

Branch retinal artery occlusion in a patient undergoing Methotrexate therapy for ectopic pregnancy: A case report

Sener Gezer,¹ Birol Vural,² Mehtap Kirsavoglu,³ Yigit Cakiroglu⁴

Abstract

Methotrexate is a commonly used agent in the treatment of an un-ruptured ectopic pregnancy. Thromboembolic events are rarely seen side effects of such a medicine. We report the case of the 22-year-old woman who underwent Methotrexate therapy for an un-ruptured ectopic pregnancy without any history of thromboembolic risk factors. A second dose (50 mg/m²) was administered to the patient showing a non-decreasing pattern of β -HCG levels after an initial standard dosage of Methotrexate (50 mg/m²). On the 12th day of the treatment, a sudden onset of painless vision loss was seen in the right eye. Fundal imaging and fluorescein angiography revealed an occlusion of the superior temporal branch of the right retinal artery. After a month of hyperbaric oxygen therapy, complete recovery without loss of vision was achieved.

Keywords: Methotrexate, Ectopic pregnancy, Branch retinal artery occlusion.

<https://doi.org/10.5455/JPMA.14284>

Introduction

Nowadays, systemic Methotrexate is frequently used in the treatment of un-ruptured ectopic pregnancy. Methotrexate is a folic acid antagonist, it inhibits Deoxyribonucleic acid (DNA) and Ribonucleic acid (RNA) synthesis by affecting the growth of rapidly dividing cells, particularly the trophoblasts, myeloid cells and gastrointestinal mucosal cells. Commonly encountered side effects of the drug depend on the duration and dosage of the induced therapy; it commonly includes stomatitis, leukopenia, nausea, vomiting, fever and malaise. While thromboembolic events are rare (<0.1%), ocular side effects such as conjunctivitis, retinopathy, transient blindness and visual loss are very uncommon (<0.01%).¹ Treatment

.....
^{1,3,4}Department of Obstetrics and Gynecology, Kocaeli University School of Medicine, Kocaeli, ²Department of Obstetrics and Gynecology, Sanliurfa Training and Research Hospital, Yenice Mananes No. 1 Eyyubiyic, Sanliurfa, Turkey.

Correspondence: Sener Gezer. Email: dr.senergezer@gmail.com

regimens prescribed for methotrexate are inclusive of single and multiple dosing. Single-dose is preferred due to the ease of administration, lower cost and no need for folic acid replacement. However, success rates are similar for both regimens.² In a single dose regimen, 50 mg/m² Methotrexate is administered intramuscularly and a β -Subunit human chorionic gonadotropin (β -HCG) level is monitored. If β -HCG values do not reduce adequately, a second dose is then given.

Acute occlusion of the retinal artery is an ophthalmologic emergency and an ocular analog of cerebral stroke. Although, branch retinal artery occlusion is a much rarer entity seen than the central retinal artery occlusion, the associated factors are however similar. Here, we present a case of acute occlusion in the superior temporal branch of the retinal artery which developed after a second dosage of systemic Methotrexate given initially for the treatment of a non-ruptured ectopic pregnancy.

Case Report

A 22-year-old woman, gravida 2 and parity 0 presented with complaints of lower abdominal pain and a history of one anembryonic pregnancy was admitted to Kocaeli University Hospital, Turkey on March, 2018. Her past medical history was insignificant. Her serum β -HCG level was found to be 46,558 IU/L (At 6'th week of pregnancy β -HCG level should not be above 1000 IU/L). Transvaginal ultrasonography revealed a 12 × 12 mm mass in the right adnexal area, which may be consistent with an un-ruptured ectopic pregnancy. No foetal cardiac activity or a yolk sac was visualized. Endometrial thickness was 3.4 mm (>5mm in healthy pregnancy). Patient was admitted to the hospital and was followed with a two-day interval β -HCG level. β -HCG values at two-day intervals were monitored (Figure-1) and a single dose of 50 mg/m² (86 mg) methotrexate was administered intramuscularly on the 10th day. Pre-treatment haemogram, platelet and liver function tests were all normal. Due to inadequate decrease in serum β -HCG levels, a second dose of Methotrexate was given intramuscularly on the 18th day (8th day after the first

