



Successful clearance of human parainfluenza virus type 2 viraemia with intravenous ribavirin and immunoglobulin in a patient with acute myocarditis

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ABSTRACT

Human parainfluenza virus (HPIV) infection as an aetiology of acute viral myocarditis is rare, with only few cases reported in the literature to date. Here we report a case of fulminant HPIV-2 myocarditis in a 47-year-old man with viraemia who was successfully treated with intravenous ribavirin and intravenous immunoglobulin (IVIG). There are currently no recommendations on the treatment of HPIV myocarditis. We are, to our knowledge, the first to report a patient with a documented HPIV-2 viraemia that subsequently cleared after the initiation of antiviral therapy. Although it is difficult to definitively attribute the patient's clinical improvement to ribavirin or IVIG alone, our case does suggest that clinicians may wish to consider initiating ribavirin and IVIG in patients with HPIV myocarditis and persistent viraemia not responding to supportive measures alone.

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1. Why this case is important

Acute myocarditis is a complex and challenging diagnosis. The pathogenesis of this disease frequently involves viral infections.¹ Amongst the viral causes of acute myocarditis, human parainfluenza virus (HPIV) infection as an aetiology is rare with only four cases reported in the literature.^{2–5} Two cases of myocarditis associated with HPIV infection were diagnosed by a rise in paired serology² and a positive viral culture on throat swab.⁴ A recent report of HPIV myocarditis demonstrated the presence of HPIV-3 ribonucleic acid (RNA) on nasopharyngeal swab, pericardial fluid and cardiac tissue.³ All of these cases however, were diagnosed retrospectively and the aetiological information did not influence case management. To the best of our knowledge, we are the first to report a case of HPIV-2 myocarditis with documented viraemia and clearance of viraemia following treatment with intravenous (IV) ribavirin and immunoglobulin (IVIG).

2. Case description

A 47-year-old previously well man presented to a regional hospital with a 7-day history of dyspnoea, chest pain, and lower limb swelling. He had a dry cough without fever 2 weeks prior to admission. On admission he was afebrile, normotensive but tachycardic and had oxygen saturations of 96% while breathing room air. Physical examination revealed signs consistent with cardiac failure. Full blood count revealed a mild leukocytosis (white cell count $12.4 \times 10^9/L$, 73% neutrophils, 20% lymphocytes and 7% monocytes) and thrombocytosis ($591 \times 10^9/L$). His C-reactive protein was marginally elevated (17.3 mg/L) and procalcitonin level was normal. He was in acute renal failure with an elevated creatinine of 155 mmol/L. The cardiac enzymes, creatine kinase (CK), creatine kinase-MB fraction (CK-MB) and troponin I were all elevated at 847 U/L, 48.8 U/L and 2.22 µg/L, respectively. Transthoracic echography showed a reduced left ventricular ejection fraction (LVEF) of only 15% with global hypokinesia. A presumptive diagnosis of viral myocarditis was made.

He deteriorated rapidly and required mechanical ventilation for respiratory failure, along with double inotropes and intra-arterial balloon pump (IABP) to support his cardiogenic shock. He developed worsening renal failure, as well as paroxysmal episodes of atrial fibrillation. Endotracheal tube aspirates were negative for influenza virus A and B, HPIV-1, 2 and 3, adenovirus

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and respiratory syncytial virus (RSV) by immunofluorescence. One week after admission, he deteriorated further and was started on extra-corporeal membrane oxygenation (ECMO) before being transferred to our hospital.

After the transfer, there was still ongoing myocardial inflammation with persistently raised cardiac enzymes. Further tests to elucidate a possible infective aetiology for his myocarditis included negative polymerase chain reaction (PCR) on serum for parvovirus B19, Epstein–Barr virus, herpes simplex virus and human herpes-6 virus (HHV-6). The human immunodeficiency virus screen, cytomegalovirus IgM, brucella and rickettsial serologies were negative, as was stool for enterovirus by PCR testing. A nasopharyngeal swab sent for respiratory virus multiplex PCR was negative for RSV, influenza A and B, metapneumovirus, rhinovirus, coronavirus and adenovirus. It was however positive for HPIV-2 by both Seeplex Respiratory Viral 12 Detection Assay (Seegene, Rockville) and Lumindex xTag Respiratory Viral Panel (Luminex Corporation). Primers specific for HPIV-1, 2 and 3 were then designed by the research laboratory under the Program in Emerging Infectious Disease (PEID) from the Duke–NUS Graduate Medical School using complete genomes of each viral serotype downloaded from GenBank and aligned with MAFFT (a multiple sequence program alignment for amino acid or nucleotide sequences) in Geneious Pro version 5.1.4. Forward and reverse primers sequences were designed to target highly conserved regions and produce amplicons of ~1–2 kb in length. Primers used were: 5′-GCCTACAGGTGGTGGAG-3′ and 5′-GCTTGATGGTCGCGCCG-3′ for HPIV 1, 5′-GCCAGCATCCACAGGTGTC-3′ and 5′-GCAGAGCGTATTATTGACCG-3′ for HPIV 2, 5′-GGAGGATATTGATCTCAATG-3′ (HPIV3 F) and 5′-GCAACTAGTGATCTCATTGTACTG-3′ for HPIV 3. The PCR reactions were carried out using Pfu Ultra™ polymerase. Utilizing these primer sets, the patient's serum also tested positive for HPIV-2 by PCR indicating an ongoing HPIV-2 viraemia (Fig. 2). Sequencing of the 1062 bp product that sits within the V gene showed 98% similarity with other HPIV-2 sequences deposited in the GenBank (accession number JX889247), confirming the aetiology of myocarditis in our patient. Following detection of HPIV-2, the patient was started on oral ribavirin (loading dose of 10 mg/kg on day 1 and 400 mg three times daily on day 2) but switched to IV ribavirin (10 mg/kg 8 hourly) on day 3 for a total duration of 7 days upon receiving the regulatory approval from the Health Sciences Authority of Singapore. Intravenous immunoglobulin (IVIG) was given concomitantly at a dose of 0.5 g/kg every other day for 1 week.

