Parafoveal acute middle maculopathy (PAMM) in sickle cell disease after discontinuation of hydroxyurea

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ABSTRACT

Purpose: Paracentral acute middle maculopathy (PAMM) is a rare ophthalmologic emergency involving the intermediate and deep retinal capillary plexus that supply the retina’s middle layers. This case report describes an episode of PAMM in a patient with sickle cell disease (SCD) to demonstrate the importance of early diagnosis, review potential pathophysiologic mechanisms, and finally discuss appropriate management in this patient population.

Observations: A 33-year-old black female with SCD, who had recently discontinued disease-modifying therapy with hydroxyurea, presented with a central scotoma of the left eye. Examination showed superficial opacification and whitening of the temporal perifoveal macula. After an initial diagnosis of central retinal artery occlusion she was admitted for a stroke workup. MRI was negative for stroke, and the patient was discharged after undergoing a red blood cell exchange (RBCX). Follow-up exam and optical coherence tomography (OCT) findings were more consistent with PAMM.

Conclusions and Importance: To our knowledge, this is the first report of PAMM after discontinuation of hydroxyurea in preparation for pregnancy. It highlights the importance of a multidisciplinary approach when treating peripartum patients with SCD and the need for further research regarding vaso-occlusive prophylactic agents and their effects in pregnancy to minimize morbidity during family planning.

1. Introduction

Herein we report a case of a 33-year-old female with a history of Sickle Cell Disease (SCD) who presented with clinical findings of unilateral central scotoma due to paracentral acute middle maculopathy (PAMM) shortly after discontinuation of hydroxyurea due to desire for pregnancy. This case highlights the need for a multidisciplinary approach in the management of such cases and the need for further studies on appropriate prophylactic management in patients undergoing preparation for pregnancy. To date, we know of no reports that have shown an acute occurrence of PAMM following discontinuation of hydroxyurea in a young female desiring pregnancy.

1.1. Case report

A 33-year-old black female with a history of SCD presented to the emergency department (ED) for evaluation of new-onset unilateral central-paracentral scotoma five days after initial onset of symptoms. This case highlights the need for a multidisciplinary approach in the management of such cases and the need for further studies on appropriate prophylactic management in patients undergoing preparation for pregnancy. To date, we know of no reports that have shown an acute occurrence of PAMM following discontinuation of hydroxyurea in a young female desiring pregnancy.
her vision and fainted. Her husband caught her and prevented her from hitting her head. When she "came to," she could not see well from her left eye. She reported episodes of vomiting and diarrhea occurring later that day. Five days after these symptoms she saw an outside retina specialist, who diagnosed her with a central retinal artery occlusion and sent her immediately to the ED at UT Southwestern Medical Center for a stroke evaluation.

On arrival to the ED, her best-corrected visual acuity was 20/20 in the right eye and 20/25 with eccentric fixation in the left eye. No relative afferent pupillary defect was noted. Fundus examination of the right eye was unremarkable, while the left eye showed superficial whitening of the temporal macula (Fig. 1). Careful evaluation did not reveal any Hollenhorst plaques, vascular sheathing or a cilioretinal artery (Fig. 1). Intraocular pressures (IOP), extraocular motility (EOM), and slit-lamp examination were normal. General medical examination was normal without any focal neurologic defects. Her vitals signs showed blood pressure 125/85 mm/Hg, with laboratory evaluation showing hemoglobin (Hb) of 7.4 g/dL, consistent with her baseline. Additionally, she had normal serum glucose levels and a negative urine pregnancy test. The patient was admitted for stroke evaluation with neurology, and the hematology team was consulted. MRI/MRA was negative for an acute infarct or carotid disease, and transthoracic echocardiogram was normal except for mild-moderate tricuspid valve regurgitation. She received one red blood cell exchange transfusion (RBCX) and was discharged four days later.

