Chronic Graft-versus-Host Disease Revealed by Lichenoid Vulvar Lesions Successfully Treated with Thalidomide

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Sir,

Chronic graft-versus-host disease (GVHD) occurs in approximately 60–80% of patients who survive for 100 days after allogeneic bone marrow transplantation (BMT) (1). The skin is affected in almost all cases of chronic GVHD, with two distinct phases: the early chronic phase, characterized by lichenoid lesions similar to lichen planus, and the late chronic phase, with sclerodermatous lesions. During the early course, the clinical spectrum of lichen planus may be reproduced, and the initial lesions are usually in the buccal mucosa. Rarely has genital mucosa been reported during chronic GVHD. We describe a case of chronic GVHD in a 40-year-old woman successfully treated with thalidomide at a dose of 100 mg per day. GVHD manifested in erosive lichen-planus-like lesions of the vulva following allogeneic BMT for chronic myeloid leukaemia.

CASE REPORT

In May 1999, after conditioning with busulfan and cyclophosphamide, the woman underwent allogeneic BMT from an HLA-matched sibling. She received cyclosporine and methotrexate as GVHD prophylaxis. On day 30 after BMT, she developed acute cutaneous GVHD (grade II), which was controlled with prednisolone. A bone marrow examination performed 3 months later showed cellular marrow in cytogenetic and morphological complete remission. In October 1999 (5 months after BMT), the patient began to complain of a burning sensation of the vulva mucosa, which was causing dysparunia. Hormone replacement therapy failed to improve these symptoms. Gynaecological examination revealed erythema and erosive areas between the labia majora and minora, associated with mild atrophy of the vulva and introitus vaginae mucosa. Examination of the oral cavity revealed asymptomatic involvement of the buccal mucosa, showing erythema, with a white reticular component, and small areas of erosions along the gingival mucosa. The patient refused biopsy, but as oral involvement was typical of chronic GVHD, and vulvar lesions were reminiscent of vulvar lichen planus, vulvar involvement was considered a manifestation of lichenoid chronic GVHD. Therapy was started with corticosteroid ointment (betamethasone 0.05%), but this topical treatment remained ineffective. The patient was therefore treated locally with a preparation of cyclosporine in olive oil (30 mg of cyclosporine, twice daily). The lesions rapidly began to improve, but the cyclosporine preparation had to be discontinued because of poor tolerance in erosive areas of both the genital and buccal mucosa. Systemic corticosteroid (prednisolone, 0.5 mg per kg per day) was then added to the topical corticosteroid, but the results remained unsatisfactory. An association of systemic corticosteroids and cyclosporine (100 mg per day) was also tried over a period of 2 months, but without success. Indeed the patient progressively developed vaginal adhesions, causing haematocolpos in April 2001 (18 months after BMT), treated by surgical lysis. It was consequently decided to start her on thalidomide (100 mg per day). Within 2 weeks the burning sensation of the vulva mucosa had stopped, and one month later oral and genital inflammation had visibly decreased. However, because of a sedatory effect, the thalidomide dose had to be decreased to 50 mg per day. Seven months later (March 2002) the patient had a recurrence, leading again to the thalidomide dose being raised to 100 mg per day and subsequent improvement after 10 days. This same dose of thalidomide has remained effective and well tolerated for 12 months. Regular use of corticosteroid ointment has been added to thalidomide to prevent any further recurrence.

DISCUSSION

Although chronic GVHD occurs frequently after allogeneic BMT, manifestations of this disorder in the genital mucosa have rarely been described in the literature, suggesting that this localization may be under-reported. A case of chronic GVHD occurring in penis mucosa, causing phimosis, was described in 1998 (2). Corson et al. (3) reported gynaecological manifestations of chronic GVHD in five allogeneic bone marrow transplanted women and Lönnqvist & Brune (4) in two. In all these cases the patients developed extensive sclerosing vaginitis, with synechiae formation leading to vaginal stenosis. The authors did not emphasize the association of vulva mucosa lesions. Furthermore, contrary to our observation, genital lesions were not the first manifestation of chronic GVHD and were associated with extensive cutaneous chronic GVHD. On the other hand, in 1999 DeLord et al. (5) reported one case of vaginal stenosis as an isolated localization of chronic GVHD. To our knowledge, no previous papers have reported the involvement of vulva mucosa as a first symptom of this disease. Genital involvement after BMT is probably multifactorial, and other potential causes of dysparunia have been eliminated in our observation. Our patient did not receive total body irradiation during conditioning before BMT. Furthermore, she received adequate hormone replacement therapy after BMT. Finally, there was no sign of Sjögren-like syndrome, which can occur in patients with the extensive form of chronic GVHD (1). In

the reports by Corson et al. (3) and DeLord et al. (5), the diagnosis of vaginal involvement was made with a mean time of 12 months after BMT. In our study, erosive lichen-planus-like lesions of the vulva mucosa appeared 5 months after BMT.

These findings suggest that the vulvar lesions may correspond to the early phase of chronic GVHD. We therefore aim to carry out regular gynaecological examinations after BMT to allow earlier diagnosis, and consequently early therapy, for chronic GVHD genital complications. Because local and systemic corticosteroids and cyclosporine have failed to improve genital and oral lesions, we decided to start treatment with thalidomide. Indeed the beneficial effect of high-dose thalidomide has been reported in the treatment of patients with refractory chronic GVHD (6,7). In our observation, the vulvar lesions rapidly decreased with a low dose of thalidomide (100 mg per day). A combination of thalidomide and regular use of corticosteroid ointment was performed over the course of 1 year and no recurrence was observed.

The efficacy of thalidomide suggests that introduction of the drug earlier in the course of this form of chronic GVHD may be beneficial, as well as in other mucosal involvement, and also that thalidomide may be added to cyclosporine as GVHD prophylaxis after BMT. However, all these propositions require further clinical study before they can be accepted. Finally, in our observation topical treatment with cyclosporine in olive oil failed to improve oral and vulva mucosal lesions because of poor tolerance in erosive lesions. Regarding the recently described efficacy of topical tacrolimus for recalcitrant erosive oral lichen planus (8), we suggest that tacrolimus ointment may also be useful in the management of chronic GVHD genital complications.

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