Case Report

IgG heavy-chain deposition disease affecting kidney, skin, and skeletal muscle

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Introduction

Immunoglobulin G heavy-chain deposition disease (HCDD) is a very rare monoclonal immunoglobulin disorder, characterized by production and deposition of defective immunoglobulin heavy chains without light chain deposition. There are nine reports in the literature describing renal involvement, and heavy-chain deposition in other organs only in one case [1–6]. We present a case of this disease with multiorgan involvement, confirmed by light (LM), immunofluorescence (IF), and electron microscopy (EM).

Case

A 73-year-old woman with history of malaise, leg oedema, exertional dyspnoea, arterial hypertension was regularly treated with antihypertensive and antiuretic drugs. She was admitted to the hospital because of persistent proteinuria, anaemia, and muscular pain. On admission to the hospital she was normotensive (blood pressure was 140/70 mmHg), although slight cardiomegaly and paroxysmal atrial fibrillation were revealed. Lung and abdominal examination disclosed no pathology. There was no lymphadenopathy.

Laboratory investigation yielded the following results: urinary protein excretion 3 g/day. Urinalysis discovered numerous erythrocytes and few leukocytes. No growth of bacteria appeared in urine culture. Haematological values: Westergren sedimentation rate was 51 mm/h, haemoglobin 111 g/l, white blood cell count 5.5 x 10⁹/l.

Serum creatinine was 204 µmol/l (creatinine clearance 48 ml/min), urea 15.3 mmol/l. Serum cholesterol was slightly elevated (6.3 mmol/l). The patient had low complement components, C3 and C4 (0.22 and 0.04 g/l respectively), positive antinuclear antibodies in low titre, positive antibodies to glomerular basement membrane (BM) antigens (21 EU), without detectable antineutrophil cytoplasmic antibodies and cryoglobulins. The antibodies against hepatitis C virus were also detected in the patient’s serum, but no antibodies against hepatitis B virus were present. Serum electrolytes, blood sugar, calcium, urate, alkaline phosphatase, aspartate aminotransferase, alanin aminotransferase and γ-glutamyl transferase were normal.

Total serum protein 55 g/l, serum albumin 30.5 g/l, γ globulins 11.1 g/l, with monoclonal spike of 5.6 g/l. Serum concentrations of immunoglobulins were normal. Immunofixation electrophoresis of serum disclosed monoclonal spike of IgG λ, and of urine monoclonal spike of λ light chain. Cytological analysis of the bone marrow aspiration showed 14% plasma cells and a biopsy revealed normocellular bone marrow, including two poorly delineated nodules of lymphoplasmacytoid cells, suggesting the diagnosis of plasmacytoma. However, bone X-ray survey did not show any lesion typical of plasmacytoma. After renal histology suggested HCDD, muscle and skin biopsies were also performed.

The patient was treated with prednisolone and melphalan. Nine months later, gross proteinuria (4 g/day) and hypoproteinaemia persisted, with minimal further deterioration of renal function (serum creatinine 226 µmol/l).

Beside routine light-microscopy, fresh tissue samples were snap-frozen in liquid nitrogen and cut to 5-μm thin sections for direct IF microscopy. The sections were incubated with antisera to human IgA, IgG and IgM heavy chains, kappa and lambda light chains, complement components C3, C1q and C4, fibrin related antigens and albumin (Dako, Denmark). After fixation in osmium tetroxide, ultrathin sections were contrasted with uranyl acetate and lead citrate.

Light microscopy of the kidney biopsy revealed hyperlobulated glomeruli, with mostly argyrophilic,
PAS positive and Congo-red negative segmental nodular glomerulosclerotic lesions (Figure 1). The latter were encircled by focal pseudoaneurysmatic dilatations of the walls of glomerular capillaries. Duplications of the capillary BM were also observed. Subtle PAS positive material was also present in the reticular dermis and muscle fascia.

**Immunofluorescence.** IgG heavy chain deposition without light chains was disclosed in glomerular mesangium and focally in glomerular capillary walls (Figure 2). Besides, IgG heavy-chain deposits were present in ‘pseudolinear’ pattern along and within tubular BM and arteriolar walls. Abundant IgG deposits were detected in the papillary and reticular dermis, in arteriolar walls, along dermal connective tissue fibres, BM of sweat glands. In skeletal muscle, deposits were found in endomysium along sarcolemmas, in vessel walls, and in perimysium (Figures 3, 4). Deposition of complement components C3, C1q, and to lesser extent C4, was apparent in the same locations.

