T-cell large granular lymphocytic leukemia associated with renal cell carcinoma

A case report

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Abstract
Rationale: T-cell large granular lymphocytic leukemia (T-LGLL) is a rare lymphoproliferative neoplasm of cytotoxic T cells and renal cell carcinoma (RCC) is the most common form of kidney cancer, but T-LGLL associated with RCC has never been reported.

Patient concerns: A 58-year-old Chinese male presented with general fatigue and intermittent-fever, accompanied by palpitations and dizziness.

Diagnosis: Radical nephrectomy was performed, and a diagnosis of clear cell carcinoma (T1N0M0, I phase) was made based on the postoperative pathological findings. With typical cellular morphology, immunophenotype and T-cell receptor gene rearrangement, a diagnosis of T-LGLL was established.

Interventions: After radical nephrectomy, this patient remained asymptomatic without any treatment.

Outcomes: To date, the patient is generally in good condition, without complaints of discomfort.

Lessons: The coexistence of these entities may not be coincidental, and it is likely that they may share a common pathogenic pathway related to immune dysregulation.

Abbreviations: BM = bone marrow, CBC = complete blood count, CT = computed tomography, Fas ligand = Fasl, KIRs = killer cell inhibitory receptors, LDH = lactate dehydrogenase, PB = peripheral blood, PCR = polymerase chain reaction, RCC = renal cell carcinoma, SH2 = Src homology 2, TCR = T-cell receptor, T-LGLL = T-cell large granular lymphocytic leukemia.

Keywords: T-cell large granular lymphocytic leukemia, renal cell carcinoma, STAT3

1. Introduction

T-cell large granular lymphocytic leukemia (T-LGLL) is a lymphoproliferative disease of cytotoxic T cells and represents 2% to 3% of all small lymphocytic leukemias. Renal cell carcinoma (RCC) is the most common form of kidney cancer (2% to 3% of all adult malignancies) and 85% of all primary renal tumors. Approximately 90% of renal tumors are RCC, and approximately 80% of these are clear cell carcinomas. The diagnosis of RCC can be made by pathology and the mainstay treatment for localized RCC is surgery. The association of T-LGLL with solid neoplasms is rare and the occurrence in primary RCC has, to the best of our knowledge, never been reported. Herein, we describe a unique case of T-LGLL associated with RCC, and the clinicopathology characteristics were also reported, as well as the clonal cytogenetic and molecular abnormalities.

2. Case report

A 58-year-old Chinese male, Han ethnic, was referred to the hematology department of the First Affiliated Hospital of Nanjing Medical University with general fatigue and intermittent-fever in December 2011, accompanied by palpitations and dizziness, and he had been complaining these since December 2006. In 2008, he received abdominal computed tomography (CT) scan due to back pain, which revealed a heterogeneous enhancing mass lesion including areas of necrosis and specks of calcification in the lower pole of the left kidney. Preoperative blood routine inspection showed that elevated lymphocyte (WBC 10.6 × 10^9/L, lymphocyte ratio 41.7%, ALC 5.0 × 10^9/L, ANC 4.4 × 10^9/L), hemoglobin 133g/L, platelet 216 × 10^9/L, but the cause of lymphocytosis was unclear. Radical nephrectomy was performed, and histological findings of the resected surface of the tumor in the left kidney revealed a yellow-white, solid lesion that measured 3.5 × 2.5 × 2.8cm in size limited to the renal parenchyma with negative margins. The resection of lymph nodes revealed no nodes with metastasis. On microscopic examination,
Nucleoli are conspicuous and eosinophilic at \( \times 400 \) magnification (Fig. 1). Based on the postoperative pathology findings, a diagnosis of clear cell carcinoma (T1N0M0, I phase) was made, according to the American Joint Committee on Cancer 2009 cancer staging. Following the removal of tumors, the patient recovered without complication. A follow-up CT scan was performed 4 months postoperatively and showed no evidence of metastasis. No sweating, weight loss or dizziness except fatigue and fever could be found during this period of time.

