Nephrol Dial Transplant (1998) 13: 2142–2146

Nephrology
Dialysis
Transplantation

The Interesting Case

Proteinase-3-antineutrophil cytoplasmic antibody (PR3-ANCA) positive crescentic glomerulonephritis in a patient with Down's syndrome and infectious endocarditis

Toshiyuki Haseyama[1], Hirokazu Imai[1], Atsushi Komatsuda[1], Keiko Hamai[1], Hiroshi Ohtani[1], Satoshi Kibira[2], and Akira B. Miura[1]

[1]Third and [2]Second Department of Internal Medicine, Akita University School of Medicine, Akita, Japan

Key words: crescentic glomerulonephritis; PR3-ANCA; endocarditis; Down's syndrome

Introduction

ANCA-positive glomerulonephritis is mostly idiopathic, but occasionally it may be associated with other underlying conditions, e.g. scleroderma [1], rheumatoid arthritis [2,3], Goodpasture's syndrome [4], pulmonary aspergillosis [5], relapsing polychondritis [6], and infectious endocarditis [7–9]. It is particularly important to be aware of these conditions and to make the diagnosis in time, because this may have important consequences for patients' management. We present a patient with Down's syndrome, who had PR3-ANCA-positive crescentic glomerulonephritis and infectious endocarditis and who illustrates the above points.

Case report

A 24-year-old man was admitted to Akita University Hospital on 13 September 1996 because of generalized fatigue, nausea, and vomiting. One month after birth, he was diagnosed with Down's syndrome. At 5 years of age, he was diagnosed with Fallot's tetralogy, and he underwent surgery for an endocardial cushion defect in our hospital at 7 years of age. In August 1996, he visited a neighbourhood doctor because of fever and appetite loss after dental care in July, and he was referred to our hospital on 4 September. Laboratory data revealed that WBC was 9000/μl, haemoglobin was 9.7 g/dl, platelets were 112 000/μl, BUN was 25 mg/dl, creatinine was 2.3 mg/dl, uric acid was 6.3 mg/dl, and CRP was 8.4 mg/dl. Urinalysis showed urinary protein was 2+ for dipstick, and occult blood reaction was 4+ with hyaline and granular casts. Urine volume decreased gradually, and he was admitted to our hospital as an emergency case on 13 September 1996.

Physical examination on admission revealed massive oedema of the extremities, purpura of the upper extremity, a distended cervical vein, and a surgical scar on his anterior chest. Blood pressure was 80/44 mmHg, pulse rate was 150/min with arrhythmia, and body temperature was 37.8°C. A medical interview was poor for mental retardation. A holosystolic murmur (Levine 3/6) was audible in the mitral and pulmonary areas. Moist rales and wheezing were also audible in the bilateral lower lung. The abdomen was swollen and flabby. The liver and spleen were impalpable. No abnormal signs were observed in the lymph nodes.

Relevant laboratory data were: erythrocyte sedimentation rate 40 mm/h; red blood cell count 282×10^4/μl; haematocrit 24.2%; haemoglobin 8.0 g/dl. The leukocyte count was 11 200/μl with a differential count of 39% bands, 47% segments, 1% eosinophils, 0% basophils, 6% lymphocytes, 0% monocytes, and 3% myelocytes. The platelet count was 69 000/μl. Lactate dehydrogenase was 316 U/l (normal range, 203–413), aspartate aminotransferase 17 U/l (normal range, 5–26), alanine aminotransferase 10 U/l (normal range, 1–23). Blood urea nitrogen (BUN) was 84 mg/dl, serum creatinine was 8.0 mg/dl, and uric acid was 10.9 mg/dl. Sodium was 135 mEq/l, potassium was 6.7 mEq/l, chloride was 108 mEq/l, Ca was 7.7 mg/dl, and inorganic P was 6.8 mg/dl. Total protein was 6.1 g/dl, albumin was 2.8 g/dl, IgG was 5211 mg/dl, IgA was 380 mg/dl, and IgM was 219 mg/dl. ASO was 154 Todd units. C-reactive protein was 7.6 mg/dl (normal range, 0–0.5). Rheumatoid factor was 80 IU/ml (normal range, below 10).