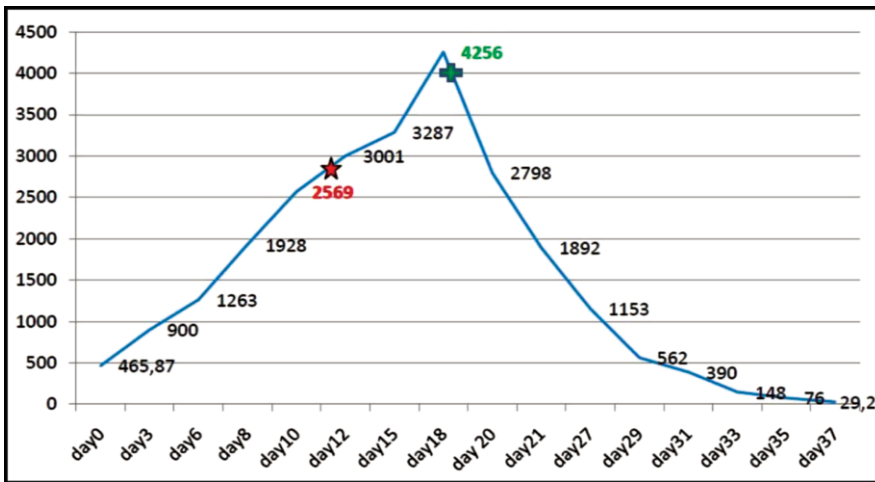


Figure-1: β-HCG levels during treatment and follow-up. On day 10 first dose of methotrexate (red star) and on day 18 second dose of methotrexate (green plus) was employed.

the appearance of the left eye was normal. Carotid-vertebral Doppler ultrasonography, electrocardiography and colour doppler echocardiography were all normal. No pathology was assessed on protein C & S, anti-thrombin 3 and factor 5 Leiden mutation analysis. Hyperbaric oxygen therapy was then started for the occluded retinal artery. Patient was discharged with decreasing levels of serum β-HCG and a hyperbaric oxygen therapy was continued for nearly a month. Visual and fundal examinations were normal at one and six month's followup. Also, fundus auto fluorescence imaging revealed no



Figure-2: Color fundus photograph (Big photo-arrow shows occlusion of the branch retinal artery) and Fundus fluorescein angiography of the right eye (Small photo-arrow shows delay in the arterial filling).

dose). Sufficient reductions were achieved following the second dose and the patient was then followed with serial β-HCG. On the 30th day of follow-up (12th day of 2nd dose), a painless sudden loss of vision developed in the right eye. Visual activity was 20/40. Optical coherence tomography and fundus fluorescein angiography were performed by an ophthalmologist, occlusion was detected in the superior temporal branch of the right central retinal artery (Figure-2). In contrast,

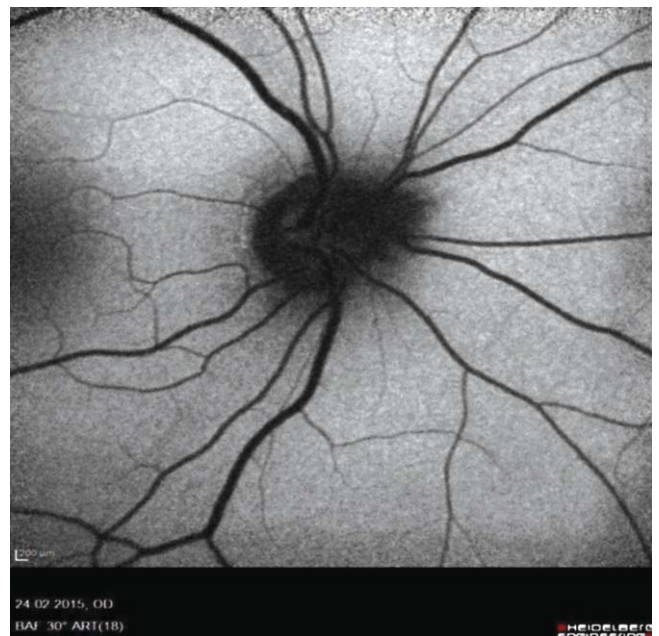


Figure-3: Normal Fundus Autofluorescence Imaging of the right eye at sixth month follow-up.

abnormality at six month follow-up (Figure-3). Informed consent was obtained from the patient.

Discussion

Treatment options for ectopic pregnancy include expectant, surgical or medical management. Methotrexate is less expensive, minimally toxic and protects fertility, hence, it is widely used in the treatment of ectopic pregnancy. Doses of Methotrexate used for ectopic pregnancy are relatively low compared to its

other indications. Results of a meta-analysis³ showed greater effectiveness, however, more side effects were also seen with the multi-dose protocol as compared to the single-dose protocol. A randomized prospective study comparing two protocols in un-ruptured ectopic pregnancy gave similar results with the success rate lower than the single-dose protocol.²

