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Case Report

Primary Immunodeficiency Screening in an Infant with Cytomegalovirus Disease Reveals HIV Infection

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Abstract

Cytomegalovirus is widely spread worldwide, and it is not uncommon for it to complicate the congenital human immunodeficiency virus (HIV) disease as an acquired or congenital coinfection. However, the association of the two infections is not common amongst infants with primary immune deficiencies.

We describe a case of a 6-month-old infant with acquired cytomegalovirus and HIV infections, diagnosed in the course of the patient's clinical and laboratory workup for a presumed primary immunodeficiency. To date, this is the first reported case of such a combination in a child from Bulgaria.

Keywords

congenital immune disorder, children, flow cytometric workup, complex viral illness

INTRODUCTION

Cytomegalovirus (CMV) is the commonest congenital infection, affecting approximately 0.6%-0.7% of all newborns in the developing countries.[1] Significant differences exist in the incidence of congenital or early acquired CMV infection in HIV-positive or HIV-exposed but HIV-negative children.[2] Congenital CMV-disease can cause considerable morbidity, whereas acquired infection is usually asymptomatic in healthy full-term infants. However, in resource-limited settings, CMV has significant sequelae, including decreased growth and neurodevelopment, in infants of HIV-infected or HIV-uninfected mothers, requiring comprehensive care.[3,4] On the other hand, the right of non-disclosure of the parent's HIV status is legally guaranteed, but may hamper the timely diagnosis of an affected child, thus postponing the beginning of an adequate therapy.[5,6] Hereby, we report a clinical case of an infant with acquired CMV-infection as a cause for the detection of a congenital HIV infection.

CASE REPORT

A 6-month-old boy was brought to our hospital by his grandmother for a second time, with fever (up to 38°C), mild

cough, and transient macular rash. The previous hospitalization was a month before for otitis. The family history, according to the grandmother, was unremarkable. Past history: born abroad, after an uneventful pregnancy and normal delivery on term, with small-for-date anthropometric measurements: birth length 48 cm and birth weight 2400 g. The child was fed formula milk since birth, but with poor weight gain. At the age of three months, he was admitted to a hospital in Germany because of vomiting, failure to thrive, and chest X-ray proven interstitial pneumonia. Then an acquired CMV infection was detected by RT-PCR CMV-replication tests in blood and urine and negatives such in the stored neonatal screening heel-prick filter paper. After 15 days of antibiotic and supportive treatment, the patient still did not improve and the parents decided to leave the hospital, neglecting doctors' warnings.

Physical examination: alert, but in poor general condition with moderate dehydration signs and normal capillary refill. A generalized non-itchy erythema-macular rash was seen. There was bilateral coarse vesicular breathing. The liver was palpated at 3.5 cm below the costal margin, soft and non-tender, and the spleen was at 1 cm below the costal margin, with similar characteristics. The rest of the physical exam was normal for the age. Anthropometrics: weight – 4900 g (below the 3rd percentile), height – 61.5 cm (the 3rd percentile), head circumference – 38.5 cm (below the 3rd percentile).

Laboratory studies

Complete blood count: HGB: 102 g/L; RBC: 3.9×10^{12}/L; HCT: 0.33; MCV: 80.1 fl; PLT: 640×10^{9}/L; WBC: 25.24×10^{9}/L; Reticulocytes: 1.11%; ESR: 50 mm/h. ***Table 1*** *and* ***Table 2*** *show the differential blood counts (DBC) and biochemistry tests, respectively.* ***Table 3*** *gives details on the flow-cytometric lymphocyte subpopulations (T, B lymphocytes, and NK cells).*

Table 1. Differential blood counts, in % and absolute counts

Tests	%	Reference range (%)	Absolute count ($\times10^{9}$/l)	Reference range ($\times10^{9}$/l)
Neutrophils	**15.6**	22-45	3.93	2.2-4.5
Eosinophils	1.3	0-4.1	0.32	0-0.6
Basophils	1.3	0-2	**0.32**	0-0.1
Monocytes	5.8	5.8-11.8	**1.47**	0.4-0.8
Lymphocytes	69.7	35-74	**17.6**	3.5-7.3

Table 2. Biochemistry laboratory tests

Test	Result	Reference range
Total protein, g/l	77.1	57-80
Albumin, g/l	41.0	35-55
Total bilirubin, mcmol/l	13.3	3.4-21
Direct bilirubin, mcmol/l	5.6	0.8-8.5
CRP, mg/l	**17.5**	0-10
AST, U/l	**456.0**	0-60
ALT, U/l	**502.0**	0-45
LDH, U/l	862.0	230-975
GGT, U/l	**129.0**	0-55
Alkaline phosphatase, U/l	307.0	42-362
Urea, mmol/l	4.6	3.2-8.2
Creatinine, mcmol/l	32.0	35-75
Glucose, mmol/l	5.3	2.8-6.1
Fibrinogen, g/l	2.91	2.0-4.5
aPTT, seconds	28.1	24-35
PT, %	109.8	70-120
IgG, g/l	**14.4**	3.72-12.7
IgM, g/l	1.492	0.35-2.42
IgA, g/l	0.319	0.0-0.83
IgE, IU/ml	**35.3**	0-12.7

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Table 3. Flow cytometric lymphocyte subpopulations, TBNK-panel results (T, B lymphocytes and NK cells)*

Tests	%	Reference range %	Absolute count (×10⁹/l)	Reference range (×10⁹/l)
Lymphocytes			**17.025**	3.8-9.9
CD3+ T cells	58	50-77	**9.837**	2.4-6.9
CD3+CD4+T helper cells	**11**	33-58	1.803	1.4-5.1
CD3+CD8+T cytotoxic/suppressor cells	**39**	13-26	**6.596**	0.6-2.2
CD19+ B cells	34.9	13-35	**5.945**	0.7-2.5
CD3-CD16+CD56+NK cells	6.7	2-13	**1.134**	0.1-1.0
CD4/CD8 index	-	-	**0.27**	1.6-3.8

*Flow cytometry was performed at the Centre of Competence "PERIMED" of Medical University of Plovdiv, on BD FACS Aria III machine, according to a standardized procedure and using commercial TBNK-multitest reagent kit and national age-adjusted reference ranges of lymphocyte subsets.

