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Bosutinib and Membranous Nephropathy in Chronic Myeloid Leukemia: Coincidence or Drug-Related Injury?

Bosutinib y Nefropatía Membranosa en Leucemia Mieloide Crónica: ¿Coincidencia o Lesión Relacionada con el Fármaco?

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RESUMEN

Los inhibidores de tirosina quinasa (ITKs) han mejorado significativamente los resultados en la leucemia mieloide crónica (LMC), aunque los efectos adversos renales son cada vez más reconocidos. Se describe un varón de 32 años con LMC que desarrolló proteinuria en rango nefrótico dos años después de iniciar tratamiento con bosutinib. Los análisis mostraron creatinina sérica elevada, hipoalbuminemia y proteinuria grave. La biopsia renal reveló nefropatía membranosa con positividad granular gruesa para PLA2R e IgG4, acompañada de inflamación intersticial compatible con nefritis túbulo-intersticial aguda. El bosutinib se suspendió temporalmente y luego se reanudó bajo supervisión multidisciplinaria estrecha, asociado a rituximab y tacrolimus. A los seis meses, la función renal y la proteinuria mejoraron significativamente. Este caso cuestiona el impacto del bosutinib en el daño glomerular y tubular en el riñón. El reconocimiento temprano, la biopsia renal y el manejo multidisciplinario individualizado son esenciales. En casos seleccionados, la continuación del ITK junto con terapia inmunomoduladora adyuvante puede ser una estrategia factible.

Palabras Clave: Bosutinib; Leucemia mieloide crónica; Inhibidores de tirosina quinasa; Nefrotoxicidad; Nefropatía membranosa

ABSTRACT

Tyrosine kinase inhibitors (TKIs) have significantly improved outcomes in chronic myeloid leukemia (CML), but renal adverse effects are increasingly recognized. We report a 32-year-old male with CML who developed nephrotic-range proteinuria two years after starting bosutinib. Laboratory tests showed elevated serum creatinine, hypoalbuminemia, and severe proteinuria. Renal biopsy revealed membranous nephropathy with coarse granular PLA2R and IgG4 positivity, accompanied by interstitial inflammation consistent with acute tubulointerstitial nephritis. Bosutinib was temporarily discontinued and then resumed under close multidisciplinary supervision, combined with rituximab and tacrolimus. At six months, renal function and proteinuria had significantly improved. This case questions the impact of bosutinib on glomerular and tubular damage in the kidney. Early recognition, renal biopsy, and individualized

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multidisciplinary management are crucial. In selected cases, continuing TKI with adjunct immunomodulatory therapy may be a feasible strategy.

Keywords: Bosutinib; Chronic myeloid leukemia; Tyrosine kinase inhibitors; Nephrotoxicity; Membranous nephropathy

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by the BCR-ABL fusion gene resulting from the Philadelphia (Ph) chromosome translocation. Although renal involvement in CML is rare, paraneoplastic glomerulopathies or treatment-related nephrotoxicity can occur. Adverse drug reactions (ADRs) affecting the kidneys due to tyrosine kinase inhibitors (TKIs) used in CML are relatively uncommon, and no standardized management protocol currently exists for these complications[1].

The introduction of the first-generation TKI, imatinib, significantly improved prognosis and overall survival in patients with CML. Subsequently, second-, third-, and fourth-generation TKIs, including bosutinib, dasatinib, nilotinib, ponatinib, and asciminib, further increased response rates and enabled individualized treatment selection [2,3]. Less than 4% of bosutinib is recovered in the urine, with approximately 1% excreted unchanged, indicating minimal renal clearance of the active drug and increased risk of accumulation and nephrotoxicity in patients with impaired renal function [4].

TKIs can induce a range of glomerular diseases, including IgA nephropathy, minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), thrombotic microangiopathy (TMA), and membranous nephropathy (MN), as well as tubular/interstitial injuries such as acute tubular necrosis (ATN) or acute tubulointerstitial nephritis (TIN). MN is particularly rare in patients with CML and usually manifests several years after diagnosis [1]. Here, we present a unique case of simultaneous MN and acute TIN in a patient with CML receiving long-term bosutinib therapy, highlighting the diagnostic challenges and therapeutic considerations.

