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CASE REPORT

Juvenile Myelomonocytic Leukemia in a Premature Neonate Mimicking Neonatal Sepsis

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Juvenile myelomonocytic leukemia (JMML) is a rare hematologic malignancy in children. Its presentations include anemia, thrombocytopenia, monocytosis, skin rash, marked hepatomegaly, and/or splenomegaly. Fever and respiratory involvement are common. Here, we report a case of a premature neonate with initial symptoms of respiratory distress. She gradually developed clinical manifestations of JMML that mimicked neonatal sepsis. Three weeks after birth, JMML was diagnosed. This is the first reported case of JMML presenting in a premature infant in Taiwan.

1. Introduction

Juvenile myelomonocytic leukemia (JMML) is a very rare pediatric hematopoietic malignancy. The median age of diagnosis is about 2 years old.[1,2] Infants or children with JMML clinically present with pallor, fever, infection, and skin rash. Accompanying clinical findings include lymphadenopathy and hepato-splenomegaly. It has been defined as a myelodysplastic/myeloproliferative neoplasm by the

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World Health Organization (WHO) classification in 2008 but due to recent identification of novel gene mutations in JMML, the diagnostic criteria of JMML were further modified in 2011.[3,4] Although the diagnosis of JMML is facilitated, early diagnosis remains a challenge. This is a report on a premature neonate with JMML.

2. Case Report

A female newborn was delivered at 35 weeks of gestation to a 33-year-old female (gravida 4, para 2) in a tertiary teaching hospital. The baby had a birth weight of 2730 g and measured 44.5 cm in length. Her APGAR scores were 4 at 1 minute and 5 at 9 minutes. Because she presented with mild respiratory distress, the baby was admitted.

On review of her prenatal history, thickened nuchal translucency was noted at 17 weeks of gestational age, although the prenatal cytogenetic study was normal. However, multiple congenital abnormalities were found after birth, including a boat-shaped head, ear anomaly with bilateral low-set ears, high arch palate, micrognathia, short neck, left simian crease, and edema over the bilateral hands, feet and the labia major. A pediatric geneticist was consulted, but no definite syndrome of chromosomal abnormality was suspected.

Complete blood count (CBC) on the 1st day of life revealed a white blood cell (WBC) count or 22.8 $\times$ 10^9/L (segments 40%, lymphocytes 30%, and monocytes 6%), hemoglobin (HGB) 13.9 g/dL, and platelets (PLT) 253 $\times$ 10^9/L (Table 1). The baby had progressive respiratory distress with tachypnea on her 3rd day of life. Patent ductus arteriosus 0.35 cm with left to right shunt was found by ultrasonography and she received oral Ibuprofen twice. However, fever, poor activity, cutis marmorata, hypotension, and bradycardia developed later. The baby was intubated and provided ventilator support. Repeated laboratory workup showed WBC 45.07 $\times$ 10^9/L, monocytes 36%, HGB 8.3 g/dL, PLT 232 $\times$ 10^9/L, and C-reactive protein (CRP) $<$0.05 mg/dL.

On her 9th day of life, the baby still appeared pale despite aggressive blood transfusion for severe anemia (HGB 5.1 g/dL) and thrombocytopenia (PLT 86 $\times$ 10^9/L). Peritoneal dialysis was initiated for acute renal failure. Brain ultrasonography showed left intra-cerebral hemorrhage (3 $\times$ 4 cm). Meanwhile, aggressive supportive care and empirical antibiotics were administered.

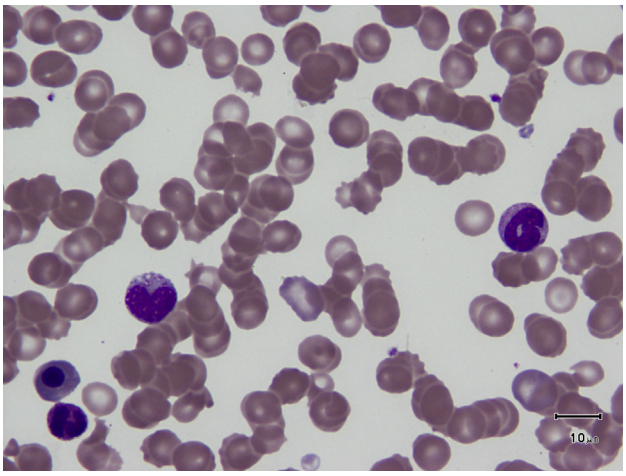

Figure 1 Peripheral blood smear showed leukocytosis with increased monocytes. Wright stain; magnification, $\times$1000.

