Sticky Platelet Syndrome as a Cause of Recurrent Miscarriages: A Rare Case Report

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ABSTRACT

Sticky platelet syndrome (SPS) is a hereditary disorder. SPS can cause pregnancy complications, such as recurrent miscarriages. However, proper management can prevent the incidence of recurrent miscarriages. Here, we describe a case of a woman who lost her fifth first-trimester pregnancy, and upon assessment, we discovered SPS. The 33-year-old woman underwent consultation with an obstetrician because of her history of five first-semester miscarriages. Gynecology ultrasound, infection parameters, hormonal and metabolic panels, and autoimmune workup were all found to be normal; however, vitamin D deficiency was identified as was SPS from a platelet aggregation test. The patient was then treated with clopidogrel and vitamin D3 supplementation. She became pregnant after five months of treatment. Her pregnancy was normal and she went into delivery at 40 weeks gestation with no maternal or fetal complications.

Keywords*: Sticky platelet syndrome, hyperaggregability, pregnancy, recurrent miscarriages, clopidogrel*

INTRODUCTION

Holliday et al. first reported sticky platelet syndrome (SPS) in 1983 at the 9th Conference on Stroke and Cerebral Circulation.[1,2] The authors described a patient with ischemic stroke/TIA who experienced elevated platelet aggregation following low-dose administration of adenosine diphosphate (ADP) and/or epinephrine (EPI).[3] Another publication in 1984 reported a 24-year-old pregnant woman in her seventh month of gestation surviving an acute myocardial infarction. She did not have any known risk factors for thrombosis, and coronary angiography revealed no signs of atherosclerosis or other vascular lesions.[3]

SPS is thought to be responsible for roughly 20% of otherwise unknown arterial events and 13% of unclear venous thrombotic events.[4] It is the second-most prevalent inherited thrombophilia status after resistance to activated

protein C, with an incidence of 21%. It is by far the most frequent thrombophilia linked to thrombosis of the arterial system.[4] According to reports, compared to patients in the general population, women with SPS undergo noticeably more spontaneous abortions.[5] SPS, which is underappreciated as a cause of spontaneous abortion, has also been reported in women who have experienced repeated pregnancy loss but do not have a personal history of thrombosis.[6]

Here, we describe a case of a woman with a history of five miscarriages all within the first trimester. After a thorough evaluation, she was diagnosed with sticky platelet syndrome.

CASE ILLUSTRATION

A 33-year-old woman underwent consultation with obstetrics-gynecology due to having a history of five first-semester miscarriages and no successful pregnancies. No other symptoms were found: no history of smoking or alcohol consumption, and her menstrual cycle was normal. She did not have any other past illnesses and physical and gynecological examinations were normal. Her aunt also had a history of repeated miscarriages.

Laboratory examinations revealed immunological workup (antinuclear antibody test, anti-dsDNA, lupus anticoagulant, IgM and IgG anticardiolipin antibody, and IgM and IgG anti-Beta 2-Glycoprotein) and infection markers (antirubella IgM, cytomegalovirus IgG and IgM, and toxoplasmosis IgG and IgM) to be negative, except a positive antirubella IgG result. Other results were also within normal ranges, including complete blood count, erythrocyte sedimentation rate (ESR), prolactin, luteinizing hormone (LH), testosterone level, Thyroid Stimulating Hormone (TSH), Free T4, Free T3, fasting insulin, fasting blood glucose, lipid profile, prothrombin time (PT), activated partial thromboplastin time (aPTT), D-dimer, and international normalized ratio (INR).

The abnormal laboratory test results were 25-OH vitamin D, which was below the normal level (19.9 ng/mL), and platelet aggregation, which showed hyperaggregability to adenosine diphosphate (ADP) (**Figure 1**). The patient was then given vitamin D3 supplementation of 1,000 IU per day and clopidogrel of 75 mg once daily for three months.

After three months, the patient was permitted to plan for pregnancy. The level of 25-OH vitamin D in blood had increased to 35 ng/mL. She was instructed to continue clopidogrel and vitamin D3 supplementation.