The patient's family history was insignificant. At the present visit, his physical examination revealed his vital signs were in the normal range, normal skin color without icterus and the abdomen was soft to palpate without apparent lymphadenopathy or hepatosplenomegaly. A complete blood cell (CBC) count showed a leukocyte count was \( 12 \times 10^9/L \) with 41.7% lymphocytes, ANC \( 4.4 \times 10^9/L \), hemoglobin of \( 133g/L \), and a platelet count of \( 222 \times 10^9/L \). The peripheral blood (PB) smear revealed lymphocytosis (50%) and showed an increased number of LGL (27.5%) with pale cytoplasm and fine prominent azurophilic granules (Fig. 2). The patient's serum chemistry panel, coagulation test, tumor markers, lactate dehydrogenase (LDH), and \( \beta_2 \)-microglobulin were all in the normal range. Further laboratory investigations excluded rheumatoid factor, cryoglobulins, and antinuclear antibodies. CT scans of neck, thoracic, and abdominal regions showed no lymph node, liver, or spleen enlargement. Upper and lower gastrointestinal endoscopy showed no abnormalities.

Lymphocyte subtype analysis of PB by flow cytometry showed an abnormal ratio of the total lymphocytes with 50.3% (normal range: 20%–40%), and a slightly increased number of CD3+ cells with 76.4% (normal range: 65%–75%), a prominently exceptionally elevated number of CD3+CD8dim+ cells with 41.8% (normal range: 21%–29%). Flow cytometry illustrated abnormal T-cell immunophenotype was CD2+CD3+CD4-CD8+CD5-CD7+TCRab+. The clonal expansions were assessed with the IO Test Beta Mark TCR Vbeta Repertoire Kit (PN IM3497, Beckman Coulter Immunotech, Marseille, France), which is a kit for the quantitative determination of the TCR Vbeta repertoire of human T lymphocytes using flow cytometry. The results showed TCR Vbeta 13.2 was 91.6% (normal: 3%). The expression of KIR was evaluated by gating on the total population of CD3+CD8dim LGLs, using fluorescein isothiocyanate conjugated antibody [CD158e1/e2 (DX9)] and the following phycoerythrin conjugated antibodies [CD158a/b (EB6), CD158b1/b2, j (GL183) and CD158i (FES172)], which were all obtained from Beckman Coulter (Miami, FL, USA). Restricted KIR expression was observed (CD158a+: 86.8%, CD158b+: 10.7%, CD158i+: 0.8%, CD158e+: 1.5%). Representative tetramer staining is shown in Figure 3.

A bone marrow (BM) aspirate was performed to flow cytometry, cytogenetics, and molecular biology studies. The BM showed lymphocytosis (55%) and 28% of lymphocytes exhibited morphological aspects of LGLs. The cytogenetic analysis by G-banding revealed a 46, XY karyotype with no chromosomal abnormalities. Immunophenotyping analysis of BM cells by flow cytometry showed abnormal ratio of lymphocytes with 50.2%, and abnormal T-cell immunophenotype was CD2+CD3+CD4-CD8+CD5-CD7+CD16+CD56-CD57+. The cytogenetic analysis by G-banding revealed a 46, XY karyotype with no chromosomal abnormalities. Immunophenotyping analysis of BM cells by flow cytometry showed abnormal ratio of lymphocytes with 50.2%, and abnormal T-cell immunophenotype was CD2+CD3+CD4-CD8+CD5-CD7+CD16+CD56-CD57+.
The EBV-DNA and CMV-DNA examined by polymerase chain reaction (PCR) were both negative. TCR gene rearrangement by PCR was positive for TCR\(\beta\) (Fig. 4), indicating the clonal nature of the LGL proliferation. We also examined exon 20 and 21 of the STAT3 Src homology 2 (SH2) domain by direct sequencing; however, no mutations were detected (Fig. 5).

