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OXIDANT-ANTIOXIDANT PARADOX OF SERUM URIC ACID AND ITS RESPONSE TO DEXAMETHASONE CYCLOPHOSPHAMIDE PULSE THERAPY IN PATIENTS WITH PEMPHIGUS VULGARIS. A HOSPITAL BASED STUDY.

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ABSTRACT

Background: Pemphigus vulgaris (PV) is an autoimmune blistering disease of the skin and mucus membranes in which increased production of reactive oxygen species(ROS) leading to a decline of antioxidants in plasma and red blood cells and hence oxidative stress is one of the proposed mechanisms in pathogenesis. There are very scarce studies regarding the role of antioxidants in pemphigus vulgaris. The role of serum uric acid which can act both an antioxidant as well as an oxidant and its response to DCP therapy was evaluated in this study. **Aim and objectives:** To evaluate the serum level of uric acid in patients with pemphigus vulgaris and its response to dexamethasone – cyclophosphamide pulse therapy. **Material and Methods:** This was a prospective hospital based study conducted in the department of Dermatology and Biochemistry, Government medical college Srinagar in which new(freshly diagnosed)cases of pemphigus vulgaris were recruited and the serum levels of uric acid was determined by calorimetric method. The level of uric acid was then again determined after the achievement of clinical remission with DCP therapy. **Results:** A total of 15 successively admitted patients were recruited in the study. The serum level of uric acid was elevated in three patients, decreased in one patient only and the rest had uric acid levels within normal limits. However the levels returned to normal with DCP therapy following the achievement of clinical remission in patients with both elevated and decreased uric acid levels. **Conclusion:** The decreased levels of uric acid in pemphigus vulgaris as found in some previous studies was found in only one patient in our study and the rest had normal to elevated levels,thus explaining the oxidant-antioxidant paradox of uric acid. However larger studies are needed to establish the role of uric acid (antioxidant or oxidant) in pemphigus vulgaris.

KEYWORDS: ROS-Reactive oxygen species; Antioxidant system; Oxidative stress; uric acid, pemphigus vulgaris, DCP-Dexamethasone-cyclophosphamide pulse therapy.

What is known: Various studies have shown that uric acid acts as an antioxidant in different diseases including pemphigus and its level is decreased in pemphigus vulgaris.

INTRODUCTION

Skin is one of the major targets of oxidative injury due to reactive oxygen species (ROS) that originate in the environment and skin during various physiological and pathological processes. Normally a complex of antioxidant defence system in our body scavenges ROS, maintaining a balance.Imbalance in the oxidant-antioxidant systems due to increased reactive oxygen species production and/or deficient function of the antioxidant system, leads to oxidative stress, which may be involved in the pathogenesis of many dermatological diseases such as, systemic sclerosis, psoriasis, skin cancers, vitiligo, chronic urticaria, Behcet's disease, lichen planus, atopic dermatitis, to mention a few, as well as their association with non dermatological

diseases such as cardiovascular disorders, diabetes mellitus, rheumatoid arthritis, all of which are associated with oxidative stress. However there are very few studies regarding the role of antioxidants and oxidative stress in pemphigus vulgaris[1,2,3].

Pemphigus vulgaris (PV) is an autoimmune blistering disease of the skin and mucus membranes in which increased production of reactive oxygen species(ROS) leading to a decline of antioxidants in plasma and red blood cells and hence oxidative stress is one of the proposed mechanisms in pathogenesis. Uric acid has been demonstrated to act as an antioxidant in various dermatological disorders such as psoriasis vulgaris, vitiligo, acne vulgaris, pemphigus vulgaris (PV), lichen planus, and alopecia areata by various previous studies. Some of the previous studies have shown a decline in the level of serum uric acid but no change in the level of other antioxidants such as glutathione peroxidase, selenium, vitamin C and bilirubin in pemphigus vulgaris; however there are very scarce studies regarding the role of antioxidants in pemphigus vulgaris. The exact role of uric acid(oxidant or antioxidant) in the pathogenesis of pemphigus vulgaris is not known. This is a novel study in which the role of serum uric acid which can act both an antioxidant as well as an oxidant and its response to DCP therapy was evaluated.

