

SEXUAL DYSFUNCTION WITH COMPLEX ETIOPATHOGENESIS CENTERED ON VULVAR CANCER

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Abstract

Normal sexual activity is conditioned by the morphophysiology of the integrity of the genital organs and of the human brain, respectively by the absence of associated pathology.

In the reported case, the 57-year-old female patient presented for a gynecological consultation, having very intense vulvar itching.

Previously, the patient addressed the dermatology department, where she was diagnosed with "vulvitis with significant edema and erythema" for which she underwent local treatment for 4 weeks. After dermatological therapy, the itching improved slightly, but persisted in association with the local stinging sensation.

The vulvar itching became very intense, and the patient solicited a gynecological reexamination.

It has to be noted that the patient believed, at that time, that the itching was due to psoriasis, a disease she had been suffering from since she was 10 years old. The emergency investigations established the existence of vulvar cancer, due to bilateral vulvar tumor.

It should also be mentioned that the patient was undergoing therapy for the diagnosis of paranoid schizophrenia, for that of chronic peripheral venous insufficiency, respectively for manifest menopausal disorders.

In this context, sexual intercourse has completely disappeared, due to complex sexual dysfunction, so that the libido, the erection, the copulation and the orgasm no longer existed.

Keywords:

Intense vulvar pruritus, vulvar squamous cell carcinoma, biopsy, complex sexual dysfunction

Introduction

Psoriasis, a chronic autoimmune dermatological condition, has a negative impact on the determinism of sexual intercourse, decreasing the libido, because of the existence of itchy and painful inflamed skin, including in the genital area.

The psoriasis characteristic lesions are the result of malpighian skin cells turnover, the basal cells reaching the stratum corneum in 4 days, instead of 28 days, as is normal.

But mitotic cell proliferation activity is non-tumoral. This aspect is important because in vulvar cancer, in a proportion of 27%, its coexistence with a second form of cancer was described (Berek/Holschneider), which, in the present case, did not exist.

In psoriasis, the rapid growth of the dermal layer, including because of apoptosis deficiency or of blocking of anti-apoptotic genes, from the protein group of Bcl-2 genes or at the level of cytokines, in which the keratinocyte is involved, is both a source of and a target for interleukin 15 (9).

A severe autoimmune disease of the skin, psoriasis changes the woman's physical appearance, being often accompanied by associated diseases, in the presented case the question is whether vulvar cancer is associated, or a comorbid pathology?

Vulvar cancer, having starting points in the skin and the mucosae, it has a prevalence of, according to some authors, 2-3% or even 4% of malignant tumors of the genital organs, respectively 0.6% according to Berek and Novak.

The lesion occurs at the level of the labia minora, at the base of the labia majora and in the clitoral area, on the background of vulvar dystrophic lesions, which may cause itching, atrophy, leukoplakia and vulvar kraurosis.

The left labia majora, (Fig.1), brownish coloured, is edematous. The right labia majora shows slightly bleeding lesions due to scratching, which present intense itching.

Local skin and adipose tissue alterations reduced the regional sensuality significantly.

Normally, the clitoris has an increased sensitivity with an obvious erogenous character, which, in the presented case, no longer exists.

The vulvar slit is open inferiorly, a situation that allowed vulvo-vaginal infection with E.coli.

Above the posterior commissure, between the bridle of the labia minora and the hymenal remains, the navicular fossa is much smaller, an aspect that determined, among other things, the patient's very low libido.

The small labia are transformed into tumoral formations (thickened) of intense red color, that reduce the vaginal vestibule aperture, (Fig.2a,b).

The external urethral orifice is indistinguishable, as is the glans clitoris, which forms a common body with the anterior commissure of the labia minora.

The morphological changes of the surfaces of the labia minora have destroyed both the special tactile corpuscles and the local

sebaceous and perspiratory glands, thus they no longer have any erogenous value.

In fact, the glands are hyposecretory and without pheromones, an aspect already noted by the patient.

Besides these, the anterior commissure of the labia minora forms a common body with the clitoral area (the foreskin of the clitoris, the bridle of the clitoris and the clitoris – structures that can no longer be delimited from each other).

Later, throbbing pain appeared in the labia majora.

