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Case Report

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An Unusual Case of Seronegative Cryoglobulinemic Glomerulonephritis with Dominant Organized IgA Deposits Associated with Staphylococcal Infection: Casual or Causal Relationship?

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Abstract
Introduction: Cryoglobulinemia refers to the presence of cryoglobulins (CGs) in the serum, encompassing a group of diseases caused by the type of circulating GC. Cryoglobulinemic glomerulonephritis (CryoGN) is the principal manifestation of renal involvement. The diagnosis may be challenging because the hallmark of cryoglobulinemia is the detection of CG in the serum. However, cases of CryoGN without serological evidence of CGs are not uncommon in clinical practice, often diagnosed by anatomopathological findings in the renal biopsy. ***Case Presentation:*** We report the case of an 86-year-old male who developed renal impairment, nephritic syndrome, and nephrotic-range proteinuria, without serological evidence of CGs, associated with staphylococcal bacteremia without apparent focus. Renal biopsy and pathological examination showed a membranoproliferative glomerulonephritis pattern with CD61-negative pseudothrombi. Immunofluorescence microscopy showed atypical IgA-dominant deposits. Electron microscopy revealed amorphous subendothelial and mesangial deposits and organized electrodense deposits within capillary loops (pseudothrombi) with microtubular substructure measuring 20–40 nm in thickness. These findings were consistent with seronegative CryoGN and microtubular organized atypical

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IgA-dominant deposits. ***Discussion:*** In this report, we discuss the clinical, analytical, and histopathological findings of a rare case of CryoGN without serological evidence of CGs. Regarding the etiology that triggered the glomerular disease in our patient, we conducted an exhaustive study in order to determine the underlying cause of CryoGN. At the time of biopsy, the patient had an active staphylococcal bacteremia. There are reports that postulate that staphylococcal antigens drive activation of immune system and in consequence, could cause this rare form of IgA-dominant glomerulonephritis with cryoglobulinemic features. After ruling out other causes of cryoglobulinemia, we discuss a plausible causal relationship of the staphylococcal infection in the pathogenesis of CryoGN in our patient.

Introduction

Cryoglobulins (CGs) are immunoglobulins (Igs) that precipitate or form a gel when exposed to temperatures below 37°C and re-solubilize when rewarmed. Cryoglobulinemia refers to the presence of CGs in the serum (positive results in qualitative tests and/or >0.05 g/L concentration in quantitative tests determined by cryocrit) without pathological involvement. The term cryoglobulinemic disease/syndrome or cryoglobulinemic vasculitis (CryoVasc) is reserved for the clinical manifestation of tissue deposition of these aberrant Igs [1]. Three main types of CGs have been described: type I CGs comprise one monoclonal Ig (typically IgG or IgM and rarely IgA), which accounts for 10–15% of cases and is usually associated with lymphoproliferative disorders. Types II and III are also called mixed cryoglobulinemia (MC) because they consist of two types of Igs [1]. Type II CGs are composed of monoclonal IgM (IgM kappa in more than 90% of cases) with rheumatoid factor (RF) activity and polyclonal IgG, which accounts for 50–60% of cases, and type III CGs are constituted by polyclonal IgM with RF activity and polyclonal IgG, which accounts for 25–30% of cases [2]. Occasionally, it has been reported that MCs were not composed of IgM-IgG but of other Ig combinations, such as IgG-IgG, IgA-IgG, or IgM-IgG-IgA [3, 4]. Autoimmune diseases often cause MC. In addition, infections caused by various pathogens, such as viruses, bacteria, fungi, protozoa, and parasites, may induce MC [5]. Hepatitis C virus (HCV) infection is the most frequent pathogen among them. It must be noted that up to 15% of the cases of cryoglobulinemia have no defined cause and are therefore called "essential" or "idiopathic" cryoglobulinemia.