The patient came back to the clinic three months later and said that she was in her sixth week of pregnancy. She was not experiencing any symptoms. She continued taking 75mg of clopidogrel once daily and vitamin D3 supplementation. Clopidogrel was stopped at 36 weeks of pregnancy. She routinely visited the obstetrician and no abnormalities were detected during her pregnancy. Vaginal delivery occurred spontaneously at 40 weeks of gestation. Both

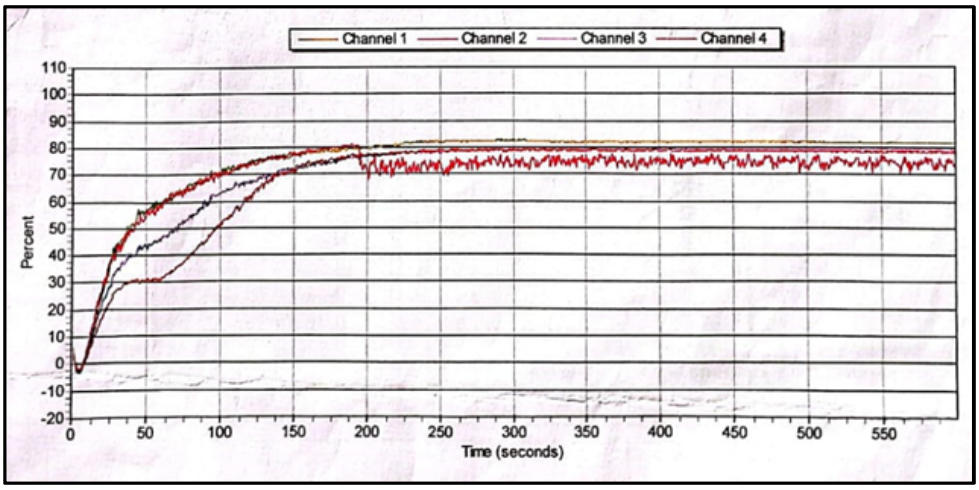

Figure 1. Platelet aggregation report of the patient

the patient and the infant were healthy and no complications were experienced.

DISCUSSION

Since pregnancy is a prothrombotic condition, pregnant women who have a history of thrombophilia might have a greater risk of complications during pregnancy.[7] Pregnancy-related hypercoagulability is caused by a variety of factors, such as decreased anticoagulant activity (protein S and acquired protein C resistance) and increases in clotting factors (VII, VIII, X, von Willebrand factor, and fibrinogen). There is also a decrease in fibrinolytic activity. The rate of venous thromboembolism in pregnancy increases fivefold as a result of these alterations in addition to venous stasis in the lower extremities.[7]

In our case, the patient had already had five miscarriages all in the first trimester. Three consecutive pregnancy losses before 20 weeks after the last menstrual period are considered recurrent pregnancy loss, also known as recurrent miscarriage (RM).[8] According to the Royal College of Obstetricians and Gynecologists, three or more consecutive pregnancy losses are considered RM, while the American Society for Reproductive Medicine Practice Committee defines RM as two or more pregnancy losses that are verified by histology or ultrasound, even if they are not sequential. The prevalence of RM is about 1-3% of all couples attempting to conceive.[9]

Antiphospholipid antibody syndrome (APS), untreated hypothyroidism, poorly controlled diabetes mellitus, some uterine anatomic abnormalities, and parental chromosomal abnormalities are recognized etiologies for RM.[5,8,10] Other endocrine disorders, immunologic abnormalities, acquired and/or heritable thrombophilia, and environmental causes are among the other likely or plausible etiologies. Over 33% of cases are still unsolved even after these potential causes have been considered.[8] Nevertheless, it has been demonstrated that about 55% of RM cases are caused by prothrombotic defects that cause placental artery thrombosis and infarction.[5] In our case, a comprehensive workup determined that our patient had SPS, a heritable thrombophilia.[11,12,13]

SPS is a procoagulant condition that can cause artery, venous, or capillary thrombi by hyperaggregability and hyperresponsive platelets.[14] When extremely low levels of adenosine diphosphate (ADP) and/or epinephrine (EPI) are added, in vitro platelet aggregation increases, indicating a qualitative platelet disorder known as SPS.[15,16] This platelet aggregation can be measured by PFA-100 devices. The patient's platelet count must be >100,000/μL and hematocrit must be >30% to perform the test.[17] If a patient demonstrates hyperaggregability responses to at least two concentrations of one reagent or at least one hyperaggregability response to both reagents, a firm diagnosis of SPS may be made.[18]

