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RETINAL VEIN THROMBOSIS ASSOCIATED WITH HYPERHOMOCYSTEINEMIA IN A KIDNEY TRANSPLANTED PATIENT TREATED WITH VITAMIN B AND BEVACIZUMAB

Nephrology

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ABSTRACT

Retinal vascular occlusion in patients having hyperhomocysteinemia is a known entity. However its treatment still controversial especially after organ transplantation. The objective of this work is to report a case of retinal vein thrombosis in kidney transplanted patient and discuss the management of this case by B vitaminotherpy and bevacizumab. A 47 year old Moroccan patient flowed for unknown end stage kidney disease on hemodialysis from september 2005 have been transplanted by the kidney of his wife on july 2013. After five months the patient presented with a great decrease of visibility related to retinal venous thrombosis and all explorations were negative except hyperhomocysteinemia. Firstly we decided to start B vitaminoterpy and oral folic acid for three months with decrease the Hcy serum level but without improving clinical status. Thus, we prescribe intraocular bevacizumab (dose) every thre weeks conducting to a spectacular evolution. However there was a treatment dependence and patient still on the same treatment. The management of this situation still unknown but we conclude that B vitaminotherapy is not effective leading us to use intraocular anti VEGF. The use of bevacizumab was effective to improve visibility of our patient whereas dependence and cost of treatment. Our result still an only observational case and prospective randomized studies are necessary to prove effectiveness of this treatment and help us to make decision easier.

KEYWORDS

INTRODUCTION :

Cardiovascular disease is a major source of morbidity and the most common cause of death following kidney transplantation, with event rates two to four-fold higher than expected based on population estimates [1,2]. Distinct etiological factors lead to endothelial dysfunction. Generally, more than one of these factors (systemic arterial hypertension, diabetes mellitus, obesity, dyslipidemia, smoking, and family history) are found in renal transplant recipients [3-5]. Homocysteine (Hcy), as a cardiovascular risk factor, was studied over 30 years ago and has been investigated as a factor in the genesis of atherosclerosis (6). Today, hyperhomocysteinemia is a well-established cardiovascular risk factor in the general population, and some studies suggest that this association is also present among renal transplant recipients. In 50-70% of the patients, serum Hcy concentration is increased (7-9)

Ducloux et al showed a positive correlation between serum Hcy and LDL-cholesterol in clinically stable renal transplant recipients (10). In this context, endothelial damage occurs due to the predominance of oxidized forms of Hcy in plasma, thus generating reactive oxygen species and tissue toxicity (11-12).

Retinal vascular occlusion in patients having hyperhomocysteinemia is a known entity, particularly in young patients (30). However its treatment still controversial especially after transplantation. The objective of this work is to report a case of retinal vein thrombosis in kidney transplanted patient and discuss the management of this case by B vitaminotherpy and bevacizumab.

CASE REPORT:

A 47 year old morocan patient flowed for unknown end stage kidney disease (ESRD) on hemodialysis from september 2005 have been transplanted by the kidney of his wife on july 2013. In induction he receive basiliximab and maintained by association of corticosteroids (tapered rapidly and stopped after three momths), tacrolimus and mycophenolate mofetil. The post operative period was marqued by a late graft function related to an arterial stenosis treated by antiplatet with a good evolution. At three months the patient had a normal graft function with no surgical, infectiueous or immunological complication and particularly controlled hypertension by conversion enzyme inhibitor . In the fifth month the patient presented with a great decrease of visibility related to retinal venous thrombosis (picture 1) and all explorations were negative except hyperhomocysteinemia. We performed thrombophilic tests, body CT scan, immunological tests (C3, C4, AAN, Cryoglobulinemia), dermatological exam searching melanoma. The cerebral MRI did not show any central venous thrombosis

Firstly we decided to start B vitaminoterpy and oral folic acid for three months wicjh decreases the Hcy serum level but without Improving clinical status. Thus, we prescribe intraocular bevacezumab (dose) every thre weeks conducting to a spectacular evolution. However there was a treatment dependence and patient still on the same treatment

DISCUSSION:

