

Case Report

Sequential occurrence of PTCL-NOS and T-ALL in the same patient – A rare observation suggesting possible transformation

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ABSTRACT

We report here the first case of sequential occurrence of peripheral T-cell lymphoma (PTCL)-not otherwise specified and T-lineage acute lymphoblastic leukemia (T-ALL) in a 50-year-old male diagnosed with the former on lymph node biopsy. He went into complete remission with 6 cycles of etoposide-based chemotherapy; however, he presented after 8 months with fever and generalized weakness. Peripheral smear showed 90% blasts, and his total leukocyte count increased to 80,000/cu mm over the next 2 days. Flow cytometry on peripheral blood showed 84% blasts, which were CD45 bright and positive for cytoplasmic CD3, CD8, CD5, CD7, and CD1a, and negative for surface CD3, CD34, and TdT. He was diagnosed with T-ALL in a treated case of PTCL and started on induction chemotherapy, to which he responded dramatically. However, he developed neutropenic colitis on day 14 of his illness and died.

Keywords: Peripheral T-cell lymphoma, T-lineage acute lymphoblastic leukemia, Transformation

INTRODUCTION

Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), is a heterogeneous group of non-Hodgkin lymphomas with variable clinical course and prognosis. The disease usually presents in males in the sixth decade of life with nodal presentation and an advanced stage in about 70% of cases. Extra-nodal presentation commonly involving the skin and gastrointestinal tract with eosinophilia, hemophagocytosis, and pruritus is common.^[1] Gene expression profiling (GEP) has identified two distinct molecular subtypes - PTCL-T-box Transcription factor 21 (*TBX21*) and *GATA3*, of which the latter has a more aggressive clinical course and adverse prognosis.^[2] The transformation of T-lineage acute lymphoblastic leukemia (T-ALL) to PTCL is rarely reported;^[3] however, ours is the first reported case of T-ALL occurring in a treated case of PTCL to the best of our knowledge.

CASE REPORT

A 50-year-old male presented to the hematology department of a tertiary care center with a history of intermittent low-grade fever and progressive increase in swelling in the right cervical region for 3 weeks. On examination, the patient had a 5 × 4 cm firm, mobile, and non-tender swelling in the right cervical region with multiple palpable level II, III, and IV cervical lymph nodes, the

largest measuring 2 × 1.5 cm on the left, and splenomegaly of 2 cm below the costal margin in the splenic axis. The rest of the general and systemic examination was normal. His laboratory parameters were as follows: hemoglobin 12 g/dL, total leukocyte count (TLC) 5600/cu mm, differential leukocyte count: neutrophils 65, lymphocytes 30, monocytes 3, eosinophils 2, platelet count 3,25,000/cu mm, and serum lactate dehydrogenase (LDH) of 990 IU/L. The peripheral blood smear was normal and did not show any blasts or atypical cells. He did not have any evidence of laboratory tumor lysis syndrome (TLS), and all other biochemical investigations were normal. Positron emission tomography-computed tomography showed numerous metabolically active lymph nodes with increased uptake in the liver and spleen. Bone marrow aspirate and biopsy showed trilineage differentiation without any evidence of hematolymphoid malignancy.

Excision biopsy of the right cervical mass was done, which showed diffuse effacement of architecture by monomorphic medium-sized lymphoid cells with pale cytoplasm, large irregular vesicular nuclei, and prominent nucleoli, has been shown in Figure 1a. There was hyperplasia of high endothelial venules. No Reed-Sternberg-like cells were seen. Immunohistochemistry (IHC) as shown in Figure 2 showed diffuse CD3 positivity. These cells were positive for CD4, CD8 (CD4>CD8), and CD5 and were negative for CD7, CD10, CD1a, CD99, CD56, bcl-6, PD-1, CD23, ALK, CD34, and TdT and showed variable positivity for CD30. The Ki-67 proliferation index was more than 90%. In view of the above, a diagnosis of CD4+/CD8+ PTCL-NOS was made. The patient was administered six cycles of etoposide-based chemotherapy, to which he responded well. His clinical condition improved with the disappearance of lymph nodes, and he was advised to undergo follow-up every month initially followed by every three months.

