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Editorial

Focus on HPV-driven head and neck cancers

A brief search on Pubmed.org reveals a continuous increase in the number of publications regarding HPV (Human Papillomavirus) in Head and Neck Cancers (HNC): from less than 10 per year in the 1990's to over 100 in the present decade, with about 10 review articles solely in 2017! Many reasons account for such significant change, remarkably the recognition of high-risk HPVs (mainly HPV-16) as the etiological agent of a substantial proportion of HNC, although highly heterogeneous by cancer anatomical site, geographical region and gender. In fact, several features are being explored in diverse studies and trials around the World, which reflect on the large number of papers on the subject presented at the 31st International Papillomavirus Conference held in Cape Town (South Africa) last March. This Editorial highlight the reasons for the increased focus on HPV-related HNC.

HNC is a relatively common cancer that affects more males than females with an estimated incidence of about 700,000 cases per year and a high mortality rate worldwide. Although undoubtedly the main etiological factors for HNC are tobacco and alcohol consumption, a subset of oropharyngeal cancers (OPC) have been shown to be induced by high-risk HPVs, particularly HPV-16[1]. A steady raise in OPC is observed in the last decade in Northern Europe and in the US, which seems to reflect not only the reduction of smoking and drinking among these populations, but also an increase in HPV related OPCs (especially among men).

It is important to highlight that the fraction of HPV-driven OPCs clearly varies among geographical regions: whereas most OPC in the US (60%) are HPV-16 positive, in Europe this proportion is 31%, and solely 4% in Brazil[2]. Previous reports have pointed out for the low prevalence of HPV in HNC from Brazil, as compared to the HNC from other countries[3,4]. Significant differences in the prevalence of HPV in HNC have also being recorded in hospital series from the city of São Paulo[5]. Moreover, a wide variation is observed within European sub-regions, with globally higher detection in Northern Europe and lower in Southern Europe[1]. The clinical relevance of such divergence remains to be determined.

Geographical divergence in HPV-16 induced OPC rates could be attributed to differences in tobacco and alcohol use throughout different countries. Indeed, Anantharaman et al.[2] reported that ever smokers and ever drinkers were less likely to be HPV-16 positive. However, smoking prevalence reported in the general population of these regions does not clearly support this hypothesis. Alternatively, differences in oral sex behavior could contribute to the variability in the incidences observed, although this is a controversial issue.

Another intriguing aspect in the viral etiology of some HNC refers to the marked heterogeneity of HPV across anatomical sites. It has been estimated that the HPV attributable fraction in cancer of the hypopharynx, larynx and oral cavity is about five times lower than OPCs[1]. Interesting to note that even within the oral cavity, subsites more proximal to the oropharynx hold higher HPV attributable fractions as compared to those more distal from the oropharynx. Even so, geographical variation in HPV induced non-oropharyngeal HNC is maintained ranging from 7% in the US and 5% in Europe, to 0% in South America. Taken together, these data points towards a substantial contribution of HPV-16 for OPCs, which is however limited for oral cavity and laryngeal cancers.

Evidence is accumulating that links HPV-positivity to a better prognosis and response to treatment in comparison to alcohol and smoking related HNC[6]. Of note, the use of different HPV detection assays hampers the comparability of results stemming from different studies and, even more important, testing HPV in tumors is not routinely performed. In this direction, the search for additional biomarkers is crucial to early diagnosis and proper clinical management of patients.

Several studies in HNC have shown that the detection of HPV DNA alone is an insufficient proof for viral causality, thus requiring the evaluation of other individual or combined biological markers for the definition of truly HPV-driven tumors. A variety of algorithms have been proposed, including the detection of HPV RNA, antibodies against viral early and late oncoproteins, and $p16^{ink4a}$, pRb, p53 and Cyclin D1 protein expression as surrogate markers of HPV-induced transformation. Advantages and limitations for each of these markers have been described. Of note, Castellsagué et al.[1] reported that using either or both E6*I mRNA or $p16^{ink4a}$ together with viral DNA yielded comparable HPV attributable fractions for oropharyngeal, oral cavity or laryngeal cancers, and that differences between methods derived mostly from the lack of $p16^{ink4a}$ expression in a small fraction of HPV DNA and mRNA positive tumors. Nevertheless, others argue that the specificity of $p16^{ink4a}$ for non-oropharyngeal HNC is low. Moreover the pattern of HPV-16 status and $p16^{ink4a}$ expression in OPC has been shown to differ by race, being significantly higher in Whites as compared to Black and Asian individuals[7]. This trend was not observed in non-oropharyngeal HNCs.

HPV-16 serology has been assigned as a very sensitive and specific biomarker capable of predicting OPC onset. For instance, recently Kreimer et al.[8] analyzed the kinetics of HPV-16 E6 antibodies preceding OPC development and showed that stable antibody levels can be detected more than 10 years prior to cancer diagnosis. In addition, detection of viral HPV DNA in oral rinses and of HPV antibodies in the sera of patients with OPC could contribute to determining the potential risk of recurrence of HPV-positive HNC.

Further studies and clinical trials are warranted to better elucidate the diagnostic and therapeutic implications of HPV in HNC. The identification of additional biomarkers is in fact the subject of several ongoing studies, some of which were presented at the last International Papillomavirus Conference (www.hpv2017.org). Information on the different etiologies of HNC is seminal to develop more precise guidelines to benefit patients with HNC. Last but not least, the accumulated knowledge will contribute to understand the impact of HPV prophylactic vaccination in the reduction of HNC worldwide.

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Editorial

Manipulation of autophagy by sexually transmitted infections: new opportunities for intervention

Autophagy, from the Greek words meaning "self-eating", is an evolutionarily conserved multistep process preserved amongst all eukaryotes to maintain cellular homeostasis[1]. It is an intracellular, catabolic process whereby dysfunctional organelles such as mitochondria and inflammasomes, aggregated or unneeded proteins as well as intracellular bacteria and viruses and their components are degraded[2,3]. The entities marked for destruction become surrounded by a double membrane structure called an autophagosome. The autophagosome fuses with a lysosome and the sequestered components are catabolized by lysosomal enzymes[4-6]. The resulting amino acids, fatty acids, carbohydrates and nucleic acid components are returned to the cytoplasm to provide additional nutrients for various metabolic processes.

Under physiological conditions; autophagy is maintained at a low basal level in most cells[7]. Its induction is primarily inhibited by a compound called mammalian inhibitor of rapamycin (mTOR) that senses the availability of nutrients, oxidative stress as well as other deviations from intracellular homeostasis[8-10]. When non-physiological conditions that increase cellular stress develop mTOR is inhibited and the pathway to autophagy is activated[11]. More specifically, the pathway of autophagy is induced by nutrient and oxygen deprivation, decreased levels of growth factors, the presence of a cytotoxic environment, oxidative stress due to defective mitochondria, and intracellular changes induced by infection or malignancy[12-14].

In addition to its central role in the clearance of intracellular pathogens autophagy, it has an additional role in the regulation of both innate and adaptive immunity. Peptides produced by the lysosome-mediated degradation of microorganisms that have been sequestered in autophagosomes combine with major histocompatibility complex molecules and migrate to the cell surface. Their subsequent binding to receptors on the surface of T lymphocytes results in the activation of peptide-specific acquired immunity[15]. Activated T cells as well as antibody production by activated B lymphocytes require additional energy and this is provided by activation of autophagy within these immune cells[16]. Autophagy also prevents the induction of excessive inflammation that can harm healthy cells. It inhibits the activation of NFκB, the transcription factor that turns on genes coding for pro-inflammatory cytokines[13,17]. In addition, it down-regulates production of the primary pro-inflammatory cytokine, interleukin (IL)1β, by sequestering and degrading an intracellular structure called an inflammasome that is responsible for production of biologically active IL-1β[18-20].

The contribution of autophagy in eliminating sexually transmitted viruses and bacteria that infect the female genital tract has received only limited attention. This editorial highlights the role of autophagy in the defense against these infections and the mechanism utilized by sexually transmitted pathogens to circumvent autophagy-mediated destruction. Novel studies are proposed, based on these interactions to facilitate autophagy-mediated destruction of female genital tract pathogens.

CHLAMYDIA TRACHOMATIS

C. trachomatis is the most common sexually transmitted bacterial pathogen, a major cause of infertility and ectopic pregnancy as well as the leading cause of preventable blindness worldwide[21]. According to the Centers for Disease Control in the United States there was a 5.9% increase in the rate of chlamydial infections from 2014 to 2015, resulting in 478.8 cases per 100,000 people[22]. *C. trachomatis* has a unique biphasic developmental cycle. The extracellular elementary body infects epithelial cells by binding to a heparin-containing surface component and is subsequently internalized[23]. It then converts into an intracellular form, the reticulate body, which replicates within inclusion bodies in the host cell cytoplasm. Autophagy-related proteins do not assemble into autophagosomes in response to the inclusion body and so *C. trachomatis* replication is resistant to autophagy[24].

The role of interferon (IFN)-γ is pivotal in combating chlamydial infections; its introduction eliminates this bacterium[25]. IFN-γ depletes intracellular tryptophan and iron, induces production of nitric oxide, and activates host autophagy[8,13,26]. Recent data have shown that IFN-γ induces the fusion of autophagosomes with chlamydial inclusion bodies via a mechanism involving induction of guanylate binding proteins[27].

There remains a still largely unmet need to identify the role of autophagy in a chlamydial genital tract infection. What is the mechanism by which an intracellular chlamydial infection prevents autophagy induction and how can this be reversed? Are women with an inherited or acquired deficit in autophagy induction at increased susceptibility to this infection and its sequelae? Can we identify compounds that can safely induce autophagy and/or IFN-γ production in women newly infected with *C. trachomatis* to prevent harmful consequences of this infection?

CANDIDA ALBICANS

C. albicans is a dimorphic fungus that can exist in either a yeast-like or a filamentous form. It is a harmless commensal organism in about 20% of healthy reproductive age women. Under conditions of a transient local immune suppression or the administration of antibiotics that disrupt the vaginal microbiome, endogenous *C. albicans* proliferates, converts from the yeast to the filamentous form, becomes invasive and causes a symptomatic infection. The mechanism that this organism utilizes to resist immune destruction and to persist in the female genital tract involves autophagy. In response to *Candida* proliferation in the genital tract, the Th17 class of CD4+ T lymphocytes is activated and the cytokine interleukin (IL)-17a is released. IL-17a recruits neutrophils and macrophages to the genital tract to engulf and destroy the fungal invader[28]. However, *Candida* has a cell surface receptor that binds IL-17a and induces autophagy in the yeast[29]. This results in conversion to the filamentous form and formation of a biofilm that resists engulfment. Once the extracellular infection is resolved and phagocytic cells are no longer present the yeast forms are again

produced and recolonize the vagina. Thus, activation of autophagy in *C. albicans* in response to anti-candidal immunity ensures its survival.

Recurrent vulvovaginal candidiasis (RVVC) is a frustrating consequence of a *C. albicans* infection in about 5% of infected women. A symptomatic episode is usually resolved with anti-fungal treatment, but the infection returns shortly after treatment cessation. It remains untested whether the interference with autophagy in *Candida* has the potential to allow the immune system to totally eliminate this organism from the genital tract, and, thus, prevent recurrent infections. An antibody that blocks the IL-17a receptor on yeast and/or introduction of an exogenous compound that activates yeast mTOR and prevents autophagy induction are attractive options that remain to be tested.

HERPESVIRUS

Type I and type 2 herpes simplex virus (HSV) are double stranded DNA viruses that infect the female genital tract. They can cause painful lesions and, in pregnancy, are major inducers of neonatal morbidity and mortality. Their intracellular replication should be inhibited and the virus destroyed by autophagy. However, both HSV 1 and HSV 2 produce a protein, infected cell protein 34.5 (ICP34.5), that inhibits formation of the autophagosome and, thereby, prevents viral elimination[30]. Human cytomegalovirus (CMV) produces an analogous protein, TRS1, that also inhibits autophagy in CMV-infected cells[31]. Thus, herpesviruses persist within host cells by inhibiting autophagy. The introduction of exogenous agents capable of inducing autophagy in herpesvirus-infected cells appears to be a logical option worthy of evaluation.

