Primary Cytomegalovirus Infection, Atypical Kawasaki Disease, and Coronary Aneurysms in 2 Infants

Charlotte Catalano-Pons,1 Pierre Quartier,1 Marianne Leruez-Ville,2 Florantia Kagogelidou,3 Dominique Gendrel,4 Gérard Lenoir,5 Jean-Laurent Casanova,6,* and Damien Bonnet**

1Unité d’Immunologie et d’Hématologie Pédiatriques, 2Laboratoire de Virologie, and Services de 3Cardiologie Pédiatrique and 4Pédiatrie Générale, Hôpital Necker-Enfants Malades, 5Service de Pédiatrie Générale, Hôpital Saint-Vincent-de-Paul, and 6Onatoire de Génétique Humaine des Maladies Infectieuses, Université de Paris René Descartes-INSERM U550, Faculté Necker, Paris, France

We describe 2 infants who developed atypical Kawasaki disease and coronary aneurysms during primary cytomegalovirus infection. These observations suggest that children with coronary aneurysms and Kawasaki-like disease should be tested for cytomegalovirus. Conversely, children with unusually severe primary cytomegalovirus infection should be tested for coronary aneurysms.

Acquired coronary abnormalities in children are mostly due to Kawasaki disease [1], the diagnosis of which is still based on nonspecific clinical criteria [2]. It is an acute vasculitis, affecting small- to medium-sized vessels, especially coronary arteries, and occurring mostly in children aged <5 years. The immunopathological mechanisms involved in the pathogenesis of the disease are unclear. Although its etiology remains unknown, the clinical and epidemiological characteristics of the disease suggest that it is infectious [3]. We describe here 2 infants who developed primary cytomegalovirus (CMV) infection and atypical Kawasaki disease with coronary aneurysms.

Patient 1. A 3-month-old boy, who did not have a medical history, was admitted to the hospital because of 2 days of fever, asthenia, and anorexia. On physical examination, pharyngitis and conjunctivitis were observed. Laboratory findings revealed leukocytosis (WBC count, 15,700 cells/mm³), with 51% polymorphonuclear neutrophils, 33% lymphocytes, 11% monocytes, and 2% cells with basophil cytoplasm, anemia (hemoglobin level, 110 g/L), thrombocytosis (platelet count, 543,000 platelets/mm³), and inflammatory syndrome (C-reactive protein concentration, 69 ng/mL). CSF findings showed aseptic meningitis (9 WBCs/μL; protein level, 0.19 g/L; glucose level, 3 mmol/L; IFN-α level, <2 IU; a negative bacterial culture result; and no detection of CMV DNA by PCR-based methods). No bacterial or fungal agent grew on cultures of blood and urine samples. The patient was treated with cefotaxim and vancomycin for 2 days and then with amoxicillin and clavulanic acid for 5 days, with no response.

Echocardiography on day 9 of fever showed an aneurysm of the main left stem (5 mm in diameter) and 3-mm dilatations of the left anterior descending and circumflex branches and of the right coronary artery (normal dilatation, <2 mm). Kawasaki disease was suspected, and 2 high-dose (2 g/kg iv) immunoglobulin infusions were administered, along with acetylsalicylic acid (100 mg/kg/day) and an anticoagulant (fludione, 0.5 mg/kg/day), which had a transient effect on the fever and inflammatory syndrome. Four days later, a third immunoglobulin infusion was required. The patient’s condition improved, with a decrease in fever and levels of inflammatory markers, but he developed hepatosplenomegaly with mild cytolyis. The coronary lesions did not improve.

