

## Case Report

# Juvenile idiopathic arthritis in X-linked agammaglobulinemia with a novel in-frame deletion: a case report and functional analysis

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**Abstract:** Introduction: X-linked agammaglobulinemia (XLA) is a rare primary humoral immunodeficiency caused by mutation of Bruton tyrosine kinase (BTK), featuring early onset and repeated bacterial infections. Arthritis is an intriguing presentation because despite the constant threat of infection, inflammatory and rheumatic arthritis occur in rare cases, suggesting that unregulated autoimmunity can arise in the context of immunodeficiency. Case presentation: A 17-year-old Chinese male presented with a 4-month course of arthritis in his right knee and right hand. The clinical features and laboratory findings were consistent with juvenile idiopathic arthritis. He had many prior infections and received antibiotic treatment at various local clinics without a definite diagnosis. Immunological studies revealed severely decreased level of serum immunoglobulin and circulating B lymphocytes. Sequencing of the BTK gene in this pedigree identified a novel 3 base pairs deletion in exon 3 resulted in a glutamine deletion, and established the diagnosis of XLA. The patient responded well to oral naproxen and maintained asymptomatic on monthly intravenous immunoglobulin. Conclusions: This case strengthened the importance of early and accurate diagnosis and careful management of XLA patients to maintain the *Yin-Yang* balance of immunodeficiency and autoimmunity.

**Keywords:** X-linked agammaglobulinemia, juvenile idiopathic arthritis, immunodeficiency, autoimmunity, Bruton tyrosine kinase, B lymphocytes

## Introduction

X-linked agammaglobulinemia (XLA) is a rare disorder of primary humoral immunodeficiency, featuring the severe decrease of serum immunoglobulin of all isotypes, and a circulating B cell count < 2% normal level [1]. Upon the completion of heavy-chain rearrangement in pro-B lymphocytes, the mutation of a single gene encoding Bruton tyrosine kinase (BTK) at the Pleckstrin homology (PH) domain blocks downstream BCR signal and halts pre-B cells' proliferation. B lymphocytes fail to mature and cannot produce immunoglobulin, thus exposing patients to higher risk of infections. Periodic intravenous immunoglobulin (IVIG) would be sufficient to prevent infection in most cases.

Arthritis is not uncommon in XLA (reported incidence ranging from 7% to 30%) [2-5], but it is a rather interesting presentation because less

than 7% of all cases were clinically diagnosed with rheumatic diseases, including rheumatoid arthritis (RA) [6, 7], spondyloarthritis (SpA) [8-10] and juvenile idiopathic arthritis (JIA) [11, 12]. These cases represent a subgroup of patients in whom autoimmunity developed from the background of immunodeficiency. Such cases are clinically challenging not only for diagnosis but also for the life-long management to balance immune homeostasis.

In this case report we described a 17-year old male presenting as oligoarticular JIA, and established the diagnosis of XLA by identifying a novel deletion of BTK gene in his pedigree.

## Case presentation

A 17-year-old male presenting with a 4-month course of joints pain and swelling was admitted to our center for the first time. The symptoms

**Table 1.** Summary of the patient's laboratory studies

Test	Value	Reference	Unit
Complete blood count	Within normal range		
Coagulation function	Within normal range		
ANA, ENAs, RF, CCP, AKA	(-)		
HLA-B27	(-)		
Antibodies against HBV, HCV, HIV & TB	(-)		
ESR	2	< 21	mm/h
C-reactive protein	29.22	< 5	mg/L
Serum globulin	13.8	20.0-40.0	g/L
Uric acid	625	240.0-490.0	µmol/L
Ig G	< 0.33	8.0-15.5	g/L
Ig A	< 66.7	836-2900	mg/L
Ig M	337	700-2200	mg/L
Ig E	1.72	0.1-150.0	IU/ml
Circulating B cell	6 (0.2)	175-332 (3.91-8.59)	cell/µl (%)
Circulating T/NK cell	Within normal range		

ESR: erythrocyte sedimentation rate. Ig: immunoglobulin. ANA: antinuclear antibody. ENAs: anti-extractable nuclear antigens. RF: rheumatoid factor. CCP: anti-cyclic citrullinated peptide antibodies. AKA: anti-keratin antibodies. HLA: human leukocyte antigen. HBV: hepatitis B. HCV: hepatitis C. HIV: human immunodeficiency virus. TB: Mycobacterium Tuberculosis.