Tests for hepatitis B antigen, hepatitis C antibody, cryoglobulin and antinuclear antibody were negative. Anti-DNA, -RNP, -Sm, -SS-A, and -SS-B antibodies were negative. Complement C3 was 23 mg/dl (normal range, 60–116), C4 was 5 mg/dl (normal range, 15–44), and CH_{50} was 14 U/ml (normal range, 30.0–40.0).

Correspondence and offprint requests to: Hirokazu Imai MD, Third Department of Internal Medicine, Akita University School of Medicine, 1-1-1, Hondo, Akita 010-8543, Japan.

Immune complex (C1q) was 3.8 mg/ml. MPO-ANCA was negative; however, PR3-ANCA was 97 EU/ml (normal range, below 10). Urinalysis showed 1+ for protein (0.7 g/day) and 4+ for blood on dipstick examination, and microscopic study proved 50–99 RBC/HPF and 3–5 WBC/HPF. Blood culture revealed no growth of bacteria. Chest X-ray showed bilateral pleural effusion, increased vascular shadow in the lung field, and severe cardiomegaly with 69% CTR. Electrocardiogram showed complete right bundle branch block (CBBB) and supraventricular arrhythmia. Ultrasonic cardiogram revealed 2–3 cm sized vegetation in the posteromedial side of the mitral valve.

Hospital course

Haemodialysis was started for severe congestion, oedema, and hyperkalaemia on the first hospital day. Since symptoms such as fever, and pulmonary congestion occurred after dental treatment, the cardiac anomaly, and abnormal ultrasonic cardiogram suggested infective endocarditis. We administered antibiotics, carbapenem and aminoglycoside, to target oral and dental bacteria inducing endocarditis. Since we had observed a positive result of PR3-ANCA in the outpatient clinical examination, we added intravenous methylprednisolone, 500 mg/day, for 3 days under the diagnosis of PR3-ANCA-positive crescentic glomerulonephritis showing rapidly progressive nephritis syndrome. Haemodialysis continued 3 times per week. Five weeks after treatment, the fever was down and CRP decrease to 1.5 mg/dl. However, the ultrasonic cardiogram revealed not only mitral valve but also pulmonary and tricuspid valve involvement in the vegetation (Figure 1). Cardiosurgeons commented that this patient was not suitable for surgery, because he had received an operation for cardiac disorders and had renal failure. On 1 November he lost consciousness during defaecation. The resuscitation was not effective.

Examination of the kidney at postmortem

Light microscopic study demonstrated 48 glomeruli in the specimen, 14 glomeruli showed global sclerosis with fibrocellular and fibrous crescents and nine had segmental necrosis (Figure 2). Residual glomeruli showed mild mesangial proliferation, but no abnormal findings in the basement membrane. Architecture of tubulointerstitium was abrupt, mononuclear cells infiltrated massively, and atrophic tubuli were observed. Round cells were present around the small artery and arteriole with partial necrosis of the small artery. Immunofluorescence study revealed faint linear pattern of IgG and IgA along the basement membrane. The predominant depositions of IgM and C3 were observed as granular patterns in the mesangial area.

Discussion

We report a case of Down's syndrome, which developed infectious endocarditis after dental care, and rapidly progressive glomerulonephritis accompanied by PR3-ANCA positive. In 1991, Wagner *et al.* [7] showed a patient with infectious endocarditis associated with cytoplasmic-ANCA positive 4 weeks after admission, even though it was negative on admission. Kidney biopsy revealed focal segmental glomerulonephritis with frequent crescent formation. Immunofluorescence demonstrated massive deposition of IgM and C3 in the mesangial area. In 1994, Soto *et al.* [8] also reported a case of PR3-ANCA-positive RPGN with underlying endocarditis. However, they did not analyse renal pathology. Recently, two more cases were reported [9]. One was membranoproliferative glomerulonephritis with hypocomplementaemia and PR3-ANCA (12 U/ml; normal range is below 10), another was focal segmental glomerulonephritis with mild extracapillary proliferation with PR3-ANCA (25 U/ml). In both cases, intravenous administration