Vulvar cancer is lymphophilic, invading the regional lymph nodes by spreading in the lymphatic capillaries.

In the presented case, the external inguinal nodes were palpable.

In general, if there are no inguinal lymph node metastases, the 5-year survival has been found to be over 90%.



Figure 1 Obvious morphological changes in the labia majora and labia minora. The urethral opening and the structure of the clitoris are no longer differentiated (glans clitoris)



Figure 2a. Tumoral transformation of the labia minora and of the clitoral region



Figure 2b. Overview of tumorigenesis of labia minora and of the posterior commissure

Here, due to the presence of secondary inguinal nodal determinations, the 5-year survival is reduced by half (Christine H. Holschneider) and even less.

Vulvar squamous cell carcinoma occurs in menopausal women.

The discussed female patient is 57 years old, the age at which affective, anxiety and depressive disorders increase, determined by the morpho-functional, cyclical changes of the hypothalamic-pituitary-ovarian axis.

The decrease in estrogen levels during menopause is also associated with changes at the brain level regarding certain neurotransmitters and neuropeptides, which accentuates vasomotor instability, dyspareunia, insomnia.

These changes were already clearly influenced by the medicinal treatment of the aforementioned associated pathology.

The primary malignant focus of the vulva can be on all parts of it and, more commonly, on the labia minora and clitoris, as in the presented case.

In addition to intense vulvar itching, the patient associated local pain and vulvo-vaginal discharge in significant quantity, foul-smelling, yellowish, as well as dysuria.

The itching subsides slightly after scratching, but for a very short time.

The demarcation line between the modified labia minora and the labia majora was obvious.

The labia minora were thickened, intense red in color, with an irregular surface changes that also affected the base of the labia majora, the edema and erythema

going towards the anal opening.

The local itching could not be controlled by the patient by any method.

In regard of a normal tissue shape and structure, there is a physiological balance between cell proliferation and apoptosis from a molecular and genetic point of view.

Among the genes that determine cell growth and function, proto-oncogenes and tumor suppressor genes may be the cause of the malignant structure described (5).

Oncogenic genes are actually activating mutations of proto-oncogenes, which, through increased stimulation, determined aberrant cell proliferation, respectively the malignant phenotype, with intense local itching, which, upon gynecological examination, imposed the urgency in the investigation, diagnosis and surgical treatment .

The labia are innervated by branches of the ilio-inguinal nerve, positioned anteriorly, the small abdomino-genital nerve serving the integument that covers them, and the pubic nerve, originating from the sacral plexus S2-S4, innervates the posterior part.

A perineal branch from the posterior femoral-cutaneous nerve reaches the labia majora, as well as sensitive fibers from the pubic nerve.

At the level of the labia minora, there are complex receptor cells (13), smooth muscle fibers and a well-developed vasculo-nervous system that gives erectile properties to the area.

In the reported situation, these structures are no longer functional due to local and neuro-psychological pathology, so even if a se-

xual act would had been performed, it would have been very painful and finally unacceptable to the patient.

The vulvar area contains specialized sensory receptors that have a greater representation at the brain level.

The labia minora, located between the labia majora, unite posteriorly, and superiorly are separated into two folds (anterior folds) that join, forming the foreskin of the clitoris, and the posterior folds, which form the bridle of the clitoris, on its lower part. This whole area was very itchy.

It has to be mentioned that the vulvar fibroelastic stroma is rich in neuro-vascular structures, being covered by skin and hairs, which, because of the cutaneous sores generated by pruritus, presented a markedly pink secretion.

The intense itching involved the clitoral area entirely. But, in the presented case, the itching no longer determined an erectile state through vulvar excitation, but a pathological state of significant itching, especially at the level of the labia minora and the clitoris.

It should be emphasized that the lack of estrogen hormones during menopause induces thinning of the skin, that caused itching, which, in the patient case, intensified and caused discomfort, peeling, burning sensation, and quasi-permanent local stinging.

The patient did not experience itching in other areas.

At menopause, the decrease in estrogen levels also causes urogenital changes by decreasing vulvo-vaginal trophicity and the elasticity of vaginal walls and decreasing

vaginal lubrication after performed erectile maneuvers, all of which accentuate sexual dysfunctions. In this context, the patient may even refuse sexual intercourse, as in the presented case.

