Case Reports in Clinical Medicine, 2022, 11, 116-121
https://www.scirp.org/journal/crcm
ISSN Online: 2325-7083
ISSN Print: 2325-7075

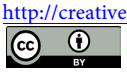
The Troll in Transplant—CMV Esophagitis in a Post Orthotopic Liver Transplant Patient Complicated with Scalp Squamous Cell Carcinoma

Alif Adlan Mohd Thabit[1], Anuradha Radhakrishnan[1], Haniza Omar[2], Tan Soek Siam[2]

[1]Infectious Diseases Unit, Department of Medicine, Selayang Hospital, Batu Caves, Malaysia
[2]Department of Hepatology, Selayang Hospital, Batu Caves, Malaysia
Email: alif.adlan@gmail.com, anurapr70@gmail.com, ohaniza@yahoo.com, tansoeksiam@yahoo.com

How to cite this paper: Thabit, A.A.M., Radhakrishnan, A., Omar, H. and Siam, T.S. (2022) The Troll in Transplant—CMV Esophagitis in a Post Orthotopic Liver Transplant Patient Complicated with Scalp Squamous Cell Carcinoma. *Case Reports in Clinical Medicine*, **11**, 116-121.
https://doi.org/10.4236/crcm.2022.114018

Received: March 5, 2022
Accepted: April 16, 2022
Published: April 19, 2022



Abstract

A liver transplant candidate who is CMV serostatus positive and is subjected to calcineurin inhibitor such as tacrolimus post transplant may increase risk of CMV disease, and may promote tumor progression in some. We report a case of a late localized CMV disease manifesting as oesophagitis after 7 years post orthotopic liver transplantation complicated with an aggressive scalp squamous cell carcinoma which recurred despite wide local excision procedure. Hence it is crucial to modulate the patient's risk factors for tumor progression without compromising the patient to graft rejection.

Keywords

Orthotopic Liver Transplant, Cytomegalovirus CMV, Esophagitis, Limited Systemic Sclerosis

1. Introduction

Solid organ transplants are constantly exposed to immunosuppressants, and it is a dilemma to strike a net state of immunosuppression vs risks of infection. Cytomegalovirus, being an immunomodulating virus, plays a significant role during the early and later part post transplantation. CMV can be related to autoimmune diseases as a cause of the disease eg systemic sclerosis. It can also be an indirect complication of systemic sclerosis presenting as CMV esophagitis, as a result of the immunosuppressants use. CMV disease can manifest at an early or late period post transplantation, particularly while on immunosuppresants, as both the virus and drugs have potential to be linked to malignancies.

2. Case Presentation

We report a case of a 59-year-old Chinese lady diagnosed with autoimmune hepatitis and limited systemic sclerosis complicated with pulmonary artery hypertension and peripheral vascular disease with history of digital ulcer gangrene and Raynaud's phenomenon. She has had an orthotopic liver transplant 6 years ago and had been on immunosuppressants of prednisolone, mycophenolate mofetil (MMF) and Tacrolimus post transplantation till date. CMV serostatus was donor and recipient positive D+/R+. However, she was given iv acyclovir 500 mg every 8 hours post transplant for 1 week and no further primary prophylaxis or pre-emptive therapy was started.

She presented to the emergency department (ED) with a 2 month history of non healing ulcerative scalp lesion, which became progressively larger especially following a history of hair dye application. She also gave a history of dysphagia and weight loss of approximately 5 kilos within 2 months.

Systemic review revealed signs of microstomia, digital pitting, Raynaud's phenomenon, and a soft ejection systolic murmur at the lower left sternal edge. A 2 × 2 cm parietal scalp lesion with center ulceration and rolled edges, hard and firm in consistency was fixed to the underlying skull bone. There was no pus or discharge. Respiratory system was unremarkable except loud P2 sound. Abdominal examination revealed a well-healed Mercedes-benz scar. The patient was a fit lady who is self-employed. She does not drink alcohol and has never used illicit drugs. There was no family history of sudden cardiac death, other liver or autoimmune diseases.

Blood investigation results as shown in **Table 1** were grossly normal, except for worsening absolute lymphocyte counts (ALC) and transaminitis, but later his ALC improved after a course of valganciclovir. CT scans showed cortical bony erosions at the skull base, maxilla, mandible and the skull vault with suspicious periosteal reaction at the bilateral humerus bones with right lung nodule. PET scan only showed irregular metabolic uptake of skin at parietal scalp, but no hypermetabolic distant or bone metastases. The patient underwent wide local excision of the parietal scalp lesion, burring of the skull with split skin graft. A 4 × 3.5 cm tumor infiltrating the periosteum was removed en bloc with a 1 cm margin. The histopathology examination of the tumor (**Figure 1**) revealed malignant squamoid cells infiltrating into the stroma and suspicious peripheral margin involvement.