At her outpatient follow-up, two weeks after initial onset of symptoms, the patient continued to endorse blurred central vision of the left eye. Her best-corrected visual acuity in the affected eye was now 20/50 on eccentric fixation. Confrontational visual field testing showed a left paracentral superior nasal defect. Pupillary exam, IOP, and EOM remained normal. Dilated fundus exam was overall unchanged with focal macular whitening involving the temporal macula in the left eye. Her right eye was unremarkable and remained stable. There was no evidence of vascular sheathing in either eye or any clinical signs of vasculitis. Macular infrared images showed an ameboid area of decreased signal corresponding to the area of ischemic retina with retinal opacification seen in the temporal macula on exam (demarcated with a white line in Fig. 2 A). Optical coherence tomography (OCT) imaging showed hyperreflective bands involving the inner nuclear layer (black asterisks in Fig. 2 B) over the area corresponding to the infrared changes. Of note, the inner nuclear layer showed its normal hyperreflective appearance in the nasal macula (white asterisk in Fig. 2 B). Also, even in the affected area, the inner retinal layers appeared normal (white arrow in Fig. 2B points to the normal hyperreflectivity of the ganglion cell layer). The outer nuclear layer was also spared (white # sign in Fig. 2B). Three separate scans (Fig. 2 B, 2D and 2F) demonstrate that these findings were true throughout the area of ischemia. No acute abnormalities were seen in the right eye. One month later, a repeat scan showed a decrease in the infrared changes (Fig. 3A). Some residual hyperreflectivity of the band that previously included the inner nuclear layer is seen in the temporal macula (black asterisk in Fig. 3B), but there is still preservation of the nasal inner nuclear layer (white asterisk). Even in the ischemic region, there is preservation of the ganglion cell layer (white arrow) and the outer nuclear layer (white # sign). Macular thickness maps show significant thinning in the area corresponding to the initial ischemic event (Fig. 3C and 3D). At the 4 month follow up visit, the vision remained subjectively stable in the left eye and was found to be 20/25 with pinhole and with eccentric fixation. Imaging revealed almost complete resolution of the infrared changes (Fig. 4A), loss of the inner nuclear layer in the temporal macula (Fig. 4B, black asterisks), but preservation of the inner retina (white arrow) and outer nuclear layer (white # sign) in the same location, and also preservation of the nasal inner nuclear layer (white asterisk). This constellation of findings supports a diagnosis of isolated PAMM secondary to underlying SCD.

2. Discussion

Sarraf et al. first described the novel findings of parafoveal acute middle maculopathy (PAMM) as the Type 1 variant of acute macular neuroretinopathy (AMN). Distinction between Type 1 and Type 2 AMN variants is based on the location of hyperreflectivity, occurring either above or below the outer plexiform layer, respectively.1 PAMM is characterized on SD-OCT by focal or diffuse hyperreflective bands occurring above the outer plexiform layer and involving the inner nuclear layer. These lesions arise due to vaso-occlusive events of the intermediate (ICP) and deep capillary plexus (DCP) and some of the superficial vascular plexus (SVP) supplying the middle layers of the retina.2-4 Vaso-occlusive events of these vessels lead to ischemic events, mainly in the inner nuclear layer and above the outer plexiform layer, while the outer retinal layers, and the innermost retina, are spared.1,5,4 Type 2 AMN, now termed AMN, consists of hyperreflective lesions involving the outer plexiform layer (OPL) the outer nuclear layer (ONL) below. It is thought to be due to reduced flow in the deep capillary plexus. Of note, the OCT findings in our patient were restricted to the inner nuclear layer and did not involve the outer nuclear layer, consistent with PAMM rather than AMN.

Although our patient was initially diagnosed with a CRAO, this entity typically leads to a severe inner retinal ischemic injury resulting in edema and hyperreflectivity involving all inner retinal layers acutely. CRAO progresses to broad inner retinal thinning in later stages with decreased hyperreflectivity.6-7 Rather than the uniform inner retinal involvement seen with CRAO, in PAMM, the hyperreflective lesions can be multiple or isolated as well as focal or diffuse and tend to respect the innermost retinal layers (e.g., nerve fiber layer and ganglion cell layer). The situation is somewhat more complex in cases of cilioretinal artery "occlusions". A large study by Pichi et al. demonstrated that most cases of so called cilioretinal artery "occlusions" are in reality cases of cilioretinal artery insufficiency (or hypoperfusion) and do not result in total inner retinal ischemia, but instead PAMM. The authors of that study are careful to explain that true cases of cilioretinal artery occlusions (as often seen in giant cell arteritis) do involve all inner retinal layers. Although careful studies have shown that up to 30% of eyes have a cilioretinal artery,8 our patient does not have one in the left eye (see Fig. 1). Furthermore, in the vast majority of cilioretinal artery occlusions, the ischemia involves most of the retinal distribution of the vessel, which almost invariably includes the nasal macula, often starting near the disc. This is not the case in our patient, in whom the ischemia involved predominantly the temporal macula (Figs. 1–4). Thus, our conclusion is that in our case the ischemic event is PAMM in the absence of either a CiRAO or a complete CRAO.

