

Atypical Infection-Related Glomerulonephritis With “Masked” IgG-Kappa Crystalline Hump-Like Deposits



Lanny T. DiFranza¹, Glen S. Markowitz¹, Vivette D. D’Agati¹ and Dominick Santoriello¹

¹Department of Pathology and Cell Biology, Columbia University Irving Medical Center, New York, New York, USA

Correspondence: Dominick Santoriello, Department of Pathology, Columbia University Irving Medical Center, 630 West 168th Street, VC14-224, New York, New York 10032, USA. E-mail: ds335@cumc.columbia.edu

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INTRODUCTION

The cardinal clinical and pathologic features of acute bacterial infection-related glomerulonephritis (IRGN) include intense staining for C3 in a “starry-sky” pattern on routine immunofluorescence, exudative endocapillary proliferation, low serum C3, subepithelial hump-shaped immune deposits, and a documented history of infection.¹ Other specific types of IRGN include necrotizing and crescentic glomerulonephritis (GN) in the setting of infective endocarditis and membranoproliferative GN in the setting of low-virulence infections of medical hardware (i.e., “shunt nephritis”). Herein, we report a unique case of diffuse proliferative and exudative GN with “masked” IgG-kappa crystalline humplike deposits in a 57-year-old man with pneumonia and negative dysproteinemia workup. The simultaneous resolution of GN and pneumonia in response to antibiotic therapy alone favored an unusual manifestation of acute IRGN.

CASE PRESENTATION

Clinical History and Laboratory Data at Presentation

A 57-year-old Caucasian male presented to an outside hospital with malaise, fevers, and chills associated with rigors and decreasing urine output. He reported initial onset of symptoms approximately 1 month prior, 24 hours after returning from extensive travel to the Middle East, including Saudi Arabia and Iraq. He was diagnosed with pneumonia by his primary care provider and was treated with a 5-day course of ciprofloxacin followed by a 10-day course of levofloxacin. In the emergency department, physical examination revealed blood pressure 174/78 mm Hg, temperature

37.8 °C, oxygen saturation 95%, and pulse rate 102, but no rash, edema, lymphadenopathy, or organomegaly. Chest radiograph showed an area of consolidation with central clearing in the right middle lobe, and chest computed tomography confirmed the cavitary nature of the lesion. He was started on piperacillin and tazobactam for suspected cavitary pneumonia.

Laboratory evaluation (Table 1) was notable for serum creatinine 7.41 mg/dl (estimated glomerular filtration rate 8.1 ml/min per 1.73 m²), serum albumin 4.0 g/dl, white blood cell count 12.1 × 10³/μl with 83% neutrophils, elevated erythrocyte sedimentation rate (117 mm/h), and hypocomplementemia with reduced serum C3 level (24 mg/dl) and serum C4 level (3.5 mg/dl). Urinalysis showed 3+ protein with 10–20 red blood cells/high-power field (hpf) and 5–10 white blood cells/hpf. Anti-nuclear antibody, myeloperoxidase anti-neutrophil cytoplasmic antibody, proteinase 3 anti-neutrophil cytoplasmic antibody, anti-glomerular basement membrane antibody, hepatitis B surface antigen, hepatitis C antibody, and rapid HIV screen were negative. QuantiFERON-TB Gold blood test and blood and sputum cultures (performed after antibiotic therapy) were all negative. A kidney biopsy was performed on the sixth hospital day.