The reduction of estrogens also decreases the titer of VIP (Vasoactive Intestinal Peptide), a neurotransmitter that, due to vascularization changes, minimizes the vaginal lubrication.

Also, the amounts of pheromones are reduced which, thus, diminish the female sexual attractiveness, by decreasing the sexoid factor which no longer stimulates the sebaceous and sweat glands that produce the pheromones (13).

All the data presented above aggravated the emotional and sexual marginalization of the patient, primarily by reducing the libido.

Added to this is the contribution of the sense of smell, through the olfactory receptor cells, located in the nasal pits on the pituitary mucosa, which lines the lamina cribrosa of the ethmoid bone.

It has to be noted that in the Schultze olfactory receptors of that mucosa there are approximately 1 million chemical receptors, undifferentiated neurosensory cells, elongated or spindle-shaped, which not only have the role of receiving volatile substances, but also of transmitting sexual excitement through the dendrites of the olfactory cells from the nasal mucosa.

By activating them, the signals reach the olfactory bulbs through the nerve fibers that cross the upper wall of the nasal cavities, and from here they reach the cerebral

cortex of the temporal lobes through the olfactory tracts (13).

It should be marked that a single filament may detect the presence in the air of 50 molecules with a specific scent, through chemical reactions at the receptor level. The intensity of the erotic sensation determined by pheromones decreases with age (the patient is 57 years old).

Pheromones are volatile chemical substances that act at the level of the olfactory area, a structure of 240-500 square mm and which has approximately 10-20 million receptor cells.

In addition, the corroboration of the absence of ovulation (due to estrogen decrease) with the associated pathology and, respectively, with the previous established treatment, which no longer stimulates the sexual behavior of the patient, accentuates her sexual dysfunctions.

After the analysis of the vulvar tissue, multiple biopsies were also taken from this level, under colposcopic control, primarily from the level of the labia minora, the morphopathological examination confirming the presence of vulvar cancer (i.e. moderately invasive, differentiated squamous cell carcinoma).

The vaginal introit had a normal macroscopic appearance.

Vulvar itching caused the decrease of the woman's libido as well as her copulation desire, and the other sexual dysfunctions listed above.

Superficial inguinal lymph nodes were palpable in the right region.

At the level of the left labia majora, in the inner area, the patient complained of stinging and prickling.

I mention that the vulvar area was swollen. At the level of the urethra, by the lower wall pressing, a discharge was eliminated, in which, through microscopic examination and microbiological tests, an *Escherichia Coli* infection was identified, for which targeted antibiotic therapy was administered.

The tumor gene most frequently involved in oncogenic mutation is p53. It has to be noted that the patient had a significant heredo-collateral history, respectively:

- the patient's father died at the age of 70 from kidney cancer
- the patient's mother died at the age of 80 from pancreatic cancer
- the maternal uncle had a colonic neoplasm operated on at 50 years old
- another maternal uncle died at the age of 59 from dermatomyositis (possibly paraneoplastic)

Taking into account the oncological pathology of her family, we can talk about the existence of the patient's genetic predisposition for malignancy, the comorbidities worsening due to immunodepression, respectively the occurrence of vulvar cancer was favored.

The 5-years survival after cancer diagnosis of the presented case is very unlikely, considering the invasion of the inguinal nodes.

About complex sexual dysfunction:

The **temporary sexual dysfunction** began with the mental illness (paranoid schizophrenia), increasing because of the psychotropic treatment and with the onset of menopause; the vulvar squamous cell carcinoma generated the appearance of **complex** sexual dysfunctions (of libido, of erection, of copulation and of orgasm).

The multilateral oncological treatment, namely radical surgery (total vulvectomy) (Fig.3 a, b, c, d, e) and local radiotherapy, no longer allowed the actual performance of the sexual act, the temporary sexual dysfunction that preceded the onset of genital cancer thus becoming permanent.

