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Caso Clínico

Vacuolated lymphocytes, a clinical finding in GM1 gangliosidosis

Linfocitos vacuolados, un hallazgo clínico en la gangliosidosis GM1

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CASE REPORT

A 7-month-old infant was brought to the emergency department of our hospital with fever and respiratory distress accompanied by cough and nasal mucus. After clinical assessment, the diagnostic orientation was compatible with pneumonia. Apart from these common symptoms, there were several clinical signs worth mentioning.

On physical examination, cherry-red spots were observed all over the thorax, as well as, hypospadias. The results of complementary tests (cranial radiography, abdominal sonography…) also confirmed macrocephaly, hypotonia, ecchymosis and hepatosplenomegaly. Biochemical analysis showed a remarkable increase in the following parameters: Aspartate amino transferase (AST) 114 UI/L (VR: 5-34 UI/L), lactate dehydrogenase (LDH) 1941 UI/L (VR: 120-246 UI/L) and alkaline phosphatase (ALP) 1632 UI/L (VR: 46-116 UI/L). Blood cell count revealed thrombocytopenia (59 x 10^9/L). Undoubtedly, the most relevant finding was the presence of vacuolated lymphocytes (41%) in the peripheral blood smear (Fig. 1).

All these physical and clinical findings could be suggestive of a mucopolysaccharidosis and point to criteria of glycogenosis vs. other storage disorders. Therefore, the study for the differential diagnosis was completed. In fact, the patient was previously diagnosed with GM1 gangliosidosis confirmed by a massive sequencing study. The patient had a homozygous mutation in the galactosidase beta 1 (GLB1) gene (OMIM*611458) classified as pathogenic. Unfortunately, he was died 6 months later due to complications of pneumonia and the aforementioned pathology.

DISCUSSION

GM1 gangliosidosis is a lysosomal storage disorder, a rare inborn error of metabolism, due to deficiency of the β-galactosidase enzyme caused by mutations in the GLB1 gene (1). The incidence of this disease is estimated to be 1 in 100 000-200 000 live births.

GM1 gangliosidosis is classified into 3 types depending on the clinical phenotype: type 1 (infantile form/

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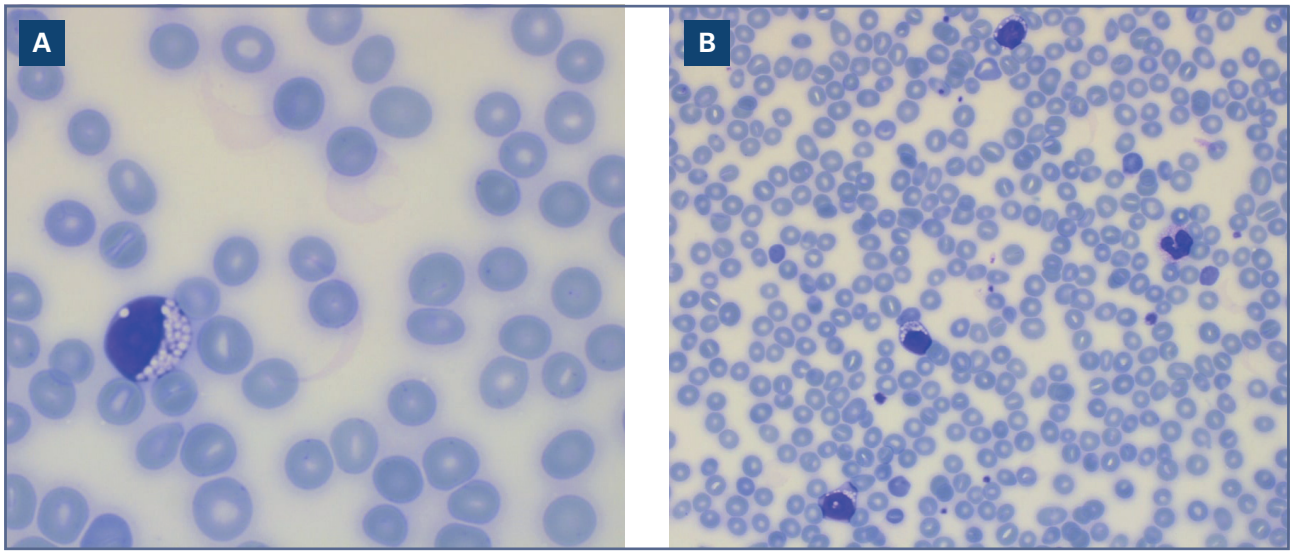

