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CASE REPORT
Cardiovascular surgery

The risks of rejection vs. infection: Ramsay Hunt syndrome, Gradenigo syndrome, and varicella meningoencephalitis in a heart transplant patient

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Background Orthotopic heart transplant (OHT) recipients are at increased risk for varicella zoster reactivation, and severe complications may arise due to their immunosuppressive regimens. Managing immunosuppression in acute infection is difficult, and specific guideline recommendations or evidence from the literature are lacking. However, patient care must involve weighing the risk of transplant rejection with the consequences of worsening infection.

Case summary An OHT patient with a history of multiple episodes of acute rejection, latent varicella zoster virus (VZV) infection, and recent completion of anti-viral prophylaxis presented with unilateral facial droop and pain, abducens nerve palsy, crusting facial rash, and ear swelling. Imaging revealed necrotizing otitis externa, with associated otitis media, and petrous apicitis concerning for Gradenigo syndrome. A VZV-positive viral panel confirmed our suspicion for Ramsay Hunt syndrome (RHS). The patient's mentation continued to decline, and subsequent lumbar puncture also revealed VZV meningoencephalitis. The patient's mycophenolate mofetil (MMF) was suspended, with continuation of tacrolimus, and initiation of intravenous acyclovir. The patient demonstrated gradual resolution of his infection, without developing any signs of acute rejection.

Discussion Varicella zoster virus reactivation is common in OHT patients, particularly when viral prophylaxis is discontinued; however, cardiologists should be aware of the rarer manifestations that can manifest in these immunocompromised patients. This is the first documented case of simultaneous RHS, Gradenigo syndrome, and VZV meningoencephalitis in any patient, regardless of transplant status. We demonstrate that even in patients at very high risk of rejection, MMF can be safely discontinued and host immunity maintained with temporary tacrolimus monotherapy.

Keywords Heart transplant • Immunosuppression • Coronary allograft vasculopathy • Case report

ESC curriculum 6.5 Cardiomyopathy • 7.5 Cardiac surgery • 8.6 Secondary prevention

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Learning points

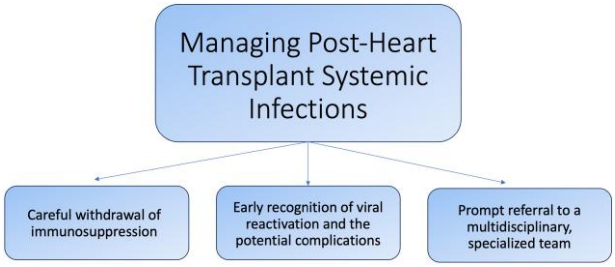
- Identify how complications of varicella reactivation can present in orthotopic heart transplant patients, including as Ramsay Hunt syndrome (facial nerve palsy with facial rash) and Gradenigo syndrome (abducens nerve palsy with otorrhoea and retro-orbital pain).
- Recognize the vulnerability of heart transplant patients who have recently finished taking prophylactic anti-viral therapy to have infections.
- Recognize potential strategies for adjusting immunosuppression in patients with acute infections also at high risk for rejection both on admission and on discharge from the hospital.

Introduction

Orthotopic heart transplant (OHT) patients require lifelong immunosuppression to prevent organ rejection and thus are at increased risk for varicella zoster virus (VZV) reactivation. Involvement of the facial nerve due to reactivation of VZV in the geniculate ganglion may lead to ear pain, facial droop, and an auricular vesicular rash characteristic of Ramsay Hunt syndrome (RHS).[1] The central nervous system can become involved, leading to VZV meningoencephalitis. Bacterial superinfection may also manifest, and when inflammation of the apex of the petrous bone and the abducens nerve occurs, the classic triad of Gradenigo syndrome may occur, consisting of abducens nerve palsy, retro-orbital pain, and otorrhoea.[2] These are exceedingly rare complications, with VZV meningoencephalitis or RHS occurring in <1% of OHT recipients[3,4] and co-occurring in just a few case reports amongst exclusively non-OHT patients.[5,6]

Here, we present a case of Gradenigo syndrome in an OHT patient occurring simultaneously with VZV meningoencephalitis, RHS, and Gradenigo syndrome. However, the challenge of this case is highlighted in the management of a patient at high risk of recurrent transplant rejection in the setting of life-threatening infection, and the balance of restoring sufficient innate immunity, while maintaining adequate immunosuppression.

Summary figure



Case presentation

A 64-year-old male presented to the emergency department with left-sided facial numbness the morning of his admission, accompanied by a left-sided facial droop. Five days prior, he had noticed left ear swelling and purulent discharge, with worsening pain and subjective fevers despite being prescribed otic ofloxacin.