The erectile dysfunction

does not, in principle, prevent a woman from having sexual intercourse, but it impedes it by:

- reduction of translucent vulvo-vaginal discharge even before the appearance of vulvar cancer; the secretion disappeared due to the local malignancy, making penile intromission impossible.
- decreasing the erotic state, so the orgasm no longer occurs
- the estrogen reduction generated the lack of copulins, which are an important factor of arousal for men.



Figure 3a. Tracing the surgical incision area



Figure 3b Extirpation of the pathological area

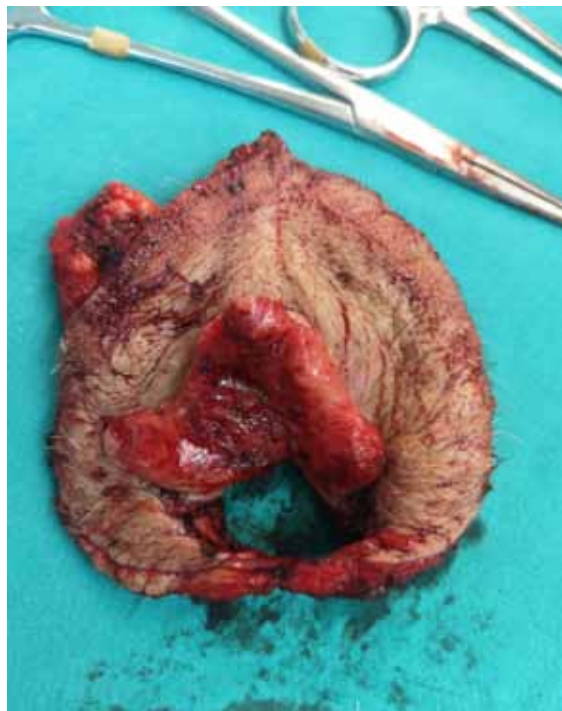


Figure 3c. Extirpated tumoral formation

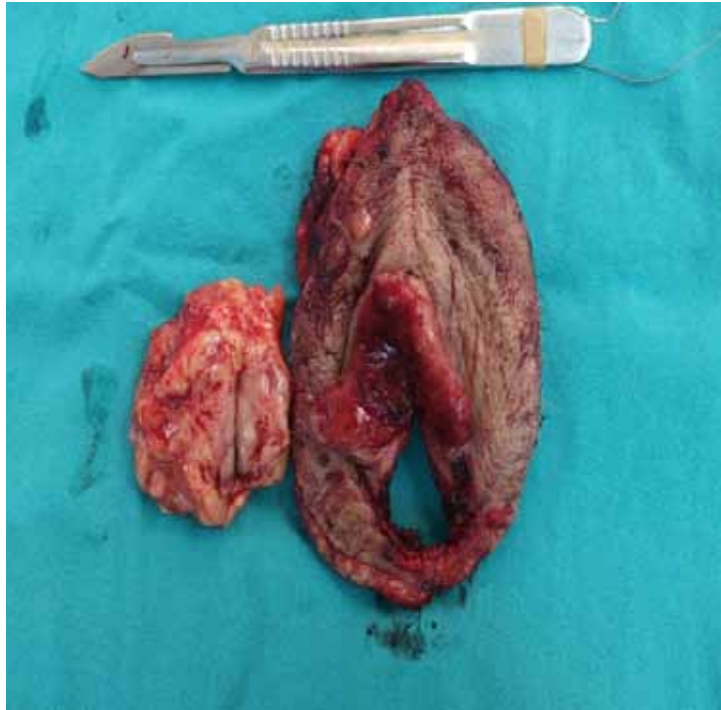


Figure 3d. Both tumoral formations excised in adjacent plane



Figure 3e. Total vulvectomy completed

In the presented patient situation, the anerection has become total, with the disappearance of the neuro-vegetative and of the emotional participation in a potential inter-human relationship.

The copulation dysfunction:

initially, with the occurrence of the vulvar cancer, the impossibility of vulvo-vaginal intromission appeared, because of the local morpho-physiological changes, and after the performed vulvectomy, the actual possibility of sexual intercourse completely disappeared.

The orgasm dysfunction: the existence of the above-mentioned data determined the patient to have total anorgasmia.

