Case Report

A Case of Recurrent Erythema Multiforme and its Therapeutic Complications

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Abstract

Introduction: We report a patient with recurrent erythema multiforme (recurrent EM) who developed iatrogenic Cushing's syndrome due to prolonged corticosteroid use. Clinical Picture: The patient had been treated with multiple courses of oral and intramuscular prednisolone over a 10-year period to suppress his recurrent and episodic symptoms. This resulted in the development of iatrogenic Cushing's syndrome with secondary adrenal suppression and steroid-induced osteoporosis. Treatment: The patient was treated with continuous acyclovir therapy in addition to azathioprine. This combination controlled his disease and enabled us to stop his requirement for high-dose prednisolone. Outcome: The patient responded well to this treatment regimen and has been in remission to date. Conclusion: This represents a severe case of recurrent EM and the side effects associated with years of chronic high-dose steroid usage. We discuss the therapeutic options to aid physicians in treating this disabling condition.

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Key words: Acyclovir, Azathioprine, Corticosteroid side effects

Introduction

Recurrent erythema multiforme (EM) is a disabling condition with a specific diagnosis and certain diagnostic criteria. Systemic corticosteroid therapy is frequently used to treat this condition. We report a case of a patient who was treated with systemic steroids for many years to control this condition and the vast number of side effects associated with chronic corticosteroid treatment. Our review of the literature shows that continuous acyclovir therapy represents a safer, more effective treatment for many patients with recurrent EM. This case also confirms that azathioprine is consistently effective in providing disease suppression.

Case Report

The patient is a 39-year-old Chinese male who was referred to our institution in August 2002 by a private dermatologist for further investigation and management. He gave a history of recurrent erosions on his lips and buccal mucosa every 2 to 3 months since 1989. He also complained of episodic blisters on his elbows every 1 to 2 months since 1992. This was associated with episodic blisters on his hands and feet every 1 to 2 months since 2000 and 2 episodes of genital erosions over the past year.

He had first presented to our institution in December 1991 with oral ulcers and rashes. At this time he gave no preceding history of "cold sores" or genital herpes. The clinical impression at the time was that of pemphigus or bullous pemphigoid. A biopsy was taken from a lower lip erosion and the histological diagnosis at the time was that of bullous lichen planus. A herpes culture taken from his lip erosion was negative. He subsequently defaulted follow-up and over the past 10 years had been treated for his condition by his general practitioner. Over this period, he had received multiple twice weekly courses of oral prednisolone 60 mg daily every 1 to 2 months supplemented by intramuscular steroid injections 1 to 2 times a year, which resulted in rapid resolution of his symptoms.

In the year prior to his referral, the patient had consulted a private dermatologist who performed a repeat biopsy from a target lesion on his finger. This confirmed a diagnosis of EM and his condition as recurrent EM. He was treated on 2 occasions over the year with a 2-week tailing course of prednisolone 30 mg daily and was worked up by the private dermatologist for side effects of chronic steroid use. He was found to have hyperlipidaemia, with a low cortisol level and abnormal liver function tests. The patient was admitted to the ward for further work-up. On examination he was found to be cushingoid with crusted erosions on his buccal mucosa (Fig. 1), healing erosions on his glans penis, target lesions on his palms (Fig. 2) and small tense blisters

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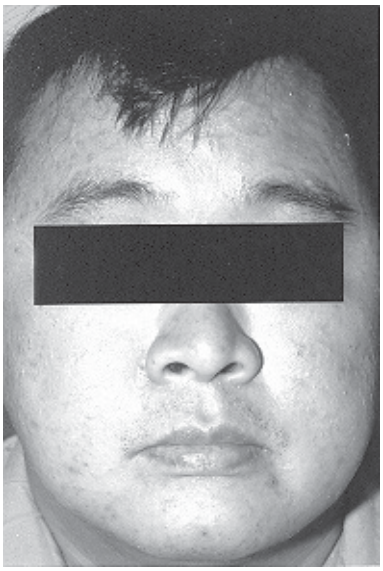

Fig. 1. Cushingoid facies with steroid-induced acne. A small tense blister is seen on the lower lip.