Eight months later, the patient reported a history of intermittent fever and generalized weakness for 7 days. On evaluation, his complete blood count was as follows:

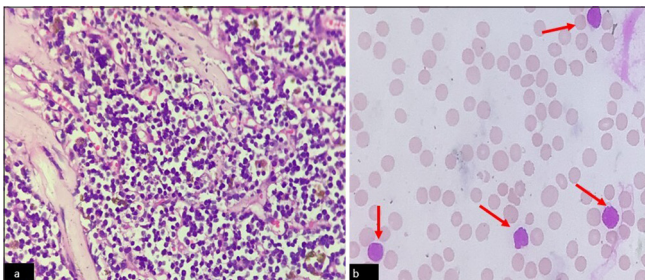


Figure 1: Photomicrographs of initial lymph node biopsy (a) [Hematoxylin and eosin (H&E), ×400], diffuse effacement of lymph node architecture by medium-sized lymphoid cells and peripheral smear after 8 months (b): Leishman–Giemsa, ×400, (red arrows show blasts with open chromatin).

hemoglobin-8g/dL, TLC = 10,000/cu mm, platelet count 1,70,000/cu mm, and the majority of the cells were blasts. These cells had a high N: C ratio with open chromatin, and few showed prominent nucleoli, as shown in Figure 1b. The patient was admitted, and his TLC rose to 80,000/cu mm over the next 2 days. He had features of laboratory TLS in the form of hyperuricemia (serum uric acid 11 mg/dL) and hyperkalemia (serum potassium 6.2 mg/dL). The patient was immediately started on intravenous hydration, rasburicase, and prophylactic antibiotics with insulin glucose infusion for hyperkalemia. Flow cytometry done on peripheral blood, as shown in Figure 3 showed 90% blasts that were CD45 bright and positive for cytoplasmic CD3, CD8, CD5, CD7, and CD1a and negative for surface CD3, CD4, CD56, CD34, TdT, CD117, CD19, CD10, cytoplasmic CD79a, CD13, CD33, CD14, CD64, human leukocyte antigen-DR and Myeloperoxidase. In view of the above phenotype, a diagnosis of T-ALL was made, and the patient was started on dexamethasone. The patient responded dramatically to steroids, and his counts crashed to 9000/cu mm over the next 3 days, and blasts disappeared from peripheral blood on day 5. Unfortunately, molecular studies could not be done for the patient due to resource constraints. The patient was started on induction chemotherapy for T-ALL and was doing well till he developed neutropenic colitis on day 14 of treatment and progressed to septic shock and multiple organ dysfunction syndrome despite aggressive antibiotic therapy, leading to his death.

DISCUSSION

PTCL is an aggressive lymphoma with frequent relapses and poor 5-year progression-free survival and overall survival.^[4] PTCL-NOS is a diagnosis of exclusion, and the disease is reclassified as angioimmunoblastic T-cell lymphoma (AITL) and anaplastic large cell lymphoma (ALCL) in 15% and 10% cases, respectively.^[5] The expression of two or more markers (CD10, bcl-6, PD-1, ICOS, and CXCL-13) associated with T-follicular helper (TFH) cell phenotype leads to classification of PTCL as nodal TFH cell lymphomas. This category includes nodal TFH cell lymphoma, angioimmunoblastic type, follicular type, and NOS.^[2] AITL is characterized by proliferation of high endothelial venules with clustering of medium-sized tumor cells with pale cytoplasm around them and expansion of follicular dendritic cell meshwork as evidenced by IHC with CD21 and CD23. The presence of hallmark cells positive for CD3, CD4, CD30, ALK, and epithelial membrane antigen (EMA) clinches the diagnosis of ALK-positive ALCL.^[1]

PTCL-NOS is characterized by diffuse infiltration by medium-sized lymphoid cells with irregular nuclei, which have predominantly CD4+/CD8- phenotype and T cell receptor-alpha beta restriction. However, CD4-/CD8+ and CD4+/CD8+ phenotypes or gamma delta restricted subtypes