Esophageal duodenoscopy showed reflux esophagitis with linear ulcer, superficial antral erosion and mild duodenitis. The histopathology of the oesophageal tissue (**Figure 2**) showed positivity on CMV immunohistochemistry, despite no obvious viral inclusion bodies seen on hematoxylin and eosin (H&E) stain. There were negative findings for CMV retinitis on ophthalmology slit lamp examination. She was commenced on iv ganciclovir 5 mg/kg twice daily for a period of 2 weeks. During this treatment period, 2 CMV nucleic acid amplification tests (NAAT) from blood sample in ethylenediamine tetraacetic acid (EDTA) tube taken 4 days apart detected no viral copies on polymerase chain reaction (PCR)

test. Oral valganciclovir 600 mg daily was prescribed as secondary prophylaxis for a total of 6 weeks.

Table 1. Progress of patient's relevant blood investigations throughout hospital admission.

	Normal Values	Day 1	Day 10	Day 26	Day 42
WCC (10^3/uL)	3.60 - 10.20	3.7	5.07	4.37	4.8
Platelet (10^3/uL)	152 - 347	178	177	125	206
Lymphocytes (10^3/uL)	1 - 3	0.4	0.51	0.57	1.01
Urea (mmol/L)	1.7 - 8.3	7	4.9	6.3	
Creatinine (umol/L)	80 - 115	72	72	67	
AST (U/L)	5 - 41	6	43	96	
ALT (U/L)	5 - 37		76	24	
Tacrolimus level (ng/ml)	5 - 20		5.93	5.99	
CMV DNA (units)			Not detected	Not detected	

Abbreviations: WCC: white cell count; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CMV DNA: Cytomegalovirus DNA level.

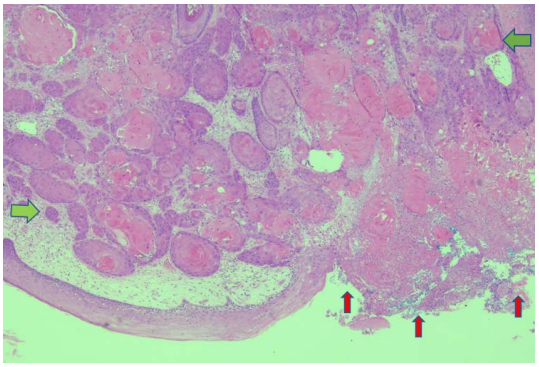


Figure 1. Tissue with ulcerated surface (red arrow). Nests of malignant squamoid cells (green arrow) are seen infiltrating into the stroma (H&E stain, x 40 magnification).

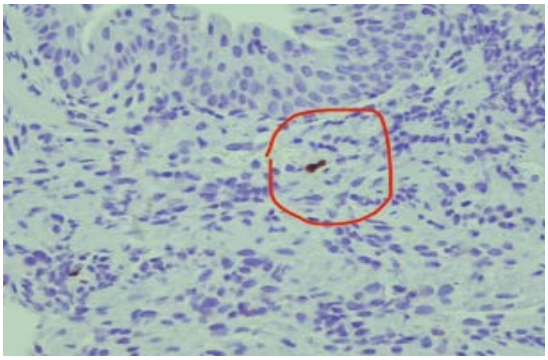


Figure 2. CMV immunohistochemistry is positive (orange circle) (x 400 magnification).

She was planned for another repeat excision biopsy surgery in view of the further involvement of peripheral margin suspicions on the histopathological examination. A repeated serum CMV genome detection test also revealed no viral load detected via the PCR method. A negative result does not conclusively rule out CMV infection either due to the timing of the collection, improper collection manner, or simply due to specimen deterioration of cold chain during storage or transportation.

3. Discussion

Cytomegalovirus, being an immunomodulating virus may have well attributed to the pathogenesis of systemic sclerosis owing to its ability to infect both endothelial and monocyte or macrophage cells, causing specific autoantibodies to cross react with endothelial autoantigens [1]. On the other hand, a systemic sclerosis patient on immunosuppressants can manifest asymptomatic severe CMV esophagitis which was detected via endoscopy as part of scleroderma investigation [2].

As part of diagnosis gastrointestinal (GI) disease, Durand *et al.* reported overall, the quantitative polymerase chain reaction (qPCR) is 85% sensitive and 95% specific [3]. Depending on CMV serostatus, among CMV D+/R−, qPCR 100% sensitive, 80% specific. It has the lowest sensitivity among CMV D+/R+, similar to our case. **Table 1** showed that it was not successful in detecting any CMV viral genome despite being repeated in this patient.

Treatment duration in GI CMV disease should be patient-specific, and guided by virologic and clinical improvement. If CMV viremia is present, it should be cleared prior to treatment discontinuation with at least two consecutive negative CMV PCR test 1 week apart to ensure viral clearance. However, our patient did not have documented CMV viremia. Consideration should be made for reduction in immunosuppressive therapy to the lowest possible safe dose, especially in patients with severe CMV disease, non-response to therapy, high viral load, or leukopenia. Bradley et al reported protective role of secondary prophylaxis from 0 - 6 weeks post treatment completion, and there are no routine virologic surveillance post treatment completion [4]. An inexpensive, readily available tool is the absolute lymphocyte count (ALC), whereby low counts upon treatment completion is an independent predictor marker for recurrent CMV disease [5]. As shown in **Table 1**, after discharge, and at day 42 after his first day of current admission, he had improving absolute lymphocyte counts (ALC). However, we still are uncertain which high risk CMV patients may benefit prolonged course of secondary prophylaxis.

