C3 Glomerulopathy Associated to HIV and Multiple Myeloma: A Challenging Mix

Joana Coutinho[1*], *Lígia Ribeiro*[1], *João Grilo*[1], *Rui Alves Filipe*[1], *Raquel Sá Chorão*[1]
1. Nephrology department, ULS Castelo Branco, Castelo Branco, Portugal

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Abstract
C3 glomerulopathy is a rare histopathologic pattern of kidney injury with an underlying pathophysiology that refers to a dysregulation of the alternative pathway of complement in the glomeruli microenvironment. We report a case of a 67-year-old male referred to nephrology by his general practitioner due to acute kidney injury associated with a two-month-long flu-like syndrome. Primary nephrologist assessment as to the possible causes revealed primary HIV infection already in the seroconversion phase and an IgG kappa monoclonal peak on serum immunofixation with an IgG plus kappa free light chain (kappa FLC) monoclonal peak on urinary immunofixation. Kidney biopsy revealed C3 glomerulopathy with cast nephropathy. A multidisciplinary team with an individualized approach to manage such a challenging mix of immune disturbances was needed to render a positive outcome. The authors describe this case to emphasize the growing relationship between two diseases that tend to become increasingly prevalent as life expectancy of both conditions increases.

Keywords: AIDS-Associated Nephropathy; Complement C3; Glomerulonephritis; HIV Infections; Multiple Myeloma

INTRODUCTION
C3 glomerulopathy is a rare histopathologic pattern of kidney injury diagnosed by kidney biopsy. The disease definition has evolved over the last two decades and is currently defined by the dominant deposition of the third component of complement (C3) in the renal glomerulus in immunofluorescence microscopy. Underlying pathophysiology refers to a dysregulation of the alternative pathway of complement in glomeruli microenvironment.
C3 glomerulopathy has been described associated both to HIV and multiple myeloma.

CASE REPORT
We report a 67-year-old male referred to the nephrology department in December 2022 due to *de novo* altered creatinine levels. The patient had a 10-year history of primary hypertension, well controlled with telmisartan 80 mg daily and bisoprolol 2.5 mg daily, and his creatinine levels in September 2022 were 0.76 mg/dL. He had no personal history of previous surgeries, no history of smoking, abusive drugs or excessive alcohol intake. He had administrative work and reported practicing regular physical exercise. Irrelevant family history.

On first consultation, he reported a two-month-long flu-like syndrome characterized by rhinorrhea, cough, fatigue, anorexia, loss of weight and foamy urine. He had blood tests performed 2 weeks earlier, which were requested by his general practitioner, revealing normocytic normochromic anemia 10.0 g/dL, raised creatinine and urea levels (2.2 mg/dL and 66 mg/dL, respectively) and raised sedimentation rate velocity (130s). On physical examination, he was afebrile, normotensive, pale, well hydrated with no peripheral edema, rhythmic S1 and S2 on cardiac auscultation and no abnormalities on pulmonary auscultation; no other alterations on examination (including skin, genitals and neurological evaluation).
Renal ultrasound showed normal morphology of the kidneys with no calico-pielic dilatations. Urinalysis showed proteinuria ++, hemoglobinuria + and leucocyturia +. Urine culture was negative. Twenty-four-hour urine collection (2.5 L/24h) showed proteinuria of 4.8 g.
See Table 1 for an outline of key laboratory tests performed.

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* **Corresponding Author:** Joana Coutinho | joanacoutinho_@hotmail.com | Hospital Amato Lusitano. Morada – Avenida Pedro Álvares Cabral, 6000-085 Castelo Branco

Table 1. Outline of the main results of the primary analysis panel ordered by the nephrologist.