HUMAN PAPILLOMAVIRUS

HPV, a double stranded DNA virus, is the etiological agent of cervical carcinoma as well as a causative factor for anal cancer and head and neck malignancies[32]. HPV infects terminally differentiated epithelial cells in the female genital tract. The induction of autophagy in these infected cells is essential for the production of amino acids needed for HPV replication as well as for the continued survival of the host cell. The HPV E7 protein has been shown to induce autophagy in epithelial cells. Uninfected epithelial cells that have been transfected with the E7 protein undergo autophagy[33].

The inhibition of autophagy in HPV-infected genital tract epithelial cells to limit the consequences of this infection is an attractive but unexplored area of research. Development of protocols to target HPV-infected cells with agents that inhibit autophagy and/or activate mTOR might be useful adjuncts to conventional treatments. In addition, contrary to the situation with *C. trachomatis*, we predict that women with a reduced capacity for autophagy would be relatively resistant to an HPV infection or development of a cervical malignancy. This possibility is easily amenable to testing.

HUMAN IMMUNODEFICIENCY VIRUS

HIV is a retrovirus that infects monocytes/macrophages and $CD4^+$ T lymphocytes in the female genital tract. Like herpesviruses, the intracellular replication of HIV should be disrupted by autophagy. However, unlike herpesviruses, HIV uses autophagy to facilitate its replication in monocytes/macrophages. The HIV gag protein binds to an essential autophagy component, LC3, and facilitates the assembly of HIV within autophagosomes[34]. A second HIV protein, nef, binds to another autophagy component, Beclin 1, and inhibits the autophagosome from interacting with a lysosome[34]. A third HIV protein, tat, prevents IFN-γ from inducing autophagy in HIV-infected cells[35]. When HIV infects $CD4^+$ T cells the HIV env protein is released into the extracellular milieu where it binds to uninfected $CD4^+$ T cells. This results in the induction of autophagy in these cells and their subsequent destruction by apoptosis[36]. This elimination of uninfected T cells down-regulates anti-HIV immunity and facilitates viral persistence.

Thus, HIV has evolved an amazing repertoire of mechanisms that target autophagy. This suggests that autophagy has a major role in HIV biology. However, focusing on the development of mechanisms to promote autophagy to eliminate HIV in infected monocytes/macrophages and to prevent autophagy in uninfected T cells has received scant research attention.

CONCLUSIONS

Autophagy is a major mechanism to eliminate microorganisms that reside within the cytoplasm of infected cells and to promote effective anti-microbial immune responses. Microorganisms that successfully invade the female genital tract have evolved mechanisms to prevent their autophagy-mediated destruction, utilize autophagy to promote their survival and/or promote their ability to replicate within host cells. The testing of novel protocols to prevent or reverse the microorganism-directed subversion of autophagy remains an under-appreciated area of research. It is our hope that this editorial will facilitate laboratory investigations that result in development of novel means to combat the initiation, development and consequences of sexually transmitted infections.

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Evaluation of syndromic approach of vaginal discharge flowchart to diagnosis of trichomoniasis

Avaliação da abordagem sindrômica do corrimento vaginal para o diagnóstico de tricomoníase

Mateus de Paula von Glehn[1,2], Eleuza Rodrigues Machado[3]

ABSTRACT

Introduction: *Trichomonas vaginalis* infection is the most prevalent non-viral sexually transmitted disease in the world. Among the different methods for diagnosis, the World Health Organization and Ministry of Health of Brazil proposes the use of flowcharts in the syndromic approach. **Objective:** To evaluate the syndromic approach of vaginal discharge to diagnosis of *T. vaginalis* infection. **Methods:** Transversal study with sample of outpatient population consisting of women in reproductive age. After exclusion of pregnant women and minor girls, the final sample consisted of women between 18 and 49 years old. The participants answered a questionnaire where the complaints were registered. They were examined, had the vaginal pH assessed and sample tested with 10% KOH solution to verify the exhalation of amine odor (whiff test). After this proceeding, a vaginal secretion sample was inoculated in a specific *T. vaginalis* culture medium. The culture results were used as the gold standard to evaluate the syndromic approach flowchart. The algorithm was evaluated according sensitivity, specificity, accuracy, and predictive values. **Results:** Among women with *T. vaginalis* infection, 10% were asymptomatic; among them, dyspareunia was significantly higher, if compared to women with no infection. Flowchart proposed by the syndromic approach had low specificity and accuracy, leading to unnecessary treatment in two-third of women. **Conclusion:** The diagnosis of trichomoniasis based only on the discharge complaint had low accuracy; the whiff test result improves the specificity of diagnosis of *T. vaginalis* infection, regardless of the vaginal pH value.

Keywords: sexually transmitted diseases; Trichomonas vaginalis: vaginitis; vaginal discharge.

RESUMO

Introdução: A infecção por *Trichomonas vaginalis* é a doença sexualmente transmissível não viral mais prevalente no mundo. Entre os diferentes métodos para seu diagnóstico, estão os fluxogramas previstos pela abordagem sindrômica. **Objetivo:** Avaliar o fluxograma de corrimento vaginal para o diagnóstico de tricomoníase em mulheres atendidas em equipe de saúde da família. **Métodos:** Estudo transversal feito com amostra consecutiva de população ambulatorial, composta por mulheres em idade fértil, exceto gestantes e menores de idade. As participantes responderam a um questionário onde foram registradas as queixas ocorridas nas últimas quatro semanas. Também foram examinadas e submetidas à medição do pH vaginal e teste das aminas. A cultura em meio específico foi considerada como padrão-ouro. **Resultados:** Dez por cento das mulheres infectadas pela *T. vaginalis* estavam assintomáticas; entre as infectadas, a dispareunia foi significativamente maior do que entre as mulheres negativas. O esquema proposto pela abordagem sindrômica tem baixa especificidade e acurácia. **Conclusão:** O diagnóstico de tricomoníase embasado apenas na queixa de corrimento tem baixa acurácia; o resultado do teste das aminas melhora a especificidade do diagnóstico da infecção por *Trichomonas vaginalis*, independentemente do valor do pH vaginal.

Palavras-chave: doenças sexualmente transmissíveis; *Trichomonas vaginalis*; vaginite; descarga vaginal.

INTRODUCTION

Among non-viral sexually transmitted infections (STIs), the *Trichomonas vaginalis* infection is estimated to be the most prevalent throughout the world[1], with different occurrences in various contexts. Associations between *T. vaginalis* infection and damage to sexual and reproductive health have been cited in several studies[2-8], including the increased risk of contracting and transmitting HIV[9-15].

The clinical condition of this infection is wide and varies from asymptomatic to intense vaginitis[16,17]. Among symptomatic women, it is usual the complaint of abnormal vaginal discharge, that is a common symptom of other infections or vaginal microenvironmental disorders. Any abnormalities of the vaginal exudate, either in quantity, appearance, or odor[18], which may be accompanied by other symptoms such as pruritus, burning, or dyspareunia are referred to as vaginal discharge[19].

The causes are diverse and can originate from idiopathic changes of endogenous microbiota or from exogenous infections, including the sexually transmitted infections (STIs). The term STI has been used to replace the term STD (sexually transmitted disease), considered to be wider, and encompassing the asymptomatic infections[20]. In this study the two terms are taken as synonyms. Preference is given to the second, once the emphasis is on the symptomatic cases.

The diagnosis and treatment of trichomoniasis are contemplated in the syndromic approach of sexually transmitted diseases, more specifically in the vaginal discharge algorithms. The syndromic approach of STDs has been recommended by the World Health Organization (WHO) since 1991[20] and adopted by the Ministry of Health of Brazil since 1993[21]. Its use has the advantage of timely diagnosis and treatment in a single contact, even in the absence of laboratory facilities.

While recommending the adoption of the syndromic approach as a strategy for the control of sexually transmitted diseases[20], WHO recommends that flowcharts must be adapted to the local epidemiological reality. Two flow charts – with and without microscopy – are available for the management of vaginal discharge.

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OBJECTIVE

To evaluate the accuracy of vaginal discharge flowchart for the diagnosis of trichomoniasis.

METHODS

The sample examined in this research is part of a larger study of the prevalence of *T. vaginalis* conducted in a family health clinic of the Federal District, Midwest region of Brazil.

Type of study

A cross-sectional study was conducted between November 2014 and March 2015 in a Primary Health Unit, located in the Estrutural City, one of the administrative regions of the Federal District.

Ethical Considerations

The study was approved by the Research Ethics Committee of the State Health Department of the Federal District (CAAE 28186514.5.0000.5553).

Sample Population

The outpatient population sampled consisted of women of reproductive age, except pregnant women and minor girls (less than 18 years of age). The final sample consisted of women between 18 and 49 years.

The invitation to participate in the research was made to all women who were within these criteria, regardless of the reasons that led them to seek medical assistance at the clinic. The team has about 700 women registered in this age group. Considering this number of women as a finite population, assuming a 10% prevalence of infection and a 5% confidence interval, the sample should be composed of 116 participants. Anticipating loss of 20%, the calculation was extended to 139 women. At the end, 201 women agreed to participate, and 193 were examined.

Data collection

After obtaining the signature of participant in the consent form, a trained female interviewer applied a questionnaire, and the participants were asked about the presence of some gynaecological complaint. They subsequently underwent a genital examination for measuring the vaginal pH and realization of whiff test. The pH was measured using graduated strips at intervals of 0.3 units and range from 3.6 to 6.1 (pH-Fix®, Macherey-Nagel, Ref. 92130).

The whiff test was performed by adding a drop of 10% KOH to vaginal discharge, previously disposed on a glass slide. The test was considered positive if was perceived a characteristic fishy odor.

For the culture of *T. vaginalis*, a sterile swab was applied to the posterior side wall of the vagina and plated in TYM (Trypticase - Yeast extract - maltose) culture medium, as proposed by Diamond[22]. The samples were transported to the Laboratory of Parasitology and Vector Biology of the Faculty of Medicine at the University of Brasília where they were placed in an incubator at 37º C.

The plates with TYM culture medium were viewed after 24, 48, and 72 hours. After 96 hours, the culture was instilled with 5 mL of 0.9% saline solution, transferred to test tubes, and centrifuged at 2,500 g for five minutes. The supernatants were discarded and the remaining pellets were examined. For each sample, 100 µL of the pellets were placed on glass slides and examined using an optical microscope at 40x. A second slide was prepared and allowed to dry at room temperature. This second slide was fixed with methanol, stained with Giemsa, and examined under a microscope at 100x. The result was considered positive when the presence of the parasite was observed on either of the slides.

Flowchart Evaluation

We evaluated the vaginal discharge flowchart without microscopy for the management of vaginal discharge. The algorithm was evaluated according its sensitivity (S), specificity (E), positive predictive value (PPV), negative predictive value (NPV), and accuracy (Ac) for the diagnosis of trichomoniasis. It was also calculated the positive and negative likelihood ratios (PLR) and (NLR). These measures are defined below:

- True positive (TP): individuals diagnosed as positive by the test and the gold standard;
- False positive (FP): individuals diagnosed as positive by the test, but negative by the gold standard;
- False negative (FN): individuals diagnosed as negative by the test, but positive by the gold standard;
- True negative (TN): individuals diagnosed as negative by the test and the gold standard;
- Sensitivity (S): proportion of individuals diagnosed by testing among the infected; the result can be found by the formula (TP/TP+FN) x 100;
- Specificity (Sp): proportion of individuals with negative results among uninfected; the result can be found by formula (TN/FP+TN) x 100;
- Accuracy (Ac): proportion of correct results (TP and TN) among all individuals in the sample, or (TP+TN/n) x 100;
- Positive predictive value: probability of an individual with positive test actually being infected - (TP/TP+FP) x 100;
- Negative predictive value: probability that an individual with a negative test is not infected – (TN/FN+TN) x 100.

RESULTS

The calculated values of S, Sp, PPV, NPV, and Ac are expressed as percentages in **Table 1**. RVP and RVN are expressed in whole numbers.

The prevalence of women infected with *T. vaginalis* was 16% (30 of 193). In general, gynaecological complaints were more frequent among those with positive cultures. However, the difference was significant only among those who complained of dyspareunia. Of the 30 women with positive culture, three (10%) were asymptomatic. Among those with negative cultures (n=163), the proportion of asymptomatic was the double (20%), with a significant difference (**Table 2**).