The patient, therefore, with typical cellular morphology, immunophenotype and TCR gene rearrangement, was diagnosed as T-LGLL according to 2008 WHO classification for tumors of haematopoietic and lymphoid tissues scheme.[5] In correlation with clinical history and morphologic review, a diagnosis of RCC plus underlying T-LGLL was made.

His follow-up visits showed persistent lymphocytosis. On his follow-up in January 2013, CBC revealed Hb, 135 g/L; WBC count, \(10.3 \times 10^9/\text{L}\), with ALC of \(5.8 \times 10^9/\text{L}\), and platelets, \(201 \times 10^9/\text{L}\). He remained asymptomatic throughout the disease course without any treatment. The latest follow-up CBC (June 2013) test revealed WBC: \(10.0 \times 10^9/\text{L}\), with ALC of \(5.4 \times 10^9/\text{L}\), Hb: \(133\text{g/L}\), PLT: \(230 \times 10^9/\text{L}\) without symptoms and normal size of spleen. To date, the patient is generally in good condition, without complaints of discomfort.

This study was approved by the ethics committee of the First Affiliated Hospital of Nanjing Medical University, and a written informed consent was obtained from the patient for publication of this case report.

3. Discussion

The occurrence of multiple primary malignant tumors in a single patient is particularly rare and the incidence is 0.73% to 11.70%.[6] Although the mechanisms underlying the occurrence of multiple primary malignancies are not fully understood, certain factors have been implicated, including genetic factors, carcinogenic viruses, immunological and environmental factors.

In this case, we made diagnosis of T-LGLL with RCC by the morphology, flow cytometry, immunohistochemistry, and TCR rearrangement studies. It is reported that T-LGLL could be seen in the concurrence with other B-cell neoplasm, such as chronic lymphocytic leukemia and follicular lymphoma.[7] There are also some case reports about T-LGLL coexistence with some solid tumor, just like the prostate cancer and lung cancer.[7] The disease of T-LGLL coexisted with RCC is a unique neoplasm, which requires us to master the clinical features and explore the biological characteristics deeply.

As to this patient, the most common presentation was persistent lymphocytosis. General fatigue and intermittent-remittent fever are the main clinical demonstration, and the patient did not present with anemia or splenomegaly. There was no clinical or serological evidence of RA or other autoimmune disorder. It remains unclear if the incidence is truly low or the disease has been underdiagnosed because most cases are asymptomatic on presentation. This enhances the significance of reviewing the PB smears in asymptomatic patients who have persistent lymphocytosis and raises the necessity of systematic long-term follow-up studies.

Immunophenotyping is essential for the diagnosis of T-LGLL. Over the last few years, the increasing technological advances in flow cytometry have made it possible to recognize subtle subclinical conditions in patients with few or no symptoms. Normal T-LGL is a CD8+ T cell with CD2+, cytoplasmic and surface CD3+, CD5+, CD7+, CD16-, CD56- and T-cell receptor (TCR)\(\beta\)+.[3] Leukemic proliferation has an aberrant immunophenotype. CD3+CD8+CD16+CD57+ is the most common phenotype of T-LGLL. CD5 and CD7 are most commonly down regulated antigens.[5]
Figure 4. TCR gene rearrangement was analyzed for clonality by GeneScanning analysis. TCR gene rearrangement was positive for TCR β. TCR = T-cell receptor.

Figure 5. STAT3 SH2 domain by direct sequencing and no mutations were detected.
After the widespread availability of TCR and flow cytometry, it became much accurate to distinguish the LGL lymphocytosis as a neoplastic disease or reactive lymphocytosis. The malignant LGLs were shown to carry functional inhibitory MHC class I receptors, killer cell inhibitory receptors (KIRs).[8] In this patient, restricted KIR expression was observed. At present, only a few small-scale researches have evaluated the expression of KIR in T-LGLL patients. One striking feature of the KIR in T-LGLL patients was the lack of detectable KIR expression, and an absence or the predominant expression of KIR appears to be a hint for a clonal proliferation rather than a reactive process. Reactive LGL lymphocytosis and LGLs of healthy individuals has also been shown to be multiclonal or oligo-clonal.

