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Case Series.

Rituximab Therapy for Idiopathic Chronic Urticaria with Recurrent Angioedema

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ABSTRACT

We report on 4 patients with severe and idiopathic chronic urticaria with recurrent attacks of angioedema. Initially, they responded initially to high dose corticosteroids yet relapsed on high-maintenance dose. Subsequently, trial to use steroid-sparing drugs viz. intravenous immunoglobulin then mycophenolate mofetil with hydroxychloroquine and tacrolimus had failed to maintain a remission. Hence, Rituximab was given. One month after Rituximab infusions, Prednisone dose was successfully tapered down and was discontinued. Subsequently, all patients remained in complete remission for 14-24 months of follow up.

Key Words: Angioedema, Prednisone, Rituximab, Urticaria.

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INTRODUCTION

Urticaria is a common dermatological condition which typically presents with intensively pruritic, well-circumscribed, raised wheels ranging from several millimeters to several centimeters or larger size. Urticaria can occur with angioedema, which is localized non-pitting edema of the subcutaneous tissue that can be painful and obstructs the air way. Chronic urticaria (CU) is defined as urticaria persisting almost daily for more than six weeks.[1] It generally lasts 1 to 5 years, but can have a prolonged course beyond 5 years in roughly 14% of patients.[2] The latter is considered a major health burden since the persistent pruritis impairs daily functions, disturbs sleep and hence the quality of life.[3] In general population the prevalence of CU is 0.5-5%.[4] According to the GRADE system, the mainstay of treatment of urticaria is avoidance of identified triggers, second-generation H1 antihistamines, Leukotriene antagonists, short course corticosteroids and Omalizumab if severe with or without angioedema.[1] In the present article, we describe our experience with treatment of systemic and idiopathic CU with Rituximab in patients who had failed multiple corticosteroid-sparing agents.

CASES PRESENTATION

In the past 2 years, a total of 4 patients, with generalized purpuric wheals with surrounding erythema which persisted for > 6 weeks (Fig.1) and recurrent angioneurotic oedema (Fig.2) were seen. Their demographical data is summarized in table 1. All patients had the following criteria: (a) high IgE levels with/without previous history of atopy and/or bronchial asthma. (b) none had secondary cause for allergy viz. malignancy, infections and parasitic infestations (c) no evidence of physical cause for their illness (heat, cold, solar, vibration, delayed-pressure, dermatographism, aquagenic and cholinergic induced urticaria) which was confirmed with skin testing. The latter included; wet cloth, hot bath, prick/patch tests (d) no clinical evidence of food-association (e) no evidence of new drug addition especially ACEI, ARB, oral contraceptives and all drugs were tested by a 2-weeks discontinuation period. (f) skin biopsy that did not show vasculitis (g) normal TSH, CRP, IgA level, hepatitis B & C serology, Helicobacter antibodies, Anti-microsomal antibodies, serum protein electrophoresis, RA, ANCA, ANA, and serum complements.

Treatment Protocol

All patients were treated with Prednisone 1 mg/kg for a minimum of 1 month. Subsequently, the dose was decreased by 5 mg/week. If fails to maintain a remission for > 2 weeks; intravenous immunoglobulin (IVIG) is used. If the latter fails, another 2-weeks trial of Mycophenolate mofetil with

Hydroxychloroquine and Tacrolimus is used. If fails again; Rituximab infusions are to be given.

Rituximab Infusions

The patients were treated with four weekly infusions of 500 mg of Rituximab (mabthera). The patient was pre-medicated with two 500 mg Paracetamol and one Piriton tablets followed by an infusion of 125 mg of Solumedrol in 50 ml of D5W over 30 minutes before infusions.

The 500 mg of Rituximab was diluted in 450 ml of NS leading to a concentration of 1 mg/ml. The first infusion rate was 20 ml/h for the first 30 minutes followed by 20 ml increments/hour every 30 minutes till the total dose is achieved. The second infusion was a rate was started at 40 ml/hour, the third at 80 ml/hour and the fourth at 120 ml/hour. Flow cytometry showed that her CD19 lymphocytes dropped to zero after one week of therapy and remained < 0.5% for 8 months. Interestingly, the patient is asymptomatic and up to 12 months after normalization of her CD19 i.e. total of 20 months following the start of Rituximab therapy.

