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ORIGINAL ARTICLE

Acute hantavirus infection presenting as haemolytic-uraemic syndrome (HUS): the importance of early clinical diagnosis

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Abstract The European prototype of hantavirus, Puumala virus (PUUV), isolated from a common wild rodent, the bank vole (*Myodes glareolus*), causes nephropathia epidemica (NE). NE can perfectly mimic haemolytic-uraemic syndrome (HUS), progressing from an aspecific flu-like syndrome to acute kidney injury with thrombocytopaenia, and presenting with some signs of haemolytic anaemia and/or coagulopathy. Moreover, both NE and HUS can occur in local outbreaks. We report an isolated case of NE, initially referred for plasmapheresis for suspected HUS, although signs of overt haemolysis were lacking. Early suspicion of hantavirus infection, later confirmed by serology and reverse transcription polymerase chain reaction (RT-PCR), prevented subsequent excessive treatment modalities.

Introduction

Despite the increasing incidence of rodent-borne hantavirus infections (approximately 10,000 cases/year in West Europe [1]), Puumala hantavirus (PUUV)-induced nephropathia epidemica (NE) and other forms of so-called haemorrhagic fever with renal syndrome (HFRS), are still heavily underdiagnosed in Europe and in the Americas, probably due to insufficient medical awareness and because of the multiple diagnostic pitfalls. HFRS and its milder variant NE can mimic other non-tropical infectious illnesses, such as leptospirosis [2, 3] and haemolytic-uraemic syndrome (HUS), which, moreover, can all present in local outbreaks, mostly in summertime [4, 5]. Misdiagnosis and subsequent invasive treatment for HUS was reported previously [4]. According to a German multi-clinic study, NE cases can end up hospitalised in 12 different clinical departments, and undergo several unnecessary diagnostic procedures [6]. In the here described case of a flu-like syndrome followed by acute kidney injury (AKI) and thrombocytopaenia, prior contact with bank voles, evoked during anamnesis by the consulted nephrologist, was practically diagnostic from the start.

Case report

A 58-year-old Belgian male patient developed a flu-like syndrome with respiratory and gastrointestinal complaints. Three days post onset of symptoms (POS), his fever reached 40 °C, accompanied by shivers, diaphoresis and oliguria. A progressive decline of renal function with thrombocytopaenia prompted referral to the Antwerp University Hospital, Belgium, on day 10 POS for suspected HUS. The patient mentioned nausea, epigastric pain, diarrhoea and food intolerance since day 4 POS, plus dry coughing with mild dyspnoea since day 5 POS. There were no relevant medical antecedents or chronic medication. He smoked a package of tobacco every 3 days. No medication had been taken, except acetaminophen, when in pain. The patient had a horse-breeding farm. When asked about potential contact with rodents, he admitted having

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cleaned a nest of bank voles 3 weeks before the onset of symptoms.

Examination at admission (day 10 POS) withheld stable haemodynamics, a blood pressure of 113/92 mmHg, a pulse of 96/min and fever of 39 °C. Minor lung crepitations were heard. Abdominal examination was normal. Peripheral oedema was absent.

Initial blood anomalies comprised a mild coagulopathy (Table 1). Peripheral blood smear revealed a mild but misleading presence (0.8%) of schistocytes (Fig. 1a), neutrophilia and 4% of immunoblasts (Fig. 1b, c). Arterial sampling at admission yielded a pH of 7.40, desaturation with a pO_2 of 64 mmHg and hypocapnia with a pCO_2 of 31 mmHg. Urine sediment showed mild microscopic haematuria and discrete pyuria. However, nephrotic-range proteinuria of 14 g/L was found on day 10 POS, while 24-h urine collection on day 11 POS yielded only 3.2 g. Chest radiograph and renal ultrasound were normal. Bone marrow examination showed normocellularity with active trilinear haematopoiesis and an elevated amount of immunoblasts (Fig. 1d), compatible with reactive plasmacytosis.

While platelets were spontaneously recovering after one day of hospitalisation, renal function showed a maximal decrease to an eGFR of 20 mL/min/1.73 m^2 on day 13 POS. Given the new clinical suspicion of a hantavirus infection, the only therapy consisted of optimising fluid balance and routine supporting care.