Kidney Biopsy

Sections for light microscopy were stained with hematoxylin and eosin, periodic acid–Schiff, trichrome, and Jones methenamine silver. Seventeen glomeruli were identified, none of which were globally sclerotic. Glomeruli were enlarged and displayed mild diffuse and global mesangial and severe endocapillary hypercellularity with abundant infiltrating neutrophils and monocytes, causing luminal narrowing or obliteration

Table 1. Initial laboratory findings

Parameter	Value (reference range)
SCr, mg/dl	7.41 (0.6–1.3)
eGFR, ml/min per 1.73 m ²	8.1 (>60)
Serum urea nitrogen, mg/dl	86 (6–22)
Serum potassium, mmol/l	5.4 (3.5–5.0)
Serum calcium, mg/dl	8.7 (8.5–10.5)
Serum albumin, g/dl	4.0 (3.0–5.0)
Hemoglobin, g/dl	13.1 (13.5–17.0)
WBC count, ×10 ³ /μl	12.1 (3.9–10.6)
Urine dipstick protein	3+
Urine RBC, /hpf	10–20 (0–2)
Urine WBC, /hpf	5–10 (0–2)
Blood culture	No growth
Urine culture	No growth
QuantiFERON Gold	Negative
ESR, mm/h	117 (0–22)
C3, mg/dl	24 (90–207)
C4, mg/dl	<1.5 (12–45)
ANA	Negative
MPO-ANCA	<1:20
PR3-ANCA	<1:20
Hepatitis C antibody	Negative
Anti-GBM antibody	Negative
Hepatitis B surface antigen	Negative
Serum cryoglobulin	Negative
SPEP and UPEP with IFE	No M-spike

ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; anti-GBM, anti-glomerular basement membrane; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; IFE, immunofixation electrophoresis; MPO, myeloperoxidase; PCR, protein-to-creatinine ratio; PR3, proteinase 3; RBC, red blood cell; SCr, serum creatinine; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis; WBC, white blood cell.

Conversion factors for units: SCr in mg/dl to μmol/l, ×88.4; SUN in mg/dl to mmol/l, ×0.357.

(Figure 1a and b). Trichrome stain delineated numerous subepithelial, humplike, fuchsinophilic immune-type deposits (Figure 1c). No fibrinoid necrosis or cellular crescents were seen. Proximal tubules exhibited diffuse degenerative changes, including luminal ectasia, loss of brush borders, and enlarged nuclei containing nucleoli. There was diffuse interstitial edema associated with patchy mild interstitial inflammation by lymphocytes, plasma cells, monocytes, and rare neutrophils and eosinophils. Mild tubular atrophy and interstitial fibrosis involved approximately 10% of the cortex sampled. Arterioles exhibited mild hyalinosis. No arteritis was identified.

Routine immunofluorescence performed on frozen tissue (IF-F) revealed 3+ granular global mesangial and glomerular capillary wall staining *solely* for C3 in a “starry-sky” distribution (Figure 1d). Ultrastructural examination revealed global mesangial and subepithelial humplike electron-dense deposits without glomerular basement membrane spike formation, as well as scattered small subendothelial electron-dense deposits (Figure 2a). The subepithelial humplike deposits were unusual in that they contained highly

electron-dense crystals forming angulated, geometric shapes admixed with amorphous, moderately electron-dense immune-type material (Figure 2b and c). Examination at high power (>50,000 magnification) revealed a latticelike repeating substructure with 16-nm periodicity within the crystals (Figure 2d). By contrast, the mesangial and subendothelial electron-dense deposits appeared entirely amorphous without identifiable organized substructure. Podocytes displayed 80% foot process effacement. No intracellular podocyte crystals were identified.

In light of the distinctive ultrastructural findings, immunofluorescence was repeated on formalin-fixed, paraffin-embedded tissue sections following pronase digestion (IF-P). IF-P revealed 2+ staining for C3 in a granular global mesangial and glomerular capillary wall distribution (Figure 3). In addition, IF-P unmasked 3+ staining for IgG and kappa light chain, with negative lambda light chain, in a subepithelial glomerular capillary wall distribution corresponding to the organized deposits (Figure 3). IgG subclass staining, which requires frozen tissue, was not performed because of technical constraints given the absence of detectable IgG by routine IF-F. An immunoperoxidase stain for serum amyloid P was performed and was negative.

Diagnosis

Diffuse proliferative and exudative GN with masked IgG-kappa crystalline humplike deposits.

