A Case of Erythema Nodosum Associated with *Mycoplasma pneumoniae* Infection: Pathologic Findings and a Presumed Pathogenesis

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Erythema nodosum (EN) is a painful skin disease characterized by erythematous tender nodules located predominantly over the extensor aspects of the legs. Various etiological factors, including infection, drug administration, and systemic illness have been implicated as causes of EN. *Mycoplasma pneumoniae* is one of rare infectious agents to cause EN in children. We report a case of a 7-year-old boy with context of respiratory illness and skin lesions with arthralgia. From stepwise approaches, IgM antibody against *M. pneumoniae* was positive with titers of 12.18, consistent with respiratory infection of *M. pneumoniae* and histopathology showed findings of septal and lobular inflammation without vasculitis consistent with EN. In addition, we reviewed the pathogenesis of this disease based on our case and the previous reports.

**Key Words:** Erythema nodosum, *Mycoplasma pneumoniae*, Type IV hypersensitivity, Pathogenesis

**Introduction**

Erythema nodosum (EN), the most common type of panniculitis seen in children, is characterized by inflammation of subcutaneous fat septa without vasculitis, which manifests as tender and erythematous nodules. There are various causes of EN, but their histopathologies show the identical results of deposition of immune complexes in the venules of the septae of subcutaneous fat. In this regard, whatever etiologies of EN, the disease might have common pathogenic mechanism.

Among infectious agents, *Streptococcus* spp. account for most cases of EN in children; however, few studies have investigated the role of *Mycoplasma pneumoniae* in the etiology of EN. From the previous cases and our case, we review characteristics of *M. pneumoniae* induced EN and pathogenic mechanisms of *M. pneumoniae* associated EN.
Case Report

A 7-year-old boy was hospitalized with painful skin nodules and a burning sensation on both lower legs for the previous 2 days. He had had a fever (>38°C) and cough for 5 days, which had subsided 2 days before admission, and the fever was not present at admission. We found no evidence of sore throat, vomiting, diarrhea, or weight loss, and his only symptom was joint pain in the knees and ankles. The patient was born at 38 weeks gestation by normal delivery with an uncomplicated pregnancy. He had received intravenous immune globulin (IVIG) treatment for Kawasaki disease 2 months before admission to our hospital. He had not travelled and had no familial history of illness. From 2 months before admission, there were many patients who were treated with mycoplasma infection. The physical examination showed multiple tender, erythematous papulo-nodular lesions on both lower legs (Fig. 1). Coarse breath sounds were present in both lungs. The patient’s movement was not limited by the swelling in his knees and ankles. Laboratory tests were performed to identify the cause of respiratory symptoms accompanied by a rash and arthralgia. They showed white blood cell count of 9,600/µL, C-reactive protein level of 1.96 mg/mL (normal, <0.05 mg/mL), erythrocyte sedimentation rate of 52 mm/h (normal, <15 mm/h), total protein of 7.2 g/dL, albumin of 3.8 g/dL, and IgE of 200.7 IU/mL (normal range, 1.9–170 IU/mL). The antistreptolysin O titer, rheumatoid factor, and antinuclear antibodies were within normal limits. The blood, throat, urine, and stool cultures were negative, Multiplex polymerase chain reaction (PCR) to detect respiratory virus was negative. The serological tests for Chlamydia pneumoniae and Yersinia pseudotuberculosis were negative. The specific serum IgM antibodies for Mycoplasma pneumoniae (enzyme-linked immunosorbent assay, ELISA test) were positive with titers of 12.18 index (normal range, <9 index). Six weeks ago, when he had been hospitalized with Kawasaki disease, the result had been negative. The tuberculin skin test was less than 5 mm. A chest X-ray revealed mild infiltration in both perihilar areas. A skin biopsy was taken from the patient’s lower right leg to assess the erythematous rash on his lower extremities. The histopathological results showed septal panniculitis with a small non-caseating granuloma (Fig. 2). Based on the clinic-pathological findings and lower respiratory signs and symptoms, we concluded that M. pneumoniae infection was the cause of the EN in our patient. We treated the patient with clarithromycin, and he was discharged on the third day after admission to the hospital. The EN lesions improved gradually over 2 weeks, with several new lesions on the arms or buttocks. Ibuprofen was administered to relieve his pain. The respiratory symptoms, including the cough and wheezy lung sounds, persisted beyond 3 weeks. Conservative treatment and clarithromycin were continued for 2 weeks.