Recuperation of the kidney function occurred spontaneously on day 15 POS and the patient was discharged from hospital two days later. After 6 weeks, a complete renal recovery, without any proteinuria, was confirmed during follow-up. PUUV ELISA IgM on admission (day 10 POS) appeared strongly positive with optical density (OD) 2.78 (normal < 0.80), while IgG was already slightly positive (OD 0.86, normal < 0.80). Of interest, while reverse transcription polymerase chain reaction (RT-PCR) on the acute serum sample on admission (day 10 POS) was already negative, repeated RT-PCR with subsequent sequencing on a hyperacute (7 days POS) serum sample, still available upon request via the general practitioner (GP), disclosed PUUV RNA, thus confirming the diagnosis [3, 7] (Fig. 2).

Discussion

This patient was referred for suspected diarrhoea-associated (D+) "typical HUS" because of AKI, concomitant with thrombocytopaenia, schistocytes, raised lactic dehydrogenase (LDH) and coagulopathy, after an episode of gastrointestinal complaints. However, haemolytic anaemia, characteristic for D+ HUS, was absent. Moreover, instead of the expected lowering of haptoglobin, a rather elevated level of this haemolysis indicator was found, and instead of anaemia, an initially slightly raised haemoglobin and haematocrit (Table 1) was present on admission, the latter indicating haemoconcentration and reduction of the intravascular volume, secondary to endothelial hyperpermeability [3, 8–10]. This temporary "capillary leak" is common to all hantavirus infections, and is far more pronounced than in the endothelial dysfunction, also linked to HUS. Extravasation of exudate, extremely rich in proteins, to third spaces can result in substantial weight gain, without noticeable peripheral "classic" oedema, e.g. in the lower limbs,

Table 1 Blood results on admission or 10 days after the onset of symptoms. Mild coagulopathy was suggested by decreased levels of antithrombin activity, protein C and protein S, together with thrombocytopaenia and slightly elevated level of schistocytes and D-dimers

Parameter	Result (reference value)	Parameter	Result (reference value)
Creatinine (mg/dL)	**2.06** (0.62–1.10)	PT (%)	83 (70–120)
eGFR (mL/min/1.73 m^2)	**33** (> 90)	APTT (s)	36 (30–42)
Sodium (mmol/L)	**131** (136–145)	Fibrinogen (mg/dL)	**466** (200–400)
Chloride (mmol/L)	98 (98–107)	D-dimers (ng/dL)	**4.399** (< 500)
Urea (mg/dL)	**67** (13–43)	Lupus anticoagulans	**Positive**[a] (negative)
Thrombocytes (×10E9/L)	**50** (140–440)	Cardiolipin IgG/M	Negative (negative)
Haemoglobin (g/dL)	**17.6** (13–17)	APC resistance (ratio)	**3.26** (> 2.1)
Haematocrit (%)	**50.5** (40–50)	Protein C (%)	**64** (70–130)
Schistocytes (%)	**0.8%** (< 0.5%)	Protein S (%)	**38** (70–130)
Haptoglobin (mg/dL)	**244** (30–200)	Antithrombin (%)	**69** (80–120)
Leucocytes (×10E9/L)	**15** (4.3–10.0)	Direct Coombs test	**Positive**[a] (negative)
Leucocyte differential (%)	Neutrophils: **77** (40–75) Immunoblasts: **4** (0–2)	LDH (U/L)	**323** (84–246)
CRP (mg/dL)	**6.4** (< 0.30)	Albumin (g/dL)	**2.5** (3.5–5.2)
ANA	Negative (negative)	ANCA[a]	**Positive**, 1/20 (negative)

Results higher or lower than the norm, indicated in parentheses, are marked in bold

