Title of manuscript : Forme fruste of scleroderma and autoimmune hearing loss in a young adult with X linked agammaglobulinemia

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To the Editor,

X-linked agammaglobulinemia (XLA) is an antibody deficiency disorder characterized by recurrent sinopulmonary infections, absent B cells and immunoglobulins (Ig). It has recently been observed that patients with XLA have defects in other arms of the immune system and are also predisposed to develop autoimmune complications and malignancy. With improvement in care, these patients are now surviving longer and a spectrum of other complications are being recognized. Arthritis may be seen in up to $1/3^{rd}$ of all cases. We report a young adult with XLA who had inflammatory polyarthritis, skin thickening and autoimmune sensorineural deafness.

A 24-year-old boy was symptomatic since the age of 3 years with recurrent episodes of ear discharge and pneumonia. He was evaluated elsewhere at the age of 10 and was found to have low IgG, IgA and IgM. He was diagnosed to have hypogammaglobulinemia and was initiated on immunoglobulin replacement therapy. He started developing pain and swelling in multiple small and large joints since the age of 13. He was prescribed naproxen in an another health care facility. At the age of 18, he developed sudden onset sensorineural hearing loss. He was evaluated elsewhere and was prescribed hearing aids. He was referred to us for evaluation at the age of 24.

In his family history, his elder sibling died at the age of 25. He had had history of recurrent infections since early childhood. There was also history of death of three maternal uncles in early age because of recurrent infections. However, sibling and maternal uncles were not evaluated.

On examination, he was cachectic with shiny skin over fingers and lower limbs. The skin was noted to be thickened. There were deformities (swan neck and boutonniere deformities) on multiple joints of fingers and toes (Figure 1). Knee joints were swollen along with restriction of movements. He had multiple contractures leading to restriction of movements of knee joints, ankle joints and elbow joints. Respiratory, cardiovascular and nervous system examination was unremarkable. Laboratory examination showed normal inflammatory parameters such as C-reactive protein and erythrocyte sedimentation rate. Rheumatoid factor was negative. Immunoglobulin profile of the patient revealed normal serum IgG (914) low serum IgA (<26 mg/dl) and IgM (<18mg/dl). Flow cytometry revealed markedly reduced proportion of B cells (<1%) with normal proportion of T cells and NK cells. T cell immunophenotyping showed that activated T cells (CD3+HLADR+) were increased in the patient as compared to control(46.91% VS 10.50%) and follicular helper T cells (CD45RA+ CXCR5+) were decreased in number (1.42% VS 7.11%).

Nail fold capillaroscopy showed no capillary dropout or haemorrhages. Skin biopsy revealed changes of fibrosis. Ultrasound knee joints revealed synovial hypertrophy along with minimal effusion.

Whole exome sequencing revealed hemizygous missense variation in exon 15 of the BTK gene (chrX:g.101356060G>C) that resulted in the amino acid substitution of glycine for arginine at codon 554. This variant has previously been reported in patients affected with XLA.

He was diagnosed to have XLA with polyarthritis presenting as*forme fruste of scleroderma* . He was continued on monthly intravenous immunoglobulin replacement (400mg/kg) and cotrimoxazole prophylaxis. For arthritis, he was advised naproxen and physiotherapy. He also underwent cochlear implant on follow up and is currently doing well.

Patients with XLA usually present with recurrent sino-pulmonary and gastrointestinal infections, while autoimmune features are infrequent as compared to patients with common variable immunodeficiency[1]. Index patient presented with features of both recurrent infections as well as autoimmunity. He had features of deforming inflammatory arthritis (*forme fruste of scleroderma*) along with autoimmune sensorineural hearing loss (SNHL).

Previously published reports have suggested that juvenile chronic arthritis in males may be the initial clinical presentation of XLA.[2] Index case had previously been diagnosed to have hypogammaglobulinemia and he developed arthritis while he was on immunoglobulin replacement therapy. When he presented to us, he had already developed a chronic deforming arthritis that resembled the clinical presentation of *forme fruste of scleroderma.*

Even though scleroderma has rarely been reported in patients with XLA[3.] Index patient likely had *forme fruste of scleroderma* as other clinical features of scleroderma were not seen.

Index patient also had features of autoimmune SNHL as hearing loss developed acutely. Several authors have reported SNHL in patients with agammaglobulinemia and have proposed following mechanisms[4,5]: Impaired clearance of apoptotic cells; diminished B cell tolerance as Bruton tyrosine kinase (Btk) is essential for B cell tolerance (Absence of Btk leads to inappropriate continuous receptor editing by B cells. This enables B cells to overcome Btk-responsible maturation defects and escape to the periphery); and compromised regulatory T cell function.

To conclude, we report a young adult with XLA who presented with unusual constellation of autoimmune manifestations.

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4. Berlucchi, Marco & Soresina, Annarosa & Redaelli de Zinis, Luca & Valetti et al. Sensorineural Hearing Loss in Primary Antibody Deficiency Disorders. The Journal of pediatrics.2008;153. 293-6.
5. Richter D, Conley ME, Rohrer J, Myers LA et al . A contiguous deletion syndrome of X-linked agammaglobulinemia and sensorineural deafness. Pediatr Allergy Immunol. 2001(4);12(2):107-11. Figure legend: Figure1: Shiny thickened skin with deformities in small joints of hands in the index patient