The clinical manifestations most frequently involve the skin, joints, peripheral nervous system, and the kidney (in approximately 30% of cases) [6, 7]. Cryoglobulinemic glomerulonephritis (CryoGN) is the principal manifestation of renal involvement [5, 7]. Cryoglobulinemia-associated renal disease is challenging to diagnose because the hallmark of cryoglobulinemia is the detection of CG in the serum. However, the cases of CryoGN without the serological evidence of CGs are not uncommon in the clinical practice [8], often diagnosed by anatomopathological findings in the renal biopsy. CryoGN is a distinct pathological entity that can show various proliferative or sclerosing patterns on light microscopy (LM). However, certain features help to distinguish them from other proliferative GN such as the presence of intracapillary CG deposits called "immune thrombi" or "pseudothrombi" in the LM and organized deposit substructure (usually microtubular) on electron microscopy (EM) [9]. CryoGN with IgA-dominant deposits is a rare presentation and has been described mainly in association with underlying IgA-lambda-expressing lymphoproliferative disorder [10, 11]. Herein, we describe an unusual case of seronegative CryoGN with dominant organized IgA deposits associated with staphylococcal infection.

Case Report

Our patient was an 86-year-old Caucasian male, without relevant previous medical history, who was diagnosed in October 2019 with acute myeloblastic leukemia secondary to myelodysplastic syndrome by refractory anemia with excess of blasts type-II (RAEB-II). He was treated with monthly cycles of decitabine and venetoclax with interruptions due to complications of lymph node tuberculosis and COVID-19 infection. In March 2022, he was admitted to hematology for febrile neutropenia associated with methicillin-sensitive *Staphylococcus aureus* bacteremia without apparent focus. Subsequently, nephrology consultation was requested for non-oliguric acute kidney injury (Cr 3.56 mg/dL and urea 148 mg/dL), uncontrolled arterial hypertension (180/90 mm Hg), progressive edema with nephrotic proteinuria (3.7 g/24 h), and micro-hematuria (25 red blood cell per high power field with dysmorphic cells). The physical examination revealed a respiratory rate of 24 breaths/min, an oxygen saturation of 96% while breathing ambient air, pulmonary rales, peripheral pitting edema 3+, and purpura skin associated with burning pain in the lower limbs (skin biopsy not performed). There was no lymph node involvement, splenomegaly, arthralgia, bone pain, or Raynaud´s phenomenon. Complementary tests showed the following: hemoglobin of 9 g/dL, severe thrombocytopenia (43×10^9 L), LDH 385 U/I, normal haptoglobin, reticulocytes 2.53%, blood smear without schistocytes, negative Coombs test, negative RF, and normal ADAMTS-13. The rest of the study showed hypoalbuminemia (2.3 g/dL) without

Table 1. Laboratory findings on admission

		Reference range/unit
WBC	1,240	U/L
Hemoglobin	9	12–16 g/dL
Platelet count	43	10^3/μL
Reticulocyte count	2.53	2–4%
Lactate dehydrogenase	385	135–214 IU/L
Coombs test	Negative	NA
Total protein	6.1	6.4–8.7 g/dL
Serum albumin	2.31	3–5.5 g/dL
Total cholesterol	107	110–200 mg/dL
GOT	14	5–32 IU/L
GPT	32	5–33 IU/L
Urea	148	17–60 mg/dL
Creatinine	3.56	0.6–1.2 mg/dL
C-reactive protein	26.1	0.1–0.5 mg/dL
Procalcitonin	2.88	<0.10 ng/mL
HBs-Ag	Negative	NA
HCV-Ab	Negative	NA
HIV	Negative	NA
Syphilis total antibodies test (IgM/IgG)	Negative	NA
Epstein-Bar virus antibodies (IgM/IgG)	Negative	NA
Herpes virus 1 antibody IgG	Positive	NA
Cytomegalovirus antibody IgG	Positive	NA
SARS-CoV-2 antibody IgG	18	6.7–15 g/L
SARS-CoV-2 antibody IgM	Negative	0.27–2.1 g/L
CH50 (CH50/mL)	41	25–48
C3	10.3	90–180 mg/dL
C4	18.9	10–40 mg/dL
RF	10	<15 IU/mL
ANA and anti-ds-DNA	Negative	NA
PR3/MPO ANCA	Negative	NA
CG	Negative	NA
Anti-GBM	Negative	<1 AI
Anti-PLA2R Ab (ELISA)	Negative	NA
ADAMTS13 activity	68	50–160%
IgG	1,810	800–1,600 mg/dL
IgA	406	70–400 mg/dL
IgM	123	90–180 mg/dL
UPCR	4,300	<20 mg/g
UACR	3,300	<30 mg/g
Urine red blood cells	25	/HPF
24-h urine total protein excretion	3.7	<0.15 g/24-h
SPEP and SIF	No monoclonal bands	NA
Urine protein electrophoresis/IFE	No monoclonal bands	NA, mg/dL
FLC κ	47.2	4.90–13.70 mg/L
FLC λ	36.1	7.60–19.50 mg/L
FLC κ/λ	1.31	0.27–1.67

