CASE REPORT

Responses to Treatment According to the Cytokine Profiles of Pericardial Effusion in Two Children with Idiopathic Pericarditis

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Summary

Acute pericarditis is inflammation of the pericardium with or without pericardial effusion. In the pediatric population, most patients with acute pericarditis are diagnosed with idiopathic pericarditis. Herein, we present two children with idiopathic pericarditis who underwent immunological assessment of pericardial effusion for the first time. Both patients showed equally high levels of interleukin-6 in the pericardial effusion. However, they had different treatment responses, in accordance with the pericardial effusion and serum interleukin-10 concentrations. Our present cases suggest that interleukin-10 may be associated with the response to anti-inflammatory therapy in idiopathic acute pericarditis.

Key words: Acute pericarditis, Non-steroidal anti-inflammatory drugs, Steroid, Pediatric population, Proinflammatory cytokine

Acute pericarditis (AP) is an inflammation of the pericardium with or without pericardial effusion (PE).1-4 The incidence of AP has been reported as 27.7 cases per 100,000 people per year.1 The etiology is varied and depends on the epidemiological background, patient population, and clinical setting. Moreover, the etiologies for AP are often unclear especially during the acute phase. Hence, they are generally labeled as “idiopathic”.5 According to previous reports, idiopathic pericarditis (IP) accounts for 37% of the inpatient admissions for PE in children, and some of them proved to be “viral” afterward.5,6

Treatment options for PE in patients with AP have not been well established because of its unknown pathomechanism.1,2 Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) (generally ibuprofen and indomethacin) should be used as first-choice drugs for the treatment of AP.3 In addition, colchicine, steroids, azathio-prine, intravenous immunoglobulin (IVIG), or anti-interleukin (IL)-1 therapy are considered in cases of intractable PE.4 To determine the optimal treatment for each patient, immunological assessments of PE have been performed in previous studies.3,4 However, those studies mainly targeted adult populations with non-IP.7,8 To the best of our knowledge, the immunological assessment of PE in children with IP has not yet been reported.

Herein, we report the cases of two children with IP who underwent immunological assessment of their PE. Notably, the treatment responses of the two cases differed in accordance with their PE cytokine profiles.

Case Report

Patient 1: A previously healthy 4-month-old Japanese male was hospitalized because of a 4-day history of poor sucking, grunting, and tachypnea (Figure 1A). He was born as a full-term infant from non-consanguineous healthy parents. On admission, he presented with pallor and coldness. Grunting and retraction of the chest were remarkable. Heart rate, respiratory rate, and blood pressure were 170 beats per minute, 42 breaths per minute, and 108/52 mmHg, respectively. Heart sounds were diminished. His hematological parameters of venous blood (oxygen at a flow rate of 10 L/min) on admission were as follows: pH, 7.462; partial pressure of carbon dioxide (pCO2), 29.7 mmHg; partial pressure of oxygen (pO2), 188 mmHg; bicarbonate (HCO3−), 20.8 mmol/L; base excess (BE), −4.4 mmol/L; lactate, 1.4 mmol/L; leukocyte count, 12.0 × 109/L with 53.0% segmented neutrophils; hemoglobin concentration, 10.0 g/dL with 31.0% hematocrit; platelet count, 752 × 109/L; albumin, 4.6 g/dL (reference range [RR]: 3.8-5.2 g/dL); lactate dehydrogenase (LDH), 222 U/L (RR: 115-245 U/L); creatine kinase (CK)-MB, 17.8 U/L (RR: < 25.0 U/L); C-reactive protein (CRP), 0.70 mg/dL (RR: < 0.30 mg/dL); brain natriuretic peptide (BNP), 77.2 pg/mL (RR: < 18.4 pg/mL); cardiac troponin-T (cTnT), 0.010 ng/mL (RR: < 0.014 ng/mL); prothrombin time-international normalized ratio (PT-INR),...
Figure 1. Clinical course of patients 1 (A) and 2 (B). CRP, C-reactive protein; CTX, cefotaxime; DOA, dopamine; DOB, dobutamine; MEPM, meropenem; WBC, white blood cell.

Figure 2. Chest X-ray, echocardiogram, and pericardial aspirate on admission in the two patients (A-C, patient 1; D-F, patient 2). A, D: Chest X-rays show remarkable cardiomegaly with pulmonary congestion (cardiothoracic ratio is 0.75 and 0.70, respectively). B, E: Echocardiograms reveal a large amount of pericardial effusion (asterisk) causing atrial compression (arrow). C, F: Bloody pericardial aspirate is obtained in both patients.

12.3 (RR: 0.85-1.15); activated partial thromboplastin time (APTT), 34.2 s (RR: 24.3-36.0 s); and D-dimer, 1.9 mg/L (RR: < 1.0 mg/L). Chest X-ray showed remarkable cardiomegaly with pulmonary congestion (cardiothoracic ratio 0.75) (Figure 2A). Echocardiogram revealed a large amount of PE causing atrial compression (Figure 2B).