CASE PRESENTATION

A 32-year-old male patient diagnosed with CML was initially treated with imatinib 600 mg daily. Following an insufficient response at 8 months, the regimen was switched to bosutinib 400 mg daily. Two years into the bosutinib therapy, the patient was referred to the nephrology clinic for newly onset proteinuria. Laboratory evaluation revealed a serum creatinine level of 1.76 mg/dL, an estimated glomerular filtration rate (eGFR) of 50 mL/min/1.73 m², proteinuria of 14536 mg/g, albuminuria of 8377 mg/24h, and a serum albumin level of 16.50 g/L. Urinalysis demonstrated 4+ proteinuria, with a spot urine protein-to-creatinine ratio of 12716 mg/g and an albumin-to-creatinine ratio of 7848 mg/g, consistent with nephrotic-range proteinuria. The hemogram showed an eosinophilia of 5.7%. Microscopic examination of the urine sediment for eosinophils was not performed. The patient had no history of diabetes mellitus or hypertension.

A percutaneous renal core biopsy was performed. Light microscopy revealed diffuse thickening of the glomerular basement membranes (GBM) in all glomeruli (**Figure 1**). Crescent formation and glomerular necrosis were absent. Hematoxylin and Eosin staining demonstrated diffuse GBM thickening (**Figure 1A**), Masson trichrome staining revealed fine eosinophilic granular deposits (**Figure 1B**), and Jones methenamine silver staining showed characteristic spike formations along the GBM (**Figure 1C**). Congo red and crystal violet stains were negative for amyloid deposition. Immunohistochemical staining for myeloperoxidase showed no evidence of tumor cell infiltration in the interstitium. Further immunohistochemical analysis demonstrated linear C4d positivity along the GBM (**Figure 1D**) and coarse granular positivity for PLA2R (**Figure 1E**) and IgG4 (**Figure 1F**) along the GBM. DNAJB9 staining, used to differentiate from fibrillary glomerulonephritis, was negative. The interstitium showed moderate inflammatory infiltration predominantly composed of lymphocytes and polymorphonuclear leukocytes, with focal tubular epithelial infiltration (**Figure 2A-2B**). Immunofluorescence could not be evaluated due to the presence of only medullary tissue. Based on these findings, the biopsy was reported as membranous nephropathy concomitant with acute tubulointerstitial nephritis.

Figure 1: Diffuse Thickening of the Glomerular Basement Membranes (GBM) and Corresponding Immunohistochemical Staining Results.

Fig 1A: Diffuse thickening of the GBMs (Hematoxylin and Eosin, X200)

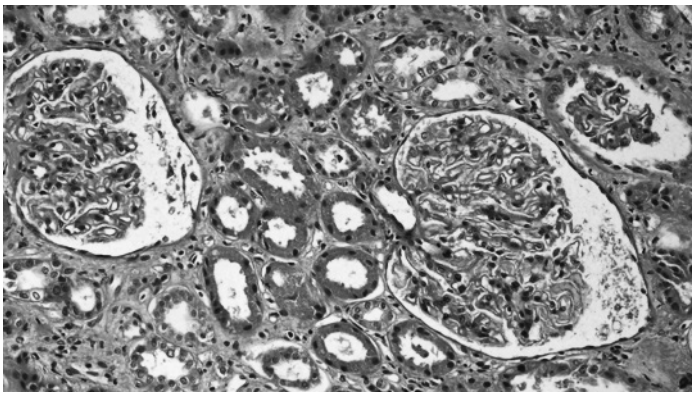


Fig 1B: Eosinophilic deposits along the thickened GBMs (Masson's Trichrome, X400)

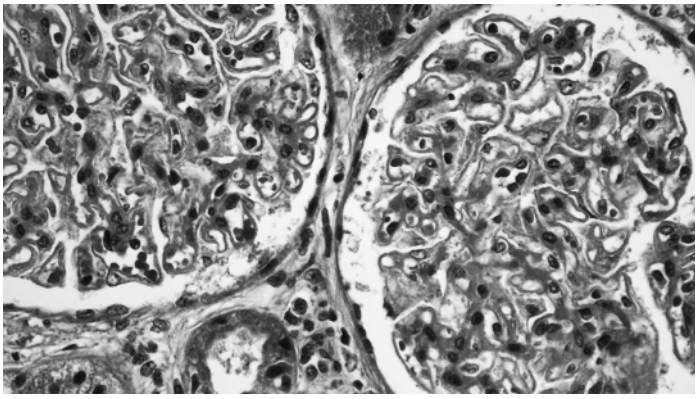


Fig 1C: Spikes formation within the thickened GBMs (Jones Hematoxylin Eosin, X400)

