Bilateral Conjunctival Mucosa-Associated Lymphoid Tissue Type Lymphoma in a Kidney Transplant Recipient

Eun-Young Ji, M.D.¹, Ji-Yeun Chang, M.D.¹, Chul Woo Yang, M.D.¹, Seok-Goo Cho, M.D.² and Byung Ha Chung, M.D.¹

Divisions of Nephrology¹, Hematology², Department of Internal Medicine, Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Lymphoproliferative disorder in a posttransplant setting has emerged as a difficult problem in kidney transplantation (KT). Lymphoma involving adnexa of the eye has rarely been reported due to scarcity of lymphoreticular tissue in the ocular area. This report presents a case of a 37-year-old KT recipient who was diagnosed with conjunctival mucosa-associated lymphoid tissue lymphoma with a chief complaint of seeing black spots. Unlike other post-transplant lymphoproliferative diseases associated with the Epstein-Barr virus (EBV) reactivation via immunosuppression, the lesion was not related to the virus. The patient received radiotherapy with concomitant conversion from the tacrolimus to the sirolimus. Overall, the results presented herein indicate lymphoma may be an important differential diagnosis when KT recipients complain of ocular discomfort.

Key Words: Kidney transplantation, Marginal zone B-cell lymphoma, Lymphoproliferative disorders

Case Report

INTRODUCTION

Kidney transplantation (KT) is an emerging option for renal replacement therapy that improves the quality of life, as compared to dialysis. However, immunosuppressive therapy for the prevention of rejection can lead to lymphoproliferative disease after KT up to 1% to 20%(1). The extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) type that belonged to the indolent B-cell lymphomas which is mainly an observed gastric mucosa and it is associated with the Helicobacter pylori infection(2-5), has been rarely reported as originating from other sites. We herein report a case of a KT recipient who is diagnosed with extranodal marginal zone lymphoma involving both conjunctivae.

CASE REPORT

A 37-year-old woman with end-stage renal disease due to lupus nephritis received a living-donor KT after 5 years of peritoneal dialysis. The donor was her mother, and the human leukocyte antigen mismatch number was 2. She underwent induction therapy by using basiliximab, and thereafter maintained immunosuppression with tacrolimus, mycophenolic acid, and deflazacort. The trough level of tacrolimus has been maintained between 4~5 ng/mL. The allograft function was kept stable with an estimated glomerular filtration rate of 60 mL/min/1.73 m², and there was no surgical or immunological complication except for urinary tract infection over a 4-year post-transplant period.

Three years and eight months after KT, the patient was admitted to the hospital because of a black spot in her left
eye vision. There were no accompanying symptoms, such as loss of vision, eye pain, or inflammation signs. There was also no recent eye trauma or eye surgery. On admission, her blood pressure was 130/80 mmHg, heart rate was 90 beats/min, and body temperature was 36.7°C. She did not complain of any systemic symptom, such as weight loss, night sweat, or fatigue. There was no palpable mass, subcutaneous nodule, or organomegaly. The admission laboratory examination showed normal complete blood count (CBC), normal levels of lactate dehydrogenase and liver function tests, and minimally elevated erythrocyte sedimentation rate. The tests for human immunodeficiency virus and viral hepatitis A, B, and C were all negative. Cytomegalovirus and Epstein-Barr virus (EBV) were not detected in the real-time polymerase chain reaction test. In the ophthalmic examination, multiple cystic nodules located in both lower conjunctivae were found. The cystic nodules were biopsied and diagnosed with extranodal marginal zone lymphoma of MALT type (Fig. 1). During the staging workup for lymphoma, orbital magnetic resonance imaging and positron emission tomography computed tomography (PET-CT) showed hypertrophic changes in the lower conjunctivae of both eyes and tonsils (Fig. 2). The bone marrow finding was normal, and the chromosome analysis of hematology/oncology showed no atypical clone. The stain for EBV was negative. The patient also underwent esophagogastroduodenoscopy with a negative result of H. pylori infection.