Other laboratory tests

Blood gas analysis and urine tests – within reference range. Chest X-ray: increased bilateral vascularity. Upper-left sided infiltrative opacities. Mild hilar lymphadenopathy. Normal-sized heart. No effusions. Abdominal ultrasound: hepatosplenomegaly, diffuse homogenous hyperechoic liver structure. Normoechoic spleen. No ascites. Normal kidneys. No abdominal lymphadenopathy. Virology studies: serology – positive for anti-CMV IgG – 182.5 RU/ml (reference range <22 RU/ml); Anti-CMV IgM – 1.47 RU/ml (reference range <1.1 RU/ml); positive for anti-HIV1/2 Ag/Ab – ELISA and Western blot test. Negative anti-SARS-CoV-2 by PCR and antigen tests. TST (Mantoux test) <5 mm and T-Spot-TB- negative.

Treatment and disease course: proper rehydration and broad-spectrum antibiotic therapy led to improvement after two days of high fever and the rash waned, but the weight gain was poor yet. Thus, a comprehensive immune deficiency directed workup was initiated. High serum IgG, elevated CD19+B-lymphocytes and prominent CD4 lymphopenia with inverted CD4/CD8 index from the TBNK-panel were found. Consequently, HIV infection was proven. Finally, during the discussion about the HIV-testing, the parents reluctantly reported that the father had been HIV-positive for 12 years and on antiretroviral therapy (ART), but the mother had never been tested, nor had she received any ART. Accordingly, an antiretroviral therapy was started.

DISCUSSION

We describe the process of an immune deficiency screening in an infant with CMV infection. Traditionally, the serum anti-CMV IgM and IgG levels of the baby and the mother are analyzed in order to qualify the infection as congenital or acquired, together with quantitative RT-PCR for CMV replication. In unclear situations, the molecular testing of both the blood and the Guthrie card of the infant is proposed as a useful diagnostic method for accurate differentiation between congenital and acquired CMV infection, which was utilized in our case.[7] CMV is known to interfere with the clinical course of an immune deficiency and even worsen it, which holds true also for the HIV-infection.[8] In our case, we had initially no information about the HIV-status of the child and had only deceptive such for its parents. In line with the published guidelines[9], we screened the child for PID. Additional factor was the persistent hepatocytolytic activity, indicating failure to efficiently clear the CMV, also suggested by the elevated anti-CMV-Ig levels. The patient's DBC, mildly elevated CRP and the increased total and specific serum immunoglobulins indicated only the body's antiviral immune response. Flow cytometry is well established for lymphocyte subsets enumeration and functional analysis[10], and showed the aforementioned abnormalities in our patient **(Table 3)**. CMV is known to induce similar changes[11], as is the HIV infection or coinfection with CMV, which we proved[12]. Tuberculosis, the other most commonly reported infection in HIV-positive patients was ruled out via the IGRA-test.[13]

We can only speculate about the HIV status of the mother and the way of the HIV and CMV acquisition by the infant. Of note, it was born small for date and did not grow normally, despite the adequate care. ART is reported to decrease the rates of pre- and perinatal HIV transmission, so is the formula feeding of infants born to HIV positive mothers, although a horizontal transmission is also documented, which might be the case in our patient.[14]

The social sensitivity and stigmatization about HIV, especially in small societies or ethnic groups, are well documented.[5,6] These, together with the decision of the parents not to share their HIV statuses, are quite perspicuous and out of the scope of the current report. However, we also acknowledge that there should be better understanding and willingness on the part of parents to share such confidential information with the doctor responsible for their child's health, in the interest of children's wellbeing.

CONCLUSIONS

The reported case is a diagnostic challenge, further complicated by ethical issues and the overlapping clinical presentations of HIV and CMV in an infant. In any child with symptomatic CMV infection, primary or secondary immune deficiency must be considered. We acknowledge that testing for HIV should always be performed in the initial workup, then followed up by the more elaborate and expensive immunological tests. It is also appropriate to use the blood and the Guthrie card PCR-method for rapid differentiation of congenital from acquired CMV infection in the early infancy.

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Первичный скрининг иммунодефицита у ребёнка с цитомегаловирусной болезнью выявил ВИЧ-инфекцию

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Резюме

Цитомегаловирус широко распространён во всём мире, и нередко он осложняет течение врождённого вируса иммунодефицита человека (ВИЧ) в виде приобретённой или врождённой коинфекции. Однако сочетание двух инфекций не является обычным явлением среди детей раннего возраста с первичным иммунодефицитом.

Описан случай 6-месячного ребёнка с приобретённой цитомегаловирусной и ВИЧ-инфекцией, у которой в ходе клинико-лабораторного обследования был диагностирован предполагаемый первичный иммунодефицит. На сегодняшний день это первый зарегистрированный случай такого сочетания у ребёнка из Болгарии.

Ключевые слова

врождённое нарушение иммунитета, дети, проточная цитометрия, комплексное вирусное заболевание