Occlusion of the retinal artery is usually in the form of a central retinal artery occlusion (CRAO) and the incidence is reported to be 1/100,000.⁴ Branch retinal artery occlusion occurs less commonly than central retinal artery occlusion and the outcome is found to be better than that of the central retinal artery occlusion.⁵ Embolism is the most common cause of CRAO and the major source is the carotid artery atherosclerotic plaques. Risk factors for retinal artery occlusion include arterial hypertension, diabetes mellitus, carotid artery disease, coronary artery disease, transient ischaemic attacks and tobacco. Other risk factors for patients under 50 years of age are hyperhomocysteinaemia, factor V Leiden, protein C and S and anti-thrombin deficiencies, antiphospholipid antibodies, prothrombin gene mutations, sickle cell disease and paraneoplastic syndromes.⁶ Our patient had none of the above mentioned risk factors and a haemogram, platelet count, liver function test, urine analysis and hypercoagulability tests performed were all normal. No pathology was identified on the echocardiogram and duplex carotid ultrasound examination. Fundoscopic findings of retinal artery occlusion include retinal opacity, cherry-red spot, cattle trucking, optic disc oedema and pallor. Fundus fluorescein angiography showed delayed filling of the affected vessels, reduced arterial caliber and 'cattle trucking' of the blood column in the retinal branch arteries. An increased inner retinal layer thickness can be detected by optical coherence tomography due to retinal oedema and optic nerve swelling.⁷

Acute retinal artery occlusion has no standard treatment and many options have been reported in the literature. Some of these are Isosorbide dinitrate, Nitroglycerin, inhalation of Carbogen (vasodilatation), Acetazolamide, Mannitol, anterior chamber paracentesis (intraocular pressure reduction), Pentoxifylline (increased red blood cell deformability), isovolaemic haemodilution, enhanced external counterpulsation (improved retinal perfusion), ND:YAG laser embolysis/embolotomy, ocular massage, surgical removal of the clot (dislodging of an embolus), hyperbaric oxygen therapy (increased retinal oxygenation) and Methylprednisolone (reduction of retinal oedema). In two randomized controlled trials, Pentoxifylline⁸ and an

enhanced external counterpulsation combined with haemodilution⁹ was used for central retinal artery occlusion which suggested positive effects. Our patient achieved normal vision with hyperbaric oxygen therapy which may be due to a branch artery occlusion and not central artery occlusion. In the literature, atypical central retinal artery occlusion was observed in a patient using oral methotrexate and prednisolone for dermatomyositis.¹⁰

Conclusion

Occlusion in the superior temporal branch of the retinal artery in the young patient with no risk factors may be due to methotrexate therapy for ectopic pregnancy. Although methotrexate is a safe drug for the treatment of an unruptured ectopic pregnancy, it may have serious side effects.

Disclaimer: None to declare.

Conflict of Interest: None to declare.

Funding Disclaimer: None to declare.

References

1. Methotrexate side-effects. <http://www.drugs.com/sfx/methotrexate-side-effects.html> Methotrexate Official FDA information, side-effects and uses. [Online] [Cited 2018 August 10]. Available from: URL:<http://www.drugs.com/pro/methotrexate.html>.
2. Guvendag Guven ES, Dilbaz S, Dilbaz B, et al. Comparison of single and multi dose methotrexate therapy for unruptured tubal ectopic pregnancy: a prospective randomised study. *Acta Obstet Gynecol Scand.* 2010; 89:889-5.
3. Barnhart KT, Gosman G, Ashby R, Sammel M. The medical management of ectopic pregnancy: a meta-analysis comparing "single dose" and "multidose" regimens. *Obstet Gynecol.* 2003;101:778-84.
4. Rumelt S, Dorenboim Y, Rehany U. Aggressive systematic treatment for central retinal artery occlusion. *Am J Ophthalmol.* 1999;128:733-8.
5. Yuzurihara D, Iijima H. Visual outcome in central retinal and branch retinal artery occlusion. *Jpn J Ophthalmol.* 2004;48:490-2.
6. Chen CS, Lee AW. Management of acute central retinal artery occlusion. *Nat Clin Pract Neurol.* 2008;4:376-83.
7. Shinoda K, Yamada K, Matsumoto CS, Kimoto K, Nakatsuka K. Changes in retinal thickness are correlated with alterations of electroretinogram in eyes with central retinal artery occlusion. *Graefes Arch Clin Exp Ophthalmol.* 2008;246:949-54.
8. Incandela L, Cesarone MR, Belcaro G, Steigerwalt R, De Sanctis MT, Nicolaidis AN, et al. Treatment of vascular retinal disease with pentoxifylline: A controlled, randomized trial. *Angiology.* 2002; 53:S31-4.
9. Werner D, Michalk F, Harazny J, Hugo C, Daniel WG, Michelson G. Accelerated reperfusion of poorly perfused retinal areas in central retinal artery occlusion and branch retinal artery occlusion after a short treatment with enhanced external counterpulsation. *Retina.* 2004;24:541-7.
10. Sharma M, Prashar A, Tuli R, Sharma RK, Mahajan VK. Atypical central retinal artery occlusion: an uncommon cause of retinopathy and visual loss in dermatomyositis. *Int J Rheum Dis.* 2019;22:325-30.