Twelve-lead electrocardiogram (ECG) showed sinus tachycardia of 156 beats per minute with low voltage in all leads. We considered these findings were due to AP. Pericardial puncture was performed, and bloody pericardial aspirate was obtained (Figure 2C). The cytological diagnosis of PE was class II (dysplastic but not malignant).
Oral aspirin therapy was started at a dose of 75 mg/kg/day. Despite the treatment, the PE was intractable, and serum CRP levels gradually increased. Both contrast-enhanced computed tomography and bone marrow examination were normal, and viral polymerase chain reaction (PCR) analyses of the PE, blood, nasal mucus, and feces were all negative. Hence, we diagnosed the AP as IP. On the 17th day of illness, intravenous prednisolone was started at a dose of 0.5 mg/kg/day. The PE gradually decreased and disappeared on the 22nd day of illness. Serum CRP levels were within normal limits on the same day. Prednisolone was successfully tapered without recurrence of PE. The patient was discharged on the 47th day of illness.

Patient 2: A 5-year-old Japanese male was referred to our hospital with an 8-day history of high fever and cardiomegaly (Figure 3B). He was born from non-consanguineous healthy parents as a full-term infant and had no prior medical history. On admission, he presented with a high fever of 38 °C with pallor and peripheral coldness. Friction rub was audible with diminished heart sounds. Heart rate, respiratory rate, and blood pressure were 115 beats per minute, 32 breaths per minute, and 105/62 mmHg, respectively. His hematological parameters of venous blood on admission were as follows: pH, 7.462; pCO₂, 33.4 mmHg; pO₂, 44.6 mmHg; HCO₃⁻, 24.7 mmol/L; BE, 0.5 mmol/L; lactate, 0.9 mmol/L; leukocyte count, 13.1 × 10⁹/L with 30.8% segmented neutrophils; hemoglobin concentration, 10.2 g/dL; and D-dimer, 9.9 mg/L. Chest X-ray showed remarkable cardiomegaly (cardiothoracic ratio 0.70) (Figure 3D). Echocardiogram revealed medium amount of PE (Figure 3E). Twelve-lead ECG showed sinus tachycardia of 120 beats per minute. Pericardial puncture was performed, and the cytological diagnosis of the bloody pericardial aspirate was class I (normal) (Figure 3F). Oral aspirin therapy was started at a dose of 50 mg/kg/day, which successfully decreased the PE and serum CRP levels. Oral aspirin was tapered without recurrence of PE. The patient was discharged home on the 28th day of illness. Cultures and viral PCR analyses of the PE, blood, nasal mucus, and feces were all negative.

Cytokine assay: In the present cases, pericardial and serum cytokine levels were sequentially studied during the disease course (Figure 3). IL-6 and IL-10 were measured using a cytometric bead array kit (BD Biosciences, San Jose, CA, USA) according to the manufacturer’s instructions. The lower detection limits for IL-6 and IL-10 were 3.0 and 2.8 pg/mL, respectively. As shown in Figure 3A, the pericardial levels of IL-6 were remarkably elevated in both patients, whereas the IL-10 levels were higher in patient 2 than in patient 1 (66.7 versus 14.3 pg/mL, respectively). Both patients also showed elevated serum levels of IL-6 and IL-10. In patient 1, the serum levels of IL-6 and IL-10 both peaked on the 17th day of illness and then decreased after starting prednisolone (Figure 3B). In patient 2, the serum levels of IL-6 peaked on the 10th day of illness and then decreased to basal negligible levels. In contrast, the serum levels of IL-10 continued to increase throughout the disease course in patient 2 (Figure 3C).
Discussion

In this report, we demonstrated the cytokine profiles of PE in pediatric patients with IP for the first time. Despite the diagnosis and treatment, etiologies for the pericarditis had remained unclear in both patients. The two patients responded differently to anti-inflammatory drug treatment, despite having similarly elevated levels of the proinflammatory cytokine IL-6.

To date, there have been several reports regarding cytokine analysis in patients with PE. According to these reports, cytokine concentrations in the PE were higher than those in the serum or plasma, regardless of the PE etiology. In our cases, the cytokine concentrations in the PE were higher than those in the serum, in line with previous reports. These results suggest that pericarditis may arise because of local rather than systemic inflammation. According to the results of previous reports and the present study, the PE levels of IL-6 in pediatric patients range from 491 to 39,228 pg/mL, and are significantly higher than those in adult patients (up to 4,993 pg/mL).

From this viewpoint, PE in pediatric patients may require more aggressive anti-inflammatory treatments such as high-dose NSAIDs, systemic administration of steroids, or IVIG. In patient 1, intravenous steroid therapy in addition to a high dose of NSAIDs effectively reduced PE. However, the side effects of steroids, such as exacerbation of infection or growth impairment, must be considered.

