Chlamydophila pneumoniae Infection Induced Nodular Vasculitis

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Key Words
Chlamydia pneumoniae · Erythema induratum · Erythema nodosum

Abstract
We present the case history of a 48-year-old male patient with Chlamydophila (Chlamydia) pneumoniae who developed a nodular vasculitis. He developed a cutaneous vasculitis with the onset of respiratory symptoms. The diagnosis of Chlamydophila pneumoniae infection was based on serology. Since this infection is very common in our population, although often asymptomatic, it should be systematically considered as a causative agent of nodular vasculitis.

Introduction
Erythema nodosum is the most common type of panniculitis; it may be due to a variety of underlying infectious or otherwise antigenic stimuli. Nodular vasculitis (erythema induratum) is a related but distinctly different clinicopathologic reaction pattern of the subcutaneous fat. It is classically caused by an antigenic stimulus from Mycobacterium tuberculosis but may be associated with several other underlying disorders. To our knowledge, there are only a few previous case reports of manifestations of nodular vasculitis in connection with Chlamydophila (Chlamydia) pneumoniae infection.

Case Report
A 48-year-old Japanese man with diabetes mellitus and sleep apnea syndrome presented with skin eruptions on his extremities that he first noticed 2 weeks prior to his admission to our hospital. A week after the appearance of the eruptions, he developed generalized malaise and a further week after that, he developed fever. He was diagnosed as having bacterial pneumonia by another hospital and treated with β-lactam antimicrobial agents, including cefdinir and cefazidime for about 10 days,
but without effect. Thus, he visited the department of internal medicine of our hospital about 5 days before admission to our department.

Laboratory data on that day were as follows. Urine *Legionella* antigen and *Streptococcus pneumoniae* antigen were negative. Serum *Mycoplasma* antibody was negative (complement-fixation test). Anti- *C. pneumoniae* IgA 1.61 C.O.I. (negative <0.90), anti- *C. pneumoniae* IgG 2.85 C.O.I. (negative <0.90). On admission (day 1), body temperature was 37.4°C, blood pressure was 114/75 mm Hg, and pulse was regular, 101 beats/min. Laboratory results: hemoglobin 11.8 g/dl, WBC count 10 × 10^3/μl (neutrophil 71.0%), and PLT count 37.6 × 10^4/μl. CRP 6.87 mg/dl, total bilirubin 0.4 mg/dl, AST 12 IU/l, ALT 9 IU/l, creatinine 0.58 mg/dl, and albumin 3.4 g/dl. ANA and RF were negative. MPO-ANCA and PR3-ANCA were negative. Chest computed tomography (CT) showed interstitial pneumonia and alveolar pneumonia was intermingled.

Physical examination revealed crops of tender, violaceous nodules on his extremities, and their sizes ranged from 5 to 10 mm in diameter (fig. 1). Histopathological examination shows diffuse septolobular panniculitis of nearby vessels (fig. 2). Perivascular infiltrates with neutrophils, extravasation of red blood cells, and fibrinoid degeneration were identified (fig. 3). A direct immunofluorescent study showed no immunoglobulin deposition. He was diagnosed with *C. pneumoniae* infection, and this infection induced nodular vasculitis.

From the 2nd to the 17th day, he was treated with pazufloxacin, 1 g daily. The serum CRP fell gradually to become 0.57 mg/dl on the 16th day, and return to normal range by one month. After the 20th day, the indurated erythema began to improve, and seemed to run parallel with the improvement of the serum CRP. We measured it again 40 days after the first time: anti-*C. pneumoniae* IgA 0.95 C.O.I., anti-*C. pneumoniae* IgG 3.18 C.O.I.

**Discussion**

Summarizing the case, our patient presented with the signs/symptoms of pneumonia with an interstitial shadow and an infiltrating shadow on chest CT. Cephems were ineffective, whereas the newer quinolones were effective. Changes in the blood antibody titers in addition to these observations and results suggested *C. pneumoniae* infection. Nodular vasculitis subsided along with improvement of the pneumonia following antibiotic administration, suggesting that it was caused by *C. pneumoniae* infection.

