

Cytomegalovirus in Non-Melanoma Skin Cancers

Anna Sorensen^{1*}, Bruce Smoller², John Martens¹, Nicole Pecora², Jun Wang³, Kim Handley⁴ and Eugene Storzynsky¹

¹Department of Advanced Heart Failure and Transplant, University of Rochester Medical Center, USA

²Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, USA

³Department of Molecular Laboratory, University of Rochester Medical Center, USA

⁴Department of Virology Laboratory, University of Rochester Medical Center, USA

Abstract

Background: Survival time after heart transplantation continues to rise due to the use of immunosuppression therapy and other advances in care. However, this increase in patient survival and exposure to potent immunosuppression drugs comes at the expense of long-term complications such as infection and malignancy. In addition to immunosuppression exposure, viral infection has been indicated to play a role in carcinogenesis. While the presence of CMV genome or antigens has been found in malignant tumors, conflicting evidence exists regarding the independent nature of this association. Limited data are available regarding the association of Cytomegalovirus (CMV) in skin cancer development post transplant. Study to detect CMV genome specifically in Non-Melanoma Skin Cancers (NMSC's) yet to be complete in the heart transplant population.

Methods: This is a single center, retrospective, observational study of adult heart transplant recipients managed by the University of Rochester Advanced Heart Failure program. 10 BCC and 10 SCC lesions of heart transplant recipients housed at the URMIC were tested for CMV-PCR, DNA.

Results: CMV was not detected from any of the specimens.

Conclusion: We did not identify a connection between CMV DNA and non-melanoma skin cancers.

Keywords: Skin cancers; Heart failure; Virus

Abbreviations

BCC: Basal Cell Carcinoma; CMV: Cytomegalovirus; DNA: Deoxyribonucleic Acid; EBV: Epstein Barr Virus; FFPE: Formalin-Fixed, Paraffin-Embedded; HSV: Human Herpes-virus; NMSC: Non Melanoma Skin Cancers; SCC: Squamous Cell Carcinoma; UNOS: United Network for Organ Sharing; URMIC: University of Rochester Medical Center; OTTR: Transplant Care Platform

Introduction

The gold standard for treatment of end stage heart failure is heart transplantation. Survival time after heart transplantation continues to rise due to the use of immunosuppression therapy and other advances in care [1]. However, this increase in patient survival and exposure to potent immunosuppression drugs comes at the expense of long-term complications such as infection, rejection, graft vasculopathy, and malignancy [2,3].

The occurrence of malignancy secondary to immunosuppression therapy among heart transplant recipients is well documented, and is a leading cause of death in patients with a functioning allograft [4-6]. The International Society of Heart and Lung Transplant (ISHLT) has shown the cumulative prevalence of malignancy in heart transplant recipients at 1 and 10 years to be 2.9% and 31.9% respectively, with skin cancer being the most prevalent [7]. Nationally, the incidence of Squamous Cell Carcinoma (SCC) and Basal Cell Carcinoma (BCC) has increased 77% over the past 20 years in the transplant population [8].

In addition to immunosuppression exposure, viral infection has been indicated to play a role in carcinogenesis [9]. The human papilloma virus (HPV), hepatitis B (Hep B) and C (Hep C), and Epstein-Barr virus (EBV) have been associated with the development of cancer in both immunocompetent and immunocompromised patient populations [10].

Limited data are available regarding the association of CMV in

NMSC skin cancer development post- transplant. While the presence of CMV genome or antigens has been found in malignant tumors, conflicting evidence exists regarding the independent nature of this association [10-12]. Studies to detect CMV genome specifically NMSC's have yet to be completed in the immunosuppressed post-transplant population.

The aim of this pilot study is to detect the presence of CMV in NMSC lesions identified in the heart transplant population.

Materials and Methods

Approval for this study was obtained from the University of Rochester Institutional review board. This is a single center, retrospective, observational study of adult heart transplant recipients managed by the University of Rochester Advanced Heart Failure program. The source of information will include electronic records from e-Record and OTTR, internal program data, the United Network for Organ Sharing (UNOS) and URMIC specimen management. Heart transplant recipients aged 18 years or older whose post transplant care is managed by the University of Rochester, have a biopsy confirmed diagnosis of NMSC in which the biopsy was performed at URMIC were included in our study. The study included subjects from all racial and ethnic groups. This study did not aim to recruit vulnerable subjects. We did not have any restrictions on gender.

***Corresponding author:** Anna Sorensen, Department of Advanced Heart Failure and Transplant, University of Rochester Medical Center, USA, Tel: +1 585-279-5100; E-mail: Anna_Sorensen@URMC.Rochester.edu

Received: July 08, 2019; **Accepted:** July 23, 2019; **Published:** July 29, 2019

Citation: Sorensen A, Smoller B, Martens J, Pecora N, Wang J, et al. (2019) Cytomegalovirus in Non-Melanoma Skin Cancers. J Infect Dis Med 4: 136.

Copyright: © 2019 Sorensen A, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Heart transplant recipients without a biopsy confirmed NMSC, and those with biopsies performed at outside institutions were excluded from our study. We requested a waiver of consent and of HIPAA authorization as this was a retrospective study of data that had already been collected. All care provided to the subject would have already occurred in the past and would have been directed by their providers. We did not intervene to change the subject's care. No subjects were contacted.

