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CASE REPORT **OPEN ACCESS**

Safe and effective use of Dupilumab for Refractory eczema in a child with Renal disease

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A B S T R A C T

Dupilumab is now a safe treatment option for severe atopic eczema, especially in cases where other treatments have failed. There are few studies on dupilumab's safety and effectiveness in patients with kidney disease, despite known connections between nephrotic syndrome and atopic dermatitis. The quality of life is greatly impacted by pruritic disorders in patients with chronic kidney disease, highlighting the necessity for additional research to fully investigate dupilumab's potential in this population. Our case study emphasizes the significance of researching the safety of dupilumab in pediatric patients, particularly in light of its recent approval for use in children six years of age and older. We present a 6-month evaluation of the safety and effectiveness of dupilumab in a well-managed case of severe refractory atopic dermatitis in conjunction with nephrotic syndrome, and we strongly recommend the development of treatment guidelines.

Keywords: Dupilumab, Atopic Dermatitis, Nephrotic Syndrome

INTRODUCTION

Atopic dermatitis (AD) is a chronic multifactorial inflammatory skin condition that affects 1% to 3% of adults and 15% to 20% of the world's juvenile population and has a substantial impact on patients' quality of life [1]. A recent study stated the prevalence of AD in UAE to be 11.6% [2]. SCORAD is a clinical tool used to assess the extent and severity of eczema (SCORing Atopic Dermatitis). Based on the SCORAD index results, atopic dermatitis can be classified into mild (< 25), moderate (25–50) and severe (> 50) forms. In children, the Children's Dermatology Life Quality Index (CDLQI) is designed to measure the impact of any skin disease on the lives of children. A score of 0-1 signifies no effect on quality of life, 2-6 small effect, 7-12 moderate effect, 13-18 very large effect and 19-30 extremely large effect.

Study conducted in 2017 reported prevalence of End Stage Kidney Disease in the UAE population to be 11.5% [3]. Regarding nephrotic syndrome in the UAE, there is a lack of recent data. As per our knowledge, the most recent prevalence dates to 1997, indicating a rate of 26.3% [4]. The risk of nephrotic syndrome in children with atopic dermatitis is several times higher than those without atopic dermatitis [5]. Increased peripheral blood total IgE levels and a range of atopic illness clinical symptoms are present in 50–70% of children with NS. As a result, NS and atopic disorders have many characteristics [6].

With dupilumab, dermatologists now have a safe option for treating severe atopic eczema in adults and children whose condition is not well controlled by topical or systemic therapy involving corticosteroids or immunosuppressants. Dupilumab is an FDA approved human monoclonal IgG4 antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes.
Although the association of atopic dermatitis with nephrotic syndrome is documented in the literature [7], there is a paucity of studies regarding the safety and efficacy of dupilumab in kidney disease patients.

CASE REPORT

Our patient, an 11-year-old boy, being treated for steroid-dependent Idiopathic Nephrotic Syndrome (INS) since he was 4 years old. His daily medications included 100 mg of cyclosporine and 5 mg of prednisolone. Two years after the onset of renal disease, he began to experience recurrent itchy, oozing rash on the face, antecubital fossa, and popliteal fossa. After a year, the rash spread to the entire body. He was given a diagnosis of late-onset eczema and was treated with topical fusidic acid-betamethasone combination, oral prednisolone, and moisturizing creams including white soft paraffin, all of which were ineffective in treating the condition over time. He experienced two episodes of sepsis, during which staphylococcus aureus was isolated from wound cultures and blood samples from the skin. The antibiotics used were adjusted based on the patient's sensitivity. The patient had terrible quality sleep for the past year because of his persistent itching, and he was unable to go to school or play outside.

When the patient presented to us, he had a Cushingoid appearance with puffiness of the face, facial hypertrichosis, buffalo hump, and thin limbs. He was continuously itching despite being on four hourly cetrizine. Skin examination revealed generalized erythematous excoriated oozing plaques covering almost the entire body surface with areas of lichenification of the neck, antecubital fossa, and legs. The only areas with relative sparing were the central face, palms, and soles. He also had bilateral pitting pedal edema and left axillary and right non-tender inguinal lymph node enlargement (figure 1). His pruritus as measured by Pruritus visual analog scale was 10, his children's-Dermatology Life Quality Index-child (cDLQI) was 19, and Scoring of Atopic Dermatitis (SCORAD) score was 99.55 which showed the severity of the disease. Other system examinations were unremarkable.