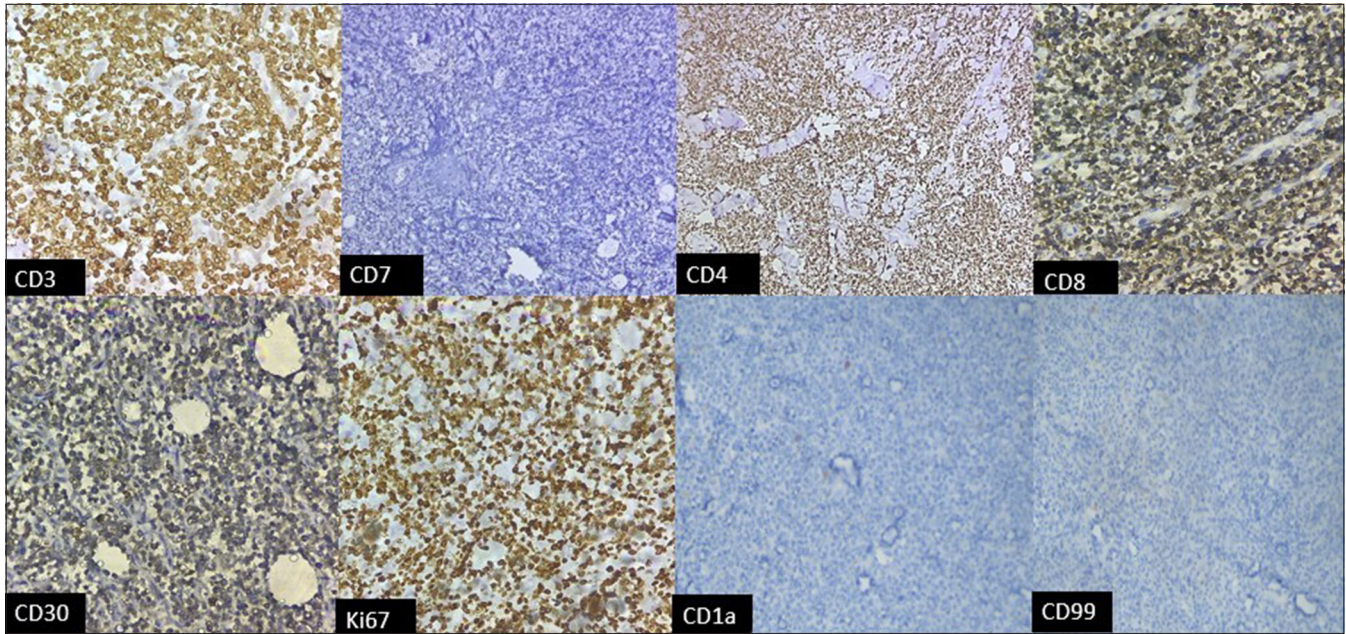


Figure 2: Photomicrographs of Immunohistochemistry on lymph node biopsy (Immunohistochemistry, $\times 400$, lymphoid cells are positive for CD3, CD4, CD8, and CD30 with high Ki67 and negative for CD7, CD1a, and CD99).