The patient’s final diagnosis was extranodal marginal cell MALT lymphoma stage IE, and she was scheduled to receive curative involved field radiation therapy on the conjunctivae with a dose of 25.2 Gy in 14 fractions. The pa-
tient’s tacrolimus was converted to 2 mg of sirolimus. At 6 months after the radiotherapy, the patient achieved a clinical complete remission without additional imaging studies. A hematologist evaluated the treatment response by careful clinical judgment including CBC, serum chemistries, and lactate dehydrogenase. The patient tolerated the local radiotherapy without extraorbital relapse or late complications, including keratitis or cataract. We planned to assess her on the risk of relapse every 6 months for at least 5 years.

**DISCUSSION**

Post-transplant lymphoproliferative disease (PTLD) is one of the potentially fatal complications after KT that has been known to be a result of immunosuppressive therapy(6). PTLD is divided into four histologic categories by the World Health Organization (WHO) classification, namely, early hyperplastic lesions, polymorphic lesions, monomorphic lesions, and classic Hodgkin-type lymphoma, and they are usually associated with EBV. However, MALT lymphoma, which is a lymphoproliferative disorder characterized by transformation from acquired marginal zone B-cell to malignant lymphocyte, is specifically excluded from the WHO category of PTLD(7-10). Recently, few post-transplantation MALT lymphomas have been reported, and they required differentiation from PTLD due to different management and prognosis(11).

It is generally known that MALT lymphoma most frequently develops in the stomach due to the *H. pylori* infection(12). Only rare nongastric MALT lymphomas with lung, salivary gland, small bowel, colon, or cutaneous involvement have been described in the post-transplant setting(13,14). Reports of post-transplant orbital and ocular lymphomas were rarely reported probably due to the scarcity of lymphoreticular tissue in these areas(15). Therefore, the present case was noteworthy to be reported in view of the extranodal marginal zone MALT lymphoma that occurred in the conjunctivae in the post-transplant setting.

The major etiology of PTLD is the detrimental effect of immunosuppressive agents on the immune control of EBV and 60%~80% of PTLD was associated with the virus (16,17). However, the pathogenesis of it is still unclear and very complex due to the interplay of many different factors, especially in EBV non-associated lymphoma(18). The patient of this case had a past infection of EBV, but there was no evidence of viral reactivation or invasion to the tissue. Therefore, the authors concluded that the present case was EBV non-associated lymphoma. In cases of EBV-related PTLD, the reduction of immunosuppression has been a mainstay of PTLD treatment(19). Rituximab, which is an anti-CD20 monoclonal antibody, is strongly suggested in a systemic disease(20). This case was an EBV-negative lymphoma and the disease extent was limited to the eye; therefore, we decided that a local radiotherapy would be the treatment modality because radiotherapy is one of the competent options among the treatment modalities for orbital MALT lymphoma(21-25). Recent studies reported that a radiotherapy dose range of 25~35 Gy achieved ex-
cellent survival rates for stage IEA orbital MALT lymphoma(26). In addition, we changed tacrolimus to sirolimus for its anti-proliferative effect. Sirolimus is a macrolide antibiotic with immunosuppressive properties, and it was shown in vitro to suppress the growth of a number of lines of B-cell lymphomas(27). The mechanism of the anti-proliferative effect of sirolimus is that the inhibition of interleukin-10 secretion induces apoptosis of the tumor cells. Furthermore, the use of sirolimus instead of tacrolimus is safer than the reduction of immunosuppression in view of allograft rejection. Several cases reported a complete remission with good allograft function via sirolimus conversion without any chemotherapy(28,29). The patient of this case has maintained her allograft function without any sign of rejection during the treatment. PTLDs with EBV negativity have been known to have a poor prognosis with late onset(30). However, orbital MALT lymphomas have a good prognosis in comparison with other ocular adnexal lymphomas despite EBV negativity(31).

The patient achieved a complete remission after radiotherapy by careful clinical judgment. No additional radiologic studies were performed other than CT simulation for involved field radiation therapy. According to previous reports, follow-up CT or PET is not routinely performed in lymphoma to evaluate response(32).

