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Xanthomas and Macrothrombocytopenia: Sitosterolaemia is the Answer

Xantomas y macrothrombocitopenia: sitosterolemia es la respuesta

Alfonso Ragnar Torres-Jiménez,∗ Eunice Solís-Vallejo, Berenice Sanchez-Jara, Adriana Ivonne Cespedes-Cruz, Maritza Zeferino-Cruz

Reumatología Pedíatrica, Hospital General Centro Médico Nacional la Raza, Mexico City, Mexico

A R T I C L E   I N F O

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Sitosterolemia is an extremely rare autosomal recessive disease. The main characteristic is the absence of the routes that normally impede absorption and retention of noncholesterol sterols, like those found in plants and shellfish. The gene responsible for sitosterolemia is on chromosome 2p21, and mutations in any of the genes that comprise the locus encoding the adenosine triphosphate (ATP)-binding cassette (ABC) transporter, subfamily G (ABCG) proteins, ABCG5 or ABCG8, cause this disease.1–7

Case Report

The patient was a 9-year-old boy who was referred to our department to be evaluated for probable juvenile idiopathic arthritis. He was the child of consanguineous parents (cousins), although the remainder of his hereditary and/or family background was unremarkable. At the age of 3 years, he began to complain of generalized arthralgia, at no predominant time of day or night, that did not change with physical activity or rest. It did not limit his daily activities, but would sometimes wake him up at night, and was relieved with massages and paracetamol. Our findings were increased volume in his knees, as well as the appearance of skin lesions on the extensor surfaces of elbows and knees and thrombocytopenia of 45,000/mm³; epistaxis was ruled out. On physical examination, he was pale and had no abdominal organomegaly;

there were painless nodular skin lesions of soft consistency on extensor surfaces of elbows and knees; they were not attached to deep layers of 2–3 cm and thus, were suggestive of tuberous xanthomas; the Achilles tendon was enlarged due to subcutaneous nodular lesions (Fig. 1). The rest of the physical examination was unremarkable. The laboratory analyses showed leucocytes of 5270/mm³, hemoglobin 11.4 g/dL, reticulocytes 4.28%, peripheral blood smear with stomatocytes + schistocytes + large platelets ++ (Fig. 2), direct Coombs test negative, platelets 106,000/mm³, mean platelet volume of 20 fl, cholesterol 223 mg/dL and triglycerides 132 mg/dL. In Spain, the determination of serum phytosterol levels and the analysis of the ABCG5 and ABCG8 genes are not performed. Based on the presence of macrothrombocytopenia, hemolysis, elevated reticulocyte count, tuberous xanthomas and slightly elevated cholesterol and triglyceride levels, the diagnosis of sitosterolemia was established and treatment was begun with a diet low in phytosterols and ezetimibe at a dose of 10 mg/day.

Discussion

In 1974, Bhattacharyya and Connor reported a new disease in 2 Caucasian sisters who had been referred to them because of the presence of tendon xanthomas since their childhood. Surprisingly, the plasma cholesterol in these patients was within normal ranges, but they found elevations of the phytosterols (specifically β-sitosterol) and, thus, named the new disease β-sitosterolemia.3

Sitosterolemia is a rare autosomal recessive disease, characterized by markedly high levels of phytosterols, with a slight increase in the plasma cholesterol. It is caused by mutations in the ABCG5 or ABCG8 genes (adenosine triphosphate-binding cassette [ABC] transporter), located on chromosome 2p21, which helps
to prevent sterol absorption and promote the excretion of phyto-
sterols (sitosterol, campesterol and stigmasterol), preventing their
accumulation in blood and tissues.1–4 The exact prevalence of sitos-
terolemia is unknown, but there are 80–100 cases worldwide.4–8

Plant sterols include the phytosterols and the phytostanols.
Phytosterols are closely related to cholesterol, the main differ-
ce being the configuration of the side chain. The phytosterols
most widely found are sitosterol, campesterol and stigmasterol.
As humans are incapable of synthetizing phytosterols, their only
source is the diet. Usually less than 5% of the phytosterols in the
foods we consume is absorbed, in contrast to 55% of the choles-
terol. The liver, rapidly and preferentially, excretes phytosterols
into the bile. This leads to a low level of retention of noncholesterol
sterols. In 1998, Patel mapped the locus of sitosterolemia, STSL, to
chromosome 2p21. This locus is comprised of 2 adjacent genes,
ABCG5 and ABCG8, which encode 2 intestinal sterol transporters,
sterolin-1 and sterolin-2. Mutations in either of them lead to the
development of sitosterolemia. These transporters are found in the
apical membrane of enterocytes and in the biliary tract. ABCG5 and
ABCG8 regulate the network of absorption and excretion of phyto-
sterols and cholesterol. In enterocytes, they promote the flow of
phytosterols back into the intestinal lumen and, in the liver, they
promote the excretion of sterols into bile.4,6,7,9,10

