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Case Report Open Access

Concomitant Secondary Peripheral T-cell Lymphoma with Therapy-related Chronic Myelomonocytic Leukemia in a Patient with History of High-grade Follicular Lymphoma

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Abstract

A secondary myeloid or lymphoid neoplasm is not infrequently associated with a primary tumor, solid or hematopoietic, post cytotoxic treatment or radiation. Concurrent secondary neoplasms derived from distinct myeloid and lymphoid cell origins are rare. It is not only a diagnostic challenge, but makes for difficult treatment management. We report a very rare occurrence in 63-year-old male with a history of high-grade follicular lymphoma who was treated with multiple courses of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and then developed a concurrent secondary peripheral T-cell lymphoma, not otherwise specified (sPTCL, NOS) and therapy-related myeloid neoplasm (tMN), under an umbrella of myelodysplastic/myeloproliferative neoplasm, namely chronic myelomonocytic leukemia (CMML). Despite aggressive therapeutic management, the patient passed away secondary to disease progression, complications of infection, and multi-organ failure. An appropriate diagnostic approach for complicated cases as described aided in providing the correct diagnosis.

Keywords: Secondary peripheral T-celllymphoma; Therapy-related myelodysplastic/ myeloproliferative neoplasm; Chronic myelomonocytic leukemia

Introduction

Therapy-related myeloid neoplasms (tMN) are well documented in patients receiving alkylating agents, topoisomerase II inhibitors, or radiation [1-3]. The latency period of developing tMN varies, but is most commonly between 2-5 years [4]. Therapy-related chronic myelomonocytic leukemia (tCMML), with features overlapping myelodysplastic syndrome (MDS) and myeloproliferative neoplasm (MPN) may occur, but is infrequent [5] Clinically, secondary T-cell non-Hodgkin lymphoma (sT-NHL) especially B-cell lymphoma has also been reported in patients receiving immunosuppressants or bioimmunotherapy [6,7]. However, a concurrent tMN and sT-NHL in spleen, lymph node, and bone marrow (BM) is a rare diagnostic scenario, which could result in a diagnostic dilemma and impact immediate treatment.

Case Report

A 63-year-old male was found incidentally to have generalized lymphadenopathy after receiving a computed tomography (CT) scan for nephrolithiasis. A right inguinal lymph node biopsy was performed, confirming a grade 3A follicular lymphoma. He received six cycles of R-CHOP and attained complete remission. Approximately 3.5 years later, a follow-up CT and positron emission tomography (PET) scan revealed new lymphadenopathy involving the right neck, chest, abdomen, and pelvis with mild splenomegaly and standardized uptake value (SUV) ranging from 3 to 5. Because the patient was asymptomatic, observation was recommended. The patient was stable until 5 months later when he developed malaise, weakness, and weight loss. Subsequent imaging studies showed similar lesions with markedly increased SUV ranging from 8.1 and 12.7. Laboratory investigations showed a white blood count of 7.0×10^9/L, hemoglobin of 127 g/L, and platelet count of 54×10^9/L. A staging bone marrow biopsy showed hypercellularity (90%) with mild granulocytic dysplasia and monocytosis, and several small atypical T-cell aggregates which were of unclear clinical significance at that time. Although the restaging bone marrow biopsy was negative for B-cell lymphoma, the overall bone marrow biopsy findings and monocytosis (1.0×10^9/L) raised the possibility for tMN or tCMML. Deletion of 20q was noted in 5/20 cells using conventional karyotyping. JAK2- V617F mutation was also detected.

The patient received external beam radiation to the spleen and single-agent rituximab therapy with poor response. Despite treatment, the patient complained of left abdominal pain. CT scan showed an enlarged spleen. The patient was subsequently started on hydroxyurea with little improvement. A splenectomy was performed, which revealed a 2001. 2 g spleen measuring 23.0×17.0×8.0 cm. Microscopic examination demonstrated expansion of the white pulp, consisting of nodules of atypical lymphoid cells intermingled with monocytes (Figures 1A-1H). Extramedullary hematopoiesis was evident and focal, but no overt blastosis was observed.

Flow cytometry analysis of the splenic lymphoid population essentially showed no B-cells. However, there was a T-cell subpopulation showing pan-T-cell marker and CD4 and CD8 coexpression (Figures 2A and 2B). Additional needle core biopsy of right inguinal lymph node showed diffuse replacement by atypical T-cells (Figure 1B) highlighted by CD3 (Figure 1C) and lacking B-cells

(Figure 1D). Flow cytometry analysis also demonstrated a distinct subpopulation of dual CD4/CD8 positive T-cells within the inguinal lymph node (Figures 2C and 2D). A diagnosis of concurrent tCMML and secondary peripheral T-cell lymphoma, not otherwise specified (sPTCL, NOS) was rendered.

