Introduction

Congenital panhypopituitarism is a condition that results from partial or complete loss of anterior pituitary function and its symptoms stem from the absence of pituitary hormones. The onset of pituitary failure is heralded clinically by growth hormone (GH) deficiency and thyroid failure, followed by hypogonadism and subsequent adrenal insufficiency. Neonates with congenital anomalies of the pituitary gland or hypothalamus may have hypoglycemia, midline deficiency (e.g., cleft palate), and micro penis whereas GH deficiency usually results in growth failure, thyroid stimulating hormone deficiency in hypothyroidism with symptoms that include weakness, hoarseness, and bradycardia, and adrenocorticotropic hormone (ACTH) deficiency in hypofunctioning adrenal glands associated with hypotension and infectivity. The diagnosis requires imaging and measurement of basal and evoked pituitary hormone levels. Treatment is generally with hormone replacement. Some reports suggest that adrenal insufficiency exacerbates infection. Septic shock as a consequence of cytomegalovirus (CMV) infection is rare in term infants. We encountered such a case that was complicated by congenital panhypopituitarism. Written informed consent was obtained from the parents of the patient for publication of this report.

Clinical Case

The patient was a male neonate born to nonconsanguineous Japanese parents with no significant family history of birth defects or fetal wastage. His mother was a 27-year-old woman, gravida 2, para 1. A diagnosis of cleft lip was made during the pregnancy. He was born by induced vaginal delivery at 41 weeks of gestation with a birth weight of 2,848 g. Apgar scores were 5 at 1 min and 7 at 5 min; he was subsequently transferred to our hospital because of respiratory distress and hypotonia after birth. At our hospital, his respiratory status deteriorated at 12 h after birth, requiring mechanical ventilation with 100% oxygen therapy. Systolic blood pressure dropped to 20 mmHg and serum interleukin-6 level was elevated to > 5000 ng/dL. We suspected septic shock and treated him promptly with antibiotics, hydrocortisone, and polymyxin-B-immobilized fiber column direct hemoperfusion (PMX-DHP) (Fig. 1). Oxygenation index was high at 28 and worsening pulmonary hypertension was documented on repeat echocardiogram, which raised suspicion for a right-to-left ductus arteriosus shunt with right ventricular
hypertrophy. Inhalational nitric oxide and inotropic therapy were then introduced. Inhalational nitric oxide therapy was completed at 15 days of age with extubation at 17 days and completion of inotropic therapy at 18 days of age.

He was diagnosed with congenital hypopituitarism by magnetic resonance imaging of the pituitary gland and examination of pituitary hormones at 19 days. Hormone replacement therapy was started at this point. Fever and inflammatory response did not improve; at 34 days of age, white blood cell count was 15,100/μL with 41.5% dysmorphic lymphocyte expansion. The diagnosis was congenital cytomegalovirus (CMV) infection based on a positive polymerase chain reaction (PCR) test for CMV DNA in dried umbilical cord blood. CMV DNA PCR was positive in both blood and urine at 48 days of age. Ganciclovir was administered for 3 weeks, after which conversion of CMV-positive cells was confirmed to be negative. Auditory brainstem response test at 98 days of age and fundus examination showed no abnormality. The patient was discharged at 108 days of age.

**Congenital hypopituitarism**

Routine newborn screening was normal in this patient. However, in view of the findings of cleft lip, micro penis (Fig. 2A, B), hyponatremia at completion of hydrocortisone therapy, and delayed appearance of the epiphyseal center at the distal femoral edge, we measured thyroid hormone levels at 19 days of age.

Thyroid stimulating hormone and T4 levels were significantly decreased (to 0.01 µIU/mL and 0.02 ng/l, respectively). We made a diagnosis of central hypothyroidism and investigated the levels of other hormones secreted by the pituitary gland. ACTH, follicle-stimulating hormone, luteinizing hormone, and GH levels were very low (< 0.02 pg/mL, < 0.1 mIU/mL, < 0.1 mIU/mL, and < 0.03 ng/mL, respectively; Table 1) and glucagon loading test on day 23 confirmed complete deficiency in GH secretion (Table 2).

Magnetic resonance imaging showed agenesis of the anterior pituitary gland (Fig. 3). Therefore, we made a diagnosis of congenital panhypopituitarism and started hormone replacement therapy consisting of hydrocortisone 24 mg/m², levothyroxine 14 µg/kg/day, and recombinant human growth hormone 0.38 mg/kg/week (Fig. 4).
CMV infection

Blood examination soon after birth revealed normal white blood cell count (8,200/µL (I/T 0.25) and total IgM and C-reactive protein (CRP) levels were within normal range (8 µg/dL and < 0.10 mg/dL, respectively; Table 3). His mother had not been checked for maternal serum CMV antibodies during the pregnancy. The patient showed a gradual increase in CRP (from 0.1 mg/dL at birth to 3.74 mg/dL at 7 days). We started antibiotics but CRP did not return to the normal range. Atypical lymphocytes were found to be elevated at 20 days. PCR at 23 days detected CMV DNA in urine and blood. We started him on oral ganciclovir 5 mg/kg twice daily for 2 weeks followed by 5 mg/kg once daily for 1 week. Subsequently, the mother’s blood and breast milk were found to be positive for CMV DNA. After treatment with ganciclovir, CRP level and liver function improved and CMV antigen was negative. We also examined the dried umbilical cord for CMV DNA using PCR to establish the time of infection. The result was positive and showed that he had contracted CMV infection just after birth via vertical mother-to-child transmission.

