Challenging the Paradigm: Severe Rheumatoid Arthritis and Anti-TNF Failure in an X-Linked Agammaglobulinemia Patient

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INTRODUCTION

X-linked agammaglobulinemia (XLA) is the most common type of agammaglobulinemia, a rare inherited immunodeficiency disorder caused by mutations in the Bruton tyrosine kinase (**BTK**) gene on the X-chromosome.(1,2)

- BTK was identified in 1993 and produces an enzyme known as Bruton's tyrosine kinase.(3)
- It is the first known immune deficiency and is classified as a primary immunodeficiency disorder and an inborn error of immunity.
- Patients with XLA typically present after 6-9 months of life with reduced or undetectable B-lymphocytes once maternal antibodies diminish. Clinical manifestations often include recurrent sino-pulmonary and gastrointestinal infections.(1)
- XLA patients cannot produce antibodies and are vulnerable to infections from encapsulated bacteria.
- Management involves immunoglobulin replacement therapy to prevent infections.

Objectives: To describe a rare case of autoimmune erosive polyarthritis with anti-TNF therapy failure in a patient with genetically confirmed XLA, and to explore the role of T cell-mediated inflammation in the absence of B cells..

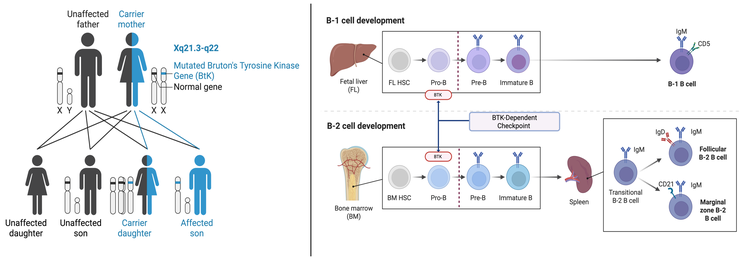


Figure 1a. *X-linked recessive inheritance pattern of Bruton's tyrosine kinase (BTK) gene mutations in X-linked agammaglobulinemia (XLA). The affected male in our case (bottom right) inherited the pathogenic BTK variant (c.1932C>G, p.Phe644Leu) from a carrier mother.* BTK deficiency results in a block in B cell development. Figure 1b: Without BTK, **pre-B cells fail to proliferate and differentiate**, leading to **developmental arrest and agammaglobulinemia.** Created in https://BioRender.com

CASE PRESENTATION

56-year-old male diagnosed with XLA at age 5 following multiple respiratory tract infections

- Currently on weekly Hizentra SCIG with no recent infections
- Diagnosed in November 2022 with symmetric chronic additive seronegative polyarthritis involving small and large joints, fulfilling the 2010 ACR/EULAR classification criteria for rheumatoid arthritis (RA).
- Symptoms began in early 2022, with ultrasound evidence of erosions in right D2, D5 MCP joints with PIP irregularities in November 2022

Treatment history:

- MTX (escalated to 25 mg/week by January 2023) + HCQ (since November 2022)
- SSZ trial from January 26 to March 2, 2023
- Adalimumab (Hadlima) from March 2023 to July 2024, with failure due to persistent active synovitis
- Switched to Rinvoq in July 2024 with significant improvement and resolution of synovitis, RA in remission (HAQ score of 0.25)

Treatment failure of anti-TNF therapy is unusual in this context as XLA results in no circulating B-cells (4, 5)

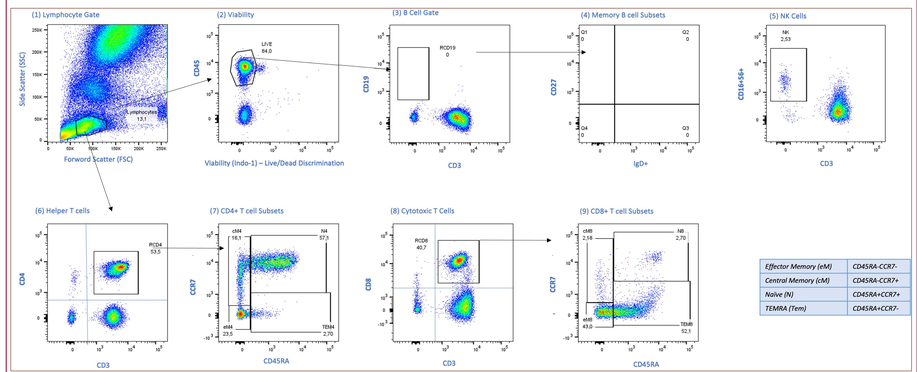
METHODS

- Lymphocyte subset analysis using multicolor flow cytometry T cell identification (CD3+) with CD4/CD8 characterization, B cell analysis using CD19, CD27, IgD, IgM, and CD38 markers, NK cell identification (CD3-CD56+)
- Lymphocyte Proliferation Assay (LPA) using CFSE-labeled PBMCs Stimulation with mitogens (PHA, pokeweed, anti-CD3/CD28) and recall antigens. 7-day culture with analysis of proliferative responses by CFSE dilution
- Genetic testing initially performed at ARUP Laboratories in 2015 using massively parallel sequencing with Sanger confirmation. Invitae Primary Immunodeficiency Panel (429 genes) sent in 2024. Variant classification following ACMG criteria established by Richards et al.(6)
- **Rheumatologic Evaluation:** Musculoskeletal ultrasound assessment, comprehensive autoantibody screening, and radiographic examination of hands and feet