The clinical signs vary, and can include the presence of
tendon xanthomas, premature atherosclerosis, early myocardial
infarction, arthritis, arthralgia, hemolysis, thrombocytopenia and
hypersplenism. Sitosterolemia differs from familial hypercholes-
terolemia in that the cholesterol levels are normal.4–6,11

Macrothrombocytopenia associated with the absence of ABCG5
is caused by the increase in plasma phytosterol levels, not by any
intrinsic defect of the megakaryocytes. Hemolysis is secondary to
an increase in the osmotic fragility of the erythrocytes. As the
ABCG5 and ABCG8 proteins are not present in platelets or eryth-
rocytes, the accumulation of plant sterols in plasma and their
insertion into the blood cell membranes is a better explanation
for the abnormalities in morphology and function in patients with
sitosterolemia. The xanthomas in the patellar, plantar and Achilles
tendons and in the extensor tendons of the hands are present in
all the cases that present during childhood. There can be recur-
rent arthralgia or arthritis in knees and ankles, which are due to
sitosterol deposits.7,12,13

Blood tests show plasma cholesterol levels ranging from normal
to slightly elevated, thrombocytopenia, chronic hemolytic ane-
mia with a negative Coombs test and high liver enzyme levels.8
A peripheral blood smear aids in the diagnosis of sitosterolemia
and is characterized by the presence of stomatocyte hemolysis,
thrombocytopenia and macrothrombocytes.2,12

The plasma phytosterol levels in normal individuals do not
surpass 1 mg/dL, whereas the concentration in patients with
sitosterolemia can be over 20–30 mg/dL. Enzymatic methods or
colorimetry are usually employed to quantify sterols, but they do
not differentiate between cholesterol and plant sterols. The latter
are detected using gas chromatography or high-performance liquid
chromatography.1,5

The disease should be suspected in patients with tendon or
Tuberous xanthomas, early cardiovascular disease associated with
normal cholesterol levels, or inexplicable hemolysis.4,6,9,11

The treatment of sitosterolemia includes a diet that avoids foods
that are high in phytosterols (vegetable oils, margarine, olives, nuts,
avocado, chocolate and shellfish).4,9,13 Improving the intestinal and
hepatic routes of elimination of phytosterols in patients with sitos-
terolemia reduces the levels of plant sterols. Ezetimibe binds to
NPC1L1, which is a sterol transporter in the small intestine, and
blocks sterol absorption and reabsorption, resulting in low chole-
terol and phytosterol levels.1,4,5,8 A recent study in 8 patients with
sitosterolemia indicates that ezetimibe is effective, as it reduces
the phytosterol levels in plasma and erythrocytes and improves
the platelet count. The combination of ezetimibe with bile acid
sequestrant resins, statins or diets low in phytosterols promotes
a decrease in the plasma campesterol and sitosterol levels. Ezetim-
ibe leads to a marked improvement in plasma sterol concentration,
regression of the xanthomas and resolution of the cardiovascu-
lar disease.4,5,7,9,11 Liver transplantation was recently performed in
a patient with sitosterolemia in whom the normalization of the
plasma phytosterol levels were completely normalized.4

It was not possible to determine the phytosterol concentra-
tions, but the clinical signs and peripheral blood smear led us to
the diagnosis. Sitosterolemia should be considered in patients with
xanthomas and thrombocytopenia, and the peripheral blood smear
must be examined specifically to establish the presence or absence
of macrothrombocytes and stomatocytes.

Ethical Disclosures

Protection of human and animal subjects. The authors declare
that no experiments were performed on humans or animals for
this study.

Confidentiality of data. The authors declare that they have fol-
lowed the protocols of their work center on the publication of
patient data.

Fig. 1. Tuberous xanthoma in elbow.

Fig. 2. Peripheral blood smear showing macrothrombocytes, stomatocytes and
schistocytes.
Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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