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GYNECOLOGIC GRAFT-VERSUS-HOST DISEASE

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GYNECOLOGICAL ADJUVANT THERAPY

The incidence of genital GVHD varies according to published studies, ranging of 24.9% to 69% of the HSCT recipients affected.[1-5] However, it is likely that this prevalence is underestimated because it only included patients who reported symptoms, and there might be underreporting.[3]

The median time to presentation of genital symptoms ranges from 7 to 10 months after transplantation; whereas, late-onset is not uncommon after one year. It is usual for oligosymptomatic patients who are sexually inactive to have a slow/delayed diagnosis if there is no systematic genitals examination, risk factors valuation, and preventive guidance.[2,7]

The pre-transplant clinical evaluation of women includes recommendations about genital GVHD, including early manifestations and complications and the importance of regular gynecological check-ups to help prevent severe gynecological complications, which often can become irreversible and have a significant negative impact on the quality of life.[8]

RISK FACTORS FOR FEMALE GENITAL GVHD

The main risk factor for the development of genital GVHD is the use of peripheral blood as the source of the progenitor cells for the transplant, representing a risk three times higher than that obtained from bone marrow cells[.9]

Type of conditioning, donor, parity, age, and presence of vaginal infection at the time of transplantation do not appear to have an impact on the incidence of genital GVHD.[8] However, oral mucosa and/or ocular conjunctiva involvement, as well as extensive areas of skin, are signs of genital injuries by the association[.9]

CLINICAL FEATURES

In 68% of cases, the symptoms affect only the vulva, whereas, in 26%, both the vulva and the vagina are involved, so in that case, vulvar lesions usually precede the vaginal lesions.[8] Isolated vaginal involvement is very rare and often asymptomatic, which makes limiting sequelae more common.[9]

The time lag between the start of vulvar and vaginal symptoms offers an opportunity to start prophylactic measures to prevent the occurrence of more severe complications, such as vaginal stenosis, with consequent impairment of sexual function.[3,8]

The genital GVHD symptoms may include dysuria, vaginal and vulvar dryness, vulvar buring, sensitivity of the vulva and vaginal introitus to touch or when washing, vulvar pain, vaginal bleeding after intercourse, and dyspareunia.[6,10,11]

Discharge is mentioned by 25% of patients with vaginal involvement, especially in the early stages, but in its mild form, it may be asymptomatic and detected only in the gynecological exam.[3]

Vulvar dryness is reported by up to 80% of women with genital GVHD and dyspareunia by up to 50% of them, impacting sexual activity.[3] Introital pain results from inflammation of the vestibular glands openings (Bartholin's and Skene's glands), erosions or vulvar fissures, and less frequently, from labial fusion. Deep dyspareunia occurs in patients with synechiae or vaginal shortening. Amenorrhea and pelvic pain, especially in women with cyclic hormone replacement, might be a vaginal synechiae sign or internal and/or external cervix os stenosis, resulting in hematocolpos and hematometra, and they are considered severe symptoms, respectively.[12,13]

TABLE 1 - Graft-versus-Host Disease main symptoms and signs in the Female Genital Tract

Symptoms	Signs
- Vulvar and vaginal dryness - Vulvar hyperemia - Discharge - Dyspareunia - Dysuria - Postcoital bleeding - Sensitivity and pain on touch the vulva.	- Vulvar erosions and fissures - Labial Fusion - Leukeratoses - Introital stenosis - Complete vaginal occlusion

The findings at physical examination resemble the symptoms of erosive lichen planus, and in the early stages, it can see erosions, erythema and tenderness around Bartholin`s and Skene's glands with increased pain sensitivity apart from interlabial fissures.[9]

Since other mucous membranes' involvement might increase genital involvement risk, women with oral and/or ocular involvement need to be submitted to gynecological examination even if asymptomatic. If a gynecologist is not available, the clinician should perform the physical examination, although vaginal involvement may be underdiagnosed.[9]

In the later stages, the studies include loss of vulvar architecture caused by labial adhesions narrowing of the vaginal introitus, clitoral agglutination, vaginal sinechiae, and circumferential fibrous banding. There may be decreased elasticity and shortening of the vaginal canal, mainly synechiae, making it difficult or impossible to visualize the cervix and get Pap test. These symptoms also make sexual intercourse difficult or impossible[1]. GVHD main signs and symptoms in the female tract genitals summarized in Table 1.