SPS is multifactorial and mostly silent until there is another insult to the coagulation system or vasculature. Then, it predisposes to thrombosis.[19] The condition most frequently manifests clinically as arterial thrombosis.[20] Coronary or cerebral arteries are the typical sites of arterial thrombosis.[20] Venous thrombosis, graft-versus-host disease, pregnancy complications, and migraine have been noted as risks associated with SPS.[19] Positive family history of thromboembolism is present in two-thirds of people with the syndrome.[3]

Intrauterine growth retardation and fetal loss are two issues linked to impaired placental vascularization that are frequently experienced by pregnant women with SPS. According to Bick and Hoppensteadt's research, 18.2% of the 351 women who were tested and had recurrent miscarriages in their study met the requirements for SPS.[20]

SPS has historically only been determined by aggregation testing in laboratories.[20] The gold standard for measuring platelet aggregation is light transmission aggregometry (LTA).[2,20] However, this is not advised for pregnant women due to the normal rise of platelet aggregation in pregnancy and the drop in the number of circulating platelets.[20]

Three distinct laboratory forms of the syndrome have been identified based on platelet aggregation patterns.[14] These three forms of SPS are known as type I, which exhibits platelet

hyperaggregability with both ADP and EPI; type II, which only shows this behavior with epinephrine; and type III, which only shows this behavior with ADP.[14,21]

Studies have shown that the majority of SPS patients respond well to small dosages of acetylsalicylic acid (ASA) (80–100 mg/day), which also causes the aggregation pattern to return to normal.[17,20-21] For patients who do not respond well to the initial low-dose ASA, elevating the daily dose to up to 325 mg has been successfully used with positive clinical outcomes.[20] There have also been some published reports of effective usage of regular doses of 75 mg daily of clopidogrel or dual anti-platelet treatment (ASA and clopidogrel) in the management of SPS.[15] Clopidogrel can be used to treat patients who are allergic to or intolerant of aspirin.[19]

Clopidogrel is a proven antiplatelet medication for acute coronary syndrome, peripheral artery disease, and secondary stroke prevention.[22] Clopidogrel works by blocking fibrinogen binding to the adenosine diphosphate receptor, thereby preventing platelet aggregation and activation.[23] Although there aren't enough adequate and carefully controlled studies on pregnant women, clopidogrel, which the Food and Drug Administration (FDA) has classified as a category B substance, hasn't been shown to have any negative effects on the fetus.[24]

Based on currently available data, the use of clopidogrel during pregnancy does not appear to pose significant toxicity to either the mother or the unborn child.[22] There is no proof that clopidogrel causes antepartum obstetric bleeding events or placental abruption. Furthermore, it is unlikely that clopidogrel will be able to pass through the placenta.[23] Thus far, there have been no reports of excessive neonatal bleeding or fetal bleeding events.[23] According to studies conducted on animal models, pregnancy-related clopidogrel use is unlikely to raise the risk of congenital defects.[25] These studies showed no evidence of clopidogrel-related fetal toxicity in reproduction studies conducted in rats and rabbits at doses up to 500 and 300 mg/kg/day, respectively (65 and 78 times the advised daily human dosage).[25] Based on estimates, the background probability of congenital defects is 3%, which means that this anomaly is probably small statistically.[24] To date, there are no reports on clopidogrel use during human breastfeeding.[23]

Since clopidogrel is a persistent platelet inhibitor with a long rate of elimination, full recovery of platelet activity doesn't occur for seven days following the final dosage. Current recommendations for surgical procedures propose stopping the medication for 5 to 7 days before a procedure due to the drug's pharmacodynamics.[24] Hematologists have advised stopping treatment one week before a cesarean section.[25] The European Society of Cardiology's latest recommendations on the treatment of cardiovascular disease during pregnancies suggest a multidisciplinary strategy and individualized treatment, but they do not provide a specific timeframe for stopping the medication before delivery.[24] The main pregnancy risk associated with clopidogrel use is the greater likelihood of intrapartum and postpartum bleeding.[23] It is important to understand that the overall incidence of clopidogrel-induced postpartum hemorrhage is approximately 2% for severe bleeding—defined as blood loss exceeding 1000 mL—and 6% for mild to moderate bleeding, defined as blood loss exceeding 500 mL.[24]

Due to the limited data, the optimal duration of antiplatelet therapy remains uncertain. However, because of the unique characteristics of the syndrome, lifelong antiplatelet therapy has been recommended.[15] Another challenge is determining the long-term management strategy for asymptomatic individuals, such as children identified through family screening of affected patients, and pregnant women who present with conditions unrelated to thromboembolism. In cases of pregnancy and puerperium, immobilization, or invasive procedures, antithrombotic prophylaxis is unequivocally advised.[15]

CONCLUSION

Our patient was diagnosed with SPS. SPS is considered one of the causes of recurrent miscarriages. Treatment of this patient with

clopidogrel resulted in successful pregnancy with good maternal and fetal outcomes.