Fig. 1. Fundus photo of the left eye showing retinal whitening in the temporal macula at presentation, 5 days after symptom onset. Note the absence of Hollenhorst plaques, vascular sheathing or a cilioretinal artery.
Fig. 2. Spectralis infrared (A, C, E) and OCT (B, D, F) images of the left eye at three different macular locations 2 wks after symptom onset. A) Decreased infrared signal is seen over the area of ischemia (white demarcation). B) Strong hyperreflectivity of the inner nuclear layer is seen in the temporal macula (black asterisk), but not the nasal macula (white asterisk). The inner retina (white arrow) and outer nuclear layer (white # sign) are preserved. C-F) Similar findings are seen over the involved retina in two other locations.

Fig. 3. Spectralis findings of the left eye one month after presentation. A) Decreased but persistent infrared changes in the temporal macula. B) Persistent hyperreflectivity in the temporal macula (black asterisk) at the level previously occupied by the inner nuclear layer, but respecting the ganglion cell layer (white arrow) and the outer nuclear layer (white # sign). The nasal inner nuclear layer is also preserved (white asterisk). C-D) Macular thickness maps show thinning in the temporal macula, corresponding to the area of ischemia.
Differentiating between ischemic events caused by CRAO versus PAMM is important for clinicians when determining long-term visual prognosis and clinical management. In CRAO, the diffuse infarction and irreversible damage to inner retinal layers of the sensory retina lead to a more severe effect on long term visual acuity, with studies showing that the majority of cases result in a BCVA of 20/400 or worse, especially in those without a cilioretinal artery. This is in contrast to PAMM, where Sarraf et al. showed individuals might have a persistent scotoma but with overall cases showing better preservation of visual acuity, ranging between 20/20-20/30. Differentiating between the diagnosis of CRAO and PAMM also helps with subsequent management. Retinal ischemia and infarction in CRAO require close follow-up (usually monthly) for at least 6 months to monitor for ocular neovascularization, as some studies have reported an 18% risk of developing ocular neovascularization within 2–16 weeks and subsequent neovascular glaucoma. While there is still some debate surrounding this issue, with some suggesting that neovascular glaucoma mainly occurs in the setting of ocular ischemic syndrome, vigilance is needed. In addition, there is recent evidence suggesting that if acute CRAO is diagnosed within the first few hours of onset, there should at least be a discussion regarding possible therapy with intravenous tissue plasminogen activator (tPA).

Multiple systems can be simultaneously affected by a sickle cell crisis. Analyzing data from 120 autopsies, evidence of chronic organ failure was found in 75% of patients but clinically noted in only 25% of clinical histories. In our case, the fact that the lesion was PAMM makes it more likely that this was part of a multi-organ SCD-related vaso-occlusive issue rather than a carotid or cardiac embolus seen commonly in cases of CRAO. The negative embolic workup supports this conclusion. However, at the time of her ED visit, the referring diagnosis was CRAO, which in conjunction with the episode of loss of consciousness triggered the stroke workup. Given the fact that cardiovascular disease is the leading cause of CRAO and mortality is highest in the first week of patients presenting with a retinal arterial occlusion, prompt evaluation for cardioembolic and thrombotic etiologies are warranted in events of acute ischemia. This evaluation includes carotid imaging and echocardiography to evaluate for valvular disease, vascular aneurysms, and atherosclerotic plaques. It is essential to consider the hypothetical scenario of an isolated diagnosis of PAMM in the setting of SCD. Even in that scenario, and even in the absence of other neurologic symptoms, a new diagnosis of PAMM should also trigger a stroke workup. The American Academy of Ophthalmology preferred practice pattern guidelines for Retinal and Ophthalmic Artery Occlusions specify that acute, symptomatic arterial occlusions represent urgent ophthalmic evaluation. Furthermore, they state that PAMM can progress to a more complete CRAO picture in some cases. Finally, SCD is a significant risk factor for stroke due to carotid stenosis, arrhythmias, and other comorbidities, reinforcing the importance of a low threshold for a stroke workup in these patients.

