



CASE REPORT

Nephrotic syndrome associated with metastatic melanoma: a case report

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Abstract

Nephrotic syndrome (NS) may occur after or concomitantly with malignancy. The use of immunosuppressive approaches in patients with cancer and NS is controversial, especially when the association between the pathologies is unclear. The aim of this study was to report the case of a patient with metastatic melanoma who developed NS and to examine the association between NS and neoplasia. A 56-year-old woman diagnosed with right hallux melanoma, removed by marginal resection with no sign of metastasis, developed NS after 6 months without the detection of another associated disease. The histological diagnosis was focal and segmental glomerulosclerosis (FSGS). The patient was older than most patients with FSGS and was treated with immunosuppressive agents (prednisone and cyclosporine) concomitantly with melanoma treatment. Nephrotic syndrome was the first manifestation of metastatic melanoma recurrence in this patient. Proteinuria was controlled adequately after immunosuppression and melanoma treatment. Although NS has been associated with cancer, laboratory and histological markers correlating it with melanoma are needed.

KEYWORDS

immunosuppressive agent, melanoma, neoplasm, nephrotic syndrome, paraneoplasm

1 | INTRODUCTION

Paraneoplastic syndrome is defined by clinical manifestations that are not related directly to the tumor burden, metastasis, or invasion, but are the results of tumor cell secretions such as cytokines, tumor antigens, hormones, and growth factors.^{1,2} These substances can damage the kidneys, generating paraneoplastic glomerulopathy. The prevalence of cancer in patients with nephrotic syndrome

(NS) is 11–13%; it is greater in patients aged >50 years and in men.³

The tumors most commonly associated with this type of paraneoplastic syndrome are carcinomas, mainly pulmonary, gastrointestinal, and of hematopoietic origin (e.g., Hodgkin's lymphoma). Among the most common paraneoplastic glomerulopathies are membranous glomerulonephritis (GN), GN with minimal injury, focal and segmental glomerulosclerosis (FSGS), membranoproliferative GN

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(all manifesting clinically as NS), immunoglobulin (Ig) A nephropathy, and rapidly progressive GN.^{1,4–7}

The diagnosis of paraneoplastic glomerulopathy is suggested by the lack of an alternative NS etiology, the remission of clinical and histological manifestations after complete treatment of the neoplasia by surgical removal or chemotherapy, and neoplasia recurrence associated pathophysiologically with glomerulopathy recurrence. The diagnosis is confirmed, and the treatment and prognosis are determined, by renal biopsy.^{1–3,8}

Glomerulonephritis may develop before, concurrently with, or after cancer; a temporal relationship is suspected when proteinuria occurs 6 months before or after the diagnosis of malignancy, but the risk of cancer persists for more than 10 years after the diagnostic confirmation of glomerulopathy.^{1,2,8,9} Thus, investigation for neoplasms in patients with idiopathic NS, especially those aged >50 years, is extremely important.¹⁰

Paraneoplastic membranous nephropathy (MN) is the most common form of NS in adults, with 70% of cases occurring in men. Its prevalence is 2%–11% in patients with malignancies and up to 22% in patients aged >60 years.^{1,2,11,12} Complete tumor resolution by surgery, chemotherapy, and/or radiotherapy promotes MN and proteinuria remission.^{10,13}

Paraneoplastic FSGS is rare, and the literature contains few case reports describing its association with cancers [lymphoma (particularly Hodgkin's lymphoma), leukemia, thymoma, hematological malignancies, and non-small cell lung carcinoma]. Cancer cells can synthesize growth factors, including fibroblast growth factor and transforming growth factor-beta, which have been associated with the emergence of FSGS in experimental animal models.^{5–7,14–18} FSGS is defined by the involvement of only a few glomeruli (focal) in one glomerular segment (segmental), with areas of glomerular sclerosis, tubular atrophy, and interstitial fibrosis. Extracellular matrix containing different types of collagen and laminin, and IgM and C3 deposits, are present in a few cases. FSGS can be treated with corticosteroids, but this therapy is effective in <50% of patients; thus, immunosuppressants are also indicated. Immunosuppression should be induced as soon as possible, as FSGS may progress to renal failure under inadequate treatment.¹⁹