Diagnosis of primary CMV infection was based on the detection of CMV-specific IgM antibodies at a high level (IgM titer, 1:100, by CMV IgM EIA PCS assay; BMD) associated with a low IgG level (3400 UA/mL, by Enzygnost Anti-CMV/ IgG assay; Dade Berhing) and on the detection of the virus in blood and urine cultures. Serological tests were negative for influenza A and B viruses; parainfluenza viruses 1, 2, and 3; adenovirus; respiratory syncytial virus; Epstein-Barr virus; and parvovirus B19. Ganciclovir treatment was initiated (at day 28 after the first symptoms) at a dosage of 10 mg/kg/day and was continued for 3 weeks, which resulted in the resolution of fever, inflammatory syndrome, and thrombocytosis. Blood cultures were negative for CMV on day 4 after treatment; results of tests for CMV-specific IgM antibodies were negative at month 2 (IgM positive; IgG level, 47 U/mL, by Vidas CMV IgM and CMV IgG; bioMérieux); liver transaminase levels had normalized at month 1; and the hepatosplenomegaly had regressed at month 5. The right coronary artery was normal after 1 month, whereas the left coronary artery aneurysm regressed more slowly, over 7 months. One year later, findings of selective coronary angiogram were normal. We suspected impairment of the immune control of CMV, but findings were normal for...
immunological examination, which included tests of serum immunoglobulin levels; antibody responses to tetanus, diphtheria, and poliovirus vaccines; T cell and B cell subset counts; and the CMV-driven proliferation of T cells in vitro.

**Patient 2.** An 18-month-old girl was admitted to the hospital because of 2 days of fever, thoracic macular cutaneous lesions, edema of the extremities, conjunctivitis, and redness of the lips and pharyngeal mucosa. Biological tests showed leukocytosis (WBC count, 15,600 cells/mm³, with 85% polymorphonuclear neutrophils, 8% lymphocytes, and 3% monocytes), anemia (hemoglobin level, 7.8 g/dL), normal platelet count (315,000 platelets/mm³), and inflammatory syndrome (C-reactive protein level, 581 ng/L). CSF findings showed aseptic meningitis (27 WBCs/µL, with 42% polymorphonuclear neutrophils and 58% lymphocytes; protein level, 0.51 g/L; glucose level, 0.43 g/L; and negative culture results). No bacterial or fungal agent was isolated from urine or blood culture.

A 2.6-mm dilatation of both coronary arteries (normal dilatation, <2.2 mm) was diagnosed by echocardiogram on day 6 of fever. The patient received 3 infusions of high-dose (2 g/kg) immunoglobulin and acetylsalicylic acid (100 mg/kg/day). The C-reactive protein concentration decreased, but fever persisted, with a high erythrocyte sedimentation rate, and thrombocytosis developed (platelet count, 1,243,000 platelets/mm³). The patient received 3 infusions of methylprednisolone, with a transient response after 2 days. Oral corticosteroid treatment (2 mg/kg/day) was administered for 3 weeks. An echocardiogram (figure 1) revealed aneurysms of the left anterior descending artery (3.8 mm in diameter) and of the main left stem (4 mm in diameter). The patient was treated with a fourth immunoglobulin infusion and an anticoagulant (fluindione, 0.5 mg/kg/day). The patient's condition responded well to this treatment, with normalization of clinical and biological signs after 1 week. The coronary lesions, however, did not improve.

Serologic testing for CMV was performed on a sample that, unfortunately, was collected after the first immunoglobulin infusion; IgG levels and IgG avidity index results were therefore not interpretable. The diagnosis of primary CMV infection was based on the presence of specific CMV IgM at a very high level (index 3.6, by the Vidas CMV IgM assay; bioMérieux) and of CMV DNA detected by PCR in blood (viral load, 2700 copies/mL) and urine (viral load, 344,000 copies/mL). There was no specific IgM against Epstein-Barr virus, adenovirus, parvovirus B19, or human herpesviruses 6 and 7. Ganciclovir therapy (10 mg/kg/day for 8 days) was initiated at day 53. At the start of the treatment, an echocardiogram showed aneurysms of the left anterior descending artery (5 mm in diameter) and the main left stem (4 mm in diameter). Negative results were obtained for CMV PCR of blood plasma at day 25 and for CMV-specific IgM antibodies at month 6 (IgM negative; IgG level, 35 U/mL, by VIDAS CMV IgM and CMV IgG assay; bio-Mérieux). After 1 month of treatment, the main left stem displayed a dilatation of only 2.6 mm. Seven months later, echocardiogram findings were normal. After 1 year, selective coronary angiogram findings were normal. We suspected impairment of the immune control of CMV, but findings were normal for immunological examination, which included tests of serum immunoglobulin levels; antibody responses to tetanus, diphtheria, and poliovirus vaccines; T cell and B cell subset counts; and the CMV-driven proliferation of T cells in vitro.

