Mycophenolate-Associated Alopecia in an Adolescent Girl Mycophenolate and Alopecia

Adölesan Bir Kız Hastada Mikofenolat İlişkili Alopesi Mikofenolat ve Alopesi

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ABSTRACT

PURPOSE: To report a patient treated with enteric-coated mycophenolate sodium (EC-MPS), in whom infrequent side effects developed.

CASE REPORT: A 14-year-old girl presented with hair loss after starting EC-MPS. She had her first nephrotic syndrome attack when she was 7 years old. During the next six years, she had six attacks and two biopsies without findings of segmental sclerosis. She received steroids and 55 months of CsA. She was evaluated as steroid and CsA dependent when she had a relapse a month after cessation of treatment. The last biopsy showed CsA toxicity. EC-MPS was instituted (1080 mg/d). Alopecia developed at the second month. The dose was decreased by two third and hair loss stopped within a month. Her menstrual cycles also ceased after EC-MPS treatment and resumed two months after dose reduction. She remained in remission during the following 8 months and had a new relapse thereafter, which responded to a short term of high dose steroid treatment. She is still on the 20th month of EC-MPS and had no relapse.

CONCLUSION: This is the first adolescent with alopecia and menstrual irregularity during EC-MPS treatment, which may be effective even at a two third of the suggested dose.

KEY WORDS: Mycophenolate, Alopecia, Menstrual irregularity, Nephrotic syndrome, Adolescent

ÖZ

AMAÇ: Enterik kaplı mikofenolat sodyum (EC-MPS) ile tedavi edilen ve nadir görülen yan etkilerin geliştiği bir olguyu bildirmek.

OLGU SUNUMU: On dört yaşında kız hasta EC-MPS tedavisi sonrası gelişen saç kaybı ile başvurdu. Hastanın ilk nefrotik sendrom atağını 7 yaşında iken geçirdiği, takip eden 6 yıl boyunca 6 atak daha geçirdiği, bu sürede yapılan iki renal biyopside segmental skleroz bulgularına rastlanmadığı, steroid tedavisi ve 55 ay süren siklosporin A (CsA) tedavisi aldığı kaydedildi. Tedavi kesiminden bir ay sonra relaps olması üzerine steroid ve CsA bağımlı olarak değerlendirilen olgunun tekrarlanan biyopsisinde CsA toksisitesi izlendi. Bunun üzerine başlanan EC-MPS (1080 mg/gün) tedavisinin ikinci ayında alopesi gelişti. Doz üçte iki oranında azaltılınca saç dökülmesi bir ay içinde durdu. Ayrıca, EC-MPS tedavisinden sonra duraklamış olan adet döngüsü dozun azaltılmasından iki ay sonra tekrar başladı. Takip eden 8 ay boyunca remisyonda kalan olgunun tekrarlayan atağı kısa süreli yüksek doz steroid tedavisine yanıt verdi. Halen EC-MPS tedavisinin 20. ayında olan olgu sorunsuz izlenmektedir.

SONUÇ: Olgumuz, EC-MPS tedavisi sırasında alopesi ve adet düzensizliği bildirilen ilk adölesan olgudur. EC-MPS, önerilen dozun üçte ikisinde bile etkili olabilmektedir.

ANAHTAR SÖZCÜKLER: Mikofenolat, Alopesi, Adet düzensizliği, Nefrotik sendrom, Adölesan

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INTRODUCTION

Mycophenolate mofetil (MMF) is an immunosuppressive agent more recently added to the therapeutic armamentarium against steroid resistant (SRNS), frequently relapsing (FRNS) and steroid or cyclosporine dependent nephrotic syndrome (SDNS, CsADNS) (1-7). It has emerged as a new agent without nephrotoxicity and gonadal toxicity (3). The most common side effects are gastrointestinal (GI) complaints (gastritis, nausea, vomiting, dyspepsia, constipation, diarrhea, abdominal distention, abdominal pain), anemia, leukopenia, and a predisposition to infection and malignancies (2,5). Alopecia and amenorrhea are infrequent side effects of MMF (8-10). To decrease the GI side effects, enteric-coated mycophenolate sodium (EC-MPS) has been designed and put into clinical use (11).

Here, we report an adolescent girl in whom sparseness of hair volume was realized at the second month of treatment with EC-MPS and responded to dose reduction by two third of the previous dose. She also experienced cessation of menstruation for four months during EC-MPS treatment.