The choice of treatment for paraneoplastic glomerulopathy depends on the etiology of this condition and may include a low-salt diet and/or water restriction; the use of diuretics, angiotensin-converting enzyme inhibitors, corticosteroids, and/or immunosuppressants (i.e., azathioprine and cyclosporine); and chemotherapy in cases of unresectable tumors or metastasis. Complete tumor resolution promotes the total resolution of paraneoplastic NS. The use of corticosteroids and immunosuppressants

for NS is highly controversial, especially in patients with cancer and cases in which the association of cancer with glomerulopathy is not well established.^{1,2,13,20}

This report describes the case of a patient with FSGS and metastatic melanoma. The diagnostic methods available for the establishment of an association of FSGS with cancer, and the role of immunosuppression as the most appropriate treatment for patients with cancer and NS, are discussed.

2 | CLINICAL CASE

A 56-year-old married female farmer from Bahia, Brazil, sought hospital service in January 2013 for an ulcerated lesion on the right first toe that had appeared 1 year previously. A biopsy of the lesion identified invasive malignant melanoma (Breslow depth =5.8 mm, Clark level =V) with marginal involvement. Nine days later, amputation of the right hallux with margin resection was performed. On physical examination, the patient was conscious but feverish. At this time, no abnormality was detected on pulmonary, cardiovascular, abdominal, and neurological examination.

In July 2013, the patient was admitted due to diarrhea, anasarca, dyspnea on minor exertion, orthopnea, dry cough, and hematuria. Physical examination revealed lower-limb edema and ascites. The diagnostic hypothesis of NS was made and investigated. The following parameters were obtained: urea, 57 mg/dl; creatinine, 1.22 mg/dl; glomerular filtration rate (GFR) measured by 24-h urine, 40.0 ml/min/1.73 m²; uric acid, 6 mg/dl; Na, 142 mEq/L; K, 5.6 mEq/L; bicarbonate, 28 mmol/L; ionic Ca, 4.7 mg/dl; P, 4.2 mg/dl; parathyroid hormone, 135 pg/ml; vitamin D, 8 ng/ml; blood glucose, 79 mg/dl; glycated hemoglobin, 5%; 24-h urinary protein excretion, 10.76 g; and serum albumin, 2 g/L. Investigations conducted for differential diagnosis revealed the following: native anti-DNA antibodies, 16 U/ml; antinuclear antibody (ANA) homogeneous nuclear standard with titer 1/160 and nucleus 1/160; fibrinogen, 1067 mg/dl; rheumatoid factor, 11.9 IU/ml; negativity for *Treponema pallidum*, hepatitis B and C, and HIV; nonreactivity for anti-viral capsid antigen IgM and IgG; C3 complement fraction, 147 mg/dl; C4 complement fraction, 31.1 mg/dl; and immunofixation with the absence of anomalous proteins. A renal biopsy was performed to determine the etiology of NS and revealed FSGS (tip lesion variant; Figures 1–3) with focal regenerating acute tubular necrosis and negative immunofluorescence.

Treatment with prednisone (0.5 mg/kg) and cyclosporine (100 mg every 12 h) was initiated in August 2013. After 3 months of this treatment, reduction in the proteinuria was observed (24-h urinary protein excretion <1 g).

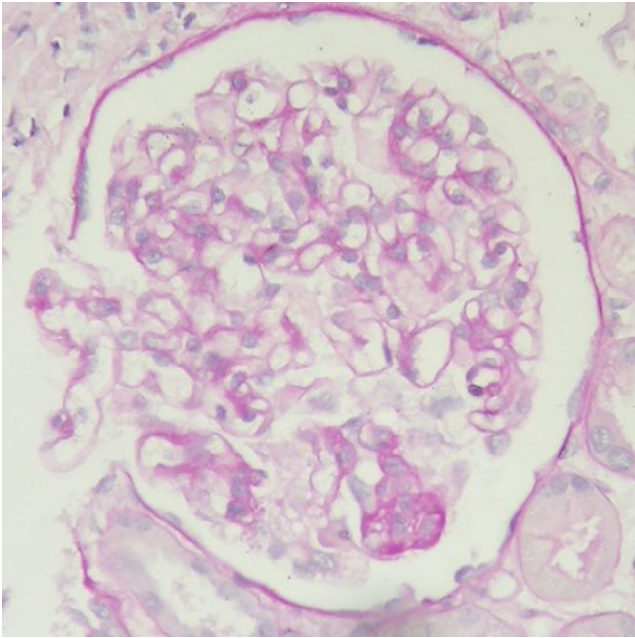


FIGURE 1 Glomerulus with segmental and focal sclerosis in a patient with melanoma (period acid–Schiff staining, 400× magnification)

