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**Case Report** **Nephrology**

# Lupic Glomerulonephritis in a Patient Presenting with Hyperimmunoglobulin E Syndrome: A Case Report

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## Abstract

Hyper-IgE syndrome (also known as Job or Buckley syndrome) is a hereditary immune deficiency of autosomal dominant inheritance. It is clinically characterized by the occurrence of recurrent staphylococcal, skin abscesses, bacterial and fungal pneumopathies, and a significant increase in immunoglobulin E. Its association with systemic lupus erythematosus has been described, the mechanism of which involves the deposition of immune complexes. We report the case of an 11-year-old girl with hyper IgE syndrome who was admitted to our clinic with severe renal failure, diagnosed as lupus glomerulonephritis on kidney biopsy.

**Keywords:** Immune complexes, immune dysregulation, systemic lupus erythematosus, lupus nephritis, hyper IgE syndrome.

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## INTRODUCTION

Hyperimmunoglobulin E (IgE) syndrome, or Buckley's syndrome, is a complex genetic disorder whose most likely pattern of inheritance is autosomal dominant with variable penetrance, although many cases appear to be sporadic. Recurrent staphylococcal skin abscesses, sinus-pulmonary infections and severe eosinophilic pruritic dermatitis characterize it. The association of Buckley syndrome with other conditions has been described, including neoplasia and autoimmune diseases. This article describes the case of an 11-year-old patient followed for a hyper IgE syndrome and admitted to our department for severe renal failure.

## CASE REPORT

We present the case of an 11-year-old patient, the eldest of four siblings from a first-degree consanguineous marriage. She has been followed for 6 years in the pediatric department of CHU Mohammed VI in Marrakech for Buckley's syndrome, diagnosed by diffuse pruritic skin lesions, recurrent pleurisy secondary to staphylococcal pulmonary infections and a very high serum immunoglobulin E level.

The patient was put on cotrimoxazole-based preventive antibiotic therapy. Until 2020, the evolution was marked by no improvement in the skin lesions, with recurrent respiratory infections requiring multiple hospital admissions (4 to 6 per year).

Since 2020, the patient had been lost to follow up due to the worldwide confinement of the SARS Cov-2 pandemic. Renally, during the follow-up period, the patient had normal renal function and an inactive urine sediment.

On November 23, 2023, the patient was admitted to our department with severe diuresis-preserved renal failure and a creatinine level of 169 mg/l (according to the Acute Kidney Injury Network AKIN classification), complicated by a uremic syndrome with 4 g/l urea and acute lung edema requiring emergency dialysis.

On admission, the general clinical examination revealed a conscious patient, hypertensive to 160/90 mmHg, polypneic at 30 cycles per minute, with soft, bilateral, bucketing edema of the lower limbs and an active urine sediment consisting of proteinuria and hematuria, with no staturo-ponderal development delay. Mucocutaneous examination revealed keratosis lesions on both the upper and lower extremities (Figure 1). The rest of the clinical examination was unremarkable.


**Figure 1: Keratosis lesions of the upper extremities (A) and lower extremities (B)**

Biological workup revealed normochromic normocytic anemia, lymphopenia and thrombocytopenia on CBC. Blood ionogram showed hypocalcemia, hyperphosphatemia and metabolic acidosis. The infectious workup was negative.

The etiological work-up for renal failure, carried out after the patient had been stabilized, revealed normal-sized kidneys with no pyelo-caliceal dilation on renal ultrasound. Serologies (HIV, HBV, and CVH) were negative, with an impure nephrotic syndrome consisting of massive proteinuria at 11g/24h, hypo albuminemia at 22 g/l and hypoprotidemia at 45 g/l.

In view of the haematological, cutaneous and renal involvement, an immunological work-up was requested, which showed a C3 serum complement and a positive antinuclear antibody level.

According to the new EULAR/ACR 2019 classification, our patient was diagnosed with systemic lupus erythematosus.

A renal biopsy was indicated, in view of the impure nephrotic syndrome showing an aspect of lupus glomerulonephritis class VI according to the ISN/RPS 2003 classification (Figures 2 and 3). Investigation of other disorders, notably cardiac, neurological and psychological, was unremarkable.

In view of the biological and histological findings, the diagnosis of end-stage renal failure due to lupus nephropathy associated with Buckley's syndrome was accepted. Treatment consisted of dialysis using a right jugular tunneled catheter, with symptomatic treatment including oral calcium supplementation and blood pressure control.