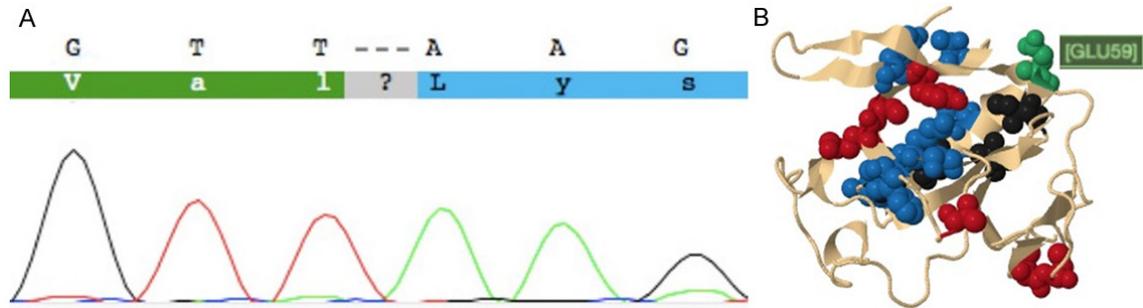
started in his right knee, and then involved the third to fifth metacarpophalangeal joints of his right hand. Recent trauma was denied. He reported having bilateral synovitis of the hip 7 years ago, which lasted five months until a full recovery was achieved with unknown management. He had meningitis six years ago and pulmonary infection with bilateral bronchiectasis last year. His parents recalled him having many moderate episodes of respiratory and skin infections ever since he was two years old. He received antibiotic treatments for most of these episodes at various local clinics without continuous medical records and definite diagnosis. His parents and a younger sister were all apparently healthy and reported nothing unusual on family history. Upon physical examination, his right knee was moderately swelling and tender, with increased local temperature and limited motion. He was afebrile and ambulant, without other abnormal physical findings.

A normal complete blood count and slightly elevated C-reactive protein level suggested of a non-septic course. Arthrocentesis of the patient's right knee found the joint fluid to be yellowish red, viscous and contained > 2000 leukocytes/ml (25% lymphocytes and 75% neutrophils). No crystals were found. Gram stain, acid-fast stain and pathogen culture of the joint fluid were all negative, deeming the arthritis aseptic.

Ultrasound and X-ray of the right knee suggested non-erosive synovitis. These findings combined with his sub-acute feature without signs of local or disseminated infections, suggested the patient's arthritis was inflammatory and pathogen-free.

Based on the patient's clinical presentation and laboratory findings (**Table 1**), arthritis due to trauma, gout, or hemophilia was unlikely. Rheumatic arthritis including rheumatoid arthritis, ankylosing spondylitis, enteritis related arthritis, spondylitis with inflammatory bowel disease, Reiter's syndrome, and psoriatic arthritis were excluded as well. The patient fulfilled the International League of Associations for Rheumatology classification criteria of oligoarticular juvenile idiopathic arthritis [13]. On 200 mg/daily oral naproxen and 5 gm/monthly IVIG infusion, the patient's serum globulin level raised within normal range. His arthritis disappeared within a month, and he had not relapsed on his follow-up visits six month later.

The patient's past medical history raised strong suspicion of primary immunodeficiency. Immunological evaluation (**Table 1**) revealed severely decreased serum immunoglobulin of all isotypes, and a nearly absent circulating B cell level indicating a B lymphocytes abnormality. Subsequent bone marrow biopsy, as well as



**Figure 1.** The Patient's BTK gene sequencing. A: Sequencing showing a 3 bp deletion of GAG (represented by ---) at exon 3 in the patient's cDNA transcript, resulted in a deletion of a glutamine at position 59 (represented by a question mark) between a Valine (Val) and a Lysine (Lys). B: The mutated amino acid [Glu59] is located on protein surface represented in green color. Other known mutated residues on the same chain were also shown, including location either buried inside (black) or on the surface (blue) with unknown protein interface, or known interface (red).

flow cytometry of peripheral blood and bone marrow confirmed absent CD19<sup>+</sup> (mature B) lymphocytes. When specifically inquired again, the patient's mother recalled that two of her brothers died of unknown reason within the first year of life. The low immunoglobulin levels, absent B cells and maternal family history strongly suggested of X-linked agammaglobulinemia.