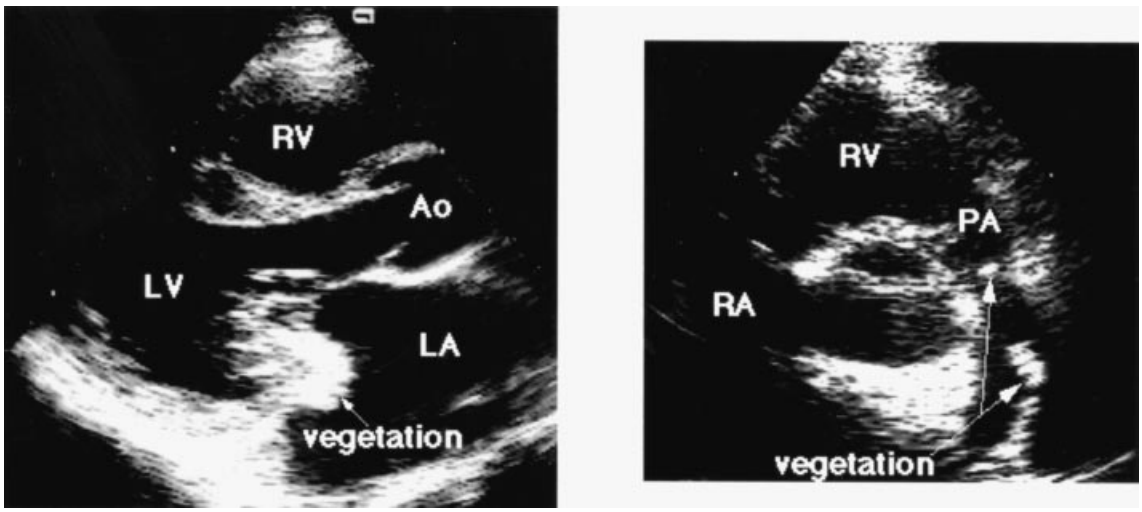
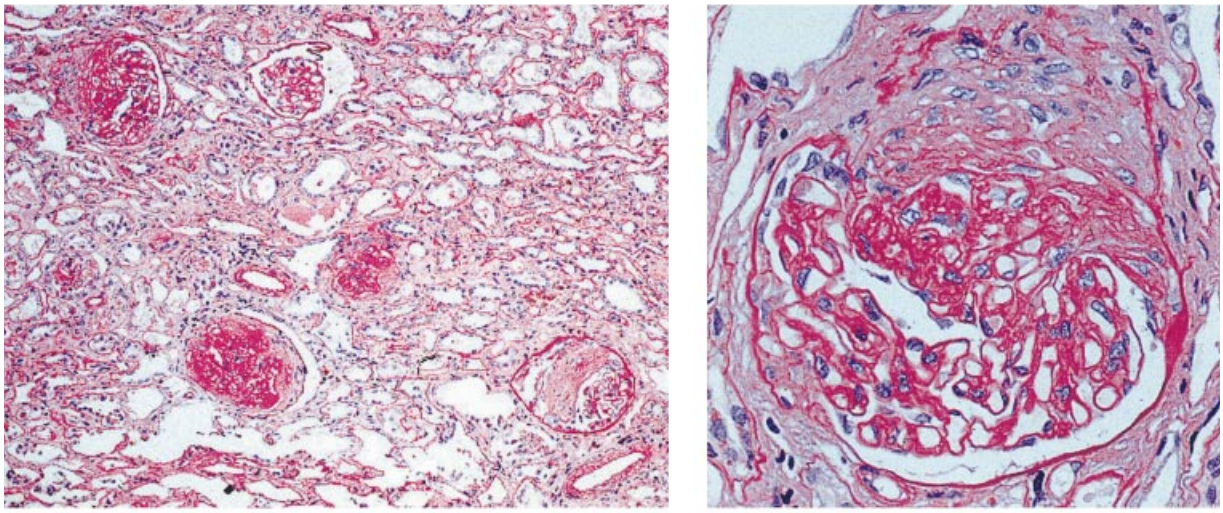