Oncological Evaluation and Monitoring Dr. Băcanu Florin

57 years old female patient

21.02.2022: Tumor biopsy from the labia minora, the histopathological examination showing invasive squamous cell carcinoma, moderately differentiated

10.03.2022: MRI imaging evaluation of the vulvar region revealed the presence of a nodular formation of 42/16 mm at the level of the labia minora, with right inguinal lymphadenopathy with a 26/15 mm diameters.

25.03.2022 Bucharest surgery clinic:

- Diagnosis: Bilateral vulvar tumor T2N1M0, stage IIIA, single right inguinal lymphadenopathy

- Surgical treatment: bilateral total vulvectomy + right inguinal lymphadenectomy.

- Histopathological examination: ulcerated tumor 4/4cm, non-keratinized squamous carcinoma, ulcerated, moderately differentiated, G2.

T1b: maximum tumor thickness=8mm, absent lymphovascular invasion (LVI-), absent perineural invasion (PNI-), non-invaded resection margins.

Initial staging in the Surgery Clinic = III A pT1b N1b G2

2 inguinal lymph nodes were examined, one invaded (2 cm diameter squamous cell carcinoma metastasis), with extracapsular extension present. It should be mentioned that the rupture of the tumor-invaded ganglion capsule places the neoplasm in the **N2c stage**

Thus, the post-surgical TNM staging becomes: p(postoperative), T1b (lesion over 2cm thick, stromal invasion over 1mm), respectively **pT1b pN2c M0, i.e. stage III C.**

26.05.2022 The local MRI re-evaluation 2 months postoperatively reveals left inguinal adenopathy with diameters of 32/21 mm.

08.06.2022 PET CT is performed for the characterization (from the point of view of metabolic imaging) of the left inguinal adenopathy and for the assessment of the actual extent of the disease, highlighting:

- Centrally necrotic left inguinal-femoral adenopathic block, peripherally metabolically active with diameters of 31/20 mm, with Standard Uptake Volume (SUV) = 7.77.

- Another moderately sensitive adenopathy for the radiotracer, located in the left external iliac, with dimensions of 13/9mm and SUV = 2.22.

- Moderate capture at the level of the right labia (to be followed-up!) with diameters of 15/11 mm and SUV=4.94, interpreted as having an inflammatory/infectious substrate (recent local staphylococcal infection).

N.B.: the invasion of the external iliac lymph nodes has the significance of a distant metastasis.

The patient underwent post-operative complex oncological treatment, namely concurrent radio-chemotherapy (with weekly administration of cisplatin), the total irradiation dose being of 70 Gy.

The patient will be clinically and imaging monitored. If the disease recurs, surgical reintervention i.e. pelvic exenteration ± palliative systemic chemotherapy (having modest results) could be helpful.

Conclusions:

In the presented case, given the neoplastic invasion of the inguinal lymph nodes, enlarged bilaterally, but mobile on the right side, and subsequently of the iliac lymph nodes, it is not possible to discuss the possible 5 years survival after the diagnosis establishment and the oncological treatment initiation.

In the most favorable situation, although this case of vulvar cancer was promptly operated, the occurrence risk of cardiovascular pathology and of diabetes mellitus is at least 2 times higher than that of the reference population due to the coexistence of the autoimmune disease i.e. psoriasis, although, after

radio- and chemotherapy, the intensity of its activity decreased.

The labia are innervated by branches of the ilio-inguinal nerve: by the small abdomino-genital nerve for the skin that covers them anteriorly, respectively by the pudendus nerve (coming from the sacral plexus S2-S4), for the posterior part. A perineal branch from the posterior femoral-cutaneous nerve reaches the labia majora, as well as sensitive fibers from the pudendus nerve. Complex receptor cells (13), smooth muscle fibers and a well-developed vasculo-nervous system are all found in the labia minora and give the area its erectile quality. The vulvar area contains a multitude of specialized sensory receptors that have an important representation at the cerebral level.

In the patient's current situation, her erectile capacity has disappeared both because of the local malignant pathology and of the previous psychiatric one, so even if the woman had tried to perform a sexual intercourse, this approach would have been very painful and, thus, unacceptable .

Conflict of interest

The authors have no conflicts of interest to declare. They also had full access to all study data and assume responsibility for the accuracy of the analysis of the data presented.

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