Shunt Nephritis and Pyogenic Spondylitis With a Positive PR3-ANCA Associated With Chronically Infected Ventriculoatrial Shunt

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INTRODUCTION

Shunt nephritis is a rare complication mostly described in the setting of chronic infection of ventriculoatrial (VA) shunts inserted for the treatment of congenital or acquired hydrocephalus.1,2 The diagnosis of shunt nephritis is challenging and may be overlooked. We report a case of successfully treated shunt nephritis and pyogenic spondylitis with positive antiproteinase 3 antineutrophil cytoplasmic antibody (PR3-ANCA) in a patient who presented with acute kidney injury.

CASE PRESENTATION

A 56-year-old Japanese man presented with hematuria, proteinuria, progressive kidney dysfunction, and a persistent low grade fever for 4 months. The patient also had mild spontaneous lower back pain. He had a medical history of alcoholic liver cirrhosis and secondary hydrocephalus due to non-HIV cryptococcal meningitis at the age of 50, initially treated by a ventriculoperitoneal shunt. The shunt was subsequently replaced with a VA shunt because of an intra-abdominal abscess.

On physical examination, his vital signs revealed a temperature of 37.2 °C, a pulse of 71/min with regular rhythm, and a blood pressure of 115/77 mm Hg. No abnormalities were detected in the patient’s lungs, heart, abdomen, or extremities.

Laboratory data revealed an elevated creatinine (2.35 mg/dl, baseline 0.86 mg/dl; 5 months before admission), anemia (hemoglobin 9.8 g/dl), mild elevation of liver enzymes (γ- aspartate aminotransferase 67 U/l, alanine aminotransferase 46 U/l), low complement (complement component 3 66 mg/dl, 50% hemolytic unit of component 28 U/ml), elevated C-reactive protein (4.33 mg/dl), and positive PR3-ANCA (67.4 U/ml; reference range <3.5 U/ml). Urinalysis showed proteinuria (1.63 g/gCr) and hematuria (>100 erythrocytes/high power field), both new findings. Blood culture and cerebrospinal fluid culture were positive for oxacillin-resistant Staphylococcus capitis (Table 1). Transthoracic echocardiography showed no vegetation. Transesophageal echocardiography was not performed, because infectious endocarditis was not high in our differential diagnosis. There was increased uptake in the lumbar spine L3-L4 disc on gallium scintigraphy. Lumbar-spine plain magnetic resonance imaging findings were consistent with pyogenic spondylitis.

We suspected a VA shunt infection with pyogenic spondylitis. The VA shunt was removed and antimicrobial therapy was immediately started (Figure 1). The VA shunt was not cultured. Initially, based on the guideline,3 i.v. vancomycin (0.5–1.0 g/d determined by the daily trough value) was given for 25 days until the patient developed a drug eruption. We then switched to a combination of minocycline (200 mg/d) and clindamycin (1800 mg/d). We continued parenteral antibiotics for a total of 9 weeks. Blood cultures turned negative on day 10 of antibiotic treatment. During the antibiotic therapy, his proteinuria and hematuria resolved, and renal function returned to his baseline. Complement and C-reactive protein normalized over the treatment course (Figure 1). His lower back pain also improved. Symptoms of hydrocephalus remained absent even without a VA shunt. There were no signs or
symptoms of granulomatosis with polyangiitis (Wege-
ner’s granulomatosis), although serum levels of PR3-
ANCA did not decrease. After 5 months from the
beginning of treatment, titers for PR3-ANCA remain
high (85.1 U/ml).

**DISCUSSION**

Shunt nephritis, an infection-related glomerulone-
phritis, is a dreaded complication of a VA shunt.
Although the incidence of VA shunt infection is rela-
tively high, approximately 12%, only 0.7% to 2.3% of
infected patients develop shunt nephritis. Therefore,
its diagnosis is sometimes difficult and often delayed or
missed. Although 160 cases have been reported in the
literature, the number of patients with shunt nephritis
is decreasing because VA shunts are being replaced with
ventriculoperitoneal shunts.