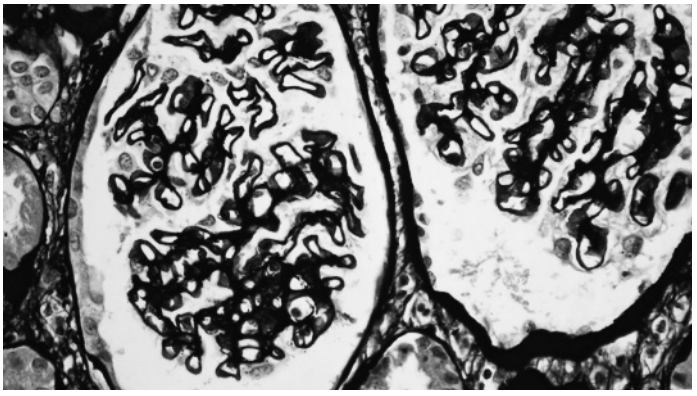


Fig 1D: C4d positivity along the GBM (X200)

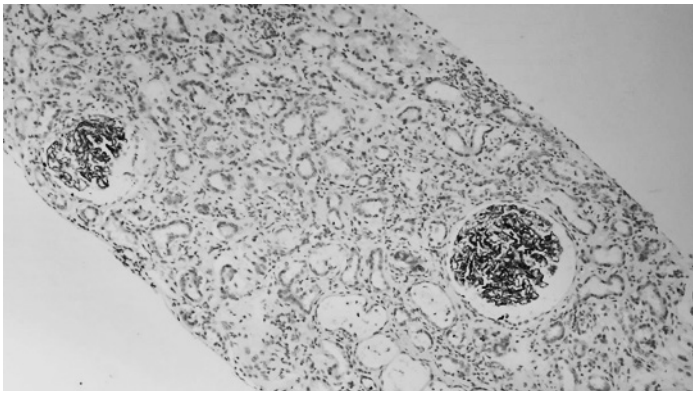


Fig 1E: PLA2R positivity along the GBM (X100)

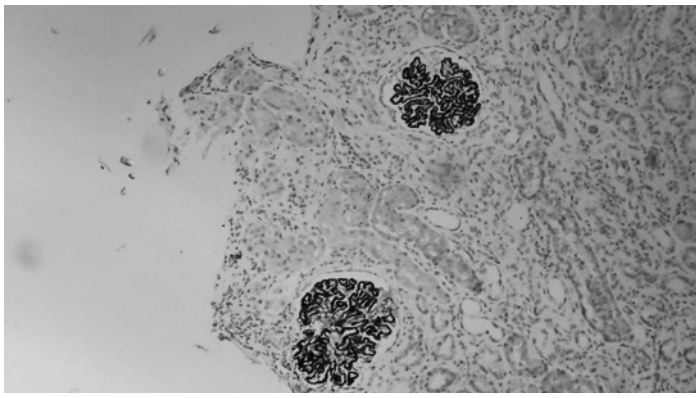


Fig 1F: IgG4 positivity along the GBM (X100)

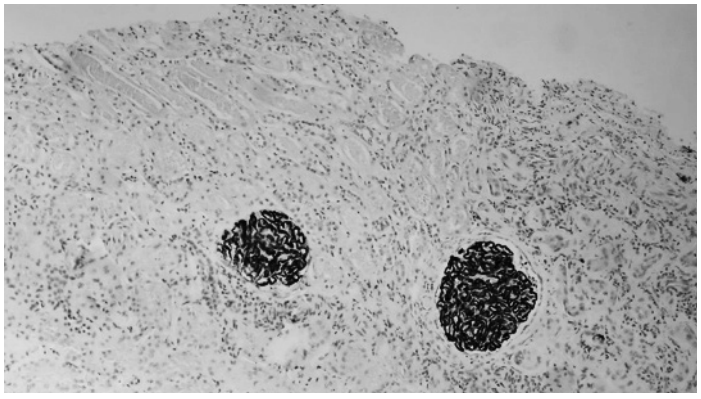


Figure 2: Interstitial Inflammation Infiltrating the Tubular Epithelium.

