IA1 MICROINVASIVE CERVICAL ADENOCARCINOMA IN A YOUNG WOMAN: CONSERVATIVE PROCEDURE AND REPRODUCTIVE OUTCOME

ADENOCARCINOMA MICROINVASOR IA1 DO COLO DO ÚTERO EM MULHER JOVEM: CONDUTA CONSERVADORA E RESULTADO REPRODUTIVO

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ABSTRACT

Introduction: The expansion of cytological screening programs for cervical cancer leads to an increase in the proportion of both adenocarcinomas and diagnoses in young women with reproductive intention. Conservative treatment is not fully established. **Objective:** to report the conservative management and follow-up difficulties of a real case of microinvasive cervical adenocarcinoma in a young woman. **Case report:** This is a case report of a 23-year-old patient with stage IA1 microinvasive cervical adenocarcinoma related to HPV18. The patient was vaccinated against HPV 16/18 at 16 years of age and conservatively treated. She became pregnant during follow-up with a favorable outcome. **Conclusion:** We discuss the difficulties and uncertainties regarding follow-up and opportunity for hysterectomy, emphasizing the need for a multidisciplinary approach to make a balanced decision between conservative treatment and oncological safety, as well as mitigate follow-up difficulties in real life.

Keywords: adenocarcinoma; uterine cervical neoplasm; conization; conservative treatment; pregnancy outcome; treatment outcome.

RESUMO

Introdução: A ampliação dos programas de rastreamento citológico de câncer do colo uterino resulta em aumento na proporção de adenocarcinomas e de diagnósticos em jovens ainda com desejo reprodutivo. O tratamento conservador não está totalmente estabelecido. **Objetivo:** descrever a condução conservadora e as dificuldades de seguimento em caso real de adenocarcinoma microinvasor do colo em uma jovem. **Relato de caso:** É relatado o caso de uma paciente de 23 anos com adenocarcinoma microinvasor IA1 do colo uterino relacionado ao HPV 18, mesmo vacinada contra HPV 16/18 aos 16 anos. Foi tratada conservadoramente, com gestação e desfecho favorável. **Conclusão:** São discutidas as dificuldades e incertezas em relação ao seguimento e à oportunidade para histerectomia, ressaltando a necessidade de abordagem multidisciplinar para decisões equilibradas entre tratamento conservador, segurança oncológica e, ainda, amenizar as dificuldades de seguimento na vida real.

Palavras-chave: adenocarcinoma; câncer do colo do útero; conização; tratamento conservador; resultado da gravidez; resultado do tratamento.

INTRODUCTION

Cervical cancer results from an infection caused by Human Papillomavirus (HPV), usually sexually acquired[1]. The most prevalent viral types of this cancer are HPV-16 (55%) and HPV-18 (15%)[2,3].

The currently recommended strategy to control this neoplasm is the regular screening test in women over 25 years of age associated with HPV vaccination before beginning sexual activity[4]. The coverage expansion of screening programs has resulted in the anticipation of diagnoses, with more cases of cancer in reproductive-age women. In addition, cytological screening has a lower impact on adenocarcinoma diagnosis[5-7].

Diagnosis in young women is a particular situation that needs to find a balance between reproductive maintenance and oncological safety. The literature still debates conservative treatments.

The present report is an update on the case of a young woman, previously vaccinated against HPV at 16 years of age, who developed a microinvasive cervical adenocarcinoma treated conservatively. Follow-up difficulties before and after the reproductive outcome stood out.

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CASE INTRODUCTION

The preceding history was previously published as a case report[8] and briefly describes this 16-year-old patient participation (2005) in a multicenter, international, randomized, and double-blind phase III study that assessed the effectiveness of the HPV-16/18 vaccine (GlaxoSmithKline Biologicals) compared to the Hepatitis A vaccine as a control, regardless of cytological status and HPV-DNA test in the initial cervicovaginal sample and serological status for HPV.