CASE REPORT

A 14-year-old girl presented with hair loss after starting EC-MPS. She was first admitted with nephrotic syndrome when she was 7 years old. She was treated with steroids for the following two attacks. A year after the last attack, she had another one while on low-dose steroid treatment (0.25 mg/kg/alternate day). Her kidney biopsy revealed mesangial proliferation and cyclosporine A (CsA) was added. On the second year of low-dose steroid and CsA treatment, she had a new relapse that was managed with pulse methylprednisolone (MP). Nine months later, she had another attack and the second biopsy revealed no toxic effect of CsA or findings suggestive of segmental sclerosis. CsA was started with tapering doses (from 5 mg/kg/day to 3 mg/kg/day) in addition to low-dose steroid for another two years and then it was stopped. However, a month after cessation, she presented with a new relapse and high levels of urea (215 mg/dL) and serum creatinine (1.1 mg/dL). Serum complement levels were in the normal range and anti-nuclear antibody and anti-double stranded DNA levels were negative as they were throughout the clinical course. A new biopsy was performed and showed chronic changes including dilated tubules filled with hyaline casts, interstitial fibrosis, interstitial inflammatory cell infiltration, periglomerular fibrosis around all glomeruli and complete hyalinization in 20-30% of the glomeruli. She was evaluated as steroid and CsA dependent. As the total CsA treatment duration reached 55 months and because of the pathological findings compatible with CsA toxicity, EC-MPS was started with an equivalent dose of 1000 mg/m^2 (1080 mg/d) divided into two daily doses in addition to pulse MP. At the end of the second month of EC-MPS treatment, proteinuria levels and other laboratory parameters reached normal levels, but the patient recognized scarcity in her hair (Figure 1A,B). The dose was decreased by 30% (720 mg/d). A month later, hair loss stopped and new hair in the scalp was observed (Figure 2A,B). Hair density became abundant in the following months (Figure 3A,B). Her menstrual cycles ceased after EC-MPS treatment although she had been having regular cycles for the last two years. Her laboratory findings including follicle stimulating hormone, luteinizing hormone, prolactin, estradiol, free thyroxine, thyroid stimulating hormone were in the normal range and pelvic ultrasonography was normal. Her menstrual irregularity improved two months after dose reduction.

She remained in remission during the following 8 months after dose reduction, but then had a new attack, which responded to steroids. She is still on EC-MPS (720 mg/d) for the last 20 months without any other side effects and we are planning to stop the treatment at the end of 2 years.

DISCUSSION

MMF is a reversible inhibitor of inosine monophosphate dehydrogenase and *de novo* purine synthesis. This leads to selective inhibition of both T- and B-lymphocytes (1,8,12). As idiopathic NS is thought to be a T-lymphocyte dysfunction, MMF has been used for the treatment.

In children with FRNS, SRNS and SDNS, CsA and cyclophosphamide (CYC) have been the treatment of choice. Although they have beneficial effects, CsA has a significant risk of nephrotoxicity along with cosmetic effects and CsA-dependency, while CYC may cause gonadotoxicity and malignancy (13). Recently, MMF has emerged as an immunosuppressive agent devoid of nephrotoxicity and gonadal toxicity, which is beneficial in managing children with FRNS (3,4,9), SRNS (1,2,13,14), SDNS (5,7,12,15) and CsADNS (6,7). However, it has compromising side effects including GI disturbances, anemia, leukopenia, predisposition to infection and malignancies, which may lead to dose reduction or even medication withdrawal (2,5). Enteric-coated mycophenolate sodium (EC-MPS) has been designed to reduce MMF-related GI adverse effects (11). We started EC-MPS in our case as the patient had renal impairment at the time of admission, had evidences for CsA nephrotoxicity at the last kidney biopsy and as she was accepted as steroid and CsA dependent because of having a relapse a month after cessation of steroids and CsA.

The advantage of MMF compared with CYC is the reduced incidence of drug related adverse effects including alopecia and amenorrhea (10). In a study on 12 patients with lupus nephritis, who had both CYC-treated and MMF-treated episodes, alopecia and amenorrhea were seen only in CYC-treated periods (16). In a meta-analysis including 618 adult patients with lupus nephritis, a significant reduction in alopecia and amenorrhea has been reported with the use of MMF compared to CYC (17). Our patient had no clinical, laboratory or histopathological features of lupus, and both alopecia and transient menstrual irregularity developed while on MMF. Although the latter may be associated