Fig 2A: Inflammatory cells in the interstitium have infiltrated some tubules, entering the lumen

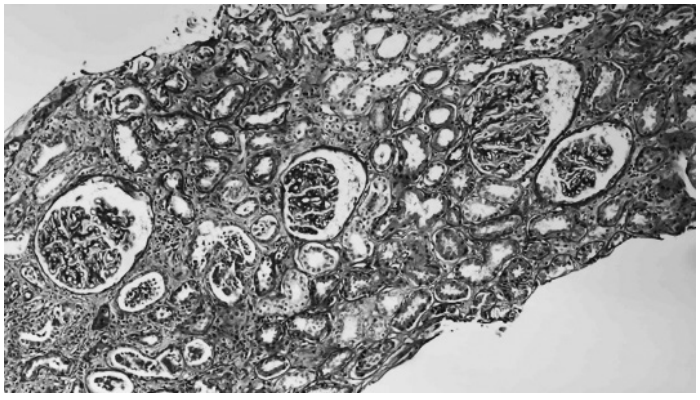
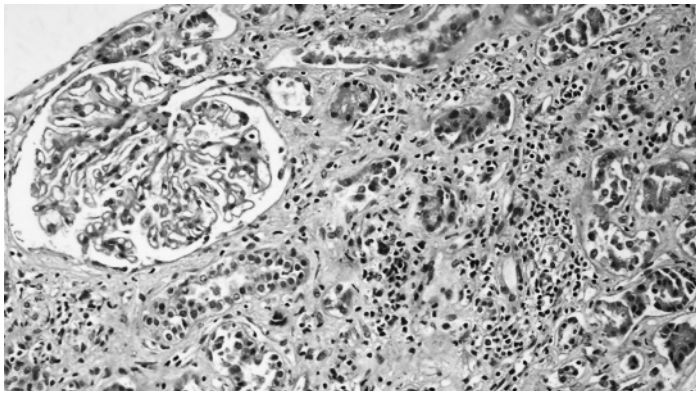


Fig 2B: Inflammatory cells have caused damage to certain tubules. Regenerative atypical changes were observed in the epithelial cells lining the other tubules.



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Bosutinib treatment was temporarily discontinued for one month; however, no improvement in renal function was observed. Following a multidisciplinary consultation with the hematology department, bosutinib was restarted due to the critical need for continued hematologic control. Immunosuppressive therapy with rituximab and tacrolimus was initiated based on the renal biopsy diagnosis of membranous nephropathy. The treatment regimen consisted of two doses of rituximab 1 g administered 15 days apart, combined with tacrolimus 2 mg/day (1 mg twice daily) for a total duration of 12 months. The patient received no nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids.

At six-month follow-up, significant clinical improvement was observed, with serum creatinine of 1.03 mg/dL, eGFR of 94 mL/min/1.73 m², serum albumin of 36.2 g/L, spot urine protein-to-creatinine ratio of 2074 mg/g, and albumin-to-creatinine ratio of 1517 mg/g.

DISCUSSION

TKIs have revolutionized the treatment of hematologic malignancies such as CML, significantly improving patient survival and quality of life. These agents primarily target the BCR-ABL fusion protein, but they may also inhibit other tyrosine kinases expressed in renal tissue, including vascular endothelial growth factor receptors, platelet-derived growth factor receptor beta (PDGFR), c-KIT, and SRC family kinases, thereby contributing to nephrotoxicity [5]. Bosutinib inhibits PDGFR, which is expressed in glomeruli, tubules, renal interstitium, and arteries, playing a role in tubular cell repair, as well as c-KIT, which is expressed at low levels in collecting ducts and distal tubules. Additionally, bosutinib inhibits SRC family kinases, predominantly expressed in renal tubules and, to a lesser extent, in vascular structures [6].

