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Renal Failure in a Patient with Ibrutinib Refractory Chronic Lymphocytic Leukemia

*Paola Casciani[1], Massimiliano Postorino[1], Francesca Rossi[2], Sergio Tripodi[3], Annalisa Biagi[1], Lisa Mercante[1], Roberta Laureana[1], Enrico Santinelli[1], Maria Ilaria Del Principe[1], Valter Gattei[2] and Giovanni Del Poeta[1]**

[1]*Department of Biomedicine and Prevention, Università Tor Vergata, Italy*

[2]*IRCCS Centro di Riferimento Oncologico, Italy*

[3]*UOC Pathological Anatomy, Azienda Ospedaliera Universitaria, Italy*

Abstract

The incidence of a renal lymphocytic infiltration in Chronic Lymphocytic Leukemia (CLL) is a fairly common phenomenon, found in a variable percentage of cases, as a result of autopsy studies. However, it is uncommon the association of the infiltrate with specific renal histopathological alterations, such as a Granulomatous Interstitial Nephritis (GIN), with severe kidney function impairment. We describe a patient with progressive TP53 mutated CLL who developed acute renal failure due to leukemic infiltration associated with GIN during treatment with ibrutinib, the new inhibitor of the Bruton's tyrosine kinase. After stopping ibrutinib, the patient obtained a complete remission with high doses of prednisone plus chemoimmunotherapy, but recently he underwent relapse treated now with venetoclax plus prednisone.

Introduction

Chronic Lymphocytic Leukemia (CLL), a low grade malignancy consisting of CD5+CD23+CD200+ small B lymphocytes, is the most frequent leukemia in the western world. The treatment landscape for CLL is rapidly evolving. Combination chemoimmunotherapy regimens like FCR (Fludarabine, Cyclophosphamide, Rituximab) and BR (Bendamustine, Rituximab) have been the frontline therapies for CLL, whereas Chlorambucil remained the standard frontline therapy for older patients (65 years or older) with CLL until recently [1,2]. Targeted therapy with small molecule inhibitors against Bruton Tyrosine Kinase (BTK) such as ibrutinib and acalabrutinib are playing a major role for treatment of patients with either treatment-naïve or refractory/relapsed CLL [3-5].

The Bruton's tyrosine kinase inhibitor ibrutinib showed an impressive and sustained Progression Free Survival (PFS) and Overall Survival (OS) benefit both in first line and in relapsed or refractory CLL. Nevertheless, patients with specific high risk features like *TP53* mutations showed a trend toward shorter PFS, and altogether, only half of the enrolled patients were still receiving ibrutinib at the end of the observation period [6]. Here, we report a peculiar case of acute renal failure associated with leukemic infiltration and Granulomatous Interstitial Nephritis (GIN) occurring in a CLL patient with *TP53* gene mutations, refractory to ibrutinib in first line, but subsequently responding to chemoimmunotherapy.

Case Presentation

In February 2014, a 59-year-old male patient presented with asymptomatic widespread lymphadenopathy (cervical, axillary, supraclavicular, mediastinal and inguinal) and splenomegaly (18 cm on imaging). His white cell count was higher than normal with differential count showing 16.0 × 10^9/L lymphocytes. The immunophenotypic study carried out on peripheral blood lymphocytes by flow cytometry showed a CD19+/CD20+/CD5+/CD23-/CD200+ homogeneous phenotype with a IGL-Lambda clonal restriction, confirming the diagnosis of atypical (CD23-) CLL. The prognostic biomarker CD38 was negative (10% of positive CLL cells). FISH analysis revealed the deletion of the long arm of chromosome 13 (del13q-) and the deletion of the short arm of chromosome 17 (del17p-). Clonal mutations of the *TP53* gene were also found (variant allele frequency, VAF, 78%, mutation on exon 8 c.916C>T, p.R306X). This pathogenic variant is denoted *TP53* c.916C>T at the cDNA level and p.Arg306Ter (R306X) at the protein level. The substitution creates a nonsense variant, which changes an Arginine to a premature stop codon (CGA>TGA), and is predicted to cause

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Correspondence:
Giovanni Del Poeta, Department of Biomedicine and Prevention, Università Tor Vergata, Viale Oxford, 8100133 Rome, Italy; Tel: +39-0620903407; E-mail: g.delpoeta@tin.it

