OPEN

Syphilis and parvovirus B19 co-infection imitating a lupus nephropathy

A case report

Eric Jaunin, MD[a], Sebastien Kissling, MD[b], Samuel Rotman, MD[c], Gérard Waeber, MD[a], Matthieu Halfon, MD[b,*]

Abstract

Rationale: Syphilis can share clinical features with autoimmune diseases, such as cutaneous Lupus or rheumatoid arthritis. Moreover, secondary syphilis can have visceral involvement, thus affecting the kidney. Syphilitic nephropathy causes nephrotic syndrome with a classic membranous pattern. We present a unique presentation of a co-infection by syphilis and parvovirus B19 sharing all the biological and histological features of proliferative lupus nephritis (LN).

Patient concerns: We present a case of a 71-year-old Caucasian male returning from a trip to Asia presenting with nephrotic syndrome with antinuclear antibodies (ANA) positivity.

Diagnoses: Because of nephrotic syndrome a kidney biopsy was performed. It demonstrated a membranous nephropathy with extracapillary proliferation and a full house pattern (presence of IgA, IgG, IgM and C1Q deposits) on immunofluorescence (IF), highly suggestive of LN class III and V. However, several atypical clinical features notably the age, sex of the patient and the history of travel prompt us to search for another cause of nephropathy.

Interventions: A serology was positive for syphilis and a PCR in the renal biopsy was also positive for parvovirus B19. Thus, a co-infection by syphilis and parvovirus B19 was funded to be the cause of the renal lesions.

Outcomes: The proteinuria improved; a course of antibiotic was administrated because of neurologic syphilitic involvement (presence of headache with positive syphilis serology in the CSF).

Lessons: A co-infection by syphilis and parvovirus B19 can share all the biological and histological features of proliferative LN and must be recognized as a cause of pseudo-lupus nephritis.

Abbreviations: ANA = antinuclear antibodies, ANCA = anti-*neutrophil* cytoplasmic antibodies, Anti- GBM = anti Glomeruli basal membrane antibodies, Anti-sDNA = anti double stranded DNA, CSF = cerebrospinal fluid, FSGS = focal segmental glomerulosclerosis, IF = immunofluorescence, LN = lupus nephritis, RPR = rapid plasma reagin test, RPS/ISN = Renal Pathology Society/International Society of Nephrology, SLE = systemic lupus erythematosus, TPHA = Treponema Palladium Hemagglutinations Assay.

Keywords: glomerulonephritis, lupus nephritis, parvovirus, syphilis

1. Case

1.1. Introduction

Syphilis is a venereal disease caused by treponema pallidum. It is divided into 3 stages: primary (painless chancre at the site of inoculation), secondary (systemic infection with rash, lymphadenopathy, fever), and tertiary (gummatous stage with neurosyphilis and cardiovascular involvement). There is a variable latency period between stages.

Even though the incidence of syphilis has become quite low in the western world, it is re-emerging since the early 2000's. Kidney involvement is rare but can occur at any stage from secondary to latent and tertiary syphilis.[1] Membranous nephropathy, probably due to an immunological cross-reactivity between a syphilis and a kidney antigen, is the most common manifestation. But patients may present with other histopathological patterns, such as focal segmental glomerulosclerosis (FSGS).[2] Syphilis is also widely known to share clinical features with systemic disease; especially cutaneous syphilitic lesions can clinically look like cutaneous lupus.

In terms of renal histology, membranous syphilitic nephropathy can be easily distinct from lupus membranous nephropathy

Editor: N/A.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

The authors have no funding and conflicts of interests to disclose.

[a] Department of Medicine, [b] Service of Nephrology and Hypertension, [c] Service of Clinical Pathology, Lausanne University Hospital and University of Lausanne, Switzerland.

[*] Correspondence: Dr Matthieu Halfon, Service of Nephrology and Hypertension, University Hospital of Lausanne (CHUV), Rue du Bugnon 17, 1011 Lausanne, Switzerland (e-mail: matthieu.halfon@chuv.ch).

How to cite this article: Jaunin E, Kissling S, Rotman S, Waeber G, Halfon M. Syphilis and parvovirus B19 co-infection imitating a lupus nephropathy. Medicine 2019;98:36(e17040).

