Female genital tract graft-versus-host disease following allogeneic bone marrow transplantation

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Background and Objectives. Graft-versus-host disease (GVHD) is a complex syndrome observed after bone marrow transplantation (BMT) affecting several organs including the lower genital female tract. We tried to evaluate the incidence of genital tract involvement and whether there are specific risk factors.

Design and Methods. A retrospective study was conducted in order to describe genital manifestations of GVHD and evaluate its incidence, severity and remission among 213 females who underwent BMT. The risk factors studied were previous pregnancies, vaginal cultures just before BMT and hormonal replacement therapy (HRT).

Results. Genital lesions considered as expression of GVHD were found in 53 patients (24.9%). They appeared in the first 100 days after BMT in 12 women and beyond in 41 cases. Seventy-three percent of patients with such lesions showed some evidence of chronic GVHD elsewhere. The proposed grading, the first attempt of its kind, showed that genital chronic GVHD was minimal in 66%, moderate in 22% and severe in 12% of patients. Vaginal fibrosis, sometimes with complete obstruction, was seen in this last form. This occurred in 86.8% of patients after 2-157 months (median 22) while persistent GVHD was observed in 7 of them. In our sample no significant association was found between genital GVHD and previous pregnancies or vaginal infections at BMT, while HRT seems poorly associated with gynecological manifestations of GVHD (p=0.049).

Interpretation and Conclusions. Genital GVHD is not unusual after BMT. It can seriously affect female sexuality and the overall quality of life. We suggest stressing the importance of early detection of genital involvement in order to prevent the most serious lesions. Further studies are needed to identify the triggering factors associated with the development of genital GVHD.

Key words: graft-versus-host disease, gynecological manifestations, allogeneic transplantation.

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Graft-versus-host disease (GVHD) is a disorder affecting several organs such as liver, skin, lachrymal and salivary glands as well as the mucous membranes. It is an inflammatory reaction to donor lymphocytes and may cause fibrosis, stricture and obliteration of the involved tissues.[1-3]

Little is known about GVHD of the female lower genital tract. The first report in 1982[4] described five cases. A recent review of literature shows some sporadic reports, but no studies have addressed the incidence and the influencing factors involved. Awareness of symptoms can allow early detection in order to avoid disabling lesions which can affect sexual and interpersonal relationships and eventually the overall quality of life of patients.[5]

Design and Methods

A retrospective study on 213 patients undergoing bone marrow transplantation (BMT) between April 1980 and November 1999 at S.Martino Hospital (Genova) was carried out in order to evaluate the incidence, severity and change over time of genital GVHD.

The median age at BMT was 31 years (range 7-65) and the follow-up was 7-242 months (mean 78). Fifteen patients had transplants for severe aplastic anemia (SAA), the others for hematologic malignancies. The patients' characteristics and conditioning regimens are shown in Table 1. The incidence of acute and chronic global GVHD as well as immunosuppressive prophylaxis are presented in Table 2.

The potential risk factors studied were vaginal cultures just before BMT, previous pregnancies, including abortions, and hormonal replacement therapy .

All data describing gynecological findings came from our clinical records. They consisted of an extensive interview and gynecological examination performed for 109/213 patients in the first 100 days after BMT and in all patients after this period as well as clinical changes checked three times a year by the same two specialists. Children received frequent and thorough clinical follow-up without gynecological examinations which started in adult age.

The symptoms patients referred and gynecological findings are shown in Table 3. Cases of complete vaginal obliteration were confirmed by ultrasound.

The attempt to grade genital GVHD, as done for global GVHD, led to the definition of three levels: minimal, moderate and severe (Table 4).

Table 1. Patients' characteristics at BMT.