For the diagnosis of trichomoniasis, the isolated complaint of vaginal discharge confers sensitivity, specificity, and accuracy below 60% (diagnosis 1). Higher sensitivity (73%) occurred when the discharge complaints were associated with the pH value or test of amines (diagnosis 5). Higher specificity (85%) occurred in diagnosis 4, which included only women who presented vaginal pH values above 4.5 and positive results on the test of amines, simultaneously.

DISCUSSION

Infection with *T. vaginalis* is considered the most prevalent curable STI in the world[23]. Nevertheless, the proper diagnosis of this infection still faces barriers that start because there are many asymptomatic carriers[24]. Even among symptomatic women, complaints are invariably nonspecific. Such complaints are common for many different conditions that affect the female genital tract[7].

In this sample, if the complaints of vaginal discharge were taken solely into consideration for the diagnosis of trichomoniasis, 46% of women would receive a wrong diagnosis, with 75 negative women receiving a positive diagnosis (FP) and 13 positive women diagnosed as negative (FN). This demonstrates that the vaginal discharge complaint alone is not sufficient for the adequate diagnosis of trichomoniasis.

The pH values above 4.5 increased the diagnostic specificity (77%), which also reflects in accuracy (70.5%). However, there was a 24% lower sensitivity, with two-third of the women undiagnosed.

Table 1 – Evaluation of trichomonas diagnoses according to the results of cultures for *T. vaginalis*, 2015.

Trichomoniasis	Growing of *Trichomonas vaginalis* Diamond medium						
	S	Sp	PPV	NPV	Accuracy	PLR	NLR
Diagnostic 1	57	54	18,5	87,1	54	1,2	0,8
Diagnostic 2	33	77	21,3	86,3	70,5	1,5	0,9
Diagnostic 3	33	84	27,8	87,3	76,2	2,1	0,8
Diagnostic 4	27	85	24,2	86,3	75,6	1,7	0,9
Diagnostic 5	73	59	24,7	92,3	61	1,8	0,5

Diagnostic 1: vaginal discharge; Diagnostic 2: vaginal discharge AND pH above 4.5, regardless whiff test result; Diagnostic 3: vaginal discharge AND positive whiff test, regardless pH value; Diagnostic 4: vaginal discharge AND positive whiff test AND pH above de 4.5; Diagnostic 5: vaginal discharge AND positive whiff test AND/OR pH above de 4.5; S: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; PLR: positive likelihood ratio; NLR: negative likelihood ratio.

Table 2 – Distribution of women according vaginal complaints and culture results for *T. vaginalis*, in 2015.

Complaint	Positive (n=30)		Negative (n=163)		Variation
	n	%	n	%	
Discharge	17	57	75	46	11
Dyspareunia	15	50	53	33	17
Lower abdominal pain	15	50	86	53	-3
Malodorous discharge	12	40	54	33	7
Burning	11	37	43	26	10
Pruritus	10	33	46	28	5
Asymptomatic	3	10	33	20	-10

The test of the amines provided similar sensitivity (33%) to the measurement of pH, but had greater specificity and accuracy, and was a better discriminator among women with negative cultures, preventing them from being wrongly diagnosed as carriers of trichomoniasis. By this procedure, 24% (46 of 193) of the women would be incorrectly diagnosed, with 26 of them receiving positive diagnoses without effectively being carriers the parasite.

Similar findings have been reported in the literature[25]: the test of amines increased the predictive value for diagnosis, at the expense of increase in specificity, although the adequacy of testes for sensitivity was reduced. There are, therefore, some limitations in the comparison of results. In the study mentioned above, the population was composed of pregnant women and the gold standard was considered the wet mount.

The scheme proposed by the flowchart of syndromic approach (diagnostic 5) had the higher sensitivity, but moderate specificity and accuracy (around 60%), with an elevated number of negative women diagnosed with trichomoniasis (67 of 193). Among the women diagnosed with trichomoniasis by flowcharts and negative cultures, many may have had bacterial vaginosis (BV), as this is also associated with positive test of the amines and higher values of pH[19].

The drug and recommendations for its use in the treatment are the same: metronidazole in a single dose of 2 g or 14 doses of 400 mg divided into twice daily doses during 7 days. The difference is that in the case of trichomoniasis, women should be instructed to refer their partners to treatment, a situation that can be delicate considering the stigma surrounding sexually transmitted diseases. In this case, the greater sensitivity of the flow chart would have better predictive value and accuracy in situations of high prevalence.

As mentioned, clinical cases of trichomoniasis and BV are similar. It is also common the occurrence of BV accompanying the infection by *T. vaginalis*[26,27]. In both cases, positive results from the test of amines and higher pH values can be expected. That said, the value of microscopy cannot be denied for the distinction between these two nosological entities since microscopic examination permits a view of moving parasites[28]. Although presenting less sensitivity in comparison to culture[29], the relative practicity of its use and the possibility of immediate diagnosis can improve the resoluteness of care provided in family health teams.

The increased specificity made possible by the use of the microscope in the diagnosis of trichomoniasis has been demonstrated by Vishwanath et al. (2000)[30]. Although there may be no increase in sensitivity, the increased specificity improves the predictive value for a positive diagnosis. As explained above, the syndromic approach strategy has two flowcharts for the management of vaginal discharge – with and without microscopy. The latter is not used in the primary care units of the Federal District, because there are no available microscopes. To implement this method, an analysis of the cost of equipment, training, and the necessary changes in the work processes of the teams would need to be considered.

This study is not the first evaluation of flowcharts proposed by the syndromic approach in Brazil. However, most studies of the vaginal discharge flowchart have been more focused on infection by *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Among the studies that examined *T. vaginalis*, the gold standard used was the wet mount of discharge[25,31]. In research reported in Scielo, Pubmed,

and Google Scholar, no flowchart validation studies for the diagnosis of *T. vaginalis* using culture as the gold standard in primary health care were found.

CONCLUSION

The diagnosis of trichomoniasis based only on complaints regarding vaginal discharge has low accuracy. The test results of the amines improve the specificity of the diagnosis of *T. vaginalis* infection, independently of the value of the vaginal pH. The flowchart proposed by syndromic approach led, in this study, to unnecessary treatment in more than one third of symptomatic women.

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Conflict of interests

The authors declare no conflict of interests.

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The stigma of HIV positive users of the public health system

O estigma de usuários do sistema público de saúde brasileiro em relação a indivíduos HIV positivo

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ABSTRACT

Introduction: The initial idea of AIDS as a disease that affects individuals with attitudes disapproved by society has caused stigmatization and prejudice among HIV positive individuals. **Objective:** To analyze the existence of prejudice and discriminatory attitudes of Unified Health System ("Sistema Único de Saúde" – SUS) users towards HIV positive individuals, according to socioeconomic class. **Methods:** This is a cross-sectional, descriptive research, with quantitative approaches. We categorized the population according to the Brazilian Criterion of Economic Classification, and applied a structured questionnaire related to prejudice, discrimination, and perceptions regarding sterilization and infectious diseases; as well as questions from a relevant Ministry of Health publication. **Results:** The study population consisted of 150 individuals, 77.3% of which asserted they would agree to be treated immediately after an HIV positive patient and 92% after a prisoner. However, 42% preferred being examined before HIV positive individuals, and 23.3% before a prisoner. The majority reported concern about the sterilization of dental material (98%), though 42% did not know how the procedure was carried out. There was significant difference between individuals who initially said they would not mind being received after HIV positive patients (p=0.0029) or inmates (p<0.0001), and those who later said they would rather be received before individuals in these conditions. There was no association between socioeconomic class and prejudice. **Conclusion:** SUS users show prejudicial and discriminatory attitudes toward HIV patients, often expressed in subtle manners, regardless of economic class of the individual.

Keywords: discrimination; HIV positive; acquired immunodeficiency syndrome.

RESUMO

Introdução: O conceito inicial de que a AIDS era uma doença que ocorria em indivíduos com atitudes desaprovadas pela sociedade causou estigmatização e preconceito em indivíduos HIV positivo. **Objetivo:** Analisar a existência de preconceito e atitudes discriminatórias de usuários do Sistema Único de Saúde (SUS) em relação a indivíduos soropositivos, considerando sua classe socioeconômica. **Métodos:** Trata-se de uma pesquisa descritiva, com caráter transversal e abordagem quantitativa. Aplicou-se o Critério de Classificação Econômica Brasil, para a classificação econômica da população, e um questionário estruturado com questões relacionadas ao preconceito e à discriminação, à percepção sobre esterilização e ao contágio de doenças; além de questões de manual do Ministério da Saúde que aborda o assunto. **Resultados:** A população estudada foi composta por 150 indivíduos, dos quais 77,3% afirmaram que aceitariam ser atendidos após um paciente soropositivo, e 92%, após um presidiário. Entretanto, 42% prefeririam o atendimento antes de um indivíduo soropositivo, e 23,3%, antes de um presidiário. A maioria relatou preocupação quanto à esterilização do material odontológico (98%), embora 42% não soubessem como o procedimento ora realizada. Existiu diferença significativa entre os indivíduos que inicialmente afirmaram aceitar o atendimento após um paciente HIV positivo (p=0,0029) ou um presidiário (p<0,0001) e os que posteriormente disseram preferir o atendimento antes. Não houve associação entre classe econômica e preconceito. **Conclusão:** Os usuários do SUS apresentam preconceito e atitudes discriminatórias em relação a pessoas soropositivas, expressa, às vezes, de maneira velada, independentemente da classe econômica do indivíduo.

Palavras-chave: preconceito; soropositividade para HIV; síndrome da imunodeficiência adquirida.

INTRODUCTION

In the early 1980s, the first AIDS cases were reported in the United States, showing clinical characteristics of immune system impairment in male homosexual patients, raising suspicions about a relation between homosexuality and the disease.[1]

AIDS was conveyed through the media as a lethal and incurable illness[1] associated with homosexuals, drug users and sex workers, reinforcing the stigmatization of these groups by all strata of society, regardless of educational level and knowledge on the epidemic, raising fear and distrust among the population[2].

The subsequent spread of the disease among heterosexuals, children and infants revealed that the idea of a homosexual risk group was mistaken[1]. Today, we can see the progression of the AIDS epidemic and the human suffering caused by stigma, prejudice, and discrimination, which are processes of devaluation and intolerance towards those individuals, causing social inequity.[3]. For this reason, asymptomatic individuals often do not reveal their condition.[2]

The term "stigma" was created by the ancient Greeks to refer to bodily traits that manifested because of an individual's unworthy moral behavior. Thus, people considered "normal" often promoted discriminatory attitudes against individuals who bore some difference unaccepted by society[4]. The stigma attached to HIV goes far beyond individual effects, and is directly linked to the reproduction of social inequalities, leading to prejudice, rejection and loss of *status*[5].

In turn, prejudice is a form of thought in which a person reaches conclusions which pre-judge another person, leading to discrimination[6].

Studies show reports of sick individuals who were denied professional treatment after revealing they had HIV, or after manifesting some of the disease's clinical characteristics[1,2]. However, few studies have tried to identify the different forms of prejudice shown by public health system users towards individuals with HIV.

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OBJECTIVE

To verify the existence of prejudicial and discriminatory attitudes of users (in different economic classes) of the Unified Health System (SUS) towards HIV-positive patients, in a city in Northwestern São Paulo State, Brazil.

METHODS

The research was approved by the Human Research Ethics Committee of the School of Dentistry of Araçatuba, Universidade Estadual Paulista "Júlio de Mesquita Filho", within the standards required by Resolution no. 466/12.

This is a cross-sectional, descriptive research, with quantitative approaches. Initially, the city Secretary of Health was contacted to be informed about the study's objectives, in order to obtain support for the conduction of the research.

Participants were users of "basic health units" (BHU) of Américo de Campos, in Northwestern São Paulo State.

Previously, a pilot study was conducted on 10 patients with the purpose of verifying the need to rectify the questionnaires.

Data collection took place on an individual basis, in a private room at the only BHU of the city, on the same day as patients' appointments, and every day from July to October, 2014.