Received: 10 February 2019 / Received in final form: 9 July 2019 / Accepted: 12 August 2019

http://dx.doi.org/10.1097/MD.0000000000017040

by the nature of the immune deposits, especially the presence of C1Q deposit which is nearly pathognomonic of lupus nephritis (LN).

However, parvovirus B19 is one of the few other causes of C1Q deposition in kidney tissues.[3] Therefore, in case of a co-infection by syphilis and parvovirus B19, histological renal lesions could overlap leading to pseudo-lupus nephritis.

1.2. Case

A 71-year-old Caucasian male was referred for an abrupt onset of a nephrotic syndrome. His past medical history was significant only for hypercholesterolemia, which was treated with a statin. After a 2-3-month stay in Thailand a few months prior to hospitalization, he reported the onset of fatigue, episodes of fever and night sweats and generalized muscle and joint pain. Blood work ruled out HIV, HCV, HBV, EBV, and CMV infections. A thoracic and abdominal CT scan was unremarkable. Screenings for malaria and other parasitic infections were negative. Upon suspicion of polymyalgia rheumatica and Horton disease in the context of a new onset right-sided headache, his general practitioner initiated a 5-day course of prednisone without any improvement. A temporal artery biopsy showed no sign of giant cell arteritis. Symptomatic treatment with nonsteroidal anti-inflammatory drugs was later prescribed with little benefit. Given the rapid progression of inferior limbs edemas with a proteinuria of up to 9 grams per day, the patient was eventually referred to the tertiary hospital. He was then asymptomatic except for fatigue. He denied taking any other medication or recreational drugs and affirmed not having any unprotected sexual intercourse over the last years. He did not experience any macroscopic hematuria. Upon physical examination, blood pressure was 130/60 mmHg, with no fever. Both lower limbs were markedly edematous and presented a bilateral pretibial maculo-papular rash. Blood tests showed a mild inflammation (leucocytes 15 G/L, CRP 21 mg/L). The plasma creatinine level was 117 μmol/L and albuminemia was 24 g/L. Urine analysis confirmed a proteinuria of nephrotic range (protein to creatinine ratio 510 g/mol, albumin to creatinine ratio 355 mg/mmol) with a bland sediment. The urine culture remained sterile. A renal ultrasound did not show any abnormalities. anti-*neutrophil* cytoplasmic antibodies (ANCA) and anti Glomeruli basal membrane antibodies (anti-GBM) were negative, but antinuclear antibodies (ANA) were positive at the 1/640 dilution with a mottle aspect. C3 and C4 were in the normal range. Supportive treatments that included a loop diuretic, an ACE inhibitor and a statin were initiated, and a kidney biopsy was performed. Histology showed deposits within capillary loops with some degree of extracapillary proliferation (Fig. 1A). The IF showed IgA, IgG, IgM, C3, and C1Q deposits ("full house" pattern, IgA (+), IgG (+++) IgM (+) C3 (++), C1Q (++)) and sub-epithelial deposits were observed on electron microscopy (Fig. 1B and Fig. 2). The pattern of the renal lesion along with ANA positivity was highly suggestive of LN class III (i.e., proliferative focal glomerulonephritis) associated with LN class V (i.e., Lupus membranous nephropathy). However, this quite a peculiar picture for lupus (i.e., patients' sex and age at presentation, lack of typical extra-renal features of lupus, history of travel) prompted us to request a complementary microbiological workup, including a serology for syphilis. The Treponema Palladium Hemagglutinations Assay (TPHA) and the rapid plasma reagin test (RPR) were highly positive with 10240 (norm < 80) and 32 (norm < 2), respectively. Moreover, skin biopsy of the pretibial lesions revealed a spirochete infection (presence of spirochetes in the epiderma and superficial derma with positive anti T. palladium antibodies). Even though syphilis nephropathy could explain the membranous pattern on the kidney biopsy, the observed IF pattern is not typical of

