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ADVANCED-STAGE HPV- NEGATIVE CERVICAL CANCER IN A YOUNG PATIENT: A CASE REPORT

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Abstract: INTRODUCTION: Cervical cancer is one of the most common cancers in women and has one of the highest incidences in the world. According to data from the National Cancer Institute (INCA), cervical cancer is the 3rd most common type of neoplasm among women, with around 16,710 registrations by 2022 in Brazil and a ratio of 15.38:100,000 women. ¹ Prevention is therefore essential and is carried out through the cytopathology test, which detects cellular alterations that are precursors to cancer. Although the HPV virus has been identified as the main etiological factor behind these changes, between 3 and 8% of cancers are proven to be HPV-negative. **OBJECTIVE:** To report the case of a patient with poorly differentiated squamous cell carcinoma with stage IIIB at diagnosis and a negative HPV test. **METHOD:** The data contained in the study came from the patient's electronic medical records, anamnesis, physical examination and complementary exams carried out between May 15, 2022 and September 7, 2022. **CONCLUSION:** The results obtained in this study contribute to improving care for patients with cervical cancer, contributing to treatment assistance and the construction of prevention strategies. **Keywords:** HPV. Pap smear. Cervical cancer. Neoplastic metastasis. Young adult.

INTRODUCTION

Cervical cancer is one of the most common cancers in women and has one of the highest incidences in the world. According to data from the National Cancer Institute (INCA), cervical cancer is the 3rd most common type of cancer among women, with around 16,710 cases recorded in Brazil so far in 2022, with a ratio of 15.38:100,000 women (INCA, 2022).

As a form of prevention, screening is indicated through the cytopathology test, also known as the Pap smear, which allows the identification of cellular alterations that are

precursors to cancer. According to the recommendations of the World Health Organization (WHO), screening should be carried out from the age of 25 to 64, and after two normal tests, with an interval of one year each, the interval is three years (THULLER et al., 2012).

Although the HPV virus has been identified as the main etiological factor, between 3 and 8% of cancers are proven to be HPV-negative. ³ Therefore, we must highlight other important causes, such as early sex, multiple sexual partners and high parity, factors that increase the chance of developing neoplasia (SCHORGE & Co, 2014).

Since the virus cannot grow in conventional cell culture media, and serological media have low sensitivity, the best research methods for its detection are carried out by evaluating the genome of cervical samples (KOLIOPOULOS et al., 2017). When research is carried out, patients who are identified as HPV-negative are related to a higher incidence of squamous cell carcinoma compared to adenocarcinoma. Women who are classified as HPV negative have a significantly worse prognosis and may even progress to lymphatic invasion when compared to HPV positive patients (KALIFF et al., 2020).

The aim of this paper is to present the case of a 20-year-old woman who came to the Gynecology department of the Santa Casa de Misericórdia Hospital in Vitória complaining of abnormal uterine bleeding, in addition to an ulcerated, friable lesion on the cervix, affecting its entire length. In view of the patient's age, she was tested for HPV, and the result was negative. This paper will discuss how the diagnosis was made and the patient's follow-up and prognosis.

CASE REPORT

A 20-year-old patient, G4 P4 A0, living in the metropolitan region of Espírito Santo, from the interior of Bahia, smoker, menarche at 10 years old, sexarche at 12 years old, 20 sexual partners throughout her life, denied using contraceptive methods and/or condoms, reported never having had an oncotic Pap smear and had a poor social background. She went to the emergency room in her home town due to severe abdominal pain associated with intermittent vaginal bleeding of insidious onset. She reported that she had started complaining after the pregnancy of her youngest daughter, who was 1 year old. During hospitalization, she required blood transfusion due to acute post-hemorrhagic anemia. Physical examination revealed a vegetating lesion on the uterine cervix with a stony consistency, and heavy bleeding to the touch. A contrast-enhanced abdominal CT scan was carried out for complementary propaedeutics, which revealed significant bilateral hydronephrosis, markedly dilated ureters in practically their entire length and a slightly enlarged uterus. During hospitalization, the patient experienced a progressive increase in renal sludge and a decrease in diuresis, compatible with acute kidney injury, left lower limb edema and congestion compatible with deep vein thrombosis. A vena cava filter was also suggested due to the impossibility of anticoagulation, as the patient had active vaginal bleeding. Because of these complications, the patient was transferred to a gynecology referral service in the state of Espírito Santo.