Hcy appears to be an independent risk factor for arteriosclerotic outcomes in general populations of men and women (13,14) with a 6% increase in the relative risk of cardiovascular complications for each µmol/L increase in blood Hcy (15). Factors associated with hyperhomocysteinemia are age, smoking, systemic arterial hypertension, folate and vitamin B12 levels, elevated cholesterol, sedentary lifestyle and, especially, renal function. However, after renal transplant, the decrease in serum Hcy levels seems to be lower than expected with the improvement in renal function. Other factors, such as chronic graft dysfunction, dyslipidemia or the effect of immunosuppressive drugs, may influence Hcy, thus increasing cardiovascular risk in these individuals (16-22)

Hyperhomocyst(e)inemia in renal transplant patients is independent of the scheme of immunosuppression they are taking. The older the patients are and the higher are their serum creatinine levels, the more susceptible they are to hyperhomocyst(e)inemia following renal transplantation (23). Winkelmayer et al found an association between elevated serum Hcy levels and risk for renal graft loss and death in renal transplant recipients. In this single-center sample, baseline fasting plasma tHcy levels were independently associated with the risk of death and kidney allograft loss (24). Moreover Stable renal transplant recipients (RTRs) have an excess prevalence of both fasting and post–methionine loading hyperhomocysteinemia, which may contribute to their increased risk for arteriosclerotic cardiovascular disease (25,26).

High homocysteine levels have been associated with cardiac allograft coronary artery disease and arterial graft thrombosis , but the risk of venous thrombosis with hyperhomocysteinemia has not been

extensively studied. Investigation of apparently normal patients with otherwise unexplained venous thrombosis has demonstrated a greater than expected number of individuals with blood homocysteine levels above the 95th percentile [27,28]. Den Heijer and al found that hyperhomocysteinemie increase 3 times the risk of venous thrombosis and by 21 times if associated with other thrombosis factors (29).

Retinal vein occlusion (RVO) is the second most common sight-threatening retinal vascular disorder after diabetic retinopathy. It is a multifactorial disease, which may affect small, medium, and large ocular vessels, with central occlusion representing the most dangerous clinical entity. Arterial hypertension, diabetes mellitus, cigarette smoking, atherosclerosis, and increased plasma lipoprotein (a) have been reported as systemic risk factors for RVO [30-34].

Patients with RVO have a higher prevalence of stroke and a greater risk of cardiovascular disease than similarly aged individuals without RVO.[35]

Homocysteine is an amino acid derived from methionine, which can be converted into cysteine. The metabolic pathways involving homocysteine require vitamin B_{12}, vitamin B_6, and folate for proper functioning. Various reports on hyperhomocysteinemia depict that arterial as well as venous vessels are involved in the disease.[36]

Several studies have shown that the level of plasma total homocysteine (tHcy) is elevated in RVO patients and it is a risk factor for RVO with a RR between 16 and 47 in comparison with a control group[37-39]. Any list of investigations for a case of RVO should include total plasma homocysteine (tHcy) levels however , RVO can be the first manifestation of an undiagnosed hypertension more than thrombophilic factors (30) and it is still unclear whether hyperhomocysteinemia is a causal factor in the occurrence of thrombosis, a consequence of full-fledged disease, or only a biochemical marker of its development. The authors disputing the homocysteine hypothesis postulate postulate that the association between hyperhomocysteinemia and thrombosis is only an indirect one, via factors affecting both homocysteine levels and cardiovascular risk. The latter assumption is supported by the data indicating that the relative risk associated with moderately elevated homocysteine levels has been found to be greater in retrospective than in prospective studies (40-42). Moreover, While there is an excess prevalence of mild to moderate hyperhomocysteinemia in hemodialysis patients, some studies did not demonstrate a relationship between total homocysteine concentrations and risk of VAT in patients with end-stage renal disease on hemodialysis and only Aspirin intake was associated with a lower incidence of VAT (43)

tHcy , until recently, was an attractive potential target of therapeutic interventions to reduce the cardiovascular disease burden in CKD patients, given that hyperhomocysteinemia typically responds to high-dose B-vitamin therapy. While the past decade has witnessed large clinical trials of B-vitamin therapy to reduce cardiovascular disease and mortality in individuals with CKD, these have largely been disappointing [44, 45]. Similar trials in the general population have also demonstrated no significant impact of B-vitamin therapy on cardiovascular disease and all-cause mortality, despite significant lowering of tHcy associated with B-vitamin therapy [46].