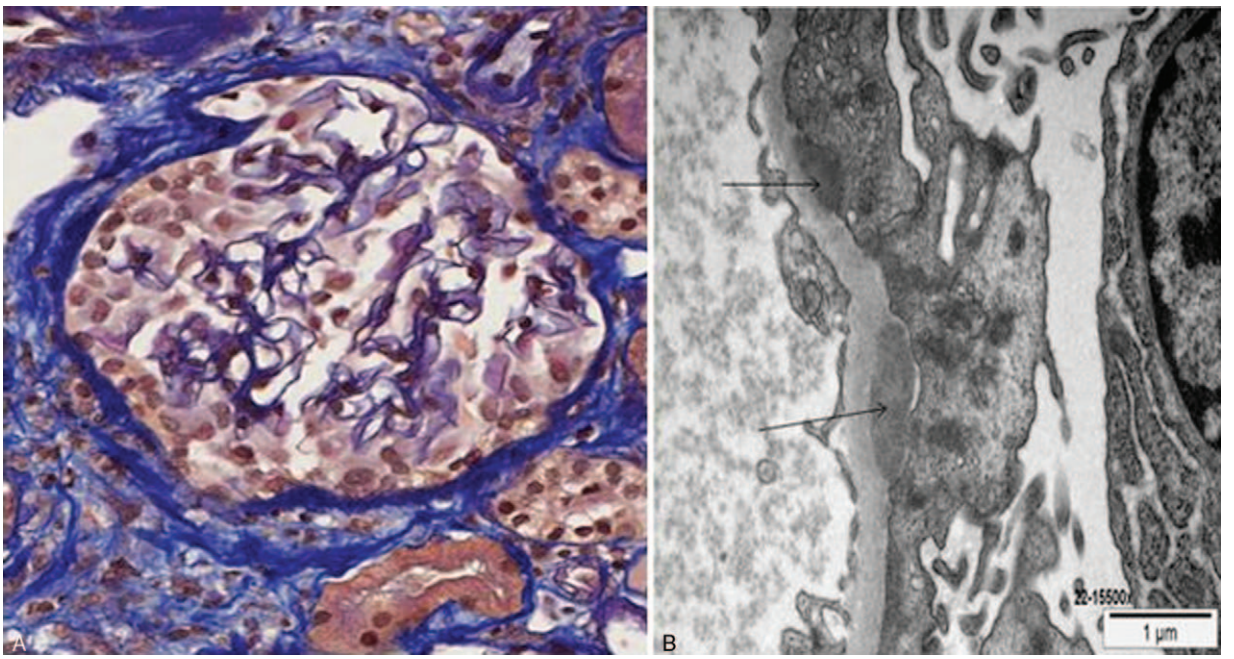

Figure 1. A: Renal biopsy showed 3 cellular crescents on 24 glomeruli with "full house" pattern depositions within capillary loops. (FAOG, 400×). B: Electron microscopy revealed electron-dense deposits (black arrow) between the lamina densa of the glomerular basement membrane (GBM) and the visceral epithelial cell (subepithelial deposits) characterizing membranous glomerulonephritis.