The clinical trial "PATRICIA" provides details on the methodology of this study[9]. In 2012, the breaking of the blinding revealed that this patient had received three doses of the HPV vaccine in 2005 when she already had a positive HPV-DNA test for HPV-18 and negative cytology. This same pattern of exams was maintained (positive DNA-HPV-18, negative HPV-16 and other 23 types, negative cytology, and colposcopy without suspicious images) up to the end of the study in 2010. In the 2005–2010 period, the patient underwent five annual tests for *Chlamydia trachomatis* and two tests for *Neisseria gonorrhoeae* (HC2 CT/GC DNA Test, Hybrid Capture®2, Digene, Gaithersburg, USA), all negative. The patient remained with a single partner until 2012 and used oral hormonal contraceptive. After 2010, she continued with an annual follow-up, and, in 2012, at the age of 23 and with a positive HR-HPV test (HC2 High-Risk HPV DNA Test, Hybrid Capture®2, Digene, Gaithersburg, USA), she showed ASC-H cytology (atypical squamous cells of

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undetermined significance which could not exclude high degree)[6]. The colposcopy carried out at the time was adequate, with a type 1 transformation zone and a thin acetowhite area in the endocervical mucosa, whose biopsy revealed an "adenocarcinoma in situ" (AIS).

Afterward, an Excision of the Transformation Zone (ETZ) was performed, and the definitive diagnosis was IA1 microinvasive adenocarcinoma (FIGO, 2014)[10], presenting microinvasion of less than 1 mL depth, endocervical margin, and channel reinforcement free of neoplasia. The immunohistochemical study identified the presence of HPV-18 DNA. The patient underwent a conservative procedure with periodic follow-up to preserve fertility.

About three months after ETZ, she had a planned pregnancy. A cerclage was conducted at 16 weeks, indicated by her obstetric history of isthmus cervical incompetence in a previous pregnancy, at the age of 15, which required cerclage and resulted in premature vaginal delivery (1,700 g live-born).

Regular prenatal care continued and progressed with premature rupture of membranes at 33 weeks and 5 days. The cerclage point was removed, followed by the vaginal delivery of a preterm newborn, with 2,010 g, 41 cm, and Apgar 8/9. **Figure 1** describes the oncological follow-up during pregnancy and after delivery.

During pregnancy, an HPV test (PapilloCheck®, Greiner Bio-One, Frickenhausen, Germany) detected the viral types HPV-52 (high-risk),-42, -43, and -44 (low-risk). Six months after delivery (14 months after ETZ), the patient underwent the latest HPV test in the case, with a negative result for HPV-16 and -18, and positive for the group of 12 other HR-HPV (HPV test Cobas®, Roche Molecular Diagnostics, Pleasanton, USA).

At that time, the cancer cytology test and colposcopy showed no changes. Follow-up continued, and after an additional 12 months, the patient presented AGC-FN cytology (atypical glandular cell; favor neoplasia)[6]. The patient was reviewed with colposcopy – which revealed suspicious endocervical images (**Figure 2**) – and biopsy, and a cytology review was requested. The biopsy was negative, and the diagnosis of the cytology review was AGC-NOS (not otherwise specified)[6].

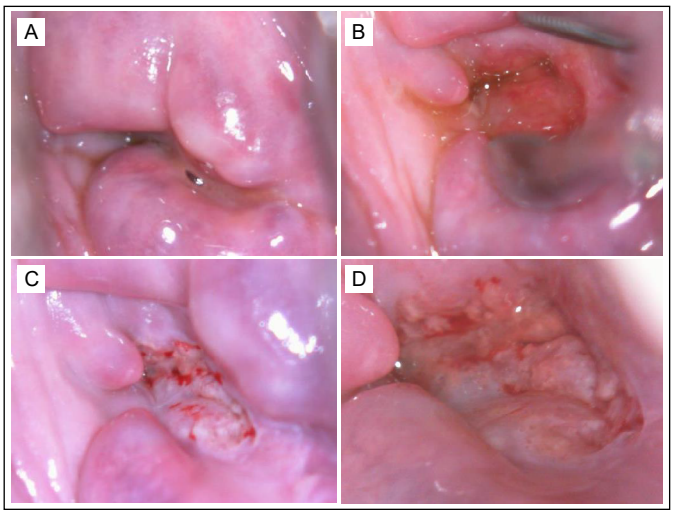

Figure 2 – Irregular cervix observed after two cerclages and prior loop conization (A). Columnar squamous junction located at the level of the external orifice (type 1 transformation zone) (B), presenting several discrete yellowish focal areas in the endocervical mucosa, with discrete relief and becoming acetowhite (C, D). Impression of suspected high-grade abnormalities (colposcopic images obtained in Full-HD through the ICONOS® video colposcopy prototype).