Treatment with a high-dose folic acid, B6, and B12 multivitamin in kidney transplant recipients did not reduce a composite cardiovascular disease outcome, all-cause mortality, or dialysis-dependent kidney failure despite significant reduction in homocysteine level (47,48).

So, To day there is no current evidence to support the use of homocysteine lowering therapy for cardiovascular disease prevention in kidney transplant recipients from all great studies and societies (49-53).

The first anti VEGF agent was approved in intraocular use in 2006 in USA (54) and ranibizumab approved by the food and drug administration for treating RVO after a phase 3 randomized clinical trial (55) in 2010 including 397 patients showing a satisfactory results in ranibizumab. Bevacizumab is a humanized anti VEGF monoclonal antibody that was first approved by the FDA for the treatment of metastatic colorectal cancer (56) and its use of intravitreal bevacizumab improved the treatment of ocular diseases related to VEGF including RVO (57,58). However, at this time, bevacizumab still, treatment is within the realm of an accepted “standard of care” Because of the lack of large randomized clinical trial data and despite the advances in vision gain with anti-VEGF agents, challenges remain such as macular ischemia, high treatment burden, and progression to neovascular glaucoma (59). In our case, we find a spectacular improve of vision and any adverse effect but the burden of treatment and dependence to ocular injection was the most challenges.

CONCLUSION

We show in this case that retinal vein occlusion after kidney transplantation is a big challenge with various aetiologies related to cardiovascular risk and can be associated to hyperhomocysteinemia as only risk factor. The management of this situation still unknown but we conclude that vitaminiterapy is not effective leading us to use intraocular anti VEGF. The use of bevacizumab was effective to improve visibility of our patient whereas dependence and cost of treatment. Our result still an only observative case and prospective randomized studies are necessary to prove effectiveness of this treatment and help us to make decision easier.

REFERENCES:

1. Kasiske BL. Risk factors for accelerated atherosclerosis in renal transplant recipients. Am J Med. 1988; 84(6):985–992. [PubMed: 3287917]
2. Levey AS, Beto JA, Coronado BE, et al. Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. Am J Kidney Dis. 1998; 32(5):853–906. [PubMed: 9820460]
3. Bostom AG, Shemin D, Gohh RY, Beaulieu AJ, Bagley P, Massy ZA, et al. Treatment of hyperhomocysteinemia in hemodialysis patients and renal transplant recipients. Kidney Int Suppl. 2001;78: S246-52.
4. Massy ZA, Chadefaux-Vekemans B, Chevalier A, Bader CA, Drueke TB, Legendre C, et al. Hyperhomocysteinaemia: a significant risk factor for cardiovascular disease in renal transplant recipients. Nephrol Dial Transplant. 1994;9 (8): 1103-8.
5. Ducloux D, Ruedin C, Gibey R, Vautrin P, Bresson-Vautrin C, Rebibou JM, et al. Prevalence, determinants, and clinical significance of hyperhomocyst(e)inaemia in renal-transplant recipients. Nephrol Dial Transplant. 1998; 13 (11): 2890-3.
6. Perna AF, Ingrosso D, Castaldo P, Galletti P, De Santo NG. Homocysteine and transmethylation in uremia. Kidney Int Suppl. 2001;78: S230-3.
7. Fonseca I, Queiros J, Santos MJ, Mendonça D, Henriques AC, Sarmento AM, et al. Hyperhomocysteinemia in renal transplantation: preliminary results. Tansplant Proc. 2000; 32(8): 2602-4.
8. Beaulieu AJ, Lapane KL, Gohh RY, Selhub J, Monaco AP, Dworkin L, et al. Short-term reproducibility of total homocysteine determinations in stable renal transplant recipients. Tansplant Proc. 1999; 31 (5): 2121-3.
9. Sunder-Plassmann G, Floth A, Fodinger M. Hyperhomocysteinemia in organ transplantation. Curr Opin Urol. 2000; 10 (2): 87-94.
10. Ducloux D, Motte G, Nguyen NU, Abdelfath A, Gibey R, Chalopin JM. Homocysteine, nutritional status and insulin in renal transplant recipients. Nephrol Dial Transplant. 2002; 17 (9): 1674-7.
11. Kes P. Hyperhomocysteinemia in end-stage renal failure. Acta Med Croatica. 2000; 54 (4-5): 175-81.
12. Mangoni AA, Jackson SH. Homocysteine and cardiovascular disease: current evidence and future prospects. Am J Med. 2002; 112 (7): 556-65.
13. Boushey CJ, Beresford SA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease: probable benefits of increasing folic acid intakes. JAMA. 1995;274: 1049–1057.
14. Graham IM, Daly LE, Refsum HM, Robinson K, Brattstrom LE, Ueland PM, Palma-Reis RJ, Boers GH, Sheahan RG, Israelsson B, Uiterwaal CS, Meleady R, McMaster D, Verhoef P, Witteman J, Rubba P, Bellet H, Wautrecht JC, de Valk HW, Sales LA, Parrot-Rouland FM, Tan KS, Higgins I, Garcon D, Andria G. Plasma homocysteine as a risk factor for vascular disease: the European Concerted Action Project. JAMA. 1997; 277:1775–1781.
15. Ducloux D, Motte G, Challier B, Gibey R, Chalopin JM. Serum total homocysteine and cardiovascular disease occurrence in chronic, stable renal transplant recipients: a prospective study. J Am Soc Nephrol. 2000; 11 (1): 134-7.
16. Locsey L, Asztalos L, Dan A, Kinces Z, Berczi C, Sziki G. Changes in cardiovascular risk factors after renal transplantation. Magy Seb. 2001; 54 (2): 101-4.
17. Ducloux D, Fournier V, Rebibou JM, Bresson-Vautrin C, Gibey R, Chalopin JM. Hyperhomocyst(e)inemia in renal transplant recipients with and without cyclosporine. Clin Nephrol. 1998; 49 (4): 232-5.
18. Van Guldener C, Stam F, Stehouwer CD. Homocysteine metabolism in renal failure. Kidney Int Suppl. 2001; 78: S234-7.
19. Arnadottir M, Hultberg B, Wahlberg J, Fellstrom B, Dimeny E. Serum total homocysteine concentration before and after renal transplantation. Kidney Int. 1998; 54 (4): 1380-4.
20. Bostom AG, Gohh RY, Beaulieu AJ, Han H, Jacques PF, Selhub J, et al. Determinants of fasting plasma total homocysteine levels among chronic stable renal transplant recipients. Transplantation. 1999; 68 (2): 257-61.
21. Fonseca V, Guba SC, Fink LM. Hyperhomocysteinemia and the endocrine system: implications for atherosclerosis and thrombosis. Endocr Rev. 1999; 20 (5): 738-59.
22. Kim SI, Yoo TH, Song HY, Hwang JH, Lee Hy, Han DS, et al. Hyperhomocysteinemia in renal transplant recipients with cyclosporine. Tansplant Proc. 2000; 32 (7): 1878-9.
23. David José de Barros Machado, Flávio Jota de Paula, Emil Sabbaga and Luiz Estevan Ianhez. HYPERHOMOCYST(E)INEMIA IN CHRONIC STABLE RENAL TRANSPLANT PATIENTSREV. HOSP. CLÍN. FAC. MED. S. PAULO 55(5):161-168, 2000
24. Winkelmayer WC, Kramar R, Curhan GC, Chandraker A, Endler G, Fodinger M, et al. Fasting plasma total homocysteine levels and mortality and allograft loss in kidney transplant recipients: a prospective study. J Am Soc Nephrol. 2005;16 (1): 255-60.
25. Kasiske BL, Guijarro C, Massy ZA, Wiederkehr MR, Ma JZ. Cardiovascular disease after renal transplantation. J Am Soc Nephrol. 1996;7:158–165.
26. Bostom AG, Gohh RY, Tsai MY, Hopkins-Garcia BJ, Nadeau MR, Bianchi LA, Jacques PF, Rosenberg IH, Selhub J. Excess prevalence of fasting and postmethionine-loading hyperhomocysteinemia in stable renal transplant recipients. Arterioscler Thromb Vasc Biol. 1997;17:1894–1900.
27. Heijer M, Koster T, Blom H, et al. Hyperhomocysteinemia as a risk factor for deep-vein thrombosis. N Engl J Med 1996;334:759–762.
28. Jorge Vega S, Helmuth Goecke S, Alejandro Vásquez G1, Armando Peña M1.Renal artery thrombosis after withdrawal from anticoagulation therapy in a kidney transplant recipient with thrombophilia. Report of one caseRev Méd Chile 2007; 135: 98-102