His labs showed leukocytosis (23.3 x103 /µL), neutrophilia 11000 x103/µL and eosinophilia (2.3x103/µL). The total IgE was >5000 KU/L (the upper limit of the test) with specific tests showing Class 5 allergy to House Dust Mite and Class 4 allergy to egg white. Stool analysis was negative for parasites or ova. The patient was investigated for underlying immunosuppression as a cause for persistent eczema and sepsis with HIV test, Immune Status Screen, Lymphocyte subset
analysis, immunoglobulin screen, STAT3 gene (for Hyper IgE syndrome) which was normal. Renal parameters like random urine protein was 15.4 mg/dl (normal <15.0 mg/dL), random urine creatinine [119.2 mg/dL], serum creatinine [0.3 mg/dL) and blood urea [11mg/dL] levels were normal. Cyclosporine trough levels were checked and it was within the therapeutic range for the disease [42.8 ng/mL] and due to good control of proteinuria, the nephrologist preferred not to increase
cyclosporine dose. Skin biopsy showed parakeratosis, a prominent granular cell layer, spongiosis, and elongated rete ridges, and perivascular inflammatory infiltrate composed of neutrophils, a few eosinophils, lymphocytes, and histiocytes,
and dermal fibrosis.

He was diagnosed with erythroderma secondary to late-onset atopic eczema but treatment was a challenge due to ongoing sepsis. During the sepsis phase, we treated him with topical mometasone cream, desloratidine, and white soft paraffin without success and advised him on an egg-free diet. We did not consider dust mite allergen desensitization for fear of exacerbating his already severe rash. Once the patient was systemically stable, we increased the dose of prednisolone from 5mg to 40mg daily (1.25 mg/kg; body weight 32 Kg) without increasing his cyclosporine levels. Within one week his skin condition improved and he was able to sit up. At discharge from the hospital, his SCORAD had improved to 54.75. We tried a very slow taper of steroids but the patient still flared up at 25mg prednisolone. We did not consider increasing the cyclosporine dose further as it was already in the therapeutic range for atopic eczema (3.12 mg/kg dose).

Due to severe adverse effects from steroids caused by cushingoid habitus and stunted growth, as well as recurrent sepsis attacks on inflamed skin and progression to erythroderma, dupilumab was considered as a life-saving medicine provided the FDA recommends dupilumab for use in uncontrolled Atopic dermatitis. Given the renal issues, cyclosporine was not an option. As a result, following an interdisciplinary meeting with pediatrics and nephrology, we decided on a dupilumab trial, considering previous case reports demonstrating the safe use of dupilumab in uremic pruritus, as well as its product summary stating that population pharmacokinetic analysis did not identify mild or moderate renal impairment as having a clinically meaningful influence on systemic exposure to it. Written consent was obtained from the patient's father and the medication was started. After starting the patient on Dupilumab pediatric dose of 200mg every 2 weeks, his skin condition
progressively improved (figure 2). After 6 weeks of treatment, his total IgE count was 1944 KU/L, his SCORAD reduced 17.45 and his cDLQI improved to 4 (small effect on patient's QoL). His sleep improved drastically and his itch became better. At 6 months follow up his eczema was still under control. However, he experienced mild flare-ups of itching a few days before the ensuing dose of dupilumab which was continued with topical mometasone, regular moisturizers and cetirizine syrup. The patient could resume his normal activities and enroll in school again. Throughout 6-month treatment follow-up, his renal parameters (blood urea, serum creatinine, and proteinuria) were well controlled.