AI, activity index; AU, arbitrary units; NA, not applicable; WBC, white blood cells; GOT, glutamate-oxaloacetate transaminase; GPT, glutamate pyruvate transaminase; HVBs-Ag, hepatitis B virus surface antigen; HCV-Ab, hepatitis C virus antibody; HIV, human immunodeficiency virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; CH50, complement hemolytic activity-50; C3, complement 3; C4, complement 4; RF, rheumatoid factor; ANA, antinuclear antibody; anti-ds-DNA, anti-double-stranded-DNA antibody; ANCA, antineutrophil cytoplasmic autoantibody; PR3, proteinase 3; MPO, myeloperoxidase; anti-GBM, anti-glomerular basement membrane; anti-PLA2R Ab, anti-phospholipase A2 receptor antibody; Ig, immunoglobulin; UPCR, spot urine protein-to-creatinine ratio; UACR, spot urine albumin-to-creatinine ratio; ELISA, enzyme-linked immuno sorbent assay; ADAMTS13, a disintegrin-like and metalloproteinase with a thrombospondin motif-member 13; HPF, high-power field; SPEP, serum protein electrophoresis; SIF, serum immunofixation; FLC, free light chain; κ, kappa; λ, lambda.

hypercholesterolemia. The 24-h urine protein excretion was 3.7 g with a spot urine protein-to-creatinine ratio and urine albumin-to-creatinine ratio of 4,300 and 3,300 mg/g, respectively. Serum protein electrophoresis with immunofixation (IFE) revealed a polyclonal distribution with hypergammaglobulinemia IgG (1,810 mg/dL) and IgA (406 mg/dL). Urine IFE was negative to monoclonal bands. Serum free light chain kappa (FLCκ) and lambda (FLCλ) were 47.2 mg/dL and 36.1 mg/L, respectively, with kappa/lambda free light chain ratio of 1.31. Complement 3 (C3) was 10.3 (90–180 mg/dL), and complement 4 (C4) was 18.9 (10–40 mg/dL). Other laboratory results included negative antinuclear antibody, negative antineutrophil cytoplasmic antibody, and negative serum CGs in up to 4 studies. Serology was negative human immunodeficiency virus, hepatitis B virus, and HCV. The rest of laboratory test results are shown in Table 1. Abdominal sonography revealed normal-sized kidneys.

A renal biopsy was performed, and 24 glomeruli were examined under LM, 1 of which (4%) was globally sclerotic. The rest showed mesangial expansion, associated with endocapillary and mesangial proliferation with the presence of double contours in the methenamine silver staining (Fig. 1a–d). Focally, the glomerular capillary lumens were occupied by large intraluminal PAS-positive material without platelet aggregates (CD61-negative), compatible with pseudothrombi (Fig. 1a–c). A mild degree of interstitial collagen fibrosis (20%) and tubular atrophy, accompanied by minimal inflammatory infiltrate, predominantly lymphoid without atypia, with patchy distribution and nonspecific histological appearance, was observed. Congo red and thioflavin stainings were negative. The immunohistochemistry technique for DNAJB9 was negative. The frozen tissue immunofluorescence (IF-F) was positive for IgA (3+), IgG (1+), C3 (3+), C4d (3+), lambda (3+), and kappa (3+) light chains without restriction, localized segmentally to the capillary walls with more intense staining in pseudothrombi (Fig. 2a, b). IF-F was negative for IgM, C1q, and fibrinogen. IgG subtyping was not performed. The IF on pronase-digested paraffin-embedded sections showed similar results to that obtained by IF-F. EM showed amorphous subendothelial and mesangial deposits and organized electrodense deposits within capillary loops (pseudothrombi) with microtubular substructure measuring 20–40 nm in thickness (Fig. 2c, d). These findings are compatible with a membranoproliferative glomerulonephritis (MPGN) pattern of injury, with intravascular microtubular atypical IgA-dominant immune deposits with features consistent with CGs.

