LETTER TO THE EDITOR

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Ibrutinib-Associated Kaposi Sarcoma and Reversible Renal Manifestation in Chronic Lymphocytic Leukemia

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To the Editor,

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) causes immune dysregulation, which increases the risk of autoimmune disorders and secondary malignancies (1,2). Bruton's tyrosine kinase inhibitors, particularly ibrutinib, have improved outcomes in high-risk CLL, including cases with del(17p) or TP53 disruption (3). However, rare virus-associated malignancies, including human herpesvirus 8 (HHV-8)-associated Kaposi sarcoma, have been reported during treatment with agents that alter immune function (4). Renal involvement associated with CLL/SLL may result from leukemic infiltration or several glomerular lesions (5). To our knowledge, no previous report from Türkiye has described Kaposi sarcoma arising during ibrutinib treatment, together with a reversible renal manifestation after subsequent CLL-directed therapy.

A 70-year-old man with hypertension and no history of HIV infection or organ transplantation presented to our hospital with nephrotic-range proteinuria (5.2 g/24 h) and hypoalbuminemia (26 g/L). Kidney biopsy revealed interstitial infiltration by small mature lymphocytes, consistent with CLL/SLL. Detailed glomerular findings from light microscopy, immunofluorescence, and electron microscopy were not available; therefore, the histologic basis of the nephrotic-range proteinuria could not be established. Fluorescence in situ hybridization detected del(13q) in 20% of nuclei and del(17p) in 9% of nuclei. The laboratory cut-off used to define del(17p) positivity could not be retrieved, and TP53 mutation analysis was not available. In April 2024, after a suboptimal response to four cycles of R-CHOP and two cycles of fludarabine, cyclophosphamide, and rituximab (FCR), the patient started on ibrutinib at 420 mg/day. After three months, proteinuria decreased to 2.8 g/24 h.

In October 2024, he developed violaceous plaques on his lower extremities. Skin biopsy confirmed Kaposi sarcoma, with positive staining for CD34, CD31, and HHV-8 latent nuclear antigen 1. A numerical Ki-67 proliferation index was not reported. The CD4 count was not measured at the time of diagnosis. Proteinuria was not measured on the date that ibrutinib was discontinued. Ibrutinib was stopped, and localized radiotherapy at 20 Gy in 10 fractions led to marked regression of the lesions. The patient was then started on venetoclax plus obinutuzumab, with prophylaxis for tumor lysis syndrome. At the last documented

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assessment in March 2025, approximately five months after the diagnosis of Kaposi sarcoma and the treatment change, proteinuria had decreased to 0.6 g/24 h, serum albumin had normalized to 38.7 g/L, and the absolute lymphocyte count had returned to the normal range. No recurrence of Kaposi sarcoma was observed during this period.

This clinical observation suggests two potentially relevant associations. Ibrutinib inhibits interleukin-2-inducible T-cell kinase and has been shown to produce Th1-selective pressure in T lymphocytes (6). Because Th1 immunity contributes to control of latent herpesviruses, this observation does not directly establish a mechanism for HHV-8 reactivation. A contribution from ibrutinib should therefore be regarded as a hypothesis rather than a demonstrated causal relationship. Prior exposure to FCR may also have contributed to persistent immune dysfunction. Classic Kaposi sarcoma should also be considered. Regression occurred after both ibrutinib discontinuation and concurrent local radiotherapy; therefore, the effect of either intervention could not be isolated.

In this patient, venetoclax plus obinutuzumab produced a hematologic response after ibrutinib discontinuation. The fall in proteinuria from 5.2 to 0.6 g/24 h during effective CLL/SLL-directed treatment suggests a potentially reversible, disease-associated renal manifestation (7). However, the absence of detailed glomerular pathology and a proteinuria measurement at the time of ibrutinib discontinuation prevents attribution of the findings to a specific glomerulopathy or to the treatment. The absence of Kaposi sarcoma recurrence during the documented follow-up is reassuring but should be considered preliminary.

The interpretation of this clinical observation is limited by concurrent radiotherapy, prior fludarabine exposure, classic Kaposi sarcoma as an alternative explanation, unavailable CD4 and detailed glomerular data, the missing proteinuria value at ibrutinib discontinuation, and limited follow-up. The clinical course suggests a possible association between ibrutinib exposure and Kaposi sarcoma, while improvement in proteinuria accompanied the response to subsequent CLL/SLL-directed therapy. Clinicians should evaluate new cutaneous lesions during ibrutinib treatment and investigate renal abnormalities with appropriate clinical and pathologic correlation.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of the clinical information presented in this letter.

Footnotes

Conflict of Interest: No conflict of interest was declared by the author.

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