All patients who attended the BHU during the collection period were invited to participate in the research. Those who agreed signed the Informed Consent Form (ICF) and responded to two questionnaires, applied by a trained researcher:

1. the Brazilian Economic Classification Criteria (for short, BECC, or "Critério de Classificação Econômica Brasil"), drafted by the Brazilian Association of Research Companies,[7] as a way to categorize the population: in this scale, the educational level of the head of the household is worth 0 to 8 points; the remaining points are provided by the amount of durable consumer goods owned by the family (vehicle, color TV, radio, refrigerator, freezer, washing machine, etc.); the number of rooms and bathrooms in the house and the number of maids working in the house. The sum of these indicators divides the population in several classes, "Class A1" (from 42 to 46 points) being the highest, and "Class I" (from 0 to 7 points) the lowest; and b);
2. a questionnaire on stigma and discrimination, with questions from the Ministry of Health's *Knowledge, attitudes and practices survey of the Brazilian population*[8]. Additionally, questions regarding: the acceptability of being treated by an HIV-bearer dental surgeon; the perception of the possibility of acquiring diseases at the dental office; the relative infectiousness between HIV and hepatitis; the concern for cleanness and sterilization of the equipment used by dental surgeons; the acceptability of being treated after patients with AIDS or inmates; and whether respondents would prefer, given the choice, to be treated before HIV patients or prisoners.

As a number of penitentiaries are present in neighboring towns, inmates receive dental treatment at the city's public health units, justifying their inclusion in the research. Studies show a high rate of prison inmates with sexually transmitted diseases (STDs), such as HIV and syphilis, in addition to drug injection and history of blood transfusion, fostering discriminatory attitudes against these groups[9].

Collected data was handled using the *Epi Info™ 7* software and presented as absolute and relative frequencies. Statistical analysis was performed using the test for comparing two proportions as well as the χ^2 test with 5% significance level, using the *BioStat 5.0* software[10].

RESULTS

The population studied consisted of 150 users of the public health system, of which 74% were female; 31.3% were aged between 18 and 27 years, 17.3% between 28 and 37 years, 20% between 38 and 47 years, 16.7% between 48 and 57 years and 8% were older than 58 years. By BECC, the population was divided into economic classes: 10% belonged to class A2, 22% to class B1, 37.3% to class B2, 22.7% to class C1, 6.7% to class C2 and 1.3% to class D1.

Forty percent of the respondents reported having suffered some form of discrimination, due to color or race (0.7%); gender (6.7%); social condition and lack of money (22.7%); sexual orientation (4%); profession or occupation (12.7%); or HIV diagnosis, if applicable (3.3%); due to illness or disability (6.7%); age (12%); physical appearance (12.7%); or other reasons (14%).

Also, 32.7% of respondents said they did not agree with the adoption of children by homosexual couples; 13.3% said they would not have homosexual friends; 91.3% thought that if a person had AIDS, he or she should receive treatment at home; 24.7% asserted they would stop buying vegetables if the vendor was revealed to be infected with HIV; 8.7% believed that a teacher with the AIDS virus should not continue to give lessons; 38% believed that, if a family member was infected with HIV, the family should keep this a secret; and 5.3% claimed knowing someone close with HIV or who died of AIDS.

23.4% said they would not agree to receive treatment from a dental surgeon infected with HIV; 86% believed infections could be acquired at the dental office; and 80.7% thought that HIV easier to contract if compared to hepatitis B. In addition, 98% showed concern about the sterilization of the dental surgeon equipment, although 42% did not know how this procedure was performed.

77.3 and 92% reported agreeing to receive treatment after a patient with HIV or an inmate, respectively. However, when questioned whether they would prefer being treated before or after an individual with AIDS or an inmate, 42 and 23.3%, respectively, answered "before." A statistically significant difference was observed, by comparing the ratios, between individuals who initially said they would accept being treated after a patient with HIV ($p = 0.0029$; power=0.8672) or an inmate ($p<0.0001$; power=0.9970) and those who later said they would prefer being treated before (**Tables 1 and 2**). There was no statistical relation between economic classes and the prejudice revealed by the preference of being treated before an individual with AIDS ($p=0.1036$) or an inmate ($p=0.6034$) (**Tables 3 and 4**).

DISCUSSION

The prevention of HIV/AIDS and hepatitis is a crucial aspect in dentistry; therefore, preventive measures should be used during treatments[11]. A survey of dentistry students revealed they represent the main danger to the patient, as they tend to neglect the importance of cleaning and disinfecting materials and equipment used during the procedure[12], highlighting a flaw in the training of future professionals. In our study, many people showed concern for the cleanness and sterilization of materials used during dental treatment, but did not know how the process was carried out.

Furthermore, the risk of contracting HIV is much lower than that for the hepatitis virus, with estimates of 0.3% for HIV, 1 to 10% for hepatitis C and 40% for hepatitis B.[13] However, the present study shows that many respondents held inaccurate views regarding the transmission risks of these viruses. Rather, they were more concerned with the cross-transmission of HIV, as it causes an incurable disease, affects one's quality of life and leaves visible marks that lead to prejudice[11].

The different forms of stigma and discrimination related to AIDS occur due to the disease's characteristics, and cause great impact on people's lives, [14] resulting in self-stigmatization, in which case individuals tend to accept society's negative beliefs about them and isolate themselves from social life. Self-stigmatization is considered the most difficult stigma to overcome[15]. In turn, relatives and those who are closest to patients suffer from what has been called a "co-stigma", receiving the same treatment as infected individuals and being excluded from society[16].

Therefore, patients' families are often not a center of support; but rather a focus of stigmatization, discrimination and exclusion[17]. In our study, many people believed that a family member's HIV infection should be kept a secret, probably due to the exclusion suffered by both the infected person and their relatives and closest friends through the co-stigma. This may have led to fewer people reporting to know someone who is HIV positive.

Table 1 – Comparison between the proportion of individuals who initially said they would agree to being examined after an HIV-positive patient and those who later said they preferred being examined beforehand. Américo de Campos, 2014.

Initial agreement						Later preference					
Yes		No		Total		Irrelevant		Before		Total	
n	%	n	%	n	%	n	%	n	%	n	%
116	77.3	34	22.7	150	100	87	58	63	42	150	100

P=0.0029.

Table 2 – Comparison between the proportion of individuals who initially said they would agree to being examined after an inmate and those who later said they preferred being examined beforehand. Américo de Campos, 2014.

Initial agreement						Later preference					
Yes		No		Total		Irrelevant		Before		Total	
n	%	n	%	n	%	n	%	n	%	n	%
138	92	12	8	150	100	115	76.7	35	23.3	150	100

P<0.0001.

Table 3 – Comparison between economic class and preference for being examined before HIV-positive individuals. Américo de Campos, 2014.

Preference for examinations before HIV-positive patients						
Economic class	Before		Irrelevant		Total	
	n	%	n	%	n	%
A2	8	5.3	7	4.7	15	10
B1	15	10	18	12	33	12
B2	20	13.3	36	24	56	37.3
C1	11	7.3	23	15.3	34	23.6
C2	7	4.7	3	2	10	6.7
D1	2	1.4	0	0	2	1.4
Total	63	42	62	58	150	100

P=0.1036.

Table 4 – Comparison between economic class and preference for being examined before inmates. Américo de Campos, 2014.

Preference for being examined before prisoners						
Economic class	Before		Irrelevant		Total	
	n	%	n	%	n	%
A2	5	3.3	10	6.7	15	10
B1	10	6.7	23	15.3	33	22
B2	11	7.3	45	30	56	37.3
C1	6	4	28	18.6	34	23.6
C2	2	1.4	8	5.3	10	6.7
D1	1	0.7	1	0.7	2	1.4
Total	35	23.4	115	76.6	150	100

P=0.6034.

Many individuals choose not to reveal their true diagnosis, fearing embarrassment and various distressing feelings such as fear, shame, stigma and social isolation[18]. According to a survey conducted in Mozambique, several women who lived with HIV were afraid to disclose their condition, for different reasons, against a strong discriminating environment in which AIDS raises moral objections and is associated with death. These women worked hard in concealing their diagnoses, even among relatives, retreating from social relations as a way to protect themselves and preserve their family members and acquaintances. In their situation, disclosing their condition would mean losing their identity, being seen by society as "discreditable" and doomed to death[17].

In our study, most respondents reported suffering some type of discrimination throughout their lives, due to their color or race, gender, social status, sexual orientation, profession, disease, age or physical appearance. Stigma and discrimination cause low self-esteem, depression, psychiatric disorders, post-traumatic stress disorders, and stress, affecting the individuals' mental health due to insults and social exclusion. Another study, conducted in South Africa and China, showed that people with HIV had feelings that may lead to suicide[14].

Prejudice against homosexuals is still strongly related to AIDS, even though the disease is widely spread among heterosexual individuals nowadays[2], showing that the knowledge about HIV is insufficient. The lack of knowledge regarding contamination and risk transmission of HIV means people's views are grounded on myths, beliefs, emotions and folk discussions distant from scientific knowledge.[19] This is shown in the present study, in which people associate homosexuality with promiscuity and a greater risk of acquiring AIDS.

Aware of this reality, the Ministry of Health makes great efforts to spread information on the disease through the National STD/AIDS Program[8], providing data on its true transmission risks and prevention measures. This information is reaching the population, as demonstrated in a study with adolescents who reported believing that the most common form of HIV transmission is through unprotected sexual intercourse and by sharing needles among injectable drug users[20].

Health professionals, especially dental surgeons, due to fear and ignorance about the disease's transmission mechanisms, are often unwilling to treat HIV-infected patients[1]. Discrimination and prejudice on the part of health professionals toward HIV-positive patients are commonly reported. That is especially the case for dental surgeons, who reportedly refuse treatment by fear of contracting pathogens during procedures[2.11].

Refusals happen less often as dental surgeons' knowledge regarding the risks of occupational infection increases, and among those who are familiar with the protocols of post-exposure to biological materials and thus maintain their equipment adequately sterilized[21]. Confirming this, the present study observed prejudice and discrimination on the part of patients who would not accept being treated by a professional with HIV. This highlights the importance for the general population to have access to adequate information on the matter, so as to minimize or eliminate discriminatory attitudes and practices.

Our research also revealed that part of the respondents would prefer being treated before inmates, due to the stigma revolving around this population. It is estimated that 20% of Brazilian prisoners are infected with HIV, a scenario that results from prison overcrowding, with substandard and insanitary cells – an environment prone to the spread of epidemics and infectious diseases, mainly through homosexual relations, sexual violence, and the use of injectable drugs[22].

Prejudice, sometimes, is not shown explicitly; in a survey that asked adolescents about the forms of discrimination, one of the answers was: "[It's] not that I do anything, I don't go as far as excluding people or mistreating them, but I'm always a bit wary." Remarks like this show that prejudice is not always evident, but is also expressed in more subtle ways[23]. This probably happens due to the fear of punishment, as Brazilian law forbids any form of discrimination[24]. According to Law no. 12,984, discrimination against HIV carriers or AIDS patients is a crime, punishable by up to four years in prison and a fine[25]. In our research, this reason may have initially led respondents to show less prejudice (when asked about how comfortable they were to be examined after HIV patients or inmates) than when asked the question later.

Among different economic classes, there was no statistically significant relation between those who preferred to be treated before inmates or patients suffering from HIV, and those who were indifferent, revealing the existence of a subtle prejudice throughout the whole population, regardless of economic class, probably due to the possibility of legal sanctions.

Further studies should be carried out with larger populations, so as to confirm the existence of different forms of discrimination by public health system towards HIV-positive individuals.

CONCLUSION

The data obtained in this study suggests that the SUS users of the city analyzed (regardless of economic class) show prejudice and discriminatory attitudes toward people with HIV, that often manifest subtly.

Conflict of interests

The authors declare no conflict of interests.