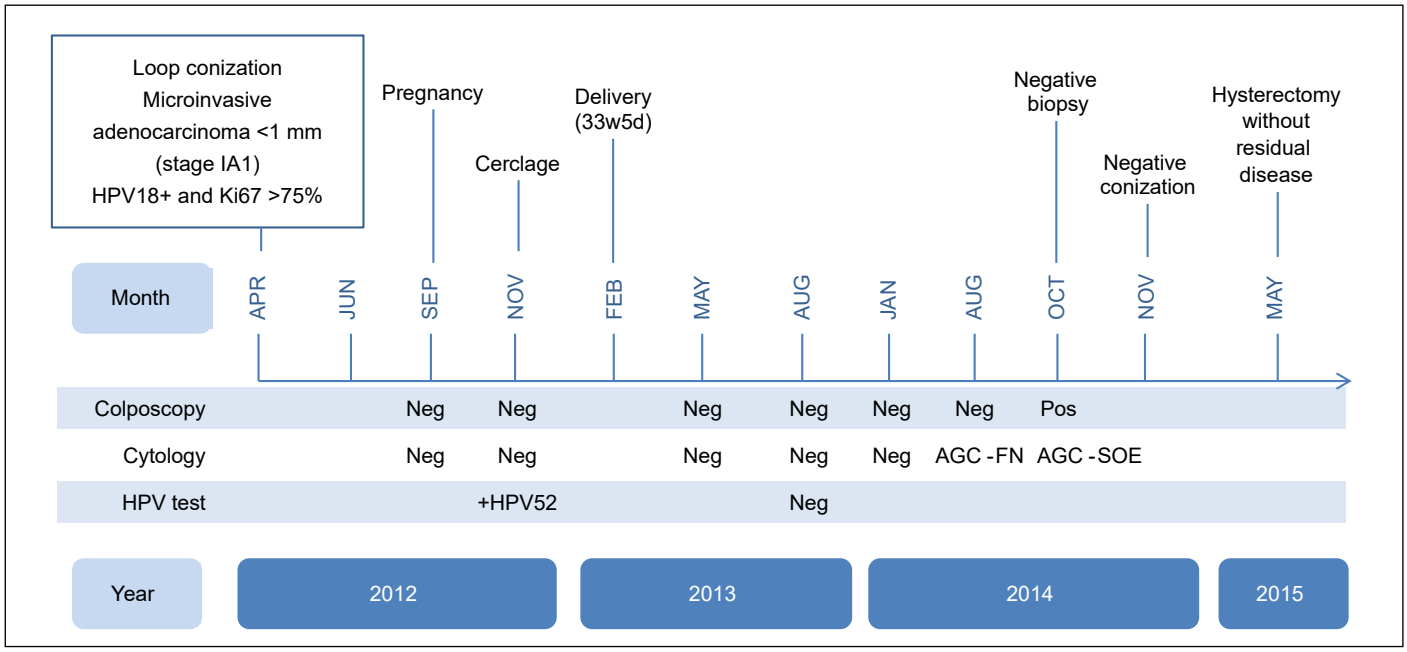

Figure 1 – Chronology of events and test results since the initial treatment in 2012.

Cervical conization with cavity and remaining channel curettage was performed – with negative histopathological results – to obtain a more accurate diagnosis of the situation at that moment and due to the case progress characteristics and the pattern of glandular lesions of the cervix. In a multidisciplinary meeting with the patient, and at her request, a hysterectomy was chosen. The surgery (total hysterectomy and bilateral salpingectomy) had no complications, and the anatomopathological result did not show residual disease. The follow-up continued until 2018 without further changes. The patient authorized the publication.

DISCUSSION

The follow-up after conservative treatment for microinvasive cervical adenocarcinoma can cause insecurity, anxiety, and disagreement among assistant team members since few similar cases are described and there is no consensus in the literature.

The issues found in the procedures for glandular lesions of the cervix are related to their characteristics and may be multifocal, endocervical, and less accessible to colposcopy, added by difficulty in defining glandular atypia in the cytological test, which presents low agreement between cytopathologists[11,12].

In carcinoma follow-up, biomolecular tests related to HPV do not have a defined value as screening has. The present case identified the persistent presence of HPV-18 DNA throughout screenings from 2005 to 2012, which disappeared after microinvasive treatment. There was only a transitory detection of other types of HPV during pregnancy, mostly of low risk, which subsequently disappeared, a situation considered common during pregnancy.

The detection of cervical adenocarcinoma is generally late, occurring in advanced stages and with worse prognosis compared to squamous cell carcinomas[5]. The tendency, when faced with a diagnosis of glandular lesion of the cervix, is to adopt a more aggressive treatment[13]. These difficulties related to the initial diagnosis can increase in case of follow-up after treatment.