MATERIAL AND METHODS

This was a prospective hospital based study conducted in the department of Dermatology Government medical college Srinagar in which new(freshly diagnosed)cases of pemphigus vulgaris were recruited. The diagnosis of pemphigus vulgaris was made by clinical examination(mucocutaneous blisters and erosions), histopathology (intraepidermal suprabasal acantholysis) and direct immunofluorescence(fishnet pattern of immunoglobulin deposition), which is considered as gold standard for the diagnosis. However ELISA or immunoblot analysis to detect the antibodies to desmogleins (3& 1) or the titre of these antibodies was not determined as the facility is not available at our centre. Hence the correlation between serum uric acid level and the titre of anti-Dsg-3 antibodies was not determined before and after treatment. Patients who were on systemic steroids, immunosuppressants, smokers or were suffering from diseases associated with increased oxidative stress such as diabetes mellitus or cardiovascular diseases were excluded from the study. A 2ml sample of venous blood was drawn to determine the serum uric acid level(by calorimetric method). The level of uric acid was then again determined after the achievement of clinical remission with DCP therapy.

RESULTS

The study comprised of 15 patients (8 males and 7 females). The age group ranged from 20-70 years with a mean of 42.600±15.801.The duration of the disease ranged from 1-36 months with a mean of 14.733±11.461.The normal level of serum uric acid ranges from 3.5-7.2mg/dl. The serum uric acid levels in the pre-treatment period ranged from 3.100-8.200 with a mean of 5.860±1.235.Three patients had elevated serum uric acid, one had less than the normal and the rest had normal levels) and in the post-treatment period(after achieving clinical remission) the levels normalised in patients with both elevated as well as decreased levels and ranged from 4.500-6.200 with an arithmetic mean of 5.227±0.5329. (Table 1). An average of 6 months was the period of achieving the clinical remission.

Table1.Showing the age, duration of disease and serum uric acid levels before and after treatment.

	Age(Years)	Duration in months	Uric acid before treatment_	Uric acid after treatment
No of Cases	15	15	15	15
Minimum	20	1.000	3.100	4.500
Maximum	70	36.000	8.200	6.200
Arithmetic Mean	42.600	14.733	5.860	5.227
Standard Deviation	15.801	11.461	1.235	0.539

DISCUSSION

Pemphigus comprises of a group of autoimmune intraepidermal blistering disorders of skin and mucous membranes caused by pathogenic immunoglobulin autoantibodies against transmembrane desmosomal glycoproteins, desmoglein (Dsg) 1 and Dsg 3. Pemphigus is divided into two major types: pemphigus vulgaris (PV) and pemphigus foliaceous (PF). Clinically mucocutaneous blisters and erosions are seen.One of the proposed mechanisms leading to blistering in pemphigus vulgaris is the oxidative pathway.[4] Inflammatory pathways leading to complement activation which in turn activate neutrophils and cause the release of reactive oxygen species (ROS), which exert their adverse effect through lipid peroxidation, inflammatory cytokines, and the disruption of dermal–epidermal junction in PV[5,6]. Antioxidants are physiological defense mechanisms in alleviating ROS toxicity in human skin problems. The effect of serum/RBC selenium,bilirubin, and uric acid as potential antioxidants have been measured in several diseases. There have been a few studies considering antioxidants levels in patients with PV[7,8,9].

