

IgA-dominant infection-related glomerulonephritis (IgA-IRGN) secondary to osteomyelitis in a patient with diabetes and very high cardiovascular risk

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ABSTRACT

Background: *Staphylococcus aureus* is a non-typical cause of glomerulonephritis. **Aim:** We present a case of *Staphylococcus*-related glomerulonephritis secondary to osteomyelitis in a patient with diabetes and very high cardiovascular risk. **Case summary:** A 63-year-old man with diabetic foot ulcer presented to the Emergency Department complaining of right lower limb swelling and vasculitic rash on both lower limbs. He had a history of 2nd right metatarsal joint osteomyelitis due to methicillin-sensitive *Staphylococcus aureus* and had been receiving ciprofloxacin and clindamycin during the last 7 days before presentation. Urine analysis revealed proteinuria and hematuria and 24-hour urine protein of 5 g/day. Renal biopsy showed *Staphylococcus*-related glomerulonephritis with IgA deposits, mostly in the mesangium. **Conclusion:** Although post-infectious glomerulonephritis is well documented, its relationship with *Staphylococcus aureus* osteomyelitis has been rarely reported.

KEY WORDS: *Staphylococcus-associated glomerulonephritis, osteomyelitis, diabetic foot, vasculitic rash, high cardiovascular risk*

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INTRODUCTION

The term post-infectious glomerulonephritis has primarily referred to post-streptococcal glomerulonephritis. Immunocompromised background, most commonly diabetes or malignancy and aging have emerged as risk

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factors of *staphylococcus*-associated glomerulonephritis^{1,2}. *Staphylococcus*-associated glomerulonephritis develops with a concurrent *staphylococcal* infection, such as endocarditis, cellulitis, pneumonia, visceral abscesses, urinary tract infection, and less commonly osteomyelitis³. *Staphylococcus*-associated glomerulonephritis has been reported in 7 diabetic patients with foot ulcer and osteomyelitis^{4,5-8}. Of note, only in 2 patients (1 with diabetes and cervical osteomyelitis and 1 non-diabetic with wrist osteomyelitis) vasculitic rash was evident^{9,10}. We report here the case of *staphylococcus*-associated glomerulonephritis in a patient with diabetic foot ulcer and osteomyelitis.

Case Report

A 63-year-old man at very high cardiovascular risk due to a history of type 2 diabetes, dyslipidemia, atrial fibrillation, smoking (40 pack-years) and diabetic foot ulcer on the right foot presented to the Emergency Department complaining of right lower limb swelling and rash on both lower limbs. He had a history of diabetic foot ulcer (Figure 1) and 2nd right metatarsal joint osteomyelitis (Figure 2) due to methicillin-

sensitive *Staphylococcus aureus*. He had been receiving ciprofloxacin and clindamycin during the last 7 days before presentation. Furthermore, he was on stable doses of alogliptin 25 mg, metformin 1000 mg twice daily, rosuvastatin 40 mg, ezetimibe 10 mg, apixaban 5 mg twice daily and nebivolol 5 mg.

On physical examination, the patient was hemodynamically stable and afebrile. The right lower limb was swollen, and vasculitic rash was evident on both lower limbs. Laboratory results are shown in Tables 1-3.

Renal ultrasonography showed normal findings. Due to lab results (Tables 1-3) and especially proteinuria [protein-creatinine ratio (PCR) = 5390.0 mg/g] and urine sediment, kidney biopsy was performed. Renal biopsy showed diffuse proliferative glomerulonephritis whereas co-dominant IgA and C3 deposits in the mesangium as well along the glomerular basement membranes were observed in immunofluorescence staining (Figure 3).

During hospitalization, patient was administered meropenem and tigecycline. After 14 days of hospitalization, right lower limb edema was improved and vasculitic rash had abated. Inflammatory markers were also improved, and most recent lab tests are shown in the Tables 1-3.