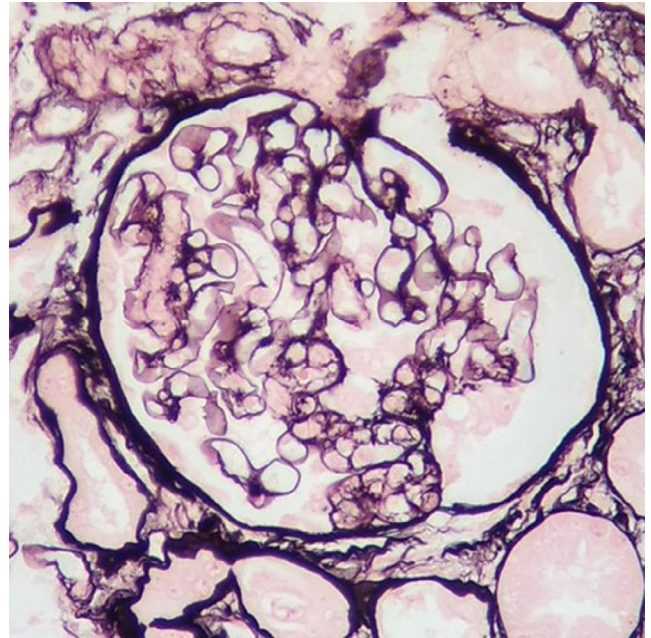


FIGURE 3 Glomerulus with segmental and focal sclerosis in a patient with melanoma (periodic acid–silver methenamine staining, 400× magnification)

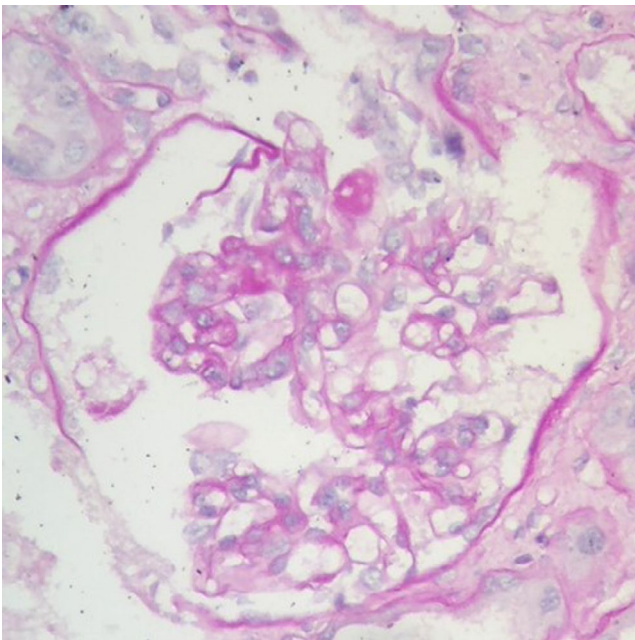


FIGURE 2 Glomerulus with segmental and focal sclerosis and a tip lesion in a patient with melanoma (period acid–Schiff staining, 400× magnification)

In March 2014, when she presented to the hospital due to the appearance of a right foot injury, this lesion was resected, and the possibility of metastatic lesions was investigated. In October 2014, the patient presented with right inguinal lymph-node enlargement. An ultrasound examination was performed and revealed focal cortical