CASE DISCUSSION

Our case had an occurrence of severe Atopic Dermatitis (AD) after diagnosis of INS. A consistent relationship has been shown between atopic diathesis and INS in several clinical reports, population-based studies, and immunological research [7-9]. However, the question remains regarding the exact relation and temporal relationship between these two seemingly different clinical diseases. Both diseases have immune dysfunction with Th2-mediated immune enhancement, Th1-mediated immune weakening, and T-regulatory cell function downregulation [6] . Immunologically similar pathway for INS and AD exemplified by upregulation of IL-4 and IL-13 [6]. Dermatologists are familiar with these interleukins as important
mediators of atopic disease and newer studies suggest a role for IL-13 to mediate proteinuria in patients with Minimal Change Disease (MCD) [7]. An exome sequencing analysis in five patients with frequently relapsing MCD associated with the allergic disease showed that heterozygous 'prohibitin 2 gene' variant may contribute to susceptibility towards the recurrence of MCD as well as atopic skin disease [10]. These are small studies and it is too early to reach definite conclusions
about the relationship between the two diseases. Diagnosis of AD in our patient was based on clinical findings of flexural eczema, lichenification, intense pruritus, and allergic rhinitis with high IgE levels. There was no family history or personal history of infantile eczema. Despite taking immunosuppressive treatment for renal disease, his eczema wasn't controlled but contrarily progressed to erythroderma and recurrent sepsis.

According to the FDA drug leaflet for dupilumab, 'no formal trial of the effect of hepatic or renal impairment on the pharmacokinetics of dupilumab was conducted' [11]. According to the product summary of Dupilumab adopted by the European Medicines Agency (EMA), no dosage adjustment is needed in patients with mild or moderate renal impairment; however very limited data are available in patients with severe renal impairment; nonetheless dupilumab, being a monoclonal antibody, is not expected to undergo significant renal elimination [12]. Literature is sparse regarding the real-life use of dupilumab in patients with renal disease. In a retrospective analysis, studying off-label use of dupilumab in recalcitrant pruritus patients, Zhai LL et al. found that all five of their uremic pruritus patients reported improvement in itch score [13]. They noted that the response was slower, and the rate of recurrence was higher than other patients with renal disease in this series who had prurigo nodularis or idiopathic chronic pruritus. There are two case reports for successful use of dupilumab to treat a flare-up of AD in a patient having uremic pruritus from a failing renal transplant and severe uremic pruritus alone without eczema [14,15] . In a recent report, there was an improvement of both atopic dermatitis and IgA nephropathy when dupilumab was started for severe AD refractory to weekly methotrexate [7] . It is also to be highlighted that, the financial burden of Dupilumab on the population should be considered. In our patient, we fortunately were able to secure humanitarian aid considering his severe clinical status.

CONCLUSION

Pruritic disorders like prurigo, renal pruritus, and severe xerosis cutis form a major burden of skin diseases and adversely affect the quality of life in an estimated 55% of chronic kidney disease patients [16] . It is therefore imperative that we have further studies to explore the possibility of dupilumab in these patient populations and treatment guidelines are made available. Similarly, the association of pediatric INS with atopic eczema necessitates studies regarding the safety of dupilumab which has recently been approved for use in children 6 years and above. Our case report demonstrates the 6-month safety and efficacy of dupilumab pediatric dose in a case of well-controlled INS associated with severe refractory AD.

Statement of ethics:

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Author Contributions: The co-authors analysed medical records, laboratory and imaging reports to write the case report. The co-responding author reviewed and adjusted the report with great consideration.