In a bone marrow biopsy specimen, the proportion of plasma cells was 1.1%, therefore excluding plasma cell myeloma and monoclonal gammopathy of unknown significance. Based on the characteristic LM, IF, and EM findings of the renal biopsy and the clinical characteristics of the patient, seronegative CryoGN with atypical IgA-dominant deposits (IgA-IgG MC) associated with staphylococcal bacteremia was suspected. However, *Staphylococcus* infection-associated glomerulonephritis (SAGN) with cryoglobulinemic features was considered in the differential diagnosis. Antibiotic treatment was continued according to antibiogram, and later, chemotherapy for acute myeloblastic leukemia was initiated. The patient evolved with a progressive decline of kidney function and poor hematological response despite the established treatment, and hemodialysis was initiated. The patient died 9 months later, due to extrarenal infectious causes.

Discussion

Herein, we report an unusual case of HCV-unrelated CryoGN without the serological evidence of serum CGs, typical renal histopathological findings of CryoGN with microtubular organized atypical IgA-dominant deposits, and clinical manifestation of purpuric skin rash on the lower extremities. Renal involvement occurs in 30% of patients with CryoVasc, especially in the context of MCs and HCV [4]. Patients usually present with nephritic syndrome and severe hypertension. CryoGN is a type of immune complex-mediated GN. The generation of CGs depends on the host's predisposition and environmental triggers [12]. Demonstration of serum CGs mainly confirms the diagnosis of CryoVasc. However, histologically, typical cases of seronegative CryoGN are not uncommon. The absence of CGs in the serum is attributed to the practical difficulty of detecting serum CGs, especially in the temperature-sensitive pre-analytical phase or by the presence of small traces of CGs (hypocryoglobulinemia) or cyclical variation in the number of circulating CGs. This makes detection of CGs prone to mistakes or artifacts, producing false-negative results [13]. In our case, serum CGs remained negative on four repeated tests. In a recent publication, Javaugue et al. [8] described a series of 81 patients diagnosed of CryoGN, comparing the etiology, clinical and anatomopathological findings, as well as extrarenal characteristics, treatment, and evolution between two groups with seronegative and seropositive non-hepatitis-associated CryoGN (59 and 22 patients, respectively). The authors showed that non-hepatitis CryoGN was more frequent in the setting of type II CG, and glomerular involvement was rare in type III CG, accounting for less than 10%. However, half of the seronegative group had type I CG based on IF findings of renal biopsies. An interesting fact described by this study is that hematological disorders were the major cause in 89% of CryoGN, and in the seronegative group, despite the absence of detectable CGs, blood and/or urine IFE allowed identification of a monoclonal Ig in around 80% of cases, most commonly IgG. In our patient, we performed a complete hematological study, including BMO and peripheral blood flow cytometry with negative results, thus ruling out hematological disorders as a cause of cryogenesis. On the other hand, our patient had purpuric skin lesions as extrarenal manifestations of a CryoVasc, which is not in agreement with the findings of Javaugue et al. [8] that reported that seronegative CryoGN was more likely a kidney-limited disorder. In contrast, the extrarenal manifestation was common in patients with seropositive CryoGN. Extrarenal manifestations, mainly cutaneous, were present in 64% and were significantly less frequent in seronegative CG.