Discussion

Preterm low birth weight infants have a 3–10 times higher incidence of CMV infection than full-term normal birth weight infants. An immature immune system and
lack of transplacentally acquired maternal IgG antibodies might increase the risk of infection in premature infants\(^6\). So, there are few reports of severe congenital CMV infection in full-term infants.

Our patient developed severe complications, including pulmonary involvement (pneumonia, persistent pulmonary hypertension, pneumothorax), liver dysfunction, and septic shock as a result of CMV infection. A previous study found no significant demographic differences between infants with recurrent infection and infants born to mothers with either primary CMV infection during pregnancy or unclassified maternal infection\(^5\). The main infection routes for CMV are transplacental, vaginal delivery, breast milk ingestion, and blood transfusion. In our case, CMV DNA PCR was positive in maternal blood and breast milk and all CMV IgM antibodies in blood were negative. CMV DNA PCR of dried umbilical cord confirmed the infection\(^6\). Our report describes an infant who became infected at the time of delivery by vertical transmission from a mother who did not develop active CMV infection during pregnancy. He had no hepatosplenomegaly or intracranial calcification and was infected after the organogenesis period. We searched for other causes of atypical lymphocytes but obtained negative results for all viruses except for CMV.

The usual treatment for CMV infection is oral ganciclovir or its prodrug, valganciclovir. Some researchers have suggested that ganciclovir and valganciclovir may have clinical benefit in symptomatic newborns with central nervous system involvement\(^7\). Our patient was treated with ganciclovir for 3 weeks, after which he was confirmed to be negative for CMV-positive cells. Moreover, in this case, PMX-DHP was effective in the acute phase of treatment. CMV causes cytokine storm leading to septic shock and PMX-DHP reduces its mediators, including interleukin\(^8\). We regularly checked the value of CMV-positive cells but no reactivation was noted.

CMV infection can be fatal in patients with compromised immunity. Our patient also had congenital hypopituitarism. Hypopituitarism results from a deficiency of hormones produced by the anterior pituitary or those released from the posterior pituitary. Hypopituitarism has a high mortality rate and is a major risk factor for mortality in patients with cortisol deficiency as a consequence of ACTH deficiency\(^9\)\(^–\)\(^11\); such patients develop low blood pressure and eventually circulatory failure, which may be fatal unless treated promptly with cortisol and a vasopressor agent. The hypothalamic-pituitary-adrenal system was disrupted in our patient because of hypopituitarism and led to septic shock occurred.

Hypopituitarism is often accompanied by cleft lip and cleft palate, dysplastic in the midline. The genetic origins of these abnormalities are thought to be the same\(^12\)\(^–\)\(^14\). Mutations in transcription factors can be also accompanied by ocular abnormalities, such as septo-optic dysplasia. However, he had no optic abnormalities. Although particular genetic patterns could affect these mutations, he did not have specific family history. Failure of testosterone secretion associated with luteinizing/follicle-stimulating hormone deficiency caused the micro penis

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**Table 3** Glucagon loading test (day23)

|          | 0 min | 30 min | 60 min | 90 min | 120 min | 150 min | 180 min |
|----------|-------|--------|--------|--------|---------|---------|---------|
| GH (ng/mL) | < 0.03 | < 0.03 | < 0.03 | < 0.03 | < 0.03 | < 0.03 | < 0.03 |

GH, growth hormone

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**Fig. 4** Hormone replacement therapy during the hospital stay
in our patient. The septic shock in this case was treated with hydrocortisone, which also corrected the hypotension caused by the panhypopituitarism. A radiograph of the femur revealed no epiphyseal growth plate in this patient. Hypothyroidism causes growth retardation and impaired bone maturation. Thyroid hormone receptors are expressed on chondrocytes at the epiphyseal growth plate, where T3 regulates the expansion and differentiation of chondrocytes\(^{15}\). Furthermore, thyroid hormone has been shown to contribute to the control of serum growth hormone and insulin-like growth factor-1 levels\(^{16}\), and it is thought that hypothyroidism arrests growth, causes epiphyseal dysgenesis, and delays bone age because of the effects of thyroid hormone. We treated our patient with hydrocortisone, levothyroxine, and human growth hormone, after which he achieved good growth and weight gain.

The patient was screened for complications at the time of discharge from hospital. Investigations for intracranial calcification, chorioretinitis, and sensorineural deafness as sequelae of CMV infection were negative. At follow-up at the age of 1 year, his physical development is normal.

We encountered a case of septic shock due to CMV infection complicated by panhypopituitarism. Hypoglycemia or micro penis in the cleft lip should be suspected of complications of panhypopituitarism. It is plausible to keep CMV infection in mind when a neonate presents with severe septic shock.

**Conflicts of Interest**

The authors have no affiliations with or involvement in any organization or entity with any financial interest, or nonfinancial interest in the subject matter or materials discussed in this manuscript.

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