Hypertrichosis: the possible side effect of cyclosporin in an infant with hemophagocytic lymphohistiocytosis receiving HLH-2004 chemotherapy protocol

Hipertrikoz; hemofagositik lenfohistiositozu olan ve HLH-2004 kemoterapi protokolü uygulanan hastada siklosporine bağlı gelişen olası yan etki

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Abstract

Hemophagocytic lymphohistiocytosis is a life-threatening condition of severe hyperinflammation that results from an uncontrolled proliferation of activated lymphocytes and histiocytes secreting high amounts of inflammatory cytokines. The immediate treatment strategies include immune suppressive therapy such as corticosteroid, etoposide and cyclosporin A. Herein, we present a 13-month-old infant who developed severe hypertrichosis after the administration of HLH-2004 treatment protocol. We discuss the various hypotheses regarding the causal relationship between cyclosporin A and hypertrichosis, emphasizing the importance of patient follow up. *(Turk J Hematol 2009; 26: 154-6)*

Key words: Cyclosporin A, hypertrichosis, hemophagocytic lymphohistiocytosis, corticosteroids

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Özet

Hemofagositik lenfohistiositoz yüksek düzeylerde enflamatuvar sitokin salgılayan, kontrol edilemeyen histiosit proliferasyonu ile seyreden ağır enflamasyonun görüldüğü hayatı tehdit eden bir hastalıktır. Tedavi stratejileri arasında korikosteroid, etoposid, ve siklosporin gibi immünsupresif tedaviler yer almaktadır. Bu raporda hemofagositik lenfohistiositoz tanısı alan ve HLH-2004 protokolüne uygun tedavi sonrası ağır hipertrikoz gelişen 13 aylık bir hasta anlatılmıştır. Siklosporin A ve hipertrikoz arasındaki nedensel hipotez tartışılmış ve hasta takibinin önemi anlatılmıştır. *(Turk J Hematol 2009; 26: 154-6)*

Anahtar kelimeler: Siklosporin A, hipertrikoz, hemofagositik lenfohistiyositoz, kortikosteroid

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is characterized by fever, hepatosplenomegaly, cytopenia, hyperferritinemia, hypertriglyceridemia, and/or hypofibrinogenemia, increased CD 25 level, and decreased natural killer activity [1]. HLH can be analyzed in two groups, including primary and secondary [1,2], both of which are not rare in Turkey [3,4]. Primary HLH is an inevitably fatal disorder without specific treatment. The only curative treatment in primary HLH is the induction of remission with initial immunosuppressive treatment, including corticosteroid, etoposide and cyclosporin A (CsA), followed by hematopoietic stem cell transplantation [1,2]. The secondary form of the disease usually resolves after recovery of the primary insult; however, in severe forms, such as Epstein-Barr virus-related HLH, immunosuppressive treatment may be life-saving.

Cyclosporin A and corticosteroid therapy are widely used immunosuppressive agents, often known to have unpleasant side effects, particularly cosmetically undesirable cases such as hypertrichosis [5,6]. However, as far as we know, no other case of HLH associated with hypertrichosis has been previously reported, and the exact mechanism of this condition is unknown. Herein, we present a 13-month-old boy with HLH, who developed severe hypertrichosis during the course of HLH-2004 treatment protocol [1]. We discuss the various hypotheses regarding the causal relationship of CsA and hypertrichosis, emphasizing the importance of patient follow-up.

Case Report

A 13-month-old boy was referred to Hacettepe University, Division of Pediatric Hematology from a local hospital. His symptoms had started seven months before with the loss of head control and ability to sit, with pallor, fatigue and intermittent fever reported for the last one month. There was first-degree consanguinity between parents, but no similar history or infant death among siblings and relatives. The physical examination revealed hepatosplenomegaly and developmental delay. Since laboratory evaluation showed pancytopenia, hypertriglyceridemia and hypofibrinogenemia, a bone marrow aspiration was obtained, revealing increased histiocytes and hemophagocytosis. The diagnosis of HLH was established, and HLH-2004 treatment protocol [1] was initiated, including CsA, dexamethasone and etoposide. CsA was administered at a dose of 6 mg/kg/day; dexamethasone was started at a dose of 10 mg/m^2/day and was slowly tapered to 2.5 mg/m^2/day by the end of the eight weeks. The plasma CsA level was measured weekly and found to be within the therapeutic range of 150-200 ng/ml. The patient was discharged by the 8th week of treatment and therapy was continued in a local hospital. However, CsA levels could not be measured at that time because of the lack of availability.