In conclusion, this report presents a case of conjunctival MALT lymphoma that produces visual discomfort in KT recipients. The patient received a lymphoma treatment with the conversion of the tacrolimus to sirolimus and a local radiotherapy without major complications or disease progression. We suggest that the lymphoma should be suspected as a possible cause of visual disturbance in KT recipients when other common etiologies are ruled out.

ACKNOWLEDGEMENTS

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (grant number: HC15C1129).

REFERENCES

1) Bosly A, Coiffier B. Recent data on the epidemiology of non-Hodgkin lymphoma. Groupe d’Etudes des Lymphomes de l’Adulte (GELA). Pathol Biol (Paris) 1997/45:449-52.
2) Hsi ED, Singleton TP, Swinnen L, Dunphy CH, Alkan S. Mucosa-associated lymphoid tissue-type lymphomas occurring in post-transplantation patients. Am J Surg Pathol 2000;24:100-6.
3) Le Meur Y, Pontoizeau-Potelune N, Jaccard A, Paraf F, Leroux-Robert C. Regression of a gastric lymphoma of mucosa-associated lymphoid tissue after eradication of Helicobacter pylori in a kidney graft recipient. Am J Med 1999;107:530.
4) Shehab TM, Hsi ED, Poterucha JJ, Gunaratnam NT, Fontara RJ. Helicobacter pylori-associated gastric MALT lymphoma in liver transplant recipients. Transplantation 2001;71:1172-5.
5) Vardiman JW. The World Health Organization (WHO) classification of tumors of the hematopoietic and lymphoid tissues: an overview with emphasis on the myeloid neoplasms. Chem Biol Interact 2010;184:16-20.
6) Smith JM, Rudser K, Gillen D, Kestenbaum B, Seliger S, Weiss N, et al. Risk of lymphoma after renal transplantation varies with time: an analysis of the United States Renal Data System. Transplantation 2006;81:175-80.
7) Achuthan R, Bell SM, Leek JP, Roberts P, Horgan K, Markham AF, et al. Novel translocation of the BCL10 gene in a case of mucosa associated lymphoid tissue lymphoma. Genes Chromosomes Cancer 2000;29:347-9.
8) Enno A, O'Rourke J, Braye S, Howlett R, Lee A. Antigen-dependent progression of mucosa-associated lymphoid tissue (MALT)-type lymphoma in the stomach. Effects of antimicrobial therapy on gastric MALT lymphoma in mice. Am J Pathol 1998;152:1625-32.
9) Hamoudi RA, Appert A, Ye H, Ruskone-Fournestraux A, Streubel B, Chott A, et al. Differential expression of NF-kappaB target genes in MALT lymphoma with and without chromosome translocation: insights into molecular mechanism. Leukemia 2010;24:1487-97.
10) Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1984;1:1311-5.
11) Gibson SE, Swerdlow SH, Craig FE, Surti U, Cook JR, Nalesnik MA, et al. EBV-positive extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue in the posttransplant setting: a distinct type of posttransplant lymphoproliferative disorder? Am J Surg Pathol 2011;35:807-15.
12) Suarez F, Lortholary O, Hermine O, Lecuit M. Infection-associated lymphomas derived from marginal zone B cells: a model of antigen-driven lymphoproliferation. Blood 2006;107:3034–44.
13) Bates WD, Gray DW, Dada MA, Chetty R, Gatter KC, Davies DR, et al. Lymphoproliferative disorders in Oxford renal transplant recipients. J Clin Pathol 2003;56:439–46.
14) Goldfarb JM, Larson ML, Venugopal P, Gregory SA. Posttransplant lymphoproliferative disorder: extranodal marginal zone lymphoma occurring after renal transplantation. Clin Adv Hematol Oncol 2006;4:600–4.