RESULTS

Category	Parameter	Result	Reference Range	Interpretation
Immunoglobulins	IgA	<0.10 g/L	0.7 – 4 g/L	*Deficient*
	IgG	9.52 g/L	7 – 16 g/L	*on adequate IgG Replacement*
	IgM	<0.20 g/L	0.4 – 2.3 g/L	*Deficient*
	IgE	<5 ug/L	0 – 240 ug/L	
B Cells	**Total B cells**	**0%**	7 – 16 %	***Absent***
	Total B cells (absolute)	**0**	97 – 270 cells/cu mm	"
B Cell Subsets	**CD27+IgD- Memory B cells**	**0%**	11 – 33 %	"
	CD27+IgD- Memory B cells (absolute)	**0**	10 – 73 cells/cu mm	"
	CD27+IgD+ Non-switched memory	**0%**	7 – 24 %	"
	CD27+IgD+ Non-switched memory (absolute)	**0%**	10– 46 cells/cu mm	"
	CD27-IgD- Double negative B cells	**0**	1– 10 %	"
	CD27-IgD- Double negative B cells (absolute)	**0**	4 – 15 cells/cu mm	"
	CD27-IgD+ Naive B cells	**0%**	42 – 71 %	"
	CD27-IgD+ Naive B cells (absolute)	**0**	44 – 158 cells/cu mm	"
T Cells	Total T cells	97%	65 – 80 %	*High* ▲
	Total T cells (absolute)	1048	805 – 1606 cells/cu mm	*Normal*
	CD4+ T cells	36%	34 – 52 %	*Normal*
	CD4+ T cells (absolute)	389	474– 1009 cells/cu mm	*Decreased* ▼
	CD8+ T cells	61 %	18 – 34 %	*High* ▲
	CD8+ T cells (absolute)	659	208 – 635 cells/cu mm	*High* ▲
	CD4/CD8 ratio	0.6	1 – 3	*Inverted*
	CD4-CD8- T cells	1.2%	0–1%	*Elevated* ▲
NK Cells	CD16+56+ cells	3 %	6–23%	*Decreased* ▼
	CD16+56+ cells (absolute)	32	83– 372 cells/cu mm	*Decreased*
T Cell Function (LPA)	Proliferation to anti-CD3/CD28 (CD4)	89 %	78– 90 %	*Normal*
	Proliferation to anti-CD3/CD28 (CD8)	81 %	78– 90 %	*Normal*
	Proliferation to PHA (CD4)	81 %	83 – 94 %	*Normal*
	Proliferation to PHA (CD8)	87 %	83 – 96 %	*Normal*
	Proliferation to Pokeweed (CD4)	5 %	44 – 77 %	*Decreased* ▼
	Proliferation to Pokeweed (CD8)	72 %	44 – 77 %	*Normal*
	Tetanus response (CD4)[1]	0%	1 – 15 %	*Absent* ▼
	Tetanus response (CD8)	0%	1 – 19 %	*Absent* ▼

Table 1: Immunological Results. Pan-hypogammaobulinemia, with absent IgA and IgM, and low IgE. Flow Cytometric Analysis: Despite an inverted CD4:CD8 ratio (0.6), both CD4⁺ and CD8⁺ T cells showed preserved numbers. **B cell analysis** revealed **complete absence of CD19⁺ B cells**, and downstream subset analysis confirmed undetectable naive ($CD27^-IgD^+$), memory ($CD27^+IgD^-$), and double-negative ($CD27^-IgD^-$) B cell populations. **Lymphocyte Proliferation Assay (LPA):** Responses to **mitogens** were intact across both CD4⁺ and CD8⁺ subsets. (1)Antigen-specific responses were absent for tetanus toxoid despite vaccination.



Effector Memory (eM)	*CD45RA-CCR7-*
Central Memory (cM)	*CD45RA-CCR7+*
Naïve (N)	*CD45RA+CCR7+*
TEMRA (Tem)	*CD45RA+CCR7-*

Figure 2: Flow cytometric immunophenotyping of peripheral blood lymphocytes . Immunophenotyping was performed at the **Flow Cytometry Laboratory of the Montreal General Hospital, McGill University Health Centre**, using multicolor flow cytometry panels.**(1)** Lymphocytes were gated using forward scatter (FSC) versus side scatter (SSC). **(2)** Viable leukocytes were identified as CD45⁺ cells negative for a viability dye detected in the Indo-1 channel.**(3)** B and T cells were gated using CD19 versus CD3. CD19⁺ B cells were completely absent (0%), while CD3⁺ T cells comprised the majority of events (96.8%), consistent with XLA. **(4)** CD27 versus IgD gating showed no definable memory B cell subsets, as expected in the absence of CD19⁺ cells.**(5)** Natural killer (NK) cells were identified as $CD3^-CD16^+CD56^+$, comprising 2.53% of lymphocytes.**(6)** CD4⁺ T helper cells were identified among CD3⁺ cells.**(7)** CD4⁺ T cells were further categorized into memory subsets using CD45RA and CCR7 expression.**(8)** CD8⁺ cytotoxic T cells were gated from the CD3⁺ population. **(9)** CD8⁺ T cells were similarly classified into memory subsets by CD45RA and CCR7.