[a] Not reproducible/negative after a few days

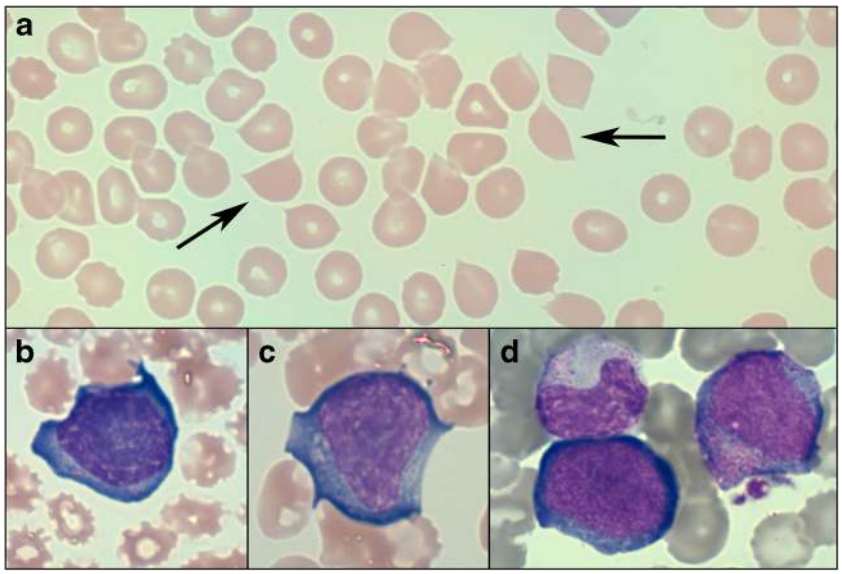

Fig. 1 **a** Schistocytes in peripheral blood smear (arrows). **b**, **c** Peripheral immunoblasts defined as enlarged lymphoid cells with little, moderate to deep basophilic cytoplasm, a large reticular nucleus with uniform chromatin and variably prominent nucleoli. **d** Bone marrow with the presence of an immunoblast (*lower left*), a band neutrophil (*top*) and a promyelocyte (*right*)

but is illustrated in this case by frank hypoalbuminaemia (Table 1). Finally, flu-like symptoms with high fever prior to admission are not suggestive for D+ HUS.

Endothelial dysfunction is postulated as being mediated amongst other by an "inflammatory cytokine storm" caused by hantavirus-specific cytotoxic CD8+ T lymphocytes,