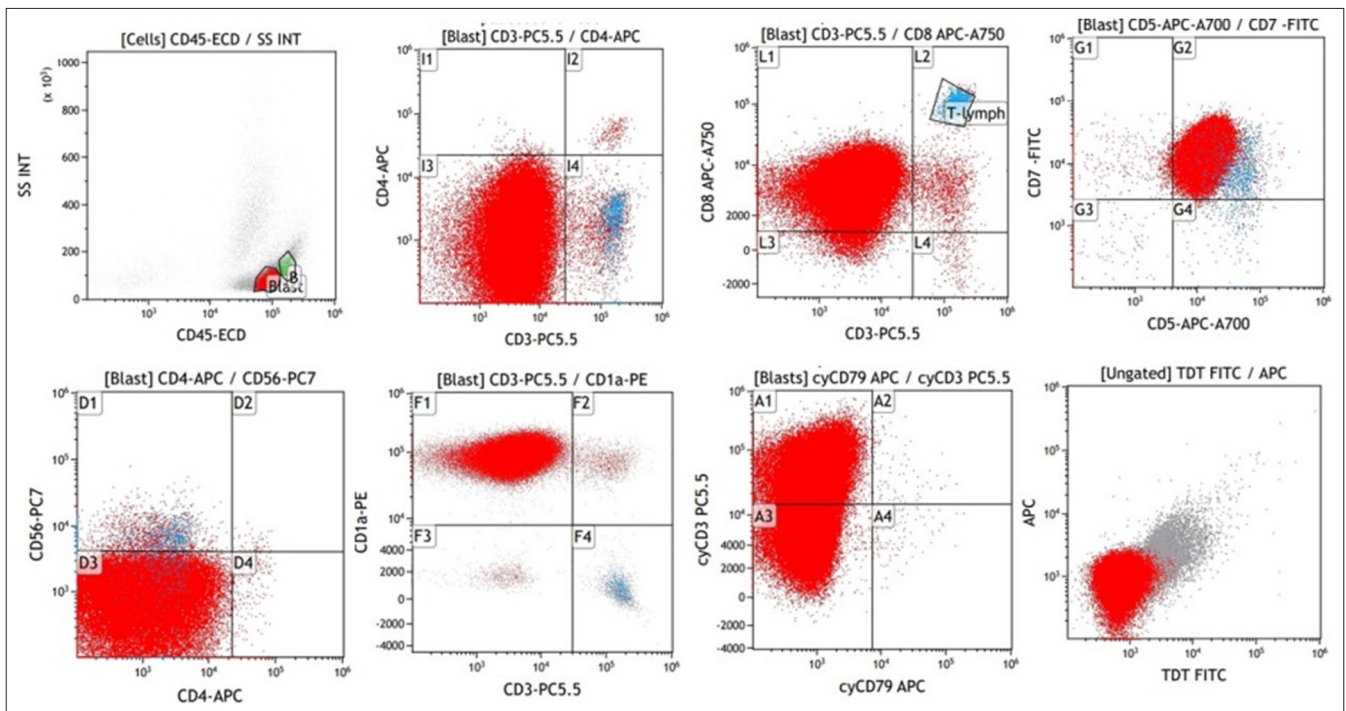


Figure 3: Dot-plots of flow cytometry on peripheral blood showing CD45 bright blasts gated on CD45-SSC plot negative for surface CD3, CD4, positive for CD8, CD7, CD5, CD1a, cytoplasmic CD3, and negative for CD56, TdT, and cytoplasmic CD79a. SSC: Side scatter.

may also be seen. Polymorphous infiltrate comprising histiocytes, eosinophils, plasma cells, and transformed B-cells resembling Reed-Sternberg (RS) cells may be seen.^[1] Our patient had a CD4+/CD8+ phenotype on lymph node biopsy without any polymorphous infiltrate or RS-like cells.

Expression of at least one cytotoxic molecule (CM): Perforin, TIA-1, or granzyme B leads to subclassification as nodal CM-positive PTCL, which has frequent Epstein-Barr virus (EBV) positivity and adverse prognosis, though not seen in our patient.^[6]

The poor prognostic factors are advanced stage at presentation, high international prognostic index score, CD8 positive phenotype, Ki-67 >70%, transformed cells more than 70%, GATA3 profile, positivity for EBV, and expression of CD30 in the majority of cells.^[1] Molecular studies were not done in our patient due to financial constraints; however, he had multiple adverse prognostic markers such as a Ki-67 index >90%, CD4+/CD8+ phenotype, advanced stage, and high LDH. Our patient developed T-ALL after 8 months of receiving chemotherapy while on follow-up. The immunophenotype of T-ALL was CD8+/CD4-/CD7+/CD1a+, which was distinct from the phenotype of PTCL (CD4+/CD8+/CD5+/CD7-/CD1a-/TdT-/CD99-) at initial presentation. The absence of immaturity markers (CD1a, TdT, CD99) on lymph node biopsy confirms that it was not a T-lineage lymphoblastic lymphoma of the lymph node on initial presentation.

Molecular profiling suggests a distinct demarcation between PTCL and T-ALL, which is corroborated by the cell of origin: T-cell progenitors or thymocytes in T-ALL and mature T-lymphocytes in PTCL. T-ALL is characterized by expression of oncogenes (*TAL-1*, *LMO-2*, *TLX-1*) and activation of the NOTCH signaling pathway. The TBX21 type PTCL on GEP are marked by defects in the epigenetic regulators such as *DNMT3A*, *IDH2*, *TET2*, and recurrent mutations in the *RHOA* gene, and lack gene fusions seen in T-ALL. The GATA3 subtype on GEP is characterized by copy number alterations in *TP53*, *PTEN*, and *CDKN2A* genes.^[7] Few studies report similarities between PTCL with Th1/cytotoxic signatures and T-ALL.^[8,9] The activation of NF- κ B, JAK/STAT, and PI3K-mTOR pathways is seen in both PTCL and T-ALL, and a second hit upstream of the mutated gene in a case of PTCL affecting the differentiation of immature thymocytes could hypothetically lead to transformation. In the absence of molecular studies, we do not have evidence of transformation and a plausible explanation for the occurrence of T-ALL in a previously diagnosed and managed case of PTCL.

This is an unusual case in which the patient developed T-ALL within 8 months of chemotherapy. The absence of molecular studies in our case is a major limitation, as a similar clonal signature and appearance of T-ALL-associated genes in the background of PTCL-associated genes would indicate transformation to T-ALL from PTCL. We hence describe this as a peculiar case of sequential appearance of T-ALL in a case of PTCL reported for the 1st time in the literature to the best of our knowledge.

CONCLUSION

The sequential occurrence of PTCL and T-ALL in a patient is extremely rare and genetic studies must be done in such cases to establish clonality and possible transformation which unfortunately could not be done in our patient.

Author Contribution: PM: Drafting manuscript, Intellectual content development; PS: Final version approval; SK: Analysis and Interpretation; AD: Acquisition of clinical and laboratory data.

Ethical approval: Institutional Review Board approval is not required.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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