thickening of an inguinal lymph node, which measured 13×6 mm, and diffuse cortical thickness of a globular inguinal lymph node, which measured 15×9 mm. Aspiration of a right inguinal lymph node revealed neoplastic cells. Chest computed tomography performed for staging detected micronodule lung pulses, non-specific neural plate and pleural thickening, and an increased number and irregularity of the left axillary lymph nodes. Thus, right inguinal lymphadenectomy, right inguinal radiotherapy for 4 months, right hallux radiotherapy, and carboplatin and paclitaxel chemotherapy were instituted for four months. Due to a new elevation of urinary protein excretion ($2.5 \text{ g}/24 \text{ h}$) and tumor recurrence, the cyclosporine treatment was prolonged, with gradual withdrawal and cessation after 19 months (on April 2015). The patient was discharged with outpatient follow-up and remains asymptomatic. Currently, her 24-h urinary protein excretion level is $<0.4 \text{ g}/24 \text{ h}$ and her GFR is $92 \text{ ml}/\text{min}/1.73 \text{ m}^2$ (Figures 4 and 5).

3 | DISCUSSION

The case reported here exemplifies a rare association of FSGS with malignant neoplasia, specifically melanoma. The onset of NS occurred months after the diagnosis of melanoma in the right hallux region, with a clear association, but no evidence of metastasis at that time. Due to the clinical picture of hematuria, anasarca, and symptoms thereof (i.e., orthopnea and dyspnea on exertion),

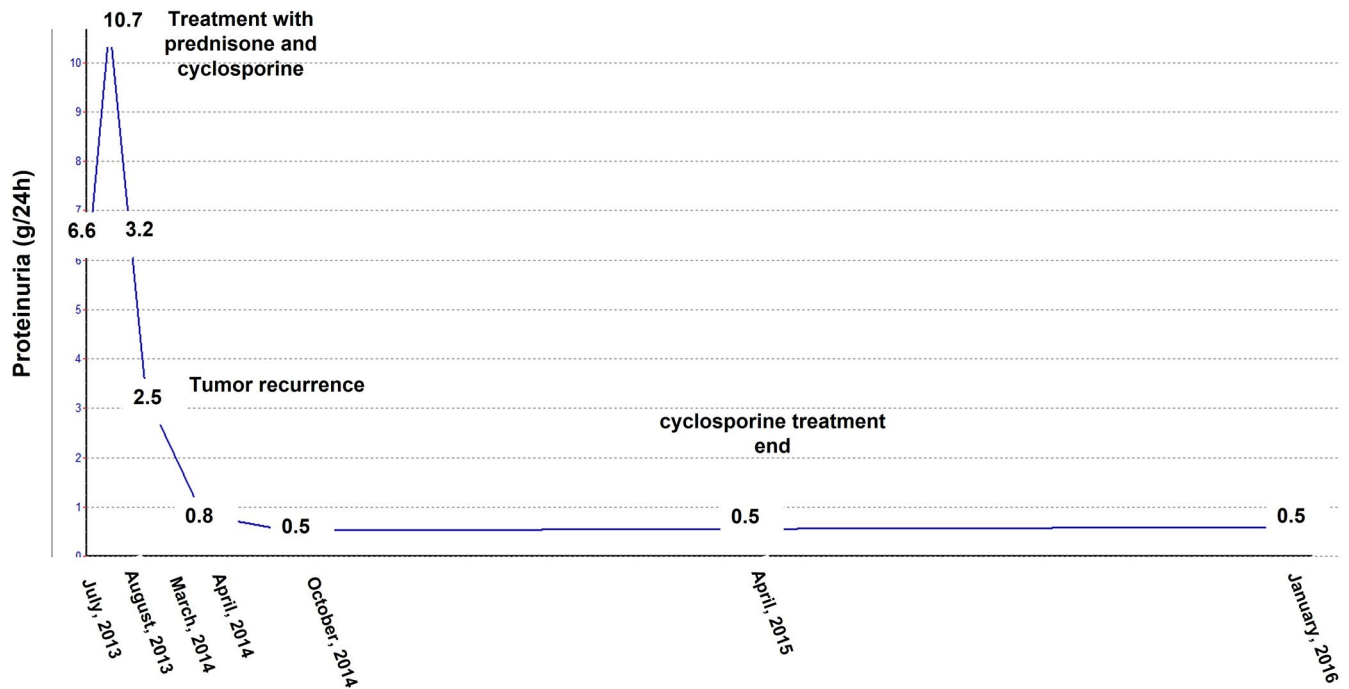


FIGURE 4 Evolution of proteinuria in a patient with melanoma and glomerulus with segmental and focal sclerosis