Fig. 1. The ultrasonic cardiogram revealed not only mitral valve but also pulmonary and tricuspid valve involvement in the vegetation. RV, right ventricle; LV, left ventricle; RA, right atrium; LA, left atrium; PA, pulmonary artery; Ao, aorta.

Table 1. Case reports of PR3-ANCA positive glomerulonephritis and infectious endocarditis

Author	Age/sex	Cardiac disease	Clinical course	Onset of endocarditis	Bacteria	ANCA
Wagner	26/F	ASD	1971: closure of ASD	1991: aortic valve	*Streptococcus viridans*	c-ANCA (160-fold)
Soto	79/M	NA	NA	1991: aortic valve	*Streptococcus bovis*	c-ANCA (2000-fold): PR3-ANCA
Subra	48/M	NA	diabetes	1994: mitral valve	NA	c-ANCA (320-fold): PR3-ANCA 12 U/ml
	46/M	NA	NA	1993: aortic valve	NA	c-ANCA (160-fold): PR3-ANCA 25 U/ml
This case	26/M	Down's syndrome 1975: surgery for ECD	1996: August: dental care	1996, September: Mitral, pulmonary valves	Unknown	PR3-ANCA (97 EU/ml)

NA, not available; ECD, endocardial cushion defect; ASD, atrial-septal defect.



(a) (b)

Fig. 2a,b. Histopathology of the kidney. (**a**) Four of five glomeruli showed fibrous crescents (PAS stain, ×100). (**b**) Mild mesangial proliferation was observed with fibrous crescents (AZAN stain, ×400).

of antibiotics improved physical findings and laboratory data. The present case is similar to Wagner's case, as both cases had infectious endocarditis, PR3-ANCA-positive crescentic glomerulonephritis, and a moderate degree of IgM and C3 deposition (Table 1).

PR3-ANCA is well known to be a specific marker of Wegener's granulomatosis, which has a sensitivity and specificity of more than 90% [10,11]. PR3 antigen is present in the primary granules of neutrophils and monocytes. PR3 kills bacteria and is a growth factor forcing the myeloid series. After activation of neutrophil, PR3 moves from cytoplasmic granule to the cell membrane, and is released into the extracellular fluid. Released, the PR3 is neutralized by the alpha-1 proteinase inhibitor [12,13].

The previous two cases [7,8] had endocarditis as a result of infection with bacteria of the streptococcus group. Unfortunately we could not detect any bacteria in the blood culture on admission. The fact that endocarditis occurred following dental care suggests that infection was caused by Gram-positive bacteria in the present case.

Regarding the therapy for infectious endocarditis with PR3-ANCA, previous reports and the present case suggest that in patients with low titres of PR3-ANCA (e.g. below 25 U/ml), it is sufficient to administer antibiotics alone. In contrast, it is better to use either antibiotics and corticosteroid or antibiotics and immunosuppressants in patients with high titres of PR3-ANCA above 50 U/ml, at least when they do not respond to antibiotics within a normal period of time. Surgical replacement of valves may be necessary and is efficient to protect systemic embolism and heart failure following the treatment of bacteraemia. In the present case, we could not perform cardiac surgery, because the patient had already undergone surgery for an endocardial cushion defect, and since multiple valves were involved. The clinical course was presumably adverse because of this complex situation.

Kidney diseases such as mesangiocapillary glomerulonephritis, amyloidosis, and immunotactoid glomerulopathy have been reported in association with Down's syndrome as well as kidney malformation such as horseshoe kidney and cystic dysplasia. Two cases of Down's syndrome with crescentic glomerulonephritis accompanied by MPO-ANCA have been reported in the past [14,15]. The present case is the first report with PR3-ANCA-positive crescentic glomerulonephritis in Down's syndrome and infectious endocarditis. This observation illustrates the importance of recognizing the possibility of coexisting bacterial endocarditis, and also the importance of making the diagnosis in time.

