Clonal CD5/CD10 negative EBV+ B-cell Lymphoma Arising During Treatment of a nTFH Lymphoma

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Background

T-follicular helper (TFH) cell lymphoma (nTFHL) is a subtype of aggressive peripheral T-cell lymphomas that arise from neoplastic transformation of T-follicular helper cells.

Dysregulated immune function of malignant helper T cells can result in unchecked proliferation and clonal expansion of EBV-infected B lymphocytes resulting in a secondary EBV+ B-cell process complicating existing nTFHL.

Key Mechanisms

- primary malignancy: neoplastic transformation and expansion of T-follicular helper (TFH) cells

- immune dysregulation: aberrant TFH–B-cell interactions and cytokine signaling alter normal B-cell homeostasis

- EBV-associated B-cell expansion: impaired immune surveillance and a permissive microenvironment may facilitate the proliferation of EBV-infected B cells

- secondary complication: EBV-positive B-cell proliferation may emerge alongside T-follicular helper cell lymphoma (nTFHL) and, in some cases, progress to a distinct B-cell lymphoma

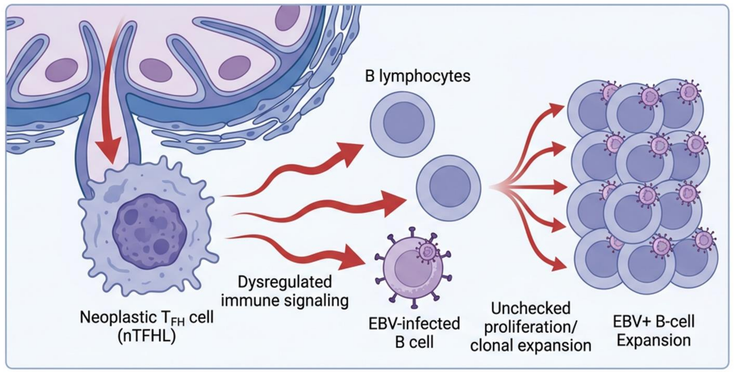


Figure 1: Representation of key mechanisms.

Case

A 57-year-old male presented to the hospital with two months of progressive B symptoms. He was found to have diffuse lymphadenopathy and pancytopenia.

Excisional lymph node and bone marrow biopsies demonstrated nTFHL.

He was treated with one cycle of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and two cycles of CV-CHP.

Interval PET demonstrated primary refractory disease for which he was subsequently started on salvage therapy with romidepsin/duvelisib.

He soon after developed a rapidly progressive peripheral lymphocytosis, worsening lymphadenopathy, and cytopenias.

Flow cytometry of peripheral blood revealed a new clonal CD5/CD10 negative EBV-positive B-cell population.

Repeat excisional lymph node and bone marrow biopsies demonstrated co-occurring clonal T and B cell populations identified by sequencing for IgH rearrangements and T-cell NGS.

immunoglobulin heavy-chain (IgH) gene rearrangement sequencing

what it detects: B-cell clonality

principle: during normal B-cell development, IgH genes undergo V(D)J recombination generating diverse antigen receptors; when a single B-cell clone expands, its descendants share the same IgH rearrangement

interpretation: detection of a dominant or reproducible IgH rearrangement supports the presence of a clonal B-cell population

T-cell next-generation sequencing (NGS)

what it detects: T-cell clonality

principle: T-cells acquire unique T-cell receptor gene rearrangements during development; expansion of a T-cell clone produces a dominant rearrangement pattern detectable by molecular sequencing.

interpretation: identification of a clonal T-cell population supports the presence of an expanded T-cell clone population

Molecular Finding	Significance
Clonal T-cell population	Supports the presence of an expanded T-cell clone associated with nTFHL.
Clonal B-cell population	Indicates expansion of B cells sharing a common IgH rearrangement.
Both populations detected	Demonstrates molecular evidence of coexisting T- and B-cell clonality, potentially reflecting the complex lymphoid microenvironment of nTFHL.

Figures 2 & 3: Identification of and understanding clonal populations is key to case presentation.

Outcome

Rituximab was added for treatment of the clonal B-cell population in addition to romidepsin/duvelisib for his T-cell lymphoma. Unfortunately, his disease continued to progress, and he ultimately passed away.

Discussion

This case highlights an example of clonal CD5/CD10 negative EBV+ B-cell lymphoma arising during the treatment for a nTFH lymphoma. Further research is needed to better understand how to best sequence therapy in such cases.

Current research indicates there is no established, evidence-based sequencing algorithm specifically for an EBV-positive clonal B-cell lymphoma arising during treatment of nTFH lymphoma.

Treatment regimens for concurrent T-cell and B-cell lymphomas is limited, and management is generally individualized.

Important considerations include:

- **Identify which lymphoma is driving the clinical course.** Compare the progression rate, symptoms, and organ involvement of each process.
- **Determine whether the B-cell lymphoma is CD20-positive.** This helps establish whether rituximab is a reasonable component of treatment.
- **Assess the response of the nTFH lymphoma to its current regimen.** If the T-cell lymphoma is responding but the B-cell lymphoma is progressing, the therapeutic strategy may need to change.
- **Review cumulative toxicity and overlapping treatment activity.** Some regimens may have activity against both lymphomas, but activity against one does not guarantee adequate control of the other. Anthracycline exposure (increased rise of cardiac toxicity), marrow suppression (neutropenic infections, severe cytopenias), and immune dysfunction are especially important.
- **Consider clinical trials and multidisciplinary review.** Taking an early, multidisciplinary approach involving hematology/oncology and hematopathology can help specialists can help guide treatment selection.

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