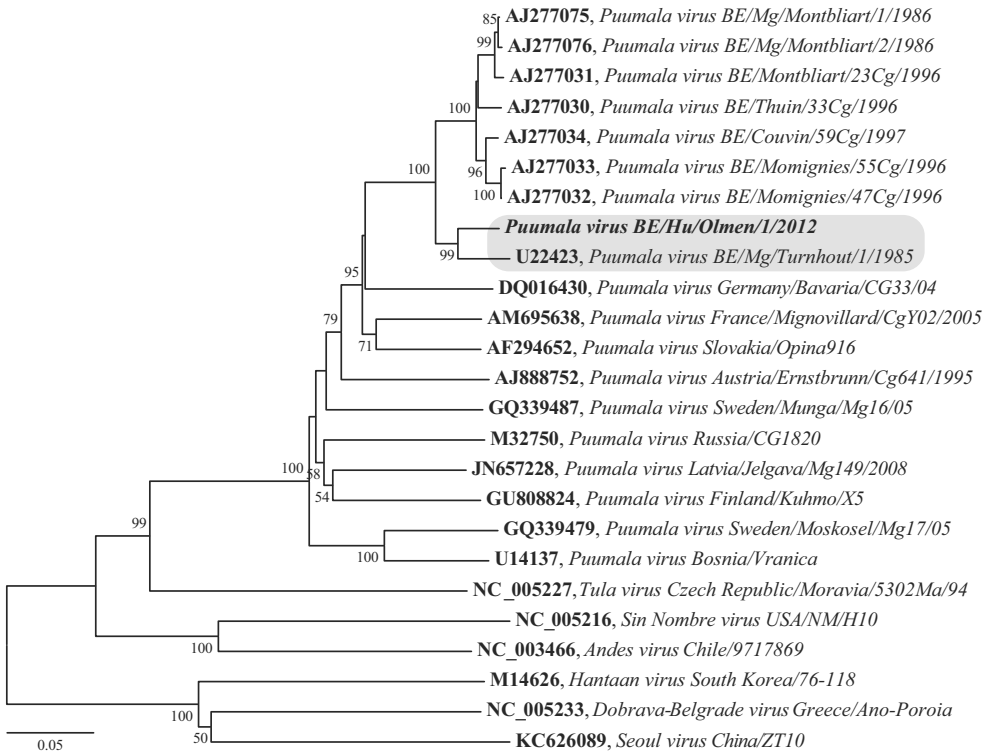

Fig. 2 Phylogenetic tree based on full-length hantavirus S segment (nucleocapsid protein) sequences. The patient lineage is designated as BE/Hu/Olmen/2012/1. For the Belgian (BE) strains, Puumala virus isolates from different regions are used. The evolutionary history was inferred using the neighbour-joining method. The bootstrap consensus tree inferred from 10,000 replicates is taken to represent the evolutionary history of the taxa analysed. The 450-bp amplicon retrieved from a serum sample taken 7 days after the onset of symptoms clusters significantly with a Puumala virus (PUUV) strain (BE/Mg/Turnhout/1/1985, formerly called CG 13891) isolated already in 1985 out of a bank vole captured in Turnhout, north Belgium. Bootstrap values less than 50% are not shown. GenBank accession numbers are shown in bold. The scale bar represents the number of base substitutions per site

attacking endothelial cells presenting viral antigens on the surface [3, 8–10]. The perceived coagulopathy implies increased thrombin generation and fibrinolysis, which, together with the presence of thrombocytopaenia and schistocytes, may suggest a mild form of disseminated intravascular coagulation in the early phase [11]. Early appearance of autoimmune antibodies like lupus anticoagulant and anti-neutrophil cytoplasmic antibodies (ANCAs, Table 1) are probably an expression of the generalised autoimmune reaction, as is the monoclonal gammopathy that is sometimes also present, and should not confuse the attending physician, since these side effects are low titred and disappear mostly within days.

Indicative for hantavirus infection, rather than a possible HUS, was the swift recuperation of thrombocytopaenia and the very rapid spontaneous disappearance of nephrotic-range proteinuria, whilst further renal deterioration occurred. In hantavirus infections, rapidly rising proteinuria invariably precedes the development of AKI and is an index of severity of subsequent renal function impediment. Indeed, in a recent Finnish study on 205 PUUV cases, the mean maximal proteinuria was noted on day 5, whereas the mean maximal serum creatinine was reached on day 9 POS [12], after which spontaneous self-remittance set in. Nephrotic-range proteinuria (> 3 g/24 h) was documented in a third of cases, but again reached near-normal levels within 11 days POS in most cases. Such a rapid self-restoration within days of initially massive proteinuria is almost, by itself, diagnostic for hantavirus nephropathy, since, to our knowledge, this is not encountered in other nephropathies, particularly if accompanied by AKI. Thus, the initial nephrotic-range non-selective proteinuria—which can be assessed upon admission by a simple urine dipstick bedside examination [12]—was strongly suggestive for hantavirus infection, but not for HUS. This sudden glomerular filtration dysfunction is now explained by a new renal pathological entity, called podocyte injury. Podocytes are highly specialised cells, tightly intertwined on the epithelial side of glomerular capillaries. Breaches in this ultimate filtration barrier, characterised by effacement of the podocytes' foot processes, can only be visualised by electron microscopic examination on kidney biopsy. This invasive procedure is not indicated for suspicion of hantavirus nephropathy a fortiori, since light microscopic and immunofluorescent glomerular findings are invariably normal [3] and since podocyte injury has now been demonstrated also in a series of other, mostly more chronic, glomerulopathies.

The kidney is the target organ in HFRS, as classically opposed to the lung in the American hantavirus pulmonary syndrome (HPS). Recent case reports, however, show a considerable overlap, and the paradigm of two different clinical syndromes (HFRS versus HPS), induced by genetically closely related emerging viruses via the same entry port (the human lung), has recently been questioned [3, 13–16]. Of note, lung involvement or acute lung injury (ALI) was also unmistakably present in this case, with coughing and dyspnoea, forthright hypoxaemia and hypocapnia, all hallmarks of HPS. Smoking as a risk factor for incurring NE was first mentioned in a Belgian case–control study [17] and confirmed later in two grand-scale Finnish studies, the latter even finding a significant correlation between the severity of PUUV-induced AKI and a current status of active smoker [18]. The underlying mechanism might be weakened upper airway defence against viral intrusion, or hand-to-mouth viral passage, as probable in the described case, using hand-rolled cigarettes. The presence of immunoblasts in peripheral blood, as well as in bone marrow, has, so far, been considered specific for HPS only. The haematological triad of leucocytosis with left shift, thrombocytopaenia and immunoblasts was shown to be diagnostic for HPS on admission [19]. This case, together with another PUUV infection acquired in France in 2004 [4], both show the presence of this criterion in NE. Moreover, "atypical lymphoid cells", as often described in early peripheral blood examination of other HFRS cases, might often be, in fact, immunoblasts, but missed as such in non-haematological departments or considered as "lymphoplasmoid cells" [20]. The normal medullary megakaryocytic cell line in the two pseudo-HUS cases [4 and current report], and in one case described by Denecke et al. [20], proves that thrombocytopaenia is caused by peripheral consumption, probably by an activated endothelium.

