AIDS presenting as focal segmental membranous glomerulopathy

P S Bass, P J Garrett, D W Ellison, P Terry, S O'Connell, J M Theaker, J R Dathan, D Fine

Abstract

The case of a young, heterosexual man who was investigated for proteinuria is reported. A renal biopsy specimen showed a focal and segmental membranous glomerulopathy. He was later found to be HIV positive and died from cerebral infarction associated with HIV vasculitis 16 months after his initial presentation. Unusual forms of immune complex mediated glomerulopathies should alert the pathologist to the possibility of HIV associated disease.

(J Clin Pathol 1994;47:179-181)

The association between HIV and renal disease is well documented.¹ Typically, HIV associated nephropathy (HIVAN) is a rapidly progressive, focal, and segmental sclerosing glomerulopathy with characteristic tubulointerstitial changes, reported to occur predominantly in black, North American, intravenous drug misusers.² Numerous other HIV related glomerular diseases, including IgA nephropathy³ and membranous glomerulopathy,⁴ have been reported in HIV positive patients with a variety of risk factors for the infection. Our patient, a heterosexual man with no apparent risk factors for HIV, had an unusual form of membranous glomerulopathy (MGN). Although the pathologist's initial differential diagnosis included infections such as syphilis and hepatitis B,⁵ his HIV infection was only discovered two months after the renal biopsy had been performed.

Case report

An asymptomatic, 38 year old, white, heterosexual, oil company engineer was found to have proteinuria at a routine employment medical examination and was referred to a renal physician. Clinical examination was normal apart from bilateral inguinal lymphadenopathy. Twenty four hour protein excretion was 3.4 g. Blood pressure and renal function tests were normal. Antibodies to smooth muscle were moderately positive and to neutrophil cytoplasm (ANCA, measured by indirect immunofluorescence) weakly positive. A renal biopsy was performed. Two months later, the renal physician was notified that an HIV antibody screen taken at the time of the employment medical examination was positive. No factors to suggest an increased risk of HIV infection had been identified. He had previously worked in north and west

Africa for short periods, but had specifically denied sexual activity or possible parenteral exposure during these times.

The tests were repeated and HIV antibodies detected by ELISA, gel particle agglutination, and immunoblot. HIV P24 antigen ELISA was negative. A full blood count and CD₄ lymphocyte count were normal. Serological tests for syphilis and hepatitis B markers were negative. A latex agglutination test for *Toxoplasma gondii* antibody was positive (titre of > 1/1024), but the toxoplasma IgM was negative, consistent with infection acquired some time in the past. Antibodies were also detected by ELISA to herpes simplex, varicella zoster, and cytomegalovirus, indicating earlier infection with these agents.

Eleven months after presentation at the renal clinic, a progressive fall was noted in his CD₄ count. Antiviral treatment with zidovudine was started. Dapsone and pyrimethamine were also given as prophylaxis against *Pneumocystis carinii* infection.

Five months later he required emergency hospital admission. He was febrile, drowsy, and confused. He had a left sixth nerve palsy and right upper motor neurone facial weakness. His right arm and leg were weak with reduced tone, and both plantar responses were extensor.

A brain computed tomogram on the day of admission was normal, but the electroencephalogram (EEG) was highly abnormal, with suppression of the rhythms over the left cerebral hemisphere and additional θ waves anteriorly. These findings suggested an underlying encephalopathy or early infarction. Microscopic examination, culture, and measurement of the glucose and protein content of the cerebrospinal fluid were unremarkable. Tests performed on serum again showed a toxoplasma latex agglutination titre of > 1/1024 and a negative IgM. Complement fixation tests showed herpes simplex, cytomegalovirus, and varicella zoster antibody titres of 1/40, 1/160, and 1/640, respectively. Cryptococcal antigen and antibody tests were negative.

Stroke secondary to a primary vascular pathology or possibly herpes zoster infection was diagnosed. Toxoplasma encephalitis was considered unlikely because of the normal computed tomography brain scan appearance. Despite aggressive treatment, including steroids, sulphadiazine, acyclovir and pyrimethamine, he died three days after admission. A necropsy, limited to examination of the brain, was performed.

