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Chronic lymphocytic lymphoma and concomitant renal cell carcinoma (Clear Cell Type): Review of the literature

Burak Uz [a], Ilhan Dolasik [a,*], Ozlem Ucer [b], Adile Ferda Dagli [b], Sercan Simsek [b]

[a] Fırat University Faculty of Medicine, Department of Internal Medicine, Division of Adult Hematology, Elazığ, Turkey
[b] Fırat University Faculty of Medicine, Department of Pathology, Elazığ, Turkey

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ABSTRACT

In the present report, a 73 years-old male patient who developed clear cell type renal cell carcinoma (RCC) 5 years after the diagnosis of chronic lymphocytic lymphoma (CLL) and plausible explanations for this association were discussed by the authors. The incidence of CLL and RCC occurring in the same patient is higher than that expected in the general population. Various explicative hypotheses of this concurrence include treatment-related development of a second malignancy, immunomodulatory mechanisms, viral aetiology, cytokine (interleukin 6) release from a tumor, and common genetic mutations. Further investigations are warranted.

1. Introduction

The increased incidence of second primary solid tumors and hematological malignancies have been reported in the setting of Non-Hodgkin lymphoma (NHL) [1,2]. The observed rates of renal cell carcinoma (RCC) developing in the NHL patients was 1.86-fold greater, and conversely, NHL developing in RCC patients was 2.67-times higher than that the expected rates in the general population [3]. There appears to be an association between lymphoid malignancies and RCC that cannot be explained by chance alone. This co-existence should be attributed to prior treatment modalities such as alkylating agents, long-term survival of elderly patients, close monitorization of NHL with imaging studies, immunosuppression due to underlying lymphoproliferative disorder, genetic alterations predisposing to both malignancies, environmental factors, and viral aetiology [1,2,4]. However, the exact mechanism has not been clarified yet.

2. Case report

A 73 year-old man was diagnosed with chronic lymphocytic lymphoma (CLL) in December 2009, where he presented with a servical mass at another state hospital. He was treated with 6 cycles of cyclophosphamide, vincristine and prednisone (CVP). On follow-up he received 6 cycles of fludarabine because of relapsed disease. His past history showed a 60 year/pack cigarette usage. His family and social histories were unremarkable. He was referred to our center with B symptoms, and axillary lymphadenopathies in December 2012. His physical examination was unremarkable except bilateral axillary and left posterior servical lymphadenopathies. His blood count parameters were as follows: hemoglobin (Hb): 14.5 g/dL, MCV: 90.3 fL, leukocyte: $20.08 \times 10^3/mm^3$, lymphocyte: $14.19 \times 10^3/mm^3$, platelet count (Plt): $168 \times 10^3/mm^3$. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values were 71 mm/h and 6 mg/L (normal range: 0–5), respectively. All other laboratory tests including serum electrolytes, liver and renal function tests, and coagulation profile were normal. Bilateral multiple axillary lymphadenopathies ($7 \times 3.5\ cm^2$ in the right, $6 \times 3.5\ cm^2$ in the left) were noted in the superficial ultrasonography. Six cycles of fludarabine and cyclophosphamide (FC) combination were applied from December 11, 2012 to April 30, 2013, resulting in relief from symptoms and achieving a partial remission in lymphadenopathies. The patient applied with deep anemia (Hb: 3.6 g/dL) and thrombocytopenia (Plt: $35 \times 10^3/mm^3$) in April 2014, one year from the last chemotherapy. However, erythropoietin (EPO) level was 2030 mIU/mL (normal range: 4.3–20). ESR and CRP values were 136 mm/h and 221 mg/L, respectively. Bone marrow biopsy revealed hypercellularity (%60), and grade III increment for iron and reticular fibers. There were no abnormality in erythrocytic and granulocytic series in terms of differentiation and maturation. No infiltration or granuloma was noted. In addition, dismegacaryopoiesis and an increase in the number of the megacaryocytes were also reported (Fig. 1). Direct and indirect antiglobulins tests (initial and repeated) were negative, and reticulocyte correction index was 0.04. Detailed laboratory investigations including viral aetiology, rheumatological parameters, and tumor markers were unremarkable. JAK2 (V617F) mutation

* Corresponding author.
E-mail address: ilhand.dr@hotmail.com (I. Dolasik).