Discussion

EN is the most common type of panniculitis found
in children and is thought to be the result of a reactive process that can be triggered by a wide variety of stimuli. Various pathogens, including infections (particularly streptococci, tuberculosis, yersinia, and mycoplasma), drugs, chronic inflammatory diseases (such as sarcoidosis, Behcet’s disease, and chronic intestinal disease), malignancy and idiopathic condition, are known to be causative agents of EN. On the basis of the same histopathologic findings from various pathogens, EN is not caused solely by pathogens themselves or pathogen-induced substances.

Histologically, EN is the prototype of the septal panniculitides. The septa of the subcutaneous fat are thickened with an inflammatory cell infiltrate. Neutrophils predominate in acute lesions, whereas mononuclear cells and histiocytes predominate in chronic lesion. In our patient, his histological findings revealed an inflammatory process involving the septa between subcutaneous fat lobules and the presence of non-caseating granulomas without vasculitis consistent with EN.

*M. pneumoniae* can cause respiratory illness and extrapulmonary complications, including neurological, cardiac, dermatological, musculoskeletal, hematological, and gastrointestinal symptoms. Cutaneous manifestations occur in 10–25%, and include non-specific exanthems, urticaria, vasculitis, Steven-Johnson syndrome, toxic epidermal necrolysis, pityriasis rosea, and erythema nodosum. However, EN is rarely reported as a cutaneous manifestation of *M. pneumoniae* infection.

In 2001, Kakourou et al. were the first to describe EN caused by *M. pneumoniae* in a pediatric population. They found that *M. pneumoniae* serology was positive in 3 of 35 children with EN. Blanco et al. described a 4-year-old child who presented with a tibial rash that was compatible with EN approximately 15 days after the onset of pulmonary symptoms. Shimuzu et al. reported the case of an 8-year-old girl who developed a diffuse maculopapular rash like erythema multiforme followed by Henoch-Schönlein purpura in the absence of pulmonary manifestations 7 days after the onset of EN. Furthermore, a retrospective study found that of 39 patients with EN, two were infected with *M. pneumoniae* and one had a concomitant acute streptococcal infection. Greco et al. described two children with EN caused by *M. pneumoniae*, one of whom had no respiratory symptoms. Studies of EN associated with *M. pneumoniae* found that the condition commonly appeared on the shins or arm and buttocks of females around 10 years of age and typically occurred 15 days after prodromal symptoms, such as fever. EN was occasionally accompanied by arthralgia and persisted less than 2 weeks without recurrence. A review of the English literature revealed that EN caused by *M. pneumoniae* did not necessarily include respiratory symptoms, and that the prognosis was benign (Table 1).

The precise mechanisms underlying the spectrum of *M. pneumoniae*-induced cutaneous symptoms are poorly understood; however, the mechanisms can
be divided into three types. Most cutaneous lesions associated with *M. pneumoniae* are thought to be caused by the organism itself and are referred to as the direct type. The bacteria can be hematogenously disseminated to the dermis, causing hypodermal inflammation. The indirect type involves the host response to antigens on the microbes. Investigators have speculated that host immune responses, including immune complex-mediated injury and cytotoxic T-cell-mediated responses, play an important role. It is suggested that each host immune cell may recognize and respond to substances of microbial agents, including pathogenic proteins depending on their size and property. Those substances may bind to receptors on specific cells via systemic circulation and the corresponding immune cells may be responsible for the inflammatory processes. It could be explained why a pathogen itself is not found in target lesions and systemic immune modulators (corticosteroids and IVIG) are effective in rapid progression. It could be in line with EN by *M. pneumoniae*.

Generally, EN tends to be self-limited. The most common approach is treatment of any underlying disorders and supportive therapy, including bed rest and use of nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen or naproxen. In this case, we treated the patient with clarithromycin and conservative treatment including ibuprofen without systemic immune modulators.