Patients transplanted or managed by the program from 2001 to Aug 30, 2018 were identified using eRecord, OTTR and internal program databases. Patients with biopsy confirmed NMSC were identified using the documentation in e-Record, OTTR, and UNOS data for our program.

All biopsy samples had been collected from heart transplant recipients with expressed consent as part of standard post transplant care. Stored biopsy specimens were obtained from specimen management. A member of the clerical staff in surgical pathology identify the surgical pathology numbers, pulled the paraffin tissue blocks and brought them to histology. The histology laboratory cut additional slides as needed for CMV testing and labeled the slides with numbers specific to the study with no relationship to patient information. These numbered slides were assayed for CMV and presented to the investigators with patient identifiers. Formalin-fixed, paraffin-embedded (FFPE) scrolls (3 X 10 µm thick) were received from surgical pathology. The Maxwell RSC DNA FFPF Kit (Promega AS1450) was used to extract DNA from FFPF scrolls according to manufacturer's protocol. DNA quality and quantity were measured by Nanodrop spectrophotometer. CMV was amplified according to standard laboratory procedure using the Focus (Diasorin) RT-PCR platform.

Results and Discussion

The target of this assay is the CMV *UL83* gene detected with a FAM labeled forward primer. This assay was validated clinically for respiratory and urine specimens. To confirm that it would also work on fixed tissue the following specimens with gastrointestinal CMV disease were extracted and amplified (using 5 ul of extract). CMV was detected in all of them. Note that an internal control is added to all specimens.

Patient information was secured utilizing a numbered identification system held secure in a locked drawer in the PI's office.

CMV was not detected from any of the specimens. Of our 10 SCC samples, four had a previous diagnosis of CMV viremia. Of the 10 BCC, six had a previous diagnosis of CMV. None of the subjects had active CMV viremia at the time the NMSC was diagnosed and removed.

Conclusion

While exposure to UV sunlight has been shown to contribute significantly to NMSC other studies have identified a contribution made by viruses. We also understand many other genetic and environmental factors may play a role as well. Although our study did not identify a connection between CMV DNA and NMSC, we realize this is a small sample size in a single institution. We would like to further research HSV, HPV and EBV potential contribution to NMSC. As noted above other studies have suggested a correlation with viruses and NMSC. We feel with this highly susceptible group of patients, more research needs be completed.

References

1. Metra M, Ponikowski P, Dickstein K, McMurray JJ, Gavazzi A, et al. (2007) Advanced chronic heart failure: A position statement from the Study Group on Advanced Heart Failure of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 9: 684-694.
2. Kittleson MM, Kobashigawa JA (2014) Long-term care of the heart transplant recipient. *Curr Opin Organ Transplant* 19: 515-524.
3. Lateef N, Abdul Basit K, Abbasi N, Kazmi SM, Ansari AB, et al. (2015) Malignancies After Heart Transplant. *Experimental and Clinical Transplantation. Official Journal of the Middle East Society for Organ Transplantation* 14: 12-16.
4. Doesch AO, Müller S, Konstandin M, Celik S, Kristen A, et al. Malignancies after heart transplantation: incidence, risk factors, and effects of calcineurin inhibitor withdrawal. *Transplant Proc* 42: 3694-3699.
5. Fuchs U, Klein S, Zittermann A, Ensminger SM, Schulz U, et al. Incidence of malignant neoplasia after heart transplantation--a comparison between cyclosporine a and tacrolimus. *Ann Transplant* 19: 300-304.
6. Rivinius R, Helmschrott M, Ruhparwar A, Schmack B, Klein B, et al. (2015) Analysis of malignancies in patients after heart transplantation with subsequent immunosuppressive therapy. *Drug Des Devel Ther* 9: 93-102.
7. Roussel JC, Baron O, Périgaud C, Bizouarn P, Pattier S, et al. (2008) Outcome of heart transplants 15 to 20 years ago: graft survival, post-transplant morbidity, and risk factors for mortality. *J Heart Lung Transplant* 27: 486-493.
8. Brewer JD, Colegio OR, Phillips PK, Roenigk RK, Jacobs MA, et al. (2009) Incidence of and risk factors for skin cancer after heart transplant. *Arch Dermatol* 145: 1391-1396.
9. Molina BD, Leiro MG, Pulpón LA, Mirabet S, Yañez JF, et al. (2010) Incidence and risk factors for nonmelanoma skin cancer after heart transplantation. *Transplant Proc* 42: 3001-3005.
10. Desai R, Collett D, Watson CJ, Johnson PJ, Moss P, et al. (2015) Impact of Cytomegalovirus on Long-term Mortality and Cancer Risk After Organ Transplantation. *Transplantation* 99: 1989-1994.
11. Courivaud C, Bamoulid J, Gaugler B, Roubiou C, Arregui C, et al. (2012) Cytomegalovirus exposure, immune exhaustion and cancer occurrence in renal transplant recipients. *Transpl Int* 25: 948-955.
12. Couzi L, Levaillant Y, Jamai A, Pitard V, Lassalle R, et al. (2010) Cytomegalovirus-induced gammadelta T cells associate with reduced cancer risk after kidney transplantation. *J Am Soc Nephrol* 21: 181-188.