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LETTER TO THE EDITOR

An uncommon RBC membranopathy: two case reports

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Abbreviations

MCV	Mean corpuscular volume
WBC	White blood cell
LDH	Lactate dehydrogenase
EMA	Eosin-5'-maleimide
PS	Peripheral smear
NGS	Next-generation sequencing
GC-MS	Gas chromatography-mass spectroscopy

Sitosterolemia is a rare autosomal recessive disease of plant sterol metabolism. Bhattacharyya and Connor first described this disease in 1974 [1]. To date, there are only about 100 known cases worldwide [2].

We describe two patients diagnosed with sitosterolemia at our center. Patient A is a 12-year-old male, presented with complaints of short stature, abdominal distension, and gradually progressive paleness since 2 months. He had pallor and hemolytic facies, and both weight (25 kg) and height (130 cm) were less than the 3rd centile and had spleno-hepatomegaly.

His investigations (Table 1) were suggestive of a chronic hemolytic anemia. Since the child had giant platelets on peripheral smear and spherocytes were not seen, diagnosis of hereditary spherocytosis seemed unconvincing. So genetic work-up by next-generation sequencing (NGS) was done which revealed mutation in ABCG8 gene, suggestive of sitosterolemia. On review, his peripheral smear showed some stomatocytes (Fig. 1).

Patient B is a 12-year-old child who was referred to us for splenectomy. The child had splenomegaly and bicytopenia, diagnosed during work-up for a short febrile illness. There were stomatocytes in his peripheral smear too, and sterol levels were borderline high (Table 2); hence, genetic studies were sent, which revealed compound heterozygous variants in the ABCG5 gene, suggestive of sitosterolemia type 2.

Both patients belong to Asian background with no family history suggestive of an inherited red cell disorder. They are under regular follow-up for monitoring diet, counts, and changes of early atherosclerosis. If dietary changes are not adequate, we will consider ezetimibe for them.

Discussion

Sitosterolemia is caused by increased intestinal absorption and decreased biliary excretion of plant sterols resulting from homozygous or compound heterozygous mutations in genes encoding sterol efflux transporter ABCG5 (sterolin-1) and ABCG8 (sterolin-2) that pumps sterols out to intestinal lumen or into bile [3]. Patients with sitosterolemia can have a variety of presentations like short stature, chronic abdominal discomfort, and splenomegaly indicating a chronic hemolytic disease. Some may present with tendinous and cutaneous xanthomas, arthritis, and arthralgias. They have a strong propensity towards premature coronary atherosclerosis [4].

Laboratory features are suggestive of chronic hemolysis with presence of stomatocytic red cells and macrothrombocytopenia on blood films. Eosin-5'-maleimide test by flow cytometry (EMA) is usually abnormal. Plasma levels of plant sterols (sitosterol, cholestanol, and stigmasterol) measured by GC–MS (gas chromatography-mass spectrometry) are elevated. The identified homozygous or compound heterozygous mutations in ABCG5 and ABCG8 genes further confirm the diagnosis.

Treatment predominantly involves dietary changes and pharmacological adjuncts. All sources of vegetable fats like vegetable oils, nuts, seeds, olives, and avocados should be eliminated. Food derived from animal sources with cholesterol as the dominant source should be allowed [5]. Bile

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Table 1 Laboratory evaluation

	Hb (12–14) / MCV (70–86)	WBC (5000–15,000)	Platelets (150,000–400,000)	Reticulocyte count (0–2%)	LDH (0–250)	EMA (900–1300 MCF)	PS	Hb electrophoresis	Sterol levels	NGS
Patient A	6.1/83.7	12,420	81,000	5.8%	334	832.78	Target cells +, no spherocytes seen, few stomatocytes +	Beta thalassemia trait	High	Heterozygous mutations in ABCG8 gene
Patient B	10.8/80	6600	83,000	4.7%	550	750.60	Spherocytes +, stomatocytes +, giant platelets seen	Normal	High	Heterozygous mutations in the ABCG5 gene

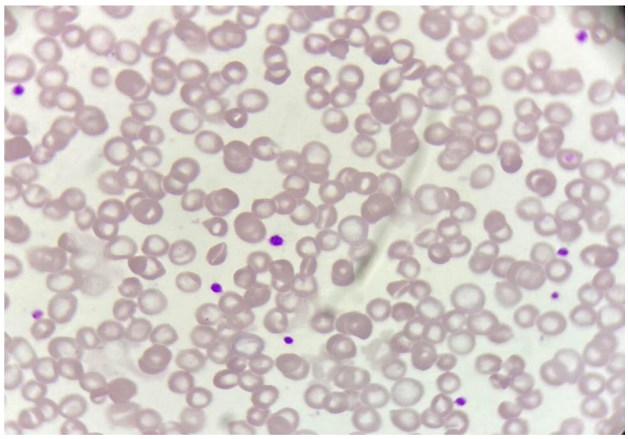

Fig. 1 Peripheral smear of child A

acid resins like cholestyramine may be useful; statins have no role [6]. Ezetimibe was US FDA approved in 2002 for use in patients with sitosterolemia. Ezetimibe alone or in combination with cholestyramine effectively reduces plant sterol levels by around 50% [7]. Some patients may require surgical interventions like ileal bypass to effectively reduce sterol levels.

We feel that this condition is under-reported as many may remain misdiagnosed as hereditary spherocytosis or hyperlipidemias. Measures as simple as dietary modification can control this condition and prevent a splenectomy (which will be detrimental in patients with sitosterolemia as it further increases risk of atherosclerosis and pulmonary hypertension). Hence, stomatocytes should be actively searched for in patients with large platelets and unexplained mild hemolysis. Consider early NGS to determine diagnosis.

Table 2 Plant sterol levels of patient B

Plant sterols	Observed values (μmol/L)	Reference range (μmol/L)
Campesterol	Not detectable	11.95 ± 4.58 (7.37–16.49)
Stigmasterol	20.59	10.51–21.26 (10.51–21.26)
Beta-sitosterol	9.22	4.23 ± 1.64 (2.59–5.89)
7DHC	3.97	1.32 ± 0.50 (0.82–1.82)
Cholesterol	3672.57	4640 ± 820 (3820–5460)
7DHC/cholesterol	0.002164	< 18 years, < 0.000287 > 18 years, < 0.00068
Lathosterol/cholesterol	0.000015	0.051–0.079%
Cholestenol/cholesterol	0.000053	< 0.051

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Purva Kanvinde—saw peripheral smears, assisted in sending investigations

Mukesh Desai—guided management of patients for genetic work-up

Nitin Shah—helped in literature search

Archana Swami—proof reading of manuscript

Minnie Bodhanwala—final approval of the version of manuscript

Sangeeta Mudaliar—planned management of both children and their follow-up

Data availability Not applicable.

Code availability Not applicable.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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