Parameter	Results (Reference Intervals)
Hemoglobin (g/dL)	8.8 (12.00-17.00)
Leucocytes (10^3/nL)	2.51 (4.00-10.00)
Erythocyte sedimentation rate	130 s (<20)
Uric acid (mg/dL)	9.10 (7.60-8.50)
Creatinine (mg/dL)	3.61 (0.70-1.30)
Blood urea nitrogen (mg/dL)	97 (10.30-49.20)
Total proteins (g/dL)	10.0 (6.30-9.20)
Albumine (g/dL)	3.9 (3.20-4.90)
Triglycerides (mg/dL)	290 (< 250)
Ferritin (mg/mL)	693.7 (22-222)
Imunoglobulin G (mg/dL)	5831 (700-1800)
Imunoglobulin M (mg/dL)	33 (70-400)
Bence Jones proteins (mg/24h)	2894
Beta2 microglobulin (mg/L)	16.4 (1.09-2.53)
Serum protein electrophoresis	Monoclonal peak in gamma region

HIV-1 serology returned positive, confirmed by immunoblot with a viral load of 4.64 million copies per milliliter. The immunoblot showed reactivity for gp120, gp41, p24 and p31, which is consistent with primary HIV infection already in the seroconversion phase. The patient reported being regularly screened for HIV, with the last screening 6 months earlier being negative. The initial CD4+ T-cell count was 115/mm3.

Due to the abnormal monoclonal peak in the gamma region on serum protein electrophoresis (SPEP) (M protein 3.69 g/dL), serum and urinary immunofixation and bone marrow aspirate were ordered. Serum immunofixation revealed an IgG kappa monoclonal peak. Urinary immunofixation revealed an IgG monoclonal peak and another kappa free light chain (kappa FLC) monoclonal peak. Urinary Bence Jones protein (BJ) was positive 2.89 g/24 h. Beta 2 microglobulin was 16.4 mg/L. Bone marrow examination had 33% plasma cells with 3.7% blasts (CD117+/CD34+). Plasma cells were 99% clonal kappa.

Renal involvement and the patient's symptoms could be attributable to both HIV primary infection and multiple myeloma. Due to the rapidly progressive decline of renal function, a kidney biopsy was performed. See Fig. 1 for kidney biopsy images, which were consistent with C3 glomerulopathy with cast nephropathy.

