Acute Hemorrhagic Pericarditis in a Child with Pneumonia Due to Chlamydia pneumoniae

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Chlamydia pneumoniae is mainly responsible for respiratory tract infections but has also been associated with endocarditis and myocarditis. We report a case of pneumonia in a child with hemorrhagic pericardial effusion with a positive result by a new C. pneumoniae TaqMan PCR, suggesting a pericardial inflammation directly induced by C. pneumoniae. C. pneumoniae should be suspected in patients with community-acquired pneumonia and concurrent pericarditis. Empirical treatment with azithromycin seems feasible.

CASE REPORT

A 13-year-old girl presented with tachypnoea and shortness of breath that was exacerbated by exertion. These symptoms worsened during the last 24 h prior to admission. In addition, she complained of throat pain and nausea. There was a history of skeletal dysplasia of unknown cause, scoliosis, generalized gingivitis, and mild aortic-valve regurgitation. No other symptoms of note were elicited, and no medication was concurrently taken.

On examination, the patient was subfebrile (38.3°C) and pale. She had severe shortness of breath when lying supine but was only mildly dyspnoeic when sitting forward. The first and second heart sounds were soft, and no murmur was heard. Coarse crackles were found on auscultation of both lungs. Abdominal palpation was painful in the epigastrium and left upper quadrant. Hematological investigation revealed a white cell count of 12.6 × 10³/liter. C-reactive protein was 20 mg/liter. Blood gases were normal. A chest X ray showed central bilateral infiltration and an enlarged cardiac silhouette (Fig. 1).

On the second day the patient deteriorated clinically; she complained of throat pain and nausea. There was a history of endocarditis and myocarditis. We report a case of pneumonia in a child with hemorrhagic pericardial effusion with a positive result by a new C. pneumoniae TaqMan PCR, suggesting a pericardial inflammation directly induced by C. pneumoniae. C. pneumoniae should be suspected in patients with community-acquired pneumonia and concurrent pericarditis. Empirical treatment with azithromycin seems feasible.

On admission, empirical antibiotic therapy with azithromycin for community-acquired pneumonia was initiated.

Known causes of pneumonia and myocarditis or pericarditis were excluded. No serological evidence of acute infection with influenza virus, parainfluenza virus, Epstein-Barr virus, adenovirus, varicella zoster virus, coxsackie virus, mumps, measles, echovirus, leptospira, listeria, streptococci (streptolysin negative), staphylococci (staphyloolysin O negative), or Mycoplasma pneumoniae was found.

On the second day the patient deteriorated clinically; she needed oxygen supplements, and the pericardial effusion increased in a repeated ultrasound study. Consequently, subxiphoideal pericardial drainage was performed and 500 ml of hemorrhagic effusion was removed. Culture of the pericardial effusion remained sterile, and cytological investigation revealed no malignant cells. The pericardial drain was left for 4 days, and additional antibiotic treatment with cefuroxime was given intravenously for 4 days; anti-inflammatory therapy with ibuprofen was also given. At 3 weeks after removal of the pericardial drain, effusion did not reaccumulate and the clinical status improved. The patient was discharged from the hospital after 14 days. Further serological workup revealed positive immunoglobulin G (IgG) and IgA antibody results for Chlamydia pneumoniae. For C. pneumoniae serology we used sandwich enzyme-linked immunosorbent assays (sELISAs) Medac (Wedel, Germany) for IgG and IgA. The sELISAs and calculations were performed according to the manufacturers’ instructions. Finally, we performed a new C. pneumoniae TaqMan PCR with the pericardial fluid to verify whether C. pneumoniae was directly involved in induction of the infection and especially the hemorrhagic pericarditis (Fig. 3).

The collected pericardial fluid was immediately transported to the diagnostic laboratory at room temperature and stored at 4°C up to the time of DNA preparation. DNA preparations were stored at −20°C. DNA was prepared from two different samplings of the pericardial effusion by use of a QIAamp DNA Mini kit (QIAGEN, Hilden, Germany) and simultaneously subjected to TaqMan PCRs specific for the atypical pneumonia-causative organisms M. pneumoniae (P1 adhesin gene), Legionella pneumophila (mip gene), and C. pneumoniae (rpoB gene).

As an external positive control, a 70-bp conserved region of the human GAPDH gene was amplified (data not shown). The reactions were performed in a final volume of 25 μl containing 0.3 μM concentrations of each primer, 0.2 μM fluorogenic probe, and 25 ng of DNA in one-fold TaqMan MasterMix, which contains 0.25 U of uracil-N-glycosylase (Eurogentec, Seraing, Belgium). PCR procedures were performed under standard conditions (10 min at 50°C, 10 min at 95°C, and 40 cycles of 15 s at 95°C and 1 min at 60°C) with an iCycler (Bio-Rad Laboratories, Hercules, Calif.).

As DNA standards for the PCRs, plasmids encompassing the amplified regions of the different TaqMan PCRs were

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created by PCR cloning and serially diluted. As an inhibition control, distinct copies of the cloned amplicons were added to the DNA extracted from the two samples of the pericardial effusion. The samples were analyzed in duplicate, and PCRs were repeated twice.