FIGURES

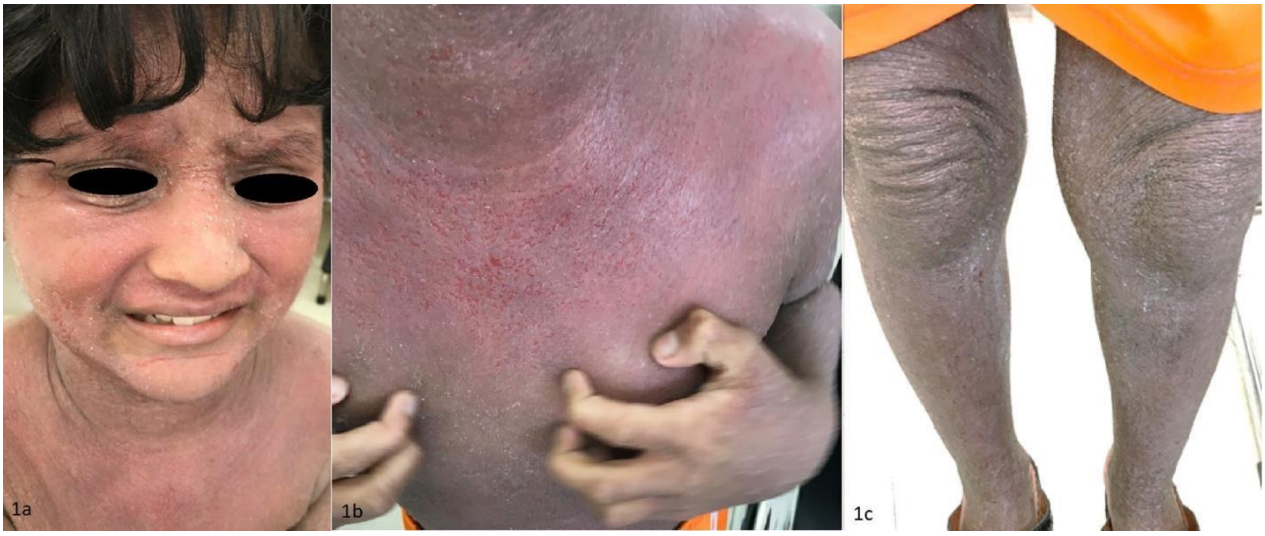

Figure 1: clinical features before starting dupilumab

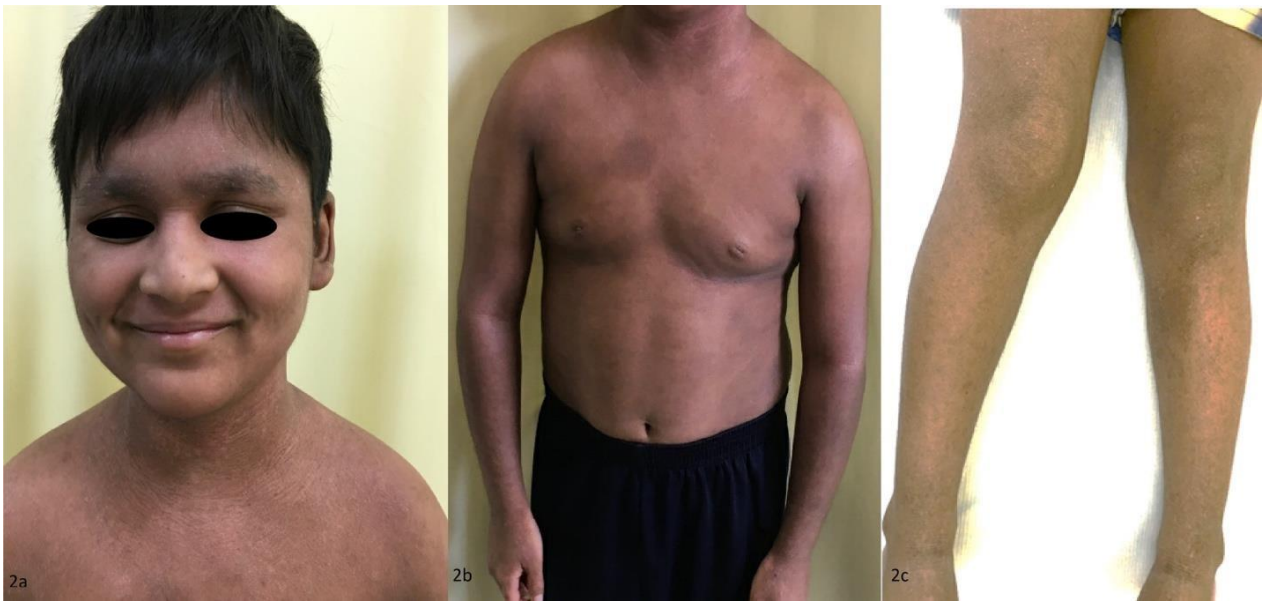

Figure 2: clinical features after starting dupilumab

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