**Electron microscopy.** Numerous finely granular deposits were disclosed, dispersed in the mesangium, within and along the outer aspect of tubular BM, and focally in the lamina rara interna of the BM of glomerular capillaries. The deposits were also found along the outer aspect of blood vessel. In the same glomerulus, glomerular capillaries showed pseudoaneurysms and gradual widening of subendothelial spaces, which were focally filled with lipid inclusions (Figure 5). The formation of neolamina was also obvious in the BM of some glomerular capillaries.

In the skeletal muscle, EM revealed abundant granular deposits along the sarcolemmas (Figure 6).

In the skin, there was peculiar ‘hairy’ transformation or splitting of the collagen fibres, without EM-evident deposits.
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Three disease entities are related to molecular abnormalities of heavy chains: light- and heavy-chain deposition disease, heavy-chain-associated amyloidosis, and HCDD [1–8]. Clinically as well as pathologically, HCDD resembles light-chain-deposition disease. The deposition of heavy chains can be explained by structural abnormalities or peculiarities of variable regions of the light and/or heavy chains [9,10]. In some patients such changes could influence the stability of biochemical properties of the immunoglobulin molecules, loosening light chains before and/or after depositing in the tissue. The correct diagnosis is provided by immunohistologic examination, using antisera to heavy and light chains and revealing monotypic heavy chain deposition with negative reaction to light chains. We assume that some cases of glomerular nodular sclerosis were misinterpreted before the use of antibodies against light chains. So far, γ1, γ3, γ4 subtypes of heavy chain have been detected in HCDD, with practically identical clinical and pathological features [1,3,4,6].

HCDD with gammaglobulin renal deposits is a rare disease with only nine reported patients until now [1–6]. There are some other cases with renal involvement, cited elsewhere under different headings, but not described in detail [11,12]. Involvement of other organs has been described in one case only [3].

Glomerular nodular sclerosis with pseudoaneurysmatic changes in glomerular capillaries is the hallmark of HCDD, although it may appear also in light-chain disease, diabetes mellitus, advanced stages of membranoproliferative glomerulonephritis, amyloidosis, cryoglobulinaemic glomerulonephritis, and idiopathic nodular glomerulosclerosis. Aneurysms of glomerular capillaries were mentioned in previous reports, but are probably in fact pseudoaneurysms, arising from gradual widening of subendothelial area.

The majority of patients did not suffer from plasmacytoma; in some cases plasmacytoma either developed during follow-up, or it was even present at the time of admission [2–3].

In our patient the diagnosis of HCDD was based on the presence of deposits of IgG heavy chain without light chains in different organs. The deposits were identified by IF, and displayed certain quantitative and qualitative features on EM examination of kidney, muscle, and skin. Granular deposits were relatively scarce, and only focally located in the subendothelial region, more numerous in mesangial matrix, and along the outer aspect of tubular BM, and very numerous along muscular sarcolemmas. But in the skin, peculiar changes of connective tissue might be associated with the HCDD, although we could not reliably identify the deposits by EM, that had been seen by IF.

Beside important renal involvement, there may be heavy-chain deposits in other organs, described in only one previous report. Deposition may be clinically silent, or obscure and unsppecific. In our patient, muscular pain, paroxysmal atrial fibrillation and cardiomegaly may be associated with HCDD. Moreover, we may speculate that the pathological changes in the BM of glomerular capillaries could induce the formation of antibodies to glomerular BM antigens, found also in our patient.

The fragmented heavy chain may activate the complement system [5]. Therefore, hypocomplementaemia with associated deposition of complement components appeared in some patients. But it was not a case in all previously presented patients [2,3]. In our patient, beside hypocomplementaemia, IF demonstrated deposition of complement components, C3, C1q, and even C4, in all three tissue specimens.

Treatment with steroids and cytostatic drugs may improve at least transiently hypocomplementaemia, proteinuria, and reduces oedema or prevent progression of disease [3,5]. Regardless of therapy, there is progressive organ dysfunction, which may be alleviated by cytotoxic chemotherapy, transfusions, and dialysis [13].

Discussion

Fig. 5. Formation of pseudoaneurysm (p) of glomerular capillary (c) with extreme widening of subendothelial area. Ultrathin sections contrasted with uranyl acetate and lead citrate. Original magnification × 1800, bar 5 μm.

Fig. 6. Abundant granular deposits (arrow) along muscular sarcolemma. Ultrathin sections contrasted with uranyl acetate and lead citrate. Original magnification × 7000, bar 2 μm.
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References


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