Patients	
Adults	202
Children	1
median age 31	(16-65)
median age 12	(7-14)
Pregnancies before BMT (including abortion):	112
Diagnosis	
SAA	15
AML	57
ALL	25
CML	86
NHL	8
HD	2
Other	20
Donor relation	
HLA identical sibling	179
Mismatch Related	7
MUD	27
Source	
BM	196
PB	17
Cells Infused (10^8/kg)	
BM	4.2 (0.7-12.6)
PB	12.7 (6.2-25)
Conditioning Regimen	
CY	13
CY+TBI / TAI	153
BU +CY	4
TT+ CY	35
FLU +CY	8

SAA: severe aplastic anemia; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; CM: chronic myelogenous leukemia; NH: non- Hodgkin's lymphoma; HD: Hodgkin's lymphoma; CY: cyclophosphamide; TBI: total body irradiation; TAI: thoraco-abdominal irradiation; BU: busulfan; TT: thiotepa; FLU: fludarabine; BM: bone marrow; PB: peripheral blood; MUD: marrow unrelated.

Table 2. Acute and chronic global GVHD and immunosuppressive prophylaxis.

Acute GvHD	
0-I	54.3%
II	44.2%
III-IV	1.5%
Chronic GvHD	
Absent	8.5%
Limited	60.6%
Extensive	30.9%
GvHD Prophylaxis	
MTX	0.5%
CsA	29.6%
MTX+CsA	64.1%
T-depl.	5.3%
No proph.	0.5%

MTX: methotrexate; CsA: cyclosporine; T-depl: donor lymphocyte-depletion; No proph: no prophylaxis.

Treatment was tailored to the clinical features. Initially, minimal and moderate vulvar lesions were managed with topical estrogen and emollient cream (Fitostimoline) with poor results. For this reason we started to treat non-responding cases with steroids, such as triamcinolone (Pevisone), which was more effective, but, in case of failure to respond, clobetasol propionate cream or ointment was given twice a day for a week and then tapered down. The most serious vaginal strictures received surgical treatment. For univariate analysis of GVHD we used Fisher's exact test (two-tailed). The overall time between BMT and the onset of GVHD as well as the regression time were estimated using Kaplan-Meier curves. All statistical analyses were performed with SPSS software release 10.0 (SPSS Inc.).

Results

Incidence

Overall, 24.9% of patients developed genital GVHD 1-107 months after BMT (median 7) (Figure 1). Of 109 who had had a gynecological evaluation in the first 100 days after BMT 12 (11%) showed clinical evidence of acute genital GVHD whereas 41 patients (19.2%) developed such lesions after that time (chronic GVHD). At the onset of genital involvement 73% of patients also showed GVHD elsewhere (Figure 3).

Grading

According to the criteria presented in Table 4, genital GVHD was minimal in 66%, moderate in 22% and severe in 12% of cases. Some serious and disabling lesions were observed in seven women. Three patients developed a soft ring stricture of the vagina, two had vaginal fibrosis with almost complete closure, one had uterine enlargement (hematometria) due to obliteration of the cervix and one, with a vaginal stricture, was diagnosed as having *in situ* vaginal carcinoma (Table 5).

Clinical remission

Complete remission, defined as the complete regression of cutaneous or mucous lesions, was seen in 46/53 of patients, 2-157 months after the onset (median 22). No improvement was seen in 7 patients (Figure 2).

Risk factors

We did not find statistical correlations between parity, vaginal infections at BMT and GVHD of the lower genital female tract. Of the 213 patients, 112 had had one or more pregnancies before their BMT (52.1%). In the subgroup affected, 19.8% were nulliparous while those who had had pregnancies before BMT were 29.5% (Fisher test not significant).

Screening for genital infections was performed just before BMT in 163/213 of the women (50 miss-

