minocycline. His fever and extremity pains drastically subsided the next day without recurrence. The patient was discharged home after 1.5 months with marked improvement in his symptoms, when the particle agglutination titer was 1:5120 and the gene of *M. pneumoniae* was no more detected in a throat swab specimen. Based on the microbiological results, laboratory data, and both echogram and MRI findings, he was diagnosed as having bilateral common carotid arteritis with probable vasculitis of the right upper and lower extremities due to *M. pneumoniae* infection, and overall treatment including tapering and cessation of steroid was completed in 2 months (Fig. 2).

Follow-up neck echogram and evaluation of serum cytokines performed 6 months after the onset revealed normalization of the intima-media thickness in the CCA and normal levels of IL-8, TNF-α, and IL-18. He was stable 17 months after the onset with no medication, which suggest Takayasu's arteritis is less likely (See Fig. 2).

3. Discussion

M. pneumoniae infection has several extrapulmonary manifestations including central nervous system (CNS) disorders in approximately 1-10% of cases [8]. However, very little is known about the pathogenesis of brain vascular occlusive diseases/vasculitis associated with *M. pneumoniae* infection. It may locally affect a vascular wall by inducing cytokines and chemokines such as TNF-α [7], and IL-8 [5] among others, which cause local vasculitis and/or thrombotic occlusion without a systemic hypercoagulable state. Alternatively, generalized thrombotic vascular occlusion can occur as a consequence of a systemic hypercoagulable state, possibly caused by immune modulation by *M. pneumoniae* through activation of chemical mediators such as complements and production of FDP-D-dimer. The present case was characterized by high complement activation, which is considered to play an important role in vasculitis in association with *M. pneumoniae* infection [1]. Specifically among the cytokines we evaluated as possible causes for vasculitis in the present case, both IL-8 and TNF-α were significantly elevated. It is highly possible that *M. pneumoniae*-induced cytokines were involved in the pathomechanism of the vasculitis. On this point, Narita et al. reported that IL-8 could be locally produced in the central nervous system, but TNF-α was never elevated in cerebrospinal fluids from patients with CNS manifestations associated with *M. pneumoniae* infection [9]. In turn, elevated serum levels of TNF-α can be associated with peculiar pathological conditions of certain extrapulmonary manifestations such as rhabdomyolysis [10]. Therefore, it is reasonably speculated that TNF-α may have played an important role as a systemic pathogenic factor in inducing the common carotid arteritis in the present case. If the vasculitis had occurred in narrower vasculature such as the middle cerebral artery, it might have led to stroke. On the other hand, elevated serum levels of IL-18 may have played an important role in the development of *M. pneumoniae* pneumonia and been directly related to disease severity [6]. But the increase of serum levels of IL-18 was not specific to patients with CNS manifestations [9].

As a diagnostic concern, it remained uncertain whether his extremity pains were due to vasculitis because of no definite abnormal findings of echogram and MRI. However, these pains drastically subsided the next day after administration of prednisolone. Myositis or arthritis was unlikely. In any case, the pains were an important clue to diagnose the common carotid arteritis in this patient. Vasculitis due to *M. pneumoniae* infection would be unrecognized unless thorough investigations are performed for some clinically overt symptoms [1].

A confounding factor for the treatment in the present case may be that the extrapulmonary manifestations of *M. pneumoniae* infection were caused by a macrolide-resistant strain of *M. pneumoniae*, but unfortunately, drug susceptibility and mutations at site 2063, 2064, and 2617 in domain V of 23S rRNA of *M. pneumoniae* [11] could not be examined in the present case. On this point, it has been considered that the resistant strains have less