Early ophthalmological symptoms, mainly acute myopia, chemosis and conjunctival injection, can occur in patients with NE [3]. Fundoscopy in our case showed elevated macular epithelium in the early phase, probably due to underlying interstitial oedema.

Treatment in NE is mainly supportive, since NE is a self-limiting condition, mostly within 2–3 weeks [3, 7, 12, 21]. Since HFRS was clinically suspected early enough in this case, no unnecessary treatment was started with immunesuppressants or plasmapheresis, which could have been deleterious to the patient, and even to subsequent serological testing. IgM titres can be false-negative due to the selective removal of heavy IgM molecules during repetitive plasmapheresis sessions [4]. Respiratory support in NE can be limited to oxygen delivery by nasal catheter or mask, as in the here described AKI + ALI case, extended if necessary to mechanical ventilation [22] or even extracorporeal membrane oxygenation (ECMO), considered hitherto as the last-step salvage therapy for HPS only [16]. Renal replacement therapy (RRT) was deemed necessary in < 5% of NE patients [1–3, 21], in sharp contrast with the 50% needing RRT for HUS [5]. Since the main indication of RRT is (predominantly pulmonary) fluid overload, it is important to respect an optimal fluid balance, a simple nursing support which often obviates the need for any RRT [3]. Treatment with icatibant, a bradykinin B2 receptor antagonist, seems to hold promise for severe HFRS disease, with life-threatening capillary leakage [23].

Remarkable for this case is the value of RT-PCR and sequencing, which not only secured a biomolecular diagnosis of PUUV infection, but also allowed tracing the geographical localisation of origin (Fig. 2) to Turnhout, in the region of the patient's residence in north Belgium, and not to the Ardennes, the forested south of Belgium, considered hitherto as the most endemic region. Such localisation of the region of infection is only possible when sufficient other sequences of the viral pathogen from different regions are available for comparison [7, 16, 22]. The here described case illustrates also a weak point of RT-PCR in hantavirology, since this diagnostic gold standard often turns out to yield negative results in hospitalised PUUV infections, because of the short viraemic phase. Similarly, in a German fulminant PUUV case needing ECMO [16], RT-PCR was positive only in the serum of day 4 POS, whereas all later samples were negative. Finally, the pivotal role of the patient's GP is also illustrated, furnishing sometimes pre-hospitalisation blood samples still containing viral RNA, along with other early clinical samples showing, in fact, the most divergent laboratory anomalies, e.g. in the degrees of thrombocytopaenia and/or proteinuria.

Conclusion

In summary, European and Russian Puumala virus (PUUV) infections, just because of their relative mildness compared to other, more severe haemorrhagic fever with renal syndrome (HFRS) forms, can constitute a diagnostic challenge, particularly on admission, whereby even the so-called "renal syndrome" is hardly or not at all in the foreground [3, 4, 6, 20, 22]. Increased medical awareness is more than ever warranted for this extremely versatile "chameleon in internal medicine", now that HFRS, until recently considered as relevant to the Old World only, has increasingly been recognised in the New World also, this time as the Seoul virus (SEOV)-induced variant. SEOV HFRS can lead to isolated acute kidney injury (AKI) and acute lung injury (ALI) forms, generally more severe than the PUUV-induced variant, but is transmitted by the omnipresent wild rat, including pet rats, which is both a global carrier and reservoir of SEOV [2, 3] (Clement et al., 2017, Rat-transmitted hantavirus infection: nil sub sole novum., submitted).

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