Currently, there is no standard treatment for patients with T-LGLL. For asymptomatic T-LGLL patients with an indolent course, a wait-and-see approach can be considered.[9] After discharge, the patient was stable and remained asymptomatic without any treatment. Since T-LGLL and RCC are relatively rare entities, their association might not be casual and there are some possible hypotheses that might explain this association: First, LGL proliferation might occur as a reaction to the presence of RCC as an antigenic trigger or immune dysregulation. The tumor could represent an antigenic trigger, and LGL expansion might have a role in tumor surveillance. In other words, a putative antigen triggers the activation and proliferation of LGLs which play an important role in the control of tumor cell proliferation. In the present case, the somewhat indolent course of RCC may indirectly support this hypothesis; Impaired signaling pathway would be required to transform the initial polyclonal/oligoclonal CTL proliferation to persistent clonal expansion. In T-LGLL, dysregulated Fas/Fas ligand (FasL)-dependent apoptosis leads to leukemic proliferation of the LGLs.[10] Normally, once antigen clearance is complete, potentially harmful antigen-primed effector CTLs are eliminated via activation-induced cell death. This process is crucial for T-cell homeostasis, and is dependent on Fas/FasL interactions. In leukemic LGLs, despite abundant and constitutive expression of Fas and FasL, cells are resistant to Fas-mediated apoptosis. The pathogenesis of RCC is complicated and still remains unclear, but the activation of Fas/FasL signaling pathway is observed in the cells of RCC.[11] and 2 diseases could share a common signaling pathway. The common signaling pathway may not only demonstrate the pathogenesis of the 2 diseases but also provide a hint for further treatment. It is believed that various deregulated signaling pathways, including NF-κB, JAK/STAT3, and PI3K/AKT are playing an important part in the happening of LGLL. RCC and T-LGLL might be 2 independent entities. LGL lymphocytosis did not subside the following filtration; A chance occurrence or an underlying genetic predisposition and the molecular pathogenesis has been described a lot by many studies in LGLL. Recent studies report that STAT3 mutations play a role in T-LGLL and most of these mutations occur in the SH2 domain of exon 21.[12] Therefore, aberrant STAT3 signaling is believed to underlie the pathogenesis of T-LGLL. The constitutive activation of JAK/STAT3 signaling pathway promotes T cells proliferation and prolongs the survival time of T cells by inhibiting apoptosis. STAT3 is also constitutively activated and promotes the development of RCC,[13] so STAT3 signaling underlies the pathogenesis of these 2 diseases. There are other possible pathogenesis, such as cytokines. Many tumor-derived factors, such as IL-10 and IL-6, are crucial for both tumor growth and immunosuppression. Sakai et al. suggested that IL-6 and related cytokine synthesis by RCC cells might enhance malignant lymphoproliferation.[14] The hypothetic pathogenesis of the concurrency is presented in this paper but additional studies on more cases are still needed for a better understanding of the occurrence of T-LGLL associated with RCC.

Our case deserves attention for several reasons: Firstly, this is the first description of T-LGLL in association with RCC. Secondly, its significance also lies in the difficulty in the exact diagnostic categorization of it. Thirdly, RCC combined with T-LGLL is very rare, and most of these tumors are of hematologic origin (non-Hodgkin’s lymphomas, acute myeloid leukemia, hairy cell leukemia), while a minority of them are epithelial neoplasms (lung, gastrointestinal tract, prostate). Lastly, the rare features of the current case are the reasons for the absence of autoimmune disease.

Though an association of RCC with T-LGLL in one patient is a rare case, it is definitely not the only one. Specialists should be alerted for the possibility of similar cases. Patients with T-LGLL may present a better prognosis than those without T-LGLL. This case adds to a growing body of evidences that highlight the need for close monitoring after the treatment of a first cancer. We wish to highlight that a revision including wider clinical presentations, with specific diagnostic markers maybe necessary to increase the diagnostic accuracy and reproducibility for such cases, as this might have profound impact on patients’ survival and disease prognostication.

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