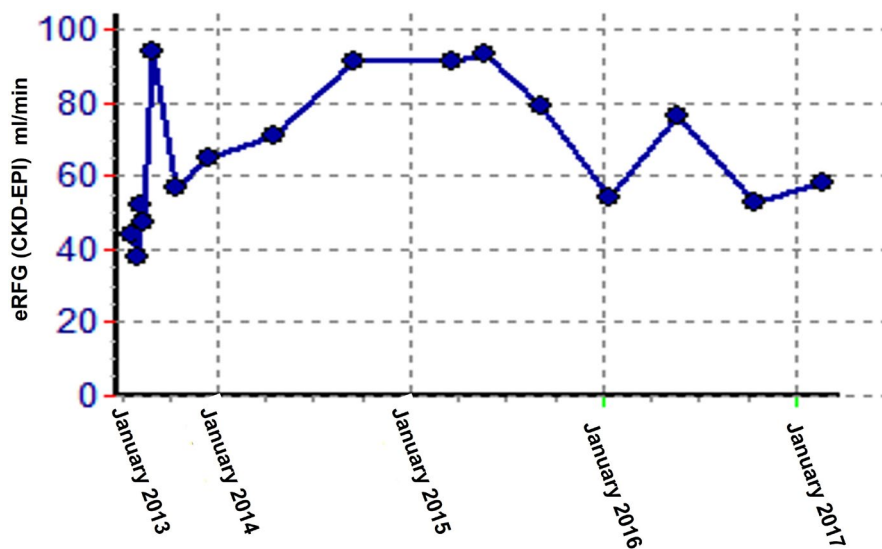


FIGURE 5 Evolution of estimated glomerular filtration rate (CKD-EPI) in a patient with melanoma and glomerulus with segmental and focal sclerosis

diagnostic tests were performed to confirm the presence of NS with proteinuria (24-h urinary protein excretion >3.5 g) and hypoalbuminemia. The etiology of NS was then investigated to guide treatment. Extensive complementary investigation revealed no contributing factor other than cancer. The association of melanoma with NS in this case became even more evident when the patient's proteinuria worsened under cyclosporine treatment, with local tumor recurrence, inguinal lymph nodes, and pulmonary metastasis. Symptom improvement was achieved with lymphadenectomy, right inguinal and right hallux

radiotherapy, and adjuvant chemotherapy with carboplatin and paclitaxel.

A therapeutic dilemma in this case was the initiation and maintenance of cyclosporine treatment to control the paraneoplastic syndrome in a patient with tumor recurrence. In this case, we used prednisone and cyclosporine, despite the patient's immunosuppression due to the neoplastic process. The initiation of immunosuppressant therapy as early as possible has been recommended, with the aim of avoiding the development or aggravation of kidney failure (and thus prognosis

deterioration), which is expected in cases of unsuitable FSGS treatment.^{19,20} Cyclosporin withdrawal was performed when the patient's proteinuria reached a non-nephrotic level, confirming FSGS control. Curative treatment of the melanoma was not possible, but the disease was controlled with the combined use of corticosteroids and cyclosporine. NS remission was achieved without the complications associated with such cases, and the patient's quality of life was improved during the period of melanoma treatment.

4 | CONCLUSIONS

This case highlights the importance of investigating possible paraneoplastic causes of NS, especially in the presence of associated risk factors. The literature contains little information on the association between FSGS and cancer, especially melanoma. Thus, serum biomarkers and histological evidence for this association need to be identified. The use of immunosuppressive therapy in such cases remains controversial, especially when cancer has relapsed or the patient requires chemotherapy, and treatment approaches need to be individualized. Our patient clearly benefitted from immunosuppression, especially with regard to the preservation of renal function and NS control during adjuvant tumor treatment.

CONFLICT OF INTEREST

The authors declare that they have no competing interest.

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AUTHOR CONTRIBUTIONS

All the authors were involved in the drafting and/or revision of the article and approved the final version to be published.



CONSENT

The authors confirm that the patient has provided written informed consent to the submission of this case report, in accordance with the journal's patient consent policy.

DATA AVAILABILITY STATEMENT

Data available on request from the authors The data that support the findings of this study are available from the corresponding author upon reasonable request.

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