

# Prolonged Symptoms in Solid Organ Transplant Recipients with Enteroviral Meningitis

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## Abstract

In both adults and children, enteroviruses are the most common cause of aseptic meningitis, and a brief and benign course is typical. We describe the first reported cases of enteroviral meningitis in Solid Organ Transplant (SOT) recipients and note a prolonged duration of symptoms. Further, our cases illustrate the utility of the rapid enterovirus Polymerase Chain Reaction (PCR) in avoiding unnecessary antibiotics and diagnostic studies.

## Introduction

Enteroviruses are in the picornavirus family and include polioviruses, coxsackie viruses and echoviruses. There are more than 70 subtypes of enteroviruses capable of causing human infection [1]. These viruses have a predilection for Central Nervous System (CNS) infection, and have been reported to cause over 75% of aseptic meningitis cases, and as many as 27% of infectious encephalitis cases [2,3]. The enteroviruses have also been associated with a number of other acute CNS infections, including transverse myelitis and flaccid paralysis [4,5]. Although these viruses have a tendency to cause infection in summer and fall, they are also associated with more than half all cases of aseptic meningitis in winter and spring [6]. Enteroviral meningitis, in most hosts, has a short self limited course and an excellent prognosis.

Recently a number of cases of viral CNS infections, including those caused by West Nile virus and Lymphocytic Choriomeningitis Virus (LCM) virus, in solid organ transplant recipients have been published [7-9]. These reports have suggested that that both the frequency of symptomatic infection and severe sequelae are greater in SOT recipients than the general population. There have been no reported cases of enteroviral meningitis in solid organ transplant recipients. It is, therefore, not known if the clinical course of this infection is different in this patient population. We report two cases of enteroviral meningitis with a prolonged duration of symptoms in SOT recipients.

## Case Reports

### Case 1

The patient is a 38-year-old man, with a history of Grave's disease and non-ischemic cardiomyopathy, for which he underwent a heart transplant six years previously. His post-transplant course had been relatively uncomplicated with no episodes of rejection and one admission 3 years prior with pneumonia. He was maintained on cyclosporine (Neoral) 75 mg every 12 hours, prednisone 5 mg daily, and sirolimus 2 mg daily for immunosuppression.

One week prior to presentation, his young children developed severe headache, fever, nausea and diarrhea. His children rapidly recovered over the course of several days. The patient, subsequently developed similar symptoms, including headache, nausea and diarrhea. Within 24 hours, he presented to the emergency department complaining of progressive severe headache (rated as a 9 on a standard 10 point pain scale), photophobia and subjective fever.

On physical examination, he was clearly uncomfortable, particularly with light exposure. His temperature was 100.3, pulse 93, blood pressure 132/88. His neck was mildly stiff with no Kernig or Brudzinski signs. His mental status was normal, and he had no other pertinent physical exam findings.

Computed Tomogram (CT) of the head was normal. A lumbar puncture was performed and Cerebrospinal Fluid (CSF) analysis revealed 100 white blood cells/cmm; 91% of these were neutrophils, 8% lymphocytes. The glucose was 62 mg/dL; the protein was 52 mg/dL. CSF HSV Polymerase Chain Reaction (PCR) was negative. CSF cryptococcal antigen was negative. Bacterial Gram stain and culture were negative. His serum laboratories were notable for comprehensive metabolic panel which was within normal limits, white blood cell count 10.9 K/mm<sup>3</sup>, hemoglobin 14.8 g/dL, platelets of 229 K/mm<sup>3</sup>. Plasma and CSF Cytomegalovirus (CMV) PCR was negative. He was started on ampicillin, vancomycin and ceftriaxone, just prior to the lumbar puncture. The following day, a qualitative PCR detected Enteroviral RNA in the CSF. Antibiotics were stopped and the patient was discharged home with plans for symptomatic treatment only. He was still complaining of a moderate headache at discharge, but was not febrile.

Twenty nine days later (30 days after symptom onset), he returned to the emergency department complaining of persistent headache (rated as a four of 10 on a standard pain scale), persisting since his hospital discharge. The headache was not ameliorated by lying flat. He had not had fever, photophobia or neck stiffness, since hospital discharge. The following day, he had a repeat lumbar puncture with CSF analysis, which revealed 13 white blood cells/cmm; 0% of these were neutrophils, 90% lymphocytes. The glucose was 60 mg/dL; the protein was 31 mg/dL. His CSF Enteroviral qualitative RNA PCR was negative. CSF HSV PCR, CSF cryptococcal antigen and bacterial culture were negative. A Magnetic Resonance Imaging (MRI) exam of his brain was performed to evaluate for other cause of persistent headache, such as cerebral venous sinus thrombosis, revealed no abnormalities. Given the Enteroviral PCR conversion from positive to negative, reduction in his CSF pleocytosis, from 100 white blood cells down to 13, as well as the shift from neutrophils to lymphocytes, his presentation was felt to be consistent with his history of resolving enteroviral meningitis.