The patient underwent OHT 15 months prior. His course was complicated by an episode of grade 2 antibody-mediated rejection 8 months prior to admission, followed by grade 1R diffuse acute cellular rejection 2 months later, and persistently elevated levels of donor-derived cell-free DNA after resolution of these episodes. He had a history of latent VZV and had completed 14 months of post-transplant viral prophylaxis, 1 month prior to presentation. Immunosuppression was maintained with mycophenolate mofetil (MMF) and tacrolimus, a standard maintenance regimen typical at 1 year post-transplantation.[7] However, due to several periods of non-therapeutic drug trough levels related to *Clostridium difficile* colitis malabsorption, he had underwent frequent dosing adjustments to his tacrolimus over the preceding 4 months. He had been on as much as 7.5 mg of tacrolimus twice daily, titrated down to his regimen on presentation of 3 mg during the day and 3.5 mg at night. He had been on a relatively stable dose of 1 mg MMF twice a day as well.

Vital signs on admission were significant for sinus tachycardia up to 110 beats per minute. Facial examination demonstrated a warm, tender, and severely swollen left auricle, parotid gland, and pre-auricular area, with serous drainage and erythema in the external auditory canal. Erythema encompassed the entire left face, with a fine crusting rash. Neurologic examination was significant for left facial droop with incomplete eyelid closure, an abducens nerve palsy, and mild trismus. His cardiac exam was unremarkable, and he denied any chest pain, shortness of breath, palpitations, or lower extremity swelling.

A brain natriuretic peptide level of 128 pg/mL was obtained; however, neither a troponin nor a creatine kinase MB was ordered. CT imaging of the face and temporal head identified oedematous otitis externa with infiltration of the pre-auricular and parotid region, suspicious for necrotizing infection (*Figure 1*). Follow-up MRI of the face revealed abnormal enhancement suspicious for neuritis, cochleitis, otomastoiditis, and petrous apicitis, raising the possibility of Gradenigo syndrome (*Figure 2*). Electrocardiogram was within normal limits, and echocardiography was without any significant abnormalities other than evidence of previous OHT, without lingering complications.

Bacterial culture and viral PCR of the left ear discharge were positive for methicillin-resistant *Staphylococcus aureus* (MRSA) and VZV, respectively. This confirmed a diagnosis of RHS with superimposed

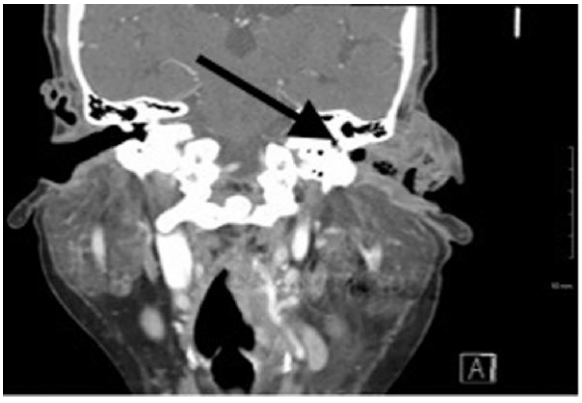


Figure 1 CT contrast coronal view demonstrating extensive left external auditory canal and ear inflammation, with mastoid effusions.

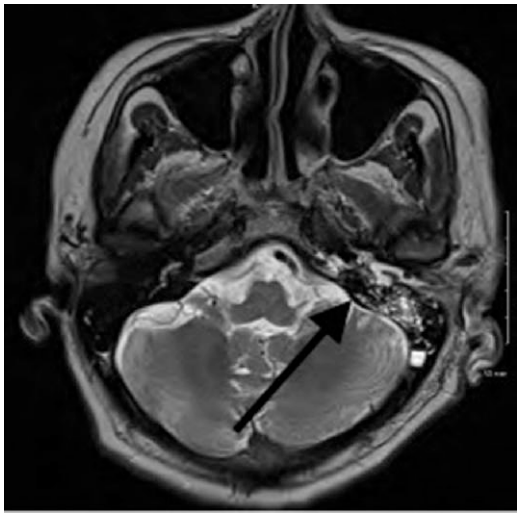


Figure 2 T2 MRI with contrast, axial view showing otomastoiditis, petrous apicitis, and otitis externa.