Efficacy of Rituximab

The drug was tolerable on such dosage despite 4-6 hour infusion time. There were no post-infusion immediate reactions and there was no report of delayed side effect. One month after the last dose of Rituximab; Prednisone dose was tapered down and the drug was discontinued without relapse of their urticaria.

Duration of Follow Up:

The patients were followed up for > 14 months in the last patient and up to 24 months in the first patient.

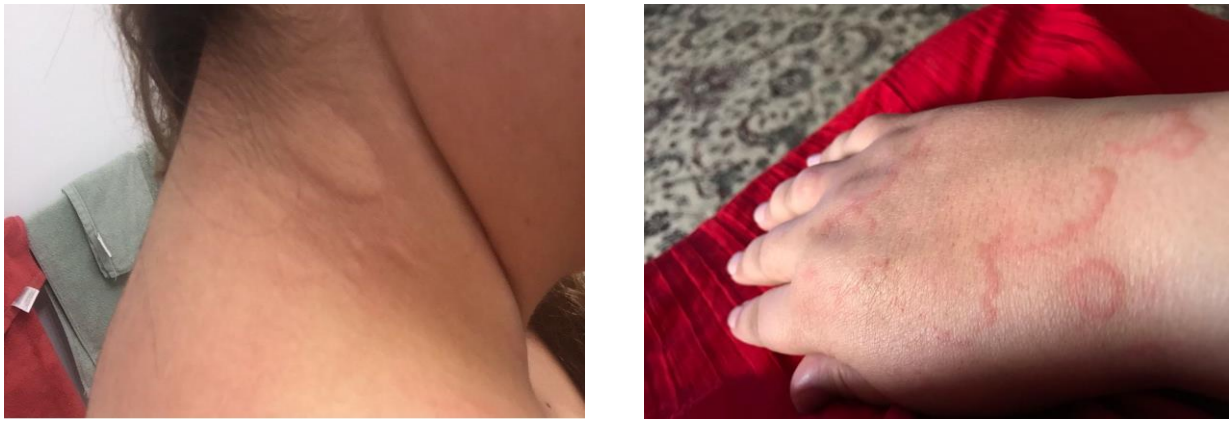

Figure 1: Wheals and maculpapular rash in 2 patients with chronic urticaria

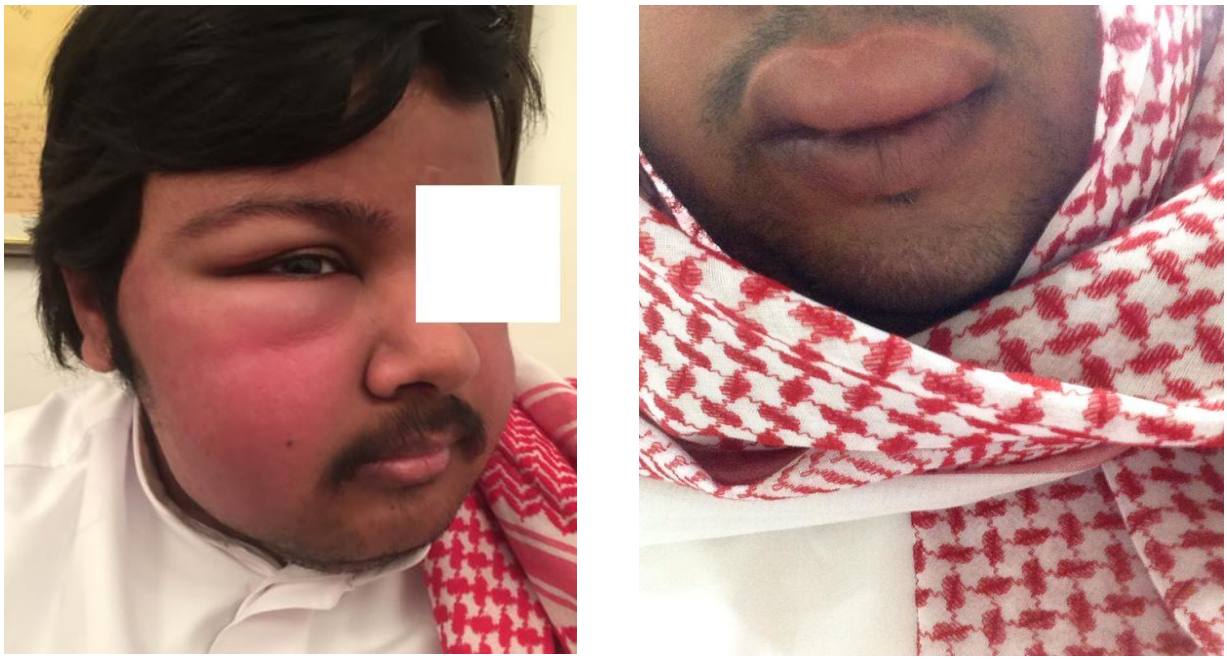

Figure 2: Angioneurotic edema in 2 patients with chronic urticaria

Table 1: Demographic characteristics of the 4 patients with persistent idiopathic urticaria

No.	Sex	Age (years)	Associated disease	Duration (Months)	Prednisone dose (mg/day)	follow up (Months)
1.	F	50	APKD	7	50	24
2.	F	45	Hypertension	8	40	18
3.	M	46	Hypertension	6	45	15
4.	M	26	Reflux Nephropathy	6	60	14

DISCUSSION

Urticaria is not a single disease but a reaction pattern that represents cutaneous mast cell degranulation. The latter results in extravasation of plasma into the dermis, forming the characteristic hives which are edematous pruritic pink wheals of variable size and shape. The lesions may be associated with angioedema which is a swelling deeper than wheals and may affect mucosal surfaces with typical sites of predilection that include the eyelids, lips, and tongue.[5] Urticaria being defined as chronic if lesions recur for longer than 6 weeks. CU includes physical urticaria, idiopathic urticaria, and urticarial vasculitis.[1] In our study, we included patients with idiopathic type of CU and excluded those with physical and vasculitic ones.[6,7] Idiopathic CU is the most common type, comprising up to 90% of all cases of CU. It has been estimated that idiopathic CU affects between 0.6% to 5% of the population during their lifetime.[8] Over half of all cases of idiopathic CU are thought to be caused by an autoimmune mechanism. This is supported by the observation that 60% of patients with idiopathic CU will have a wheal and flare reaction to intradermal autologous serum injections in the autologous serum skin test (ASST).