He was seen in clinic 40 days after his initial diagnosis and his

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**Received** September 10, 2013; **Accepted** September 28, 2013; **Published** October 07, 2013

**Citation:** Smith JA, Kaul DR (2013) Prolonged Symptoms in Solid Organ Transplant Recipients with Enteroviral Meningitis. J Infect Dis Ther 1: 116. doi:10.4172/2332-0877.1000116

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headaches had improved, but were still present. He still complained of markedly low energy and inability to participate in his usual activities. By his follow-up visit 3 months later, however, he was well without headache or excessive fatigue.

## Case 2

The patient is a 38-year-old man, with a history of polyglandular failure, diabetes and diabetic nephropathy for which he underwent a pancreas/kidney transplant six months previously with antithymocyte globulin (Thymoglobulin) induction. His post-transplant course had been relatively uncomplicated with no episodes of rejection. He was maintained on mycophenolate sodium (MYFORTIC) 720 mg twice daily, prednisone 5 mg daily and tacrolimus 3 mg twice daily for immunosuppression.

One week prior to presentation he went to a school concert with his school aged niece. She had subsequently been ill with headache, fever, nausea and upper respiratory tract infection symptoms, as had several of her classmates. The patient subsequently developed similar symptoms, including headache, coryza and nausea. Within 48 hours, he presented to his local hospital complaining of progressive severe headache (rated as a 9 on a standard 10 point pain scale), photophobia and subjective fever. His temperature in the ED was 99.9. He was admitted for 4 days and had an extensive workup, including a Computed Tomogram (CT) of the head, which was normal. A lumbar puncture was performed and Cerebrospinal Fluid (CSF) analysis revealed 12 white blood cells/cmm; 67% of these were neutrophils. The glucose was 42 mg/dL; the protein was 53 mg/dL. HIV testing, CSF HSV Polymerase Chain Reaction (PCR), CSF cryptococcal antigen, and Bacterial and fungal stains and cultures were negative. His serum laboratories were notable for comprehensive metabolic panel, which was within normal limits, white blood cell count 7.7 K/mm<sup>3</sup>. Plasma and CSF Cytomegalovirus (CMV) PCR was negative. The fourth day of his hospitalization, a qualitative PCR detected Enteroviral RNA in a nasopharyngeal swab. Antibiotics were stopped and the patient was discharged home with plans for symptomatic treatment only. He was feeling better at discharge, but shortly after, says his headache returned.

Twenty one days later (27 days after symptom onset), he returned to the emergency department complaining of persistent headache (rated as a 3-4 of 10 on a standard pain scale), persisting since shortly after his hospital discharge. The headache was not ameliorated by lying flat. He had not had fever, photophobia or neck stiffness since hospital discharge, but continued to complain of chills and light/sound sensitivity. The following day, he had a repeat lumbar puncture with CSF analysis, which revealed 29 red blood cells/cmm; 19 white blood cells/cmm; 52% of these were neutrophils, 46% lymphocytes. The glucose was 56 mg/dL; the protein was 65 mg/dL. His CSF Enteroviral qualitative RNA PCR was not performed because of a laboratory error. CSF HSV, CMV, VZV, EBV PCR, CSF cryptococcal antigen, RPR, fungal, mycobacterial and bacterial culture were negative. Serology for West Nile, endemic fungi and Lyme on the CSF were also negative. A Magnetic Resonance Imaging (MRI) exam of his brain was performed to evaluate for other cause of persistent headache revealed no abnormalities. A nasopharyngeal swab was negative for influenza, parainfluenza or RSV. Clinically, he recovered quickly. His headache and chills disappeared and he was discharged 2 days later. Given the lack of other explanations and the prior positive enteroviral nasopharyngeal swab, his presentation was felt to be consistent with slowly resolving enteroviral meningitis.

He was seen in clinic 15 days later after his last admission (42 days after symptom onset), and his headaches and chills remained gone. He

was feeling well and was back to work. He declined a repeat LP as he was feeling well.

## Discussion

Patient one had classic risk factors for enteroviral infection, in particular, exposure to ill household contacts, including an infant in diapers [10]. His initial clinical presentation, including the associated gastrointestinal symptoms, was also typical. He had the usual laboratory findings of enteroviral meningitis, including a polymorphonuclear predominance in the CSF, when examined early in the course of the illness, followed by an evolution to a lymphocytic predominance as his illness progressed. This pattern is seen in two thirds of all patients with enteroviral meningitis [11].

Patient two also had a typical initial presentation and CSF findings. He had persistence of PMN predominance in his CSF. Because of a laboratory error, his enteroviral PCR was not properly processed, so he had extensive other CSF testing, without an alternate explanation for the persistent signs and symptoms of aseptic meningitis.