The case reported had no fully defined and specific guideline for microinvasive adenocarcinoma treatment[14,15], and the cytology and colposcopic follow-up difficulties inherent in glandular lesions persisted. In addition, as this case involved a patient with an obstetric history of prematurity, her obstetric future could point to a less conservative procedure.

Hysterectomy is the most accepted and indicated procedure for cases of IA1 microinvasive adenocarcinoma[14]. In general, hysterectomy should be reconsidered when there is the option for a conservative procedure, after a reproductive success. During follow-up of the present case, a second excision procedure was indicated and carried out despite the biopsy being negative, due to the AGC-FN cytology and suspicious colposcopy, and the cytology review changed the diagnosis to AGC-NOS (not otherwise specified).

These inconstancies and disagreements are inherent in the current knowledge, with subjective criteria, less agreement about the definition of glandular atypias, and difficulty in obtaining a colposcopic image related to AIS or microinvasive adenocarcinoma[11-16]. The possibility of multifocal or hidden lesions in the channel has strengthened the choice of adopting hysterectomy for this case.

The indication of hysterectomy aiming at a "definitive treatment" was influenced by the patient's request; the possibility of a false negative in the second excision procedure; potential difficulties in continuing with follow-up due to the two ETZs and two previous cerclages; the immunohistochemical study of the initial neoplasia, which revealed high Ki67 expression related to a high rate of cell proliferation; and the exceptionality of the case, since the patient was not in the age group screened, had control frequency above the usual (clinical research protocol), and developed a neoplasia despite previous vaccination against HPV.

The reported case highlights the need to find a balance between oncological safety and reproductive maintenance. Conservative approaches to microinvasive cervical cancer are currently indicated, and the literature shows a tendency for such conduction regardless of the histological type of microinvasion, whether squamous or glandular, as there is no consistent information about a greater risk of recurrence after a conservative procedure in microinvasive adenocarcinoma[14-17].

Conservative management with cervical conization, provided that the resection margins are free and there are no signs of lymphovascular space invasion, can be considered oncologically safe[14,15], evidently aiming at some gestational success[18,19] as the case presented.

There are several studies about reproductive maintenance after cervical excision procedures, and among the most recent, the meta-analysis by Kyrgiou et al., and Papoutsis et al. indicate no changes in fertility after conization but a possible greater risk of preterm birth, as happened in the present case[18,20]. The cerclage performed in the studied patient probably contributed to the favorable outcome and was already indicated due to the previous diagnosis of isthmus cervical incompetence, which could have been aggravated by the loop conization done before the second pregnancy. It is noteworthy that despite the higher obstetric risk in patients with previous excision procedures, cerclage is not indicated routinely. In this case, the only suggestion is a more intensive follow-up with a serial evaluation of the cervix through physical and ultrasonographic examination during prenatal care[18,20].

Finally, the present case emphasizes the need to update diagnostic and therapeutic procedure teams frequently due to constant difficulties and changes concerning adenocarcinoma in young women. Particular cases, such as the one presented, should be discussed in multidisciplinary meetings to define strategies to reduce follow-up uncertainties and the anxiety associated with conservative treatment, thus avoiding approaches that may be considered excessive nowadays.

Participation of each author

Each author has participated actively and sufficiently in this work, and all had final approval of the manuscript version being submitted.

The patient authorized the publication.

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Conflict of interests

There is no conflict of interests to report.