PAMM can be idiopathic but is commonly associated with systemic comorbidities, including cardiac disease, diabetes, hypertension, vasculitis, and in combination with retinal vasculopathy such as central and branch retinal vein occlusions and Purtcher’s retinopathy. It can also be associated with other hematological conditions, including SCD. Nearly every vascular bed of the retina, including the retinal capillary plexus, can be affected in individuals with SCD leading to retinal ischemia and thinning. Based on our review of the literature there have been only a handful of cases of PAMM and SCD reported. A recent study published in 2021 is the largest reported case series and includes four patients with SCD, two of which presented with AMN and two with PAMM. A recent study also demonstrated OCT-angiography (OCTA) flow deficits in the middle and deep capillary plexus in patients with diagnosis of PAMM. Through the use of OCTA, isolated PAMM lesions were found to show reduced flow signal in middle and deep capillary plexus focally at the locations of hyperreflective lesions with preservation of flow signal in the areas surrounding the focal lesions during early stages of onset. These areas of low flow signal corresponded to parfoveal hyperreflective bands seen on SD-OCT in the inner nuclear layer. By around 4–6 weeks later in cases of PAMM there were signs of recovery of the MCP and DCP flow signal on OCT-A with corresponding improvement in hyperreflectivity of the inner nuclear layer on SD-OCT.

Interestingly, while systemic manifestations occur more frequently in patients with HbSS disease, peripheral sickle cell retinopathy, including proliferative retinopathy, is more common in patients with HbSC disease. In contrast, SCD-associated maculopathy, which develops in close to 50% of patients with SCD and is often under-diagnosed, seems to affect HbSS and HbSC patients with similar frequency. Also of note, a study by Beral et al. highlighted worse vision in patients with maculopathy due to HbSS when compared to HbSC-associated maculopathy. Furthermore, most cases of SCD-associated PAMM reported in the literature are associated with HbSS, while reported AMN cases included both Hb variants. Given the low number of SCD-related PAMM case reports, more information is needed to determine if HbSS vs HbSC disease can lead to different types and/or severity of vascular events in the macula.

Finally, patients with SCD have an increased risk of vaso-occlusive events during pregnancy due to a physiologic increase in blood viscosity and hypercoagulability. Unfortunately, many medications aimed at prophylaxis of vaso-occlusive events are contraindicated during pregnancy. Hydroxyurea, is a cytotoxic agent with multifactorial mechanisms of action which include: inhibiting the S phase of DNA synthesis, increasing vasodilation by inducing nitric oxide, leading to decrease in sickling by increasing HbF and decreasing abnormal intra-cellular HbS polymerization, and improving hydration of erythrocytes and macrocytosis. It is classified as Category D with instructions to discontinue 3 months prior to conception due to risk of teratogenicity and risk of perinatal mortality, CNS malformation, cardiac defects, and growth retardation, shown in animal studies. Interestingly, a
recently published study looking at the effects of hydroxyurea on birth outcomes in women with SCD concluded that use of hydroxyurea up until the time of conception may be safe. This study showed that individuals who used hydroxyurea both in conception and pregnancy had higher odds of having miscarriages, stillbirth, and lower birth rates, but this was not the case for those who only used it until conception. Also, when analyzing the live birth outcomes, neither group showed an association with birth defects.\(^\text{48}\)

Endari, approved by the FDA in 2017, is an L-glutamine oral powder shown to decrease RBC adhesion and maintain RBC structural integrity via antioxidation production.\(^\text{49,50}\) Endari is classified as Category C in pregnancy; caution is advised, and there are no available data to inform a drug-associated risk of birth defects or miscarriage. Voxelotor (Oxbryta),\(^\text{51,52}\) approved in 2019, is a Hb S polymerization inhibitor with no human data and no pregnancy category, and it is generally discontinued during pregnancy.

Adakveo (Crizanlizumab), also approved by the FDA in 2019, is a monoclonal antibody that binds to P selectin inhibiting RBC adhesion to the vascular endothelium. Adakveo is the only treatment agent aimed at preventing vaso-occlusive events in patients with SCD that is listed as Category B with limited studies evaluating risk during pregnancy.\(^\text{40}\) Although animal studies in monkeys did not show a risk of increased fetal abnormalities, there was an increased incidence of fetal loss at doses 2.8 times the recommended clinical dose. The potential risk to the mother is unknown, and the potential risk to the fetus must be considered.

