Rebound phenomenon to systemic corticosteroid in atopic dermatitis

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ABSTRACT

Three patients with atopic dermatitis, one boy and two girls, aged between 6 and 17 years, presented eczematous skin, pruritus, scarifications, lichenification and a family history of atopy. During exacerbations, the patients sought emergency care and were prescribed oral corticosteroids for a period of approximately 15 days. Initially, the patients improved but after cessation of therapy or dose reduction, marked worsening occurred with the development of lesions with extreme pruritus, several confluent lesions, scarification and intense exudates, as well as fever and dehydration. The patients' condition was so severe that two were admitted to the allergy unit. The medication was withdrawn and intravenous hydration was administered, together with hydrating skin creams and antihistamine therapy. In addition, weak topical corticosteroids were applied on the most severely affected areas. All three patients progressively improved.

We conclude that the patients with atopic dermatitis described herein presented a rebound phenomenon after the use of corticosteroids. We believe that systemic corticosteroids may exacerbate the acute phase of atopic dermatitis, mediated by IgE, accentuating the Th2 pattern in these patients.

Key words: Atopic dermatitis. Rebound phenomenon. Systemic corticosteroids.

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INTRODUCTION

Atopic dermatitis, also called atopic eczema, is an inflammatory process of the skin characterized by eruptions with pruritus and a tendency for recurrence usually affecting individuals with a personal and family history. Approximately 80 % of the cases begin in the sixth month of life. Pruritus is a constant aspect in the course of the disease. During the acute stage, serous or sanguineous ulcerations, vesicles and eczematous base are present. In the sub-acute stage the skin is dry, eczematous without the presence of exudates. In the chronic stage of the disease there is thickening of the corneous extract, scarification and lichenization[1]. Signs classified as major may also be present such as xerosis, ichthyosis, accentuation of the palmar lines/creases, periauricular and perioral fissures, exfoliation of the scalp, white dermatographism, sudoresis, and stigmas such as infra-orbital Dennie-Morgan folds and Hertogue sign. The diagnosis for atopic dermatitis is essentially clinical[2].

In the physiopathology there is a genetic component frequently associated to chromosome 5q. The immunologic alterations are of the Th2 pattern with receptors having high affinity for IgE (RFcε-II) in mastocytes. Currently, a sequence has been described for a pattern of Th1 chronicity. Therefore, as a characteristic of the acute phase there an increase of IgE

against antigens presented by Langerhan and dendritic cells, activating Th2 and Th3 lymphocytes, wit the production of IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13[3]. Posteriorly, there is Th1 activation and synthesis of IL-2, TNF-β and INF-γ, leading to chronic inflammation[4]. It is likely that the disequilibrium between Th1 and Th2 cells is due to interactions between APCs and antigens. Histological study of the chronic eczematous lesion shows an inflammatory infiltrate similar to that found in contact dermatitis and positive to contact tests suggesting an associated cellular hypersensitivity.

The main treatment consists in the attempt to suppress the inflammation and hydrate the skin, mainly using topical corticosteroids in the most affected regions and emollients through the entire body. Antihistamines are important to suppress itching, once that the itching alone may lead to the release of IL-2, worsening the process. Antibiotics are prescribed whenever necessary, especially for infections by Staphylococcus aureus, which may behave as a super-antigen, without needing antigenic presentation by MHC. Skin atopy is more susceptible to any irritant, such as soaps and synthetic clothing. Currently, it is known that in atopic dermatitis there is the sensitization to environmental acari either through the superior airways or the injured skin[5], thus we can cite the importance of avoiding such allergens. It is necessary to remember the possibility of food allergies manifesting as atopic dermatitis and, in such cases, removal of the food allergen.

Immunosuppressants or modifiers of the immune –inflammatory response have been used in cases of atopic dermatitis. The topical immunosuppressors pimecrolimus and tacrolimus have shown encouraging results when used without associated infections. Cyclosporine is reserved for more sever cases acting by reducing the itching mainly through cytokine suppression, especially IL-2, while not affecting the levels of IgE, INF-γ, and TNF-α. Therefore its mechanism of action is linked to IL-2 producing T-cells. Cyclosporine may present a rebound phenomenon after its removal.