INFORMED CONSENT STATEMENT

Informed consent was obtained from the patient involved in this case report.

CONFLICT OF INTEREST

The authors declare that there is no potential conflict of interest.

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REFERENCES

1. Kubisz P, Stasko J, Holly P. Sticky platelet syndrome. Semin Thromb Hemost. 2013;39:674–83. Available from: http://dx.doi.org/10.1055/s-0033-1353394. [cited 8 September 2023]
2. Ruiz-Arguelles GJ, Garces-Eisele J, Camacho-Alarcon C, et al. Primary thrombophilia in Mexico IX: The glycoprotein IIIa PLA1/A2 polymorphism is not associated with the sticky platelet syndrome. Phenotype Clinical and Applied Thrombosis/ Hemostasis. 2012; 19(6):689-92. DOI: 10.1177/1076029612448418. [cited 8 September 2023]
3. Kubisz P, Stanciakova L, Stasko J, Dobrotova M, Skerenova M, Ivankova J. Sticky platelet syndrome: an important cause of life-threatening thrombotic complications. Expert Review of Hematology. 2015; 1747-4094. DOI:10.1586/17474086.2016.1121095. [cited 28 August 2023]
4. Ruiz-Delgado GJ, Cantero-Fortiz Y, Mendez-Huerta MA, et al. Primary Thrombophilia in Mexico XII: Miscarriages are more frequent in people with sticky platelet syndrome. Turk J Hematol. 2017;2017;34:239-43. DOI: 10.4274/tjh.2016.0411. [cited 1 September 2023]
5. Stanciaková L, Žolková J, Vadelová L, et al. DNA Polymorphisms in pregnant women with sticky platelet syndrome. J. Clin. Med. 2022;11:6532. https://doi.org/10.3390/jcm11216532. [cited 1 October 2023]
6. Skerenova M, Sokol J, Biringer K, et al. GP6 haplotype of missense variants is associated with sticky platelet syndrome manifested by fetal loss. Clinical and Applied Thrombosis/Hemostasis. 2018;24(1):63-9. DOI: 10.1177/1076029616685428. [cited 1 September 2023]
7. Alecsandru D, Klimczak AM, Garcia Velasco JA, Pirtea P, Franasiak JM. Immunologic causes and thrombophilia in recurrent pregnancy loss. Fertil Steril. 2021;115(3):561-6. doi: 10.1016/j.fertnstert.2021.01.017.[cited 1 October 2023]
8. Ford HB, Schust DJ. Recurrent pregnancy loss: Etiology, diagnosis, and therapy. Reviews in Obstetrics & Gynecology Spring. 2009;2(2):76-83. PMCID: PMC2709325. [cited 14 September 2023]
9. van Dijk MM, Kolte AM, Limpens J, Kirk E, Quenby S, van Wely M, Goddijn M. Recurrent pregnancy loss: diagnostic workup after two or three pregnancy losses? A systematic review of the literature and meta-analysis. Hum Reprod Update. 2020;26(3):356-367. doi: 10.1093/humupd/dmz048.[cited 10 October 2023]
10. Shehata H, Ali A, Silva-Edge M, Haroon S, Elfituri A, Viswanatha R, Jan H, Akolekar R. Thrombophilia screening in women with recurrent first-trimester miscarriage: is it time to stop testing? - a cohort study and systematic review of the literature. BMJ Open. 2022;12(7):e059519. doi: 10.1136/bmjopen-2021-059519. [cited 1 October 2023]
11. Sokol J, Skerenova M, Biringer K, Simurda T, Kubisz P, Stasko J. Glycoprotein VI gene variants Affect Pregnancy Loss in Patients With Platelet hyperaggregability. 2018. Clinical and Applied Thrombosis/Hemostasis. 2018;24(9S):202S-208S. DOI: 10.1177/1076029618802358. [cited 1 September 2023]
12. Hayes C, Kitahara S, Tcherniantchouk O. Decreased threshold of aggregation to low-dose epinephrine is evidence of platelet hyperaggregability in patients with thrombosis. 2014. Hematology Reports. 2014;6:5326. DOI:10.4081/hr.2014.5326. [cited 10 September 2023]
13. Vallejo-Villalobos MF, Gomez-Cruz GB, Cantero-Fortiz Y, et al. Primary thrombophilia XIV: Worldwide identification of sticky platelet syndrome. Semin Thromb Hemost. 2019;45:423–8. DOI https://doi.org/10.1055/s-0039-1688498. [cited 10 September 2023]
14. Moncada B, Ruíz-Arguelles GJ, Martínez CC. The sticky platelet syndrome. Hematology. 2013;18:4, 230-2, DOI: 10.1179/1607845412Y.0000000068. [cited 10 September 2023]
15. Kubisz P, Holly P, Stasko J. Sticky platelet syndrome: 35 years of growing evidence. Seminars in Thrombosis & Hemostasis. 2019;45(1):61-8. DOI https://doi.org/10.1055/s-0038-1676581. [cited 10 September 2023]
16. Kubisz P, Ruiz-Argüelles GJ, Stasko J, Holly P, Ruiz-Delgado GJ. Sticky platelet syndrome: History and future perspectives. Semin Thromb Hemost. 2014;40:526–34. DOI http://dx.doi.org/10.1055/s-0034-1381235. [cited 8 September 2023]
17. Yagmur E, Bast E, Mühlfeld AS, Koch A, Weiskirche R, Tacke F. High prevalence of sticky platelet syndrome in patients with infertility and pregnancy loss. J. Clin. Med. 2019;8:1328; doi:10.3390/jcm8091328. [cited 10 September 2023]
18. Bick RL. Platelet-function defects. In: Bick RL, ed.

