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Membranoproliferative glomerulonephritis complicating *Propionibacterium acnes* infection

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Abstract

Background. *Propionibacterium acnes* (*P. acnes*) is a common microbe of the skin and mucosal surfaces rarely considered a true pathogen. However, it has been reported to cause serious infections. Subsequent ongoing low-grade antigenaemia may, in turn, lead to an immune-mediated glomerulonephritis with various renal histologies including that of membranoproliferative glomerulonephritis (MPGN).

Methods. Here, we describe two cases of *P. acnes* infection-induced MPGN and their treatment.

Results. Both patients were successfully treated by the eradication of the infection. One patient also received immunosuppressive medication prior to the correct diagnosis.

Conclusions. A vigorous exclusion of infection is warranted in MPGN type I or immune-complex-mediated MPGN and may sometimes yield a diagnosis of secondary MPGN.

Keywords: membranoproliferative; glomerulonephritis; *Propionibacterium acnes*

Introduction

Propionibacterium acnes (*P. acnes*) is an anaerobic, gram-positive microbe with relatively low virulence commonly found on the skin flora and mucosal surfaces [1]. It is rarely considered a true pathogen, but it has been reported to cause serious infections including those of heart valves, both prosthetic and natural, pacemakers and shunt infections [1–3].

An intracranial ventricular shunt is used to drain an excess of cerebrospinal fluid (CSF) from the brain. The most significant shunt complication is infection affecting ∼3–11% of the patients at some point [4]. Only a minority of these patients develop nephritis and published cases mediated by *P. acnes* are rare, although the true incidence can be higher due to the lengthy incubation period and poor growth of the organism [1, 4].

Immune-mediated glomerulonephritis complicates infective endocarditis in ∼20% of the cases [5]. Observations made predominantly in the pre-antibiotic era suggested that infections with less virulent organisms favoured an antibody response predisposing to immune-complex glomerulonephritis [5]. Only two *P. acnes* endocarditis and subsequent immune-mediated glomerulonephritis have been reported, and in the publication of Kimmel *et al*., diagnosis of kidney disease was set on clinical grounds only [6, 7].

Membranoproliferative glomerulonephritis (MPGN) denotes an easily recognized pattern of glomerular injury by light microscopy. It has traditionally been subdivided into three types (MPGN type I, II (dense deposit disease) and III) based on electron microscopy, but a recently proposed classification suggests a more practical approach to view MPGN as immune-complex-mediated or complement-mediated. Immune-complex-mediated MPGN results from the deposition of glomerular immune complexes forming as a result of chronic infections, autoimmune diseases or paraproteinaemias. Complement-mediated MPGN occurs due to the disorders associated with dysregulation of the complement pathway. The former typically has immunoglobulin and complement on immunofluorescence and the latter has only complement. Electron microscopy is then needed to differentiate between the two complement-mediated MPGN types: C3 glomerulonephritis and dense deposit disease [8–10].

Here, we present two cases of MPGN secondary to *P. acnes*—bacteraemia in one patient with infected shunt and in another patient with endocarditis in a prosthetic valve both successfully treated by the eradication of the infection.

Materials and methods

Patient 1 is a man, currently 25 years of age, diagnosed with a pilocyte astrocytoma at the age of 3. An operation was withheld due to the location and large size of the

tumour and radiation therapy was given. Due to the subsequent obstructive hydrocephalus, a ventriculo-peritoneal shunt was inserted.

A craniotomy was performed in June 2002 at the age of 15 as marked enlargement of the tumour was noticed and symptoms of increased intracranial pressure were evident. Total removal of the tumour was not possible and a shunt infection developed postoperatively with *P. acnes* growth in the shunt system. With broad-spectrum antibiotics, temporary externalization and transformation of the shunt system into a ventriculo-atrial system he made a full recovery.