Gene	Variant (cDNA/Protein)	Zygosity	Classification	Chromosomal Location	Interpretation
BTK[1]	c.1932C>G (p.Phe644Leu)	Hemizygous	Likely Pathogenic	Xq21.3-q22	Novel nucleotide change affecting conserved residue; not found in population databases; predicted damaging by SIFT/PolyPhen/MutationTaster; located in BTK kinase domain; satisfies ACMG criteria
BTK[2]	c.1932C>G (p.Phe644Leu)	Hemizygous	Likely Pathogenic	Xq21.3-q22	Supports diagnosis of XLA; variant previously observed in patients with XLA; *GnomAD no frequency.* ClinVar ID: 1047473

Table 2. Genetic Testing Results: The BTK variant c.1932C>G (p.Phe644Leu) was first identified by ARUP Laboratories[1] in 2015 using a targeted X-linked agammaglobulinemia panel including sequencing of 9 genes and deletion/duplication analysis of 6 genes, followed by Sanger confirmation. The variant was later confirmed in 2024 by Invitae[2] using a 429-gene primary immunodeficiency (PID) panel with next-generation sequencing and bioinformatic modeling. Computational predictions (SIFT, PolyPhen-2, MutationTaster) support a damaging effect. Based on available evidence, the variant is classified as likely pathogenic, consistent with a diagnosis of X-linked agammaglobulinemia (XLA).

Test Category	Test	Result
Autoantibodies (RA-related)	Rheumatoid Factor (RF)	Negative
	Anti-Cyclic Citrullinated Peptide (anti-CCP)	Negative
Connective Tissue Disease	Antinuclear Antibodies (ANA)	Negative
	Anti-dsDNA	Negative
	Anti-cardiolipin IgG / IgM	Negative
Vasculitis Markers	Anti-Proteinase 3 (PR3)	Negative
	Anti-Myeloperoxidase (MPO)	Negative
Paraneoplastic Panel	Anti-Hu (ANNA-1), Anti-Ri (ANNA-2), Anti-Yo (PCA-1), Amphiphysin, CV2, PNMA2	Negative
Myositis Panel (Line Blot)	Jo-1, Ku, MDA5, Mi-2α, Mi-2β, OJ, SAE1, SRP, $TIF1\gamma$, PM-SCL100, MJ, EJ, $PL\text{-}12$, $PL\text{-}7$	Negative

Table 3: Extensive rheumatologic workup revealed **no serologic evidence of autoimmunity**, vasculitis, or paraneoplastic syndromes. Myositis antibody panel (line blot) was also completely negative. These findings support a seronegative autoimmune phenotype, occurring in the absence of detectable B cells.

DISCUSSIONS

This case presents several clinically significant and mechanistically intriguing findings:

- **B Cell-Independent Autoimmunity**: Development of seronegative erosive polyarthritis in a patient with genetically confirmed XLA and complete absence of B cells challenges conventional understanding of RA pathogenesis.
- **Anti-TNF Treatment Failure:** Failure of adalimumab despite the absence of circulating B cells is mechanistically significant, as secondary treatment failure is typically attributed to anti-drug antibody development.
- **T Cell-Mediated Inflammation:** The patient's response to Rinvoq (upadacitinib), a JAK1 selective inhibitor that primarily affects T cell function, supports the hypothesis that T cells can independently drive autoimmune inflammation in the absence of B cells.
- **Therapy Selection Implications: The** successful response to JAK inhibition after anti-TNF failure suggests that targeting T cell signaling pathways may be more effective than TNF blockade in XLA patients with inflammatory arthritis.

Previous literature suggests approximately 1.41% of XLA patients in the USIDNET registry simultaneously have inflammatory arthritis, indicating a rare but recognized association.(3)

CONCLUSIONS

This rare case of autoimmune erosive polyarthritis in a patient with genetically confirmed XLA provides several important insights:

1. **Pathophysiological Implications:**
   i. Confirms that T cells can independently drive autoimmune inflammation in the absence of B cells
   ii. Challenges the B cell-centric model of autoimmune arthritis pathogenesis
   iii. Suggests alternative pathways for inflammatory arthritis development in immunodeficiency
2. **Treatment Considerations**:
   i. JAK inhibition (Rinvoq) was effective after anti-TNF failure, indicating different mechanistic pathways
   ii. Targeted T cell pathway inhibition may be more appropriate for XLA patients with inflammatory arthritis
   iii. Treatment selection should consider the unique immune environment of XLA patients

Future Directions

- Further investigation into T cell subsets and function in XLA patients with autoimmunity
- Exploration of cytokine profiles and inflammatory mediators in this patient population
- Development of personalized treatment algorithms for primary immunodeficiency patients with autoimmune manifestations

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