Review

Female Genital Tract Chronic Graft-*versus*-Host Disease: Review of the Literature

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Abstract. Background: Chronic graft-versus-host disease (cGVHD) is the most common late complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT). Although the involvement of skin, oral cavity, eyes, liver and gut is well-described, gynaecological manifestations are rare, often undiagnosed and untreated. Materials and Methods: A selective literature search of articles in English language, published from 1982 to 2014 (indexed in PubMed) was performed. Discussion: Genital cGVHD is characterised by polymorphic clinical manifestations with sclerotic changes of the vulva and vagina. Introital stenosis or complete vaginal closure were reported in severe cases. Thus, cGVHD can seriously affect female sexual function and the overall quality of life. A prompt diagnosis and an appropriate therapy may prevent the development of severe forms and the need for surgery. Thus, a systematic specialized gynaecological consultation should be performed early in every allo-HSCT recipient as part of the routine post-transplantation management, even in asymptomatic women.

Chronic graft-*versus*-host disease (cGVHD) is a systemic immune disorder and the most common late complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT) (1). In recent years, this procedure is being used with increasing frequency to treat several haematological malignancies causing the incidence of GVHD to rise. GVHD is characterized by acute and chronic stages that are categorized based on whether symptoms developed within 100 days after the transplant (acute GVHD) or later (cGVHD). Chronic GVHD presentation can be progressive (acute GVHD merging into chronic), quiescent (acute disease completely solved but followed later by chronic) or *de novo*; a previous acute GVHD is reported to be an important risk factor for chronic disease (2). The pathogenesis of GVHD is believed to be a complex, primarily T-cell-mediated, immune response in which the grafted donor cells react against histocompatibility antigens in the host (2). In the development of chronic disease, several mechanisms seem to be implicated, including persistence of donor-derived alloreactive T-cells, autoreactive T-cells and B-cells producing antibodies against the host (3). The subsequent chronic inflammation can lead to tissue damage and organ fibrosis.

The disease can occur after both allogeneic bone marrow and peripheral blood stem cell transplantation; however, cGVHD after peripheral blood stem cell transplantation has been observed to be more protracted, less responsive to glucocorticoids and more commonly involves the skin and the female genital tract (4).

Chronic GVHD is characterized by polymorphic clinical manifestations with varying severity and clinical course with, virtually, all organs potentially involved. Approximately, 65% to 85% of patients with cGVHD have skin involvement, 60% mouth involvement, 40% to 55% liver involvement, 25% to 45% eye involvement, 20% to 30% nutritional problems and 10% to 15% have lung manifestations (5). Although the involvement of skin, oral cavity, eyes, liver, gut and lungs is well-described, gynaecological manifestations are probably underestimated.

Women with genital cGVHD often complain about annoying symptoms, such as dryness, itching, burning, pain to touch, dysuria and dyspareunia. Even if these symptoms should significantly impact the quality of life and interfere with the capacity for sexual intimacy, women seldom refer them to their care providers and, thus, this condition often remains undiagnosed. However, genital cGVHD is by far the commonest cause of vulvo-vaginal symptoms after hematopoietic stem cell transplantation, even in children (6). An appropriate management of this condition is

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mandatory, thus oncologists and haematologists should be aware of the problem and a specialised gynaecological consultation should be considered as part of the routine post transplantation follow-up.

Materials and Methods

A selective literature search of articles in English language, published from 1982 to 2014 and indexed in PubMed was performed.

Genital cGVHD

Extra-genital manifestations of cGVHD are reported in 30-70% of allo-HSCT recipients with a median onset of 4-6 months following transplantation (3). Vulvo-vaginal involvement seems to be rarer and previous studies reported an incidence of genital manifestations of cGVHD in approximately 3% of bone marrow and 15% of peripheral blood recipients (7). However, the real incidence of the disease is currently unclear and various publications report female genital involvement in 25 to 49% of allo-HSCT survivors (8, 9). Vulvo-vaginal cGVHD usually presents a median of 7 to 10 months after allo-HSCT (6, 8, 9) but first symptoms can also develop as late as 2 years after the transplantation (10).

Recently, in a series of 32 women with cGVHD who were followed after allo-HSCT in a specialized gynaecological consultation, Hirsch and colleagues (11) reported a median time before the onset of gynaecological manifestations of 13 months with a range from 5 to 47 months. The possibility of a late onset of the disease, even beyond 12 months post transplantation, indicates the need of a long-term gynaecological follow-up in these women (9).

Although most of the women diagnosed with cGVHD show involvement of the mouth or other sites, genital manifestations may sometimes be the only sign of this condition (8, 12, 13). It is currently unclear if an established extra-genital involvement could represent a potential risk factor for allo-HSCT survivors to develop vulvo-vaginal manifestations of cGVHD. Furthermore, the severity of vaginal and vulvar symptoms do not appear to be correlate with the severity of cGVHD found in other organ systems (10).