It is crucial to balance the risk and benefits with immunosuppressants with active CMV disease and concurrent skin malignancy, as calcineurin inhibitors such as tacrolimus can have dose-dependent effect on certain tumor progression via tumour growth factor (TGF) TGF-β overexpression [6]. A costly alternative treatment would be everolimus which was reported to have delayed and suppressed CMV DNA synthesis [7].

4. Conclusion

We report the case of 59-year old female patient who developed late localized CMV disease after 7 years post orthotopic liver transplantation with oesophageal involvement as an incidental finding through esophagoduodenoscopy. Apart from being immunosuppressed while on long term tacrolimus and mycophenolate, she is also diagnosed with squamous cell carcinoma of the scalp which had recurrence despite wide local excision procedure. It is essential to maintain a net balance between immunosuppression and graft rejection to minimise further risks of CMV disease recurrence, particularly when post treatment surveillance cannot be objectively assessed by detection of CMV viremia.

Acknowledgements

The authors would like to acknowledge the patient for generously allowing the use of clinical details and radiological imaging in this case report. We thank our colleague, Dr. Fatin Izni Nazri from pathology department for her expertise and assistance in selection of the figures for immunohistochemistry and histopathology, the hepatobiliary and liver transplant team, and Dr. Woo and the plastic surgery unit of Hospital Selayang.

Funding

This publication is supported by the Persatuan Pendidikan Pasca Ijazah Hospital Selayang (also known as Post Graduate Education Society of Selayang Hospital). Dr. Haniza Omar received support from the society for funds in publication.

Data Availability

The patient data used to support the findings of this case report are available from the corresponding author upon request.

Author's Contribution

AAMT was directly involved in the treatment of the patient, literature search, and scientific writing. APR, HO and TSS participated in providing expert opinion on patient care and review of the manuscript. FIN had selected the figures for immunohistochemistry and histopathology.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Ferri, C., Cazzato, M., Giuggioli, D., Sebastiani, M. and Magro, C. (2002) Systemic Sclerosis Following Human Cytomegalovirus Infection. *Annals of the Rheumatic Diseases*, **61**, 937-938. https://doi.org/10.1136/ard.61.10.937

[2] Contreras, M.Á., Salas, C., Andreu, J.L. and Mulero, J. (2001) Cytomegalovirus Eso-

phagitis as a Treatable Complication of Systemic Sclerosis. *Journal of Clinical Rheumatology*, **7**, 384-387. https://doi.org/10.1097/00124743-200112000-00007

[3] Durand, C.M., Marr, K.A., Arnold, C.A., Tang, L., Durand, D.J., Avery, R.K., Valsamakis, A. and Neofytos, D. (2013) Detection of Cytomegalovirus DNA in Plasma as an Adjunct Diagnostic for Gastrointestinal Tract Disease in Kidney and Liver Transplant Recipients. *Clinical Infectious Diseases*, **57**, 1550-1559. https://doi.org/10.1093/cid/cit521

[4] Gardiner, B.J., Chow, J.K., Price, L.L., Nierenberg, N.E., Kent, D.M. and Snydman, D.R. (2017) Role of Secondary Prophylaxis with Valganciclovir in the Prevention of Recurrent Cytomegalovirus Disease in Solid Organ Transplant Recipients. *Clinical Infectious Diseases*, **65**, 2000-2007. https://doi.org/10.1093/cid/cix696

[5] Gardiner, B.J., Nierenberg, N.E., Chow, J.K., Ruthazer, R., Kent, D.M. and Snydman, D.R. (2018) Absolute Lymphocyte Count: A Predictor of Recurrent Cytomegalovirus Disease in Solid Organ Transplant Recipients. *Clinical Infectious Diseases*, 67, 1395-1402. https://doi.org/10.1093/cid/ciy295

[6] Maluccio, M., Sharma, V., Lagman, M., Vyas, S., Yang, H., Li, B. and Suthanthiran, M. (2003) Tacrolimus Enhances Transforming Growth Factor-β1 Expression and Promotes Tumor Progression. *Transplantation*, **76**, 597-602. https://doi.org/10.1097/01.TP.0000081399.75231.3B

[7] Tan, L., Sato, N., Shiraki, A., Yanagita, M., Yoshida, Y., Takemura, Y. and Shiraki, K. (2019) Everolimus Delayed and Suppressed Cytomegalovirus DNA Synthesis, Spread of the Infection, and Alleviated Cytomegalovirus Infection. *Antiviral Research*, **162**, 30-38. https://doi.org/10.1016/j.antiviral.2018.12.004