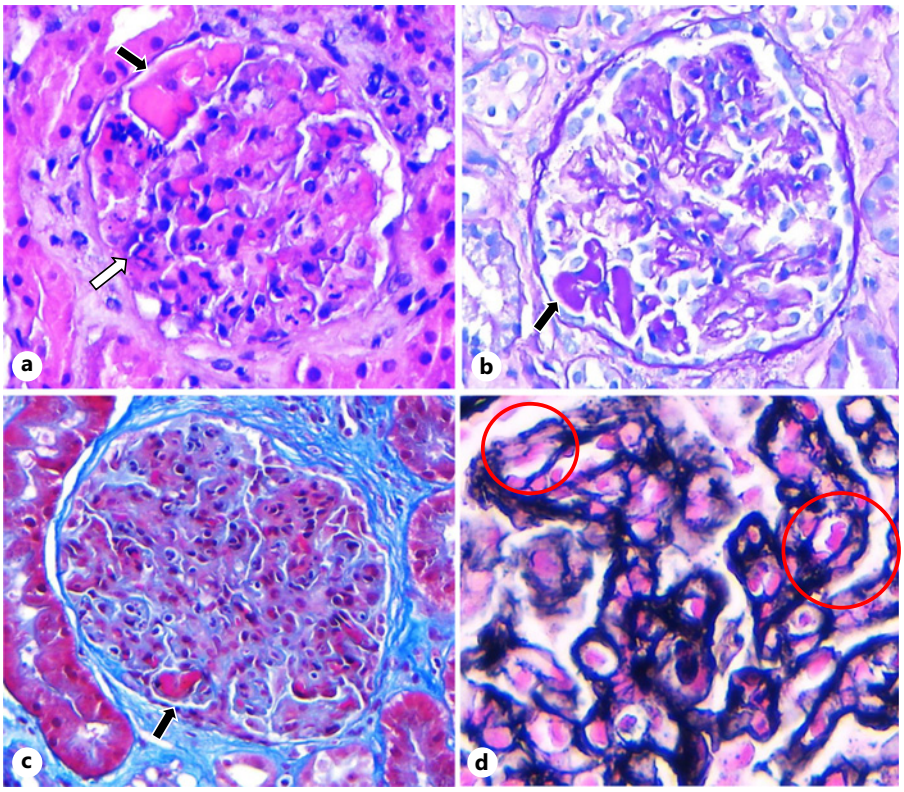

Fig. 1. a Glomeruli exhibiting a lobular appearance due to endocapillary and mesangial proliferation (white arrow) with segmental pseudothrombi (black arrow) (hematoxylin-eosin stain, ×20). **b** Pseudothrombi are positively stained with periodic acid-Schiff (PAS stain, ×20). **c** Fuchsinophilic capillary wall pseudothrombi (Masson trichrome stain, ×20). **d** Double contours of the glomerular basement membranes (red circle) (Jones silver stain, × 20).