Department of
Histopathology,
Southampton
University Hospitals,
Southampton

P S Bass
D W Ellison
J M Theaker

Department of
Nephrology
P J Garrett
J R Dathan

Department of
Genitourinary
Medicine
P Terry

Department of
Microbiology
S O'Connell

Department of
Medicine
D Fine

Correspondence to:
Dr P S Bass, University
Department of Pathology,
Level E, South Pathology
Block, Southampton
University Hospital,
Southampton SO9 4XY
Accepted for publication
29 July 1993

Pathological findings

Light microscopic examination of the renal biopsy specimen showed mild focal and segmental mesangial hypercellularity. Glomerular capillary walls and the tubulo-interstitial and extraglomerular vascular compartments were normal. Immunohistochemical staining (immunoperoxidase and avidin-biotin complex technique) showed diffuse, global, linear and finely granular glomerular capillary wall deposition of IgG, IgM, C₃ and C1_q. The mesangium did not stain.

Ultrastructurally, many glomerular capillary loops showed segmental foot process fusion as the only abnormality. An occasional segment, however, showed small, discrete, subepithelial electron dense deposits (fig 1).

At necropsy, the brain weighed 1556 g. Cerebral swelling, most obvious in the left hemisphere, was associated with transtentorial herniation of both parahippocampal

gyri and herniation of the left cingulate gyrus beneath the falx. The swollen left hemisphere was soft with petechial haemorrhages evident in the superior temporal gyrus. The rostral brainstem was compressed and contained focal haemorrhages secondary to raised intracranial pressure.

Histological examination indicated left cerebral hemisphere infarction in the territories of the middle and posterior cerebral arteries, occurring about 72 hours before death. An adventitial chronic inflammatory infiltrate and intravascular thrombosis co-existed in these vessels. Small areas of infarction in the dorsal pons were associated with an acute vasculitis of small vessels. Polymorph neutrophils invaded the walls of meningeal and parenchymal arterioles and venules, including vessels of the trochlear nerve (fig 2). No specific histological features of HIV or other viral encephalitides or opportunistic infection were seen.

Toxoplasma gondii DNA was detected in brain tissue by gene amplification using the polymerase chain reaction (PCR).⁶ Nested primers were chosen from previously published sequences producing a 97 kilobase probe. A cerebrospinal fluid sample taken two days before death was also probed retrospectively, but *T gondii* DNA was not detected.

Discussion

HIVAN is now a well characterised renal disease occurring predominantly in one HIV/AIDS subgroup. However, an ever increasing number of glomerulopathies are described in association with HIV infection. Our case highlights several interesting issues related to HIV infection and systemic disease.

Firstly, as there is a rising incidence of HIV infection in the heterosexual population,⁷ an increase in the number of patients undergoing diagnostic procedures before demonstration of positive HIV serology can be predicted. Interpretation of the histology may be influenced by knowledge of the HIV antibody status. In our patient a renal biopsy specimen showed a focal and segmental MGN. This is occasionally seen in cases of early idiopathic MGN, but, in our experience infections, such as secondary syphilis and hepatitis B, can cause this rather unusual picture. Our patient had no evidence of these diseases. We recommend that HIV infection should be added to the list of possible underlying causes for this histological appearance.

Secondly, the role of *Toxoplasma gondii* in this man's final illness remains uncertain. The histological and radiological appearances did not suggest active infection in the brain. It is likely that the PCR detected DNA from quiescent encysted organisms in the area of the brain sampled.

Finally, the patient died of intracerebral infarction associated with a vasculitis. The histological picture was consistent with that described for cerebral HIV vasculitis.⁸ Interestingly, our patient was found to have a weakly positive ANCA whilst alive. A recent

Figure 1 Ultrastructural examination of the renal biopsy specimen showed segmental, subepithelial, electron dense deposits (uranyl acetate/lead citrate).

Figure 2 Small vessel vasculitis in the trochlear nerve (haematoxylin and eosin).

study has shown that some patients with AIDS develop an HIV-ANCA.⁹ It may be that both the presenting and terminal pathological processes in our patient were immunologically mediated, with ANCA possibly playing a part.

We are grateful to Dr EC Guy, Toxoplasma Reference Laboratory, Public Health Laboratory, Singleton Hospital, Swansea, for performance of the *T gondii* PCR investigations and valuable comments.