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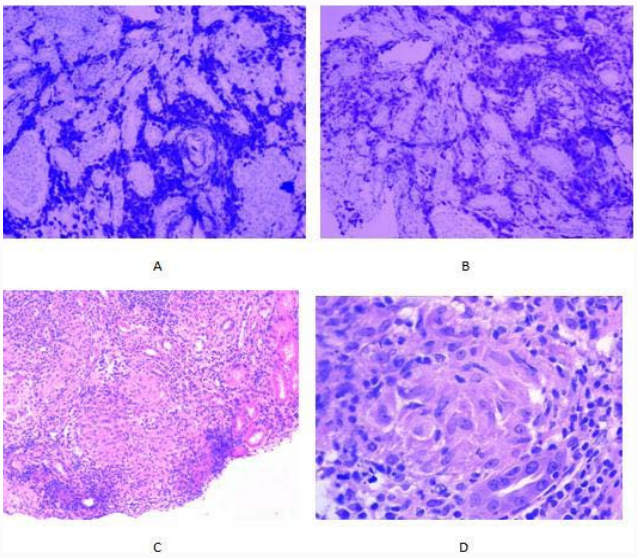

Figure 1: A and B) Immunophenotype of the B lymphocytes shows CD5 C) and CD20 D) positivity. C, Renal biopsy (haematoxylin and eosin) showing peritubular and intratubular interstitial infiltrates of small lymphoid cells associated with a large, non-necrotizing chronic granulomatous phlogosis.

loss of normal protein function through either protein truncation or nonsense-mediated mRNA decay [7]. Variable heavy chain genes of Immunoglobulins (IGHV) status resulted as unmutated, i.e. below the established cut-off of 2% of IGHV mutations (1.7% IGHV3-48*2). In April 2016, the patient presented a rapid increase in peripheral lymphocytosis (100.0 × 10^9/L), massive increase in mediastinal, abdominal lymph nodes, splenomegaly (24 cm on imaging) and B symptoms. A total Positron Emission Tomography/Computed Tomography (PET/CT) scan, showing low Standardized Uptake Values (SUV) ruled out Richter's syndrome transformation. Therefore, the patient started first-line treatment with oral ibrutinib in monotherapy at the dosage of 420 mg/d, according to the ESMO 2016 guidelines [8]. During the first month of treatment the patient showed discrete increase in total lymphocyte count and then a rapid decrease in the following three months. The values of hemoglobin and platelet remained stable as well as the hepatorenal function. A clinical and imaging re-evaluation of the disease carried out in July showed stable disease. In August 2016, the patient suddenly presented fever above 38°C together with lumbago and widespread bone pain. Creatinine (3.57 mg/dl), Azotemia (112 mg/dl), Proteinuria (0.22 gr/dl) were abnormally increased and the patient was hospitalized for the onset of an acute renal failure. Ultrasonography showed a volumetric increase of both kidneys associated with parenchymal alterations. An immunoassay screening (IgA levels, C3 and C4 complement components) was negative for autoimmune disorders. Therefore, a renal biopsy was performed showing moderate peritubular and intratubular interstitial infiltrates by a clonal subpopulation of small CD20 and CD5 positive B-lymphocytes lacking CD23, Cyclin D1 and CD10 expression (Figure 1A,1B). The histopathology was also characterized by a population of CD3+ T lymphocytes and by a large, non-necrotizing chronic granulomatous phlogosis (Figure 1C,1D). No glomerular or tubulointerstitial immune complex deposits were detected by immunofluorescence (not shown). The peripheral blood immunophenotype performed by flow cytometry showed a CD20+/CD5+/CD23- and CD200+ homogeneous B-lymphocyte population, The FISH analysis and the *TP53* mutations confirmed the same picture of the onset. After exclusion of a tuberculous or sarcoidotic nature of renal granulomas [9], the patient stopped ibrutinib and started therapy with methylprednisolone at the dose of 1 mg/Kg body weight obtaining a partial resolution of the renal failure. Afterwards, the patient was discharged from the hospital with prednisone therapy. In September 2016, he resumed oral therapy with ibrutinib at the standard dose of 420 mg per day. However, a certain degree of chronic renal failure (Creatinine 2.4 mg/dL, Azotemia 141 mg/dL), Anemia (Hemoglobin 11 g/dL), peripheral B clonal lymphocytosis (45.0 × 10^9/L), superficial and inner adenopathies persisted. For this reason, in October 2016, the patient discontinued therapy with ibrutinib and started chemoimmunotherapy according to the R-CHOP scheme (Rituximab 375 mg/m^2, Cyclophosphamide 750 mg/m^2, Vincristine 1.4 mg/m^2, Doxorubicin 50 mg/m^2 and Prednisone 40 mg/m^2) for a total of six cycles, which was successfully completed in February 2017. During this second-line therapy, the renal function showed a remarkable improvement and creatinine levels were only slightly higher than normal (about 1.5 to 1.7 mg/dL). The imaging re-evaluation, performed with TC total body, did not show either lymphadenopathies or splenomegaly. Therefore, the patient achieved a complete remission of the disease. In June 2019, the patient showed disease recurrence with increasing lymphocytosis (35.0 × 10^9/L), numerous superficial and inner lymph node swellings, splenomegaly, fair kidney failure (Creatinine 2.0 mg/dL) and bone marrow lymphocytic infiltrate. For this reason, in July 2019, the patient started treatment with venetoclax, an oral Bcl-2 inhibitor [10], and prednisone, which is ongoing.