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Analysis of congenital syphilis cases notification in a reference hospital of Niterói, Rio de Janeiro State, from 2008 to 2015

Análise dos casos de notificação de sífilis congênita em um hospital de referência de Niterói, 2008-2015

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ABSTRACT

Introduction: Congenital Syphilis (CS) is a serious public health problem in Brazil, causing death and other perinatal complications, and it is a good indicator of the quality of prenatal care as well. **Objective:** To know the frequency of CS notification registered in Hospital Universitário Antonio Pedro (HUAP, a teaching hospital of Universidade Federal Fluminense in Niterói, State of Rio de Janeiro), and to analyze a number of data of the Compulsory Notification of Infection Diseases (CNID) reports. **Methods:** Temporal retrospective study on the frequency of CS notifications in HUAP (Epidemiology Surveillance Department) during the period 2008–2015. **Results:** Fifty-six CNIDs were received. Data of CS diagnosis, treatment, symptoms and signs, among others, were analyzed. Four reports (4/56/7.14%) were not considered, as no minimum data for analysis were found. Fifty-two reports were analyzed for 8 years. Only 9 CNIDs (9/52/17.37%) were fully completed. The numbers of deliveries/CS/% in HUAP are as follows: 2008 (389/8/2.05%); 2009 (373/6/1.60%); 2010 (442/4/0.90%); 2011 (508/0/0%); 2012 (521/1/0.19%); 2013 (640/9/1.40%); 2014 (522/14/2.68%); 2015 (422/10/2.37%). The mother's age: 6 pregnant women (11.5%) between 14 and 18 years, 25 (48.1%) between 19 and 25 years, 18 (34.6%) between 26 and 40 years, and 3 (5.8%) unknown age. Prenatal care: 10 pregnant women (19.2%) assisted in HUAP, 34 (65.4%), in basic health units of Niterói and other cities in the State, and 8 (15.4%) not assisted. The maternal syphilis diagnosis took place during the prenatal period in 37 (71.0%) cases, during delivery in 12 (23.0%) cases, and in the postnatal period in 3 (6.0%) cases. Only 11 partners (21.1%) were treated. Forty-eight (92.3%) neonates were properly treated. Cases evolution: 46 (88.5%) remained alive, 3 (5.8%) stillborn, 2 (3.8%) evolved to postpartum death, and 1 (1.9%) abortion. **Conclusion:** CNIDs notification and fulfilling are extremely important to understand CS cases, pregnant women control and prenatal evaluation. As far as Congenital Syphilis is concerned, we realize that the service notification in HUAP has enough space to move forward.

Keywords: syphilis; syphilis, congenital; notice; Epidemiological Surveillance; epidemiology.

RESUMO

Introdução: Sífilis congênita (SC) é um grave problema de saúde pública no Brasil, sendo causa de óbito fetal e outras complicações perinatais, além de ser um bom indicador de qualidade do pré-natal. **Objetivo:** Conhecer a frequência de notificação de SC no Hospital Universitário Antonio Pedro da Universidade Federal Fluminense (HUAP), Niterói, Rio de Janeiro, e analisar vários dados das fichas de notificação compulsória (FNC) dessa doença. **Métodos:** Estudo retrospectivo temporal sobre a frequência de notificação de SC no HUAP (Departamento de Vigilância Epidemiológica) no período de 2008–2015. **Resultados:** Recebemos 56 FNC. Analisamos dados de diagnóstico, tratamento, sinais e sintomas de SC, entre outros. Excluímos quatro fichas (4/56/7,14%) por não conterem dados mínimos para análise. Assim, trabalhamos com 52 FNC do período de oito anos. Apenas 9 (9/52/17,37%) FNC estavam totalmente preenchidas. Os números de partos/SC/% no HUAP foram: 2008 (389/8/2,05%); 2009 (373/6/1,60%); 2010 (442/4/0,90%); 2011 (508/0/0%); 2012 (521/1/0,19%); 2013 (640/9/1,40%); 2014 (522/14/2,68%); 2015 (422/10/2,37%). A idade materna: 6 gestantes (11,5%) entre 14 e 18 anos, 25 (48,1%) entre 19 e 25 anos, 18 (34,6%) entre 26 e 40 anos e 3 (5,8%) ignorada. Sobre pré-natal: 10 (19,2%) gestantes realizaram no HUAP, 34 (65,4%) em unidades básicas de saúde de Niterói e de outras cidades do estado e 8 (15,4%) não realizaram. O diagnóstico da sífilis materna ocorreu durante o pré-natal em 37 (71,0%) casos, no parto em 12 (23,0%) e após o parto em 3 (6,0%). Apenas 11 parceiros (21,1%) foram tratados. Quarenta e oito (92,3%) recém-nascidos foram tratados adequadamente. Evolução dos casos: 46 (88,5%) continuaram vivos, 3 (5,8%) foram natimortos, 2 (3,8%) evoluíram para óbito pós-parto e 1 (1,9%) foi aborto. **Conclusão:** A notificação e o preenchimento completo das FNC de SC são de crucial importância para entendimento dos casos e controle da SC junto às gestantes e avaliação do pré-natal. No que diz respeito à sífilis congênita, nós percebemos que o serviço de notificação do HUAP tem bom espaço para avançar.

Palavras-chave: sífilis; sífilis congênita; notificação; Vigilância Epidemiológica; Epidemiologia.

INTRODUCTION

Congenital syphilis (CS) is an important potentially avoidable cause of fetal death and other adverse perinatal consequences. Its incidence is especially higher in the less developed regions of the world[1-3].

It is a sexually transmitted infection caused by the *Treponema pallidum* bacterium, and can be vertically transmitted from mother to fetus during pregnancy[4]. Syphilis is asymptomatic in many women, and screening pregnant women is essential[5].

Since penicillin was introduced for clinical use in 1943, the number of cases was progressively reduced, reaching not worth considering levels. However, a resurgence of the disease was observed during the last years, not only in under developing countries, but also in the developed ones[6]. Pregnant women are more often infected with syphilis than with HIV[7].

The Pan American Health Organization (PAHO) estimates that, every year, approximately 300,000 pregnant women with syphilis in

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Latin America received no treatment for this disease during prenatal period, and two-thirds of cases in pregnant women result from CS[8].

Early diagnosis and accurate syphilis treatment of pregnant women and their partners are simple and effective measures in order to prevent CS[9,10]. However, a series of social, political, economic and individual factors can make difficult for these population to access these measures, which contributes to the incidence of cases in the more vulnerable one[10].

For the purpose of epidemiological surveillance and banishment of CS in Brazil, the disease became a compulsory notification through the federal government Instruction 542 of December 22, 1986[7]. Obligatory notification and investigation include all detected cases, involving stillborn and miscarriage caused by syphilis. However, such notifications are still below the national reality[11].

OBJECTIVE

Analyze the notification reports of CS and quantify the number of cases in *Hospital Universitário Antônio Pedro* (HUAP) of *Universidade Federal Fluminense*, located in the municipality of Niterói, in the state of Rio de Janeiro.

METHODS

This is a temporal retrospective study on the frequency of CS notifications in newborns assisted at HUAP maternity, located in Niterói, Rio de Janeiro, from 2008 to 2015, with about 4,000 deliveries.

A data survey was carried out on 56 filed Compulsory Notification of Infection Diseases of the Notification Information System (*Sistema de Informação de Agravos de Notificação* – SINAN) during the period mentioned.

The following variables were analyzed: gender of the neonate; maternal age; prenatal location; time of syphilis diagnosis in pregnant women; neonate and mother non-treponemal tests results; treatment of the mother, the partner and the neonate; radiological changes in the long bones' tests; signs and symptoms; and place of birth of the newborn.

A database in Epi Info software was developed for the registration and the analysis of the information collected in the Notification reports.

The present study has been approved by the Ethics and Research Committee of the *Universidade Federal Fluminense*.

RESULTS

Four notifications were excluded from the total of 56 (4/56/7,14%) due to the lack of relevant information in the variables analyzed, such as partner treatment, evolution of the case, maternal and neonate non-treponemal test result, long bone X-rays result and presence of signs and symptoms. All reports were available in the Epidemiological Surveillance Department of HUAP, although these files did not contain enough information for the analysis of the problem.

The study considered 52 reports from 2008 to 2015, after the exclusion of 4 Notifications of SINAN.

Only 9 notifications (9/52/17.37%) were completely filled out; the items "education" and "mother's occupation" were not informed in the remaining reports.

A reduction in the number of notifications from 2008 to 2012 (8 cases reduced to 1, 0 reported cases in 2011) was observed, despite coinciding with a period of increase in births' number at the *Hospital Universitário* (389 deliveries in 2008 and 521 in 2012), followed by an increase of notifications from 2013 (9 cases). The largest number of reported cases occurred in 2014 (26.9%: 14); however, there is a gradual reduction in births in the period (640 births in 2013, 522 in 2014, and 422 in 2015) (**Table 1**).

Concerning maternal data: age ranged from 14 to 40 years old, 6 pregnant women (11.5%) were between 14 and 18 years old, 25 (48.1%) were between 19 and 25 years (34.6%), 18 were between 26 and 40 years, and 3 of them had (5.8%) unknown age. With regard to prenatal care, 10 pregnant women (19.2%) were assisted in HUAP, 34 (65.4%) were treated at other health units, and 8 (15.4%) were not assisted. The diagnosis of maternal syphilis occurred during the prenatal period in 37 (71.0%) cases, during childbirth in 12 (23.0%) cases and after delivery in 3 ones (6.0%).

The result of the non-treponemal testing of pregnant women during childbirth was reagent in 46 cases (88.4%), non-reagent in 2 (4.0%) and ignored in 4 (7.6%). As for treatment, 28 pregnant women (53.8%) were correctly treated and 24 (46.2%) were inappropriately treated (**Table 2**).

Regarding the partner treatment, it was observed that 11 of them (21.1%) were treated and 41 (78.9%) of them were not (**Table 3**).

Concerning the data of newborns: it was noted that 26 (50.0%) of them were male and 26 (50.0%) were female, 42 (80.8%) were born in HUAP and 10 (19.2%) in other health units. As for the result of the non-treponemal test, it was reagent in 43 newborns (82.5%), non-reagent in 6 (11.5%), and 3 (6.0%) of them were not tested. Three (5.8%) neonates did not receive treatment (due to miscarriages and stillbirths), 1 (1.9%) unknown information, 48 (92.3%) were treated properly, and 44 (91.7%) of these used crystalline penicillin and 4 (8.3%) penicillin G procaine; penicillin G benzathine was not used in any neonate (**Table 4**). After verifying the presence of signs and symptoms, it was observed that 36 newborns (69.5%) were asymptomatic, 7 (13.4%) manifested icterus and 3 (5.7%) osteochondrosis, 2 (3.8%) of them had skin lesions, 2 (3.8%) had splenomegaly, 1 (1.9%) of them had anemia, and 1 (1.9%) of them had bloody mucus rhinitis. Regarding long bone X-rays, 5 newborns (9.6%) showed changes, 36 (69.0%) did not show alterations, 4 (8.0%) were not submitted to X-rays, and results were unknown for 7 (13.4%) of them (**Table 5**).

Table 1 – Number of deliveries x cases per year (2008 to 2015).

Year	Number of deliveries	Number of cases (%)	Number of cases
	In HUAP*	HUAP	Niterói
2008	389	8 (2.056)	45
2009	373	6 (1.60)	63
2010	442	4 (0.90)	46
2011	508	0 (0.00)	56
2012	521	1 (0.19)	67
2013	640	9 (1.40)	74
2014	522	14 (2.68)	90
2015	422	10 (2.37)	135
Total	3,817	52 (1.40)	576

*HUAP: Hospital Universitário Antônio Pedro.

In relation to the evolution of cases, 46 newborns (88.5%) remained alive, 3 (5.8%) were stillborn, 2 (3.8%) evolved to death, and 1 (1.9%) resulted in abortion due to the disease in question.

DISCUSSION

In Brazil, from 1998 to 2014, 104,853 cases of CS in children under one year of age were notified to SINAN, most of them located in the Southeast and Northeast. There has been a progressive increase in the incidence rate of the disease in the last 10 years: in 2004 the infection rate was of 1.7 case for every 1,000 live births. In 2013, this rate reached 4.7 cases, *i.e.*, an increase in 100% [12].

Table 2 – Epidemiologic analysis of maternal data.

Maternal data	Frequency	
	Relative (%)	Absolute
Age (years)		
14-18	11.5	6
19-25	48.1	25
26-40	34.5	18
Unknown	5.8	3
Prenatal		
Not performed	15.4	8
In HUAP	19.2	10
Other health unit	65.4	34
Time of diagnosis		
Prenatal	71.0	37
Delivery	23.0	12
Postpartum	6.0	3
VDRL at delivery		
Reagent	88.4	46
Non-reagent	4.0	2
Unknown	7.6	4
Treatment		
Appropriate	53.8	28
Inappropriate	46.2	24

HUAP: Hospital Universitário Antônio Pedro; VDRL: Venereal Disease Research Laboratory.