He was brought for a follow-up visit in the 6th month of diagnosis. He demonstrated head control and could sit without support, and hepatosplenomegaly was absent; however, there was marked hair growth on his forehead, arms, legs, and especially back (Figures 1, 2). Minimal gingival hyperplasia was also present. No other signs of virilization were present. To eliminate endocrinological causes of hypertrichosis, serum levels of testosterone, DHEA-SO4, 17-OH progesterone, and 11-deoxycortisol were measured and were found to be within normal limits. On the other hand, plasma CsA level was 778 ng/ml, far above the therapeutic range.

After cessation of CsA, hypertrichosis decreased gradually, without any requirement of additional cosmetic interventions, and the patient is alive without any treatment and considered as secondary HLH.

Discussion

Hypertrichosis, or excess hair growth, can be troublesome for both patients and parents in the pediatric age group, as some patients may experience adverse social problems resulting from this side effect. Pediatric hypertrichosis can arise from either congenital or pharmacologic sources [7]. The overall incidence in childhood has not yet been clearly determined; however, there is reason to believe that an increase has occurred since the introduction of CsA in the early 1980s. Estimates of the frequency of hypertrichosis in patients treated with CsA, after organ transplantation, vary widely between 24 to 94%, and evidence shows that this effect is more commonly observed in the pediatric population [8]. Wysocki et al. [9] reported the rate of hypertrichosis as high as 94.6% in 56 insulin-dependent diabetics who were on long-term CsA treatment.

The effect of CsA on hair follicles has been poorly documented and its underlying mechanisms are not yet known. Studies on nu/nu mice have shown that topical, oral or parenteral administration of CsA induces macroscopically visible hair growth in these mammals via the stimulation of selected cytokines [10]. It has also been hypothesized that CsA treatment increases androgen activity. Cutolo et al. [11] reported that the use of low-dose CsA (3.5 mg/kg/day) induced dose-related hypertrichosis, and the increase in plasma androgen metabolites were concluded to be possible markers of the influence of CsA on peripheral androgen metabolism of target cells. Boudou et al. [12] measured the metabolic conversion of testosterone to 5 alpha-reduced products, and results showed a significant increased formation of 5 alpha-DHT in nude mice treated with high doses of CsA.

Figure 1-2. Marked hair growth on forehead, arms, legs, and back

Despite the aforementioned researches, several other authors have reported hypertrichosis without significant variation in normal circulating plasma androgen levels as observed in idiopathic hirsutism. To study a possible relationship between CsA-induced hypertrichosis and sex hormone patterns, Lindholm et al. [13] graded different areas of body hair growth, assessing the hormone levels before and up to six months after kidney transplantation, and reported that post-transplantation levels of hormones did not explain the increased hair growth, concluding that CsA induces hypertrichosis via a mechanism independent of sex hormones. Schmidt et al. [14] investigated ovarian, adrenal and pituitary hormones as possible mediators of increased hair growth. No significant differences in serum androgens were noted between CsA-treated patients and controls.

As with all chemotherapeutics, close surveillance of drug levels are important to monitor adverse effects. Patients using the HLH-2004 protocol are advised to have CsA levels measured weekly and the plasma level should be under 200 ng/ml. The CsA level of the presented case was extremely high at the time of the development of hypertrichosis. We believe that such intense hypertrichosis in our patient may have been caused by a CsA overdose due to insufficient drug monitorization and also due to dual usage of both CsA and corticosteroids.

Hypertrichosis is an undesirable and troublesome cosmetic problem for both patients and parents. Wysocki et al. [9] showed that cessation of CsA therapy resulted in progressive resolution of the induced hypertrichosis. The management of hypertrichosis in children is often controversial because many of the methods of treatment used are either untested or unsuitable for use in pediatric patients [15]. Thus, treatment options are few and the results of therapy are not always satisfactory. Patients should, therefore, be adequately advised of the available treatment modalities for temporary or permanent hair removal. No single method of hair removal is appropriate for all body locations or patients, and the chosen method usually depends on the character, area, and amount of hair growth, as well as the age of the patient and their personal preference. The lack of research on children makes it difficult to choose the most efficient method. When hypertrichosis is secondary to an underlying condition, eradication of the cause will frequently result in resolution of the hypertrichosis.

In conclusion, hypertrichosis is an important complication in children receiving CsA and corticosteroid treatment, particularly when used together. Monitoring plasma levels of CsA is extremely important in decreasing the possible side effects, and compliance with therapy may be achieved more easily if side effects are minimal. Educating the patient and parents prior to therapy regarding the likely occurrence of this side effect and the importance of sufficient follow-up is therefore an important aspect in the overall care of the patient. Further research should be carried out on the pathogenesis of hypertrichosis as well as the various treatment options available, particularly for the pediatric population.

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