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Connecting the dots: Xanthoma, haemolytic anaemia, stomatocytosis and macrothrombocytopenia point to phytosterolaemia

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A 20-year-old Caucasian woman was referred to the internal medicine department for investigation of unexplained chronic haemolytic anaemia (haemoglobin: 100 g/L) with negative direct anti-globulin test, thrombocytopaenia (102×10^9/L) and xanthelasma palpebrarum (Figure 1A). Clinical examination showed mild splenomegaly. Blood film examination (Figure 1B, May-Grünwald-Giemsa, original magnification ×100) revealed marked stomatocytosis and large platelets. Plasma cholesterol and triglyceride levels were normal but the levels of plant sterols measured by gas chromatography were elevated for sitosterol (500 μmol/L, control value < 3.2 μmol/L) and campesterol (196 μmol/L, control value < 6.5 μmol/L). Next-generation sequencing revealed a new splicing homozygous variant in the *ABCG5* gene (NM_022436):c.904+5G > C), confirming the diagnosis of phytosterolaemia. Treatment with 10 mg/day ezetimibe, a selective inhibitor of the Niemann-Pick C1-Like 1 protein, was prescribed in addition to specific dietary restriction banning plant fats and limiting foods rich in plant sterols. Investigation of family members was also recommended.

Phytosterolaemia (also known as sitosterolaemia) is an autosomal recessive disorder resulting from biallelic pathogenic *ABCG5* (mainly found in Caucasians) or *ABCG8* (more common among Asian populations) variants, characterized by excessive absorption of dietary sterols (cholesterol but also plant sterols). Cutaneous infiltration by lipid-loaded macrophages leads to the formation of xanthomas. The incorporation of plant sterols in the membranes of blood cells leads to structural and functional abnormalities that can cause macrothrombocytopaenia and haemolytic anaemia. Thus, an association of mild haemolytic anaemia, macrothrombocytopenia, stomatocytosis and xanthoma is highly suggestive of this rare and probably underdiagnosed inherited condition [1, 2], especially when the standard lipid profile is normal. Knowledge of clinical and haematological manifestations of phytosterolaemia is of great importance since treatment with ezetimibe can reduce haemolysis, improve haemoglobin level and platelets count and lead to regression of xanthomas. Most importantly, it can help prevent disease complications such as premature atherosclerosis [3].

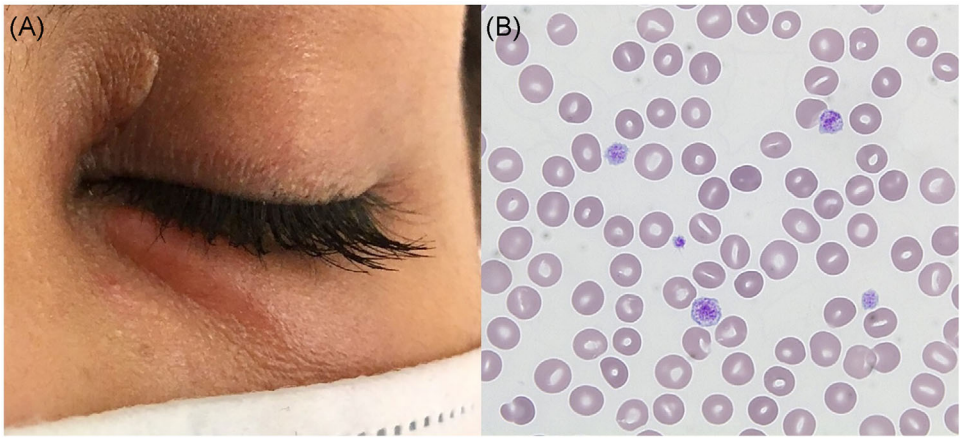

FIGURE 1 Clinical and blood film examination. (A) Clinical examination showing xanthelasma palpebrarum, (B) Blood film examination showing marked stomatocytosis and large platelets (May-Grünwald-Giemsa, original magnification ×100).

AUTHOR CONTRIBUTIONS

Jean-Baptiste Rieu wrote the paper; Jean-Baptiste Rieu took the pictures; JBR performed the blood film examination; Thibaut Jamme and Thierry Levade performed gas chromatography studies, Lamisse Mansour-Hendili performed molecular studies, Léonardo Astudillo and Pierre Cougoul performed clinical examination and follow-up of the patient. Written permission for reproduction from the copyright owners will be provided if the submission is accepted.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

This manuscript respects the ethical policy of CHU Toulouse for the treatment of human research participants.

PATIENT CONSENT STATEMENT

The authors did not obtain written informed consent from the patient but the patient did not object to his data being used for research purposes (as required by the ethical policy of CHU Toulouse).

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

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