SEQUENTIAL MULTILINEAGE HEMATOLOGIC MALIGNANCIES: A CASE OF MARGINAL ZONE B-CELL LYMPHOMA, PERIPHERAL T-CELL LYMPHOMA AND CHRONIC MYELOID LEUKEMIA

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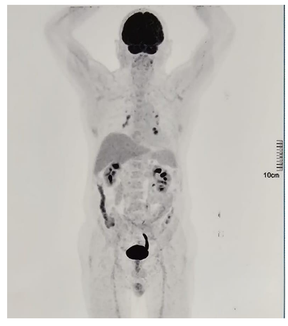
Context

The sequential occurrence of **multiple hematological malignancies of distinct cellular origin – B-cell, T-cell and myeloid –** in a single patient is a rare and clinically intriguing scenario.

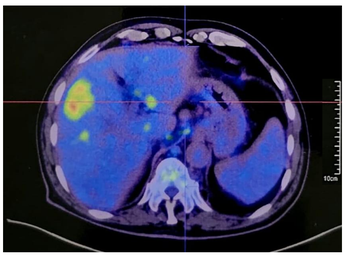
While cytotoxic therapy-related secondary neoplasms are a recognized consequence, the intersection of three genetically and immunophenotypically unrelated malignancies suggests an interplay between divergent clonal hematopoiesis, immune microenvironmental dysregulation and potentially underlying predisposition to genomic instability and mutagenesis.



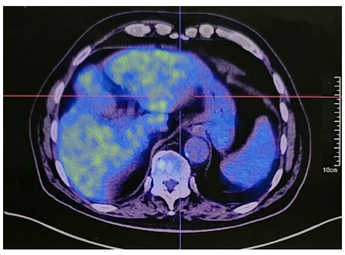
Before CHOEP



After CHOEP



Before CHOEP



After CHOEP

Patient

We report the case of a 77-year-old patient that initially presented with neutrophilic leukocytosis, generalized lymphadenopathy and night sweats. Biopsy confirmed stage III **small B-cell non-Hodgkin lymphoma**, classified as nodal marginal zone type with notable **follicular T-helper cell hyperplasia**, identified via expanded PD-1$^+$ population and a Ki-67 < 20%. Complete remission was achieved on CT scan, plus normalization of laboratory values along with clinical improvement, following 6 R-CHOP cycles and 8 cycles of rituximab maintenance.

Within three years, the patient developed systemic symptoms with nodal and hepatic involvement on PET-CT scan. Biopsy revealed **peripheral T-cell lymphoma**, small-medium cell variant CD3$^+$ CD5$^+$ and a Ki-67 < 10%. Diagnosed as Ann Arbor stage IV, he achieved a second complete remission with complete metabolic response on PET-CT scan after 6 cycles of CHOEP treatment.

One year after PTCL remission, routine laboratory workup revealed asymptomatic leukocytosis with left shift and bone marrow hypercellularity with granulocytic hyperplasia. BCR-ABL1 fusion gene was positive (75%), confirmed via cytogenetics and RT-PCR. New diagnosis of **chronic-phase CML** was established. The patient started on nilotinib, a second-generation TKI, with complete hematologic and molecular response achieved within 6 months.

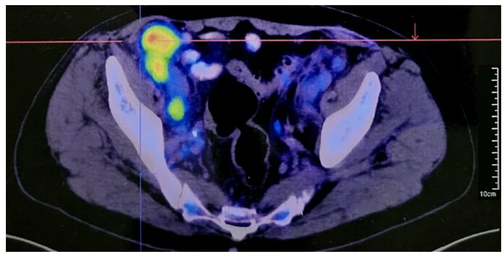
Discussion

The absence of shared immunophenotypic or genetic hallmarks between the malignancies suggests that these neoplasms did not arise through stepwise transformation of a single malignant clone, but rather from separate clonal events occurring within the same hematopoietic system. One possible explanation is early hematopoietic progenitor involvement, with a **common ancestral cell acquiring genomic alterations** that predisposed to multiple malignant trajectories.

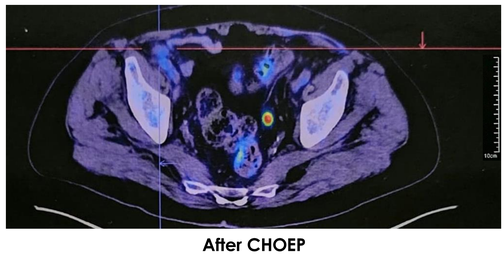
The prominent follicular T-helper cell hyperplasia identified in the initial lymphoma may represent a **permissive stromal milieu** facilitating secondary T-cell lymphomagenesis.

The emergence of BCR-ABL1–positive CML after cytotoxic chemotherapy raises the possibility of a therapy-altered bone marrow ecosystem, favoring expansion of a pre-existing leukemic clone. While t(9;22) translocation typically occurs de novo, prior treatment may have imposed **selective pressure on the hematopoietic niche**.

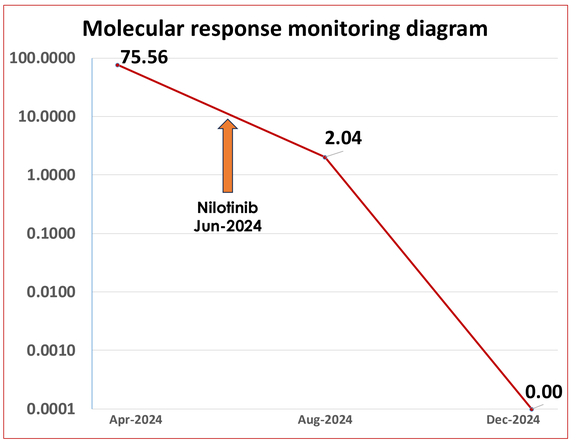
This case also emphasizes the concept of **hematopoietic plasticity**, with the bone marrow retaining the capacity to generate malignant populations across multiple lineages despite repeated interventions. The patient's complete responses to lineage-specific regimens demonstrate the ongoing therapeutic vulnerability of each dominant clone, even in a potentially unstable hematopoietic background.



Before CHOEP



After CHOEP



Conclusions

The hematologic course involving three sequential, distinct lineage malignancies within a single individual represents a compelling model of **hematopoietic clonal diversification**.

This case raises the possibility of early pluripotent hematopoietic stem cell involvement, with divergent clonal trajectories shaped by intrinsic genomic alterations, therapy-related selective pressure, and immune microenvironmental modulation.

The sustained complete remissions with lineage-specific therapies shows the efficacy of targeting the dominant malignant pathways and the resilience of hematopoietic plasticity.

This case advocates for integrative genomic and immunologic profiling to elucidate the pathophysiology of multilineage malignancies and to identify shared vulnerabilities for future therapeutic interventions.