Clinical Follow-Up

In light of the masked, apparently monoclonal IgG-kappa staining in the distribution of the crystalline deposits, a hematologic-oncologic evaluation was obtained. Serum and urine protein electrophoresis with immunofixation failed to detect a monoclonal protein. The serum free kappa-to-lambda light chain ratio was mildly elevated (3.61) but consistent with the degree of renal failure. Serum cryoglobulin testing was negative on 2 separate determinations. A bone marrow biopsy and flow cytometry on peripheral blood showed no evidence of plasma cell neoplasia or B-cell lymphoproliferative disorders.

Given the absence of detectable plasma cell or B-cell clone and the temporal association with suspected cavitory pneumonia, accompanied by fever, tachycardia, and leukocytosis, a diagnosis of atypical infection-related GN was entertained. He was continued on broad-spectrum antibiotics and did not receive any immunosuppressive or immunomodulatory therapy. His symptoms of infection abated. Over the course of the next month, renal function improved (serum creatinine 1.5 mg/dl at 1-month post-biopsy) and serum complement levels normalized. Thirteen

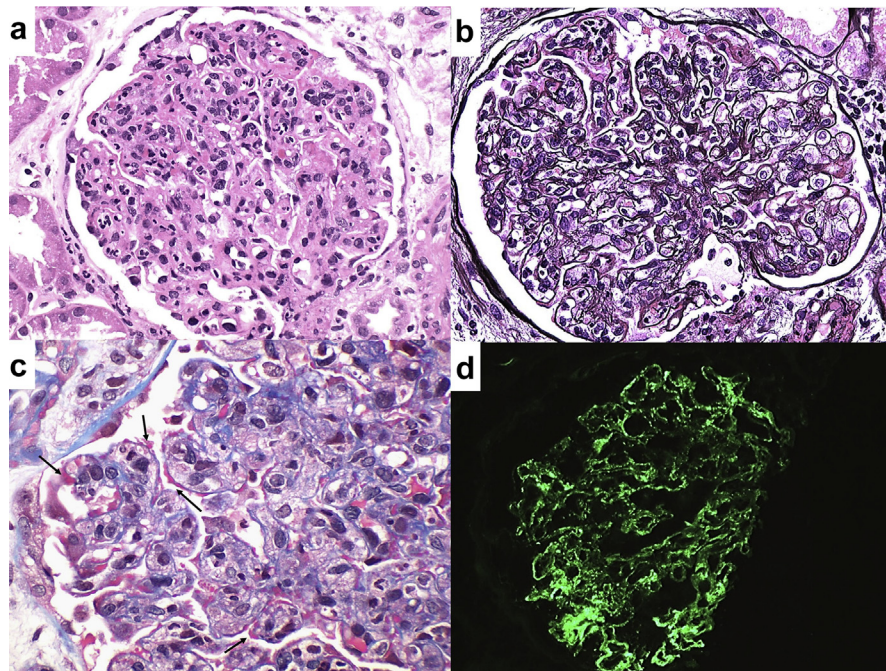


Figure 1. Glomeruli were enlarged and displayed diffuse and global endocapillary hypercellularity with abundant infiltrating neutrophils, causing luminal narrowing or obliteration (a; hematoxylin and eosin, original magnification $\times 400$). A glomerulus exhibiting global severe endocapillary hypercellularity with infiltrating neutrophils and monocytes (b; Jones methenamine silver, original magnification $\times 400$). Trichrome stain delineated numerous subepithelial, hump-shaped, fuchsinophilic immune-type deposits (arrows) (c; Trichrome, original magnification $\times 600$). Immunofluorescence performed on frozen tissue showed intense granular global mesangial and glomerular capillary wall staining solely for C3 (d; immunofluorescence microscopy, original magnification $\times 400$).

months after kidney biopsy, laboratory workup showed serum creatinine 1.21 mg/dl, urinalysis negative for blood and protein, normal serum complements, serum free kappa-to-lambda light chain ratio 2.4, and no evidence of active infection or dysproteinemia.