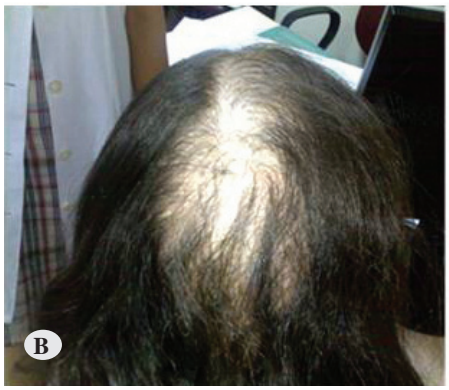
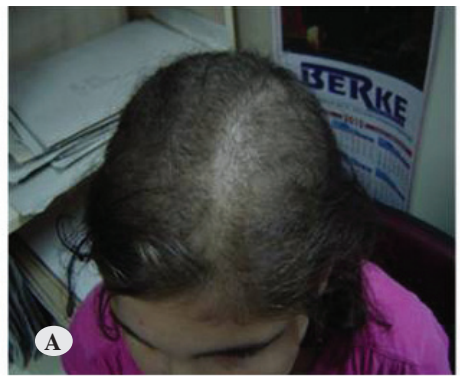


Figure 1 A,B: *Hair and scalp of the patient at the second month of treatment with enteric-coated mycophenolate sodium (EC-MPS) at a dose of 1080 mg/d.*



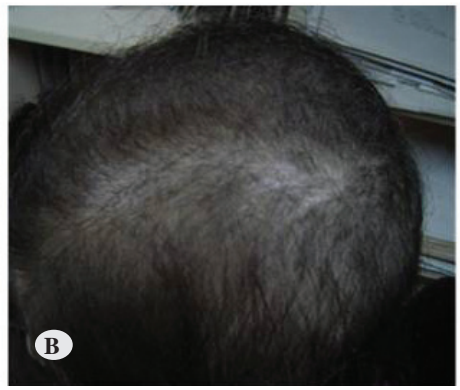


Figure 2 A,B: *Short, thin hair around the vertical area one month after EC-MPS dose reduction.*

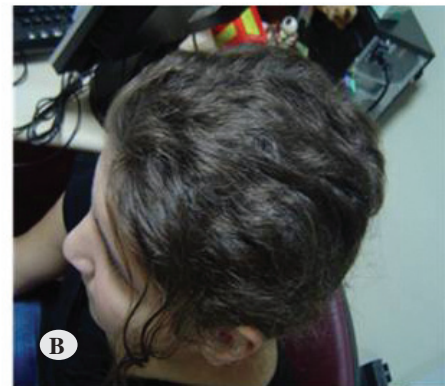


Figure 3 A,B: *Stronger and longer hair at the same area three months after dose reduction.*

with her physiological maturity, alopecia seems to be directly related to MMF treatment.

In some types of alopecia, MMF is even used for treatment. For instance, MMF was found effective in patients with lichen planopilaris (LPP), which is a cicatricial alopecia characterized by chronic lymphocytic inflammation of the hair follicle (18,19). However, in seven patients with alopecia areata, an autoimmune disorder involving activated CD4 (+) T-lymphocytes that infiltrate the hair follicles, MMF was not found to be beneficial (20).

MMF-associated alopecia has been rarely reported in the literature. In a study on 33 patients with lupus nephritis, one developed alopecia during MMF treatment (21). Besides, alopecia has been reported in an adult patient using MMF for uveitis at the tenth month of treatment (22). Among 30 adults with primary glomerulonephritis, alopecia developed in one patient with lupus nephritis, and in another with IgA nephropathy (8). In children, only slight alopecia has been reported in a child treated with MMF for resistant NS (9). In our patient, hair loss was marked and responded to dose reduction.

In NS, the usual dose is 1200 mg/m^2/d divided into two doses. Lower doses were also used and found to be beneficial as well in some studies (2,7,9). We started EC-MPS as an equivalent MMF dose of 1000 mg/m^2 and then the dose was decreased to 700 mg/m^2 when hair sparsity was noted. No relapse was observed during the following 20 months. The absence of diarrhea, serious infections, and hematological adverse effects in our patient might be attributed to a lower but therapeutically effective dosage of the medication.

In conclusion, our case is the first one with severe hair loss and menstrual dysregulation among children treated with MMF. This case is reported to emphasize that these patients require close follow-up for these infrequent side effects. Besides, alopecia may be reversible by dose reduction and even two third of the suggested dose may be effective to keep a patient with steroid- and CsA-dependent nephrotic syndrome in remission.

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