Only the C. pneumoniae PCR gave positive results with both samples. For detection of the C. pneumoniae-specific region of the rpoB gene (AE002228), primers Cp3-for (5′-GCT CCC AGC TTT CGC AGT T-3′) and Cp3-rev (5′-GCA CAA AGA CGT CTG TGG TGA GT-3′) were used, delimiting a 72-bp DNA segment and flanking the binding region of the fluorogenic probe (5′-6-carboxyfluorescein-TGG ACC AAA CCA ACC CTG TAG CTG AGT T-3′/6-carboxytetramethylrhodamine). Species specificity of the PCR was ensured, as DNA of C. trachomatis and C. psittaci was not amplified (data not shown).

As depicted in Fig. 3 the sensitivity of the C. pneumoniae TaqMan PCR was found to be <50 copies/assay. With regard to the dilution used in PCR, the detected 30 copies of C. pneumoniae genomes in sample 1 corresponded to 2.4 × 10⁴ C. pneumoniae cells per ml of pericardial effusion, while the copy number in sample 2 amounted to one-fourth of that amount.

Chlamydia pneumoniae, recently renamed C. pneumoniae (2), is a frequent cause of community-acquired respiratory tract infections, including pneumonia and bronchitis. It has also been associated with endocarditis and myocarditis (4, 6, 10), but there is just one report of an immunocompromised adult patient with C. pneumoniae pneumonia and concurrent acute hemorrhagic pericarditis (15). Our patient showed serologic signs of a C. pneumoniae infection, with positive test results for IgA and IgG antibodies in the serum and a positive PCR result for the pericardial effusion. Chronic infection with C. pneumoniae has been considered a risk factor for coronary heart disease, since a close association was reported between high levels of C. pneumoniae-specific IgA antibodies and an increased risk of myocardial infarction (9). Gnarpe et al. found a significantly increased level of IgA antibodies in patients with myocarditis, perimyocarditis, or pericarditis compared to the results seen with healthy blood donors of the same age (4).

Although no quantitative IgA antibody levels were measured for our patient, this case report supports the notion that C. pneumoniae may be associated with inflammatory heart disease. There is still discussion concerning the diagnostic “gold standard” of C. pneumoniae infection, and the choice of diagnostic tests is of utmost importance when evaluating a possible relationship between C. pneumoniae and a particular disease (7, 12). Hermann et al. showed that ELISAs are fast and objective and deliver seroprevalence results, sensitivities, and specificities that are very similar to those of the microimmunofluorescence assay, which is widely used as a serological test for demonstration of the presence of C. pneumoniae antibodies (5). With an IgA and IgG seropositivity result and the detection of C. pneumoniae genome equivalents in the pericardial fluid by PCR, we describe for the first time the uncommon finding of C. pneumoniae acting as a probable direct inducer of pericardial inflammation during C. pneumoniae infection.

For children with community-acquired pneumonia it is commonly difficult to obtain specimens for culture, and results may be misleading due to contamination with unrelated infective agents. Culture and subsequent PCR testing for C. pneumoniae, which is the most sensitive method for detection of C.
*Chlamydia pneumoniae*, are not generally available and take many days before results are confirmed. Acute- and convalescent-phase serum specimens for antibody titer determinations to selected pathogens can be obtained to confirm etiology, but results are not available during acute illness. The most common causes of pericarditis in children are purulent disease (40%), collagen vascular disease (30%), viral disease (20%), and neoplastic disease (10%) (8). Empirical antibiotic treatment of pneumonia with concurrent pericarditis should be directed towards the most common causes (3). Wubbel et al. found no difference in effectiveness of antibiotics (azithromycin versus amoxicillin) in patients with community-acquired pneumonia, even among those with infection attributed to *M. pneumoniae*, *C. pneumoniae*, and *S. pneumoniae* (14). Until additional information is available the selection of an antimicrobial agent for therapeutic treatment of children with community-acquired pneumonia should be based on clinical judgment. Azithromycin is active against a wide range of organisms responsible for community-acquired pneumonia and has pharmacokinetics and tolerance superior to those of erythromycin (11, 14). Moreover, results from initial studies conducted with cystic fibrosis patients suggest anti-inflammatory action resulting from macrolide therapy (13). For our patient with concurrent hemorrhagic pericarditis, azithromycin therapy led to complete resolution of clinical findings.

Pericardial drainage may also be required for treatment of patients with pericardial effusion with cardiac tamponade and may provide diagnosis of the causative agent. It must be emphasized that antimicrobial therapy alone would be mostly insufficient for the treatment of purulent pericarditis (13). There are no data about standardized treatment of hemorrhagic pericarditis. Although percutaneous pericardial drainage is a rather straightforward procedure, there is an ongoing discussion whether pericardial drainage should routinely be performed with patients who have a large pericardial effusion without tamponade (1).

The presented case report suggests that differential diagnosis of hemorrhagic pericarditis in patients with pneumonia should include *C. pneumoniae* as a causative agent. In addition to diagnostic and therapeutic pericardial drainage, empirical therapy with azithromycin seems appropriate.

**REFERENCES**