There have been some recent reports about immune-
complex-mediated glomerulonephritis related to in-
fections of long-term central venous catheter usage,
often placed for extensive cancer chemotherapy treat-
ment. Cases of shunt nephritis may increase because of
the increased usage of these indwelling central
venous catheters. Physicians should be aware of the
diagnosis and management of this condition.

Kidney biopsy often suggests a diagnosis of shunt
nephritis. A typical kidney biopsy of shunt nephritis
shows membranoproliferative glomerulonephritis with
immune-complex deposition. In this case, we did not
perform a kidney biopsy because of the presence of
persistent bacteremia and prioritization of shunt
removal by the neurosurgeons. In this case, the clinical
improvement with antibiotics, resolution of proteinuria
and hematuria, and improvement of renal function
strongly support the diagnosis of shunt nephritis.

It is unclear how long antibiotics should be used for
this situation. In this case, we followed the recom-
manded antibiotic treatment period for pyogenic
spondylitis. A total duration of 6 weeks of parenteral or
highly bioavailable oral antimicrobial therapy is rec-
ommended. In another literature review, criteria for
discontinuation of antimicrobial treatment include
symptom resolution or improvement and the normali-
zation of erythrocyte sedimentation rate or C-reactive
protein. Considering this information, the period of
bacteremia before treatment, and the possibility of

| Table 1. Laboratory findings on admission |
|----------------|----------------|----------------|----------------|----------------|
| Hematology     | Reference range | Serology        | Reference range | Urinalysis     |
|----------------|----------------|----------------|----------------|----------------|
| WBC            | 6600/µl        | IgG            | 3398³ mg/dl    | pH             | 5.0            |
| Neutrophils    | 73.6%          | lgG4           | 21⁷ mg/dl      | 870–1700       |
| Lymphocytes    | 16.5%          | lgA            | 344 mg/dl      | RBC            | 48–106         |
| Eosinophils    | 0.3%           | IgM            | 305¹ mg/dl     | Hyaline cast   | 33–190         |
| Hb             | 9.8⁸ g/dl      | lgE            | 35.7 mg/dl     | Granular cast  | <170           |
| Plt            | 179 × 10⁹/µl   | C3             | 66 mg/dl       | j2MG           | 150–350        |
| Biochemistry   |                |                | 65–135         | 189.7 µg/l     |
|                |                |                |                | <360           |
|                |                |                |                |                |
| TP             | 8.1 g/dl       | Protein        | 16 mg/dl       | 1.63 g/l       |
|                | 6.5–8.2        |                | 14–45          |
|                |                |                |                | <0.15          |
| Alb            | 2.5⁵ g/dl      | UA             | 2.0 U/ml       |
|                | 3.9–4.9        |                | 2.0 U/ml       |
|                |                |                | 15–30          |
|                |                |                |                |
| Cr             | 3.2³ mg/dl     | Cr             | 8.2 mg/dl      |
|                | 0.5–1.1        |                | 3.0 mg/dl      |
|                |                |                |                |
| Na             | 138 mEq/l      | No             | 1.0 U/ml       |
|                | 135–146        |                |                |
|                |                |                | 135–146        |
| K              | 4.9³ mEq/l     | MPO-ANCA       | 1.3–3.5        |
|                | 3.5–4.8        |                |                |
|                |                |                |                |
| Co2            | 8.6³ mg/dl     | Proteinuria    | 18 mg/dl       |
|                | 8.8–10.1       |                | 18 mg/dl       |
|                |                |                |                |
| UA             | 7.3³ mg/dl     | Proteinemia    | 2.0 U/ml       |
|                | 3.0–7.0        |                | <2.0 U/ml      |
|                |                |                | <3.0          |
| AST            | 67¹ U/l        | Proteinuria    | 10–35          |
|                | 10–35          |                |                |
| ALT            | 46¹ U/l        | Proteinuria    | 5–40           |
|                | 5–40           |                |                |
| CK             | 26¹ U/l        | Proteinuria    | 40–200         |
|                | 20–200         |                |                |
| T-Bil          | 0.6 mg/dl      | Proteinuria    | 0–1.0          |
|                | 0–1.0          |                |                |
| T-Chol         | 142 mg/dl      | Proteinuria    | 0.0 U/ml       |
|                | 120–220        |                |                |
|                |                |                | <8.0 pg/ml     |
| HDL-C          | 35¹ mg/dl      | Proteinuria    | 40–100         |
|                | 30–100         |                |                |
| TG             | 100 mg/dl      | Proteinuria    | 35–150         |
|                | 35–150         |                |                |
| HbA1c          | 5.8%           | Proteinuria    | 4.8–6.2        |
|                | 5.5–5.6        |                |                |
| Creatinin      | 296° ng/ml     | Proteinuria    | 21–275         |
|                | 21–275         |                |                |
| CRP            | 4.33¹ µg/ml    | Proteinuria    | <0.3          |