MRSA malignant otitis externa, complicated by Gradenigo syndrome. Given his severe infection, the patient's 500 mg of twice daily MMF was held while continuing tacrolimus 3.5 mg at night and 3 mg during the day to maintain background immunosuppression. Broad-spectrum intravenous antibiotics, including 500 mg of vancomycin every 2 days, 1 g cefepime, daily, and four drops of intraotic ciprofloxacin twice daily, was initiated in combination with enteral valacyclovir 500 mg daily.

On hospital Day 4, the patient developed increased lethargy and neck stiffness. A lumbar puncture was performed, with cerebrospinal fluid studies suspicious of viral meningitis. A viral panel was positive for VZV, confirming the diagnosis of VZV meningoencephalitis. Intravenous acyclovir 5 mg/kg was started and continued through 14 days, with resolution of his encephalopathy. The swelling of his ear receded, and his facial rash resolved. Throughout his hospitalization, our patient did not demonstrate any cardiac complications and specifically was without signs or symptoms of acute rejection or vasculopathy. Despite residual left-sided facial droop and abducens palsy, he was successfully discharged in good condition with home antibiotics. His regimen included 500 mg of vancomycin and 1 g ceftazidime dosed every 2 days, along with continuation of 250 mg of MMF twice a day. At follow-up 6 months later, despite a persistent facial nerve palsy, he demonstrated complete resolution of his left ear infection and abducens nerve palsy, without any episodes of acute rejection.

Discussion

Up to 7.8% of patients develop VZV infection within the first year after OHT.[8] Mycophenolate mofetil is an independent risk factor for reactivation, and thus, cardiologists should heighten their awareness for the varied manifestations of VZV in these patients, particularly when viral prophylaxis is discontinued.[8] Anti-viral prophylaxis is continued typically for 6–12 months following transplant; however, the median time to VZV reactivation has been demonstrated to occur upwards of 2.1 years following transplant.[4] This period between completion of prophylactic therapy and time to viral reactivation provides a vulnerable window for OHT patients, and thus, in patients with concerning symptoms, there should be a low threshold to initiate early anti-viral therapy during this time.

Reduction in immunosuppressive therapy, active infection, and a history of multiple rejections in the past are all associated with recurrence of acute cellular rejection.[9] However, we demonstrate that during severe multi-organ infection, temporary tacrolimus monotherapy with MMF discontinuation, even in a patient at very high risk of rejection, allowed for the clearance of the infection while providing enough immunosuppression to protect the transplanted heart. Guidelines regarding the specific method in which to reduce immunosuppression during acute viral infections are lacking, with a wide range of practice variation observed in the limited trials that included OHT patients.[10] Complete cessation of immunosuppression, discontinuation of a single agent (either the calcineurin inhibitor or MMF), or a reduction in dose have all been tried with varying degrees of success, further highlighting the need for randomized control trials.[11] Furthermore, the impact of continuing viral prophylaxis beyond 12 months has not been tested and, as demonstrated in our patient, may only delay the onset of disease rather than reduce the incidence[12]. Lastly, the timing of re-implementing immunosuppression following an acute illness deserves further study. Given our patient's high risk for developing acute rejection, the patient's advanced heart failure cardiologist, in conjunction with our infectious disease consultant, agreed to reinstate MMF upon discharge from the hospital, even while completing outpatient intravenous antibiotics for his infection. However, in a patient at lower risk for rejection, and a higher risk of developing a recurrent infection, it may be reasonable to further delay reimplementation of dual-agent immunosuppression until further into the antibiotic course. Thus, for patients presenting to hospitals with less experience treating OHT patients, timely consultation with the patient's transplant centre and heart failure cardiologist is crucial in ensuring appropriate care is delivered.

Conclusion

This is a novel case of RHS, Gradenigo syndrome, and VZV meningoencephalitis occurring simultaneously in a single patient, highlighting the susceptibility of OHT recipients to widespread and atypical presentations of viral reactivation. Management of a patient's immunosuppression should be approached with a careful consider of a patient's risk of rejection, balanced against the impetus to restore an adequate host response.

Lead author biography

Kevin Benavente is a resident at the University of Hawaii Internal Medicine Residency Program, with a passion for cardiology, cardiomyopathies, and advanced heart failure. He completed his undergraduate education at the University of Hawaii at Manoa and medical school at Marian University College of Osteopathic Medicine. He is committed to advancing the field via research and showing patient the respect, kindness, and love they deserve.

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Consent: The authors confirm that consent was obtained from the patient prior to submission and publication, including for all figures and information contained in this report in line with the Committee on Publication Ethics (COPE) guidelines.

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Data availability

No new data were generated or analysed in support of this research.

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