Her clinical condition remained poor but stable in the following weeks. All viral studies, including virus serological survey [i.e., toxoplasma, cytomegalovirus (CMV), herpes simplex virus, human immunodeficiency virus EIA test, Epstein-Barr virus (EBV)] and viral cultures were negative. Successive bacterial cultures of blood, cerebral spinal fluid, and ascites did not yield any bacteria.

Severe anemia and thrombocytopenia persisted, with increased monocyte count to more than 10.0 $\times$ 10^9/L since the 7th day of life. Marked hepato-splenomegaly developed in the 3rd week. A peripheral blood smear showed 2% erythroblasts with the presence of myeloid precursors (Figure 1). Bone marrow aspiration revealed increased granulopoiesis, markedly increased monocyte series to 20%, no giant pro-erythroblasts with prominent intra-nuclear inclusions, and no excess of blasts. (Figure 2). Cytogenetic study of bone marrow and Southern blotting of the *BCR/ABL* fusion gene also had normal results. She had an elevated serum vitamin B12 level ($>$2000 pg/mL) and post-transfusion hemoglobin electrophoresis demonstrated 1.3% HbF and 2.5% HbA2. Juvenile myelomonocytic leukemia (JMML) was diagnosed.

Table 1 Complete blood counts of the patient.

Age*	WBC (10^9/L)	HGB (g/dL)	PLT (10^9/L)	DC (%)						Monocytes (10^9/L)	NRBC/100WBC (%)
				BAND	SEG	LYM	MON	EOS	BASO		
1	22.8	13.9	253	0	40	30	6	24	0	1.368	3
7	45.1	8.3	232	2	33	17	36	12	0	16.225	
15	15.3	11.0†	35	0	67	19	12	2	0	1.836	17
22	24.1	15.6†	76†	0	28	21	50	1	0	12.050	8
25	40.6	9.8	104†	0	45	27	28	0	0	11.359	9
33	39.7	8.9	32	0	58	11	30	1	0	11.904	2
46	23.7	13.3†	60†	0	82	8	9	1	0	2.133	1

BAND = bands; BASO = basophils; DC = differential count; EOS = eosinophils; LYM = lymphocytes; MON = monocytes; NRBC = nucleated red blood cells; SEG = segments.

* Age in days.

† Post-transfusion laboratory report within 3 days of transfusion.

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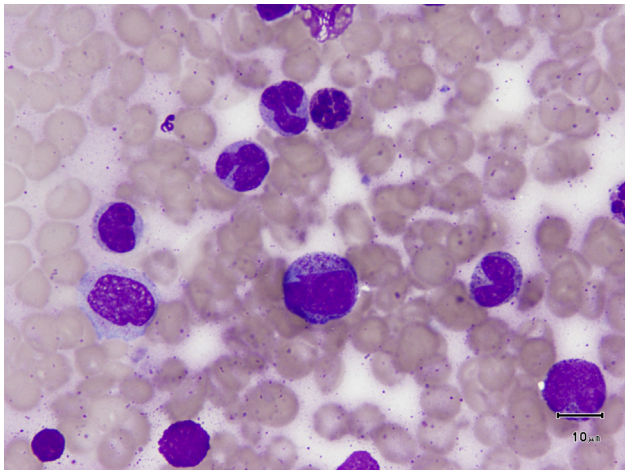

Figure 2 Bone marrow smear showed increased precursor cells of myeloid and monocytes series, without any excess of blasts. Wright stain; magnification, ×1000.

On the 23rd day, a consciousness change and flaccidity with upward gaze were noted. Brain magnetic resonance imaging (MRI) revealed multiple intra-cranial hemorrhages with hydrocephalus. Despite emergency extraventricular drainage, the baby's condition further deteriorated. Her deranged hemogram also persisted. The parents refused further transfusion and the baby died after 58 days of life.

3. Discussion

Juvenile myelomonocytic leukemia (JMML) is a clonal hematopoietic disorder of childhood that has features of both myeloproliferation (leukocytosis and monocytosis) and myelodysplasia (anemia and thrombocytopenia).[5]

Pallor, fever, infection, skin rash, bleeding problems, and cough are the most common presenting symptoms.[1] Like most patients with JMML, the present case initially presented with fever and signs of respiratory involvement. However, severe neonatal infectious diseases, sepsis, and JMML often present with a similar clinical picture. The manifestations of several microbial infections, such as EBV, CMV, human herpes virus-6, histoplasma, mycobacteria, and toxoplasma, may mimic JMML.[6] Parvovirus B19 infection can also reportedly cause symptoms and signs mimicking JMML in newborns.[7] Thus, infectious diseases should be carefully excluded before the diagnosis of JMML is made.