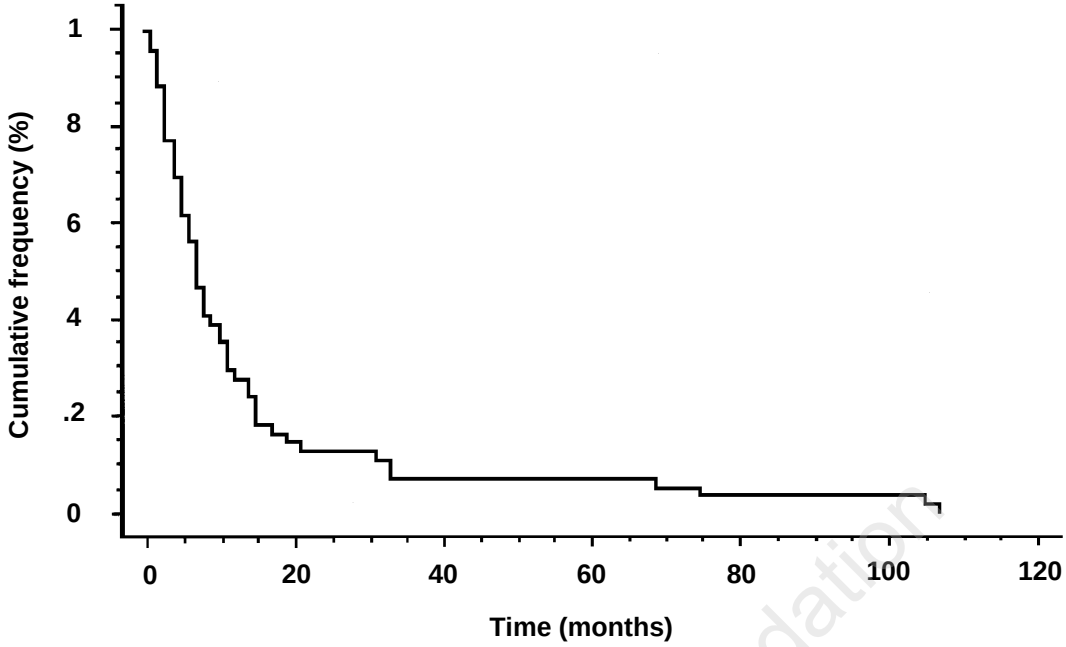

Figure 1. Kaplan-Meier estimates of the overall time from BMT to the onset of genital GVHD The median time to onset of genital GVHD was 7 months.