References

1. Endo H, Hosono T, Kondo H. Antineutrophil cytoplasmic autoantibodies in 6 patients with renal failure and systemic sclerosis. *J Rheumatol* 1994; 21: 864–870
2. Savige JA, Gallacchio MC, Stockman A, Cunningham TJ, Rowley MJ. Anti-neutrophil cytoplasmic antibodies in rheumatoid arthritis. *Clin Exp Immunol* 1991; 86: 92–98
3. Bosch X, Llena J, Collado A *et al.* Occurrence of antineutrophil cytoplasmic and antineutrophil (Peri) nuclear antibodies in rheumatoid arthritis. *J Rheumatol* 1995; 22: 2038–2045
4. Dobos GJ, Grotz W, Gondolf KB, Rohrbach R, Peter HH, Schollmeyer P. Einseitige diffuse Lungenbeteiligung bei Vaskulitis mit Anti-Neutrophilen Zytoplasma Antikörpern sowie Antikörpern gegen glomeruläre Basalmembranen. *Dtsch Med Wochenschr* 1994; 119: 1071–1075
5. Milesi-Lecat AM, Aumaitre O, Deusebis T *et al.* Aspergillose pulmonaire semi-invasive avec anticorps-anti-cytoplasme des polynucleaires de type diffus. Deux observations. *Ann Med Interne (Paris)* 1994; 145: 140–146
6. Geffriaud-Ricouard C, Noel LH, Chauveau D, Houhou S, Grünfeld JP, Lesavre P. Clinical spectrum associated with

ANCA of defined antigen specificities in 98 selected patients. *Clin Nephrol* 1993; 39: 125–136
7. Wagner J, Andrassy K, Ritz E. Is vasculitis in subacute bacterial endocarditis associated with ANCA? *Lancet* 1991; 337: 799–800
8. Soto A, Jorgensen C, Oksman F, Noel LH, Sany J. Endocarditis associated with ANCA. *Clin Exp Rheumatol* 1994; 12: 203–204
9. Subra JF, Michelet C, Laporte J *et al.* The presence of cytoplasmic antineutrophil cytoplasmic antibodies (C-ANCA) in the course of subacute bacterial endocarditis with glomerular involvement, coincidence or association? *Clin Nephrol* 1998; 49: 15–18
10. Niles JL, McCluskey RT, Ahmad MF, Arnaout MA. Wegener's granulomatosis autoantigen is a novel serine proteinase. *Blood* 1989; 74: 1888–1893
11. Merkel PA, Polissom RP, Chang Y, Skates SJ, Niles JL. Prevalence of antineutrophil cytoplasmic antibodies in a large inception cohort of patients with connective tissue disease. *Ann Intern Med* 1997; 126: 866–873
12. Rao JK, Weinberger M, Oddone EZ, Allen NB, Landsman P, Feussner JR. The role of antineutrophil cytoplasmic antibody (c-ANCA) testing in the diagnosis of Wegener granulomatosis. *Ann Intern Med* 1995; 123: 925–932
13. Daouk GH, Palsson R, Arnaout A. Inhibition of proteinase 3 by ANCA and its correlation with disease activity in Wegener's granulomatosis. *Kidney Int* 1995; 47: 1528–1536
14. Robson WLM, Leung AKC, Woodman RC, Trevenen CL. Anti-neutrophil cytoplasmic antibody associated glomerulonephritis in a patient with Down's syndrome. *Pediatr Nephrol* 1995; 9: 204–205
15. Schwab M, Böswald M, Ludwig K, Wittekind C, Waldherr R, Ruder H. A patient with Down's syndrome and anti-neutrophilic cytoplasmic antibody-positive vasculitis. *Pediatr Nephrol* 1996; 10: 249–251