29. Den Heijer M., Brouwer I.A., Bos G.M. et coll. Vitamin supplementation reduces blood homocysteine levels. A controlled trial in patients with venous thrombosis and healthy volunteers. Arterioscler Thromb Vasc Biol 1998 ; 18 : 356-61.
30. Martínez F1, Furió E, Fabiá MJ, Pérez AV, González-Albert V, Rojo-Martínez G, Martínez-Larrad MT, Mena-Martín FJ, Soriguer F, Serrano-Ríos M, Chaves FJ, Martín-Escudero JC, Redón J, García-Fuster MJ. Risk factors associated with ret inal vein occlusion. Int J Clin Pract. 2014 Jul;68(7):871-81
31. Risk factors for branch retinal vein occlusion. The eye disease case–control study group. Am J Ophthalmol 1993, 116:286–296.
32. Lip PL, Blann AD, Jones AF, Lip GY: Abnormalities in haemorheological factors and lipoprotein (a) in retinal vascular occlusion: implications for increased vascular risk. Eye (Lond) 1998, 12(Pt 2):245–251.
33. Stem MS, Talwar N, Comer GM, Stein JD: A longitudinal analysis of risk factors associated with central retinal vein occlusion. Ophthalmology 2013, 120:362–370.
34. Sofi F, Marcucci R, Fedi S, Giambene B, Sodi A, Menchini U, Gensini GF, Abbate R, Prisco D: High lipoprotein (a) levels are associated with an increased risk of retinal vein occlusion. Atherosclerosis 2010, 210:278–281.
35. Laouri M, Chen E, Looman M, Gallagher M. The burden of disease of retinal vein occlusion: Review of the literature. Eye (Lond) 2011;25:981–8
36. Ratra D, Dhupper M. Retinal arterial occlusions in the young: Systemic associations in Indian population. Indian J Ophthalmol. 2012;60:95–100
37. Martin SC, Rauz S, Marr JE, Martin N, Jones AF, Dodson PM: Plasma total homocysteine and retinal vascular disease. Eye (Lond) 2000, 14(Pt 4):590–593.
38. Lahiri KD, Dutta J, Datta H, Das HN: Hyperhomocysteinemia, as an independent risk factor for retinal venous occlusion in an Indian population. Indian J Clin Biochem 2013, 28:61–64.
39. Fahad Al Wadani, Rajiv Khandekar,1 Gigani Salim, Mohammed Al Ali, and Salman Ramzi Hyperhomocysteinia is a risk factor for retinal venous occlusion: A case control studyIndian J Ophthalmol. 2014 Mar; 62(3): 291–294.
40. Mirkovic D, Majkic-Singh N, Ignjatovic S. Homocysteine: chemistry,metabolism and role in pathophysiological processes [in Serbian].Jugoslav Med Biohem. 2003;22:127-40. doi:10.2298/JMH0302127M
41. Jacques PF, Bostom AG, Williams RR, Ellison RC, Eckfeldt JH, Rosenberg IH, et al. Relation between folate status, a common mutation in methylentetrahydro-folate reductase, and plasma homocysteine concentrations. Circulation. 1996;93:7-9.
42. Verhoeff BJ, Trip MD, Prins MH, Kastelein JJP, Reitsma PH. The effect of a common methyleneterahydrofolate reductase mutation on the levels of homocysteine, folate, vitamin B 12 and on the risk of premature atherosclerosis. Atherosclerosis. 1998;141:161-6.
43. Chadi Saifan ; Elie El-Charabaty , Suzanne El-Sayegh Hyperhomocysteinemia and vascular access thrombosis in hemodialysis patients: a retrospective study Vascular Health and Risk Management 2013:9 361–364