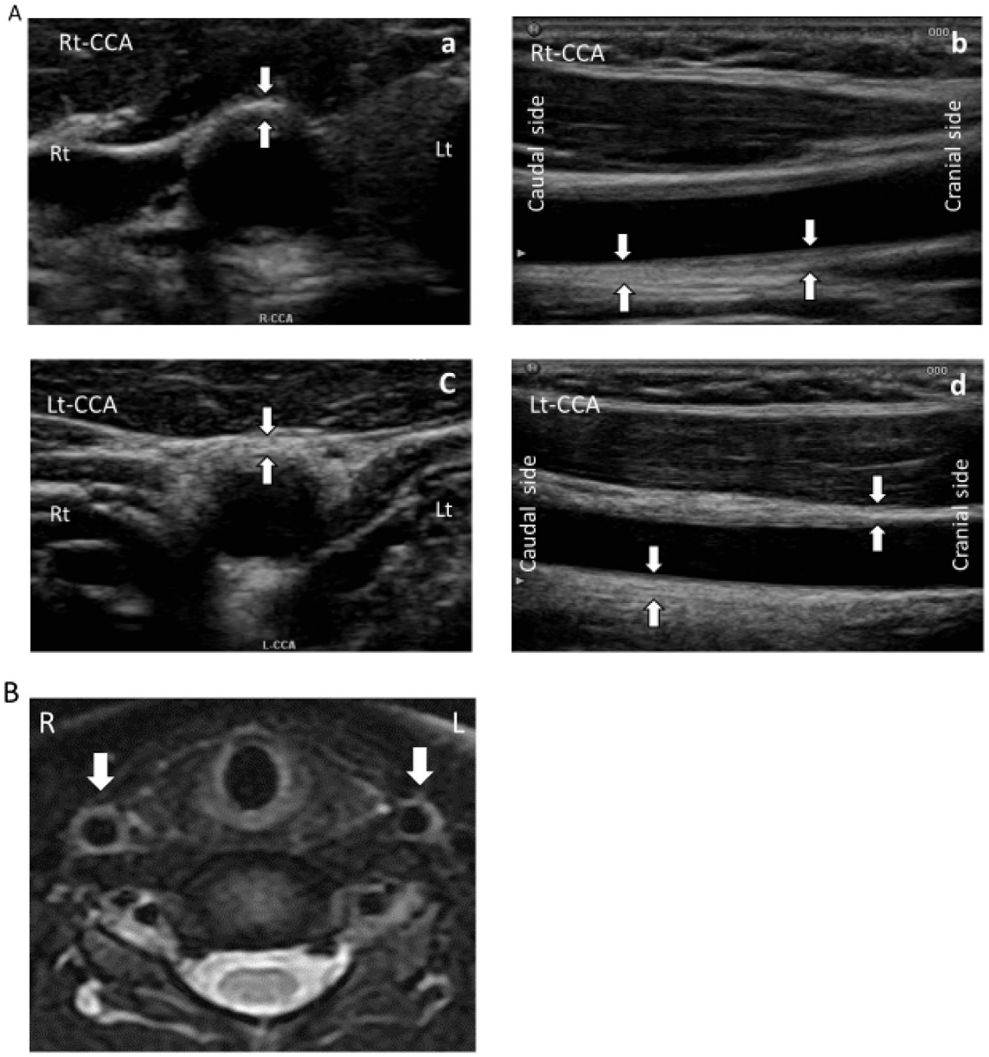
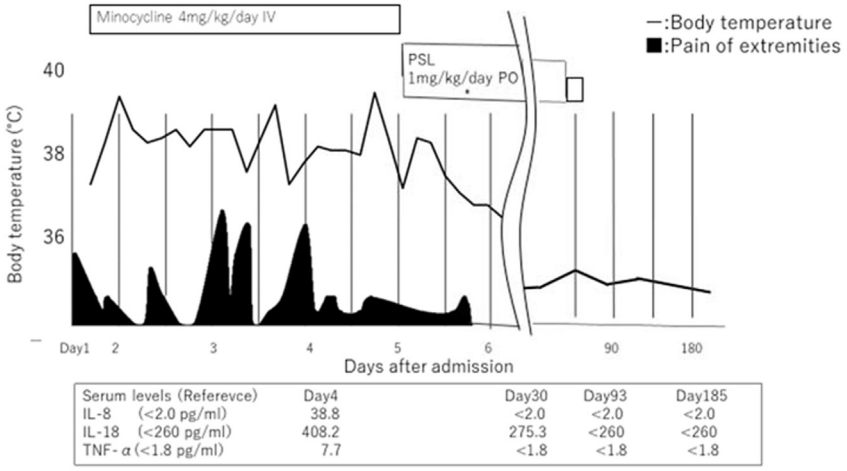


Fig. 1. A. Vascular echogram of bilateral common carotid arteries. Areas between the arrows show increasing intima-media thickness of bilateral common carotid arteries (CCAs). a: a short-axis image of right CCA, b: a long-axis image of right CCA, c: a short-axis image of left CCA, d: a long-axis image of left CCA. B. T2-weighted with lipid suppression magnetic resonance imaging of the neck. Arrows show increased signals in the walls of the common carotid arteries.



Serum levels (Refererevce)	Day4	Day30	Day93	Day185
IL-8 (<2.0 pg/ml)	38.8	<2.0	<2.0	<2.0
IL-18 (<260 pg/ml)	408.2	275.3	<260	<260
TNF-α (<1.8 pg/ml)	7.7	<1.8	<1.8	<1.8

Fig. 2. Clinical course after admission. PSL: prednisolone, IV: intravenous administration, PO: per os administration.

efficient protein synthesis and are deficient in growth ability [2]. No excess morbidity has been particularly ascribed to the drug resistance in reported cases [2,10], and the emergence of macrolide-resistant *M. pneumoniae* must not be a significant clinical threat with respect to the extrapulmonary manifestations of *M. pneumoniae* infection. In addition, the resistance rate has fundamentally been decreasing according to the current data obtained from 2013 to 2015 in Japan [11]. The present case was not

severe and did not have a life-threatening clinical course with stroke or thrombosis. Certainly one possible reason for his favorable outcome might be that tosufloxacin and minocycline were to some extent effective to *M. pneumoniae* infecting the present case, but it must be premature to conclude that an antimicrobial treatment is effective to vasculitis caused by *M. pneumoniae*. Clinically, steroid was highly efficacious against the vasculitis in this case.

In conclusion, common carotid arteritis in the present case could have been the result of local production of cytokines, particularly TNF-α, and chemical mediators such as complements activated by *M. pneumoniae* infection. Further accumulation of data particularly on cytokines and various chemical mediators is expected to fully understand the pathogenesis of, and to construct appropriate treatment modality for, this kind of rare diseases, vasculitis with *M. pneumoniae* infection.

Contributors' statement

Dr Takahashi and Prof Fujieda conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

Drs Ishihara, Oishi, and Yamamoto designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript.

Dr Narita conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflicts of interest

None.

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None.

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