The diagnosis of vulvo-vaginal cGVHD is based on symptoms and physical findings; the typical clinical manifestations and the rapid response to superpotent topical corticosteroid therapy are usually sufficient for diagnosis (14, 15). However, histological confirmation is recommended in the absence of diagnostic manifestations of cGVHD in other organs (16).

Symptoms may include dryness, itching, burning, pain to touch, dysuria and dyspareunia and, in case of minimal or moderate disease, they can overlap with those of genital tract atrophy caused by premature ovarian failure commonly associated with myeloablative therapies (9). Although these symptoms should significantly impact the quality of life and interfere with the capacity for sexual intimacy and normal voiding, women seldom refer them to their care providers and, thus, this condition remains undiagnosed.

Physical findings include mucosal abnormalities and sclerotic changes of the vulva and the vagina. In order to allow a standardised description of the disease and even a better comparison between studies, a grading system for genital lesions was established. This grading system, first described by Spinelli *et al*. (8) in 2003, was subsequently modified by Stratton *et al*. (6) and includes three grades of disease. (I) Grade I (minimal disease) characterised by generalized erythema and edema of the vulvar structures; (II) Grade II (moderate disease) characterised by erosions of mucosal surfaces of the vulva or fissures in the vulvar folds, such as interlabial sulci and fourchette; and (III) Grade III (severe disease) characterised by sclerosis of the vulvar and vaginal tissues that can lead to architectural changes, such as agglutination of the clitoral hood, introital stenosis, vaginal synechiae or complete vaginal closure.

The literature shows some sporadic reports but very few studies have addressed the incidence and the risk factors involved in the genesis and progression of the disease. Previous published data by Spinelli *et al*. (8) and Spiryda *et al*. (10) reported no significant association between genital cGVHD and age, previous haematological malignancies, vaginal infections at the time of transplantation and previous pregnancies. However, further studies are needed to clarify the role of potential risk factors in the development of genital cGVHD.

Corson and colleagues (12) were the first to describe the potential gynaecological complications in five patients who had undergone allogeneic bone marrow transplantation with subsequent development of cGVHD. Subsequently, published reports concerned severe vulvo-vaginal stenosing lesions often requiring surgical therapy (17-22). Although these studies have led to a better description of the clinical aspects of the disease, especially in the severe cases, genital cGVHD still remains often undiagnosed and untreated.

Management of cGVHD

In 2006 Couriel and colleagues (16) established guidelines for ancillary therapy and supportive care in patients with cGVHD, including treatment for symptoms and recommendations for patient education, preventive measures and appropriate follow-up. First of all, the authors recommended specific hygiene measures for the prevention or alleviation of vulvar and vaginal symptoms: avoid mechanical and chemical irritants; clean genital area with warm water; sparing use of simple emollients to the vulva (not vagina); using water-based lubricants.

Several authors reported that a combination of topical superpotent glucocorticoids and estrogen was effective in the treatment of vulvo-vaginal cGVHD (6, 8, 9, 11, 16).

Topical estrogen therapy, with or without the use of a vaginal dilator, may be useful to improve symptoms resulting from ovarian failure-related genital atrophy and use of topical steroids. Estrogen is applied when erosions and fissures are healed, every day for 2 weeks and then decrease to one application 2 to 3 times a week (23).

Topical immunosuppressive agents may constitute an adequate primary therapy for controlling mild clinical manifestations and application of ultrahigh potency corticosteroid is actually the mainstay of therapy (16). For example, clobetasol propionate 0.05% ointment locally applied once a day, every day at bedtime, usually results in improvement within 2-4 weeks. Then, a reduction to a maintenance dose 2 to 3 times a week can be applied (23). If the response to topical steroids is inadequate, topical cyclosporine or tacrolimus ointment 0.1% can be added (9, 10, 16).

In order to prevent the formation of adhesions and vaginal stenosis, Zantomio *et al*. (9) recommended also prophylactic vaginal self-examination or dilator insertion (or intercourse) twice weekly to maintain vaginal capacity.

Treatment of vaginal scarring depends on its severity and severe sclerotic lesions should be treated aggressively with topical corticosteroids and dilators. Fine scars can be lysed manually during vaginal examination; then, an ultralow dose estrogen vaginal ring (75 μg/24 hours) can be used to mechanically open opposing sides of the upper vagina and can be replaced every 3 months (6). If a vaginal estrogen ring cannot be placed, dilators coated with topical immunosuppressive drugs (steroids, cyclosporine or tacrolimus) and estrogen, can be successfully used. Dilator size can be adjusted and used 2 to 3 times a week until the vaginal scarring lessens and a normal vaginal caliber is restored (23). However, surgical lysis with or without vaginal reconstruction may be necessary for patients with extensive synechiae and complete obliteration of the vaginal canal (16). After surgical treatment, the use of topical immunosuppressive therapy with dilators or sexual intercourse can prevent the developing of new scarring and maintains vaginal capacity (24).

