Education-Family Physician Corner

A Trisomy 21 Neonate with CMV Infection Mimicking Acute Myeloid Leukemia Fab-M5

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Hyperbilirubinemia could be a part of Down syndrome; some will develop Transient Abnormal Myelopoiesis (TAM), which present with hepatosplenomegaly. TORCH screening is a group of blood tests which include testing for congenital cytomegalovirus (cCMV) infection, toxoplasma, rubella, cytomegalovirus, and herpes simplex virus.

We present a case of Down syndrome who had symmetrical intrauterine growth retardation, intrauterine growth restriction (IUGR), anemia, leukocytosis, thrombocytopenia, hepatosplenomegaly and blast cells in the peripheral smear. A diagnosis of TAM was confirmed initially. TAM had resolved spontaneously in a month and the patient developed direct hyperbilirubinemia and progressive hepatosplenomegaly with elevated liver enzymes and persistent thrombocytopenia with no blast cells. A diagnosis of cCMV infection was confirmed. Congenital infection in Down syndrome may mimic leukemia. It is important for cCMV to be diagnosed and treated early to avoid the complications.

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Down syndrome (trisomy 21) is the most common chromosomal abnormality. The incidence is approximately 1/800[1].

Individuals with Down syndrome have a high incidence of developing malignancy, especially leukemia. Down syndrome is a high risk of developing acute myeloid leukemia (AML), especially in those who are under the age of 5 years compared to a lesser risk of developing acute lymphoblastic leukemia (ALL)[2].

The most common type of AML in Down syndrome is acute megakaryoblastic leukemia FAB-M7 (70%)[2]; other types are rarely seen in Down syndrome[3]. It was noticed that AML-DS has proceeded with transient abnormal myelopoiesis (TAM) that is resolved spontaneously in most of the cases; however, 10% of these cases will progress to AML-DS. Thirty percent of Down syndrome are found to have a special mutation called GATA 1 that is responsible for developing AML. DS neonate with this mutation has a silent clinical and hematological presentation[4]. This makes AML in Down syndrome unique because TAM is uncommon in AML without Down syndrome[5].

Cytomegalovirus infection is the most common congenital viral infection worldwide; it is a human-specific DNA virus, belonging to the Herpesviridae family[6]. The majority of Cytomegalovirus cases are asymptomatic, however, this virus causes many complications in immunocompromised patients and in the fetus[6].

A primary CMV infection has a high transmission rate, 30–35%; a non-primary infection has a lower transmission rate, 1.1–1.7%[6].

The aim of this presentation is to report a case of a Trisomy 21 neonate with CMV infection mimicking Acute Myeloid Leukemia FAB-M5

THE CASE

A term baby boy was born from a non-consanguineous marriage (the mother is from Indonesia and the father is from Turkey), at full term 37 weeks, 37 weeks plus 4 days of gestation. The mother is a 40-year-old G3P3L3 who delivered by spontaneous vaginal delivery. The antenatal course had no complications. At birth, Apgar score was 9, 10 at 1 and 5 minutes, respectively. According to the growth chart for boys with Down syndrome, he showed symmetrical intrauterine growth retardation (IUGR) with all parameters below the 5th centile.

The patient was transferred to the neonatal intensive care unit (NICU) at the age of 6 hours due to reduced activity, respiratory distress and hypoglycemia. On physical examination, he was showing a phenotype of Down syndrome, confirmed by karyotype, male 47, XY, +21. In addition, he had hepatosplenomegaly.

Laboratory evaluation at birth showed leukocytosis with WBC count of 45.37x10^9/L. The peripheral blood smear revealed blast cells 24.0%, metamyelocytes 5%, myelocytes 2%, lymphocytes 27%, see figure 1 (A and B).

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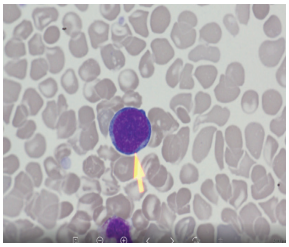

Figure 1 (A)

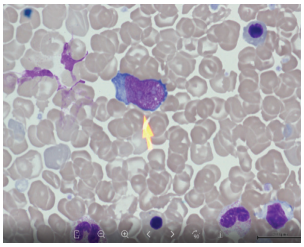

Figure 1 (B)

Figure 1 (A-B): Peripheral Blood (PB) Smear shows Blast Cells (Arrowed)

Flow cytometry study revealed CD45 dim/low SSA (blast cells) 28.14% with positive (bright) CD117: 81.7%, CD33: 97.6%, HLA-Dr: 46.4%, CD7: 79.7% & CD38: 90.1%, positive (dim) CD11b: 30.0% & CD13: 26.5% and negative CD34, MPO, CD14, CD15, CD16, CD41, CD42, CD61, CD56, CD64, TdT, CD3, CD5, CD10, CD19, CD20 & CD22; giving impression of AML FAB-M5 versus TAM for follow-up of blast cell count, see figure 2.