December 2002 onwards outbreaks of fever every 2 to 3 weeks started to occur. These episodes were typically of short duration and self-limited with C-reactive protein (CRP) moderately elevated, 40–60 mg/L. In November 2003, a blood culture taken during an acute phase revealed *P. acnes* growth. As the same bacteria had grown in the shunt system over a year earlier, it was likely that the system was permanently colonized causing the periodic fever. An operation was seen as too risky and a permanent daily oral prophylactic antibiotic (doxycycline 150 mg) was initiated. However, the outbreaks of fever continued.

In April 2009, gradually increasing lower limb oedema with simultaneous weight gain of several kilograms developed. The first urine specimen was taken in August revealing both haematuria and proteinuria later diagnosed to be of nephrotic range (9.09 g/24 h). Plasma creatinine was normal. A renal biopsy in September 2009 showed the typical features of MPGN type 1, or according to a newer classification, immune-complex-mediated MPGN (Figure 1). As he was known to have a chronically infected ventriculo-atrial shunt, the diagnosis of shunt nephritis was established without detailed exclusion of other causes.

Given the major risk of permanent loss of kidney function, reoperation of the shunt was planned after careful consideration. The infected shunt system was removed in December 2009 with subsequent *P. acnes* growth from the removed device. After 5 days of contemporary ventriculostomy and intravenous antibiotic treatment, a new shunt with antibacterial hoses was inserted. Ten days after the surgery, the leg oedema had vanished completely, the weight was reduced by 13 kg and proteinuria was diminished to a level of 1.69 g/24 h. Serum complement levels were taken only after the operation and were normal. In the latest control in March 2012, he was asymptomatic with proteinuria <300 mg/24 h and normal plasma creatinine. The microscopic haematuria disappeared 20 months after the successful operation.

Patient 2 is a 68-year-old man with a history of hypertension, hypercholesterolaemia and coronary artery disease. IgA glomerulonephritis had been diagnosed in 1977, but kidney function was only slightly impaired without progressive deterioration, the amount of proteinuria was controlled (<1 g/24 h) and microhaematuria persisted. A calcified aortic valve was replaced by mechanical prosthesis in 1998. A coronary angiography was performed in May 2007 with subsequent infected groin pseudoaneurysm. In summer 2008, anaemia, hypersedimentation and eosinophilia of unknown aetiology developed. Extensive examinations including gastroscopy, colonoscopy, serum protein electrophoresis, bone marrow aspiration and abdominal ultrasound revealed no major findings. However, blood cultures were not taken, transthoracical echocardiography was normal in January 2009.

From March to April 2009, his health progressively deteriorated and inflammatory variables were slightly elevated. Several blood cultures were negative, echocardiography showed a minor paravalvular leak in the aortic valve. Proteinuria had increased to a level of 2.04 g/24 h, but kidney function was stable (p-creatinine 125 μmol/L). A renal biopsy was taken in April 2009 revealing MPGN type I, or according to a newer classification, immune-complex-mediated MPGN as immunofluorescence had complement 3 and some IgM and electron microscopy showed subendothelial deposits. As thorough investigations only a few months earlier revealed no malignancies, virus, bacterial infections or cryoglobulinaemia, the renal disease was labelled as primary MPGN. A course of corticosteroids was started, but gradually tapered and eventually stopped after 7 months in October 2009 with no major impact on renal or suspected autoimmune disease of unknown aetiology.

During autumn 2009, lower limb oedema developed, the weight increased almost 15 kg and dyspnoea was experienced in light everyday tasks. Outbreaks of fever emerged in early December 2009. Kidney function remained stable and proteinuria was slightly decreased. In December 2009, symptoms of congestive heart failure developed leading to the patient's admittance to the hospital. There was no evidence of acute ischaemia, but a profound paravalvular leak and a clear vegetation in the prosthetic aortic valve were noticed. On admittance, plasma creatinine was increased to 192 μmol/L, the initial blood cultures were reported to be negative and broad-spectrum IV-antibiotics were started. However, 5 days later, blood cultures taken during an outbreak of fever were positive for *P. acnes*. Despite aggressive antibiotic treatment, diuresis diminished, creatinine rose to 275 μmol/L, vegetation in the valve grew and the paravalvular leak increased with repeated episodes of ventricular tachycardia. In an operation in January 2010, the prosthetic valve was attached to the aorta with only few stitches and aortic annulus was completely destroyed. The whole calcified aortic root was removed and replaced by prosthesis. The cultures from the removed prosthetic valve were positive for *P. acnes*.