In pregnant women with SCD, one treatment modality is prophylactic RBCX with a reported decline in rates of painful crisis.\(^\text{31,41,42}\) Although many studies have shown the benefits of prophylactic RBCX in the context of SCD-associated pain crisis, more information is needed regarding the efficacy of RBCX as a treatment modality in patients with macular ischemia. Moreover, the risks associated with RBCX and transfusion therapy in general should be considered, including alloimmunization and delayed transfusion reactions. Our patient received an exchange transfusion shortly after presentation to the ED; however, it is difficult to determine whether this transfusion had any additional benefit in visual acuity. She described some subjective improvement in vision following RBCX. While a few cases in the literature suggest a benefit of RBCX secondary to the restoration of blood flow and improvement in final visual acuity following treatment, some studies looking at SCD individuals with acute macular ischemia have also shown spontaneous improvement in macular function and final visual acuity without any treatment.\(^\text{35,47}\) As in our patient, significant scotomas often persist.

3. Conclusion

To our knowledge this is the first case to be reported where a patient with SCD suffered from PAMM following discontinuation of hydroxyurea in preparation for pregnancy. Our patient suffered from an acute vision-altering event following discontinuation of hydroxyurea secondary to family planning. There are limited options for prophylactic management of vaso-occlusive events in women with SCD during pregnancy. In our patient’s case, she has been actively followed by Hematology/Oncology with the initiation of daily low dose aspirin and folate acid since admission. Placement of a subcutaneous port for chronic RBCX procedures was attempted but was removed after one month due to port-associated bacteremia. Given her desire to conceive and history of port-associated bacteremia, the patient had opted against hydroxyurea and port replacement. She subsequently underwent chronic RBCX every six weeks utilizing peripheral intravenous access, along with the continuation of her daily low dose aspirin and folate acid.

One limitation in our patient’s case was the timing of presentation. Given that the patient presented 5 days after onset of symptoms we were unable to evaluate retinal OCT findings or fundus findings at time of initial onset. Although OCT findings clearly depict PAMM, another imaging modality we could have considered was OCT-A imaging to depict vascular flow signal. Also, since this is a case report of only one patient, there is limitation in establishing a cause-effect relationship between discontinuation of hydroxyurea and PAMM. Further studies are needed to better understand the effects of various new drug treatments and their impact on pregnancy. The family planning concerns also extend to men with SCD, since they have decreased sperm count and sperm motility at baseline. There is evidence that hydroxyurea may further decrease the quality of sperm.\(^\text{53}\) In consequence, often men also hold hydroxyurea therapy when attempting to conceive. However, studies of male fertility in patients with SCD receiving hydroxyurea have been limited, and some have argued that these have significant design limitations.\(^\text{54}\) Also, some studies have documented male patients with SCD that were able to procreate while on hydroxyurea and had healthy babies.\(^\text{46}\) Therefore, for better-informed family planning, there is an urgent need for research to better understand the risks and benefits on patients, their ability to conceive, and the health of their progeny, associated with the use of both established and new medications for SCD. Millions of people worldwide are afflicted by SCD; in America, the CDC estimates that SCD affects 1 out of 365 black or African American births and 1 out of 16,300 Hispanic-American births. Diversity and inclusion in research and the need to report on health conditions such as SCD impacting blacks and other minorities is paramount for patient care and education.\(^\text{55}\) This case report also highlights the importance of communication between ophthalmologists, hematologists, and transfusion specialists in these multidisciplinary cases to improve patient outcomes.

Patient consent

Patient verbally consented for publication of the case.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