DISCUSSION

This case demonstrates all of the cardinal clinical and pathologic features of acute bacterial IRGN, namely, intense staining for C3 in a “starry-sky” pattern on routine IF-F, exudative endocapillary proliferation, hypocomplementemia, subepithelial hump-shaped immune deposits, and a documented history of infection (Table 2).¹ Although a causative organism could not be cultured after antibiotic exposure, the clinical resolution of both the GN and pneumonia (including attendant fever and leukocytosis) following antibiotic therapy alone, without resort to immunosuppressive therapy, further supports an infectious etiology. However, the subepithelial humps, which stained strongly for C3 by IF-F and IF-P, contained highly electron-dense crystals exhibiting IgG-kappa restricted staining by IF-P. This unique feature, which has not been described previously in the setting of IRGN, raises intriguing mechanistic questions.

The differential diagnosis for a proliferative GN with monoclonal IgG deposits on routine IF-F includes

immunotactoid GN, the monoclonal variant of fibrillary GN, type 1 cryoglobulinemic GN, and proliferative GN with monoclonal IgG deposits (Table 2).² The monoclonal deposits in immunotactoid GN, monoclonal variant of fibrillary GN, and proliferative GN with monoclonal IgG deposits do not typically require unmasking by IF-P. The deposits in type 1 and some type 2 cryoglobulinemic GN may exhibit organized (including crystalline) substructure and may require IF-P to demonstrate staining for monoclonal immunoglobulin.³ A depressed C4 level, as seen in our patient, is also common in cryoglobulinemia; however, the deposits of type 1 and type 2 cryoglobulinemic

Table 2. Teaching points

- The cardinal pathologic findings of infection-related glomerulonephritis include exudative endocapillary proliferative features, C3-dominant staining in a starry-sky pattern by immunofluorescence, and subepithelial humplike deposits.
- Glomerulonephritis with monoclonal immunoglobulin deposits by IF-F raises a differential diagnosis that includes type 1 cryoglobulinemic glomerulonephritis, immunotactoid glomerulonephritis, monoclonal fibrillary glomerulonephritis, and proliferative glomerulonephritis with monoclonal IgG deposits.
- Pronase immunofluorescence is a valuable diagnostic technique that may be required to unmask staining for immunoglobulin in the setting of deposits with highly organized substructure.
- In this unique case, the simultaneous resolution of glomerulonephritis and pneumonia in response to antibiotic therapy alone favors an unusual manifestation of acute IRGN in which the subepithelial humps may have been enriched for oligoclonal or monoclonal IgG-kappa produced in response to infection.

IF-F, immunofluorescence on frozen tissue; IRGN, infection-related glomerulonephritis.