Ab, antibody; Ag, antigen; Alb, albumin; ALT, alanine aminotransferase; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; AST, L-aspartate aminotransferase; β2MG, beta 2 microglobulin; BUN, blood urea nitrogen; C3, complement component 3; C4, complement component 4; Ca, calcium; CH50, 50% hemolytic unit of component; CK, creatine kinase; Cr, creatinine; CRP, C-reactive protein; CSF, cerebrospinal fluid; GBM, glomerular basement membrane; Hb, hemoglobin; Hbs, hepatitis B surface; HCV, hepatitis C virus; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; HPF, high power field; K, potassium; LPF, low power field; MPO, myeloperoxidase; Na, sodium; NAG, N-acetyl-beta-D-glucosaminidase; P3, platelet; PR3, proteinase 3; RBC, red blood cell; RF, rheumatoid factor; STS, serologic test for syphilis; T-Bil, total bilirubin; T-Chol, total cholesterol; T-SPOT, a type of enzyme-linked immunospot assay used for tuberculosis diagnosis, which belongs to the group of interferon-gamma release assays; TG, triglyceride; TP, total protein; TPHA, treponema pallidum latex agglutination; U-pro/Ur-Cr, urinary protein-creatinine ratio; UA, uric acid; WBC, white blood cell.

Values that are out of normal range.
immunological impairment related to liver cirrhosis, we used antibiotics for a total of 9 weeks, while monitoring the urinalysis and C-reactive protein. After treatment his lower back pain improved and there has been no recurrence of nephritis and spondylitis.

Coagulase-negative staphylococci, especially *Staphylococcus epidermidis*, are the most common cause of foreign body infections, including shunt nephritis. *S. capitis* was the cause of nephritis in our case. It is generally considered a nonpathogenic bacterium and is rarely associated with foreign body infections.9

Cryptococcosis is an opportunistic infection that defines AIDS in HIV+ patients but is also seen in other immunocompromised situations. Our patient was previously diagnosed with cryptococcal meningitis despite the negative HIV infection. Although there was no decrease in CD4 nor impaired humoral response, it is still possible that this patient has immune deficiency related to chronic liver cirrhosis that might have allowed this nonpathogenic attenuated bacterium to cause the persistent bacteremia and nephritis.

ANCAs were originally described in 1982,10 and the PR3 antigen was discovered in 1989.11 PR3-ANCA usually causes a C-ANCA pattern and is well known as a specific marker of granulomatosis with polyangiitis. Testing for PR3-ANCA by using an indirect immunofluorescence technique or enzyme-linked immunosorbent assay has very high specificity (95%–100%) and high sensitivity (61.8%–97.1%).12 Although PR3-ANCA testing is a useful clinical tool in daily practice, it is still considered controversial because ANCA becomes positive under conditions other than vasculitis (e.g., infections or exposure to drugs). In these cases, the patient’s condition might be worsened by immunosuppression.12 ANCA formation has been reported in the course of various chronic viral (e.g., HIV, Hepatitis B, Hepatitis C), bacterial (e.g., *Streptococcus, Staphylococcus, Enterococcus*), fungal (e.g., *Aspergillus*), protozoal (e.g., *Streptococcus, Staphylococcus, Enterococcus*), and multicellular parasitic infection (e.g., *Echinococcus*).13 For example, PR3-ANCA in infectious endocarditis is a typical disease.14,15 In shunt nephritis, PR3-ANCA could also become positive. Three

![Figure 1. Clinical course. ANCA, antineutrophil cytoplasmic antibody; CH50, 50% hemolytic unit of component; CRP, C-reactive protein; HPF, high power field; PR3, proteinase 3; RBC, red blood cell; sCr, serum creatinine; U-pro/U-Cr, urinary protein-creatinine ratio.](image-url)
previously published case reports and our case of shunt nephritis with positive PR3-ANCA are shown in Table 2.16–18 Earlier reports showed that PR3-ANCA returned to normal after treatment.