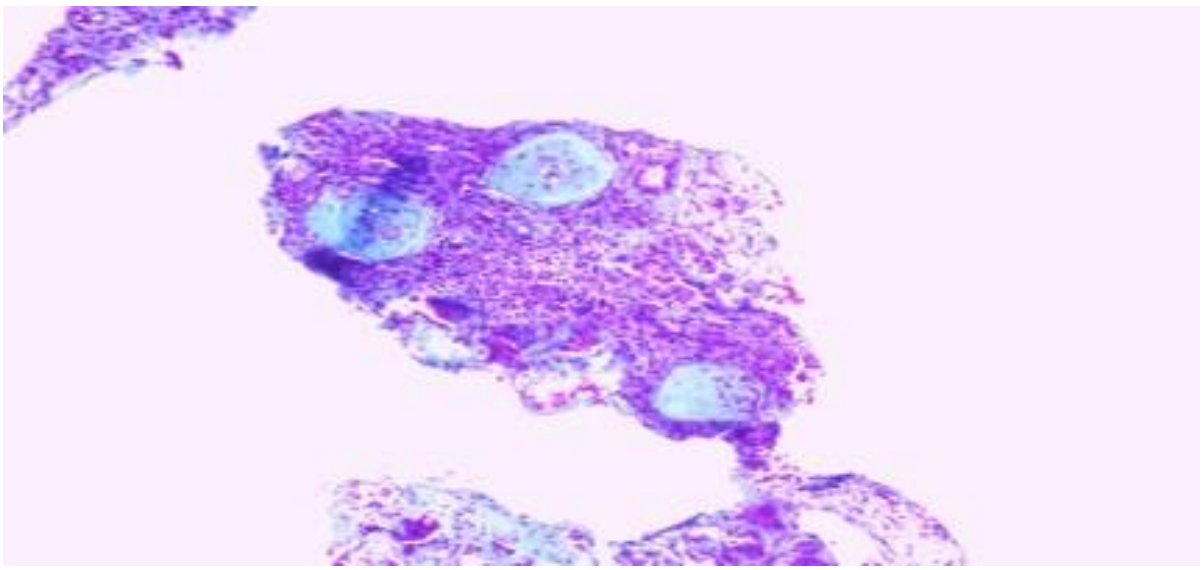

**Figure 2: Morphological aspect in optic microscopy showing diffuse glomerulosclerosis with interstitial fibrosis and tubular atrophy**