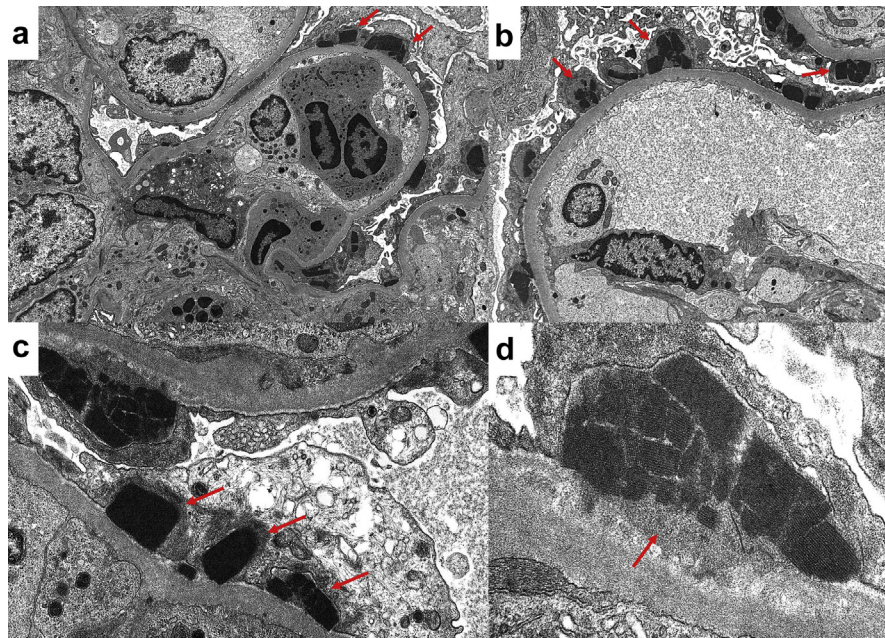


Figure 2. Ultrastructural examination revealed abundant subepithelial humplike electron-dense deposits (*arrows*) without glomerular basement membrane spike formation. An endocapillary neutrophil is seen. There were also global mesangial and scattered small subendothelial electron-dense deposits (not shown) (a; electron microscopy, original magnification $\times 6000$). The subepithelial humplike deposits were unusual in that they contained highly electron-dense crystals (*arrows*) (b; electron microscopy, original magnification $\times 8000$). The crystalline deposits formed angulated, geometric shapes singly or in clusters (*arrows*) (c; electron microscopy, original magnification $\times 25,000$). Examination at higher magnification revealed a latticelike repeating substructure with 16-nm periodicity within the crystals. The crystals were admixed with amorphous, moderately electron-dense immune-type material (*arrow*) (d; electron microscopy, original magnification $\times 60,000$).

GN are typically subendothelial and intraluminal rather than subepithelial. Cryoglobulin was not detected on 2 separate serologic evaluations, and our

patient did not exhibit other clinical features of cryoglobulinemia, such as a vasculitic rash. Nonetheless, we acknowledge the high false negative

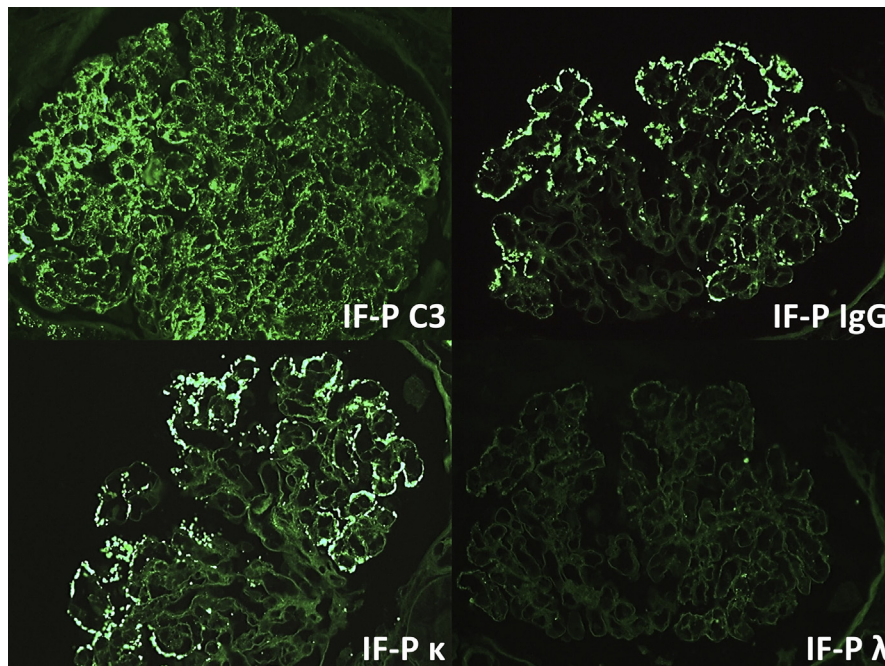


Figure 3. In light of the unusual electron microscopy findings of crystalline subepithelial humplike deposits, immunofluorescence was repeated on paraffin-embedded, pronase-digested tissue sections (IF-P). There was intense (3+) granular global mesangial and glomerular capillary wall staining for C3. In addition, a subset of the subepithelial deposits stained intensely (3+) for IgG and kappa but not lambda (immunofluorescence microscopy, original magnification $\times 400$).

detection rate of serum cryoglobulin testing, especially in type 1 cryoglobulinemia.