Table 3 – Comparative analysis of data across prenatal locations.

Maternal/ partners data	Prenatal location			
	In HUAP		Other Health Unit	
	Relative (%)	Absolute	Relative (%)	Absolute
Maternal syphilis diagnosis				
Prenatal	100.0	10	79.4	27
Delivery	0.0	0	17.6	6
Postpartum	0.0	0	3	1
Maternal treatment				
Appropriate	40.0	4	58.8	20
Inappropriate	60.0	6	41.2	14
Partner treatment				
Yes	20.0	2	23.5	8
No	80.0	8	76.5	26

HUAP: Hospital Universitário Antônio Pedro.

The present study also observed a growth of the notification cases in the last years, but it could not determine the reason of the reduction of cases notified from 2008 to 2012, which shows rates of 0.00% (2011) and 0.19% (2012). This fact does not match the reality of the city of Niterói, since there were cases of morbidity reductions in the studied years. The numbers concerning HUAP represent 9.0% of the total reported cases for that city.

The increasing number of these notifications does not occur only in Brazil, but all over the world, since syphilis affects 12 million people annually, and 90.0% of these new adult cases occur in

Table 4 – Epidemiologic analysis of neonate data.

Neonate data	Frequency	
	Relative (%)	Absolute
Sex		
Male	50.0	26
Female	50.0	26
Place of birth		
HUAP	88.8	42
Other health unit	19.2	10
VDRL		
Reagent	82.5	43
Non-reagent	11.5	6
Not performed	6.0	3
Treatment		
Not performed	5.8	3
Performed	92.3	48
Unknown	1.9	1
Medication		
Crystalline penicillin	91.7	44
Penicillin G procaine	8.3	4
Penicillin G benzathine	0	0

HUAP: Hospital Universitário Antônio Pedro; VDRL: Venereal Disease Research Laboratory.

Table 5 – Analysis of neonates' signs and symptoms.

Neonates' data	Frequency	
	Relative (%)	Absolute
Asymptomatic	69.5	36
Icterus	13.4	7
Osteochondritis	5.7	3
Splenomegaly	3.8	2
Skin lesions	3.8	2
Anemia	1.9	1
Bloody mucus rhinitis	1.9	1
Long bones X-rays		
Alterations	9.6	5
No alteration	69.0	36
Not performed	8.0	4
Unknown	13.4	7
Evolution		
Alive	88.5	46
Stillborn	5.8	3
Death	3.8	2
Abortion	1.9	1

developing countries. In Brazil, we estimate that the prevalence of syphilis in pregnant women varies between 1.4 and 2.8%, with a vertical transmission rate of 25.0%[13].

Since the consequences of CS are extremely serious, such as miscarriage, stillbirth, premature birth, low weight, blindness, deafness, mental retardation, hydrocephalus, the adequate prenatal care is of vital importance to the early diagnosis of maternal syphilis and its proper treatment[4,11-15].

The present study also observed that, although most mothers have received prenatal care, this treatment was not considered fully effective, since the disease and many of its serious consequences were diagnosed, though not avoided. It should be noted that most of these pregnant women are from the city of Niterói, which has a Human Development Index (HDI) of 0.837 — the highest HDI in the state of Rio de Janeiro —, and a Family Health Strategy (FHS) that ranged from 25.8 to 26.1% of the population involved, in 2008 and 2014, respectively[16,17].

The Centers for Disease Control and Prevention (CDCP) of the United States of America recommends serological screening in early pregnancy. In populations in which the prevalence of syphilis is high or in high-risk patients, screening should be repeated in the third quarter and at the time of delivery.[14,18,19] According to the Ministry of Health of Brazil, screening should be carried out in the first prenatal appointment, preferentially in the first trimester of pregnancy, in the beginning of the third trimester (28 weeks) and at the time of delivery, regardless of previous examinations' results[20,21]. In some populations, syphilis detection at the time of delivery is quite common, especially if the woman was not properly assisted during the prenatal period[14,18,19]. In cases studied in HUAP, 23.0% (12 cases) of diagnosis at the time of delivery were observed, showing the need for an improvement in the monitoring of pregnant women, since 50.0% of them (6 pregnant women) were not assisted during prenatal care in HUAP and 50.0% (6 pregnant women) did not receive prenatal care.

The effectiveness of treatment and the manifestations of CS are dependent on many variables, including maternal syphilis stage, gestational age at time of infection, fetal infection severity (degree of maternal spirocheatemia), adequacy and timing of maternal treatment and fetal immune response[22].

The therapeutic failure is usually associated with the use of inadequate doses of penicillin to the clinical stage, when treatment is done in the later stages of pregnancy, with the disuse of penicillin or when the partner is not treated, and pregnant women is considered inappropriately treated[5,18].

The present study evidences therapeutic failure, since most partners did not receive any treatment (41/52/78.9%) and a relevant amount of pregnant women were inadequately treated (24/52/46.2%), including those held in prenatal HUAP. It is essential that pregnant women with syphilis are orientated regarding the illness and its serious consequences, and the importance of an adequate treatment. It is also of utmost importance the inclusion of the partner's treatment, once that despite the correct treatment of women during pregnancy, they may suffer reinfection and then perpetuate the risk of new cases of CS[15].

The study showed another very serious character affecting a significant portion of the population of the metropolitan region II of Niterói, which covers the cities of Niterói, Itaboraí, Maricá, Rio Bonito, São Gonçalo, Silva Jardim, and Tanguá: the occurrence of a disturbing rate (11.5%) of the worst outcomes caused by the disease — abortion, stillbirths and neonatal death. During this period the occurrence of 40 cases of miscarriage and 29 stillbirths by the disease was observed in Niterói[23]. These cases and their mentioned consequences, reported in HUAP, correspond to 2.5 and 10.3%, respectively, of cases occurred throughout the municipality.

Limitations

This retrospective design of this study is one of its limitations, as it makes difficult the analysis of some of its factors, such as maternal behavioral characteristics, data of some mothers and their partners' treatment, and reasons for non-adherence to treatment. The fact that the reports are often filled out when the mother has already been released from the hospital and her data are sought in her medical record (which does not contain all the information) was an additional limitation, since some forms were not completely filled out.

CONCLUSION

The notification and the completion of the records need to be improved, as only a few forms were completely filled out and some did not contain enough data for a minimal analysis. An adequate completion is fundamental to identify gaps in the monitoring of pregnant women and their partners, aiming to reduce the incidence of the disease.

It is also possible to verify that prenatal of pregnant women in the region assisted by HUAP has to be analyzed, as a considerable number of these women were diagnosed with maternal syphilis during the prenatal period and the Congenital Syphilis (CS) and its consequences were not avoided. Such data is extremely alarming and shows the need for improvements in maternal health care.

It is necessary that all hospital teams become aware of the relevance of this assistance in order to create more accurate mechanisms to control the CS notifications, and carry out specific training for the involved people, such as doctors and nurses. The use of the information derived from the surveillance can benefit and help the actions of health care programs and improve the rate of CS.

Conflict of interests

The authors declare no conflict of interests.

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Zoon Vulvitis as a differential diagnosis of ulcerative lesions on the vulva: case report

Vulvite de Zoon como diagnóstico diferencial de lesões ulceradas em vulva: relato de caso

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ABSTRACT

Vulvar ulcers are a frequent reason for doubt and difficulty of etiological diagnosis. Among the causes of genital ulcers, we can mention sexually transmitted infections such as herpes simplex virus infection, syphilis, chancroid, granuloma inguinale or Donovanosis, and lymphogranuloma venereum, as well as non-infectious etiologies including psoriasis, sexual trauma, Behçet's syndrome, Wegener's granulomatosis, and Zoon Vulvitis. In the present study, a case of a seven months evolution genital ulcer patient (who did not respond to the various proposed therapies) was referred to the Service of Vulvar Pathology of the Hospital Universitário Antônio Pedro (Universidade Federal Fluminense). A biopsy of the lesion was performed, and the histopathological report was compatible with Zoon Vulvitis. The treatment with corticosteroids was initiated. Patient presented a successful evolution. An extensive review of the literature on differential diagnoses of vulvar ulcers was carried out in order to guide a clinical reasoning and a therapeutic approach to the different etiologies.

Keywords: ulcer; vulvitis; sexually transmitted diseases.

RESUMO

Úlceras vulvares constituem um motivo frequente de dúvida e dificuldade no diagnóstico etiológico. Dentre as causas de úlceras genitais estão as infecções sexualmente transmissíveis, como infecção pelo vírus herpes simplex, sífilis, cancro mole, granuloma inguinal ou donovanose, e linfogranuloma venéreo e também as etiologias não infecciosas, que incluem psoríase, trauma sexual, síndrome de *Behçet*, granulomatose de *Wegener*, vulvite de *Zoon*. No presente artigo, é relatado caso de paciente com quadro de úlcera genital com sete meses de evolução, sem resposta às diversas terapêuticas propostas, encaminhada ao Serviço de Patologia Vulvar do Hospital Universitário Antônio Pedro, sendo realizada biópsia da lesão com laudo histopatológico compatível com Vulvite plasmocitária de *Zoon* e iniciado tratamento com corticoide. Paciente apresentou evolução bem-sucedida. Aproveitamos para realizar também uma ampla revisão da literatura sobre diagnósticos diferenciais de úlceras vulvares a fim de orientar o raciocínio clínico e a abordagem terapêutica das diferentes etiologias.

Palavras-chave: úlcera; vulvite; doenças sexualmente transmissíveis.

INTRODUCTION

Vulvar ulcers are a frequent cause of doubt and difficulty of etiological diagnosis. It may be associated with sexually transmitted diseases (STDs), but also with autoimmune diseases (Behçet Disease), cancer, trauma, or be related to the use of pharmaceuticals (hormonal non-steroidal anti-inflammatory drugs), among others[1].

The research into STDs is necessary for patients presenting genital ulcer; however, due to the waiting time to obtain test results, the treatment starts empirically in most cases. Even with adequate laboratory analyses, the pathogen is not identified in 25% of women with genital ulcers[2].

As a rare disease, Zoon Vulvitis is among the differential diagnosis, revealing chronic genital ulcer, probably caused by a reaction of the vulvar mucosa after lesions, trauma or infections in general. The characteristics are similar to infectious and neoplastic diseases, requiring a histopathological analysis to be confirmed[3].

The purposes of the present study are: to accomplish a literature broad revision on vulvar ulcers differential diagnosis in order to guide the clinical opinion and the therapeutic approach of this syndrome in the daily clinical practice, and to describe the case of a chronic vulvar ulcer patient who did not respond to previous proposed treatments, but was successfully diagnosed with Zoon Vulvitis and treated at the Vulvar Pathology Service of Hospital Universitário Antônio Pedro (HUAP).

CASE REPORT

VLMF, 52 years old, menarche at the age of 14, menopause at 49. The patient was sent to the HUAP Service of Vulvar Pathology in May 2013, showing extremely painful ulcers in the vulvar region started in November 2012. Novacort®, Candicort®, Nebacetin®, corticoid, antifungal and antibacterial prepared topics were administered, in addition to benzathine penicillin 2,400,000 IU in a single dose; in success. The examination showed ulcerated lesion of poor delimited borders, flat, clean and erythematosus erosive aspect fundus affecting the inner surface of right labia majore and external surface of labia minora on the same side, from the cranial portion (next to the clitoris) until lower third of the vulva. Whitish areas of membranous aspect were distributed where non-ulcerated lesions were observed (**Figure 1**). Biopsy carried out showed histopathological finding of dense plasmacytic inflammatory infiltrate, compatible with plasmacytic Zoon Vulvitis diagnosis. Prednisone 40 mg/day was prescribed. After 15 days of treatment, the patient reported improvement of symptoms and lesion in healing process.

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DISCUSSION

Sexually transmitted infections should be considered among the causes of genital ulcers, including: infection by herpes simplex virus (HSV), syphilis (*Treponema pallidum*), soft chancre (*Haemophilus ducreyi*), inguinal granuloma or Donovanosis (*Klebsiella granulomatis*), and lymphogranuloma venereum (*Chlamydia trachomatis serotypes* L1, L2 and L3). Non-infectious etiologies include sexual trauma, Lipschütz ulcer, Behçet syndrome, drug source ulcers and ZoonVulvitis[4].