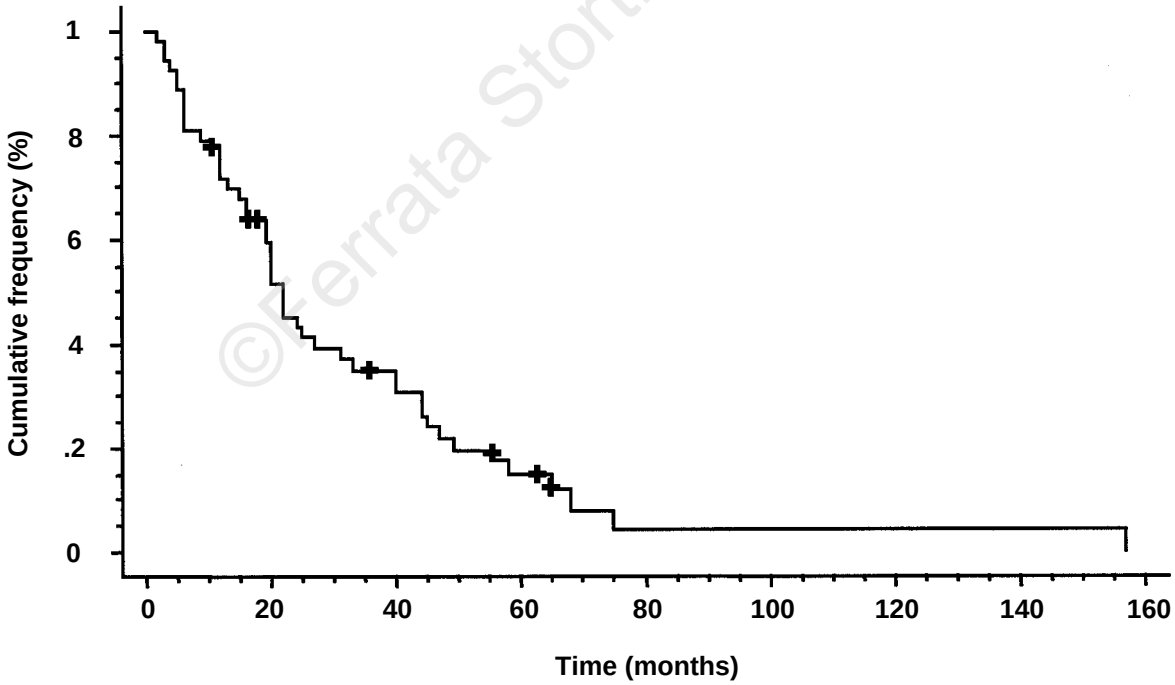

Figure 2 . Kaplan-Meier estimates of the overall time from remission as observed. The median time was 22 months. The patients who had no remission at the end of the study period were censored and are shown with a + in the graph.

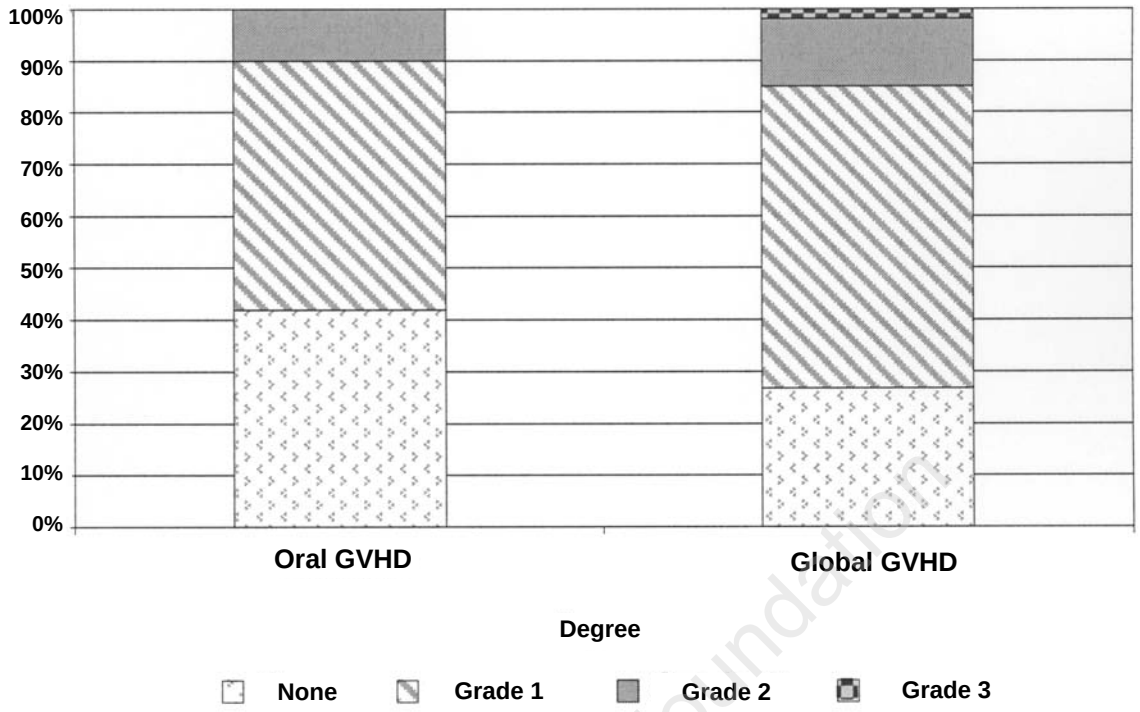

Figure 3. Oral and global GVHD in the group of 53 patients at the onset of genital GVHD. Grade 1 in 58%, grade 2 in 13% and grade 3 in 2%.

ing). In 94 cases vaginal culture was found to be positive for a variety of bacterial agents, such as streptococci, staphylococci *Proteus* and *Klebsiella* and for Ca*ndida albicans*. Among patients who developed genital GVHD, 23% had a positive result for vaginal infection while 32% were negative (Fisher test not significant). Overall, 144/213 patients were receiving estrogen therapy (67.6%).

