

Leukaemia or Leukaemoid, Down Syndrome or not?

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Case Report

Baby WM was the first live born child of the family. Her 18-year-old mother had swollen ankles, lower abdominal pain and reduced fetal movements at 31st weeks of gestation. Ultrasound scan showed fetal cardiomegaly and early hydropic changes including hepatomegaly and swollen placenta. No maternal-fetal haemorrhage could be demonstrated by Kleihauer test.

A baby girl was delivered one week later by Caesarian section. Her birth weight was 1830 grams. Apgar scores were nine at first minute and ten at fifth minute. She was phenotypically normal. She had moderate pallor but no lymphadenopathy. There were no blue-moffin rashes. A grade 2/6 ejection systolic murmur was heard over the left sternal border and of characters in keeping with flow murmur. Her abdomen was distended and the liver edge was felt at 6 cm below the costal margin. The spleen was palpable at 4 cm below the costal margin.

She had respiratory distress that necessitated nasal CPAP support. CXR showed cardiomegaly with streaky lung fields. There was no pleural effusion. Echocardiogram showed a structurally normal heart except a small patent ductus arteriosus. There was no pericardial effusion.

Blood count showed high white cell count at $73 \times 10^9/L$, with blast cell predominance ($47 \times 10^9/L$). The haemoglobin was 9.7 g/dL and platelet count was $135 \times 10^9/L$. Smear found the blast cells were morphologically undifferentiated. Circulating nucleated red cells showed features of dyserythropoiesis. The blast cells were negative for myeloperoxidase and Sudan black B on cytochemical staining. Immunophenotyping of the blast cells showed expression of megakaryocytic markers CD42b and CD61, as well as CD7. A panel of myeloid, B-cell and other T-cell lineage markers were negative. Cytogenetic study of her peripheral blood detected 47,XX,+21[16] on overnight culture and a mosaic pattern of 47,XX,+21[4]/46,XX[14] on PHA-stimulated culture.

She had severe unconjugated hyperbilirubinaemia and successfully controlled by a double volume exchange transfusion performed at 32 hours of life. The clinical course was further complicated by ileal perforation with pneumoperitonium on day 3 of life. Ileostomy was performed. Histology showed focal inflammation and haemorrhage at perforation site with suspicious leukaemic infiltration. Liver biopsy performed during the operation showed mild to moderate polymorph infiltration at portal tracts and evidence of extramedullary haemopoiesis, with focal collections of blast cells in sinusoidal areas.

She was thought to be either a mosaic Down syndrome with transient abnormal myelopoiesis (TAM) or a normal baby with acquired +21 due to a leukaemic process. She was managed conservatively without any form of chemotherapy. She became pancytopenic on day 14. The platelet count numbered $9 \times 10^9/L$, while absolute neutrophil count was $0.5 \times 10^9/L$ on day 22. Bone marrow aspiration and trephine biopsy were performed. The peripheral blood showed 15% blasts while marrow blood showed 39% blasts with similar morphology. The marrow blast cells on immunophenotyping showed expression of CD45, CD61, CD7 and CD33. A repeat cytogenetics study on bone marrow cells again showed mosaicism of 47,XX,+21[9]/46,XX[3]. While FISH with

Figure 1. A) Circulating blast cells and nucleated red cell at presentation Wright x 1000. B & C) Interphase FISH with 21q probe, showing cells with 3 signals i.e. +21 (arrows). D) Collection of blasts and a megakaryocyte (arrow) in liver biopsy. E) Interphase FISH on buccal epithelial cells showing disomy 21. F) Bone marrow aspirate showing return of normal haemopoiesis and resolution of TAM. Wright Giemsa x 1000.

21q probe (Vysis, Downers Grove, IL) showed 50.4% of interphase cells in peripheral blood harboured +21, PHA-stimulated culture showed +21 in only one cell out of 100 metaphases examined, which might represent the occasional residual blast cell in the latter culture system.