Discussion

Cases of GIN associated with kidney leukemia infiltrate are uncommon. Sometimes they may occur with acute kidney failure pictures that improve under corticosteroid treatment [11-14]. Our patient developed GIN framework associated with leukemic infiltrates leading to an acute renal failure during treatment with ibrutinib. According to the current literature, granulomatous reactions may be caused by concomitant mycobacterial infections and rare tumors including malignant lymphomas [15,16]. The participation of T cells, as in our case, in granulomatous reactions is well established, but the mechanisms underlying this phenomenon have not been yet elucidated. Noteworthy, Interleukin (IL) 17, a cytokine secreted by T-lymphocytes has been established as an important factor in T-cell-mediated IFN-gamma production and granuloma formation [17]. Moreover, the pathogenesis of GIN in patients with CLL/SLL is unknown. There is great evidence that CLL patients have T-cell dysfunction which contributes to infectious and auto-immune complications [18]. The fact that our case of GIN was accompanied by CLL interstitial infiltration suggest that GIN may be a local hypersensitivity reaction to tumor-derived antigens, which may stimulate antigen-presenting cells to produce cytokines involved in granulomatous inflammation, such as IL-12, IL-18 and/or IL-27 [19]. Moreover, our patient had not evidence by immunofluorescence of monoclonal protein or immune-complex-type deposits, providing evidence against paraprotein-mediated or immune-complex-mediated interstitial nephritis. In our patient, both the kidney function and the hematological disease improved on high dose steroids and on CLL-directed Chemoimmunotherapy (R-CHOP). It may be hypothesized that the refractoriness to ibrutinib with the subsequent GIN may be partly due to the above mentioned pathogenic variant of the *TP53* mutation. B-lymphocyte clone had an immunophenotypic pattern (CD23-/CD200+/Cyclin D1-/CD10-)

that excluded mantle cell lymphoma (Cyclin D1 negative), follicular lymphoma (CD10 negative) and marginal lymphoma (CD200+). It is possible to suppose that it is an atypical CLL refractory to ibrutinib. The vast majority of CLL patients respond to ibrutinib, as reflected by the aggregate observation of PR, CR or prolonged stable disease with nodal response despite peripheral lymphocytosis. However, there are currently no upfront clinical biomarkers to predict sensitivity or resistance to ibrutinib therapy in CLL [20]. Finally, it may be hypothesized that this clone of expanded B lymphocytes CD23-CD200+ infiltrating the kidney may have caused the histopathology of the GIN as well as the clinical picture of the next renal failure. Noteworthy, ibrutinib, by depressing some populations of B lymphocytes in CLL, may allow the expansion of other non-sensitive clones which are responsible for kidney damage as in this case. This assumption may be indirectly supported by the fact that the subsequent R-CHOP chemotherapy, eliminating the clone both in the peripheral blood and in the kidney, brilliantly resolved renal failure and allowed to obtain complete remission of the disease. This is the first CLL case reported in literature in which the appearance of GIN is described during therapy with ibrutinib. However, larger clinicopathologic studies are needed to determine the incidence and risk factors of GIN in patients with CLL.

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