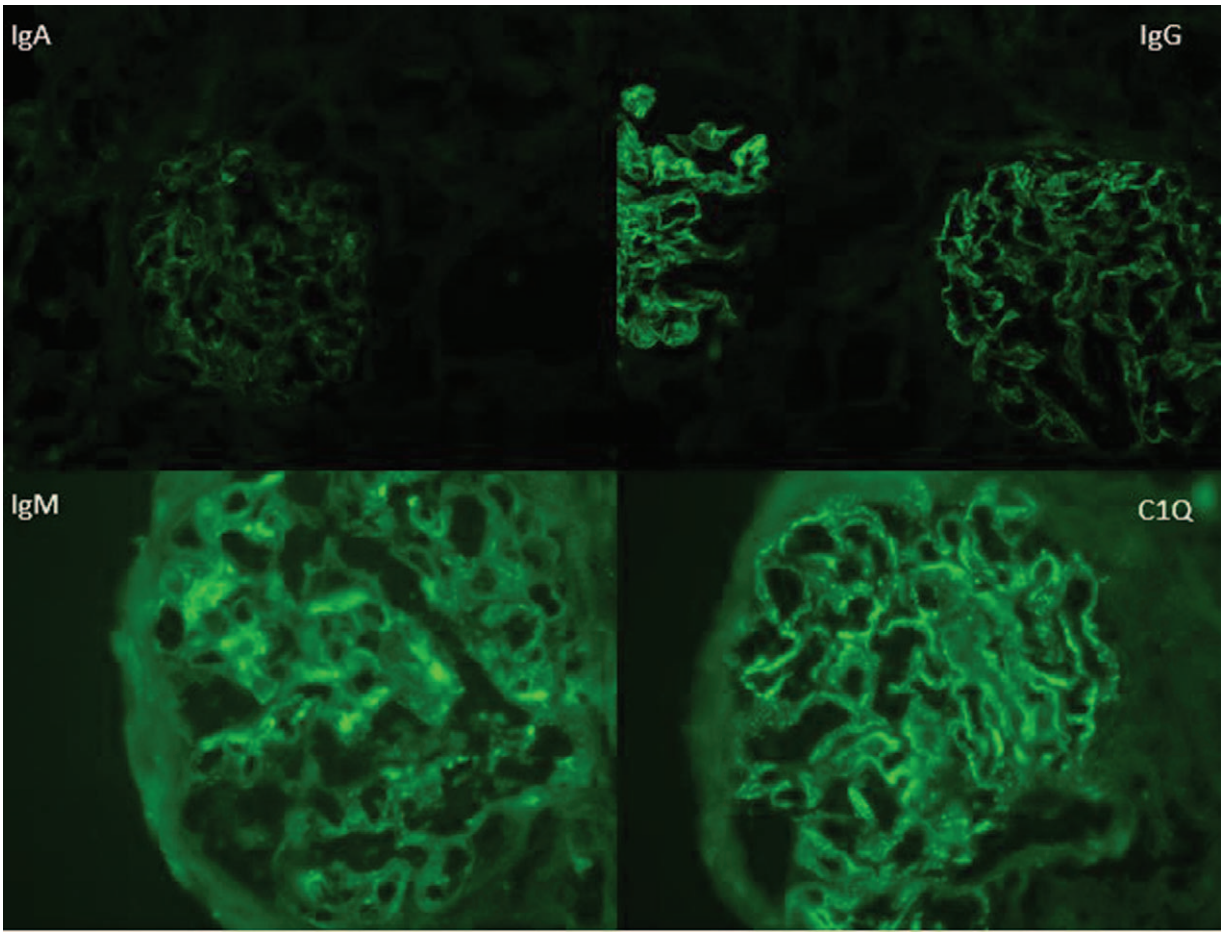

Figure 2. Immunofluorescence of glomerular immune deposits (IgA (×200), IgG (×200), C1Q (×400), IgM (×400)).

this condition. We therefore considered a concomitant parvovirus B19 infection that is well known for its ability to mimic Systemic lupus erythematosus (SLE). Actually, PCR for parvovirus B19 proved positive on the renal biopsy specimen and, therefore, confirmed a renal involvement by parvovirus B19. Thus, we made the clinico-pathological diagnosis of membranous nephropathy with nephrotic syndrome related to a syphilitic and parvovirus B19 coinfection. Shortly after the biopsy, the patient described a resurgence of headaches and loss of hearing in his left ear. A lumbar puncture was performed, and CSF analysis showed a significant protein level of (1158 mg/L), and a high leucocyte count of (74×10^6/L). Cerebrospinal fluid culture was sterile but TPHA was positive. The patient underwent a 14-day course of ceftriaxone based on the diagnosis of neurosyphilis. Interestingly, a dramatic decrease in proteinuria (to an albumin/creatinine ratio of 32.6 mg/mmol) was noted before the introduction of any antibiotic therapy. Outpatient follow-up showed complete resolution of the nephrotic syndrome and regression of the cutaneous lesions. Renal function remained stable.