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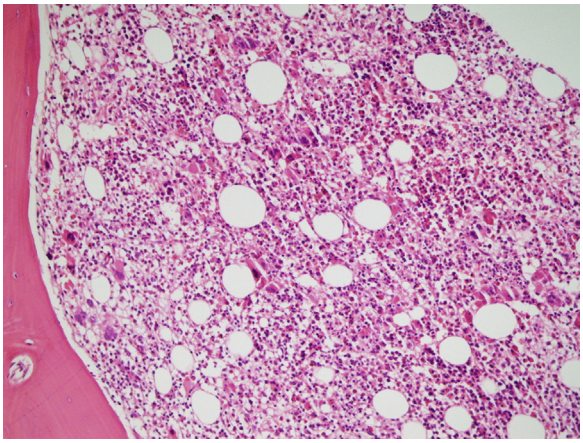

Fig. 1. The bone marrow histopathology shows hypercellularity, sparse clustering and increase in megacaryocytes, and dismegacaryopoiesis (Hematoxylin-eosin, 200 ×).

was negative. A computed tomography (CT) of the abdomen, in September 2014, revealed a mild splenomegaly (13.3 cm) without hepatomegaly, and a heterogen solid mass in 7 × 7 × 8 cm diameter bearing cystic areas in the medial lower pole of the left kidney. Tru-cut biopsy of the renal mass showed vimentin (+), CD10 (+), Ki-67: 10–20%, EMA (+), LMWK (+) cells which were consistent with clear cell type RCC (Fig. 2a–d). Torax CT to rule out a probable metastasis of RCC was found to be negative. Surgical removal of the aforementioned lesion was planned. Unfortunately, on-follow up, he developed tonic-clonic seizures for two times every other day. Electroencephalography recorded normal brain activities. Brain magnetic resonance imaging did not detect any bleeding or mass lesion. Intravenous administration of sodium valproate was initiated following improvement in seizures. However, the general condition of the patient worsened and he expired on December 2014 with active RCC.

3. Discussion

Although second malignancies are increasingly observed after NHL, the incidence of CLL and RCC in the same patient is exceptional [4,5]. Nishikubo et al. [4] reported a case series of 8 patients with lymphoid malignancies and RCC. In 2 of 8 patients, CLL and T-cell CLL were diagnosed 1 year and 8 months prior to RCC, respectively. More recently, in a series of 9 patients with lymphoma and RCC, only 1 patient had CLL [5]. This patient had carried a diagnosis of CLL for 15 years without any treatment. Finally, a case series of 5 patients with concomitant lymphoid malignancies and RCC were reported by Serefhanoglu et al. [6] Three of 5 patients had CLL. In 2 of 3 patients, the CLL was diagnosed prior (13 months and 5 years, respectively) to their RCC; while in 1 patient coincidence of CLL and RCC was reported. Our patient developed RCC after 5 years in the setting of NHL, and he had been treated with multiple courses of chemotherapy including both alkylating agents (12 cycles of cyclophosphamide) and purine analogues (12 cycles of fludarabine). Although he did not receive radiotherapy, he had multiple CT scans during his follow-up. Certain chemotherapeutic regimens have been shown to increase both the risk of NHL and RCC. Additionally, this increased risk was also attributed to radiotherapy that the patients received for NHL [2]. The actuarial risk of developing a second cancer 3–20 years after diagnosis of NHL was 21%, compared with a population expected cumulative risk of 15%. NHL patients whom underwent treatment for lymphoma are at increased risk for developing RCC, especially < 1 year and > 10 years after treatment [2]. In contrast, some authors [3,4,7] identified patients with simultaneous NHL and RCC whom did not receive any treatment at the time of presentation, and they have suggested that this association could not be attributed to treatment modalities alone. Recently, Dutcher et al. [8] have reviewed the current data about the existence of RCC and hematologic malignancies in the same patient. Among these 186 patients, the most common sequence of diagnosis was a hematologic malignancy (twelve with CLL) followed by RCC (43%), secondly,