Histological confirmation is recommended only in the absence of diagnostic manifestations of GVHD in other organs. The early and later stages with functional sequelae must be adequately corrected the estrogenic deficiency caused by a chemo-induced ovarian failure. So that the GVHD findings on physical examination are not confused with hypoestrogenism sign[1,14].

GVHD FEMALE GENITAL CLINICAL CLASSIFICATION

According to the clinical score for organ evaluation described in Table 2, genital impairment can be classified as mild, moderate, or severe.

Jagasia and his collaborators developed a consensus for GVHD's diagnosis and a severity score, adapted and published by Kornik and his collaborators, suggesting active research on asymptomatic cases[15].

TABLE 2 - Diagnosis and grading of genital chronic graft – versus-host disease - National Health Guidelines.15

	E0	E1	E2	E3
Genital Female	No signs	Mild signs and symptomsa with or without discomfort on examinationb	Moderate signs and may have symptoms with or without discomfort on examinationb	Severe signs with or without symptoms
		Any of following: Erythema on vulvar mucosal surfaces Vulvar lichen planus-like features Vulvar lichen sclerosis-like featuresc	Any of following: Erosive inflammatory chances of the vulvar mucosad Ulcersd Fissures in vulval folds d	Any of the following: Labial fusionc Clitoral hood agglutinationc Vaginal scaring c Fibrous vaginal banding Vaginal shortening Synechia Dense sclerotic changes complete vaginal stenosis

a) Symptoms are not specific and can represent premature gonadal failure or infection
b) To be determined by specialist or trained medial provider; discomfort is defined as vulvar pain elicited by gentle touch with cotton swab in any of the following sites: vestibular glands, labia majora or minora.
c) Diagnostic sign.
d) Distinctive sign.

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d Distinctive sign.

PREVENTIVE MEASURES

Hormonal therapy instituted early on, whether systemic or topical, correcting the ovarian failure caused by the use of medicines in the conditioning phase, maintains the physiological characteristics of the genital tract, facilitating early detection of symptoms of GVHD[16].

Besides, women orientation in the pre-transplant evaluation, warning them for possible complications, its initial manifestations and probable sequelae, as well as periodic gynecological evaluation , mostly when GVHD manifests in other organs, such as oral mucosa and skin; it prevents many times irreversible sexual activity impairment, and also other gynecological complications.

It is recommended estriol as a 1 mg/g cream or 1 mg vaginal suppository, applied 2 to 3 times a week during the entire transplant phase until D + 100 or until the beginning of systemic hormonal therapy. As it attenuates the vulvovaginal epithelium atrophy caused by ovarian failure and accentuated by corticosteroid action, it maintains vaginal lubrication and elasticity, allowing sexual activity and facilitating the early diagnosis of GVHD lesions6.

It is vital to encourage a return to sexual activities when possible after platelet normalization. Sexual activity favors vaginal GVHD early diagnosis, and it prevents synechiae formation in the early stages of manifestation.[1,17] Using lubricated condoms relieves discomfort and protects against contamination during sexual intercourse.[17]

EARLY TREATMENT

Vulvar and vestibular lesions often appear as very sensitive erosions, even to (the underwear touching?) the touch of underwear. Ultra-potent topical corticosteroids as ointments or creams, which have better absorption and emollient action, are the most suitable at this stage. Clobetasol propionate 0.05% can be applied directly to the lesions once or twice a day until the erosions disappear, followed by tapering dose until complete suspension. A compress, or bathing in lukewarm water before administering corticosteroids facilitates their absorption. The administration of 1mg/g estriol in the vulvar vestibule avoids atrophic changes and consequently, vaginal dryness sensation, it must be maintained to improve sexual function after controlling the condition.[14]

Support measures, such as the use of emollients and topical moisturizers, sitting in a lukewarm bath, and the application of viscous xylocaine, can ease the discomfort, particularly during sexual intercourse.[9,14]

Damage to the vaginal mucosa may include ulcerations, erosions, loose synechiae and vaginal discharge. The use of 25mg hydrocortisone in the form of vaginal suppository, once or twice a day, is recommended until early reevaluation in 15 to 30 days, decreasing the dose once the symptoms have been controlled and then maintaining twice-weekly administrations and gradually reducing the dose until complete suspension. Also, the use of 1mg/gestriol in vaginal suppository or cream is recommended at least three times a week to counteract atrophy induced by hypoestrogenism and aggravated by corticosteroids. For vaginal synechiae, stenosis and narrowing prevention, patients are encouraged to regular intercourse, and if without a partner, vaginal dilator use is recommended twice a week.[14,18,19]