A variety of infectious organisms were thoroughly investigated in this current case, and all yielded negative results. Multiple viral cultures from all sterile body fluids yielded nothing. Due to the unavailability of PCR assay or IgM of parvovirus B19 in the hospital, these were not studied in this patient. However, pathognomonic bone marrow findings of parvovirus B19 infection, including giant pro-erythroblasts with prominent intra-nuclear inclusions and cytoplasmic vacuolations, were not identified. Moreover, her poor but stationary clinical condition, deranged hemogram regardless of antibiotic use, and persistently low CRP levels made the diagnosis of infection-related myeloproliferative disorder less likely.

The diagnostic criteria for JMML include three categories (Table 2).[3,4] The baby met all four features within Category 1 (absence of *BCR/ABL* fusion gene, peripheral blood monocytosis greater than 1×10^9/L, <20% blasts in the bone marrow, and splenomegaly) and two features in Category 3 (WBC count greater than 10×10^9/L and circulating myeloid precursors). On these bases, the diagnosis of JMML was made. In the absence of features within Category 3, genetic mutation analysis (Category 2) for *NRAS*, *KRAS*, *PTPN11*, *NF1*, and *CBL* provided strong aid in diagnosing JMML.[8]

Juvenile myelomonocytic leukemia usually occurs in young children. The median interval between the onset of symptoms and diagnosis of JMML is 1.9 months (range, 0—23 months) in the study of Niemeyer et al.[1] The median age of diagnosis is about 2 years old.[1,2] Chang et al reported 16 patients with JMML in Taiwan with a median age at diagnosis of 2.5 years old.[9] The youngest patient in their study was 9 months old.[9] Chen et al also reported a Taiwanese male infant with JMML diagnosed at 6 months old who did not survive the next 2 months.[10] Most of the infants had fever as their first symptom and eventually developed marked hepato-splenomegaly with persistent monocytosis. Only two cases of JMML diagnosed in premature infants have been reported in literature.[11,12] Their presentations are similar to those of the current case report. The two previous cases were born at a gestational age of 30 and 34 weeks, respectively. Their refractory anemia and thrombocytopenia were not present until 18 days and 1 week of

Table 2 Current diagnostic criteria for juvenile myelomonocytic leukemia.*

Category 1 (All of the following)	Category 2 (At least one of the following)	Category 3 (Two of the following if no Category 2 criteria are met)
1) Absence of the *BCR/ABL1* fusion gene	1) Somatic mutation in *RAS* or *PTPN11*	1) WBC count >(10×10^9/L)
2) >1×10^9/L circulating monocytes	2) Clinical diagnosis of NF1 or *NF1* gene mutation	2) Circulating myeloid precursors
3) <20% blasts in the bone marrow	3) Monosomy 7	3) Increased Hb F for age
4) Splenomegaly		4) Clonal cytogenetic abnormality excluding monosomy 7
		5) GM-CSF hypersensitivity

Patients who have Category 2 lesions need to meet the Category 1 criteria but not the Category 3 criteria. Patients who have Category 3 lesions must meet the Category 1 and 3 criteria.

* Modified from [4].

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age, respectively. Both cases were proven to be Noonan syndrome (NS)-related JMML.

Noonan syndrome is an autosomal dominant disease characterized by facial dysmorphology, short stature, and congenital heart defects.[13] Facial dysmorphology includes a triangular-shaped face, hypertelorism, down-slanting eyes, and strabismus. Children with NS may exhibit pectus carinatum or excavatum, lymphedema, hypotonia, and seizure disorder. They are reported to display a self-resolving myeloproliferative disorder in infancy that resembles JMML.[4] Tartaglia et al identified germline mutations in *PTPN11* as causative in approximately 50% of children with NS.[14] Based on typical clinical features and/or additional genetic test, the diagnosis of Noonan syndrome can be made. Mutations in *PTPN11* are also identified as somatic lesions in *de novo*, nonsyndromic JMML and it has a frequency of up to 35% of patients in some series.[4]

Due to the co-existence of multiple anomalies and JMML, NS was suspected in this case patient. However, no typical features of NS were identified after detailed examinations by the geneticist. Unfortunately, genetic tests such as *PTPN11* mutation were not arranged due to parental refusal.

To date, this is the first case of JMML presenting in a premature infant in Taiwan. Quick infectious survey and early recognition of noninfectious etiologies in a patient with clinical presentations mimicking neonatal sepsis is crucial for the early diagnosis of JMML in premature babies.

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