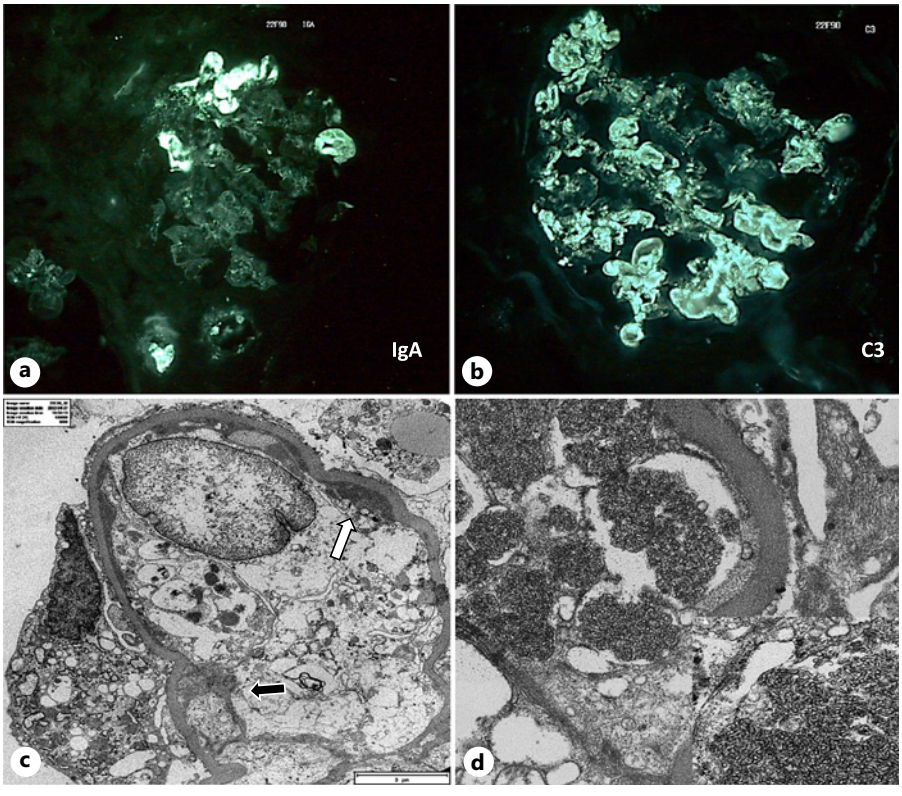

Fig. 2. a, **b** Immunofluorescence staining reveals IgA and C3 positivity in pseudothrombi (original magnification ×4,000). **c** EM shows doubles contours of the glomerular basement membranes (black arrow) and subendothelial electron-dense deposits (white arrow). **d** Intravascular immunotactoid deposits which occlude the vascular lumens (original magnification ×30,000). The image on the right displays a higher magnification view, revealing disorganized arrangement of tangle-like or tubular structures, with mean thickness of 29,94 nm (original magnification ×40,000).

The LM of the renal biopsy showed a pathological pattern of MPGN, the most common morphological pattern in CryoGN, observed in 70–90% of cases [12]. We also observed the presence of "pseudothrombi," a characteristic finding of CryoGN. Javaugue et al. [8] defined this histological finding as one of the diagnostic indices of cryoglobulinemia, even in the seronegative group. Pseudothrombi represent a large deposition of Igs or immune complex bulging into or within the capillary lumen, which can exist not only in CryoGN but also in other diseases, such as lupus nephritis, immune complex- or monoclonal Ig-mediated GN. Our patient did not meet clinical or serological criteria for lupus, and the biopsy findings were not consistent with lupus nephritis ("full-house" pattern in the IF staining was not observed, and endothelial tubulo-reticular inclusions were absent).

The IF-F and IF on pronase-digested paraffin-embedded staining of our patient showed codominance of IgA and C3 (3+) glomerular deposits over polyclonal IgG (1+), without restriction for kappa and lambda light chains. This finding does not concur with the data published by Javaugue et al. [8]; they showed in the IF dominant (84%) and polytypic (70%) glomerular IgM deposits in the seropositive group, while the seronegative CG group presented monotypic deposits in 52% of the cases. CryoGN with IgA-dominant deposits is a rare feature of the CryoGN, generally associated with lymphoproliferative disorder [10, 11]. However, recently, a series of 5 cases of CryoGN with IgA-dominant deposits has been reported in association with active staphylococcal infection at the time of renal biopsy. All cases presented acute renal failure, nephrotic proteinuria, and hematuria, requiring hemodialysis in 4/5 cases, and only one recovered renal function. The biopsies showed exudative GN, and four had focal crescents. All had prominent focal hyaline pseudothrombi and codominant staining for IgA and C3 on IF. Serological testing for CGs was performed in 3 patients and was transiently positive in 1 patient, whereas 2 patients had negative CG assay. The authors conclude that cryogenesis with dominant IgA deposition is associated with staphylococcal infection [14]. Our patient had staphylococcal bacteremia at the time of biopsy. Considering this, we excluded other causes of cryoglobulinemia (hematological disorders, HCV infection, autoimmune diseases, and other infections). We can postulate that the staphylococcal infection was the underlying cause of CryoGN. In this regard, we considered SAGN as a diagnostic possibility. SAGN is associated with glomerular immune complex deposit. In LM, SAGN typically presents as a diffuse proliferative and exudative GN with intracapillary neutrophils, much like poststreptococcal GN and less common injury-induced GN with cryoglobulinemic features. Most cases of SAGN reveal glomerular IgA and C3 (codominant) staining under IF, which is a very important diagnostics feature. Lastly, EM examination for SAGN shows the classic subepithelial humps, which are absent in GN with cryoglobulinemic features [15]. Satoskar et al. [16] compared the clinical characteristics and histological findings of sixteen renal biopsies, 8 cases of SAGN without endocarditis, and eight controls of primary IgA nephropathy (IgAN), to avoid erroneous treatment with immunosuppressive medications. The morphological findings in cases of SAGN are clearly more like those found with IgAN/Henoch-Schöenlein purpura than to those found with other postinfectious GN, including poststreptococcal GN, although there are a few distinguishing features. Under LM, endocapillary hypercellularity is significantly more common in SAGN biopsies than in IgAN. Direct IF reveals a variable intensity of IgA for SAGN biopsies, but IgAN shows strong IgA and mild-to-moderate C3. And EM of IgAN does not show the classic subepithelial humps of SAGN. In addition, Denton et al. [17] reported a case of a patient with persistent methicillin-sensitive *Staphylococcus aureus* infection, Henoch-Schönlein purpura, and GN. The authors described a third clinical presentation of SAGN, termed "staphylococcal superantigen-associated glomerulonephritis," characterized by rapidly progressive glomerulonephritis and nephrotic-range proteinuria, purpura, elevated serum levels of IgA and IgG, and normal complement levels.