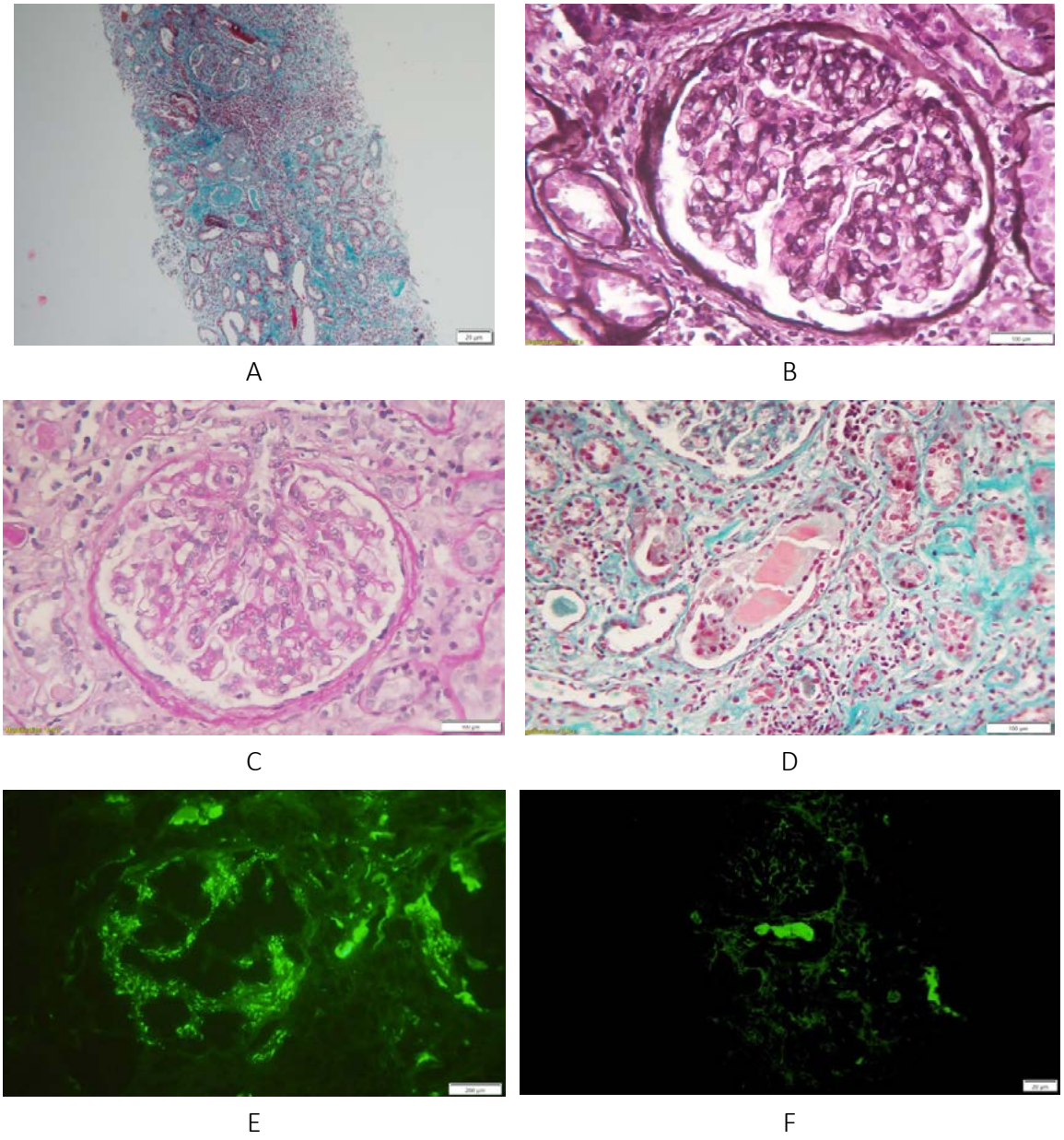

Figure 1. Kidney biopsy images with description – A: a global appreciation showing intense infiltration of interstitium with lymphoplasmacytic cells filling about 50% of the sample, with less than 30% of interstitial fibrosis. B: Optic microscopy revealed proliferative GN with mesangial expansion and hypercellularity. C: segmental duplication of the glomerular basement membrane. D: Tubes were filled with fractured polychromatic PAS-negative cylinders. E and F: Immunofluorescence stained exclusively for C3c +++ with a granular parietal pattern on GBM (E) and free light chain Kappa restriction on tubes (F).

A multidisciplinary team, including nephrology, hematology and infectious disease specialists, was put together for shared decision-making in this complex clinical case. Both conditions weaken the immune system and both therapies have to be individualized in renal dysfunction.

The final decision was to start the patient on opportunistic infections prophylaxis and highly active antiretroviral therapy (HAART) with bictegravir 30 mg + emtricitabine 120 mg + tenofovir alafenamide 15 mg daily, followed 8 days later by dexamethasone 40 mg on days 1, 8, 15, 22 of each cycle; lenalidomide 10 mg daily in 21-day cycles and cyclophosphamide 50 mg daily. The patient was kept as an outpatient, advised on avoiding public places and close contact with potentially sick individuals and given guidance on basic hygiene practices.

Meanwhile, the OncoFISH results were negative for the presence of specific chromosomal rearrangements (1q, 17p, t(4;14), and t(14;16)) in the multiple myeloma (MM)

cells. Eventually the results of genetic testing on alternative pathway complement system mutations (*(CFH, CFHR1, CFHR2, CFHR3, CFHR4, CFHR5, C3, C5, CD46 (MCP), CFB, CFI, THBD, DGKE, ADAMTS13, VTN, PLG, MMACHC, C3AR1*) came back negative, as well as C3 nephritic factor and factor H that were also normal.

The patient showed rapid improvement of all parameters, which reflects on timely treatment and favorable biopsy biomarkers, specifically the absence of crescents, interstitial fibrosis, or glomerulosclerosis. HIV copies rapidly declined, as well as M protein and BJ proteins. The patient developed a salt-losing tubulopathy, easily corrected with calcium and magnesium reposition, which improved over the first year of treatment and resolved definitively afterwards as kidney function recovered to 1.4 mg/dL serum creatinine. HIV copies, creatinine levels and M protein evolution throughout a 2-year timeline can be seen in Table 2.

Table 2. Timeline of patient's most important parameters throughout treatment.

Date / Parameter	February 2023	March 2023	May 2023	August 2023	February 2024	March 2025
HIV copies/mL	464000	52	66	92	41	<20
Serum creatinine (mg/dL)	3.8	2.03	1.53	1.54	1.42	1.39
Urine protein-to-creatinine ratio (UPCR g/g)	2.8	0.9	0.8	0.7	0.3	0.2
κ/λ FLC ratio		14.01	8.491	6.79	1.87	1.62
M protein g/dL	3.7		1.2			0.8

At 2-year follow-up, the patient maintains clinical remission and in this period, he had 1 hospitalization due to food poisoning.