Renal function and diuresis improved remarkably in just a few days postoperatively and no dialysis was needed. Plasma creatinine decreased from the pre-operative value to 130 μmol/L in a week. Recovery was otherwise very slow and complex with various non-renal complications. In the latest nephrology outpatient control in April 2012, p-creatinine was 122 μmol/L with no evidence of proteinuria or haematuria. Microscopic haematuria disappeared 5 months after the operation. Serum complement levels were otherwise normal, but complement 3 (C3) was incidentally decreased postoperatively. Doxycycline 150 mg once daily was planned to continue as a life-long therapy. The most important findings of these two patients are presented in Table 1.

Discussion

Here, we described two cases of *P. acnes*-induced low-grade chronic infections causing secondary MPGN successfully treated by eradication of the infection.

Only a minority (<3%) of shunt infection patients develop a shunt nephritis [4]. Most shunt infections are caused by different *Staphylococci* (epidermidis and

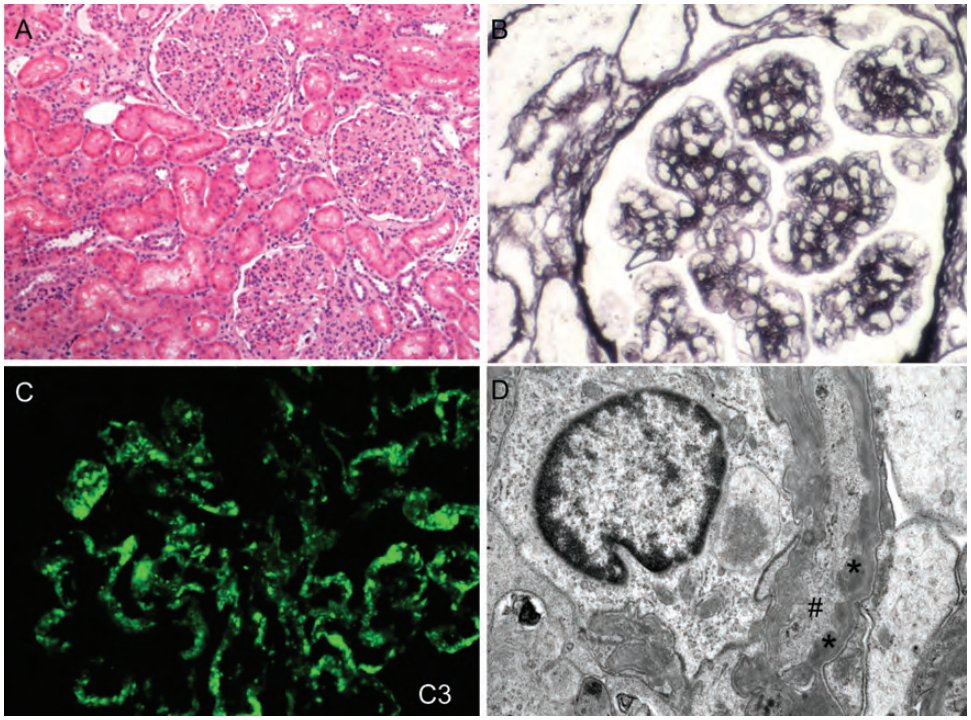

Fig. 1. The biopsy showed diffuse and global involvement of glomeruli. Cellularity was increased and lobulation was observed in the otherwise well-preserved kidney parenchyma (**A**, haematoxylin–eosin staining). Jones' silver staining (**B**) revealed duplication of the basement membrane and silver-negative vacuoles. Immunofluorescence staining (**C**) was strongly positive in glomerulus capillaries and partially in the mesangium for C3, C1q and less for IgM and IgG. Electronmicroscopy (**D**) showed subendothelial deposits (*) and mesangial interposition (#). These histological findings correspond to MPGN, type 1.