In a series of 11 patients, Spiryda et al.14 described the use of vaginal cream consisting of a 200 mg oral suspension of cyclosporine diluted in an oily base twice daily for four weeks followed by weaning for two months, until suspension. They observed healing of vaginal erosions after two weeks with its concomitant use with vaginal dilators, thereby avoiding the need of surgery to correct stenosis in 4 of the 11 women studied. The seven women who underwent surgery to correct synechiae and vaginal stenosis continued to use the medicine after surgery, and in 6-12 weeks, they were able to have sexual intercourse. Only one patient showed no improvement with clinical or surgical treatment due to thick synechiae.

Another alternative, with controversial results, is topical calcineurin inhibitors, such as 0.1% tacrolimus in ointment or cream, for vulvar and vaginal use, respectively. It would have the advantage of having less thinning epidermis. However, it is poorly tolerated because it can cause significant stinging and burning effect especially when applied to inflamed or non-intact mucosa.8 Finally, local treatment asso-

ciating corticosteroid and estrogen appeared to decrease the progression from mild to severe lesions, preventing surgical treatment. Thus, the earlier the treatment, the lower the sequelae rate.[17]

TREATMENT OF LATE COMPLICATIONS

Late complications, such as adhesions and occlusions in various segments of the genital tract, can be separated manually or incised under anesthesia with subsequent use of steroids and topical estrogen therapy.20,22 Dilation and drainage or hysterectomy may be necessary in extreme cases of collections in the cervical canal and uterine cavity (hematometra).[23]

SEXUALITY

Women undergoing HSCT develop several sexual problems that are not addressed to their doctors and experienced a decline in life quality. Deyer and his collaborators observed that 66% of women reported sexual difficulties, including decreased libido in 61.6% of them.[24]

These sexual dysfunctions have multifactorial causes such as medication, depression, estrogen, and androgen deficiency, decreased energy and self-esteem. Systemic GVHD and genital involvement worsen the condition with dyspareunia and sequelae that make sexual life impossible. It is essential to take care of triggering factors and a multidisciplinary approach valuing and seeking to resolve complaints about these women's general well-being.[11,25]

Several guidelines were published in the literature for gynecological care for women undergoing HSCT, with few differences. However, all expose the importance of blocking menstrual flow, clarifying the possibility of impaired hormonal and reproductive function after conditioning, as well as guidance on the first signs of genital GVHD, periodic gynecological examination, even in asymptomatic women, getting a Pap smear test, hormonal treatment for early ovarian failure and sexual dysfunction management.

They also address pediatric patients' evaluation for GVHD signs and pubertal status, as the lack of estrogen can prevent secondary sexual characteristics development.[1,5,6,8,9,14,16,25-30]

Besides, the presence of a gynecologist composing the multidisciplinary team of bone marrow transplant centers is of great importance for the approach in all phases, helping in the total recovery and providing an improvement in the quality of life of transplanted women.[31] Table 3 summarizes the main precautions for GVHD management in the female genital tract.

TABLE 3 - Graft-versus-host disease management in the female genital tract

Type of intervention	Score
Vulvar discomfort	
Avoid chemical and mechanical irritants (soaps and intimate hygiene products) Wash the genital area with warm water, allow air circulation, and clean from front to back. Apply emollient to the vulva Water-based lubricants	B4 B4 B4
Vulvovaginal symptoms and low estrogen level	
Topical estrogen Encourage regular intercourse for sexually active women. Orient vaginal dilators 2 to 3 times a week for women with vaginal narrowing, stenosis, or obliteration.	B4 B4 B4
Topical Therapy for DECH-c Vulvovaginal	
- Hydrocortisone 25 mg in vaginal suppository - Clobetasol propionate gel 0.05% on the vulva - Betamethasone ointment on the vulva - Tacrolimus 0.1% ointment on the vulva and cream on the vagina	B4 B4 B4 B2B
Surgical Therapy	
- Surgical lysis of adhesions with or without vaginal reconstruction followed by six months of dilator therapy.	B4
Pediatric Considerations	
Although data on GVHD genital incidence and treatment during childhood are less reported , the valuation of the same risk factors valid for adults, and care with early management through the mother or the caregiver's guidance may avoid late diagnosis with irreversible complications.	

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