A *BTK* gene sequencing was performed on the patient, his mother and sister. We found a mutation at c.175-177het\_delGAG (p.Glu59del, RefSeq NM\_000061.2) in exon 3, resulted in deletion of a glutamine at position 59 in the protein's PH domain. According to current *BTK* databases, we are the first to report this deletion and its phenotype featuring JIA. Computational prediction using Ensemble ([ensembl.org/info/docs/tools/vep/index.html](http://ensembl.org/info/docs/tools/vep/index.html)) rated its impact at a moderate level. Protein structural analysis shows that the mutated glutamine is located on protein surface (**Figure 1**). Since p.Glu59del cannot be mapped on any known protein-protein interface, we cannot show how it alters downstream signal directly. But by shifting all subsequent amino acids one position forward and cross referencing with known protein interaction using dSysMap ([dsysmap.irbbarcelona.org](http://dsysmap.irbbarcelona.org)), we found that this forward shift lead to changes including p. His362Gln and p.Arg562Trp, which have been shown to affect BTK interaction with two important molecules involved in cell proliferation, GRB2 and MET respectively.

### Discussion

Arthritis of autoimmune or autoinflammatory nature is rare in XLA patients (7%) when com-

pare with an overall population of primary immunodeficient patients (18%) [6]. Non-septic arthritis cases in XLA could be monoarthritis of a large joint, oligoarthritis or polyarthritis involving large and small joints. Pain could be mild to severe but the effusion was often prominent.

RA has been described in XLA patients with symmetric destruction of small joints and subcutaneous nodules, and was treated with disease-modifying anti-rheumatic drugs. In these patients, biopsy of synovial membrane and skin nodule found a predominant CD8<sup>+</sup> T cell infiltration, in contrast to the dominant B cell and CD4<sup>+</sup> T cell infiltration in classic RA. These findings suggested that in the absence of B cell and immunoglobulin, unregulated T cell activity probably participated in the pathogenesis of synovitis in agammaglobulinemia patients [6, 7].

SpA including reactive arthritis, inflammatory bowel disease, and enteritis-related arthritis has been reported in XLA as well. Since XLA patients are susceptible to gastroenteritis, the alteration of gut microbiome in presence of HLA-B27 increased the possibility of SpA [8-10].

JIA in XLA patients are sub-acute or chronic arthritis that responded well to IVIG and non-steroid anti-inflammatory drugs [11, 12]. Recent evidence linked the diagnosis of juvenile idiopathic arthritis to childhood antibiotic exposure, supporting the notion that repeated antibiotic usage and infection could both disturb human microbiome, and increase the incidence of autoimmunity disorders by altering immune regulation and self-tolerance [15].

Due to reoccurrence of infections, XLA patients would most likely be diagnosed in their first

decade of life. Once diagnosed with XLA, periodic IVIG should be given to maintain a protective level of serum immunoglobulin. However, it is possible for adolescent or adult patients to receive late diagnose even after several invasive infections like this case, which warrants higher awareness of primary immunodeficiency among health care providers. When these undiagnosed patients presented with rheumatic features, it is critical to thoroughly investigate and exclude infections before initiating treatment for autoimmune diseases, since delaying antibiotics or using immunosuppressant agents would put patients at significant higher risk of severe infections, even disseminated infections leading to patient's death [14]. This highlights the importance of early diagnosis and careful management of immunodeficiency, since repeated infections and excessive antibiotic usage could both contribute to the breaching of immune tolerance [6, 15], therefore protecting patients from infection could potentially protect them from the disruption of tolerance and the development rheumatic diseases.

In conclusion, X-linked agammaglobulinemia was mostly diagnosed in the first few years of life and very rarely accompanied with rheumatic arthritis. We reported a case of juvenile idiopathic arthritis in a 17-year old male and established the diagnosis of X-linked agammaglobulinemia confirmed by a novel BTK mutation in the pedigree. Immunodeficiency and autoimmunity, the Yin and Yang of immunity can be bridged when infection and antibiotic usage disrupts immune regulation.

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#### Disclosure of conflict of interest

None.

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