Because available complete blood count data showed decreased peripheral monocytes (0.437×10^9/L), reflecting partial response to therapy, the treatment regimen for tCMML remained unchanged. However, atypical circulating lymphocytes stably increased over 3 months. In addition, the absolute monocyte count rebounded (4.36×10^9/L) (Figure 1F). Post-splenectomy bone marrow biopsy revealed multilineage dyspoiesis and nearly 100% cellularity (Figure 1F) with infiltration by both atypical T lymphoid cells (30-40%) highlighted by CD3 (Figure 1G) and sheets of a myelomonocytic population (20-25%) highlighted by CD163 (Figure 1H), which were confirmed by flow cytometry. Atypical lymphoid cells in the bone marrow exhibited the same abnormal T-cell phenotype as demonstrated in the spleen with dual positive CD4/CD8 expression (Figures 2E and 2F).

PCR for T-cell gene rearrangements from multiple specimens including bone marrow, splenic tissue (Figures 3A-3D), peripheral blood, and inguinal lymph node (not shown) biopsy exhibited identical T-cell clones when analyzed for TCR-beta and gamma genes. Appropriate treatment followed after confirmation of concurrent tMN and sPTCL, NOS.

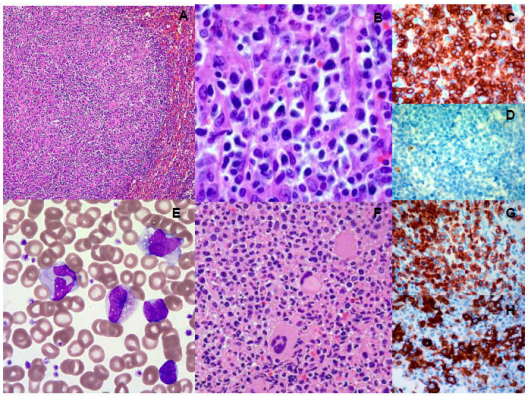

Figure 1: Spleen, lymph node and bone marrow manifestations of composite tCMML and sPTCL, NOS. A. Microscopic examination of the spleen revealed abnormal nodular proliferation of lymphocytes with expansion of both white and red pulps. B. The splenic parenchyma showed infiltration by atypical lymphocytes with dense chromatin and irregular nuclear contour in a background of prominent vasculature. C. Inguinal lymph node biopsy demonstrated complete nodular effacement by sheets of atypical lymphoid cells predominantly composed of T-cells which were highlighted by CD3. D. B-cells were virtually absent as shown by CD20 immunostain. E. Peripheral blood demonstrated monocytosis. F. Bone marrow biopsy was hypercellular showing atypical megakaryocytes and increased lymphocytes and monocytes. G. CD3 highlighted abnormal proliferation of T-cells within the bone marrow. H. CD163 stained sheets of monocytes found within the bone marrow.

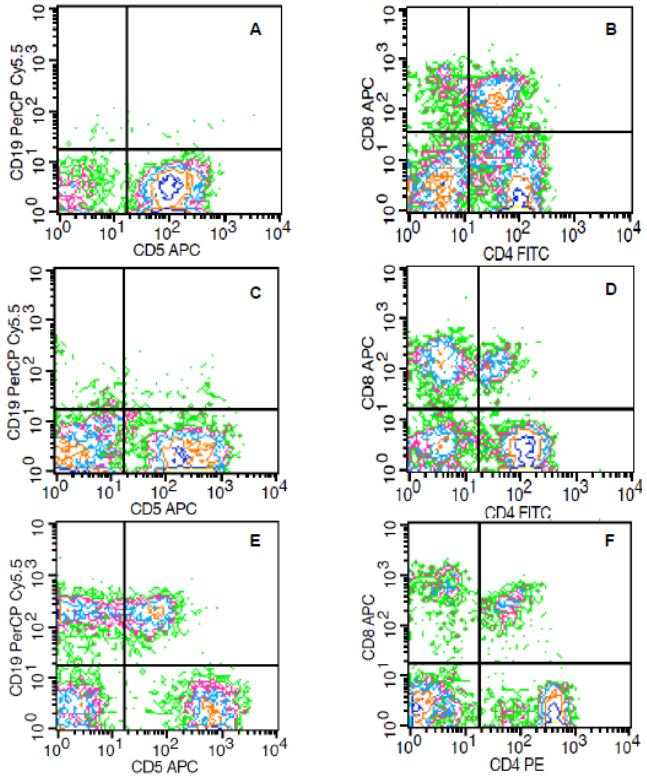

Figure 2: Flow cytometry results of the spleen (A-B), inguinal lymph node (C-D) and bone marrow (E-F) showing similar aberrant T-cell populations coexpressing CD4 and CD8.