DISCUSSION

We report here a case of *staphylococcus*-associated glomerulonephritis in a patient at very high cardiovascular risk, diabetic foot ulcer and osteomyelitis. As of 24 February 2021, *staphylococcus*-associated glomerulonephritis has been described in 7 patients with diabetes and foot ulcer and osteomyelitis, 2 patients with diabetes and vertebral osteomyelitis, and 1 patient with diabetes and olecranon osteomyelitis^{9,11-12}. IgA and C3 mesangial deposits are common among cases with reported biopsy findings.



FIGURE 1. Diabetic foot ulcer on right foot.

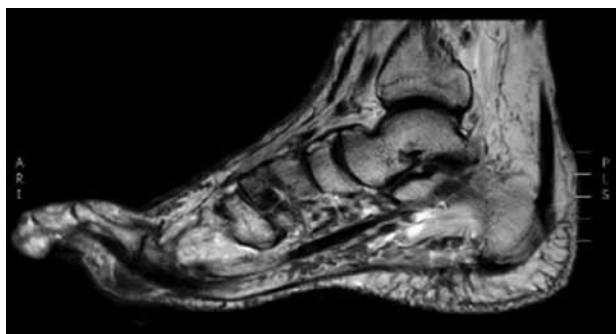


FIGURE 2. Magnetic resonance imaging shows 2nd right metatarsal joint osteomyelitis.

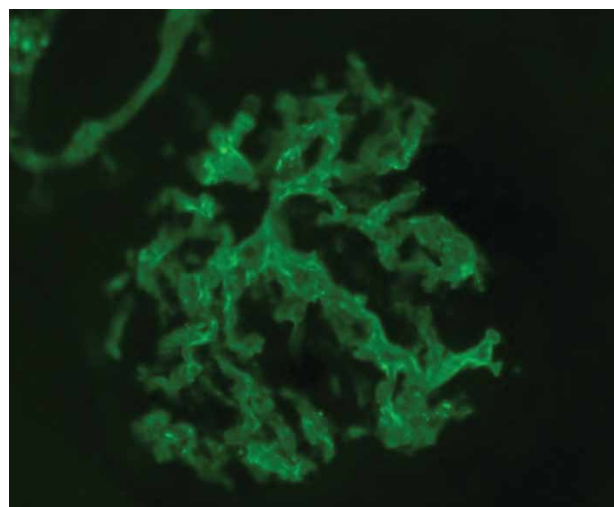


FIGURE 3. IgA deposits, mostly in mesangium in immunofluorescence examination (IgA x 400).

TABLE 1. Hematology and biochemistry laboratory reports of patient on admission, on discharge day and one year later at most recent follow-up

	On admission	On discharge day	One year later at most recent follow-up	Normal values
WBC, / μ l	11,680	11,660	9610	4000-11,000
HCT, %	41.7	45.0	43.4	36-46
Hb, g/dL	13.9	14.6	14.6	12-16
PLT, / μ L	338,000	328,000	198,000	150,000-450,000
ESR, mm/ 1st hour	87	64	11	0-30
Glucose, mg/dL	142	122	118	70-125
Urea, mg/dL	28	44	50	11-54
Creatinine, mg/dL	0.78	1.01	1.43	0.60-1.20
eGFR, ml/min/1.73 m ²	95	78	51	>60
TPR, g/dL	7.80	8.00	N/A	6.00-8.40
Alb, g/dL	3.40	3.60	N/A	3.40-5.00
AST, IU/l	21	23	21	10-35
ALT, IU/l	21	19	19	10-35
Potassium, meq/L	4.47	5.15	4.30	3.50-5.30
Sodium, meq/l	138	138	141	136-146
CRP, mg/L	103	7	3	<6

Abbreviations: WBC; white blood cells, HCT; hematocrit, Hb; hemoglobin, PLT; platelets, ESR; erythrocyte sedimentation rate, eGFR; Estimated Glomerular Filtration Rate, TPR; total protein, Alb; albumin, AST; aspartate aminotransferase, ALT; alanine aminotransferase, CRP; C-reactive protein

TABLE 2 Serological and virological laboratory reports of patient on admission day

