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Case report

A non-fatal case of hantavirus cardiopulmonary syndrome imported into the UK (ex Panama), July 2014

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1. Why this case is important

We describe a rare case of hantavirus cardiopulmonary syndrome (HCPS) diagnosed in a United Kingdom resident who returned from Panama in July 2014; this represents only the third published case of HCPS imported in Europe to date. Serological analysis identified increasing titres of hantavirus IgG antibodies over the course of illness and detection of hantavirus RNA in serum taken seven days after onset of symptoms. Sequence analysis following a pan-hantavirus diagnostic assay confirmed the presence of *Choclo hantavirus*, a species of hantavirus known to circulate in Panama and suspected of causing several cases of severe human disease in the Los Santos region of Panama during 2014. A set of molecular assays was designed to characterize the S segment of the genome and to provide rapid molecular identification for future cases.

2. Case description

A 35-year-old British woman returned to the United Kingdom (UK) on 16th July, 2014 following a nine month stay in the Los Santos province of Panama with her partner who worked locally as a rice farmer. They lived in a rural area that they had visited frequently over the last ten years. In the weeks prior to her return, she had swept out a shed that had evidence of rodent infestation and handled packaged horse feed which had evidence of rodent damage.

On 13th July, while in Panama, she developed fever, myalgia, lethargy, headache and rigors. After returning to UK, symptoms progressed to include vomiting, cough, rapidly progressive dyspnoea and chest tightness. She presented at her local Accident and Emergency department on 18th July and was admitted to hospital.

On admission she was pyrexial, hypoxic (oxygen saturation 88%) and tachycardic (heart rate 110 beats per minute). Neither rash nor bleeding were evident. Chest examination revealed bilateral crepitations. Haemoglobin levels were 191 g/L (norm: 120–160 g/L), haematocrit was 0.52 (norm: 0.36–0.46), platelet count was 65×10^9/L (norm: $150–400 \times 10^9$/L), neutrophils were 12.76×10^9/L (norm: $2–8 \times 10^9$/L) and alanine transferase levels were 160 U/L (norm: 10–40 U/L). Blood gas analysis showed arterial oxygen partial pressure of 8.9 kPa (norm: 11–13 kPa) with a pH of 7.25 (norm: 7.34–7.44); all other indices were within normal parameters.

A chest X-ray showed bilateral perihilar ground-glass opacification and normal cardiac contours. She was admitted to the intensive

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Table 1
Primer information for molecular assays used to diagnose clinical samples, produce complete S segment sequence data and monitor isolation attempts.

Primer pairs	Sequence	Position[a] (strand)	Product size	Comment
HAN-L-F1 HAN-L-R1	ATGTAYGTBAGTGCWGATGC AACCADTCWGTYCCRTCATC	L 2940 (sense) L 3391 (antisense)	451 base pairs	Pan-hanta assay[b] 1st round (nested)
HAN-L-F2 HAN-L-R2	TGCWGATGCHACIAARTGGTC GCRTCRTCWGARTGRTGDGCAA	L 2951 (sense) L 3340 (antisense)	389 base pairs	Pan-hanta assay[b] 2nd round (nested)
CHOV S 1 F CHOV S 719 R	TAGTAGTAGACTCCTTGAGAAGC CCAAAACCGATGACACCC	S 1 (sense) S 719 (antisense)	719 base pairs	CHOV sequencing Primers set 1
CHOV S 472 F CHOV S 1157R	AGAGGGAGGCAGACTGTGA CCCATAGACTGTGTCCTTCG	S 472 (sense) S 1157 (antisense)	685 base pairs	CHOV sequencing Primers set 2
CHOV S 901 F CHOV S 1480 R	GCTGAGTCTGAAGGTGCC CCCTTAACCCTAAATTAGTGC	S 901 (sense) S 1480 (antisense)	579 base pairs	CHOV sequencing Primers set 3
CHOV S 1260F CHOV S 1972R	GCAGTTAGCACAGTCCTTAGTTG TAGTAGTATGCTCCTTGAAAAGC	S 1260 (sense) S 1972 (antisense)	712 base pairs	CHOV sequencing Primers set 4
CHOV S901 F CHOV S1000R CHOV S933P	GCTGAGTCTGAAGGTGCCAC ATAGTGCTGTTGGTGGACA FAM- CATTGCTGTCCCTCAC TCTGTGTGG -BHQ1	S 901 (sense) S1000 (antisense) S933 (sense)	100 base pairs	CHOV real-time

FAM: carboxyfluorescein (reporter); BHQ1: black hole quencher 1 (quencher).
[a] Position on CHOV genome based on DQ285046 (S segment) or EF397003 (L segment). All sequences shown in the 5′ to 3′ orientation.
[b] Previously published [3].

care unit for aggressive fluid resuscitation, inotropes, and ventilatory support for respiratory distress and severe capillary leak syndrome.