[9] Approximately 50% of patients with idiopathic CU have IgG antibodies that are specific for the high affinity IgE receptor (FcεRI).[10,11] These autoantibodies activate mast cells in the skin, circulating basophils, and the complement system.[9] Additional immunological causes in CU include IgG antibodies directed against IgE antibodies and the low affinity IgE receptor (FcεRII), antiendothelial antibodies, and complement C8 alpha-gamma (C8α-γ) deficiency.[12] Our patients had severe and persistent idiopathic CU and were hardly controlled with high-dose corticosteroids. The latter has significant long-term side effects viz. osteoporosis, hypertension, glucose intolerance, obesity, stria, cushinoid appearance, growth retardation, decreased immunity, poor wound healing.[13] To avoid Corticosteroids-toxicity, multiple drugs were proposed for such condition viz. intravenous immunoglobulin, Mycophenolate mofetil, Hydroxychloroquine, and Tacrolimus.[1] All those drugs were tried in our patients and, had failed to be even steroid-sparing agents. Since CU is a disease of the mature B producing excessive amounts of autoantibodies [Vida supra], we elected to use Rituximab in such drug-refractory patients. Rituximab is a murine antibody that destroys both normal and malignant B cells B that have CD20 on their surfaces and is therefore used to treat diseases which are characterized by having too many B cells, overactive B cells, or dysfunctional B cells. The following effects have been found: (a) The Fc portion of rituximab mediates antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC. (b) Rituximab has a general regulatory effect on the cell cycle. (c) It increases MHC II and adhesion molecules LFA-1 and LFA-3 (lymphocyte function-associated antigen). (d) It elicits shedding of CD23. (e) It down regulates the B cell receptors (f) It induces apoptosis of the CD20+ cells.[14] The latter may be the basis of maintenance of long-term remission via generation of new cells without memory ones.[15]

In conclusion; our results are promising for a new hope in treatment of drug-refractory CU with Rituximab-treatment. The latter is safe and is able to produce a long-lasting remission of a disabling disease.

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