Clinical Case Reports International

Research Article
Published: 06 Jan, 2025

Unravelling the Mysteries of Sitosterolemia: Insights from a Hematologist

Harshal Mamlekar, Rajesh Kashyap, Sanjeev, Ruchi Gupta, Khaliqur Rahman, Mona V, Manish Singh, Dinesh Chandra and Poorvi Kapoor*

Department of Hematology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India

Abstract

Sitosterolemia is a disorder of lipid metabolism. It is extremely rare and is inherited in an autosomal recessive manner and is characterized by increased absorption of plant sterols from the intestinal mucosa resulting in extremely high levels within the blood. Here we present a case series of 2 patients of pediatric age group (<18 years) who presented to the outpatient department with clinical features suggestive of hemolytic anemia. Both patients did not report any stigmata of hypercholesterolemia. A thorough peripheral blood smear examination showed stomatocytes and macrothrombocytopenia in both these patients. Next generation sequencing showed a compound heterozygous mutation in ABCG5 gene (c.490C>T and c.1724G>A) in one case and homozygous mutations in ABCG5 gene (c.386C>A) in the other case. Both patients were initiated on Ezetimibe (10 mg/day) that resulted in complete resolution of symptoms. A low plant sterol diet and regular monitoring of hemoglobin and lipid profile was advised to both. Our cases highlight a rare differential diagnosis of Coombs negative hemolytic anemia that can be suspected from a thorough peripheral blood examination and confirmed by molecular genetic testing like NGS.

Keywords: Sitosterolemia; Plant sterols; Stomatocytes; Macrothrombocytopenia; Hemolytic anemia

Introduction

Sitosterolemia is a disorder of lipid metabolism. It is extremely rare and is inherited in an autosomal recessive manner. It is characterized by enhanced absorption and reduced biliary excretion of plant sterols. It results in elevated serum levels of plant sterols mainly sitosterol, campesterol, and stigmasterol. It is primarily caused by a biallelic (homozygous/compound heterozygous) loss-of-function (LOF) mutation in either ATP-binding cassette (ABC) subfamily G member 5 or member 8 (*ABCG5* and *ABCG8*, respectively) that plays a pivotal role in eliminating sterols from the liver and intestine [1]. Hence, increased absorption of plant sterols from the intestine and its reduced secretion from the liver primarily cause sitosterolaemia.

Patients mainly present with tendinous and tuberous xanthomas and premature coronary atherosclerosis, similar to those noticed in patients with familial hypercholesterolemia [2]. On rare occasions, patients may also present with haemolysis, splenomegaly, platelet abnormalities, and arthralgia/arthritis of varying severity that often impose a diagnostic dilemma [3]. Here we report 2 cases of sitosterolaemia with isolated hematologic abnormalities creating a diagnostic dilemma.

Materials and Methods

Case 1

Our first patient is a 16-year-old male born out of non-consanguineous marriage and hailing from Madhya Pradesh. He presented with complaints of generalised weakness, occasional exertional breathlessness (Grade 2 NYHA) and occasional dragging pain in the left hypochondrium for 1 year. On laboratory evaluation, he was found to have moderate anemia and thrombocytopenia; however, there was no history of any prior bleeding manifestations and no noticeable mass or lump in the body was reported. He did not have any prior transfusion history. None of his family members reported a similar illness. On Physical examination, he had pallor and hepatosplenomegaly. However, no external stigmata of hypercholesterolemia were noted.

Overall Investigations done showed features of hemolytic anemia with occasional stomatocytes and macrothrombocytes seen in the peripheral smear. Direct Coombs test was negative.

OPEN ACCESS

Correspondence:
Harshal Mamlekar, Department of Hematology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India,
E-mail: harshalmamlekar6@gmail.com

Received Date: *23 Dec 2024*
Accepted Date: *03 Jan 2025*
Published Date: *06 Jan 2025*

Citation:
Mamlekar H, Kashyap R, Sanjeev, Gupta R, Rahman K, Mona V, et al. Unravelling the Mysteries of Sitosterolemia: Insights from a Hematologist. Clin Case Rep Int. 2025; 9: 1720.

Copyright *© 2025 Harshal Mamlekar. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.*

Table 1: Shows hematological and biochemical parameters of the two cases.

