Lysinuric protein intolerance associated Hemophagocytic Lymphohistiocytosis revealed by bone marrow atypical hemophagocytosis

Intolérance aux protéines dibasiques avec lysinurie associée à une hémophagocytose lymphohistiocytaire révélée par une hémophagocytose médullaire atypique

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A 10-month-old girl was admitted to the pediatric department for early-onset pancytopenia and hemophagocytic lymphohistiocytosis (HLH) suspicion. Digestive disorders were noted in her history. Clinically, the child was initially eutrophic and exclusively breastfed upon the first examination, with findings of hepatomegaly and a spleen tip; the rest of the examination was unremarkable. During the course of the disease, she experienced growth failure, mainly affecting weight gain, falling below the expected growth curve for their age.

Laboratory tests revealed pancytopenia with normochromic normocytic anemia (hemoglobin = 10 g/dL), leukoneutropenia (White Blood Cells = 3.1 × 10^9/L; Neutrophils = 0.8 × 10^9/L), and thrombocytopenia (Platelets = 111 × 10^9/L).

Additionally, hepatic cytolysis (Aspartate Aminotransferase = 96 U/L), hemolysis markers (Lactate Dehydrogenase = 1500 U/L, Haptoglobin < 0.1 g/L), elevated ferritinemia (2076 µg/L), and hyperammonemia (190 µmol/L) were observed. Immunoglobulin assays, immunological tests, and viral tests were negative. Abdominal ultrasound showed isolated homogeneous hepatosplenomegaly.

Our patient met only four of the eight revised HLH 2004 diagnostic criteria, supporting a diagnosis of leaky HLH. Furthermore, the patient presented with additional laboratory abnormalities commonly associated with HLH, such as elevated liver enzymes and LDH. Lipid profile, NK cell activity and soluble CD25 levels were not performed due to lack of reagents.

Bone marrow examination revealed a normocellular marrow. There was an increased presence of apoptotic neutrophils (Figure 1A, all images x100, May Grünwald Giemsa stain). Additionally, selective phagocytosis of naked nuclei by immature granular cells was observed (figure 1B and 1C), an abnormal process where these cells engulfed the nuclei. Numerous hemophagocytic images were present (figure 1B et 1D), where histiocytes displayed cytoplasm filled with engulfed erythroblasts.

These findings pointed towards a rare metabolic disorder, the lysinuric protein intolerance (1,2). This rare condition is characterized by a defective transporter of dibasic amino acids (arginine, ornithine, lysine), leading to their deficient plasma levels and impaired urea cycle function (3).

The diagnosis of LPI was confirmed by the child's biological parameters. blood amino acid chromatography indicated decreased plasma levels of lysine (61 µmol/L), arginine (25 µmol/L) and ornithine (9 µmol/L), and increased levels of glutamine (1255 µmol/L), alanine (406 µmol/L), glycine (327 µmol/L), serine (263 µmol/L) and proline (278 µmol/L). The presence of urinary orotic acid was

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confirmed by chromatography. The molecular analysis to identify mutations in the SLC7A7 gene (4) has been requested but is ongoing; the result is not yet available.

In conclusion, characterized by their rarity and often limited understanding, hereditary metabolic disorders require a comprehensive evaluation. Hematological and bone marrow cytology are crucial tools in establishing an accurate etiological diagnosis. While variable, certain medullary features, such as selective phagocytosis of naked nuclei by histiocytes or granulocyte precursors, are characteristic of lysinuric protein intolerance. This condition should be considered in any patient presenting with a hemophagocytic syndrome and growth failure.

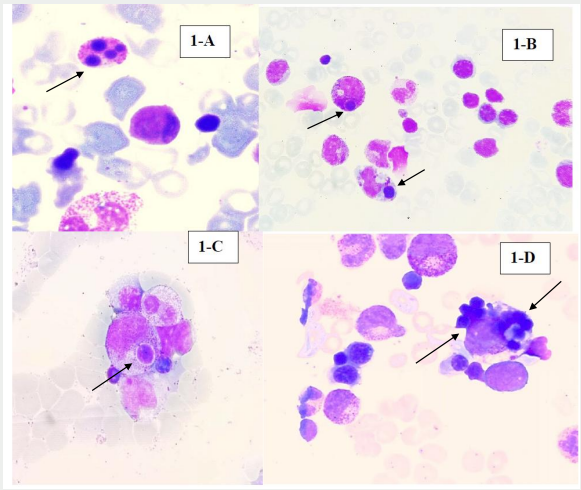

Figure 1. Medullary smear stained by May Grunwald Giemsa, x 100, showing the presence of apoptotic neutrophils and atypical phagocytosis.

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