Figure 1 – *A. Vacuolated lymphocyte in a May-Grünwald-Giemsa periphera blood smear from a 7-month-old infant with GM1 gangliosidosis (100x). B. Vacuolated lymphocytes at 50x magnification.*

acute) develops in the first 6 months of life and it is characterized by rapid progressive neurodegeneration, hypotonia, cherry-red spots, coarse facial appearance, hepatosplenomegaly, facial dysmorphism, skeletal dysplasia and often early death by 1-2 years of age. This is the most common and severe form of the disease.

Type 2 (juvenile form/sub-acute) develops between the second and the third year of age and shows slower progression presenting with delayed motor development and intellectual disability. Type 3 (adult form/chronic) emerges after 10 years of life and is characterized by a progressive extrapyramidal disorder, dystonia or skeletal involvement. It has been mostly described in Japanese population (1,2).

Our data reveal that all clinical findings, signs and symptoms were compatible with a lysosomal storage disease, which were confirmed by genetic study leading to a GM1 gangliosidosis. Among diagnostic tools for lysosomal storage diseases are those which are based not only on enzymatic assays and genetic screening but also on liquid chromatography-electrospray ionization-mass spectrometry (LC-ESI-MS) and flow-cytometric methods (3).

However, it is very useful in many cases to have biomarkers available and/or to pay attention to certain findings that allow a quick diagnostic orientation. In this way, although the examination of peripheral blood smear cannot be considered as a diagnostic tool, in this kind of pathology, it plays an important role. As we can observe in figure 1, the presence of lymphocytes showing multiple large bold vacuoles in their cytoplasms is an unusual finding and strongly characteristic of lysosomal storage disorders as reported Fenneteau et al. (4,5) In this way, it is worth mentioning that Gasser lymphocytes are typical of mucopolysaccharidosis and they can be observed in Austin disease (mucosulfatidosis) or GM2 gangliosidosis. However, we can discard their presence because their morphology is characterized by inclusions within the vacuoles which consist of dark purple large granules. In our case, the vacuoles are degranulated. Furthermore, in order to discard also a glycogen storage disease as Pompe disease, we focus again on the morphology of lymphocytes. In this kind of disorder, the glycogen within the vacuoles stains positively with periodic acid-Schiff reagent (6) and the number of vacuoles is low.

As vacuolated lymphocytes may occur in many storage disorders as it has been reported, the microscopic observation of the peripheral blood smear provides important information since it allows carrying out a first differential diagnosis.

Thus, cytological abnormalities of leukocytes are a very valuable aid for having a diagnostic suspicion and allow a fast performance of complementary tests that complete the etiological profile.

In conclusion, the prevalence of GM1 gangliosidosis is low and type 1 has an important mortality associated. So, the findings in the cytological study of the present case can be useful for supporting the diagnosis of gangliosidosis before the definitive established diagnosis by biochemical and genetic tests.

ASPECTS TO REMEMBER

- GM1 gangliosidosis is a rare inborn metabolism disease due to the deficiency of the β-galactosidase enzyme.
- The most common clinical signs are macrocephaly, hypotonia, hepatosplenomegaly, cherry-red spots and/or coarse facial appearance.

– Apart from biochemical alterations (AST, LDH and ALP), the cytological abnormalities of leukocytes are characteristic of lysosomal storage disorders, in particular, the vacuolated lymphocytes.
– The cytological study of the peripheral blood smear allows a rapid diagnostic orientation and provides very useful information to the clinicians.

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