Lessons From the Misdiagnosis of Cryopyrin-Associated Periodic Syndrome as an Infection

Importance of an Early and Precise Diagnosis

To the Editor:

Cryopyrin-associated periodic syndrome (CAPS) is a rare congenital autoinflammatory disease caused by mutations in the NLRP3 gene. Previously, CAPS was assumed to include 3 distinct diseases: familial cold-induced autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease (also known as chronic infantile neurologic, cutaneous, and articular syndrome). The general clinical features of CAPS include recurrent fever, skin rashes, joint pain, and systemic inflammation.\(^1\)

In clinical practice, there is a significant delay between disease onset and diagnosis of CAPS. The median diagnosis delay was 7.3 years (range, 0.3–76 years) according to a report by an international registry on autoinflammatory diseases in the context of the Eurofever project.\(^2\) Delayed diagnosis may result in growth retardation, economic and psychological pressure for the patient and family, and antibiotic abuse.

Here, we report a case of a 42-month-old girl who had periodic fever for 20 months and was treated as an infectious disease without any improvement; she was ultimately diagnosed as having CAPS.

CASE PRESENTATION

The patient presented with an urticaria-like rash over her face and trunk on the second day after her birth. The rash worsened in the summer and improved in the winter, but never disappeared (Figs. A and B). She had recurrent fever beginning at 23 months of age, with a maximum body temperature of 39.5°C. The patient was treated with various antibiotics for more than 1 month, but no improvement was noted. Subsequently, she experienced sudden loss of consciousness and a staring-eye gaze lasting for 1 minute, without headache or vomiting. Laboratory tests showed that she had increased peripheral white blood cell counts (17.75 \(\times\) \(10^9\) /L; 57% neutrophils and 35.4% lymphocytes), anemia with hemoglobin level of 90 g/L, and increased C-reactive protein levels (44.5 mg/L). She had normal liver and kidney functions. Her immunoglobulin

FIGURE. Urticaria-like rash over the patient’s face and trunk (A and B). Chest CT showing bilateral pneumonia (C). Cranial CT scans showing widened sulci and gyri and enlarged lateral ventricles (D). Genetic mutation in NLRP3 of the patient (E) and relative mRNA expression of (F) IL-1\(\beta\), (G) IL-2, (H) IL-8, (I) IL-10, (J) TNF-\(\alpha\), (K) MKP-1, and (L) NLRP3 of the patient and her parents. F indicates father; M, mother; P, patient.
A diagnostic antituberculous regimen with bacterium culture remained negative after 6 weeks of treatment. After 15 months of antituberculosis treatment, the fever and rash were not improved, and the patient's condition remained unchanged; there was no obvious absorption of lung lesions, and she became irritable. Examination of CSF after more than 1 month of treatment revealed 210 white blood cells/µL (32% lymphocytes and 68% neutrophils), greater than 1857 mg/L protein, 0.94 mmol/L glucose, 1.08 U/L adenosine deaminase (reference range, 0–19.6 U/L), and 175 U/L lactate dehydrogenase. Cerebrospinal fluid smears and cultures were negative for bacteria, mycobacteria, and fungi. Chest computed tomography (CT) scans showed bilateral pneumonia (Fig. C). Cranial CT scans showed widened sulci and gyri and enlarged lateral ventricles and third ventricle of the cerebrum (Fig. D). Bacterial meningitis was suspected, and empirical antibiotics, including meropenem, cefepime, vancomycin, and linezolid, were administered. The patient's condition remained unchanged; there was no obvious absorption of lung lesions, and she became irritable. Examination of CSF after more than 1 month of treatment revealed 210 white blood cells/µL (32% lymphocytes and 68% neutrophils), greater than 1857 mg/L protein, 0.94 mmol/L glucose, 3 U/L adenosine deaminase, and 175 U/L lactate dehydrogenase; all etiological evidence was obtained. She tested positive for acid-fast smear and cultures were negative for Mycobacterium tuberculosis. After 6 weeks of treatment, the plasma level of interleukin (IL)-1β in the patient was increased to 22.3 ± 0.2 pg/mL, whereas IL-1β levels in both her parents were below the lower limit of detection (4 pg/mL) of the enzyme-linked immunosorbent assay kit. Real-time polymerase chain reaction showed that IL-1β mRNA levels were markedly higher in the blood cells from the patient than in those from her father and mother (Fig. F). The relative mRNA levels of other inflammatory cytokines, including IL-2, IL-8, IL-10, and tumor necrosis factor-α, remained normal in the patient compared with those in the healthy parents. Mitogen-activated protein kinase kinase phosphatase-1 (MKP-1), a negative regulator of mitogen-activated protein kinase activity and an indirect marker of the host’s inflammation level, was also upregulated in the patient (Figs. G–K). NLRP3 mRNA was not overexpressed in the patient (Fig. L).

Based on the combination of clinical symptoms, NLRP3 gene mutation, and increased IL-1β production in the blood, the patient was finally diagnosed as having CAPS. All antituberculosis drugs were discontinued. Although IL-1β inhibition is an effective therapeutic option,3 anakinra, rilonacept, and canakinumab are available in China. Therefore, we treated the patient with prednisolone (15 mg/d, 1.5 mg/kg per day). From the second day, the patient’s body temperature returned to normal, her rash subsided, and her condition and appetite improved. Notably, the rash recurred when she had diarrhea or flu during prednisolone treatment, and it usually lasted for 4 to 5 days.

The NLRP3 gene encodes the protein cryopyrin; mutations in this gene lead to constitutive activation of caspase 1 and excessive IL-1β secretion and cause inflammatory manifestations. The G1711A mutation is a newly discovered nucleotide mutation in the NLRP3 gene; however, this mutation (previously described as G569R) was first reported in a patient with Muckle-Wells syndrome and later in a patient with neonatal-onset multisystem inflammatory disease.1 The severity of CAPS disease may be related to IL-1β production.4 It is important to precisely diagnose CAPS early and treat the disease immediately to prevent persistent inflammation-induced organ damage.

CONCLUSIONS

In our case, before the final diagnosis of CAPS, the patient had been misdiagnosed as suffering from infectious diseases and was incorrectly given different antibiotics for approximately 2 years. Physicians are expected to have sufficient knowledge on clinical symptoms of autoinflammatory diseases and list them as differential diagnoses when taken care of a patient who shows “infection-like” symptoms that cannot be explained by infection. Next, they should use available technologies, such as next-generation sequencing, to confirm the genetic diagnosis. Early diagnosis and timely treatment are of great importance to avoid irreversible and severe organ damage and disability due to autoinflammatory diseases.

Key Message

Cryopyrin-associated periodic syndrome is a rare congenital autoinflammatory disease that shows symptoms similar to those of most infections and can, therefore, be easily misdiagnosed. Genetic detection using next-generation sequencing can facilitate the early diagnosis and treatment of such rare genetic diseases.

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