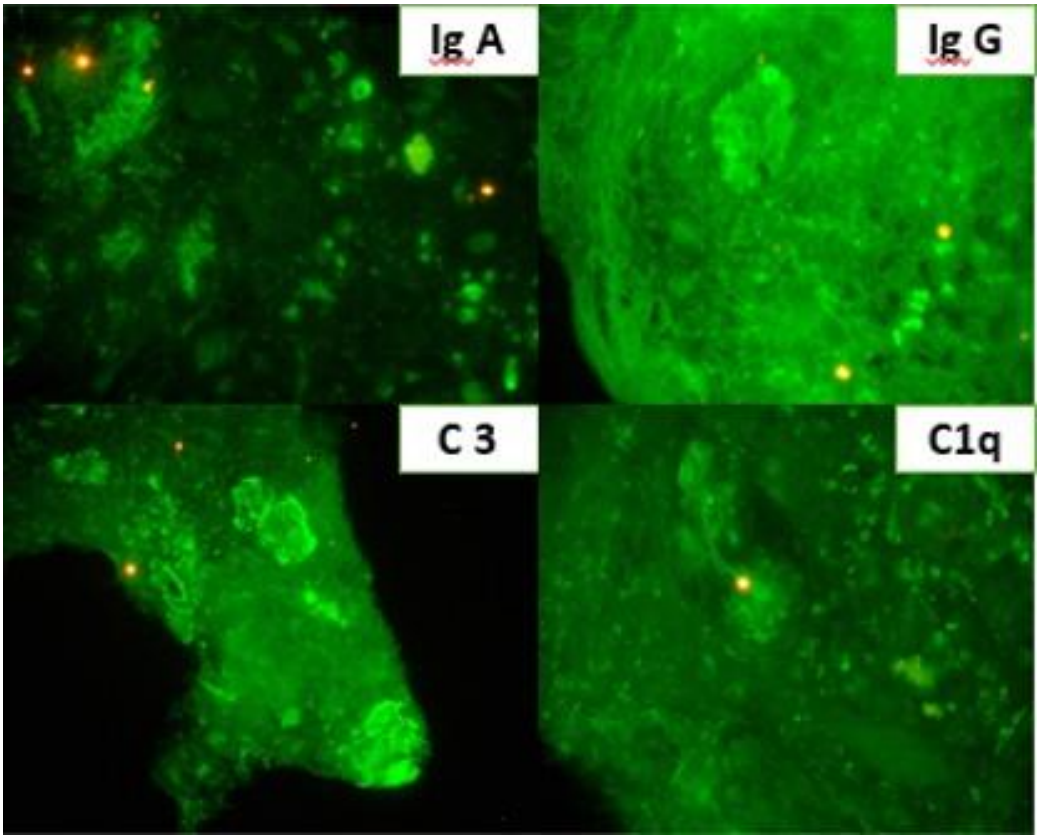


**Figure 3: Morphological aspect in immunofluorescence showing marking of Ig G, IgA, C3 et C1q**

## DISCUSSION

First described in 1966, hyper-IgE syndrome (HIES) is an inherited immune deficiency of autosomal dominant inheritance [1]. It is also known as Job's or Buckley's syndrome [2]. It is clinically characterized by the occurrence of recurrent staphylococcal "cold" skin abscesses, bacterial and fungal pneumopathies, and a significant increase in immunoglobulin E (IgE) [2]. Increased IgE levels are a constant feature of this syndrome. It is the consequence of two mechanisms [3]. The first is a decrease in IgE catabolism. However, this abnormality is not specific to Buckley's syndrome, as it also occurs in atopic eczema. The higher the IgE concentration, the lower the catabolism [4]. The second is an increase in IgE synthesis during infections.

The bacterial infections encountered in Buckley syndrome begin in the first weeks or months of life, usually in infancy at the latest [5, 6].

They are frequent and often torpid, due to an altered inflammatory response [6,7]. The most common causal agent is Staphylococcus aureus, and the sites most frequently affected are the skin, lungs and ENT tract. This was also the case in our patient. Other clinical manifestations associated with this immune deficiency include eczema, osteopenia, ligament hyperlaxity, delayed lactational tooth loss and dysmorphia [2].

Pathophysiologically, previous studies have shown that elevated IgE production secondary to disturbed immune tolerance can lead to polyclonal B-cell activation and aberrant Th2 responses, as well as autoantibody production. In addition, IgE-isotype cells are associated with overproduction of interleukins (IL)-4, IL-5, IL-10 and IgE, found mainly in patients with parasitic infections and atopic diseases [8, 9].

In addition, excessive IgE production has been reported in patients with partial T-cell immunodeficiency and autoimmune diseases, which are generally associated with hyperactivity of the adaptive immune system [9, 10]. These observations indicate that an imbalance between immunogenic and tolerogenic signals in T cells leads to increased IgE levels, which can be considered a biomarker of immune dysregulation [11, 12].

Limited studies have demonstrated an association between juvenile systemic lupus erythematosus (SLE) and elevated serum IgE levels, despite the existence of atopic symptoms or parasitic disease. However, other studies have demonstrated that the pathophysiology of SLE involves a loss of tolerance to nuclear antigens such as dsDNA, Sm and RNP, among others. This results in auto-reactivation of T and B cells by self-antigens, leading to the development of plasmablasts secreting autoantibodies [13].

The resulting pathogenic autoantibodies are predominantly of the IgG and IgE isotype, leading to elevated serum levels of IgE, which will form circulating

Immune Complexes (ICs) that deposit in target organs and trigger tissue-damaging inflammation, playing a major role in the pathogenesis of SLE [13].

No IgE deposits were observed in the immunofluorescence study of our patient's renal biopsy. However, serum IgE levels are reportedly increased in lupus patients with renal involvement, with detection of IgE immune complex deposits in renal biopsies [14]. Furthermore, elevated IgE levels have been observed in adult SLE patients without renal involvement, suggesting that IgE may contribute to the pathogenesis of SLE itself, and not just to lupus nephritis [15].

Studies of adult SLE patients have shown a significant correlation between disease activity, with IgE levels at least twice as high as in patients with inactive disease [16]. Thus, IgE levels are inversely correlated with C4 levels, suggesting that the complement cascade is activated and components are consumed [17]. This is not the case here, with normal C4 levels and no IgE deposits on renal biopsy.

Several studies have proposed the term "autoallergy" to designate autoimmune processes mediated by IgE autoantibodies [18]. There are two forms of IgE in SLE: autoreactive IgE and non-autoreactive IgE. Autoreactive IgE has been associated with high SLE activity and lupus nephritis, and promotes the production of interferon (IFN) alpha by plasmacytoid dendritic cells (pDCs) [11, 19]. Basophil activation by ICs containing autoreactive IgE amplifies autoantibody production [20].

Non-self-reactive IgE is negatively associated with the lupus erythematosus activity index (SLEDAI) and prevents IFN release from pDCs [21]. Studies have revealed that 30-50% of SLE patients with autoreactive IgE are predominantly directed against dsDNA, Ro/SSA, La/SSB and Sm [22], and anti-dsDNA IgE has been found in all lupus subtypes [16] and has been associated with SLE disease activity [23] and renal involvement. Reducing autoreactive IgE levels and inhibiting their receptors, or increasing non-autoreactive IgE, are considered promising therapeutic targets in the management of SLE [22].

## CONCLUSION

Hyper-IgE is considered an immune deficiency and may play an important role in the release of immune complexes that mediate juvenile SLE and lupus glomerulonephritis.

The specific mechanisms underlying elevated IgE levels in children with lupus remain to be clarified, and further studies are needed in this regard. Juvenile lupus nephritis with hyper-IgE may have a worse prognosis, requiring early detection.

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