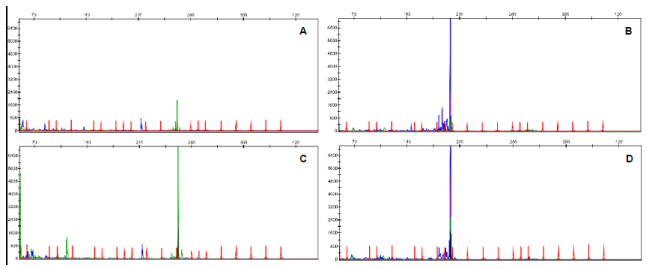

Figure 3: Identical T-cell receptor beta gene rearrangements were identified in spleen (A-B) and bone marrow (C-D) samples by PCR.

The patient developed severe colitis and after its resolution, the patient was started on a chemotherapy regimen consisting of etopside, methylprednisolone, cytarabine, and cisplatin for his PTCL, NOS. However, during treatment the patient developed deep vein thrombosis, dysrhythmia, and myocardial infarction and expired 15 months after initially developing sPTCL, NOS, and 4 months after the diagnosis of composite secondary neoplasms.

Discussion

Composite lymphomas is widely accepted concept, but rarely occurs as two distinct lymphomas, such as B-cell lymphoma/T-non-Hodgkin

lymphoma in a single anatomic site [6,7]. T-cell lymphoma secondary to B-cell lymphoma or composite T-cell lymphoma with B-cell lymphoma have been reported with uncertain incidence rate.7 To date, only one case of angioimmunoblastic T-cell lymphoma in a patient with CMML has been reported in the literature [8]. Regarding pathogenesis, a secondary T-cell malignancy could develop as a result of a dysfunction of the immune system, Epstein-Barr virus (EBV) reactivation, dysregulation of T-cell gene, or abnormal cytokine release, [7-9] whereas tMN often develops as a result of acquired cytogenetic aberrations, genomic instability or gene mutation [10]. The factors that contribute to a simultaneously abnormal proliferation of monocytes and T-cells in an individual are not well studied, and is likely attributed to dysregulated immunity and altered gene profiles. Clinically, we encountered a diagnostic challenge of composite tMN and sPTCL due to its extreme rarity.

When our patient with a history of B-cell lymphoma presented with lymphadenopathy and splenomegaly, the most likely clinical diagnosis was relapsing B-cell lymphoma. The patient was asymptomatic; however, several months later, his splenomegaly persisted and he developed pancytopenia. There was a high suspicion for tCMML in light of BM biopsy findings. Although deletion of 20q was documented in the bone marrow, this nonspecific cytogenetic abnormality was insufficient to establish a diagnosis of MDS or related disorders [11-13]. However, the presence of JAK2 V617F mutation is considered a clonal hematopoietic process, which has been seen not only in MPN, but also in MDS/MPN such as CMML with a positive detection rate of 10% [10,11]. Features of MDS/MPN were also found in the splenectomy specimen, although without significant monocytosis likely due to local radiation therapy. tCMML was verified 4 months later when the patient developed overt peripheral monocytosis and moderate dysplasia in his bone marrow. Generally it is unusual for CMML patients to present with lymphadenopathy, although myeloid/monocytic sarcoma can sometimes involve lymph nodes. When the patient's bone marrow showed T-cell proliferation, the likelihood of secondary T-cell lymphoma increased. However, it is critical to exclude reactive T-lymphocytosis secondary to viral infection when phenotypic evidence of neoplasm is equivocal, as seen in our patient. Our laboratory data showed no detectable DNA copies of cytomegalovirus or EBV thereby excluding a recent cytomegalovirus or EBV infection or reactivation. Concurrent flow cytometry and molecular studies performed on splenic tissue, inguinal lymph node, and bone marrow showed a clonal T-cell process, further supporting a diagnosis of PTCL, NOS. The incidence of PTCL, NOS, constitutes approximately 25% of all PTCL and >15% of all lymphomas [9]. However, according to one study, [14] dual CD4/CD8-positive PTCL is an uncommon variant (5.62%, 4/71 patients), which could raise a diagnostic dilemma since this phenotype often overlaps with reactive lymphoproliferative processes in autoimmune disorders that also show CD4/CD8 dual positivity [15]. Furthermore, identical clonal T-cell gene rearrangements involving various tissue specimens and at different time points confirm that the neoplastic T-cells are of the same oligoclonal origin.

In our case, treatment of our patient's primary neoplasm could have resulted in alteration of antigen presentation, cytokine release and immunomodulation of his immune system. These alterations in conjunction with acquiring cytogenetic abnormalities including del(20q) and gene mutation (JAK2), may have ultimately led to the development of concomitant lethal neoplasms.

Conclusion

In conclusion, composite myeloid and lymphoid malignancies as secondary disorders are extremely rare. Their uncommon coexistence may be easily overlooked secondary to "tunnel vision" to only one of the neoplasms. Therefore, more careful clinical and laboratory investigations and close follow-up are necessary.

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Conflict of Interest

The authors have no conflicts of interest to report.

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