Previous studies have shown improvement in renal function when patients were switched from imatinib to dasatinib or nilotinib, whereas bosutinib use has been associated with a nonsignificant trend toward declining eGFR [1]. Hirano et al. suggested that proteinuria severity may be dose-dependent, as dose reduction effectively decreased proteinuria in their cohort [7]. Literature reports indicate that the main management strategy for TKI-associated nephrotic syndrome or tubulointerstitial injury involves dose reduction or discontinuation of the offending agent, with switching to an alternative TKI, particularly in dasatinib-related cases. In contrast, continuation of the suspected TKI is rarely reported and is typically reserved for situations in which hematologic disease control is critical.

Renal adverse effects associated with bosutinib predominantly include increases in serum creatinine and reductions in eGFR, with partial or complete recovery following drug discontinuation [8]. Although these findings do not constitute strong direct evidence for bosutinib-induced nephrotic syndrome or MN, they support the concept of reversible TKI-related renal toxicity. For drug-induced acute tubulointerstitial nephritis, standard management generally involves discontinuation of the offending agent and consideration of corticosteroid therapy in selected cases.

The distinguishing feature of the present case is the simultaneous occurrence of membranous nephropathy and acute tubulointerstitial nephritis during bosutinib therapy, a combination rarely reported. Unlike most reported cases, bosutinib was not permanently discontinued in our patient. Instead, following a brief interruption, treatment was resumed after careful multidisciplinary risk–benefit assessment, and immunomodulatory therapy was initiated. This approach led to stabilization and subsequent improvement of renal function and proteinuria at six months of follow-up.

Bosutinib is a second-generation TKI used in newly diagnosed or resistant/intolerant Ph-positive CML [9]. Analyses based on 45 dysregulated IIMATs identified in MGN indicate that several anticancer drugs, including tamoxifen, bosutinib, ponatinib, and nintedanib, may represent potential therapeutic candidates for MN, and that these IIMATs are associated with critical biological processes, particularly the chemokine signaling pathway [10]. These findings support the potential nephrotoxic effects of bosutinib and its possible association with MN development in our case.

This case demonstrates that automatic discontinuation of the TKI is not always the only option when TKI-associated nephrotic

syndrome develops. Especially when alternative treatment options are limited, a clear diagnosis via renal biopsy, multidisciplinary (nephrology–hematology) risk–benefit assessment, and close monitoring may allow continuation of the suspected TKI with adjunct immunomodulatory therapy as a defensible strategy in selected cases.

MN is a common cause of nephrotic syndrome in adults; while it typically presents as a primary kidney disease, approximately 20% of cases are secondary to systemic diseases (SLE, infections, malignancies) or drug exposure [11]. In our case, PLA2R immunostaining, associated with primary (idiopathic) MN, showed coarse granular positivity along the GBM. PLA2R-positive MN associated with bosutinib has not been previously reported; however, PLA2R-positive MN has been reported in patients treated with sunitinib, another TKI. The present study reports that, while sunitinib exacerbated the underlying MN, it did not cause it [12].

The PLA2R positivity suggests an underlying idiopathic membranous nephropathy (MN); however, the concomitant development of acute tubulointerstitial nephritis (TIN) suggests a potential drug-induced component. Due to the limited literature, a definitive causal relationship between bosutinib and PLA2R-positive MN cannot be firmly established. It remains unclear whether the drug directly induced these findings or acted as a trigger in a genetically predisposed individual. Therefore, larger-scale cohort studies and additional clinicopathological evidence are required to elucidate the precise role of bosutinib in the pathogenesis of these complex renal presentations.

CONCLUSION

We present a rare case of nephrotic syndrome characterized by the coexistence of PLA2R-positive membranous nephropathy and acute tubulointerstitial nephritis in a patient receiving bosutinib therapy. While the PLA2R positivity indicates an idiopathic MN pattern, the concurrent TIN suggests a possible association with bosutinib-related nephrotoxicity. At this stage, it is not possible to definitively attribute the glomerular pathology to bosutinib, and our findings should be interpreted as a potential association rather than confirmed causality. Further studies involving larger patient populations are essential to confirm the renal safety profile of bosutinib. This case underscores the importance of renal biopsy in TKI-treated patients and highlights the need for vigilant monitoring of renal function and proteinuria to detect potential adverse effects early.

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