There remains much unknown about the precise relationship between ANCA formation and vasculitis. Previous studies revealed the relationship between ANCA-related diseases and infection.19–21 Recent studies have shown that neutrophil exudate traps may play an important role with regard to ANCA levels and tissue injury. Neutrophil exudate traps are nuclear-derived chromatin fibers released from activated neutrophil and contain PR3. Neutrophil exudate traps can not only be a cause but also be a result of inflammation.22 PR3-ANCA stimulates neutrophil exudate trap secretion, and on the other hand, bacterial PR3 enhances antibody production against PR3. This malignant cycle is considered as one of the pathogeneses underlying ANCA-related vasculitis or glomerulonephritis.13 PR3-ANCA levels in our patient remain high and have not changed over 3 months after resolution of clinical signs and symptoms. A previous single-center study indicated that patients who showed positive c-ANCA/PR3-ANCA without sufficient clinical or other evidence of a systemic vasculitis had a small risk of developing vasculitis later (Table 3).23 It is unclear whether or not an elevated PR3-ANCA is related to the pathophysiology in this case, and we will carefully observe the patient’s clinical course in the future.

Table 2. Shunt nephritis with positive PR3-ANCA in published case reports and our patients

| Case | Bonarek et al.16 | Nagashima et al.17 | Iwata et al.18 | Our patient |
|------|------------------|--------------------|---------------|-------------|
| Age, sex | 50, F | 17, F | 55, M | 56, M |
| Cause of hydrocephalus | Arachnoid cyst | Congenital hydrocephalus | Brain abscess | Secondary hydrocephalus |
| Shunt | Cystoatrial | VA | VA | VA |
| Causal organism | Propionibacterium acnes | Gemella morbillorum | Propionibacterium acnes | Staphylococcus capitis |
| Duration of shunt (yr) | 9 | 10 | 7 | 2 |
| Serum creatinine | 1.4 mg/dl | 1.1 mg/dl | 1.5 mg/dl | 2.35 mg/dl |
| Urinary protein | 3.5 g/d | 1.4 g/d | 5.4 g/d | 1.63 g/gCr |
| C3 (reference range, 65–135 mg/dl) | 55 | 39.9 | 39.9 | 66 |
| C4 (reference range, 13–35 mg/dl) | 16 | 3 | 10.3 | 18 |
| CH50 (reference range, 32–49 U/ml) | Undetectable | <8 | <5 | 28 |
| PR3-ANCA (before therapy) | 1/500 | 44 U/ml | 113 U/ml | 67.4 U/ml |
| PR3-ANCA (after therapy) | Negative | 11 U/ml (4 mo) | 6.3 U/ml (9 mo) | 85.1 U/ml (5 mo) |
| Renal pathology | MPGN | MPGN | MPGN | Not performed |
| Treatment | Shunt removal antibiotics | Shunt removal, antibiotics PSL, mPSL pulse | Shunt replacement antibiotics, PSL | Shunt removal, antibiotics |
| Outcome | Improve | Improve | Improve | Improve |

ANCA, antineutrophil cytoplasmic antibody; C3, complement component 3; C4, complement component 4; CH50, 50% hemolytic unit of component; MPGN, membranoproliferative glomerulonephritis; mPSL, methylprednisolone; PR3, proteinase 3; PSL, prednisolone; VA, ventriculoatrial.

CONCLUSION

We successfully treated a patient with shunt nephritis with antibiotic treatment and shunt removal. Hematuria, proteinuria, and progressive kidney dysfunction all improved. It is unclear why PR3-ANCA becomes positive in conditions related to chronic infection, and it will be necessary to follow the PR3-ANCA titer in this case. Physicians should be aware of the risks of infection-related glomerulonephritis in patients with VA shunts as early diagnosis and treatment initiation with antibiotics and shunt removal is a key to the successful management.

DISCLOSURE

All the authors declared no competing interests.

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