Clinical and lab features	Case 1	Case 2
Age at onset (years)	17	15
Sex	Male	Female
Hepatosplenomegaly	Yes	Yes
Xanthelesma, tendon xanthomas	No	No
Hemoglobin (g/dL)	9	8.2
Reticulocyte count (%)	10.30%	11.20%
Mean corpuscular volume (fL)	115.3	101.8
Total white blood cell count (per cu mm)	5500	6000
Differential count		
Neutrophils (%)	70	70
Lymphocytes (%)	22	21
Monocytes (%)	6	9
Eosinophils (%)	2	0
Basophils (%)	0	0
Platelet count on coulter (per cu mm)	60,000	70,000
Manual platelet count (per cu mm)	75000	80000
MPV (fL)	14.5	16.6
LDH (IU/L)	671	620
Se. Vitamin B12 levels	524	498
Direct Coomb's test	Negative	Negative
Stomatocytes and macrothrombocytes on peripheral blood smear	Yes	Yes
LFT (mg/dL)		
Total bilirubin	2.41	3.6
Direct bilirubin	0.71	0.8
Osmotic fragility Test by Flowcytometry	Mildly increased	Normal
EMA Binding assay	Normal	Normal
Hb Electrophoresis	Normal	Normal
Se. Ferritin	205	144.5
UGT1A1 promoter sequencing for Gilbert syndrome.	Normal	Homozygous for Gilbert Syndrome

Ultrasound whole Abdomen revealed a massive splenomegaly and a mild hepatomegaly. However, liver echotexture was normal and portal vein doppler did not show any evidence of portal hypertension.

Case 2

Our second patient is a 14-year-old girl, 2nd born to non-consanguineous parents hailing from Uttar Pradesh (Northern India). She presented to the outpatient department of hematology with complaints of dragging left sided abdominal pain, yellowish discoloration of eyes and occasional epistaxis (ISTH -BAT score 2) for 1.5 years. She did not receive any transfusion till date. All developmental milestones were achieved as per age and antenatal, birth and postnatal period was uneventful. None of her family members reported a similar illness. On physical examination, she had pallor, icterus, no significant lymphadenopathy. On per-abdomen examination she had a moderate hepato-splenomegaly (Liver was palpable 4 cm below right and spleen was palpable 5cm below left costal margin). No xanthelasma, tendon xanthomas or any other stigmata of hypercholesteremia were noted.

Her peripheral blood smear showed polychromasia, numerous stomatocytes and giant platelets (platelet estimated on smear to be 60,000–75,000/cu mm). Direct Coombs test was negative.

Evaluation for Hereditary spherocytosis by Osmotic fragility test (Flowcytometry) and EMA binding assay was negative.

The hematological and biochemical parameters of the 2 cases have been reported in Table 1. The findings of next generation sequencing of the 2 cases is depicted in Table 2.

Results

Both cases were confirmed as Sitosterolemia. Lipid profile was normal in both cases. Se. Sitosterol levels were not done at baseline due to logistic issues.

A diet low in plant sterols was advised. Ezetimibe at a dose of 10 mg/day was administered in both cases with symptomatic improvement. Both patients were advised a regular monitoring of hemoglobin and lipid profile. Both patients are on regular follow up at our OPD and are currently doing well. Six months post therapy, both cases showed a 2 cm reduction in spleen size with a slight improvement in platelet count and no bleeding manifestations. CT Coronary angiography and Carotid doppler did not show any features of atherosclerosis in both cases.

Discussion

Plant sterols as well as dietary cholesterol are absorbed from the brush border epithelium of small intestinal mucosa with the help of Niemann-Pick C1-like 1 (NPC1L1), a sterol influx transporter [4]. Once these lipids are esterified into chylomicrons, they are carried to the liver by the portal vein and excreted in the bile by hepatic ABCG5/ABCG8. Lipids that are left unesterified are eventually effluxed into the intestinal lumen by the intestinal ABCG5/ABCG8. Hence, if the is a mutation in the *ABCG5/ABCG8*, it will eventually lead to enhanced absorption of plant sterols from the intestine and reduced excretion in the bile causing increased levels in the blood. Genetic inactivation of *NPC1L1* protected against sitosterolemia as proven by Tang W et al. in murine models lacking *ABCG5/ABCG8* [5].