In children, to find the cause of EN is based on clinical characteristics and various tests. Our patient had respiratory symptoms, including cough, sputum, and fever accompanied by arthralgia and skin nodules with multiple lesions in the pretibial area. This patient had been given aspirin for Kawasaki disease. Although NSAIDs may cause EN, NSAIDs were not the trigger in this patient because he subsequently received aspirin without symptoms for 2 months. He also received intravenous immune globulin to treat Kawasaki disease 2 months before admission to our hospital; however, the treatment was unlikely to have caused EN. Laboratory tests were negative, with the exception of *M. pneumoniae*. Serological diagnosis for anti-Mycoplasma antibody by a single high antibody titer to *M. pneumo-

### Table 1. Summary of *M. pneumoniae* Induced EN Cases in English Literatures

<table>
<thead>
<tr>
<th>Patient age/sex</th>
<th>Period from prodromal symptoms to symptom onset &amp; Prodromal symptoms</th>
<th>Clinical feature</th>
<th>Laboratory test</th>
<th>Diagnostic method for Mycoplasma/Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.2 yr/female</td>
<td>5-15 days prodromal</td>
<td>Fever</td>
<td>WBC 9,800 (neutrophil 54%)</td>
<td>Serology(-) 3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower legs and forearms 10 days</td>
<td>ESR 84</td>
<td></td>
</tr>
<tr>
<td>13.6 yr/female</td>
<td>Fever and cough 5-15 days prodromal</td>
<td>Arthralgia</td>
<td>WBC 7,200 (neutrophil 67.5%)</td>
<td>Serology(-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower legs 10 days</td>
<td>ESR 113</td>
<td></td>
</tr>
<tr>
<td>7 yr/female</td>
<td>5-15 days prodromal</td>
<td>Lower legs and thighs 5 days</td>
<td>WBC 7,400 (neutrophil 40%)</td>
<td>Serology(-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ESR 38</td>
<td></td>
</tr>
<tr>
<td>8 yr/female</td>
<td>EN, around 10 days, accompanied with EM, HSP</td>
<td>Bilateral lower legs 9 days</td>
<td>WBC 8,440</td>
<td>Serology(-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Proteinuria</td>
<td></td>
</tr>
<tr>
<td>10 yr</td>
<td>Co-infection with Streptococcus</td>
<td>Bilateral lower legs NR</td>
<td>WBC 11,000, ESR 80</td>
<td>Serology/NR</td>
</tr>
<tr>
<td>8 yr</td>
<td>NR</td>
<td>Bilateral lower legs NR</td>
<td>WBC 11,000, ESR 37</td>
<td>Serology/NR</td>
</tr>
<tr>
<td>10 yr</td>
<td>NR</td>
<td>Bilateral lower legs NR</td>
<td>WBC 11,000, ESR 45</td>
<td>Serology/NR</td>
</tr>
<tr>
<td>7 yr/female</td>
<td>Fever for 10 days with nodule and pain in the lower limbs</td>
<td>Bilateral lower legs and arms 31 days</td>
<td>WBC 10,500, ESR 120</td>
<td>Serology(-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Proteinuria</td>
<td></td>
</tr>
<tr>
<td>9 yr 1 month/</td>
<td>Fever and cough for 5 days, 15 days interval</td>
<td>Symmetric tibia 10 days</td>
<td>WBC 14,300 (neutrophil 75%), ESR 45</td>
<td>Serology(-)</td>
</tr>
<tr>
<td>female</td>
<td></td>
<td></td>
<td>Pneumonia: rale sound on lung field</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CRP, C-reactive protein, EM, erythema multiforme, EN, erythema nodosum, ESR, erythrocyte sedimentation rate, HSP, Henoch-Schönlein purpura, NR, not reported.
niae or by a positive IgM testing would be misleading because it may include a recent past but not current infection. In our patient, there were paired tests for M. pneumoniae serology with 6 week-intervals: the first test during admission for Kawasaki disease and the second test due to EN. The results showed a significant rise of antibody titers from negative to 12.18. The clinical manifestations and the laboratory tests were consistent with mycoplasma infection.

Here, we described a patient with M. pneumoniae induced EN with type IV hypersensitivity based on histological findings. However, we were unable to identify the triggering antigens, directly. Further clinical and immunological studies are necessary to clarify the pathogenic mechanism underlying the extrapulmonary manifestations of M. pneumoniae infections.

References


요약
결절성 홍반은 소아에서 가장 흔한 피하지방층의 염증으로 하지의 압통을 동반한 결절을 특징으로 한다. 이 질환은 다양한 원인에 의해 발생되지만 공통된 조직소견을 보여준다. 저자들은 염증성 소견 및 혈청학적 방법으로 마이코플라마 패렴균에 의한 결절성 홍반을 진단하였고 조직병리적 접근을 통해 결절성 홍반의 면역반응에 대해 고찰해 보았다. 조직병리소견은 제 4형 면역반응 염증을 보였으며 이는 다양한 원인에 의한 결절성 홍반의 발생 기전을 이해하는데 도움을 줄 것이다.