IF-P, which uses formalin-fixed, paraffin-embedded tissue and requires enzymatic digestion with protease for antigen retrieval, serves as a useful salvage technique when glomerular sampling for routine IF-F is inadequate.⁴ IF-P is also required to expose sequestered epitopes in the intracytoplasmic crystals of light-chain proximal tubulopathy.⁵ As with light-chain proximal tubulopathy, inaccessibility of antigenic sites within the tertiary structure of the subepithelial crystals likely explains the need for IF-P to “unmask” immunoreactivity for IgG and kappa in our case (Table 2). Larsen *et al.*⁶ reported 16 cases of MPGN with masked monoclonal Ig deposits that would have been misclassified as C3 GN by IF-F alone. Organized substructure was reported in 7 cases, including intraluminal crystals in 1. None of the cases showed subepithelial humps or organized crystalline subepithelial deposits. Fourteen of the 16 patients had a detectable serum paraprotein matching the apparent monotypic immunoglobulin detected by IF-P, and bone marrow biopsy showed evidence of plasma cell dyscrasia or B-cell lymphoproliferative disorder in 13 patients.

Masked monotypic IgG-kappa deposits have also been described in the setting of membranous-like glomerulopathy.⁷ Biopsies show typical morphologic features of membranous glomerulopathy and lack endocapillary proliferation. Organized substructure has not been reported, and there does not appear to be an association with dysproteinemia. In contrast, these patients are typically young females with positive antinuclear antibody, but not fulfilling diagnostic criteria for a well-defined autoimmune/collagen vascular disease.

In the unique case reported herein, the resolution of GN and pneumonia following antibiotic therapy, in the absence of immunosuppression, and the lack of evidence of dysproteinemia, favor an infectious etiology (i.e., atypical IRGN) (Table 2). We hypothesize that the subepithelial crystalline deposits may have been enriched for oligoclonal or monoclonal IgG-kappa produced in response to the infectious stimulus. In this scenario, the monoclonal Ig, which may have been directed against a planted bacterial antigen or part of a preformed circulating antigen-antibody immune complex, may have self-aggregated and precipitated in the glomerular microenvironment, perhaps favored by charge interactions. The absence of crystalline substructure in the mesangial and subendothelial deposits further supports this hypothesis. Indeed, bacterial infections have been implicated in the production of immunoglobulins with unique physiochemical

properties, including cryoglobulins.⁸ Crystalline deposits, such as those observed in our case, have been reported in other reactive conditions, including mixed cryoglobulinemia and lupus nephritis.^{9,51} We cannot exclude, however, the alternative possibility of low-level production of highly nephritogenic IgG-kappa paraprotein by a small clone, below the level of detection by routine screening, perhaps occurring as part of an initially polyclonal immune response. In this scenario, monoclonal IgG-kappa paraprotein may have crossed the glomerular basement membrane, where the concentration and physiochemical properties of the paraprotein favored subepithelial self-aggregation and crystallization. Similar phenomena have been described in a patient with plasma cell dyscrasia.⁵²

In conclusion, we report a unique case of diffuse proliferative and exudative GN with “masked” IgG-kappa crystalline humplike deposits in the setting of pneumonia. The apparently monoclonal composition of the subepithelial crystalline IgG-kappa deposits prompted an extensive workup for dysproteinemia, cryoglobulinemia, plasma cell neoplasia, and B-cell lymphoproliferative disorders, which was negative. The simultaneous resolution of GN and pneumonia in response to antibiotic therapy alone favors an unusual manifestation of acute IRGN in which the subepithelial humps may have been enriched for oligoclonal or monoclonal IgG-kappa produced in response to an antigen-driven infectious stimulus. Despite this excellent outcome, the patient remains under careful surveillance for development of plasma cell neoplasia or B-cell lymphoproliferative disorder.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

[Supplementary References.](#)

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