on his elbows and feet. Investigations confirmed that he had developed iatrogenic Cushing's syndrome with secondary adrenal suppression as well as steroid-induced osteoporosis. He was found to have abnormal liver function tests (hepatitis screen negative, ultrasound of liver showed fatty infiltration) and hypercholesterolaemia. A herpes simplex virus (HSV) culture taken from a penile erosion was negative and a polymerase chain reaction (PCR) performed from his buccal lesion and finger biopsy were both negative. Serology for Epstein-Barr virus (EBV) infection was negative. A diagnosis of recurrent EM complicated by iatrogenic Cushing's syndrome and osteoporosis was confirmed. He was commenced on oral acyclovir 400 mg twice daily (suppressive dose), prednisolone 40 mg daily and Fosamax 70 mg once a week. He initially responded to the prednisolone being tailed down to 20 mg daily over 2 weeks, but when the prednisolone was tailed down to 5 mg mane and 2.5 mg nocte (as suggested by the endocrinologist), his recurrent EM got worse. He was referred for a gastroenterological opinion and his fatty liver was thought to be due to weight gain and steroid treatment. Following this, azathioprine 50 mg daily was commenced and the acyclovir was continued. He responded very well to this treatment and, over the past 9 months, has not had an episode of his recurrent EM. He has been in remission since November 2002. The patient is currently on azathioprine 100 mg daily, acyclovir 400 mg twice daily and hydrocortisone 20 mg mane, 10 mg nocte. The prednisolone was stopped recently by the endocrinologist and he was started on hydrocortisone replacement therapy.

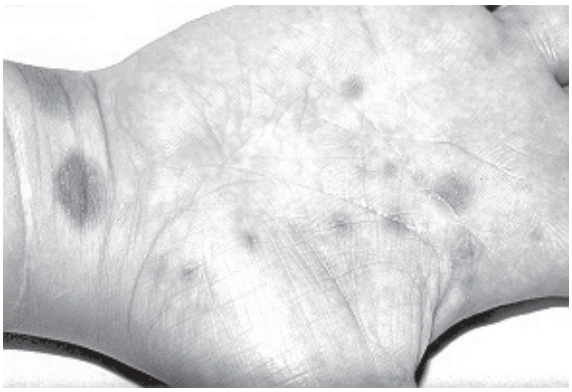

Fig. 2. Multiple target lesions on palm and wrist.

In summary, this case represents a severe case of recurrent EM and the side effects associated with years of chronic high-dose steroid usage. His condition was only partially suppressed with acyclovir (although no proven herpes simplex virus association) and it took the addition of azathioprine to suppress it completely.

Discussion

Erythema multiforme is an acute, self-limiting, mucocutaneous disorder with symmetrically distributed, erythematous skin lesions, some with concentric colour changes (target lesions), which resolve within 1 to 6 weeks and show compatible histology. There exists a subgroup of patients with recurrent EM in whom frequent episodes of the disease over several years cause significant morbidity. They experience 2 or more attacks per year, each lasting approximately 14 days as in classic EM.

Prodromal symptoms include malaise, fever, headache, sore throat, rhinorrhoea and cough which may occur approximately 1 week before the onset of EM. The typical primary lesion of EM is a round, erythematous macule that rapidly becomes papular or urticarial. Individual oedematous papules may enlarge to small plaques and may also develop concentric alterations in morphology and colour. The concentric changes produce characteristic lesions with either a central blister or a central area of necrosis resulting in target lesions. As the skin lesions resolve, they may develop some scaling but typically heal without atrophy.

The lesions are typically symmetrical and occur commonly on the dorsal surfaces of the hands and extensor aspects of the extremities. Mucosal involvement occurs in 25% to 60% of cases either simultaneously or preceding it by several days. New lesions appear over 3 to 5 days. The duration from onset to healing is less than 4 weeks (~2 weeks). In recurrent EM, the recurrent attack may occur before the lesions from the previous attack have completely resolved.

Routine tests are not diagnostic. The white cell count and erythrocyte sedimentation rate are only slightly raised. EM presents a varied histologic picture analogous to its clinical multiformity. The histopathologic changes seen are not always diagnostic of EM and the primary requirement is that they be "compatible". Recurrent EM is a specific diagnosis with certain diagnostic criteria. Cases with persistent skin lesions lasting weeks to months or a chronic nonepisodic course should not be diagnosed as recurrent EM. Also, the diagnosis of recurrent EM as an illness characterised by only acute mucosal inflammation without skin lesions is unjustified: the typical skin lesion is the sine qua non for the diagnosis of recurrent EM.

The list of aetiological associations with EM in the medical literature is endless. In view of the fact that recurrent EM is an episodic and recurrent presentation of EM, only 3 aetiologically associated EM syndromes have been well described in the literature: HSV-associated EM, mycoplasma-associated EM and drug-associated EM. However, the latter 2 are not commonly associated with recurrent EM unless, for example, the drug is repeatedly readministered. Therefore, infectious agents, commonly viruses (due to reactivation), are likely to be the main associations of recurrent EM.