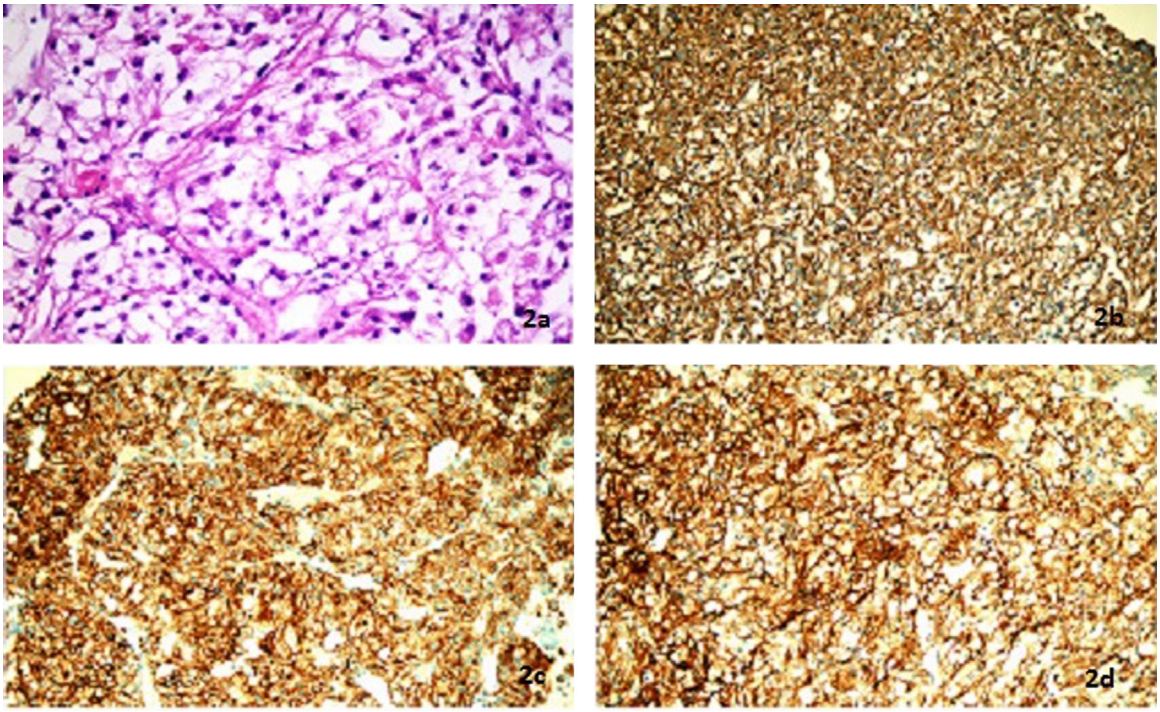

Fig. 2. (a) The tumor is characterized by malignant cells with clear cytoplasm in high magnificence (Hematoxylin-eosin, 400 ×), (b) Vimentin positivity in tumoral cells (immunoperoxidase, 200 ×), (c) CD10 positivity in tumoral cells (immunoperoxidase, 200 ×), and (d) Tumoral cells displaying positivity for low-molecular weight cytokeratin (LMWK) (immunoperoxidase, 200 ×).

synchronous (33%), and the least common pattern was RCC first and hematologic malignancy developed later (22%). The authors have also reported that these patients have common clinical characteristics, including a male predominance (2.25:1), having a hematological malignancy of B-cell origin (94%), and showing an evident risk of extranodal lymphoma (32%). The immune dysregulation via a breakdown in tumor surveillance as a result of lymphoma predisposes the patient to the development of RCC [3]. Proliferating cell nuclear antigen positivity ($\geq$ 10%) but not p53 or human papillomavirus (HPV) DNA correlated with worse clinical prognosis such as invasion or metastasis of RCC [9]. However, the role of HPV in RCC is controversial [10]. Sakai et al. [11] suggested that RCC related interleukin 6 synthesis might stimulate the proliferation of the myeloma cells. Growing evidence supports the idea that a common genetic mutation can explain the elevated incidence of second malignancies in patients with NHL. Deletions of 3p have been described in 95–98% of sporadic clear cell type RCC [12,13]. In addition, abnormalities in 11p, chromosome 13, and deletions in 17p in 11–33% of patients with advanced stage RCC have been reported [12]. Cytogenetic analysis of NHL cells by more accurate fluorescence in-situ hybridization methods such as ratio-painting and comparative genomic hybridization have enabled to identify further unsuspected chromosomal abnormalities including 17p deletions, trisomy of chromosome 7, amplification of 3 (p12) and mutations in p53 [14]. The persistently increased risk of second malignancies in the clinical setting of CLL, particularly those treated with intense courses of chemotherapy, should alert clinicians to the importance of continued medical surveillance. Future studies are needed to better clarify if this association is a causal relationship or coincidental occurrence.

Conflict of interests

None.

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