The herpetic lesions may originate from both the HSV-1 and HSV-2, which are most commonly associated with subclinical conditions. Genital herpes begins with pruritus and erythema, followed by the development of vesicular lesions on the external genitalia, and may evolve into ulcerating lesions of clean fundus[5].

Primary syphilis is characterized by a localized cutaneous lesion called chancre. The lesion begins as a papule, which is typically (but not always) painless, appearing at the site of inoculation and evolving into an ulcer with a high and hardened margin, with non-exudative basis and associated with a moderate, often bilateral, regional lymphadenopathy. Soft chancre evolves into spontaneous healing within 3 to 6 weeks, even if not treated[6].

The soft chancre arises as painful ulcerated lesions with dirty fundus with purulent exudate and may progress in suppurative lymphadenopathy by a drainage of a single orifice[7].

The granuloma inguinale or Donovanosis begins with the uprising of a subcutaneous nodulation, generally unilateral and painless, whose erosion produces well defined flat edge or hypertrophic ulceration with a granular basis of bright red appearance and easy bleeding, evolving to vegetative but painless injury, which may be single or multiple. It is not associated with adenitis, and the presence of Donovan corpuscles in the biopsy material confirms the diagnosis[8].

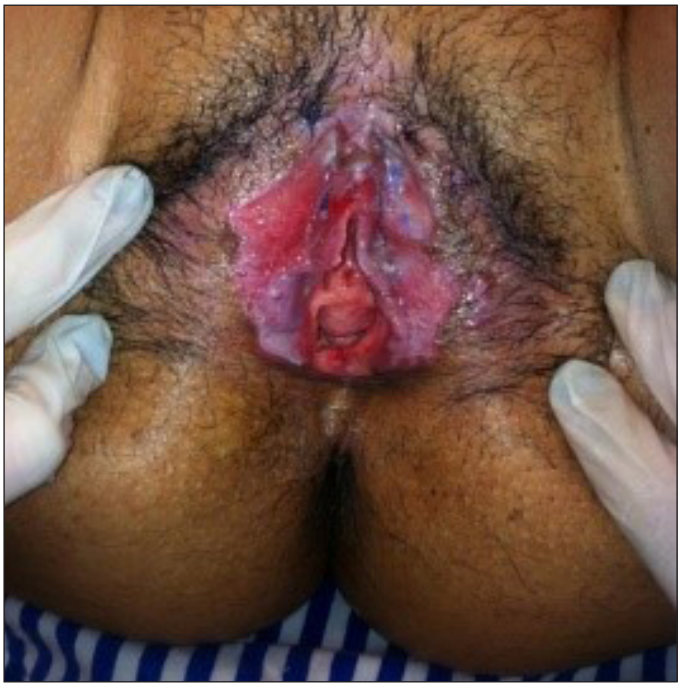

Figure 1 – Patient's genital ulcer at first appointment in Hospital Universitário Antônio Pedro.

The lymphogranuloma venereum is characterized by inoculation lesion, papule, pustule or painless ulcerations, which disappear without sequelae, followed by generally one-sided painful inguinal adenopathy, whith suppuration and fistulization of multiple holes[9].

Lipschütz ulcer, or *ulcus vulvae acutum* — a rare entity, but probably under-diagnosed disease —, is an acute painful vulvar ulcers in young women. Etiology and pathogenesis are unknown although there are reports associating the vulvar acute ulcers with infection by *Mycoplasma*, influenza A, and especially the primary infection by the Epstein-Barr virus (EBV) and *Cytomegalovirus* (CMV). This disease can be preceded with feverish symptoms and is characterized as influenza prodromal symptoms, showing lesions that affect labia majora, perineum and vaginal introitus, well-defined ulcers, and may show discreet gray exudate with adhered peseudomembranous lesions in mirror[10].

Behçet's disease is an autoimmune disease manifested by recurrent oral ulcers and may be associated or not with genital well-defined ulcers. These are usually deeper lesions than the oral ones with necrotic material in their base and an erythematous halo. The lesions in labia minora usually heal without scar evidence, however the most common ulcerations occur in the vagina and may evolve into deep ulcerations, causing tissue destruction and subsequent urethral and vesical fistulas[11].

Drug source ulcers occur 30 minutes to 8 hours, approximately, after administration of drug associated with itching and burning. These lesions tend to disappear in 1-2 weeks, followed by cicatrization with hyperpigmentation, which can persist for months. This drug reaction is mainly associated with the use of non-steroidal anti-inflammatory drugs, although medications like clotrimazole, tetracyclines and ampicillins can also initiate this type of ulcer. Intercourse with partners using these drugs can also cause the reaction[1].

It is also worth mentioning the possibility of acute aphthous ulcers triggered by immune reaction by Epstein Barr virus, Mycoplasma pneumoniae, Varicella infection, viral gastroenteritis and respiratory infections, which develop multiple painful ulcers that last from 1 to 3 weeks[1].

As already mentioned, the differential diagnosis of genital ulcers involves a number of infectious and non-infectious etiologies. Evaluation of patients during the initial approach should always take place in order to verify the presence of STDs, since these infections may be transmitted and increase the risk of contracting HIV.

Faced with the possibility of co-infection by multiple organisms, the determination of the etiology of a genital ulcer based on a classic sign can lead to misdiagnosis and inappropriate treatment.[12] In addition, immunocompromised patients may have atypical clinical symptoms, including more widespread and serious diseases[2].

Once the diagnostic tests results may not be available in the initial medical appointment and the appropriate laboratory analyses does not identify the pathogen in 25% of genital ulcers patients, the empirical treatment of these patients can be performed[2].

The empirical treatment should take into consideration the most likely diagnosis based on the patient's epidemiological and clinical history, as well as on careful physical examination. The disadvantage of an empirical treatment approach is the administration of inadequate therapy, affecting the ability to confirm the diagnosis and causing an impact on the contactants trace. This is a particular

concern when treating supposed syphilis patients. However, this situation is a compensation for the risk of unattendance of an untreated patient for monitoring or infection transmission while waiting for the diagnostic tests results[2].

The Zoom Vulvitis, the subject of our study, was first described in 1954. It is a chronic inflammation of the vulvar mucosa characterized by itching, burning, dysuria and dispaurenia affecting primarily the labia minora, clitoris, vaginal and urethral meatus. The symptoms are usually erythematous, bright, limited and symmetrical plaques affecting the patient's life quality. The lesions tend to chronicity, but the progression to malignancy was not described. The definitive diagnosis is histopathological, showing plasmocytic and vascular changes — vascular hyperplasias and extravasation of red blood cells (**Figure 2 and 3**). There are many proposed therapeutic schemes, but their results are inconsistent, including estrogens, steroids, antibiotics, antifungals, cryotherapy, laser ablation and surgical resection[13].

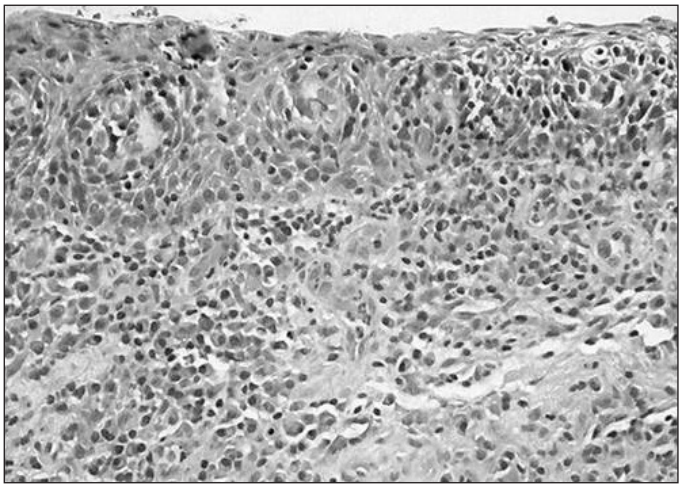

Figure 2 – Presence of spongiosis and oxycytosis with infiltrate composed basically of plasma cells.

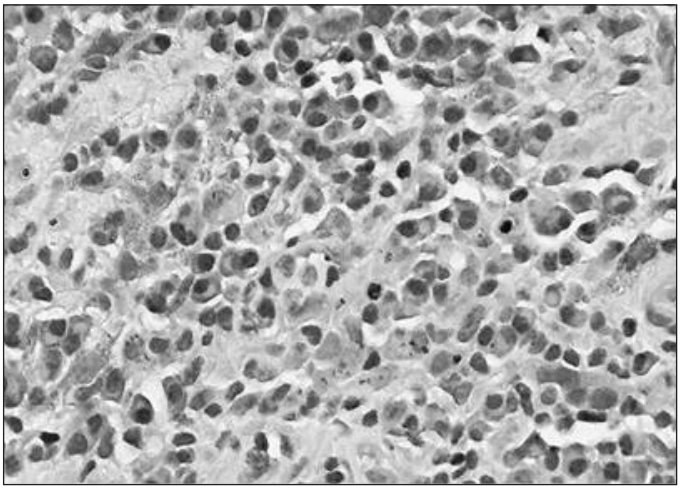

Figure 3 – Plasmocytes, ovoid-shaped cells with nucleus in the periphery.

The conclusion is that it is important to refer those genital ulcer patients who do not respond to the proposed treatment to a service of reference so that the histopathological diagnosis can be confirmed and the monitoring done properly.

Conflict of interests

The authors declare no conflict of interests.

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Chronic genital herpes: case report and literature review

Herpes genital crônico: relato de caso e revisão da literatura

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ABSTRACT
Genital ulcers are clinical manifestations of diverse etiologies, which can make diagnosis difficult. This case report is about a 64-year-old woman with a history of progressive genital ulcer pain for 4 months, despite prior antiviral use. The ulcerated lesion showed perianal involvement. Histopathology revealed neovascularization, edema and inflammatory infiltrate. Despite the use of intravenous acyclovir for 14 days, the improvement was partial. Chronic herpes simplex reveals wart or ulcer of at least one month, usually in immunosuppressed patients. A resistance to antiviral agents is a complication factor, but the treatment response to common infections is usually slower.
Keywords: genital herpes; immunosuppression; antiviral agents.

RESUMO
Úlceras genitais são manifestações clínicas de etiologias diversas, o que pode dificultar o diagnóstico. Este relato de caso trata-se de mulher de 64 anos, com histórico de úlcera genital dolorosa há 4 meses, progressiva apesar do uso prévio de antiviral. Apresentava lesão ulcerada com comprometimento perianal. Histopatológico revelou neovascularização, edema e infiltrado inflamatório. Realizou tratamento com aciclovir endovenoso por 14 dias, com melhora parcial. O herpes simples crônico manifesta-se como verruga ou úlcera de pelo menos um mês, geralmente em imunossuprimidas. A resistência a agentes antivirais é uma complicação encontrada, mas a resposta ao tratamento costuma ser mais lenta do que nas infecções comuns.
Palavras-chave: herpes genital; imunossupressão; antivirais.

INTRODUCTION

Genital ulcers are clinical manifestations of several systemic pathologies and are connected to the inferior genital tract[(1)]. The ulcers can have infectious etiology or not, most of them caused by sexually transmitted infections. The most common infectious etiologic agents are the following: *Treponema pallidum* (primary and secondary syphilis), herpes simplex viruses (HSV-1 and HSV-2 — genital herpes and perioral, respectively), *Haemophilus ducreyi* (chancroid), *Chlamydia trachomatis* serotypes L1, L2 and L3 (*Lymphogranuloma Venereum*), and *Klebsiella granulomatis* (Donovanosis)[(2)]. Sometimes, primary infection with human immunodeficiency virus (HIV) or Cytomegalovirus (CMV) can be associated with genital ulceration, as well as tuberculosis and leishmaniasis[(3)]. The prevalence of the etiological agents have influence of geographical and socioeconomic factors, as well as of gender, number of sexual partners, drug use, among others. These agents can co-exist with the same lesion[(2)].