1. Sarraf D, Rahimy E, Fawzi AA, et al. Paracentral acute middle maculopathy: a new variant of acute macular neuroretinopathy associated with retinal capillary ischemia. JAMA Ophthalmol. 2013;131(10):1275–1287. https://doi.org/10.1001/jamaophthalmol.2013.4056.
2. Rahimy E, Sarraf D. Paracentral acute middle maculopathy spectral-domain optical coherence tomography feature of deep capillary ischaemia. Curr Opin Ophthalmol. 2014 May;25(3):207–212. https://doi.org/10.1097/ICO.0000000000000445. PMID: 24614148.
3. Yu S, Pang CE, Gong Y, et al. The spectrum of superficial and deep capillary ischemia in retinal artery occlusion. Am J Ophthalmol. 2015 Jan;159(1):53–63. https://doi.org/10.1016/j.ajo.2014.09.027. e1-2, Epub 2014 Sep 22. PMID: 25244976.
4. Chen X, Denali SJ, Baumal CR. Paracentral acute middle maculopathy in pregnancy. Retin Cases Brief Rep. 2020 Summer;14(3):221–223. https://doi.org/10.1097/ICR.0000000000000679. PMID: 29252913.
5. Falkenberry SM, Ip MS, Blodi BA, Gunther JB. Optical coherence tomography findings in central retinal artery occlusion. Ophthalmic Surg Laser Imaging. 2006;37: 502–505.
23. Hussnain SA, Coady PA, Stoessel KM. Paracentral acute middle maculopathy: a review of natural history and ocular features. 
27. Leitao Guerra RL, Leitao Guerra CL, Bastos MG, et al. Sickle cell retinopathy: what we now understand using optical coherence tomography angiography. 
12. Rudkin AK, Lee AW, Chen CS. Ocular neovascularization following central retinal artery occlusion. 
18. Fawzi A, Vemulakonda GA, Adelman RA, et al. Retinal and ophthalmic artery aneurysms: a systematic review. 
6. Ozdemir H, Karacorlu M, Karacorlu SA, Senturk F. Localized foveal detachment in a patient with posterior ciliary circulation occlusion. 
7. Shinoda K, Yamada K, Matsumoto CS, Kimoto K, Nakatsuka K. Changes in retinal blood flow during red cell transfusion in sickle cell disease Part I: measurements of red cell flow and retinal blood flow. 
11. Duker JS, Sivalingam A, Brown GC, Reber R. A prospective study of acute central retinal artery occlusion. the incidence of secondary ocular neovascularization. 
9. Justice Jr J, Lehmann RP. Cilioretinal arteries. A study based on review of stereo fundus photographs and fluorescein angiographic findings. 
13. Elagouz M, Iyotli S, Gupta B, Sivaprasad S. Sickle cell disease and the eye: old and new concepts. Surv Ophthalmol. 2020;65(3):215-236. https://doi.org/10.1016/j.survophthal.2020.01.001. PMID: 31931619. 
24. Jones RL, Vemulakonda GA, Adelman RA, et al. Retinal and ophthalmic artery aneurysms: a systematic review. 
6. Ozdemir H, Karacorlu M, Karacorlu SA, Senturk F. Localized foveal detachment in a patient with posterior ciliary circulation occlusion. 
28. Beral L, Romana M, Lemone N, et al. Multifocal electroretinogram findings in sickle cell maculopathy. 
21. Jin DR, Alapat P, Nakatsuka K, Nasrallah N, et al. Retinal function in sickle cell retinopathy and sickle cell retinopathy: a review of natural history and ocular features. 
22. https://doi.org/10.1016/j.ophtha.2019.09.028. PMID: 31757501. 
33. Chutia M, Andrade RJ, Kim JH, et al. Fifty-six years of ocular thrombolytic therapy for central retinal artery occlusion: an optical coherence tomography angiography analysis. 
42. Davis BA, Allard S, Qureshi A, et al. British Society for Haematology. Guidelines on red cell transfusion in sickle cell disease. 
36. Niihara Y, Zerez CR, Akiyama DS, et al. Oral L-glutamine therapy for sickle cell anemia: I. Subjective clinical improvement and favorable change in red cell NAD redox potential. Arch Ophthalmol. 1998;116(11):117-121. https://doi.org/10.1001/archopht.1998.01080030041034. PMID: 1706177. 
38. Han J, Saraf SL, Gordevske VR. Systolic blood pressure in patients with sickle cell disease: an autopsy study. Br J Haematol. 2005;132(2):359-365. https://doi.org/10.1111/j.0007-1048.2005.01145.x. PMID: 15791362. 
29. Jain D, Atmapoojya P, Colah R, Lodha P. Sickle cell disease and pregnancy. Surv Ophthalmol. 2010;55:359-377. 
39. Jikalov AL, Slavin B, Kulkarni R, et al. The clinical utility of optical coherence tomography angiography in sickle cell retinopathy. 
43. Al-Abdulla NA, Haddock TA, Kerrison JB, Goldberg MF. Sickle cell disease and pregnancy: an analysis of maternal outcomes. 
52. Davis BA, Allard S, Qureshi A, et al. British Society for Haematology. Guidelines on red cell transfusion in sickle cell disease. 
33. Chutia M, Andrade RJ, Kim JH, et al. Fifty-six years of ocular thrombolytic therapy for central retinal artery occlusion: an optical coherence tomography angiography analysis. 
42. Davis BA, Allard S, Qureshi A, et al. British Society for Haematology. Guidelines on red cell transfusion in sickle cell disease.