Sitosterolemia can present as a totally asymptomatic disease to involvement of multiple organ systems [6,7]. Hematological abnormalities include hemolytic anemia secondary to stomatocytosis, and bleeding episodes due to dysfunctional macrothrombocytes [8,9]. Platelet hyperreactivity occurs due to accumulation of plant sterols within the platelet membrane causing macrothrombocytopenia and bleeding phenotype in murine models of sitosterolemia as shown by Kanaji et al. [10]. Xanthomas occur due to hypercholesterolemia and foam cell formation and may lead to accelerated atherosclerosis and sudden cardiac death [11,12].

A careful Peripheral blood smear (PBS) examination is essential in making a diagnosis of hemolytic anemia. If PBS reveals numerous stomatocytes and giant platelets, it should raise a suspicion of a possible diagnosis of sitosterolemia and such patients should be further evaluated by measuring blood plant sterol levels whenever possible. Mutations in the genes encoding ATP—binding cassette transporter G5 (*ABCG5*) or G8 (*ABCG8*) proven by Next generation sequencing will confirm the diagnosis [13,14]. Further evaluation for evaluation of atherosclerosis should include lipid profile, 2D echocardiogram, carotid doppler and a CT coronary angiography if feasible.

Table 2: Shows results of the Next Generation sequencing (Hemolytic anemia Panel) of the two cases.

Case No.	Gene	Location	Variant	Zygosity	Disease	Inheritance	Prediction
1	ABCG8 (+)	Exon 4	c.386C>A (p.Ser129Ter)	Homozygous	Sitosterolemia 1	Autosomal Recessive	Pathogenic
2	ABCG8 (+)	Exon 4 Exon 11	c.490C>T (p.Arg164Ter) c.1724G>A (p.Gly575Asp)	Compound Heterozygous	Sitosterolemia 1	Autosomal Recessive	Pathogenic

The aim of treatment is to reduce the levels of plant sterols in the blood. A dietary modification incorporating minimal plant sterols is advocated. Ezetimibe has shown efficacy in the management of sitosterolemia [14,15]. It inhibits absorption of plant sterols by binding to Niemann-Pick C1-like 1 (NPC1L1), a polytopic transmembrane protein in the epithelium of small intestine and reduces the levels of phytosterols in the blood. Ezetimibe used on a long term basis can increase the platelet counts and decrease mean platelet volume therby reducing the bleeding episodes [16]. Many other treatment strategies have been tried with variable results. These include bile acid binding resins, HMG-CoA reductase inhibitors and plasmapheresis which can be used in adjunct to Ezetimibe. A regular monitoring of hemoglobin and lipid profiles should be done for long term management of the disease.

The current review of literature reveals that a total of 16 cases of this disorder with isolated hematological abnormalities have been reported [8,9,17,18,19]. Our cases highlight a rare differential diagnosis of Coombs negative hemolytic anemia that can be suspected from a thorough peripheral blood examination and confirmed by molecular genetic testing like NGS.

Conclusion

Sitosterolemia is a rare, yet an important differential diagnosis for Coombs negative hemolytic anemia. A careful peripheral blood smear examination showing stomatocytes and macrothrombocytopenia should arouse a suspicion and should be further investigated by Next generation sequencing to confirm the diagnosis. Dietary modification incorporating minimal plant sterols and Ezetimibe, a lipid lowering agent are efficacious in decreasing hemolytic episodes and improving bleeding diathesis and hence are recommended in the management of sitosterolemia.

Ethical Conduct Approval

Informed consent was taken from the parent/ guardian. Ethics approval is not needed for case reports as per the institutional policy.

Informed Consent Statement

All authors and institutions have confirmed this manuscript for publication.