Another concern is the different treatment response between the two patients. Patient 2 showed a better treatment response to anti-inflammatory therapy than patient 1, although the PE and serum levels of IL-6 were higher in patient 2 than in patient 1. Patient 2 also showed a higher concentration of IL-10 in both the PE and serum. Moreover, the serum IL-10 levels gradually increased in patient 2, whereas patient 1 only showed a transient elevation. IL-10 exerts essential functions to maintain tissue homeostasis during infection and inflammation through restriction of excessive inflammatory responses, upregulation of innate immunity, and promotion of tissue repair mechanisms. In patients with aseptic meningitis, IL-10 in the cerebrospinal fluid increases relatively late compared with the proinflammatory cytokines and plays an immunoregulatory role. Accordingly, higher local and systemic concentrations of IL-10 may confer anti-inflammatory effects, which may have contributed to the better treatment response in patient 2. In contrast to patient 2, patient 1 might lack IL-10 to restrict inflammation due to pericarditis. Hence, patient 1 might need additional steroid that inhibits transcription factors, such as nuclear factor-kappa B and activator protein-1, which are required for transcription of proinflammatory mediators. The difference of IL-10 levels between the two patients might be partly due to low IL-10 productivity of immature immunocompetent cells including regulatory T or B lymphocytes in infants. However, our study has the limitation of having analyzed a small repertoire of cytokines and no immunocompetent cells in only two cases.

These present cases suggest that pediatric patients with acute IP tend to show more severe inflammation than do adult patients with AP. Moreover, IL-10 may be associated with the response to anti-inflammatory therapy for acute IP. Further investigation is warranted to establish the pathogenesis and optimal treatment of acute IP.

Disclosure

Conflicts of interest: There are no conflicts of interest to declare.

Informed consent: Written informed consents were obtained from the patients’ parents.

References

1. Adler Y, Charron P, Imazio M, et al. ESC Scientific Document Group. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: the Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2015; 36: 2921-64.
2. Tombetti E, Giani T, Brucato A, Cimaz R. Recurrent pericarditis in children and adolescents. Front Pediatr 2019; 7: 419.
3. Imazio M, Lazaros G, Brucato A, Gaita F. Recurrent pericarditis: new and emerging therapeutic options. Nat Rev Cardiol 2016; 13: 99-105.
4. Shitara Y, Peters J, Marx GR, Breitbart RW. Etiology, management, and outcome of pediatric pericardial effusions. Pediatr Cardiol 2008; 29: 90-4.
5. Kühn B, Peters J, Marx GR, Breitbart RW. Etiology, management, and outcome of pediatric pericardial effusions. Pediatr Cardiol 2008; 29: 90-4.
6. LeWinter MM. Clinical practice. Acute pericarditis. N Engl J Med 2014; 371: 2410-6.
7. Ristić AD, Pankuweit S, Maksimović R, Moosdorf R, Maisch B. Pericardial cytokines in neoplastic, autoreactive, and viral pericarditis. Heart Fail Rev 2013; 18: 345-53.
8. Burgess JJ, Reuter H, Carstens ME, Taljaard JJ, Doubell AF. Cytokine production in patients with tuberculous pericarditis. Int J Tuberc Lung Dis 2002; 6: 439-46.
9. Hamada S, Miyamoto O, Oshiro T, et al. Possible involvement of IL-6-producing tissue-resident macrophages in early-onset pericardial effusion pathogenesis after hematopoietic stem cell transplantation. Pediatr Blood Cancer 2018; 65: e26982.
10. Shitara Y, Takahashi N, Aoki Y, et al. Cytokine profiles in pericardial effusion in a Down syndrome infant with transient abnormal myelopoiesis. Tohoku J Exp Med 2017; 241: 49-53.
11. Ouyang W, O’Garra A. IL-10 family cytokines IL-10 and IL-22: from basic science to clinical translation. Immunology 2019; 50: 871-91.
12. Ishiguro A, Suzuki Y, Inaba Y, Komiyama A, Koeffler HP, Shimbo T. Production of interleukin-10 in the cerebrospinal fluid in aseptic meningitis of children. Pediatr Res 1996; 40: 610-4.
13. Chatham WW. Glucocorticoid effects on the immune system. Available at: https://www.uptodate.com/contents/glucocorticoid-effects-on-the-immune-system?source=search_result&selectedTitle=2%7E150&usage_type=default&display_rank=2. Accessed May 31, 2020.
14. Schultz C, Strunk T, Temming P, Matzke N, Häretl C. Reduced IL-10 production and -receptor expression in neonatal T lymphocytes. Acta Paediatr 2007; 96: 1122-5.
15. Chheda S, Palkowetz KH, Garofalo R, Rassin DK, Goldman AS. Decreased interleukin-10 production by neonatal monocytes and T cells: relationship to decreased production and expression of tumor necrosis factor-alpha and its receptors. Pediatr Res 1996; 40: 475-83.