Uric acid is a final enzymatic product in the degradation of purine nucleosides and free bases in humans and Great Apes while as in other mammals the last enzymatic products of purine degradation include allantoin, allantoic acid, glyoxylic acid and urea. The pathway of purine catabolism in humans is shortest among vertebrates because of the deficient urate oxidase

(uricase, an enzyme catalyzing conversion of uric acid to allantoin). As a consequence, humans have to cope with relatively higher levels of uric acid in the blood (200–400 μM) and are prone to hyperuricemia and gout[10]. Various studies have shown that high level of uric acid is strongly associated and in many cases predicts development of hypertension[11], visceral obesity, insulin resistance, dyslipidemia, diabetes mellitus type II, kidney disease, cardiovascular and cerebrovascular events. Despite the proposed beneficial role of uric acid, hyperuricemic patients have a higher rate of cardiovascular and all-cause mortality in comparison to subjects with normal levels of uric acid[13,14,15]. The ability of uric acid to scavenge oxygen radicals and protect the erythrocyte membrane from lipid oxidation was originally described by Kellogg and Fridovich, and was characterized further by Ames et al. One of the major sites where the anti-oxidant effects of uric acid have been proposed is in the central nervous system, particularly in conditions such as multiple sclerosis, Parkinson's disease, and acute stroke. Uric acid is a powerful scavenger of carbon-centered and peroxyl radicals in the hydrophilic environment but loses an ability to scavenge lipophilic radicals in hydrophobic environment and cannot break the radical chain propagation within lipid membranes[16,17,18]. Various studies have shown that uric acid can become a pro-oxidant by forming radicals in reactions with other oxidants, and these radicals seem to target predominantly lipids (LDL and membranes) rather than other cellular components. At the same time, the hydrophobic environment created by lipids is unfavourable for the antioxidant effects of uric acid, and oxidized lipids can even convert uric acid into an oxidant. Given this background and association of hyperuricemia with obesity one may infer that uric acid has a direct effect on the adipose tissue, and this effect might have a redox-dependent component[19,20]. **Yousefi et al** in an Iranain study observed a decreased level of uric acid in patients with pemphigus vulgaris especially in those with mucosal involvement. However there is a lack of studies evaluating the role of uric acid as an antioxidant in pemphigus group of disorders[21].

Dexamethasone cyclophosphamide pulse (DCP) therapy is an established mode of treatment for pemphigus in India. It was described by Pasricha and Ramji in 1984. In this regimen, the patients are given dexamethasone 100mg in 250ml of dextrose 5% on three consecutive days with 500mg of cyclophosphamide on day-2 and repeated after 28 days(phase 1 &II).After patients achieve clinical remission using DCPs (phase I), an additional nine DCPs are given as consolidation phase (phase II), followed by only oral cyclophosphamide for nine months as maintenance (phase III).Phase IV constitutes follow up period. The duration of this therapy ranges from one patient to another due to variable length of phase-1[22]. In our study DCP therapy was very effective and the average period of achieving the clinical remission was 6month.Moreover the serum uric acid levels normalised in patients with both elevated as well as those with decreased levels**.** The normalisation in those with increased levels(oxidant role)which we observed in 3 of our patients can be explained by decreased tissue breakdown with DCP therapy and the normalisation of decreased serum uric acid level which we observed in only 1 of our patients(antioxidant role) can be explained by a decrease in the levels of lipid derived peroxidation products and abolition of the lipophilic environment, the exact explanation of which still needs extensive biochemical and pathogenetic studies. However decreased levels of uric acid was found in only one patient in our study(contrary to previous studies). The exact mechanism of action of DCP therapy is not known. Pharmacokinetic studies and studies of the effects of this therapy on serum uric acid and on the immune system may need to be done to understand the mechanism of action of DCP therapy. The normalization of serum uric acid is probably because of the steroid/cyclophosphamide therapy which is the most effective therapy for pemphigus and is responsible directly for reduction of the disease severity due to its anti-inflammatory and immunosuppressive property and inhibition of the proliferative cytokines.However the exact mechanism remains elusive.

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CONCLUSION

Uric acid can act both an antioxidant as well as an oxidant The decreased levels of uric acid in pemphigus vulgaris as found in some previous studies was found in only one patient in our study and the rest had normal to elevated levels, thus explaining the oxidant-antioxidant paradox of uric acid. However larger studies are needed to establish the role of uric acid (antioxidant or oxidant) in pemphigus vulgaris.

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