Our case presentation was characterized by a staphylococcal septicemia, palpable purpura, slightly elevated serum levels of IgA and IgG, C3 hypocomplementemia. Despite having no evidence of the presence of serum CGs and matching some clinical and histological features, we considered our case a seronegative CryoGN because the pathological findings. First, the MPGN pattern with pseudothrombi in LM is a typical finding in CryoGN, and the most important data are the findings of structured deposits by EM. Ultrastructural examination of our case showed randomly arranged intraluminal microtubular structured deposits. However, EM of SAGN biopsy specimens show small-to-medium-sized mostly mesangial immune-type non-organized deposits and occasionally few subendothelial, small subepithelial, or intramembranous deposits. Subepithelial "humps" may be present in 31% of cases [15]. This is not consistent with the EM findings in our patient; we observe typical deposits composed of short, bent microtubules arranged in a disordered fashion, findings compatible with CryoGN but not with SAGN or IgAN.

On the other hand, if we only consider the findings of microtubule deposition in EM, immunotactoid glomerulopathy should also be suspected. However, in this entity, microtubules are longer and typically arranged in parallel

arrays, with predominantly subepithelial and subendothelial localization and, conversely, positive Ig staining predominantly for IgA rather than for IgG is an unusual finding for immunotactoid glomerulopathy. Regarding other causes of glomerulonephritis with structured deposits, we should consider fibrillary glomerulonephritis. We found a case published in the literature of IgA-dominant GN and seronegative GC with polytypic fibrillar deposits of Igs of subepithelial location in the EM. The striking feature of this case was the presence of negative DNAJB9 [18]. However, fibrillar GN with a DNAJB9 negative test should be considered in the differential diagnosis. In our case, the characteristics of the deposits were different.

The pathogenesis of cryoglobulinemia in the staphylococcal infection setting is unclear. Koyama et al. [19] hypothesized a role for staphylococcal superantigens in glomerulonephritis and staphylococcal infection. The superantigens can cause over-activation of the immune system via interaction with the major histocompatibility complex on antigen-presenting cells, can result in activation of T cells, and may play a role in B-cell activation and autoantibody formation. Li et al. [20] postulated that staphylococcal enterotoxin B could result in B-cell activation and autoantibody formation. In our case, it is unclear whether the staphylococcal infection could have been related to the imbalance in immune tolerance and CG formation or acted as a precipitant of a previously undiagnosed latent condition.

Conclusion

In this case report, we present a patient with seronegative CryoGN and dominant organized IgA deposits associated with *Staphylococcus aureus* infection. Even though serological testing for CGs was negative in our case, the histopathological findings were typical of CryoGN. Therefore, in cases where other more frequent causes of CG have been ruled out, we recommend ruling out an active staphylococcal infection as a potential cause of CryoGN.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines of our Ethics Committee of the Hospital Central Defense Gomez Ulla. Written informed consent was obtained from the patient's next of kin for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare, and the co-authors confirm their co-authorship of this manuscript.

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Author Contributions

José C. De la Flor, MD (primary author), conceived the ideas of the study; performed data collection, data analysis, and interpretation; and provided revisions to scientific content of manuscript. Jacqueline Apaza, MD, provided revisions to scientific content of manuscript and provided access to crucial research components. Francisco Díaz, MD, and Edna Sandoval, MD, contributed to data analysis and interpretation and performed data collection. Francisco Valga, MD, provided revisions to scientific content of manuscript and performed data collection. Daniel Villa, MD, Alexander Marschall, MD, and Michael Cieza, MD, provided revisions to scientific content of the manuscript and provided grammatical revisions to the manuscript. Maria Luisa Abascal, MD, and Andrea Rivas, MD, provided revisions to scientific content of the manuscript.

Data Availability Statement

The data used to support the findings of this study are available from the corresponding author on request (contact J.D.F., josedelaflor81@yahoo.com). All data generated or analyzed during this study are included in this article.

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