The patient was admitted to the referral service to clarify her clinical condition. On physical examination in the emergency room, she was in good general condition, hypochloric, her abdomen was painful on deep palpation without masses or visceromegaly, and her lower limbs were swollen and edematous up to the knee, with reduced mobility and pain.

On gynecological examination, there were no lesions on the vulva, the speculum was painful, there were no lesions in the vagina, but the cervix had an ulcerated, bleeding, friable lesion affecting its entire length. The laboratory tests requested showed, in addition to significant anemia, hypokalemia. In view of this situation, the patient was transferred to the ICU where she was started on correction of the hypokalemia and anemia.

A new abdominal CT scan was requested and, in addition to the aforementioned alterations, nodules with soft tissue attenuation were found in the greater omentum, which may correspond to secondary implants, and lymph node enlargement predominantly in the para-aortic, iliac, obturator and inguinal chains, reaching around 1.8 cm in the shortest axis. The double-J implant was therefore continued.

Clinical staging revealed stage IIIB, and biopsy with histopathology and immunohistochemistry of the cervix. The results of the histopathology and immunohistochemistry showed poorly differentiated squamous cell carcinoma infiltrating the lamina propria, with positive P16, positive Cell Proliferation Antigen ki67 (81-90%), positive P63 and positive Carcinoembryonic Antigen (CEA). CitoTest was used to test for HPV, with negative results for HPV in two of the samples collected.

After being discharged from the ICU, the patient came to the clinic for her first appointment at the Clinical Oncology outpatient clinic, where MRI of the abdomen and pelvis was urgently requested for imaging staging of the disease. The imaging exam showed 9 capturing nodules larger than 4 cm, as well as a gallbladder with a 1.8 cm nodular lesion and a bladder with 3 lesions larger than 2.5 cm on the right. The uterus was enlarged with nodular lesions and a retrouterine mass measuring 8.4 x 4.0 x 6.0 cm compressing adjacent structures, peritoneal carcinomatosis and multiple bone lesions in the spine, pelvis, sacrum,

iliacus and proximal femur, as well as a small amount of free fluid and deep vein thrombosis causing edema in the left thigh.

In view of the results of the imaging tests, it was decided to start chemotherapy immediately, using the combined regimen of Carboplatin and Paclitaxel. The first chemotherapy session took place on July 18, 2022. However, approximately one week later, the patient presented with significant anemia, with Hemoglobin (Hb) levels of 4.5, which resulted in the need for a blood transfusion. After this last episode, the patient returned to the clinic with symptoms of a productive cough, pain in the right hemithorax and dyspnea. Treatment for an infectious condition was started with the use of Tazocin, after a case of pulmonary thromboembolism (PTE) was ruled out by angiotomography. After showing clinical improvement, the patient was discharged from hospital with instructions to return to the outpatient clinic for the second chemotherapy session.

After the second chemotherapy session, the patient was readmitted 10 days later complaining of abnormal uterine bleeding, requiring hospitalization. She had back pain, reduced performance and a deterioration in her general condition. A blood transfusion was performed, and Transamin and Zoledronic Acid were among the mediations, due to the hypercalcemia resulting from the malignancy.

During hospitalization, due to the progressive deterioration of the patient's clinical condition, palliative care was implemented. This aimed to address psychological distress and provide medication to relieve discomfort. In addition, the possibility of using medications by hypodermoclysis was discussed with the patient, a technique that involves the subcutaneous administration of fluids and medications when it is not possible to do so orally, either due to vascular fragility or the absence of peripheral venous access.

