

BACKGROUND

- Secondary immunodeficiencies are clinically challenging and emphasize the need for a multidisciplinary approach
- Marginal zone lymphoma is typically treated with B cell depleting agents such as rituximab, a chimeric CD20 targeting monoclonal antibody. Rituximab depletes circulating and tissue residing B cells¹
- Bruton Tyrosine Kinase (BTK) is a critical enzyme in the development and function of B cells²
- Autoimmune conditions such as systemic lupus erythematosus (SLE) can also contribute to immune dysregulation³

CASE

A 55-year-old male PMH SLE on hydroxychloroquine, antiphospholipid antibody syndrome on warfarin, anal cancer s/p resection, longstanding splenomegaly and lymphadenopathy with unremarkable core needle biopsy in 2018 was diagnosed with marginal zone lymphoma via excisional lymph node biopsy in 2023

- His clinical course was complicated by a hospitalization for septic shock secondary to *Streptococcus agalactiae* bacteremia

•Work up revealed significant immunodeficiency

CD3+	141 cells/uL
CD4+	65 cells/uL
CD8+	65 cells/uL
IgG	510 mg/dl

Of note, he had persistent lymphopenia (0.06 to 0.49 cells/uL) and intermittent neutropenia (1.26-1.72 cells/uL) since 2009

- After starting rituximab for lymphoma, he developed severe neutropenia (0.47 cells/uL), candidal esophagitis (requiring transient PEG tube placement), and a left ethmoid and sphenoid sinus abscess and orbital cellulitis due to *Aspergillus fumigatus*

MANAGEMENT

- Given the severe side effects and disease progression after rituximab, he was transitioned to a selective BTK inhibitor, zanubrutinib.

- For *Pneumocystis jiroveci* (PCP), antiviral and antifungal prophylaxis, he receives dapsone, acyclovir, and voriconazole respectively. Bactrim was discontinued due to neutropenia

- He has remained infection-free since initiating zanubrutinib despite persistent lymphopenia (in cells/uL: CD3+ 147-183, CD4+ 74-108, CD8+ 48-62, CD19+ 8).

- His IgG levels improved to 700-800 mg/dL

- Notably, genetic testing was non-diagnostic

- His most recent PET scan showed stable disease

DISCUSSION

- Our patient's secondary immunodeficiency is multifactorial from SLE, lymphoma, and rituximab
- Impact of selective BTK inhibitors on immune function is not well studied. Ibrutinib, a first generation BTK inhibitor, improves T cell exhaustion with treatment of B cell lymphomas⁴; similar findings were not observed for zanubrutinib, although studies are limited⁵
- Recommendations for opportunistic infection prophylaxis often rely on data from HIV patients, yet it is unclear if the immune dysfunction is similar in individuals with non-HIV immunodeficiencies
- Our case underscores the importance of understanding the potential impact of B cell targeting therapies, such as BTK inhibitors and rituximab, on immune function, opportunistic infection prophylaxis and clinical management

REFERENCES

1. Rituximab [package insert]. South San Francisco (CA): Genentech, Inc.; 2023. Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=some-id> [Accessed 2025 Apr 13].
2. Palma M et al. BTK Inhibitors in Chronic Lymphocytic Leukemia: Biological Activity and Immune Effects. Front Immunol. 2021 Jul 1;12:686768. doi: 10.3389/fimmu.2021.686768. PMID: 34276674; PMCID: PMC8282344.
3. Perazzo SF et al. High frequency of immunodeficiency-like states in systemic lupus erythematosus: a cross-sectional study in 300 consecutive patients. Rheumatology (Oxford). 2016 Sep;55(9):1647-55. doi: 10.1093/rheumatology/kew227. Epub 2016 Jun 5. PMID: 27274095.
4. Davis JE et al. Ibrutinib protects T cells in patients with CLL from proliferation-induced senescence. J Transl Med. 2021 Nov 22;19(1):473. doi: 10.1186/s12967-021-03136-2. PMID: 34809665; PMCID: PMC8609739.
5. Treon SP et al. A randomized, placebo-controlled trial of the BTK inhibitor zanubrutinib in hospitalized patients with COVID-19 respiratory distress: immune biomarker and clinical findings. Front Immunol. 2025 Jan 21;15:1369619. doi: 10.3389/fimmu.2024.1369619. PMID: 39906744; PMCID: PMC11791645.