REFERENCES

1. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999;189(1):12-9. https://doi.org/10.1002/(SICI)1096-9896(199909)189:1%3C12::AID-PATH431%3E3.0.CO;2-F
2. de Sanjosé S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 2010;11(11):1048-56. https://doi.org/10.1016/S1470-2045(10)70230-8
3. Castellsagué X, Díaz M, de Sanjosé S, Muñoz N, Herrero R, Franceschi S, et al. Worldwide human papillomavirus etiology of cervical adenocarcinoma and its cofactors: implications for screening and prevention. J Natl Cancer Inst. 2006;98(5):303-15. https://doi.org/10.1093/jnci/djj067
4. Instituto Nacional de Câncer José Alencar Gomes da Silva. Coordenação de Prevenção e Vigilância. Divisão de Detecção Precoce e Apoio à Organização de Rede. 2ª ed. rev. atual. Rio de Janeiro: INCA; 2016.
5. Galic V, Herzog TJ, Lewin SN, Neugut AI, Burke WM, Lu YS, et al. Prognostic significance of adenocarcinoma histology in women with cervical cancer. Gynecol Oncol. 2012;125(2):287-91. https://doi.org/10.1016/j.ygyno.2012.01.012
6. Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA. 2002;287(6):2114-9.
7. Teixeira JC, Maestri CA, Machado HC, Zeferino LC, Carvalho NS. Cervical Cancer Registered in Two Developed Regions from Brazil: Upper Limit of Reachable Results from Opportunistic Screening. Rev Bras Ginecol Obstet. 2018;40(6):347-53. http://dx.doi.org/10.1055/s-0038-1660841
8. Teixeira JC, Derchain SF, Zambelli Oliveira ER, Campos Teixeira CS, Andrade LA, Bacchi CE, et al. Microinvasive adenocarcinoma of the cervix in a young woman vaccinated against human papillomavirus: the screening must be continued. J Low Genit Tract Dis. 2014;18(2):E50-4. https://doi.org/10.1097/LGT.0b013e31829ee5df
9. Lehtinen M, Paavonen J, Wheeler CM, Jaisamrarn U, Garland SM, Castellsagué X, et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol. 2012;13(1):89-99. 10.1016/S1470-2045(11)70286-8
10. FIGO Committee on Gynecologic Oncology. FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. Int J Gynaecol Obstet. 2014;125(2):97-8. https://doi.org/10.1016/j.ijgo.2014.02.003
11. Santos AL, Derchain SF, Calvert EB, Martins MR, Dufloth RM, Martinez EZ. Performance of cervical cytology with review by different observers and hybrid capture II in the diagnosis of cervical intraepithelial neoplasia grades 2 and 3. Cad Saude Publica. 2003;19(4):1029-37. http://dx.doi.org/10.1590/S0102-311X2003000400025
12. Dalla Nora LC, Azara CZ, Pace EL, Martins CM, Zeferino LC, Westin MC, et al. Cytomorphological criteria, subclassifications of endocervical glandular cell abnormalities, and histopathological outcome: a frequency study. Diagn Cytopathol. 2010;38(11):806-10. https://doi.org/10.1002/dc.21295
13. Katanyoo K, Sanguanrungsirikul S, Manusirivithaya S. Comparison of treatment outcomes between squamous cell carcinoma and adenocarcinoma in locally advanced cervical cancer. Gynecol Oncol. 2012;125(2):292-6. https://doi.org/10.1016/j.ygyno.2012.01.034
14. Bisseling KC, Bekkers RL, Rome RM, Quinn MA. Treatment of microinvasive adenocarcinoma of the uterine cervix: a retrospective study and review of the literature. Gynecol Oncol. 2007;107(3):424-30. https://doi.org/10.1016/j.ygyno.2007.07.062
15. Baalbergen A, Smedts F, Helmerhorst TJ. Conservative therapy in microinvasive adenocarcinoma of the uterine cervix is justified: an analysis of 59 cases and a review of the literature. Int J Gynecol Cancer. 2011;21(9):1640-5. https://doi.org/10.1097/IGC.0b013e3182262059
16. Wright VC. Colposcopy of adenocarcinoma in situ and adenocarcinoma of the uterine cervix: differentiation from other cervical lesions. J Low Genit Tract Dis. 1999;3(2):83-97.
17. Baalbergen A1, Helmerhorst TJ. Adenocarcinoma in situ of the uterine cervix-a systematic review. Int J Gynecol Cancer. 2014;24(9):1543-8. https://doi.org/10.1097/IGC.0000000000000260
18. Kyrgiou M, Mitra A, Arbyn M, Paraskevaidi M, Athanasiou A, Martin-Hirsch PP, et al. Fertility and early pregnancy outcomes after conservative treatment for cervical intraepithelial neoplasia. Cochrane Database Syst Rev 2015;(9):CD008478. https://doi.org/10.1002/14651858.CD008478.pub2
19. Bai H, Liu J, Wang Q, Feng Y, Lou T, Wang S, et al. Oncological and reproductive outcomes of adenocarcinoma in situ of the cervix managed with the loop electrosurgical excision procedure. BMC Cancer. 2018;18:461. https://doi.org/10.1186/s12885-018-4386-6
20. Papoutsis D, Underwood M, Parry-Smith W, Panikkar J. Early and late pregnancy outcomes in women treated with cold-coagulation versus LLETZ cervical treatment for cervical intraepithelial neoplasia; a retrospective cohort study. Arch Gynecol Obstet. 2018;297(4):1015-25. https://doi.org/10.1007/s00404-018-4704-x

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