In studies which have reviewed recurrent EM, about 70% of cases have disease precipitated by HSV.[1,2] Even in those cases of recurrent EM where triggering by HSV is not apparent, it is believed that subclinical attacks of HSV may be important in the pathogenesis of the disease.[3] Current thinking, therefore, suggests that most cases of recurrent EM may be herpes-related.[4] Although it has been suggested that in 70% of patients with recurrent EM the disease is precipitated by HSV, recent studies indicate that the proportion of cases which are HSV-related is even greater. Using PCR techniques, viral DNA has been shown to be present in the skin lesions of EM[5] even in patients whose disease does not appear clinically to be HSV-related.[6] In our local study at the National Skin Centre, nested PCR was used to detect HSV-DNA in skin biopsies with histologically proven EM. PCR was positive in 6 out of 10 patients (60%) with HSV-related recurrent EM and in 6 out of 12 patients (50%) with idiopathic recurrent EM.[7]

Cytomegalovirus (CMV) primarily brings about subclinical and asymptomatic infection in the early stages of life. After the primary CMV infection, the virus persists in a latent stage with the potential for reactivation throughout life. A study in Japan[8] using PCR techniques on 5 non-immunosuppressed Japanese adults with EM confirmed CMV-DNA in all 5 skin biopsies. A positive IgM antibody to CMV is detected not only in primary infection but also in recurrent cases. EBV,[9] streptococcal,[10] Coxsackie[10] and adenovirus infection[11] have also rarely been associated with recurrent EM. There has also been a reported association with chronic hepatitis C infection.[12] The patient failed acyclovir therapy but the recurrent EM was effectively suppressed by IFNα.

Systemic corticosteroid therapy is frequently used to treat recurrent EM. Although it may partially suppress the disease, it may also prolong the duration of attacks and is associated with side effects. Continuous acyclovir therapy represents a safer, more effective treatment for many patients with recurrent EM. It has been shown in several studies to completely suppress recurrent EM in the majority of patients and produce partial suppression in others. Patients who have a clear-cut relationship between HSV and EM are often effectively treated with short-course acyclovir (200 mg 5x/day for 5 days) started at the earliest sign of a herpes attack, but those patients who have frequent attacks of EM, whether HSV-related or not, should receive a trial of continuous acyclovir before alternative therapies are tried. It is not clear whether failures of acyclovir are related to viral resistance to acyclovir or to non-HSV-induced recurrent EM. One case report discussed a patient with frequent post-herpetic recurrent EM resistant to continuous acyclovir treatment but responsive to valacyclovir.[13]

Valacyclovir is a prodrug of acyclovir and is converted to acyclovir by the liver. Its antiviral action is similar to acyclovir but it displays much better bioavailability. In patients with recurrent EM, failure of prophylactic continuous acyclovir treatment does not exclude a herpetic origin. It may be explained by insufficient tissue concentrations of acyclovir. The systematic use of valacyclovir in patients with recurrent EM might provide better therapeutic results and lower the risk of selecting acyclovir-resistant viral strains.

Once a diagnosis of idiopathic recurrent EM has been confirmed and if the attacks are mild, expectant therapy can be implemented. However, if the recurrent EM is severe, systemic immunosuppressive (steroid-sparing) treatment needs to be instituted.

Dapsone or antimalarials are recommended as first-line treatment. There has been an isolated case report showing the efficacy of dapsone in treating recurrent EM.[14] In this study, where acyclovir treatment failed, dapsone was shown to produce partial or complete suppression in 8 of 9 patients. Antimalarials (mepacrine or hydroxychloroquine) have also brought about partial or complete disease suppression when acyclovir treatment failed. Azathioprine has been shown to be consistently effective in producing disease suppression. However, it is recommended as second-line treatment due to its side effects. If this treatment fails, mycophenolate mofetil can be tried. It has been shown to be an effective and relatively safe[14] immunosuppressive

agent in recurrent EM; however, its use is limited by its high cost.

Conclusion

Recurrent EM is a disabling condition. Systemic corticosteroid therapy is frequently used to treat this condition. The clinical case presented depicts the vast number of side effects associated with chronic corticosteroid treatment. In view of the natural history of the disease, it is clear that effective suppression of the condition is important. The use of systemic corticosteroids should be avoided and replaced by therapy with acyclovir and or systemic (steroid-sparing) immunosuppressive treatment.

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