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LETTER TO EDITOR (VIEWERS CHOICE)

# TWO UNEXPECTED OUTCOMES AFTER AN UNMONITORED PREGNANCY

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Down syndrome (DS) is the most prevalent chromosomal abnormality in liveborn infants, with higher risk of developing haematological disorders.[1,2] Nearly 10% of this infants develop a transient myeloproliferative disorder (TMD), also designated transient leukaemia/ transient abnormal myelopoiesis, an exclusive hematologic disease in DS, clinically and morphologically indistinguishable from those of acute myeloid leukaemia (AML), establishing diagnostic challenges and demanding a distinguished approach.[3,4,5]

The molecular pathogenesis of TMD is complex, requiring a shift in GATA-1 through the acquisition of a somatic mutation in the gene encoding this hematopoietic transcription factor.[3,6] The exact incidence is undetermined because patients can be asymptomatic and no mandatory laboratorial work-up testing is needed in this patient´s subgroup. The majority of patients are diagnosed within the first weeks of life.[7,8]

The range of clinical presentations of TMD varies from asymptomatic to life-threatening.[3] The usual scenario is between the 3rd - 7th day, although there are reports of patients diagnosed later, including up to 2 months of age.[2] Some are initially noticed when circulating blasts appear in peripheral blood analyses conducted for screening purposes. Others are visibly ill, showing broad features of clinical and lab anomalies at the time of diagnosis.[3,5]

This is the report of a peculiar case of an unknown pregnancy of a newborn with a post-natal diagnosis of DS and afterwards also diagnosed with TMD.

Term newborn, 37 weeks of post-menstrual age, maternal age of 43 years, healthy parents, non-consanguineous. Unknown pregnancy (menstrual irregularities and bleeding in all trimesters), unmonitored, prenatal ultrasounds haven't been carried out. Negative serology performed in the delivery room. Admitted to the Emergency Department with amniotic fluid leaking, in expulsive stage.

A female newborn weighing 3050 g, Apgar 10/10 was born by vaginal delivery, presenting a phenotype compatible with DS, confirmed by karyotype analysis (47, XX,+21).

In day one, due to jaundice, laboratory blood test were performed, revealing a white blood count of 23.3 x $10^9$ cells (20% of blasts), haemoglobin 17.6 g/dL, platelet count 132 x $10^9$/L, LDH 1542 IU/L, uric acid 7.1 mg/dL, AST/ALT 101/59 U/L, with no other alterations. Blood gas analysis and coagulation were in the normal ranges. Immunophenotyping was performed and it suggested an acute megakaryoblastic leukaemia.

The newborn didn´t show signs of respiratory distress, hepato/splenomegaly, ascites or haemorrhagic diathesis. Echocardiogram revealed moderate interatrial communication with left-right shunt. Cerebral and abdominal ultrasound were normal.

The case was discussed with a multidisciplinary team, namely the Oncohematology Service of reference hospital, deciding expectant management and assess clinical and laboratory evolution. On day five, despite the clinical situation remained stationary, he was admitted into the reference hospital for further surveillance. GATA-1 sequence was performed, revealing two somatic mutations in different alleles.

Hospital discharge occurred on day eight. Laboratory revealed a with blood count 11.7 x $10^9$cells/L (15% of blasts), with no other alterations. Clinically well, physical examination highlights only axial hypotonia.

There was no need for directed treatment as the newborn showed a spontaneous, progressive and complete remission with no peripheral blasts in Oncology reassessment consultation after one month. There were no further complications and is currently well at twenty-two months old.

When facing a newborn with a leukemoid reaction it's essential to build a differential diagnosis around other semiologically-related entities that can mimic it, such as congenital viral infections (TORCH), neonatal leukaemia, neuroblastoma, neonatal haemolytic processes (Rh-incompatibility), histiocytosis or conditions that encompass perinatal hypoxia.[2]

Amid all patients with TMD, up to 22-42% can present with life-threatening clinical spectra caused by tumour lysis or organ infiltration, including intense leucocytosis/ leucostasis and multiorgan failure with need for hemodynamic/respiratory support.[1,2,9]

The primary treatment is supportive therapy. Since the very heterogeneous clinical presentation, it's imperative to recognise who will benefit from targeted therapeutics regimens when applicable.[2,10] Chemotherapy is reserved for patients with severe indicators like multiorgan failure function and/or severe leucocytosis as well as visceromegaly or serous effusion.[2]

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While TMD resolves spontaneously in most patients within the first 3-6 months, ~30% may develop AML, typically in the first four years of life and frequently after a prior period of cytopenias due to myelodysplastic syndrome.[7] Due to the significant risk for following acute leukemia, every patient with history of TMD should be monitored for signs and symptoms of evolution. Contrasting AML in other children, in DS it has an excellent prognosis with an expected five-year event-free survival rate of ~90%.[11]

This case illustrates the importance of prenatal screenings and the investment in structured maternal care. Unsurveilled pregnancies are, fortunately rare, however we still witness concerning cases like the one we report. Chromosome abnormalities are infrequent, but always translate in chronic morbimortality. On the other hand, myeloproliferative disorders although rare, are challenging and need to be considered, especially in DS, requiring a multidisciplinary approach, but in some cases may not be a factor of poor prognosis on the long-run.

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