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 Pediátrica, Hospital General Centro Médico Nacional la Raza, Mexico City, Mexico
Hematología Pediátrica, Hospital General Centro Médico Nacional la Raza, Mexico City, Mexico

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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 leukocytes 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- 
ence being the configuration of the side chain. The phytosterols 
most widely found are sitosterol, campesterol and stigmasterol. 
As humans are incapable of synthesizing 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- 
steroles 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 hypercholesterolemia in that the cholesterol levels are normal.4–6,11 
Macrophosphatocytopenia 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- 
ia 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.5,8 

The disease should be suspected in patients with tendon or 
tuberos 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 rich in phytosterols (vegetable oils, margarine, olives, nuts, 
avocado, chocolate and shellfish).5,9,13 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.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.
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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