References

1. Berge KE, Tian H, Graf GA, Yu L, Grishin NV, Schultz J, et al. Accumulation of dietary cholesterol in sitosterolemia caused by mutations in adjacent ABC transporters. Science. 2000;290(5497):1771–5.
2. Bastida JM, Giros ML, Benito R, Janusz K, Hernandez-Rivas JM, Gonzalez-Porras JR. Sitosterolemia: diagnosis, metabolic and hematological abnormalities, cardiovascular disease and management. Curr Med Chem. 2019;26(37):6766–75.
3. Escola-Gil JC, Quesada H, Julve J, Martin-Campos JM, Cedo L, Blanco-Vaca F. Sitosterolemia: diagnosis, investigation, and management. Curr Atheroscler Rep. 2014;16(7):424.
4. Othman RA, Myrie SB, Jones PJ. Non-cholesterol sterols and cholesterol metabolism in sitosterolemia. Atherosclerosis. 2013;231(2):291–9.
5. Tang W, Ma Y, Jia L, Ioannou YA, Davies JP, Yu L. Genetic inactivation of NPC1L1 protects against sitosterolemia in mice lacking ABCG5/ABCG8. J Lipid Res. 2009;50(2):293–300.
6. Hu M, Tomlinson B. Ezetimibe treatment should be considered for patients with sitosterolemia. Pediatr Nephrol. 2014;29(8):1469–70.
7. Wang J, Joy T, Mymin D, Frohlich J, Hegele RA. Phenotypic heterogeneity of sitosterolemia. J Lipid Res. 2004;45(12):2361–7.
8. Wang Z, Cao L, Su Y, Wang G, Wang R, Yu Z, et al. Specific macrothrombocytopenia/hemolytic anemia associated with sitosterolemia. Am J Hematol. 2014;89(3):320–4.
9. Zheng J, Ma J, Wu RH, Zhang X, Su Y, Zhang R, et al. Unusual presentations of sitosterolemia limited to hematological abnormalities: a report of four cases presenting with stomatocytic anemia and thrombocytopenia with macrothrombocytes. Am J Hematol. 2019;94(5):E124–7.
10. Kanaji T, Kanaji S, Montgomery RR, Patel SB, Newman PJ. Platelet hyperreactivity explains the bleeding abnormality and macrothrombocytopenia in a murine model of sitosterolemia. Blood. 2013;122(15):2732–42.
11. Katayama T, Satoh T, Yagi T, Hirose N, Kurita Y, Anzai T, et al. A 19-year-old man with myocardial infarction and sitosterolemia. Intern Med. 2003;42(7):591–4.
12. Yagasaki H, Nakane T, Toda T, Kobayashi K, Aoyama K, Ichikawa T, et al. Carotid intima media thickness in a girl with sitosterolemia carrying a homozygous mutation in the ABCG5 gene. J Pediatr Endocrinol Metab. 2017;30(9):1007–11.
13. Buonuomo PS, Iughetti L, Pisciotta L, Rabacchi C, Papadia F, Bruzzi P, et al. Timely diagnosis of sitosterolemia by next generation sequencing in two children with severe hypercholesterolemia. Atherosclerosis. 2017;262:71–7.
14. Tsubakio-Yamamoto K, Nishida M, Nakagawa-Toyama Y, Masuda D, Ohama T, Yamashita S. Current therapy for patients with sitosterolemia–effect of ezetimibe on plant sterol metabolism. J Atheroscler Thromb. 2010;17(9):891–900.
15. Lutjohann D, von Bergmann K, Sirah W, Macdonell G, Johnson-Levonas AO, Shah A, et al. Long-term efficacy and safety of ezetimibe 10 mg in patients with homozygous sitosterolemia: a 2-year, open-label extension study. Int J Clin Pract. 2008;62(10):1499–510.
16. Othman RA, Myrie SB, Mymin D, Merkens LS, Roullet JB, Steiner RD, et al. Ezetimibe reduces plant sterol accumulation and favorably increases platelet count in sitosterolemia. J Pediatr. 2015;166(1):125–31.
17. Bastida JM, Benito R, González-Porras JR, Rivera J. ABCG5 and ABCG8 gene variations associated with sitosterolemia and platelet dysfunction. Platelets. 2021;32(4):573-7.
18. Goodyer M, Lovey J, Menetrey MJ. Peripheral blood features of phytosterolaemia. Br J Haematol. 2015;171(5):669.
19. Desai SR, Korula A, Kulkarni UP, Menon AA, Ramachandran SV, Sindhuvi E, et al. Sitosterolemia: Four Cases of an Uncommon Cause of Hemolytic Anemia (Mediterranean Stomatocytosis with Macrothrombocytopenia). Indian J Hematol Blood Transfus. 2021;37(1):157-61.