aureus), and they are also the leading causative agents in shunt nephritis [1, 3, 4]. *P. acnes*-induced shunt nephritis is unusual, although the true incidence may be higher due to the characteristics of the microbe [1]. In general, diagnostic delays have been reported to be between 1 week and 13 years from the earliest signs of shunt nephritis [3, 11]. In Patient 1, the first signs of kidney problems were revealed in April 2009 and a shunt nephritis was diagnosed in September 2009 with a delay of 5 months. A chronic infection had persisted for 7 years prior to the development of kidney problems, originating from the operation in June 2002.

Infective endocarditis caused by anaerobic bacteria is a rare condition accounting for 2–16% of all infective endocarditis [2]. *P. acnes* is the causative agent in 0.3–4.3% with mortality rates ranging from 15 to 27% [2, 12–14]. Patients often have minimal symptoms in the early phases of the disease, and delays from symptom onset to diagnosis have varied from 3 days to 15 years [12, 13]. In most cases, the infection involved prosthetic material and the time between prosthesis implantation and symptom onset varied greatly from 1 week to 27 years [12–14]. In Patient 2, the earliest signs of kidney problems were difficult to define as he had already been diagnosed with IgA glomerulonephritis in 1977. The second kidney biopsy was taken in April 2009 due to increasing proteinuria, but a secondary MPGN was diagnosed only in January 2010, with a delay of 9 months. An entry point is rarely confirmed, but is probably cutaneous [2], and in our Patient 2, it can be suspected to have resulted from the infected groin haematoma in May 2007. In this case, the infection would have persisted for 2 years prior to the development of novel kidney problems and the time interval between the application of valvular prosthesis and the onset of *P. acnes* infection was estimated to be 9 years.

The membranoproliferative pattern of glomerular injury is most commonly seen in shunt nephritis, although various types of glomerulonephritis have been described [1, 3, 4]. Renal histology varies considerably and MPGN is also seen in infective endocarditis [5]. Once MPGN diagnosis is established, an investigation of secondary causes should be undertaken with emphasis on chronic infections, autoimmune and inflammatory diseases as well as neoplasms or genetical background [15]. MPGN has traditionally been subdivided into three types based on electron microscopy [15]. A recent proposal of new classification may be of valuable help for the clinicians, as it underlines the importance of identifying chronic antigenaemia in cases of immune-complex-mediated MPGN leading to the more focused investigation of aetiology [8–10]. Both our patients had immunoglobulin as well as complement in their biopsies and electron microscopy revealed subendothelial deposits. Therefore, our patients comply well both with the older classification (MPGN type I) and with the newer classification (immune-complex-mediated MPGN). Serum complement levels are usually decreased in all forms of MPGN, but this can also be transient [10]. Patient 1 had complement levels measured only after the successful operation and they were normal at that point. Patient 2 had a transient decrease of C3 after the cardiac operation. There is paucity of data, but some cases of suspected primary MPGN may later prove to be secondary to low-grade infections. However, it is often difficult to know whether subclinical low-grade infections lead to the subsequent glomerulonephritis or

Table 1. Major clinical and laboratory findings in two patients with secondary MPGN caused by *P. acnes* before and after the eradication of the infective agent[a]