As the patient remained in cardiogenic shock, a left ventricular assist device (LVAD) was implanted the day after IV ribavirin was started, 26 days from initial hospital presentation. Histological examination of the left ventricular apical tissue revealed features in keeping with lymphocytic viral myocarditis (Fig. 1), as well as microscopic foci consistent with myocardial ischaemia. There was also coagulation necrosis and other granulating foci showing varying degrees of organization, in keeping with acute, chronic and on-going myocardial ischaemia.

Following IV ribavirin initiation, viraemia clearance was monitored using the PEID RT-PCR assay designed to detect 1062 bp of the HPIV-2 genome and showed a serial decline in HPIV viraemia with clearance on day 4 of ribavirin therapy (Fig. 2) along with improvement in myocardial inflammation as reflected by the normalization of the cardiac enzymes (Fig. 3). The patient tolerated ribavirin with no evidence of haemolytic anaemia or worsening renal function. A transthoracic echocardiogram was performed 2 weeks after ribavirin treatment showed an improvement of the LVEF to 30%. The post-operative recovery was complicated by bleeding that caused a mediastinal haematoma and thrombosis that caused a transient dysphasic stroke. He also suffered from mediastinitis that required a prolonged course of antibiotic and antifungal therapy.

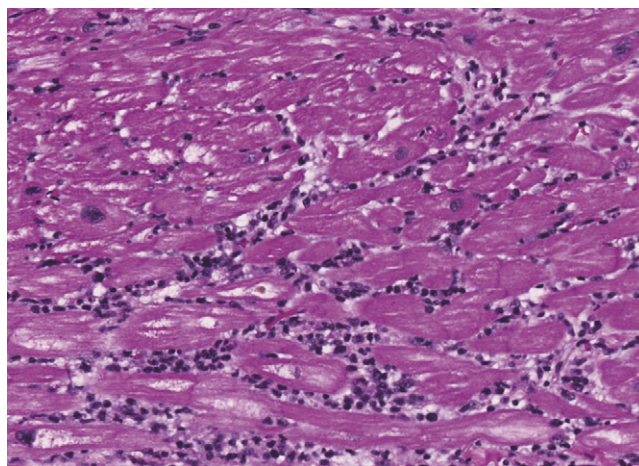


Fig. 1. Photomicrograph of left ventricular apical specimen showing lymphocytic infiltrate within the myocardium, associated with myocardial fibre damage and necrosis. H and E staining at magnification of 200×.

After undergoing 6 months of rehabilitation, he recovered his LVEF to 50% and subsequently underwent successful explantation of the LVAD one year after he first presented with myocarditis.

3. Other similar and contrasting cases in the literature

Few reports have demonstrated HPIV as the aetiology of viral myocarditis.^{2–5} In most of the previously reported cases (Table 1), the diagnosis was made by paired serology. Serology for HPIV however, lacks specificity due to cross reactivity directed against the envelope glycoproteins, HN and F proteins of other paramyxoviruses and hence may be difficult to interpret.⁷ In others, the diagnosis was established by positive immunofluorescence or culturing the virus from throat swabs.⁴ One case reported isolating viral RNA from a throat swab as well as endomyocardial tissue using molecular techniques.³ In the current report, we identified HPIV-2 by PCR in the nasopharyngeal swab and serum of a patient with acute myocarditis. Histopathological examination of the cardiac tissue also showed features consistent with a viral myocarditis. We are, to our knowledge, the first to report the successful clearance of HPIV-2 viraemia with ribavirin antiviral therapy.

4. Discussion

Myocarditis is a well-recognized sequelae of several viral infections. Coxsackie virus, parvovirus B19, HHV-6 type B and the adenovirus are the most frequent viral etiologies implicated.^{1,6} As HPIV myocarditis is a rare and seldom reported entity, it remains unclear if there are any differences in the virulence, presentation and prognosis of each of the four serotypes. Some patients appear to recover spontaneously with only minimal supportive treatment^{2,4} while others have required support with ECMO followed by heart transplant.³ Our patient developed cardiac failure requiring inotropic and ECMO support 1 week after developing an influenza-like illness. Although ventricular assist devices are becoming more widely used in patients with cardiac failure of varying etiologies with much success, implanting such a device in patients with viral myocarditis poses technical challenges. The cardiac tissues in these patients are often inflamed and friable, increasing the risk of bleeding and subsequent infection.

Antiviral agents have been evaluated for the treatment of acute myocarditis in animal models and in a few small case series.^{8–10} Ribavirin, a synthetic nucleoside, together with interferon alpha

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