Disorder of thrombosis and hemostasis: clinical and laboratory practice 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 59-85.

19. García-Villaseñor E, Bojalil-Álvarez L, Murrieta-Álvarez I, Cantero-Fortiz Y, Ruiz-Delgado GJ, Ruiz-Argüelles GJ. Primary thrombophilia XVI: A look at the genotype of the sticky platelet syndrome phenotype. Clinical and Applied Thrombosis/ Hemostasis. 2021;27:1–8. DOI:10.1177/10760296211044212. [cited 8 September 2023]
20. Sokol J, Skerenova M, Jedinakova Z, Simurda T, Skornova I, Stasko J. Progress in the understanding of sticky platelet syndrome. Semin Thromb Hemost. 2017;43(1);8-13. DOI http://dx.doi.org/10.1055/s-0036-1584352. [cited 2 September 2023]
21. Solis-Jimenez F, Hinojosa-Heredia H, García-Covarrubias L, Soto-Abraham V, Valdez-Ortiz R. Case report sticky platelet syndrome: An unrecognized cause of acute thrombosis and graft loss. 2018. Article ID 3174897. DOI: https://doi.org/10.1155/2018/3174897. [cited 6 September 2023]
22. Reilly CR, Cuesta-Fernandez A, Kayaleh OR. Successful gestation and delivery using clopidogrel for secondary stroke prophylaxis: a case report and literature review. Arch Gynecol Obstet. 2014;290(3):591-4. doi: 10.1007/s00404-014-3269-6. [cited 2 October 2023]
23. Yarrington CD, Valente AM, Economy KE. Cardiovascular management in pregnancy: Antithrombotic agents and antiplatelet agents. Circulation. 2015;132(14):1354-64. DOI: 10.1161/CIRCULATIONAHA.114.003902. [cited 2 October 2023]
24. Nana M, Morgan H, Moore S, Lee ZX, Ang E, Nelson-Piercy C. Antiplatelet therapy in pregnancy: A systematic review. Pharmacol Res. 2021;168:105547. Doi: 10.1016/j.phrs.2021.105547. [cited 2 October 2023]
25. De Santis M, De Luca C, Mappa I, Cesari E, Mazza A, Quattrocchi T, Caruso A. Clopidogrel treatment during pregnancy: a case report and a review of the literature. Intern Med. 2011;50(16):1769-73. doi: 10.2169/internalmedicine.50.5294.[cited 5 October 2023]