Non-infectious etiologies include drug reactions, Behçet syndrome, inflammatory intestine disease, bullous dermatosis (pemphigus, contact dermatitis, erythema multiforme), erosive configurations of Lichen *planus* and Lichen *sclerosus et atrophicus*, neoplasia and trauma[(2,3)].

Genital ulcers have clinical aspects quite varied, and symptoms can be preceded (or not) by painful or painless pustules and/or vesicles, burning, itching, drainage of mucopurulent material, bleeding, and lymphadenopathy in the area, indicating low sensitivity and specificity of the etiologic agent, even in cases considered classic. At least 25% of patients with genital ulcer have no laboratory confirmation of the etiological agent[(2)].

Etiological diversity and variety of presentation can delay the diagnosis of genital ulcers, slowing the adequate treatment. The authors report the case of a patient with chronic genital herpes refractory to conventional clinical treatment.

CASE REPORT

LMRS, a 64 year-old woman, divorced, dressmaker, with a history of recurrent genital ulcers for 2 years, referred to the service. Patient reports progressive painful and itchy vulvar lesions for 4 months despite previous use of acyclovir. She denied fever. Chronic lymphocytic leukemia was treated and it is in remission since the last session of chemotherapy, taken one year before this report. No other comorbidities and no use of medication were mentioned. Patient was a smoker until 50 years of age.

Physical examination revealed an extensive ulcerated lesion in the inner side of labia majora, bilaterally, hyperemic, with important perianal damage and intense local pain (**Figure 1**). In the oral cavity, an ulcerated lesion with vesicles on upper lip, compatible with oral herpes (**Figure 2**), was observed. Negative serology for HIV, syphilis and hepatitis B and C. Biopsy under sedation was carried out from the edge of the vulvar lesion due to intense local pain to manipulation. Histopathology reviewed by two pathologists revealed an ulcer with neovascularization, edema and mixed inflammatory infiltrate in the dermis, frequent eosinophilia, which might correspond to chronic herpes, although not discarding pharmacodermia as differential diagnosis.

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Patient was transferred to a joint evaluation of the Dermatology Service of the Walter Cantídio University Hospital, Universidade Federal do Ceará (UFC). Intravenous treatment with acyclovir for a period of 14 days was indicated, associated with prednisone and antibiotics due to secondary infection. After a period of treatment, patient evolved with partial improvement of the lesion (**Figure 3**). Patient was sent home in use of valacyclovir 500 mg twice a day until clinical improvement, returning every 15 days. Reassessment was carried out 30 days after hospitalization, with improvement of the pain and the aspect of injury, but still with residual ulceration (**Figure 4**).

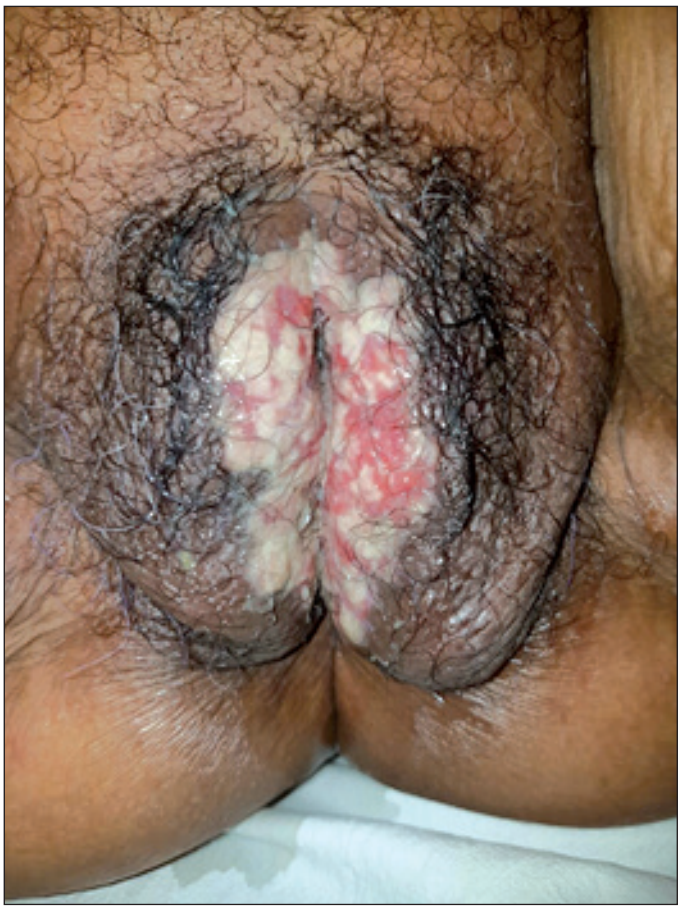

Figure 1 – Genital lesion initial appointment.

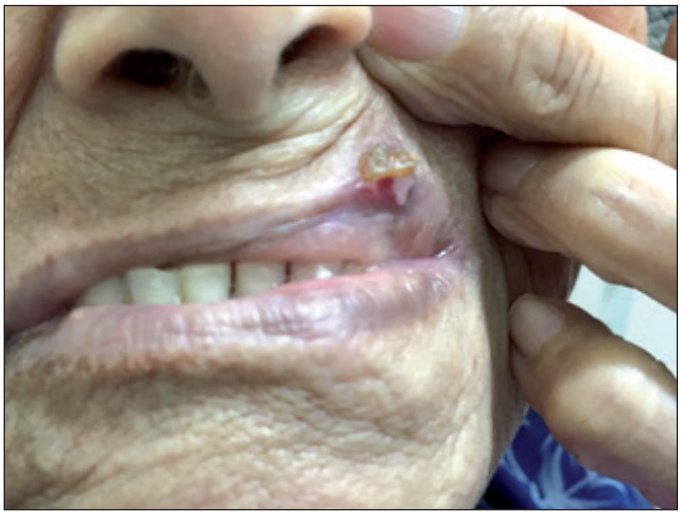

Figure 2 – Oral lesion initial appointment.

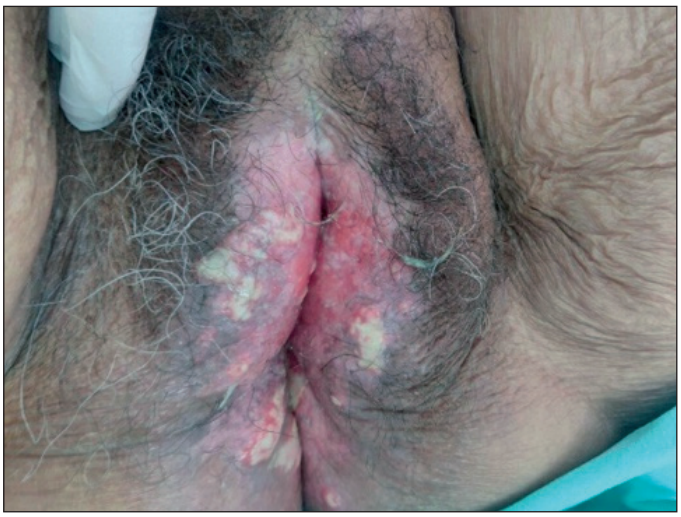

Figure 3 – Genital lesion: 10th day of antiviral treatment.

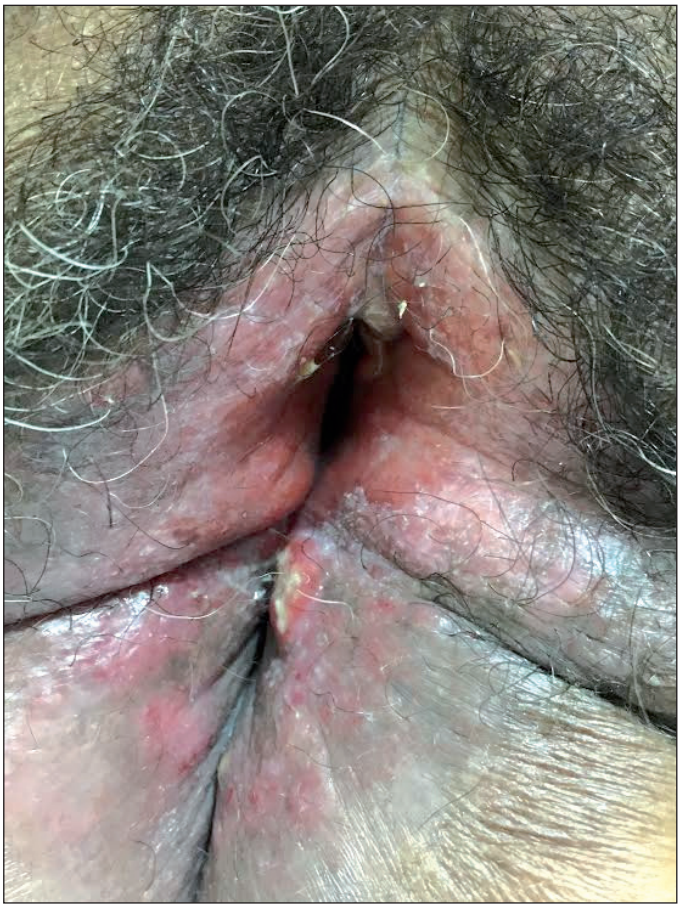

Figure 4 – Genital lesions: 30th day of antiviral treatment.

DISCUSSION

The HSV is considered the most common cause of genital ulcer[4,5]. It is a DNA virus of the *Hespesviridae* family and *Alpha-Herpesvirinae* subfamily, whose types HSV-1 and HSV-2 can cause lesions to any part of the body, with a predominance of type 2 in genital lesions, and type 1 in perioral ones[3].

The chronic herpes simplex is a symptom of HSV-2 infection in immunosuppressed patients, being defined as atypical mucocutaneous wart-like and/or ulcerative infection which can affect large areas of the perianal region and/or the genital region, persisting for a period of at least one month[6-8].

The infection with HIV is an important risk factor for the chronic herpes simplex, as it can also occur in immunocompromised patients due to other conditions, including organs transplant, hypogammaglobulinaemia, chronic lymphocytic leukemia, liver cirrhosis resulting from chronic infection by hepatitis C virus, and myeloprolipherative disorders[8,9].

Its prevalence is unknown, with most cases reported in patients infected with HIV, supposedly as an adverse effect of immunosuppression. Chronic herpes infections are apparently rare in immunocompetent patients[8].

The clinical symptoms are highly polymorphic; however, two features prevail: erosive and/or ulcerative lesions, and vegetative or hyperkeratotic lesions, and both events may occur simultaneously. The ulcerative configuration is usually the most common, characterized as single or multiple ulcerations of varied sizes and extremely painful. The hyperkeratotic configuration is uncommon, showing exhophilic and painful tumors of well-defined limits, simulating squamous cell carcinoma or other viral infections[7,9,10].

The diagnosis is based on the correlation between clinical and histological data obtained from biopsy including ulcerated edge or hyperkeratotic lesion, supported by the HSV lesion presence through immunohistochemical methods or polymerase chain reaction (PCR) and by exclusion of other infectious causes. Histologically, there is a variable hyperplasia of the epidermis with multinucleated epithelial cells and dense mixed inflammatory infiltrate composed of lymphocytes, plasmocytes and eosinophiles[7,9,10].

Infections are treated with antiviral therapy, including acyclovir, famciclovir, penciclovir and vanciclovir; however, the resistance to these agents is a complication observed[7,10]. In immunocompetent patients, acyclovir-resistant HSV is rare, with reported prevalence of 0.3%. In immunocompromised patients, this prevalence varies between 4 and 7%[11-13]. In these resistance cases, other therapeutic options include foscarnet, interferon beta, cidofovir, trifluorothymidine, and vidarabine, although with variable efficacy results[7,9,10].

The response to treatment is slower than common HSV infections, so that the treatment failure due to antiviral resistance at the outset shall not be taken into account. In addition, the susceptibility to antivirals is a dynamic process varying with time, allowing the reintroduction of antiviral drugs that have failed previously[7].

The reported case refers to a patient with chronic oral lesion associated with the anogenital lesion suggestive of herpes, with a history of chronic lymphocytic leukemia treated previously. The histopathology of the lesion showing mixed inflammatory process consistent with the diagnostic hypothesis of chronic herpes, despite being a rare variant, is a possibility that must always be considered in patients with anogenital long-term lesions, especially when associated with immunosuppression symptoms.

Conflict of interests

The authors declare no conflict of interests.

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