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Original contribution

Microvascular inflammation and acute tubular necrosis are major histologic features of hantavirus nephropathy☆

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Summary Hantavirus nephropathy (HVN) is an uncommon etiology of acute renal failure due to hantavirus infection. Pathological features suggestive of HVN historically reported are medullary interstitial hemorrhages in a background of acute interstitial nephritis (AIN). However, interstitial hemorrhages may be lacking because of medullary sampling error. This emphasizes that other pathological criteria may be of interest. We performed a retrospective clinicopathological study of 17 serologically proven HVN cases with renal biopsy from 2 nephrology centers in northern France. Histologic analysis was completed by immunohistochemistry with anti-CD3, anti-CD68, and anti-CD34 antibodies. Three control groups were not related to hantavirus infection: acute tubular necrosis (ATN) of ischemic or toxic etiology and AIN were used for comparison. Renal biopsy analysis showed that almost all HVN cases with medullary sampling (9/10) displayed interstitial hemorrhages, whereas focal hemorrhages were detected in 2 of the 7 "cortex-only" specimens. ATN was common, as it was present in 15 (88.2%) of 17 HVN cases. By contrast, interstitial inflammation was scarce with no inflammation or only slight inflammation, representing 15 (88.2%) of 17 cases. Moreover, HVN showed inflammation of renal microvessels with cortical peritubular capillaritis and medullary vasa recta inflammation; peritubular capillaritis was significantly higher in HVN after comparison with ischemic and toxic ATN controls (P = .0001 and P = .003, respectively), but not with AIN controls. Immunohistochemical studies highlighted the involvement of T cells and macrophages in

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renal microvascular inflammation related to HVN. Our study showed that microvascular inflammation, especially cortical peritubular capillaritis, and ATN are important histologic features of HVN.

1. Introduction

Hantavirus nephropathy (HVN) is a form of acute renal injury caused by hantavirus infection. Hantaviruses are RNA viruses belonging to the Bunyaviridae family [1]. Humans are infected most of the time by inhaling aerosolized contaminated rodent excreta suspended in the air. In Asia and Europe, several serotypes of hantavirus have been described responsible for various severity patterns of HVN. Puumala, the predominant serotype in northern and western Europe, is associated with a minor pattern of hemorrhagic fever with renal syndrome, spontaneously favorable in most cases, previously recognized as "nephropathia epidemica" [2,3]. Mainly observed for severe forms, typical clinical presentation comprises a 2- to 4-week incubation phase, followed by 5 well-defined phases: febrile, hypotensive, oliguric, polyuric, and convalescent [4,5]. When Puumala serotype is involved, dialysis is rarely required and evolution is usually favorable without sequelae [6]. However, a less favorable long-term renal prognosis has been reported, with evolution toward hypertension and chronic kidney disease [7,8], highlighting the importance of obtaining an accurate diagnosis. Furthermore, lethal forms have been reported with Dobrava in southeastern Europe and with New World serotypes causing severe cardiopulmonary syndrome in the Americas [1].

Pathological description of HVN, based almost exclusively on Finnish and Korean studies, classified HVN as a form of acute tubulointerstitial nephritis specifically associated with hemorrhages in the medullary interstitium [2,9–11]. However, the characteristic interstitial hemorrhages may be lacking because of sampling error [6,9], which leads to unspecific histopathologic presentation. This emphasizes that other pathological criteria may be of interest. Although microvascular injury has been previously reported in HVN [2,3,11,12], no clinicopathological study thoroughly described inflammatory changes in renal microvasculature in this setting so far.

This report describes the clinicopathological characteristics of patients with kidney biopsy and serologically based diagnosis of HVN in 2 nephrology centers from northern France, with special emphasis on microvascular inflammation.

2. Materials and methods

2.1. Patients

Inclusion criteria were both serologic confirmation of hantavirus infection and availability of renal biopsy specimen performed during acute renal failure. Between January 2000 and July 2013, 17 patients with serologically proven hantavirus infection were selected from the electronic files of the Departments of Virology and Nephrology, Lille University Hospital, Lille, France, and Valenciennes Hospital, Valenciennes, France. Serologic confirmation was established until April 2011 by the French National Reference Centre for arboviruses and viral hemorrhagic fevers, Institut Pasteur, Lyon, France and from April 2011 by the Virology Department, University Hospital, Lille, France. The serologic diagnosis of hantavirus infection was based on separate detection by enzyme-linked immunosorbent assay of IgG- and IgM-directed against Hantaan and Puumala antigens. Results showed a greater response against Puumala serotype. This study was performed in accordance with the Declaration of Helsinki. Biopsies were performed as described in our local regular protocol of care. Written informed consent was obtained for biopsy as well as for the use of clinical data and leftover histologic material for research. Clinical and laboratory data were obtained from medical reports for each patient.

2.2. Kidney biopsies

Renal biopsy specimens were collected from the Pathology Departments of Lille University Hospital, Lille, France, and Saint-Louis Hospital, Paris, France. Two biopsy specimens were obtained for each patient, one biopsy was used for light microscopy and the other one was snap frozen for immunofluorescence (IF). Kidney biopsy samples were fixed in alcohol–formalin–acetic acid and embedded in paraffin. The biopsies were cut into 3-μm sections and stained with Masson trichrome, Jones methenamine silver, periodic acid–Schiff (PAS), and hematoxylin-eosin-saffron. The direct IF assays for detection of total IgA, IgG, IgM, complement components C1q and C3, and fibrinogen were performed on cryostat section according to standard procedure.

All slides were reviewed by 2 pathologists (V. G., D. B.). The semiquantitative evaluation of inflammation in the different renal compartments was adapted from the criteria of the Banff classification for renal allograft pathology [13]. Endocapillary inflammation was graded according to the percentage of glomeruli with mononuclear cells in glomerular capillaries as follows: 0, absence; score 1, <25%; score 2, 25%-50%; and score 3, >50% of glomeruli. Considering tubules and interstitium, acute tubular necrosis (ATN), tubular atrophy, interstitial fibrosis, interstitial edema, interstitial inflammation, microvascular inflammation, and interstitial hemorrhages were assessed. ATN was diagnosed when at least