- 1 Glasscock RJ, Cohen AH, Danovitch G, Parsa KP. Human immunodeficiency virus (HIV) infection and the kidney. *Ann Intern Med* 1990;112:35-49.
- 2 Rao TK, Filippone EJ, Nicastrì AD, et al. Associated focal and segmental glomerulosclerosis in the acquired immunodeficiency syndrome. *N Engl J Med* 1984;310:669-73.
- 3 Kimmel PL, Phillips TM, Ferreira-Centeno A, Farkas-

- Szallasi T, Abraham AA, Garrett CT. Idiopathic IgA nephropathy in patients with human immunodeficiency virus infection. *N Engl J Med* 1992;327:702-6.
- 4 Guerra IL, Abraham AA, Kimmel PL, Sabnis SG, Antonovych TT. Nephrotic syndrome associated with chronic persistent hepatitis B in an HIV positive patient. *Am J Kidney Dis* 1987;10:385-8.
- 5 Heptinstall RH. Renal manifestations of various infective conditions. In: Heptinstall RH, ed. *Pathology of the kidney*. 4th Edn. Boston: Little, Brown and Co., 1992: 1935-87.
- 6 Burg JL, Grover CM, Pouletty P, Boothroyd JC. Direct and sensitive detection of a pathogenic protozoan, *Toxoplasma gondii*, by polymerase chain reaction. *J Clin Microbiol* 1989;27:1787-92.
- 7 Waight PA, Rush AM, Miller E. Surveillance of HIV infection by voluntary testing in England. *Communicable Disease Report* 1992;2:R85-90.
- 8 Budka H. Neuropathology of human immunodeficiency virus infection. *Brain Pathol* 1991;1:163-75.
- 9 Klaasen RJ, Goldschmeding R, Dolman KM, et al. Anti-neutrophil cytoplasmic antibodies in patients with symptomatic HIV infection. *Clin Exp Immunol* 1992;87:24-30.

J Clin Pathol 1994;47:181-182

Spuriously high free thyroxine with the Amerlite MAB FT₄ assay

L C Lai, J A Day, F Clark, R T Peaston

Abstract

In the Amerlite MAB FT₄ assay, as stated by the manufacturer, FT₄ values should be normal in patients with anti-thyroid hormone autoantibodies. The case of a 69 year old woman with a spuriously high FT₄ using the Amerlite MAB FT₄ assay is reported. Laboratory investigations showed that her spurious FT₄ result was likely to have been caused by anti-thyroid hormone autoantibodies.

(*J Clin Pathol* 1994;47:181-182)

It is well documented that anti-thyroid hormone autoantibodies can interfere with the measurement of free thyroxine (FT₄) and free tri-iodothyronine (FT₃).¹ In the non-isotopic Amerlite MAB FT₄ assay, FT₄ in the sample competes with a cross-reactant T₃, which is chemically bound to the well surface, for binding to a horseradish peroxidase labelled mouse monoclonal anti-T₄ antibody. The horseradish peroxidase activity in the bound conjugate is measured by an enhanced luminescence reaction. As stated by the manufacturer, FT₄ values should be normal in patients with anti-thyroid hormone autoantibodies using this assay (Amerlite MAB FT₄ assay kit insert, Kodak Clinical Diagnostics Ltd; Amersham UK).

Case report

A 69 year old woman with non-insulin dependent diabetes mellitus and primary

biliary cirrhosis had thyroid function tests performed as she had complained of tiredness and was known to have high titres of anti-thyroid microsomal autoantibodies (1/800) and anti-thyroglobulin autoantibodies (1/1600). She also had antimitochondrial IgG (greater than 1/640) and rheumatoid factor (1/40). Her serum thyroid stimulating hormone (Amerlite immunometric assay) was 3.0 mU/l (reference range: 0.15-3.2 mU/l) and her serum total T₃ (Amerlex-M T₃ radioimmunoassay) was 1.6 nmol/l (0.8-2.5 nmol/l), but her serum FT₄ (Amerlite MAB FT₄ assay) was unexpectedly and inappropriately high: 92 pmol/l (10-27 pmol/l). This spuriously high FT₄ was found on assaying subsequent serum samples from the patient over a period of one year. Her serum albumin was 35 g/l, total protein was 68 g/l, and serum protein electrophoresis was normal. The patient was receiving the following medication during the period concerned: tolbutamide, metformin, isosorbide mononitrate, glyceryl trinitrate, diltiazem, cimetidine, digoxin, spironolactone, calciferol, hydroxyapatite and bisacodyl.

Methods and results

FT₄ was measured in the patient's serum using the Boehringer Mannheim assay, which is a competitive immunoassay, and yielded a normal FT₄ value of 15 pmol/l (reference range: 10-26 pmol/l), confirming that the FT₄ value obtained with the Amerlite MAB FT₄ assay was indeed spuriously high.

Mouse IgG up to 2.5 g/l (final concentra-

Department of
Clinical Biochemistry,
Freeman Hospital,
Freeman Road,
Newcastle upon Tyne
NE7 7DN
L C Lai
J A Day
R T Peaston

Department of
Medicine
F Clark

Correspondence to:
Dr L C Lai

Accepted for publication
18 August 1993