15) Douglas RS, Goldstein SM, Katowitz JA, Gausas RE, Ibarra MS, Tsai D, et al. Orbital presentation of posttransplant lymphoproliferative disorder: a small case series. Ophthalmology 2002;109:2351–5.
16) Taylor AL, Marcus R, Bradley JA. Post-transplant lymphoproliferative disorders (PTLD) after solid organ transplantation. Crit Rev Oncol Hematol 2005;56:155–67.
17) Morscio J, Dierickx D, Tousseyn T. Molecular pathogenesis of B-cell posttransplant lymphoproliferative disorder: what do we know so far? Clin Dev Immunol 2013;2013:150835.
18) Craig FE, Johnson LR, Harvey SA, Nalesnik MA, Luo JH, Bhattacharya SD, et al. Gene expression profiling of Epstein-Barr virus-positive and -negative monomorphic B-cell posttransplant lymphoproliferative disorders. Diagn Mol Pathol 2007;16:158–68.
19) Al-Mansour Z, Nelson BP, Evens AM. Post-transplant lymphoproliferative disease (PTLD): risk factors, diagnosis, and current treatment strategies. Curr Hematol Malig Rep 2013;8:173–83.
20) Opelz G, Dohler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. Am J Transplant 2004;4:222–30.
21) Bhatia S, Paulino AC, Buatti JM, Mayr NA, Wen BC. Curative radiotherapy for primary orbital lymphoma. Int J Radiat Oncol Biol Phys 2002;54:818–23.
22) Bolek TW, Moyes HM, Marcus RB Jr, Gorden L 3rd, Mairose RL, Almasri NM, et al. Radiotherapy in the management of orbital lymphoma. Int J Radiat Oncol Biol Phys 1999;44:31–6.
23) Goda JS, Gospodarowicz M, Pintillie M, Wells W, Hodgson DC, Sun A, et al. Long-term outcome in localized extranodal mucosa-associated lymphoid tissue lymphomas treated with radiotherapy. Cancer 2010;116:3815–24.
24) Stafford SL, Kozeljski TF, Garrity JA, Kurtin PJ, Leavitt JA, Martenson JA, et al. Orbital lymphoma: radiotherapy outcome and complications. Radiother Oncol 2001;59:139–44.
25) Tsang RW, Gospodarowicz MK, Pintillie M, Wells W, Hodgson DC, Sun A, et al. Localized mucosa-associated lymphoid tissue lymphoma treated with radiation therapy has excellent clinical outcome. J Clin Oncol 2003;21:4157–64.
26) Lee JI, Kim MK, Lee KH, Hyun MS, Chung HS, Kim DS, et al. Extranodal marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue-type of the orbit and ocular adnexa. Ann Hematol 2005;84:13–8.
27) Ashrafi F, Shahidi S, Ebrahimi Z, Mortazavi M. Outcome of rapamycin therapy for post-transplant-lymphoproliferative disorder after kidney transplantation: case series. Int J Hematol Oncol Stem Cell Res 2015;9:26–32.
28) Cullis B, D’Souza R, McCullagh P, Harries S, Nicholls A, Lee R, et al. Sirolimus-induced remission of posttransplantation lymphoproliferative disorder. Am J Kidney Dis 2006;47:e67–72.
29) Boratynska M, Smolska D. Inhibition of mTOR by sirolimus induces remission of post-transplant lymphoproliferative disorders. Transpl Int 2008;21:605–8.
30) Nelson BP, Nalesnik MA, Bahler DW, Locker J, Fung JJ, Swerdlow SH. Epstein-Barr virus-negative post-transplant lymphoproliferative disorders: a distinct entity? Am J Surg Pathol 2000;24:375–85.
31) McKelvie PA, McNab A, Francis IC, Fox R, O’Day J. Ocular adnexal lymphoproliferative disease: a series of 73 cases. Clin Exp Ophthalmol 2001;29:387–93.
32) Oh YK, Ha CS, Samuels BI, Cabanillas F, Hess MA, Cox JD. Stages I-III follicular lymphoma: role of CT of the abdomen and pelvis in follow-up studies. Radiology 1999;210:483–6.