The number of circulatory blast cells slowly declined and was not detected in peripheral blood after day 40 of life, concurrent with normalization of blood count. Blood marrow aspiration repeated on day 84 showed normal haemopoietic activity. Blood count was completely normal and she was discharged on day 95. Buccal epithelial cells and cultured skin fibroblasts (each 500 cells analysed) showed absence of +21 as detected by FISH. At 8 months old, we repeated the interphase FISH study on peripheral blood and confirmed persistent absence of +21. When she was seen at 18 months old, she had completely normal haematological parameters.

Discussion

The diagnosis is a phenotypically normal but premature baby girl with TAM. The +21 abnormality was restricted to the haemopoietic cells. Cytogenetics and interphase FISH study showed presence of normal and +21 cells in peripheral blood and marrow, the latter clone disappearing with disease resolution. The failure to detect a single cell with +21 among 500 cells metaphases and interphases from stimulated lymphocytes, bone marrow and skin fibroblasts excludes 1% or more mosaicism.

In this case, some early hydropic changes could be detected. In Fact, Baschat *et al.* reported that prenatal diagnosis of TAM is possible as early as 26 week's of gestation.¹ Fetal hydrops and hepatosplenomegaly may indicate an underlying haematopoietic disorder.

TAM is a condition clinically resembling congenital acute myelogenous leukaemia. As in acute leukemias the blast cell population in this disorder may have either normal or abnormal chromosomal complement. Transient myeloproliferative disorder is well recognized in neonates with a complete or mosaic Down syndrome.²⁻⁴ Phenotypically and cytogenetically normal infant with this syndrome in whom only blast cells showed trisomy 21 had been previously reported.⁵⁻⁷ Trisomy was apparently restricted to the leukemic clone and could be detected in neither phytohemagglutinin-stimulated peripheral blood cells or bone marrow in myeloid progenitors cells after resolution of the TAM. These infants just like the mosaic Down and constitutional Down could have durable spontaneous remissions.

Congenital leukemia should be differentiated from transient leukemoid reaction or TAM, which is commonly noted in Down syndrome. Bresters et al reviewed Dutch patients and those described in the literature with congenital leukaemia in the past 25 years.⁸ This shed lights on how to differentiate leukaemia from leukemoid. Obviously, lymphoblastic blasts pointed towards leukaemia but its incidence was less common than AML (21% ALL vs 64% AML). Myeoloid blasts other than M7 type pointed towards leukaemia. For congenital leukaemia patients, most had a high leukaemic cell load with hepatosplenomegaly, leukaemia cutis and hyperleucocytosis; whereas leukemoid cases were much more stable and had fewer signs.^{8,9} Cytogenetic abnormalities were more commonly found in the majority of the leukaemia patients tested (72%); 11q23 abnormalities were found in less than half of them (42%). To the contrary, TAM or leukemoid patients had few cytogenetic abnormalities apart from +21.

Outcome in congenital leukemia is poor, but spontaneous remissions have been described. To date, 18 cases of congenital leukemia showing spontaneous remission have been described in the literature, almost exclusively myeloid leukemia (FAB M4 and M5).⁸ Because of that, some experts suggested cytostatic treatment should start only if the malignancy interferes with vital parameters. In case of relapse or progression, initial postponement of chemotherapy in these frail neonates will result in less toxicity and probably a better survival. This is even more true for patient who has + 21, be it constitutional, mosaicism or from the neoplastic clone. +21 cytogenetics together with M7 type of immunophenotyping, give much higher chance of spontaneous resolution.

The association of Down syndrome and leukaemia has been documented for over 50 years. Incidence of leukaemia in Down patients are 10-20 fold higher than that in the general population. All cytogenetic types of Down syndrome apparently predispose to leukaemia. A significant proportion of Down patients with TAM after initial resolution may subsequently develop AML. Normal child with TAM also developed subsequent AML in isolated case report but the incidence is largely unknown.¹²

TAM with +21, most probably a leukaemia-specific abnormality in this disorder, exists in three groups of neonates: Down's syndrome, constitutional mosaic Down's syndrome in which non-disjunction occurs early in embryogenesis with +21 appearing in different cell lines, and +21 restricted to blood (neoplastic) cells. The +21 abnormality may be considered as acquired in the last category, akin to other types of leukaemia. It will be most interesting to see whether the risk of progression to acute megakaryoblastic leukaemia is different among these categories.¹¹⁻¹³

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