In the genital GVHD subgroup, the percentage of patients receiving systemic or vaginal estrogen (28%) was higher than those without HRT (15%) (p=0.049) (Table 6).

Discussion

Chronic GVHD occurs in 30% of patients who survive at least 100 days after allogeneic BMT and can involve a great number of organs including the female lower genital tract. Risk factors for GVHD are well-known: an unrelated or HLA–mismatched donor; old age in the recipient; male gender associated with a female donor allosensitized through pregnancies or transfusions; positive donor and recipient CMV serologies.[6] In 1982, Corson *et al.*[4] described five cases of gynecological manifestations of GVHD with vaginal strictures and adhesions that required surgical therapy. In 1999 Yanai *et al.*[7] described a case of hematocolpus in a 25-year old female who presented with secondary amenorrhea during hormonal replacement therapy 3 years after BMT; the author referred to a similar case published by Delord *et al.*[8]

In our retrospective study 53 out of 213 patients (24.8%) showed clinical evidence of genital lesions which were considered an expression of GVHD.

Vulvar examination revealed small multiple red areas, sometimes with plaques, denudation, leukokeratosis with burning, soreness, introital pain and sticky leukorrhea. Introital stenosis and more or less extensive vaginal adhesions with insertional dyspareunia was found in severe cases. These gynecological findings could be misdiagnosed as other clinical conditions. Acute allergic vulvitis often with a precise cause is characterized by extensive erythema, with very intense itching – both absent in genital GVHD. Vulvar vestibulitis syndrome (VVS) is characterized by severe pain on introital contact with small areas of vestibular erythema. It has been observed in healthy young women and responds to local steroids,[9] but the cause is still unknown. Considering the clinical setting[2] this lesion is unlikely to be confused with GVHD. Symptoms of hypoestrogenism due to ovarian failure after the conditioning regimen can mimic or accompany genital GVHD. This condition is characterized by thin, pale genital mucous, dryness, dyspareunia; estrogen treatment

Table 3. Genital GVHD. Clinical manifestations and symtoms.

Clinical manifestations
Vaginal dryness
Vulvar redness
Pain on touching the labia
Sticky leukorrhea
Vulvar denudation
Leukokeratosis
Introital stenosis
Vaginal adhesions
Complete vaginal closure
Symptoms
Burning with urination
Burning
Soreness
Dysuria
Dyspareunia
Impossible to have sexual intercourse

Table 4. Degree of genital GVHD.

Minimal
Vulvar redness, pain on touching the labia, small areas of vulvar denudation (plaques)
Moderate
Extensive areas of vulvar denudation with or without leukokeratosis and introital stenosis
Severe
Vaginal adhesions or complete vaginal closure.

Table 5. Severe genital GVHD lesions: individual cases.

Patient	*Diagnosis*	*Age at BMT*	*Parity*	*HRT*	*Vaginal GVHD*	*Treatment*	*Outcome*
1	ALL	30	2	Yes	cervical closure and hematometria	Surgical	1
2	ANLL	30	2	Yes	soft ring stricture	Systemic steroids	2
3	ANLL	45	4	Yes	stricture and Ca *in situ*	Surgical + radiotherapy	3
4	CGL	35	2	Yes	fibrosis with closure	Surgical *	2
5	NHL	19	0	Yes	soft ring stricture	Systemic steroids	1
6	ALL	30	0	Yes	soft ring stricture	Systemic steroids	1
7	HD	40	1	Yes	fibrosis with closure	Surgical *	1

**Patients received surgical treatment after the study was completed.*
1: complete regression of fibrosis with resumption of sexual intercourse; 2: persistent small soft fornix adhesions with resumption of sexual intercourse; 3: fibrosis post-radiotherapy, no resumption of sexual intercourse.

Table 6. Risk factors.

	p
HRT	0.049
Parity at BMT	n.s.
Vaginal infections at BMT	n.s.

is dramatically effective whereas this is not the case for genital GVHD. In our study 67.6% of patients with genital GVHD were taking hormonal therapy. Therefore vulvar hypoestrogen lesions can be excluded. As GVHD can affect a great number of organs, what could be the specific risk factors for genital GVHD? According to our data, one or more pregnancies before BMT do not seem to increase the risk of genital GVHD.