Several studies reported that vulvar cGVHD precede vaginal involvement (6, 8, 10), with the latest reported cases of severe vaginal stenosis eight years after transplantation (18). The lag between vulvar and vaginal manifestations underlines the importance of early diagnosis during routine post transplantation follow-up and offers an opportunity to use prophylactic measures (*e.g*. vaginal dilator coated with topical estrogen or clobetasol, if needed) in order to prevent the need for surgery.

cGVHD and Human Papillomavirus (HPV) Infection

Theoretically, as with many viral infections, HPV can be reactivated during the immunodeficiency phase after allo-HSCT. Indeed, a lowering in specific immunity has been reported (25) and cases of cervical intraepithelial lesions are frequent. Therefore, genital HPV-related disease seems to be a significant late complication in long-term survivors. Previous studies reported an increased incidence of abnormal cervical cytology and condylomatosis following allo-HSCT (26-28); however, a relationship between the use of local immunosuppressive agents and HPV reactivation is currently discussed (29).

In 2008, Savani *et al*. (30) conducted a cross-sectional study of 35 adult women who underwent allo-HSCT for haematological malignancies; among them, 34 women developed cGVHD. The post-transplantation cervical cytology testing was abnormal in 15 women (43%). Subsequent biopsy showed high grade dysplastic lesions in 7 cases and low grade dysplastic lesions in 5 women; atypical squamous cells of undetermined significance (ASCUS) cytology was reported in the other 3 cases. The authors assumed that there was no association between genital GHVD and HPV-related cervical dysplasia but only prolonged systemic immunosuppressive treatment for cGVHD was associated with a higher risk of developing HPV-related squamous intraepithelial lesions (SIL) (odds ratio (OR): 4.6, 95% confidence interval (CI): 1.1-16.4; p=0.019) with median time to SIL of 51 months (range, 22-108 months).

Therefore, a specific follow-up with Pap smear and, if necessary, colposcopy, should be systematically performed in these women, especially when local or systemic immunosuppressive treatment is given. This specific gynaecological follow-up should be started early after the transplantation and performed yearly since the development of severe cGVHD with vaginal stenosis can strongly limit the ability to perform a routine Pap-test (31, 32). Before undergoing transplantation, adult women should be screened accordingly to the American Cancer Society guidelines for the prevention and early detection of cervical cancer in the general population (33). Therefore, if not already done, it should be appropriate to perform a Pap smear before allo-HSCT in each woman as part of the routine preoperative evaluation.

Vaccination against HPV should also be discussed since it could be a potentially important strategy for reducing the risk of reactivation of HPV infection. However, further evaluation of the immunogenicity of this kind of vaccine in allo-HSCT recipients is needed (11). Even if there is no evidence to suggest that inactivated vaccines exacerbate cGVHD, vaccination remains controversial because of suboptimal immune responses (23).

Conclusion

Genital cGVHD is an uncommon and probably underestimated complication of allo-HSCT; it is by far the main cause of vulvo-vaginal symptoms after transplantation, even in children, with an overall incidence of up to 49% of allo-HSCT long-term survivors (8, 9). The disease is

characterised by a wide variety of symptoms (dryness, itching, burning, pain to touch, dysuria, dyspareunia) and can be accompanied by sclerotic changes of the vulvar and vaginal mucosa. The sclerosis of vulvo-vaginal district can lead to progressive introital stenosis and, in severe cases, complete vaginal closure. These symptoms should significantly impact the quality of life and interfere with the capacity for sexual intimacy. As women, however, seldom refer them to their care providers, their condition often remains undiagnosed.

Most Centres do not perform systematic gynaecological follow-up in allo-HSCT survivors. However, a prompt diagnosis, followed by appropriate glucocorticoids and estrogen topical therapy, may prevent the development of severe forms and the need for surgery. Thus, early recognition and treatment are an important part of post transplantation management and a systematic, specialized gynaecological consultation should be performed in every allo-HSCT recipient. The follow-up should begin early after transplantation and be extended for years since a late onset of the disease is possible. It would be appropriate that a complete gynaecological history and examination were undertaken yearly in all females undergoing allo-HSCT, even if patients initially do not have any vulvo-vaginal symptoms.

Moreover, allo-HSCT long-term survivors seem to be at high risk of HPV-related dysplastic lesions. Thus, a specific follow-up with Pap smear and, if necessary, colposcopy, should systematically be performed in these women, especially when local or systemic immunosuppressive treatment is given. The opportunity of HPV vaccination in these women is still controversial but it could be a potentially important strategy for reducing the risk of re-activation of HPV infection; however, further studies are needed.

Conflicts of Interest

No conflicts of interest are declared. No sources of financial support are declared.

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