**Discussion.** In our 2 patients, the association of CMV detection by culture and/or PCR of blood and urine samples with high CMV-specific IgM serum titers was consistent with the diagnosis of primary CMV infection. Moreover, the 2 children were aged 3 months and 18 months, ages consistent with primary CMV infection. Most clinical features were compatible with primary CMV infection, with the exception of the coronary aneurysms. Finally, treatment with intravenous immunoglobulin was ineffective, whereas the clinical, biological, and echocardiographic abnormalities improved after intravenous ganciclovir treatment. However, a polyclonal activation of B cells has been described in patients with Kawasaki disease, with an increase in IgM serum antibodies against pathogens previously encountered. In addition, there are uncertainties as to the timing of CMV infection if the diagnosis is based on detection of IgM antibodies, which can persist for >6 months after primary infection. CMV can also be detected for >2 years in urine samples after primary infection. Finally, because Kawasaki disease and CMV infection in the normal host are typically self-limited illnesses that resolve spontaneously, it is difficult to be certain that ganciclovir therapy contributed to the resolution of the febrile illness. CMV infection is common enough (seroprevalence, 27% at the age of 7 months [4]) that occasionally there may be patients who develop both illnesses simultaneously. Overall, we nevertheless propose that the primary CMV infection in these 2 patients was involved in the development of atypical Kawasaki disease and coronary aneurysms.

It has been found that 75% of CMV primary infections in childhood occur during the first year of life [4]. The possible involvement of CMV in the pathogenesis of vascular diseases has been suggested. CMV has been shown to be involved in vascular diseases in a murine model [5]. CMV-induced vasculitis has been described in adults with acquired immune deficiencies but has also been found in patients with no known immunodeficiency, presenting as a disseminated disease with involvement of gastrointestinal tract, CNS, or skin. CMV is the only infectious agent to have been implicated in several arterial diseases in adults: atherosclerosis, postangioplasty coronary restenosis, aortic aneurysms, and cardiac allograft vasculopathy [6]. The description of a case of neonatal aortic arch thrombosis associated with primary CMV infection also suggests that CMV...
Figure 1. Echocardiogram of patient 2. A, Aneurysms of the left main stem and of the left anterior descending artery (arrows) during the acute phase of primary cytomegalovirus infection. B, Same echocardiographic view 1 month later, after treatment with ganciclovir, showing slight dilatation of the left coronary artery (arrows). One year later, findings of selective coronary angiogram were normal.
may play a role in the pathogenesis of vascular disease in children [7]. Together, these data are consistent with a role for CMV in the development of coronary aneurysms in our 2 patients. Coronary aneurysms should be sought in children with unusually severe primary CMV infection, regardless of whether those children have been shown to have an immunodeficiency.

Atypical Kawasaki disease refers to cases with only 3 of the 5 principal features (changes in extremities, polymorphous exanthema, bilateral conjunctivitis, changes in the lips and oral cavity, and cervical lymphadenopathy) or with coronary artery changes and <3 of the principal features. It is more common in infants age <6 months and adolescents and may be a different etiological entity than Kawasaki disease [8]. Our 2 patients presented with vasculitis with 2 clinical criteria (conjunctivitis and pharyngitis) and 4 clinical criteria (conjunctivitis, pharyngitis, exanthema, and edema of the extremities) of classical Kawasaki disease and appeared to experience primary CMV infection. Kawasaki disease is the usual diagnosis given when young children develop coronary aneurysms. CMV infection may have played a pathogenic role in the development of coronary aneurysms. A diagnosis of primary CMV infection should thus be considered for children with coronary aneurysms and atypical Kawasaki disease. In a series of children hospitalized for Kawasaki disease, 10% had conditions that failed to meet strict criteria, and this was particularly true for young infants, 45% of whom presented with atypical disease. This subgroup of young children has the highest prevalence of coronary aneurysms [8] (75% vs. 20% for all children), with ~5% of patients having a condition resistant to intravenous immunoglobulin therapy [9]. Our report suggests that young patients with atypical Kawasaki disease should be tested for CMV infection.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

References