44. Brady CB, Gaziano JM, Cxypoliski RA, et al. Homocysteine lowering and cognition in CKD: the Veterans Affairs homocysteine study. Am J Kidney Dis. 2009; 54(3):440–449. [PubMed: 19628319]
45. Mann JF, Sheridan P, McQueen MJ, et al. Homocysteine lowering with folic acid and B vitamins in people with chronic kidney disease--results of the renal Hope-2 study. Nephrol Dial Transplant. 2008; 23(2):645–653. [PubMed: 18003666]
46. Loscalzo J. Homocysteine trials--clear outcomes for complex reasons. N Engl J Med. 2006; 354(15):1629–1632. [PubMed: 16531615]
47. Andrew G. Bostom, MD; Myra A. Carpenter, PhD; John W. Kusek, PhD; Andrew S. Levey, MD; Lawrence Hunsicker, MD; Marc A. Pfeffer and al Homocysteine-Lowering and Cardiovascular Disease Outcomes in Kidney Transplant Recipients. Circulation. 2011;123:1763-1770
48. Szabó, Tulassay, Melegh, et al Hyperhomocysteinaemia
49. Kang A, Nigwekar SU, Perkovic V, Kulshrestha S, Zoungas S, Navaneethan SD, Cass A, Gallagher MP, Ninomiya T, Strippoli GFM, Jardine MJ. Interventions for lowering plasma homocysteine levels in kidney transplant recipients. Cochrane Database of Systematic Reviews 2015, Issue 5. Art. No.: CD007910.
50. CARI. Care for kidney transplant recipients.2012. www.cari.org.au/Transplantation/transplantation%20care%20of%20recipients/transplant˙care˙of˙recipients.html
51. Kidney Disease: Improving Global Outcomes (KDIGO)Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. American Journal of Transplantation 2009;9 Suppl 3:S1–157
52. Holt S, Goldsmith D. Cardiovascular disease in CKD.2010. www.renal.org/guidelines/modules/ cardiovasculardisease-in-ckd#Summary2
53. Bostom AG, CarpenterMA,Hunsicker L, Jacques PF, Kusek JW, Levey AS. Baseline characteristics of participants in the folic acid for vascular outcome reduction in transplantation (FAVORIT) trial [abstract no: 827]. American Journal of Transplantation 2009;9(Suppl 2):429
54. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med. 2006; 355:1432–1444.
55. Campochiaro PA, Heier JS, Feiner L, et al. Ranibizumab for macular edema following branch retinal vein occlusion. Ophthalmology. 2010;117: 1102–1112.e1.
56. Ferrara N, Hillan KJ, Novotny W. Bevacizumab (Avastin), a humanized anti-VEGF monoclonal antibody for cancer therapy. Biochem Biophys Res Commun. 2005;333:328–335.
57. Rosenfeld PJ, Moshfeghi AA, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (Avastin) for neovascular age-related macular degeneration. Ophthalmic Surg Lasers Imaging. 2005;36:331–335.
58. Rosenfeld PJ, Fung AE, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (Avastin) for macular edema from central retinal vein occlusion. Ophthalmic Surg Lasers Imaging. 2005;36:336–339.
59. Yi Jiang, MD, and William F. Mieler, MD. Update on the Use of Anti-VEGF Intravitreal Therapies for Retinal Vein Occlusion. Asia-Pacific Journal of Ophthalmology • Volume 6, Number 6, November/December 2017