2. Discussion

SLE affects the renal system in nearly 50% of patients during the first 10 years from the diagnosis, with non-Caucasians being at higher risk.[4] LN is defined as persistent proteinuria greater than 0.5 grams per day or greater than 3+ by dipstick, and/or cellular casts (red cell).[5] According to the Renal Pathology Society/International Society of Nephrology (RPS/ISN) classification, LN can be divided into 6 different classes based upon clinical and histopathological findings,[5] which guide treatment. Class III and IV (respectively focal and diffuse (endo- and extra) -proliferative LN) and class V (membranous LN) are the most clinically important classes because they require immunosuppressive therapy.[6] Despite a wide variety of optic patterns upon biopsy, some features are highly characteristic of LN, such as glomerular deposits of all the immunoglobulins classes (IgG, IgA, IgM, the so-called "full house" pattern) along with deposition of complement components (mainly C1q and C3).[5] The presence of positive ANA or anti-sDNA serology and the typical "full house" pattern on renal biopsy is sufficient to set the diagnosis of LN.[7] In the present case, the "full house" IF pattern was, therefore, highly suggestive of LN, especially considering positive ANA serology. However, several conditions may show a LN pattern on renal biopsy, such as HIV infections or in the so-called "pseudo-lupus nephritis" encountered during infectious endocarditis.[8–10] The secondary stage of syphilis infection may present with a nephrotic syndrome related to the glomerular deposition of immune complex. However, an IF full house pattern is a very uncommon observation in this setting. We found in the literature only 1 similar case of membranous nephropathy secondary to syphilis where IF showed a full house pattern but

with a negative ANA serology.[1] This atypical IF pattern is the key of our case.

The detection of parvovirus B19 viral DNA on renal tissue seems to bring the missing piece as parvovirus B19 is a known cause of pseudo LN with a full house IF pattern of the kidney biopsy.[3] However, parvovirus B19 causes a FSGS, thus the membranous pattern observed in our case could only be due to syphilis. Interestingly, antinuclear antibody positivity with a moderate mottled titer is sometimes observed during parvovirus infection, which is well known to mimic SLE.[3] Thus, identifying an infection as a cause of pseudo-lupus nephritis is crucial in order to prevent potentially harmful treatments (i.e., such as corticosteroids or mycophenolate mofetil which would have been indicated in a proliferative LN).[5] Moreover syphilis nephropathy can have a spontaneous remission as in our case.[11]

In conclusion, clinicians should keep in mind that infections can share clinical and biological features of auto-immune diseases and must pay attention to clinically atypical presentations not to misdiagnose them.

Author contributions

Formal analysis: Samuel Rotman.
Investigation: Eric Jaunin, Sebastien Kissling, Samuel Rotman, Gérard Waeber, Matthieu Halfon.
Resources: Gérard Waeber.
Supervision: Matthieu Halfon.
Validation: Sebastien Kissling, Samuel Rotman, Gérard Waeber, Matthieu Halfon.
Writing – original draft: Eric Jaunin, Sebastien Kissling, Matthieu Halfon.
Writing – review & editing: Sebastien Kissling, Samuel Rotman, Gérard Waeber, Matthieu Halfon.

References

[1] Hannawi B, Raghavan R. Syphilis and kidney disease: a case report and review of literature. Nephrol Rev 2014;4:45–7.
[2] Hartley AJ, Rajakariar R, Sheaff M, et al. Syphilis masquerading as focal segmental glomerulosclerosis. Int J STD AIDS 2014;25:529–31.
[3] Georges E, Rihova Z, Cmejla R, et al. Parvovirus B19 induced lupus-like syndrome with nephritis. Acta Clin Belg 2016;71:423–5.
[4] Kasitanon N, Magder LS, Petri M. Predictors of survival in systemic lupus erythematosus. Medicine 2006;85:147–56.
[5] Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney Int 2004;65:521–30.
[6] Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res 2012;64:797–808.
[7] Petri M, Orbai AM, Alarcon GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64:2677–86.
[8] Haas M, Kaul S, Eustace JA. HIV-associated immune complex glomerulonephritis with "lupus-like" features: a clinicopathologic study of 14 cases. Kidney Int 2005;67:1381–90.
[9] Lee LC, Lam KK, Lee CT, et al. Full house" proliferative glomerulonephritis: an unreported presentation of subacute infective endocarditis. J Nephrol 2007;20:745–9.
[10] Cheng YC, Ku WW, Wong WW, et al. The Case | A 23-year-old Asian man with HIV infection and leg pitting edema. Kidney Int 2015;88:649–50.
[11] Hunte W, al-Ghraoui F, Cohen RJ. Secondary syphilis and the nephrotic syndrome. J Am Soc Nephrol 1993;3:1351–5.