	On admission	Normal values
RF, IU/L	23	0-20
Anti-ds DNA	0	0-30
Anti-ENA	0	N/A
IgG, mg/dL	1750	751-1560
IgM, mg/dL	81	46-304
IgA, mg/dL	1020	69-517
IgE, U/ mL	459	0-165
C3, mg/dL	118	79-152
C4, mg/dL	27	16-38
ANCA-C	0	N/A
ANA, U/L	1/160	N/A
ANCA-P	0	N/A
HbsAg	Negative	0-1.00
HCV	Negative	0-1.00

Abbreviations: RF; rheumatoid factor, Anti-ds DNA abs; anti-double stranded DNA antibodies, Anti-ENA; Anti- Extractable Nuclear Antigen, Ig; immunoglobulin, C; complement, ANCA-C; Anti-neutrophil cytoplasmic antibody C, ANA; Anti-nuclear antibody, HbsAg; hepatitis B surface antigen, HCV; hepatitis C virus

However, vasculitis rash is referred in only 2 patients with *staphylococcus*-associated glomerulonephritis and concurrent osteomyelitis⁹⁻¹⁰.

Staphylococcus-associated glomerulonephritis is an immune complex-mediated disease; *staphylococcal* antigens are planted in glomeruli and activate T cells, which results in polyclonal B-cell activation and production of polyclonal immunoglobulin (Ig) A, IgG, IgM and complement activation^{10,13}. IgA antibodies often react with *staphylococcal* antigens¹⁴. This may partly explain why glomerular immune deposits in patients with *staphylococcus*-associated glomerulonephritis usually show abundant IgA deposits with IgG. Patients with *staphylococcus*-associated glomerulonephritis manifest hematuria, proteinuria of varying degrees, a rising serum creatinine, and/or peripheral edema. Cutaneous vasculitis can occur in patients with *staphylococcus*-associated glomerulonephritis, mimicking IgA vasculitis (Henoch-Schönlein purpura) or antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis⁴.

Staphylococcal antigens may activate T cells and polyclonal B cells, and thus induce the production of IgA, IgM and IgG. *Staphylococcal* antigens and IgA coexist in the circulation for prolonged time¹⁰. This prolonged antigenemia increases immune complexes formation and tissue deposition causing glomerulonephritis with IgA dominant

TABLE 3. Urine analysis

Urine analysis	On admission	On discharge day	One year later at most recent follow-up	Normal values
pH	6.0	6.0	5.0	5.5-6.5
Specific gravity	1016	1031	1023	1010-1020
Protein	3+	3+	0	0-20 mg/dL
PCR, mg/g	5390.0	7896.7	-	<150
ACR, mg/g	-	-	415.8	<30
Glucose	0	0	0	0-20 mg/dL
Nitrite	0	0	0	0
WBC/ hpf	8- 10	many	0-2	0-4
RBC, /hpf	6- 8	6-8	2- 4	0-4

Abbreviations: PCR; protein-creatinine ratio, ACR; albumin- creatinine ratio, WBC; white blood cells, RBC; red blood cells, hpf; high power field

or codominant deposits and less frequently vasculitis^{1,10,14}.

Staphylococcus-related glomerulonephritis after osteomyelitis is a rare clinical entity. Diabetes, alcoholism, cancer, or intravenous drug addiction predispose to *staphylococcal* infection^{1,2}. Renal disease can manifest 5-30 days after *staphylococcal* infection. Long-term kidney outcomes vary from complete recovery to persistent kidney function impairment, and end-stage kidney disease (ESKD)². In our case, glomerulonephritis was diagnosed following one week of osteomyelitis treatment. One year later the patient has chronic kidney disease (eGFR= 51 mL/ mL/min/1.73m²) and microalbuminuria.

Diagnosis of *staphylococcus*-associated glomerulonephritis should be taken into consideration when at least two of the following criteria are present: 1) hypocomplementemia (primarily low C3), 2) endocapillary proliferation and exudative glomerulonephritis on light microscopy, 3) C3 (with IgA or IgG) dominant or codominant glomerular staining on immunofluorescence microscopy, and 4) hump-shaped subepithelial deposits on electron microscopy¹⁵. Treatment of the disease is based on antibiotics, control of hypertension, and edema and symptom relief^{1,10}. Patients should be monitored for resolution of active infection, remission of hematuria, reduction in serum creatinine to baseline value, reduction in proteinuria, and if present, resolution of hypocomplementemia.