On 09/05/2022, the patient showed a marked worsening of her symptoms, including breathing difficulties, as well as evidence that she was terminally ill and in significant psychological distress. In this context, the social service was called in and, after discussion with the patient and her companion, it was decided to transfer her to a hospital near her home town, where she could receive care in a long-stay bed, with the aim of providing greater comfort at the end of her life. After the transfer, the patient died a few days later.

DISCUSSION

Cervical cancer is the fourth most common malignant neoplasm in women worldwide (LEE et al., 2022). Currently in Brazil, this neoplasm is considered to be the third most common type of cancer in the female population. In 2023, 17,010 new cases are expected, equivalent to 13.25 cases per 100,000 women. Regionally, it is the second most common cancer in the North (20.48/100,000) and Northeast (17.59/100,000); the third in the Midwest (16.66/100,000). In the South, it is fourth (14.55/100,000) and in the Southeast it is fifth (12.93/100,000) (INCA, 2022).

The presence of the HPV virus (human papillomavirus) and its oncogenic subtypes is considered the primary risk factor for the development of this pathology. More than 97% of cervical tumors contain HPV DNA. The most oncogenic types associated with invasive anogenital pathologies are: 16, 18, 31, 35, 39, 45, 51, 52, 56 and 58, which cause the majority of invasive tumors. Early onset of sexual life under the age of 16, a high number of sexual partners, anogenital warts, immunosuppression and smoking are the main factors involved in the history of the disease (INCA, 2022).

However, non-HPV cervical adenocarcinomas can be found in approximately 15 to 38% of cervical tumors. There is no clear definition of HPV-negative cervical cancer; some authors

define it as primary cancer diagnosed through histological characteristics (LETO et al., 2011)

Due to the high prevalence caused by HPV, non-HPV cervical cancer receives less attention, so this subtype is poorly elucidated and understood. Its literature remains obscure due to limitations in its diagnosis, imprecise methods, and it is associated with worse prognosis, clinical characteristics, diagnosed at more advanced stages, resulting in a worse prognosis for the affected population (LEE et al., 2022).

The diagnosis of HPV-negative cervical cancer may be underestimated due to the limitations of current tests for diagnosing this neoplasm. The difficulty in progressing the search for HPV-negative cervical neoplasms is the lack of definition of specific tests. Currently, the difference between HPV and non-HPV cervical neoplasms is made by means of HPV tests (hc2 and PCR). HC2 is a test based on the hybridization of viral nucleic acids. PCR, on the other hand, is highly sensitive because it can detect even low numbers of viral copies in a sample (SANTOS et al., 2016).

HPV-negative tumors are closely associated with adenocarcinomas and can be of the gastric, endometrioid and clear cell histological types. This type of neoplasm arises as a result of a different pathological pathway compared to HPV-positive types. In HPV-negative types, there is a correlation between the prevalence of p53 mutation and an aberrant pattern with overexpression of p16. Because of this, there is a poor prognosis, which is why it has more aggressive characteristics, advanced FIGO stage and is sometimes already metastatic (PETITJEAN et al, 2007). In the present study, the histopathology showed poorly differentiated squamous cell carcinoma infiltrating the lamina propria, with P16 positive, Cell Proliferation Antigen kl67 positive (81-90%), P63 positive and Carcinoembryonic Antigen (CEA) positive, corroborating the literature data of greater aggressiveness and worse prognosis.

There are currently no targeted therapies that are specific to HPV-negative or HPV-positive cancers, so treatment is predetermined by clinical staging and imaging methods. Existing therapies include: surgery, chemotherapy, radiotherapy, immunomodulators and combination therapy (SONG et al., 2019). There are two chemotherapy combination options for the treatment of cervical cancer: Cisplatin + Paclitaxel (PT) or Carboplatin + Paclitaxel (CT). Carboplatin (C) is an agent that interferes with the cell cycle, inhibiting DNA replication and transcription (HIGAMI et al., 2022). In turn, Paclitaxel (T) promotes cell death by inhibiting the stabilization of microtubules and interfering with polymerization dynamics, leading to the arrest of mitosis (HENRIQUE et al., 2013).