The shift of the immune response with IFN-γ has shown effectiveness for cases in which there was predominance of erythemas, excoriations and sanguineous eosinophilia, in other words, in the acute phase of the disease, not being cited for the chronic phase, with its efficacy being much more limited than that of immunosuppressants.

Therapy utilizing medicinal Chinese herbs is an empirical modality of treatment which may present good immediate results. However, long-term studies have shown reversible or irreversible hepatotoxicity after interruption of treatment.

Phototherapy and chemiophototherapy using UVA (long wave) radiation associated or not to chemical photosensitizers, such as 8-metoxy-psoralen, may provide positive improvement for adults reducing the expression of adhesion molecules and the recruitment of the cellular inflammatory infiltrate. Carcinogenesis must be considered in this mode of treatment.

Systemic corticosteroids are many times used in emergency care of patients with severe atopic dermatitis. However, the interruption of these drugs may lead to worsening of the disease, which is the reason why we proposed this study.

CASE REPORTS

First case

G.M., female, 17 years old presented atopic dermatitis since the age of 10 years, reposting that during the beginning of disease manifestation there were erythematous-exfoliative lesions located on the flexor regions of the superior and inferior limbs and on the cervical region. At the beginning of the follow-up in our sector the patient presented generalized exudative erythema bullosum lesions which were confluent, associated with fever and dehydration. At this time patient reported the previous use of oral corticosteroids for a period of 15 days, which was prescribed for an episode of exacerbation of the dermatitis. Initial improvement of her state with the introduction of oral corticosteroids was followed by important worsening during dose regression to 0.25 mg/kg/day. The patient required hospital admittance for six days, at which time the systemic corticosteroid was removed and treatment with antibiotics, antihistamines and topical care was instituted. There was slow improvement of her condition. However, following a four-month period, the patient again presented a worsening of the dermatitis and, during emergency care, received systemic corticosteroid and accentuated worsening was again observed during medication removal.

Second case

J.A.S.S., female, eight years old presented diagnosis of atopic dermatitis since the age of two months. Reported having control of the disease using skin moisturizers, topical corticosteroids and hydroxine. At the age of five years, during the presentation of an episode of dermatitis exacerbation sought emergency care. At such time oral corticos-

teroid was prescribed which the patient used several times during several periods of 15 days, always reporting worsening of the condition with removal of the medication characterized by an increase in the size of the affected area and exudation of the lesions, In one of the two moments during disease exacerbation after the removal of the corticosteroid, the patient sought assistance form the Allergy Sector. The patients condition was not as intense as that of the patient in the first case and improvement was more quickly achieved, presenting only exfoliative and exudative lesions on the face, trunk, and limbs 20 days after suspension of the systemic corticosteroid.

Third case

M.F.O., male, six years old, is having atopic dermatitis diagnosis since the first year of life. The mother reported erythematous and exfoliative lesions restricted to the flexor regions of the limbs, exfoliation of the cervical region and skin with intense xerosis. Corticosteroid treatment was introduced in a non-specialized Allergy service. The patient received oral corticosteroid for a period of 15 days and, during drug removal, when at a dose of 0.5 mg/kg/day there was important worsening of his condition at which time he sought assistance at the Allergy Sector presenting generalized erythematous bullosum lesions, which impeded perambulation and presented intense exudation, with the patient needing hospitalization. Treatment utilizing anti-histamines, weak topical corticosteroids only on the affected regions, skin hydration, environmental hygiene was introduced presenting improvement and control of the condition.

RESULTS

The three cases reported presented patients between six and 17 years of age, having family history of atopic dermatitis. When the patients received oral corticosteroids they initially presented improvement followed by accentuated worsening subsequent to total removal or during regression to corticosteroid treatment.

DISCUSSION

The rebound phenomenon to oral corticosteroids occurred in the three patients with atopic dermatitis that were studied. Their condition was characterized by important worsening of the skin lesions during regression from the systemic corticosteroids or few days after drug therapy was stopped. There was exacerbation of the itching, eczematous lesions, exudation, areas of lichenification, and of the extension of the affected area, which tended to conflate. The clinical worsening of the atopic dermatitis presented by the patients is similar to that described in the literature[6].