Although Bradbury *et al.*[10] reported that genital infections were associated with GVHD, the percentage of positive vaginal cultures was not statistically higher in our patients who later developed genital GVHD than in those who did not. Methodical screening for genital infections after BMT may not be meaningful because antibiotics and antifungals are given. Sexual intercourse could have a role in promoting viral or bacterial infections and possible genital GVHD. In our sample, however, genital chronic GVHD was also seen in patients who had never had sexual relationships as well as in women not sexually active for a long time. In any case patients were encouraged to use a condom in the first months after BMT. Further investigation is needed in order to determine whether genital infections related to unprotected sexual intercourse could be a risk factor in developing genital GVHD.

Some authors suggested that estrogen may have a negative influence.[11-12] We found an association, nearing the borderline, between HRT and genital GVHD that must be investigated further because of the extraordinary importance of estrogen therapy in young women with ovarian failure. This result did not confirm our previous report[13] on a smaller group.

Genital GVHD can be an isolated manifestation[8] or associated with extensive chronic GVHD.[4] In our samples 73% of patients with genital manifestations had some lesions in other organs (Figure 3). The protocol of GVHD prophylaxis included cyclosporine A (1-2mg/Kg daily i.v.) either alone or with methotrexate (8-12 mg/m^2) followed by cyclosporine (10-12mg/Kg day p.o.) Steroids were started at the first evidence of GVHD.

In more than 70% of patients who developed genital chronic GVHD, steroids had been decreased 6 months to 1 month before the onset of genital lesions. This suggests the importance of investigating symptoms of genital GVHD before and after reducing immunosuppressive therapy. Since patients without sexual activity are less likely to recognize

symptoms indicating genital GVHD, regular questioning and gynecological examination, sometimes with sonography, is recommended. Furthermore, in patients taking HRT, cessation of menstruation particularly when associated with dyspareunia and periodic cramps, should raise the suspicion of cervical or vaginal stenosis.[7]

Early detection of genital GVHD is a matter of importance because mild lesions can be successfully treated with steroids and sometimes with a program of vaginal dilators.[4] In case of vaginal adhesions, surgical intervention with a subsequent vaginal device, are recommended. Early resumption of protected sexual intercourse could be encouraged.

Gynecological examination should be suggested to all females undergoing BMT in order to detect symptoms of ovarian failure[14] and avoid disabling lesions of the low genital tract.

This study should be viewed as a first attempt to describe and grade some clinical presentations of genital GVHD, which is a neglected area. Prospective studies with more objective methods of appraisal such as colposcopy and photography are needed. Furthermore is important to determine the specific risk factors for developing genital GVHD.

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Pre-publication Report & Outcomes of Peer Review

Contributions

SS and SC: conception of the study, gynecological care of the patients, writing the paper; SC: performing the ultrasound examinations; GBR: responsible for statistical analysis and Figures 1 and 2; AB, MTVL, AMR: responsible for the hematological care of the patients. SS, SC, AMR: responsible for all others Tables and Figures. Primary responsibilitry for the paper: SS, SC. All authors gave their critical contribution to the manuscript.

Disclosures

Conflict of interest: none.

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Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Mario Cazzola, Editor-in-Chief. The final decision to accept this paper for publication was taken jointly by Professor Cazzola and the Editors. Manuscript received July 1, 2003; accepted July 23, 2003.

In the following paragraphs, Professor Cazzola summarizes the peer-review process and its outcomes.

What is already known on this topic

The majority of patients who receive an allogeneic bone marrow transplant develop chronic graft-versus-host disease (GVHD), which contributes substantially to morbidity and mortality. Despite this, our knowledge of GVHD of the lower female genital tract is still scarce.

What this study adds

Genital GVHD is not unusual after BMT. It can seriously affect female sexuality and the overall quality of life. Early detection of genital involvement is important in order to prevent the most serious lesions.