Both patients recovered eventually, but both also had unusual features, in that they had severe headaches, rated as moderate to severe persisting for greater than one month after the initial diagnosis of enteroviral meningitis. It is unlikely that either persistent headache was from any etiology, besides the enteroviral infection. Post lumbar puncture headaches are typically positional and persist from 2 to 14 days (average four to eight days) [12]. Additionally, extensive CSF testing and MRI scan failed to reveal an alternate explanations.

The natural history of enteroviral meningitis has been studied in adults [13,14]. Most patients recovered completely very quickly. Indeed, most reported return to work by 9 days and full return to usual activity by 18 days. Amongst patients with severe headache (greater than 5 on a standard 10 point pain scale), the median time to headache resolution was 9 days. No patient had evidence of a persistent headache after 28 days. These patients were therefore unusual in that symptoms persisted beyond this period. While the typical time to clearance of CSF pleocytosis in adults is unknown, both patients had persistent CSF pleocytosis (30 days and 22 days), after the first abnormal lumbar puncture.

Two factors might explain why enteroviral meningitis has not been reported previously in recipients of solid organ transplants. First, Enteroviral infections, unlike most viral infections, depend more on humoral immune response than cell mediated response for clearance. This is thought to explain the chronic enteroviral infections seen in patients with agammaglobulinemia [15]. Thus, enteroviral infections may not occur with increased frequency in most populations of SOT recipients compared to normal hosts. However, as more biologic agents with B cell depleting properties, such as alemtuzumab and rituximab are being used in patients with solid organ transplant for induction of immunosuppression and therapy for rejection [16,17], it may be that these infections will be encountered more frequently or that more severe infections may occur.

The second, and perhaps, more important explanation for the lack of previous reports of enteroviral meningitis in SOT recipients is related to the development and increasing availability of nucleic acid based assays for the diagnosis of enteroviral meningitis [18]. PCR based identification had a sensitivity 94.7% vs. 66.7% for detection of enteroviruses in CSF by viral culture alone [19,20], and rapid availability of the result makes testing much more clinically useful. Among patients with likely enteroviral meningitis and a negative CSF PCR, upper respiratory tract and gastrointestinal tract specimens for

enterovirus PCR further increase the ability of a clinician to establish a diagnosis of enterovirus infection [21].

Enteroviral meningoencephalitis has been reported in a case series of children after bone marrow transplantation, 2 of the patients were not known to have enteroviral infection, prior to transplant. Both presented with fever and seizure. Both children recovered completely within one week [22]. In another report, a child had persistently positive CSF enteroviral PCR in the setting of persistent CSF pleocytosis, prior to receiving a bone marrow transplant. He was treated with IVIG and Pleconaril (VP63843) in the peri-transplant period. On day 40 after transplant, he developed worsening of his rhombencephalitis and was found to have persistently positive CSF enteroviral PCR. Despite a 4th course of Pleconaril, he died [23].

There has been publication of a single case of acute flaccid paralysis syndrome due to Echovirus 19 in a patient who had a past medical history significant for cystic fibrosis, 2 bilateral lung transplants and renal transplantation. She was intensely immunosuppressed because of recurrent rejection of her second lung transplant, and had been treated with rabbit anti-thymocyte globulin (total dose 485 mg) and maintained with sirolimus, prednisone and tacrolimus. She was treated with IVIG and pleconaril, but died of respiratory failure [24].

The only pharmacotherapies which have been suggested for enteroviral meningitis are IVIG and pleconaril. Pleconaril is an investigational agent with activity against a range of picornaviruses. It inhibits enterovirus replication by preventing the uncoating and release of enteroviral RNA. Pleconaril is orally administered, but is an inducer of CYP 3A enzyme activity. This makes it a challenging drug to use in solid organ transplant because of the potential for drug interactions, particularly the interference with immunosuppressants and other anti-infectives [25-27].

## Conclusion

We present the first reported cases of enteroviral meningitis in SOT recipients. Both patients had a clinical course which was unusually protracted, and both continued to experience symptoms over 3-4 times, as long as immunocompetent adult patients with enteroviral meningitis. These cases suggest that patients with solid organ transplant and enteroviral meningitis may have a more prolonged course. Enteroviral meningitis and bacterial meningitis often cannot be differentiated clearly and quickly on clinical and initial laboratory studies. This is particularly true in immunocompromised hosts, where additional pathogens (e.g., *Listeria monocytogenes*, fungal and mycobacterial organisms), are of concern. Our case highlights the utility of the enteroviral PCR in confirming the diagnosis, allowing the discontinuation of other empiric antimicrobials, and possibly avoiding unnecessary diagnostic tests and lengthy hospital stays. Transplant centers should consider making this test available in their institutions.

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