DISCUSSION

Patients with HIV are at a greater risk of multiple myeloma, which seems to 2 to 5-fold the risk as compared to the general population.[1,2] In HIV patients, the M protein is most commonly IgG[3] and their clinical course seems to be more aggressive and less responsive to myeloma treatments.[4] The mechanism underlying HIV-MM association, at least in chronically infected HIV patients, may be that chronic antigenic stimulation of B cells by HIV and other viral antigens, as well as immune dysfunction via selective loss of T cells, may drive a clonal response.[5] Older literature had described several inflammatory cytokines (e.g., interleukin-6 [IL-6]), angiogenic factors (e.g., vascular endothelial growth factor [VEGF] and basic fibroblastic growth factor [bFGF]), which could play a role in the initiation, maintenance, and progression of multiple myeloma (MM) in HIV patients, but the exact mechanism remains unknown.[6]

Renal involvement is common in both HIV and MM. Both diseases have been associated with a variety of histologic patterns and the exact diagnosis can only be achieved through renal biopsy. Histologic pattern may help in understanding the pathologic mechanism of disease and eventually guide therapy. Notably, the described case had favourable biopsy findings, specifically the absence of crescents, interstitial fibrosis, or glomerulosclerosis, which, despite the intense endocapillary proliferative pattern that could reflect a highly active, inflammatory phase of disease, might explain the favourable response of this patient to therapy.

C3 glomerulonephritis (C3GN) has been very sporadically described in the context of HIV-associated glomerulonephritis and is clearly more established in association with monoclonal disease.[7,8] Definitive diagnosis of C3GN associated with HIV must exclude HIV-associated immune complex (IC) kidney disease (HIVICK) and infection-related GN. The overlapping features of such histologic patterns require careful analysis of optic microscopy and immunofluorescence patterns and correlation with laboratory parameters. Isolated strong C3 staining on a kidney biopsy with normal serum C3 levels is more suggestive of C3 glomerulopathy, in which case, a mutation in the alternative pathway of the complement system should be ruled out.[9] Electronic microscopy could also play an important role, but it was not available in this case. Considering that HIV caused such dysregulated activation of the complement system, other abnormalities in the complement pathway, such as factor H, B, I or C3 nephritic factor, should be found, which was not the case. The authors agree that in this case report, MM, specifically the free light chains, were most likely causative for dysregulation of the alternative pathway of the complement system, leading to C3GN with cast nephropathy, but further investigation is required to understand whether HIV could precipitate C3 glomerulopathy.

Limited data exist on which treatment should be started first in the case of concomitant diagnosis. Some authors have suggested that HAART should be started first, as it can reduce M protein, reduce the infectious risk of chemotherapy and possibly even improve chemotherapy efficacy, as has been documented in other cancers.[5,10,11,12] How much time in advance should HAART be initiated has not been clarified. Most authors do agree that HAART should always include a protease inhibitor for its pro-apoptotic effect on myeloma cells.[13]

Regarding myeloma choice of treatment in HIV patients, there is a general agreement that aggressive, combination therapy should be preferred, regardless of OncoFISH results. Autologous stem cell transplantation should be pursued, if indicated, in the general population, but in this specific case, it did not proceed due to persistent borderline CD4+ count levels. There is no practice guideline specifically for HIV infected patients, but some suggest that the chosen regimen should include lenalidomide due to its safety profile, immunomodulatory properties and because it has been proven to inhibit HIV RNA levels, which is crucial for viral persistence.[14]

Infections remain a major limitation to therapy and the leading cause of death. Besides appropriate prophylaxis against opportunistic agents, providing the patient with clinical information regarding preventive measures to reduce infectious disease risk is crucial.

The authors report this case due to its unique course and the novelty of an association that is meant to become more prevalent as HIV patients survive longer and multiple myeloma incidence is raising worldwide. Further research is needed into this complex interplay between HIV and plasma cell disorders, particularly on molecular mechanisms and optimal combination therapy.

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JC: Main responsible for grafting the manuscript.
LR: Co-writer of the manuscript.
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