Following discussions between on-call consultants and the UK Imported Fever Service, samples were sent to Public Health England (PHE), Porton Down, to test for potential dengue, hantavirus, leptospirosis, Q-fever, and rickettsial infection.

Doxycycline, ceftriaxone, metronidazole, oseltamivir and high dose co-trimoxazole were commenced immediately after admission; cessation of these regimens was implemented as the clinical picture became increasingly compatible with HPCS and laboratory tests ruled out specific differential diagnoses. Due to the severity of disease, ribavirin was commenced 48 h after admission but was stopped after subsequent agreement that there was lack of supporting data for ribavirin therapy in New World hantavirus infection.

The critical phase lasted 36 h after which diuresis followed. Ventilatory support was weaned over 14 days. The patient was extubated on 1st August and discharged on 5th August after making an uneventful recovery.

Initial diagnosis of HCPS was made using anti-hantavirus IgG indirect immunofluorescence test mosaic 1 (Euroimmun). A serum sample taken on 19th July (day 7 of illness) was positive for Sin Nombre and Puumala IgG at dilutions of 1:100; two days later serum titres had increased to 1:1000 for Sin Nombre IgG and 1:320 for Puumala IgG.

Molecular identification of hantavirus RNA was made in the initial serum sample utilising a modified published pan-hantavirus RT-PCR assay [3]. Sequence analysis of the second round PCR product yielded an amplicon with 96% homology to the *Choclo hantavirus* (CHOV) L segment (Genbank accession number EF397003). A set of PCR primers was designed to amplify the entire S segment using the only published sequence available on Genbank (Table 1).

RT-PCR amplification was performed using SuperScript III One-Step RT-PCR System with Platinum *Taq* (Thermo Fisher Scientific). The final mastermix (25 μL) comprised 12.5 μL of 2 × Reaction Mix 4.5 μL of PCR-grade water, 1 μL of both a forward and reverse primer at 10 μM working concentration, 1 μL of SuperScript III RT/Platinum *Taq* Mix and 5 μL of template. The cycling conditions used were 50 °C for 15 min, 95 °C for 2 min, followed by 45 cycles of 95 °C for 15 s, 52 °C for 30 s and 68 °C for 45 s, with a final extension step of 68 °C for 5 min. Bands of interest were excised from 2% agarose gel and purified using QIAquick Gel Extraction Kit (Qiagen) according to the manufacturer's instructions.

Sequenceanalysis was performed using the same primers used to produce the amplicons. Nucleotide labelling was carried out using Big Dye® Terminator v3.1Cycle Sequencing Kit (Thermo Fisher Scientific), unincorporated dye terminator was removed using DyeEx 2.0 Spin Kit (Qiagen), and sequencing of products was carried out on a 3130xl sequencer (Thermo Fisher Scientific) all according to manufacturer's instructions. Sequence data showed homology to the sole CHOV published on Genbank (98.6% across the entire segment) and significant divergence from other pathogenic New World hantaviruses (Fig. 1).

Bootstrapped maximum likelihood analysis of complete hantavirus S segments showed a close relationship between the sequenced virus and the sole CHOV sequence available on GenBank (Fig. 2).

Attempts to isolate the virus from patient serum samples were unsuccessful, presumably due to the low quantity of sample available for testing from the acute phase of illness and the apparent low levels of viral RNA present in the samples. A real-time RT-PCR assay was designed to detect the CHOV S segment (Table 1) but amplification was only seen in the initial samples. All real-time RT-PCRs were performed on the ABi 7500 (Thermo Fisher Scientific) using the SuperScript III One-Step qRT-PCR System with Platinum *Taq* (Thermo Fisher Scientific). The final mastermix (20 μL) comprised 10 μL of 2 × Reaction Mix 1.7 μL of PCR-grade water, 1 μL of both a forward and reverse primer at 18 μM working concentration, 0.5 μL of probe at 25 μM working concentration, 0.8 μL of SuperScript III RT/Platinum *Taq* Mix and 5 μL of template. The cycling conditions used were 50 °C for 10 min, 95 °C for 2 min, followed by 45 cycles of 95 °C for 10 s then 60 °C for 40 s (with quantification analysis of fluorescence performed at the end of each 60 °C step).

3. Other similar and contrasting cases in the literature

HCPS is a severe disease caused by several viruses classified within the *Hantavirus* genus of the family Bunyaviridae with a case fatality rate of approximately 30–40% [4]. CHOV is the only hantavirus associated with human disease known to circulate in Panama; case fatality rates of approximately 25% have been recorded [11] although seroprevalence studies indicate that a

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