Patient No.	1	2
Sex	Male	Male
Previous kidney biopsy result	Not existing	IgA glomerulonephritis
Site of infection	CSF ventriculo-atrial shunt	Prosthetic aortic valve
Interval between the onset of *P. acnes* infection and renal diagnosis of MPGN	7 years	2 years (estimation)
Delay between first signs of kidney disease and diagnosis of secondary MPGN	5 months	9 months
Age at renal diagnosis of MPGN	22 years	65 years
Laboratory values at renal diagnosis (reference range) unit		
CRP (<3 mg/L)	21	5
24-h proteinuria (<100 mg) g/24 h	9.09	2.08
p-Creatinine (60–100 μmol/L)	81	118
Haematuria (no/yes)	Yes	Yes
s-Albumin (36–48 g/L)	24.1	23.9
s-Haemoglobin (134–167 g/L)	102	108
s-C3 (0.71–1.41 g/L)	NA	0.97
s-C4 (0.12–0.34 g/L)	NA	0.26
s-ANA/s-DNAab (<320/<10 IU/mL)	NA/<10	<80/<10
s-HbsAg	Negative	Negative
s-HCV-ab	Negative	Negative
Laboratory values after the eradication of *P. acnes* infection at last observation (reference range) unit		
CRP (<3 mg/L)	<3	<3
24-h proteinuria (<100 mg) g/24 h	0.177 g	No proteinuria
p-Creatinine (60–100 μmol/L)	65	122
Haematuria (no/yes)	No	No
s-Albumin (36–48 g/L)	39.5	33
s-Haemoglobin (134–167 g/L)	171	165
s-C3 (0.71–1.41 g/L)	0.99	1.07
s-C4 (0.12–0.34 g/L)	0.19	0.19

[a]CSF, cerebrospinal fluid. Values in parentheses are the normal range. NA, not available.

whether infection is secondary to prolonged immunosuppressive medication due to glomerulonephritis [16].

In Patient 1, the only curative treatment for MPGN would have been the removal of the infected shunt as long-term antibiotic treatment had not been able to prevent kidney problems. The renal function was yet normal, but inevitable deterioration was to be expected should the proteinuria persist this profuse. The prognosis of secondary MPGN caused by non-curable infections with ongoing antigenaemia is not clear, but in general ∼40% of patients with MPGN progress to end-stage renal disease within 10 years and features suggestive of an adverse outcome include nephrotic-range proteinuria [15]. The prognosis in shunt nephritis can vary from complete recovery to end-stage renal failure even after optimal treatment and a delay in the removal of infected material may carry a risk of irreversible kidney damage [3, 11]. Immunomodulatory treatments with steroids and cyclophosphamides have been reported in three cases of *P. acnes*-induced MPGN, but in two cases the treatment was initiated before the diagnosis of shunt nephritis was made. No significant long-term beneficial effect was obtained with immunomodulation, but the resolution of MPGN was later achieved with shunt removal and antibiotics [1, 17]. In the third case, steroids were started simultaneously with antibiotics after the removal of the infected shunt and therefore, regression of MPGN may have been caused by several factors [18]. In cases of successful shunt removal and appropriate antibiotics, a trial of steroids may be considered to reduce glomerular inflammation and to stabilize renal function [1]. Immunomodulation was not seen as a valid option here considering the outbreaks of fever through a prophylactic antibiotic regimen. If removal of the infected shunt was not possible, another consideration of immunosuppressive medication may have been warranted.

In Patient 2, the chronic infection had greatly damaged the prosthesis and the aorta leading to cardiovascular instability with no other treatment options but urgent operation combined with antibiotics. Kidney insufficiency was gradually worsening with escalation just prior to the operation partly explained by the haemodynamic instability caused by the damaged valve. The amount of proteinuria was minimal before the operation (283 mg/24 h) possibly reflecting the immune-mediated process being somewhat under control. During spring/summer 2009, the patient received a trial of corticosteroids for 7 months with no apparent effect on renal disease. However, it is impossible to predict whether renal symptoms would have progressed without corticosteroids. In two reports of crescentic glomerulonephritis related to infective endocarditis, corticosteroids were added to antibiotic treatment with subsequent improvement of kidney function [7, 19]. Optimal treatment usually requires a combination of medical and surgical therapy [2].

In summary, the successful eradication of *P. acnes*-infected material and antibiotic treatment led to a resolution of clinical symptoms of renal disease in our patients.

Conflict of interest statement. None declared.

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