Considering the accentuated worsening of the patients' clinical condition it was necessary to exclude other diseases. Thus, hyper-IgE syndrome was excluded, that is characterized by cutaneous manifestations with pruritis, maculous-papular lesions and eczema associated to an increase in IgE production that can be associated to cellular immunity and history of skin infections by *Candida albicans* and pulmonary or skin infections by S*taphylococcus aureus*. In severe seborrheic dermatitis, the erythemaous-squamous lesions affect the scalp and face as isolated lesions or extensive erythematous-squamous-secreting plaques. In extensive psoriasis, the affected region is usually symmetric, affecting the knees, elbows, scalp and sacral region as well-defined erythematous-squamous plaques. In staphylococci scalded skin syndrome, the infection foci is not frequently found on the skin, rather they are found in distant locations in the form of otitis and conjunctivitis usually associated to fever, diffuse erythema, formation of flaccid blisters that easily rupture forming great erosive areas surrounded by epidermal patches[7]. These clinical aspects are different to those presented by the patients in our study. The patients also did not present deficiency in neutrophils phagocytic activity that may develop along with staphylococci infection[8], atopic dermatitis associated to mononuclear phagocytosis deficiency facilitating fungal infections independent of corticotherapy[9], malnutrition, which may be a cause of more severe infection due to cellular deficiency and by the reduction in phagocytic activity[10], even though malnourished patients have less tendency of presenting atopic dermatitis[11].

During or after systemic corticosteroid regression there was an exacerbation of the acute phase of the atopic dermatitis in the patients studied, which may implicate a predominance of the Th2 pattern. In fact, there are many studies in favor of this hypothesis. Thus in studies about the physiopathology of the rebound phenomenon to systemic corticosteroid in atopic dermatitis significant increases of IgE were described after the removal of the systemic corticosteroid without significant differences in IgG1, IgG2, IgG3, IgM, IgA1 and IgA2 levels[6] with IgE synthesis being regulated by Th2 cells[12,13]. In a study

evaluating the serum levels of cytokines during the rebound phenomenon, elevated values of cytokines synthesized by Th2 were observed, such as IL-4, IL-5, IL-10, IL-13 without significant differences of cytokines produced by Th1, in other words IL-2 and IFN-γ[6], denoting the important participation of Th2 cytokines in these cases.

The reports presented are similar to the acute phase of severe atopic dermatitis, which is described to course with a Th2 pattern. This hypothesis is corroborated by studies during the acute phase of the disease in question, relating that T lymphocytes in these individuals produce greater quantities of IL-4 than do healthy individuals[14,15]; among the Th2 cytokines, Il-4 was described as the main factor related to the increase of IgE production[16-19]; greater quantities of Th2 cells were found in the circulating blood and affected skin were found in the patients with acute atopic dermatitis lesions[20].

Kimata et al[12] observed that an increase in the spontaneous production of IgE by Bcells of atopic patients after treatment with oral prednisolone. Klebl et al[21], in a study concerning in vivo IgE levels during 7-day treatment with 25 mg of prednisolone did not observe an increase during this period, but report a discreet increase of IgE elevation at the end of treatment. Studies suggest that the increase of IgE production associated to prednisolone treatment observed reflects an immunomodulator effect to corticosteroids[12].

Researchers, through in vitro experimentation, using hydrocortisone added to lymphocytes of patients with atopic dermatitis, observed an increase in the spontaneous production of IgE bu plasmocytes, even in the absence of IL-4 and IL-13, as long as the hydrocortisone was added in an early stage of B cell activation. This production was not inhibited by anti-IL4 or anti-IL-13 monoclonal antibodies or by IFNγ or IFN-α, as well as not requiring T lymphocytes or monocytes. The authors reveal that hydrocortisone would stimulate IgE production by B cells by isotypic class change[12]. Studies support the hypothesis that the presence of hydrocortisone may induce the production of IgE by B cells, independent of T cell presence[22-24].

We conclude that the patients having atopic dermatitis reported in this study presented a rebound effect after of during the removal of oral corticosteroid, with accentuated worsening of the clinical condition of skin atopy. The corticosteroids may reduce the inflammatory process; however, we believe that in atopic dermatitis these drugs may exacerbate IgE mediated hypersensitivity, especially after drug suspension, accentuating the Th2 pattern typical of the acute phase of atopic dermatitis.

ACKNOWLEDGMENTS

We are grateful to the Support Center for Scientific Publications of Santa Casa de São Paulo – Faculty of Medical Sciences for the editorial assistance.

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