Severe crescentic glomerulonephritis linked to an acute Hantaan virus infection?

Sir,

We read with interest the report by Soi Kim et al. [1], describing a case of acute crescentic glomerulonephritis (ACGN) with prolonged acute kidney injury (AKI), which the authors link to a concomitant hemorrhagic fever with renal syndrome’ (HFRS), in this case, an infection with the prototype Korean hantavirus species, Hantaan virus (HTNV). Concerning the latter association, however, many questions arise as to its relevance and reliability: (A) The ‘other various glomerular diseases reported in hantavirus infections’ are in fact a total of 10 patients with membra-noproliferative glomerulonephritis (GN), one with mem-branous GN and one with mesangioproliferative GN, all reported by J. Mustonen and his Finnish coworkers after, and not during, proven acute nephropathia epidemica (NE), i.e. a milder HFRS form with the prototype European hantavirus species, *Puumala virus*. Moreover, and in contrast with the Korean case, all Finnish cases relapsed with a rapidly emerging nephrotic syndrome 1 week to 3 months after complete remission from their acute NE, and appropriate therapy induced again in all, except one case, a complete remission [2]. (B) Oliguria apparently started already from Day 1 on post onset of symptoms (POS), which may be compatible with ACGN, but not all at all with HFRS, where oliguria begins mostly at least 1 week POS, in a third phase after a prior fever and hypotensive phase [2–5]. (C) Myalgiae, a chief complaint and a presenting symptom in all Old and New World hantavirus infections, were apparently absent, suggesting an ACGN rather than an HFRS [3,5]. (D) Fever on admission (Day 4 POS) was only 37.3°C, compatible with ACGN but not with HFRS, where fever is between 38 and 41°C during several days [3,5]. (E) Thrombocytopenia, again in all Old and New World hantavirus infections, a cardinal presenting symptom, is not mentioned. Neither are the characteristic marked leukocytosis with a left shift nor the marked inflam-matory parameters [2–5]. (F) Only IgG enzyme-linked immunosorbent assay (ELISA) was used for diagnosing a recent HTNV infection. Since IgG antibodies can persist for life, and since Korea is a country highly endemic for HTNV, a positive IgG does not necessarily mean a recent infection, even less so in a 70-year-old patient. In fact, a titer of 1:2048 is unusually high for a very recent infection and should have been confirmed by IgM ELISA and preferably by other molecular-based confirmation tests. The repeated IgG ELISA 3 months POS was higher by one more dilution only (1:4096) and cannot be used as conclusive proof for a recent infection. (G) The renal biopsy showed diffuse endocapillary proliferation, with frequent neutrophil infiltration, both features highly unusual for HFRS, where slight mesangial proliferation is often the only glomerular anomaly, if any [3–10]. Some NE cases might show swelling of the epithelial cells of the Bowman’s capsule and/or adhesion of the glomerular tuft to the capsule, but crescent formation has indeed never been reported [2,3]. The most pathognomonic feature for HFRS, rupture of the peritubular capillaries with interstitial microhemorrhages in the outer medulla of the kidney, is lacking [3–5,8]. (H) Immunofluorescence (IF) staining of the glomerulus is often completely negative in HFRS, and if some IgM, IgG or C3 deposits are found indeed, they are considered aspecific, particularly after or during an episode of heavy proteinuria, which in HFRS is always aselective [4–6,8]. Predominant C3 and Ig A deposits are
such localization was so far never documented in the glomerulus with the locally most outspoken histopathological changes. Epithelial cells, particularly in the medulla, concomitant with the electron-dense deposits found with electron microscopy (EM) in the mesangium and at ‘both sides of the capillary loops’ may be compatible with ACGN but not at all with HFRS, where EM findings specific for this infection are lacking [4,6]. (J) The final outcome with a seriously amputated renal function is in line with ACGN but not at all with HFRS, where spontaneous remission to normal is the rule [2–5,9]. (K) The technique for demonstrating hantaviral antigen in the kidney is highly questionable. We feel that positive staining with a convalescent serum of a HFRS patient, which by definition is polyclonal, can nowadays not be taken as convincing argument since this older technique could stain different other antigens present in the kidney, particularly in the glomerulus of an ACGN case. An almost linear capillary IF in the whole glomerulus, as reported here, was never observed before in HFRS [8,9]. A more reliable technique would have been immunohistochemistry (IHC), using specific monoclonal antibodies or preferably highly specific reverse transcription–polymerase chain reaction (RT–PCR). Moreover, it is not even certain that the here reported case was in fact infected with HTNV since at least two different murine hantavirus species are endemic in Korea, HTNV and the rat-transmitted Seoul virus (SEOV), which are mutually heavily cross-reacting in ELISA [11]. (L) The antigen, considered here to be HTNV, was still clearly present in the capillary loops 37 days (4 + 33) POS, a record time to our knowledge never reported before. In a series of 31 Korean HFRS cases infected with HTNV or SEOV, RT–PCR positivity in serum was found in one case after an exceptionally long period of 33 days of illness [7], a lag time never documented so far in European NE cases or in American hantavirus cardiopulmonary syndrome (HCPS) cases. However, detection in renal tissue of hantaviral antigen by IHC, or viral RNA by RT–PCR, was rarely if ever positive after >30 days of illness in HFRS [8,9]. Moreover, this detection was successful only in the tubular epithelial cells, particularly in the medulla, concomitant with the locally most outspoken histopathological changes. Such localization was so far never documented in the glomeruli [4,6,8–10]. Even in a macroa model for hantavirus nephropathy, pathological changes and both viral antigen and RNA were detected only in medullary tubular cells [10]. Hantavirus pathophysiology is now generally accepted as being an overshooting immunoreaction targeting the endothelium in the human host and triggered after a sometimes very brief viremia [2,4,10–12]. Recently, microvascular leakage, the hallmark of both HFRS and HCPS, was attributed to very early-onset induction of vascular endothelial growth factor and downregulation of vascular-endothelial (VE)-cadherin [12]. In other words, a prolonged and massive presence in the kidney of pathogenic viruses, still after 37 days of illness as suggested here, could completely jeopardize the current paradigm. The original working hypothesis of an immune complex-mediated pathophysiology, as again forwarded here, has now generally been abandoned [4,11,12].

**Conflict of interest statement.** None declared.

1. Hantavirus Reference Centre, Clinical Virology Laboratory, University Hospital Gasthuisberg, Leuven, Belgium
2. Department of Internal Medicine, Tampere University Hospital, Tampere, Finland
3. Department of Anatomopathology, University Hospital Gasthuisberg, Leuven, Belgium
4. Division of Pathology and Genetics, HUSLAB, Helsinki University Hospital, Helsinki, Finland

E-mail: jan.clement@uzleuven.be


**Editorial Note:** Dr Kim et al. had been invited to reply to this letter but we did not receive a response.

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