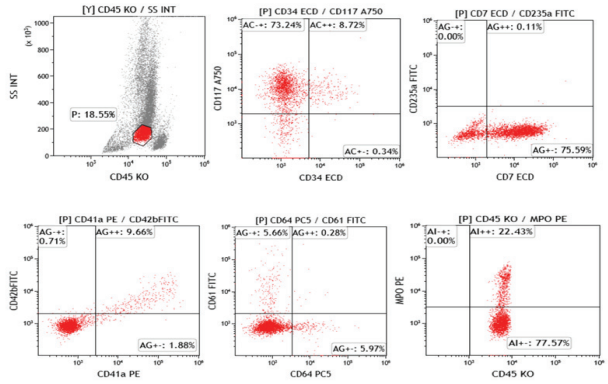

Figure 2: Flow Cytometry Analysis of PB Sample for AML Panel

Biochemical profile revealed normal liver function tests (LFT). Septic workup revealed high CRP level with 14.0 mg/L (N. 0.0-3.0). He was started on empirical antibiotics until the blood culture showed no growth. Thyroid test showed persistent high TSH level of 10.1 mIU/L. Congenital hypothyroidism was considered and thyroxine was prescribed. Echocardiography revealed tiny patent foramen ovale (PFO) and aortic regurgitation. Abdomen ultrasound showed hepatomegaly (size 6 cm). Portal vein, common bile duct and pancreas were normal. The gall-bladder was not seen. The spleen was enlarged 4.8 cm and had homogeneous parenchyma with minimal subhepatic free fluid; other organs were all within normal.

The patient started to improve clinically and his WBC and blast cell counts decreased; a diagnosis of TAM was contemplated and he was discharged.

At the age of 42 days he developed pallor and progressive hepatosplenomegaly, his CBC showed marked anemia Hb 7.0 g/dl and thrombocytopenia with platelets count of $56x10^9$/L. His peripheral smear showed absolute lymphocytosis with evident atypical features but with no blast cells. His LFT showed direct hyperbilirubinemia and elevated liver enzymes.

Serology test showed positive results for CMV, with CMV viral load PCR 1023.292 IU/mL, and CMV viral load LOG3.010 LOG/IU/mL.

The patient passed the hearing test, and the ophthalmology review revealed normal fundus, no cataracts, with bilateral epicanthus inverses. His cranial ultrasound showed normal ventricle size with no calcification or malformation.

The patient had trisomy 21 with tinny PFO and aortic regurgitation, diagnosed initially with congenital hypothyroidism for which he was kept on thyroxine and TAM resolved later. A congenital CMV was arrived at due to persistent direct hyperbilirubinemia, elevated liver enzymes, progressive hepatosplenomegaly and positive CMV viral study.

DISCUSSION

Congenital cytomegalovirus (cCMV) is the most common congenital infection worldwide[6,7]. The prevalence in developed countries is approximately 50 to 85%, while in the developing countries, it increased to 100%. The transmission of the disease is early in life through breastfeeding and crowded living conditions due to lower socioeconomic levels[6].

The diagnosis of cCMV is challenging because the majority of neonates are either asymptomatic (85-90%), or have non-specific symptoms (10-15%); therefore, cCMV is diagnosed late[7].

Neonates with symptomatic cCMV might present with: intrauterine growth restriction, small for gestational age, microcephaly, seizures, hypotonia, poor sucking/feeding, unexplained hydrops, hepatosplenomegaly, petechial rash and jaundice. The severity of these presentations vary from case to case; some cases present with life-threatening conditions[6,7]. The main laboratory findings are thrombocytopenia, direct hyperbilirubinemia, elevated transaminases, anemia with hemolysis, cerebrospinal fluid pleocytosis and elevated protein[6,7].

Additional assessments are required to detect other complications, such as cranial ultrasound, ophthalmology exam, and audiology exam[6,7]. These cases should be identified as early as possible to start the treatment with ganciclovir (GCV), which is anacyclic deoxyguanosine analog effective in the virus eradication and its complications[6].

Acute myeloid leukemia occurs as a result of abnormal proliferation and differentiation of the myeloid precursors in the bone marrow. The incidence of AML is 20% of all childhood leukemia; however, it is more likely to occur in Down syndrome 70%[2,8].

The incidence of Down syndrome with TAM is approximately 10%[9]. It could be identified by the presence of blast cells in the peripheral smear, bone marrow or in the liver[10]. However, it spontaneously regresses within 3 months[9].

After the regression, around 10-30% of these cases will develop AML after one to 30 months[10]. Down syndrome "trisomy 21" patients who present with signs and symptoms of sepsis-associated with leukocytosis should be differentiated from other differential diagnoses like sepsis, an intrauterine infection like TORCH, TAM, hemolytic diseases of the newborn and congenital leukemia[11].

French-American-British classification FAB has subdivided AML to 8 subtypes (M0-M7). M7 (Megakaryoblastic leukemia) is frequently found in Down syndrome while M5 (Monocytic leukemia) is less likely to occur in Down syndrome[3,8,10].

In this case, the diagnosis of cCMV was late because the

patient was found to have Down syndrome "trisomy 21" which explained his initial presentation; therefore, he was not screened for TORCH infection. Moreover, the presence of blast cells in the peripheral blood indicated TAM associated with Down syndrome; in addition, to the clinical improvement before discharge. A similar case reported a patient who was screened for TORCH earlier along with the genetic testing and found double pathogeneses[7].

CONCLUSION

Down syndrome (Trisomy 21) patients are challenging due to co-presentation with similar signs and symptoms of other genetic conditions, as well as the congenital infections like cCMV.

It is highly recommended to screen for TORCH infections in those newborns presenting with symmetrical IUGR even if they have a known genetic disease.

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