The patient in this study was stage IVB, which indicates the presence of distant metastases, according to the FIGO classification. In these advanced cases with an unfavorable prognosis, the recommended first-line therapy is the CT combination, as this regimen is less aggressive in terms of adverse effects compared to the PT regimen. Therefore, the patient can experience fewer side effects, have better symptom control and, where possible, prolong survival. Currently, the Brazilian Society of Clinical Oncology (SBOC) recommends treatment with CT for 6 cycles, associated with immunotherapy using Pembrolizumab or Becacizumab every 3 weeks, if available in the service (SBOC,2024).

Unfortunately, the patient in this study only underwent two cycles of chemotherapy with the CT regimen, and her condition worsened, so palliative treatment focused on symptom relief was instituted until the date of her death.

CONCLUSION

Thus, there is a clear need for further study and elucidation of this pathology due to the limitation of guidelines and protocols regarding an underdiagnosed pathology in order to establish public health strategies for the development of new studies so that the pathophysiology of the disease can be better understood.

In addition, the results obtained in this study contribute to improving care for patients with this pathology, thus contributing to treatment assistance and thereby reducing the morbidity and mortality of a disease that is so prevalent today.

REFERENCES

1. DIRETRIZES DE TRATAMENTO ONCOLÓGICO DA SOCIEDADE BRASILEIRA DE ONCOLOGIA (2024). Capítulo "Colo do útero". Disponível em: <10---Diretrizes-SBOC-2024---Colo-do-útero-v5-FINAL.pdf>
2. HENRIQUE, Á. et al. First-Line Paclitaxel and Carboplatin in Persistent/Recurrent or Advanced Cervical Cancer. *International Journal of Gynecological Cancer*, v. 23, n. 4, p. 743–748, 2 abr. 2013.
3. HIGAMI, S. et al. Acute ST-segment elevations following paclitaxel administration for uterine cervical cancer: a case report and literature review. *Cardio-Oncology*, v. 8, n. 1, 1 dez. 2022.
4. INSTITUTO NACIONAL DE CANCER (INCA), 2022. Disponível em: <<https://www.gov.br/inca/pt-br/assuntos/gestor-e-profissional-de-saude/controlado-cancer-do-colo-do-utero/dados-e-numeros/incidencia>>.
5. KALIFF, M. et al. HPV-negative Tumors in a Swedish Cohort of Cervical Cancer. *International Journal of Gynecological Pathology*, v. 39, n. 3, p. 279–288, maio. 2020.
6. KOLIOPOULOS, G. et al. Cytology versus HPV testing for cervical cancer screening in the general population. *Cochrane Database of Systematic Reviews*, v. 8, n. 8, 10 ago. 2017.
7. LEE, J.-E. et al. Untold story of human cervical cancers: HPV-negative cervical cancer. *BMB Reports*, v. 55, n. 9, p. 429–438, 30 set. 2022.
8. LETO, M. DAS G. P. et al. Human papillomavirus infection: etiopathogenesis, molecular biology and clinical manifestations. *Anais Brasileiros de Dermatologia*, v. 86, n. 2, p. 306–317, 1 abr. 2011.
9. PETITJEAN, A. et al. TP53 mutations in human cancers: functional selection and impact on cancer prognosis and outcomes. *Oncogene*, v. 26, n. 15, p. 2157–2165, abr. 2007.
10. SCHORGE & Col – *Ginecologia de Williams*. Ed. AMGH LTDA, 2ª edição, 2014.
11. SONG, D. et al. A retrospective analysis of cisplatin/carboplatin plus paclitaxel in advanced or recurrent cervical cancer. *Journal of Obstetrics and Gynaecology: The Journal of the Institute of Obstetrics and Gynaecology*, v. 39, n. 3, p. 389–394, 1 abr. 2019
12. THULER, L. C. S.; BERGMANN, A.; CASADO, L. Perfil das Pacientes com Câncer do Colo do Útero no Brasil, 2000-2009: Estudo de Base Secundária. *Revista Brasileira de Cancerologia*, v. 58, n. 3, p. 351–357, 28 set. 2012.