Staphylococcus-associated glomerulonephritis can be misdiagnosed as C3 glomerulonephritis. In patients with C3 glomerulonephritis, persistent or recurrent active glomerulonephritis over a prolonged period is common and renal disease follows an upper respiratory infection¹⁶. *Staphylococcus*-associated glomerulonephritis can also be misdiagnosed as primary IgA nephropathy as both entities may be triggered by infection. Although hema-

turia, palpable purpura or acute kidney injury might both occur with *Staphylococcus*-associated glomerulonephritis and IgA nephropathy, initial presentation at an older age or in a patient with diabetes favor the diagnosis of post-infectious glomerulonephritis. In addition, the histological pattern of the kidney biopsy provides significant clues for the differential diagnosis, such as the presence of diffuse exudative glomerulonephritis on light microscopy rather than a mesangial proliferative pattern are suggestive of post-infectious glomerulonephritis rather than IgA nephropathy. Serum ANCA was negative and therefore ANCA-associated vasculitis was unlikely.

In conclusion, we present a patient at very high cardiovascular risk, diabetic foot ulcer and osteomyelitis who developed *staphylococcus*-related glomerulonephritis with nephrotic-range proteinuria, edema, palpable purpura and acute kidney injury.

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Institutional Review Board Statement

Considering the non-interventional design of a case-report and the anonymity of the presented data, ethical review and approval were waived for this study.

Informed Consent Statement

Written informed consent has been obtained from the patient to publish this paper.

Data Availability Statement

Data not available on request due to restrictions of privacy.

Conflict of interest

None to declare.

ΠΕΡΙΛΗΨΗ

IgA μεταλοιμώδης σπειραματονεφρίτιδα μετά από οστεομυελίτιδα σε ασθενή με σακχαρώδη διαβήτη πολύ υψηλού καρδιαγγειακού κινδύνου

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Εισαγωγή: Η μετασταφυλοκοκκική σπειραματονεφρίτιδα συνιστά σπάνια κλινική οντότητα. **Σκοπός:** Η περιγραφή ενός περιστατικού μετασταφυλοκοκκικής σπειραματονεφρίτιδας μετά από οστεομυελίτιδα σε ασθενή πολύ υψηλού καρδιαγγειακού κινδύνου με σακχαρώδη διαβήτη. **Περιγραφή περιστατικού:** Ο ασθενής, ένας άνδρας 63 ετών με διαβητικό έλκος στο δεξί πέλμα, προσήλθε στο Τμήμα Επειγόντων λόγω αμφοτερόπλευρου οιδήματος και αγγειϊτιδικού εξανθήματος στα κάτω άκρα. Είχε ιστορικό οστεομυελίτιδας του 2^{ου} μεταταρσίου του δεξιού άκρου ποδός οφειλόμενης σε ευαίσθητο στη μεθικιλίνη χρυσίζοντα σταφυλόκοκκο, για την οποία ελάμβανε σιπροφλοξασίνη και κλινδαμυκίνη τις τελευταίες 7 ημέρες. Από τον εργαστηριακό έλεγχο αναδείχθηκε πρωτεϊνουρία, αιματουρία και αποβολή πρωτεϊνών 5 γρ/ ημέρα σε συλλογή ούρων 24ώρου. Στη βιοψία του νεφρού παρατηρήθηκε μετασταφυλοκοκκική σπειραματονεφρίτιδα με εναποθέσεις IgA κυρίως στο μεσάγγειο. **Συμπέρασμα:** Η σταφυλοκοκκική οστεομυελίτιδα στο διαβητικό πόδι μπορεί σπάνια να επιπλακεί με μεταλοιμώδη σπειραματονεφρίτιδα.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: Μετασταφυλοκοκκική σπειραματονεφρίτιδα, οστεομυελίτιδα, διαβητικό πόδι, αγγειϊτιδικό εξάνθημα, υψηλός καρδιαγγειακός κίνδυνος

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