Several studies showed that *C. pneumoniae* infection could be involved in the pathogenesis of MPO-ANCA-associated glomerulonephritis, reactive arthritis, SLE, and adult onset of Still’s disease [1]. Much less is known about the role of *C. pneumoniae* in the pathogenesis of systemic diseases. One explanation is molecular mimicry [2]. Immune responses and/or antibodies against it are unknown. *C. pneumoniae* antigen might cross-react with several body tissues such as the kidney, blood vessels, skin, joint, and muscle. Alternatively, *C. pneumoniae* can survive and replicate within the epithelial cells, macrophages, and neutrophils. *C. pneumoniae*-infected cells may then trigger abnormal signal transduction, resulting in changes of the cytokine profiles and activation and/or deactivation of immunocytes such as B cells, T cells, macrophages, and NK cells [3].

Nodular vasculitis has been associated with infectious tuberculosis and/or nontuberculosis and noninfectious disorders. Infectious nontuberculous cases have been associated with *Nocardia, Pseudomonas*, and *Fusarium* [4]. There may also be an association with hepatitis B virus and hepatitis C virus [5]. Noninfectious associations may include previous episodes of superficial thrombophlebitis of the lower legs,
hypothyroidism, chronic lymphocytic leukemia, rheumatoid arthritis, and Crohn’s disease [5].

Some reports in the past have shown that all cases of exanthema caused by Chlamydia pneumoniae are of the erythema nodosum type [6–12] (table 1). However, the histopathological findings in 3 [6, 11, 12] of the 7 exanthema cases have been reported previously, and these 3 cases showed features of vasculitis. Although omitted in those papers, the other 4 cases may also have been histopathologically found to show findings of vasculitis. It is therefore possible that the eruption reported as erythema nodosum is actually nodular vasculitis.

**Disclosure Statement**

We have no conflict of interest in relation to the publication of this paper.

**Table 1.** Review of the literature concerning the association of Chlamydia pneumoniae infection with erythema nodosum

<table>
<thead>
<tr>
<th>Reference number</th>
<th>Age/sex</th>
<th>Type of infection</th>
<th>Associated disease(s)</th>
<th>Diagnostic criteria of Chlamydia pneumoniae infection</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>[7]</td>
<td>17/M</td>
<td>Lower respiratory</td>
<td>None</td>
<td>MIF</td>
<td></td>
</tr>
<tr>
<td>[7]</td>
<td>11/F</td>
<td>Lower respiratory</td>
<td>None</td>
<td>MIF</td>
<td></td>
</tr>
<tr>
<td>[8]</td>
<td>37/M</td>
<td>Lower respiratory</td>
<td>Myocarditis, reactive arthritis</td>
<td>MIF</td>
<td></td>
</tr>
<tr>
<td>[9]</td>
<td>37/M</td>
<td>Meningitis</td>
<td>Hepatitis, iritis</td>
<td>MIF</td>
<td>Clinical diagnosis: atypical erythema nodosum or vasculitis</td>
</tr>
<tr>
<td>[10]</td>
<td>Not specified</td>
<td>Löfgren’s syndrome</td>
<td>MIF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[12]</td>
<td>42/F</td>
<td>None</td>
<td>None</td>
<td></td>
<td>Histology: infiltrations around the vessels</td>
</tr>
<tr>
<td>Present study</td>
<td>48/M</td>
<td>Lower respiratory</td>
<td>None</td>
<td></td>
<td>Histology: vasculitis</td>
</tr>
</tbody>
</table>

CF = Complement fixation; MIF = micro-immunofluorescence.
**Fig. 1.** Several indurated erythema on the patient’s thigh.

**Fig. 2.** Diffuse septolobular panniculitis of nearby vessels.
Fig. 3. Necrotizing vasculitis in the lower dermis.

References