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Cytopathologic follow-up of women with cervical cancer post-radiotherapy: case series

Citopatologia de seguimento em mulheres com câncer de colo do útero após radioterapia: série de casos

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ABSTRACT

Cytopathology, in addition to its role in cervical cancer screening programs, is also an important tool for controlling the efficacy of treatment in women with cervical cancer by monitoring and early detecting residual, recurrent neoplasms or benign reactive changes. In this study, we report eight cases of cytopathologic follow-up of women with cervical cancer post-radiotherapy, assisted by a Center of Oncology in Pernambuco. The main cytological findings post-treatment were described, as well as the histopathological characteristics at diagnosis and the treatments performed.

Key words: radiotherapy; neoplasms of the cervix; radiation effects.

INTRODUCTION

Cervical cancer is the third most frequent neoplasm in the female population and 16,340 new cases was estimated for the biennium 2016-2017, with risk of 15.85 for every 100,000 women[1].

The most common treatments for cervical cancer are radiotherapy combined with chemotherapy and hysterectomy[2]. The control of treatment efficacy should be performed by cytopathological examination, which presents sensitivity ranging from 28%-51%, monitoring and early detecting possible residual or recurrent neoplasms, which allows immediate clinical and/or surgical intervention[3, 4].

Radiotherapy is capable of promoting morphological changes, not only in neoplastic epithelial cells, but also in normal squamous and glandular epithelial cells, making it difficult to diagnose residual lesions, since they need to be well differentiated from reactive changes, avoiding the release of false positive or false negative results[4, 5].

Considering the importance of the cytopathological analysis of the cervix post-treatment and the difficulties of this investigation for the pathological follow-up, this paper aims to report a series of eight cases of cytopathologic evaluations following radiotherapy for cervical cancer treatment.

MATERIAL AND METHOD

This is a case-series descriptive study, carried out after approval by the Human Research Ethics Committee of the Centro Universitário Tabosa de Almeida (Asces-Unita), under no. 2.008.129.

Data were collected and cytopathologic follow-up analysis was performed by conventional cytology in women with cervical cancer after the radiotherapy, assisted by an oncology center in Pernambuco between June and October, 2017, after the signing of the Free and Informed Consent Form (FICF).

The sample was defined for convenience, including all the women assisted in the proposed period, in any age group, with diagnosis of cervical cancer confirmed by histopathology and who underwent radiotherapy. Data were also collected from the medical records of women who underwent cytopathologic follow-up in the proposed period, among which, the age group, histopathological result at diagnosis and treatment data were highlighted.

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CASE REPORTS AND RESULTS

Case 1

A. M. B. S., 65 years old, smoker, multiparous, with histopathological examination evidencing undifferentiated squamous cell carcinoma. Subjected to three cycles of chemotherapy with cisplatin and 5-fluorouracil, total hysterectomy and 28 cycles of teletherapy. The cytopathologic follow-up examination was negative for intraepithelial lesion and malignancy (NILM), showing smear with predominance of intermediate squamous epithelial cells, with mild reactive changes (pseudoeosinophilia and polychromasia) and maintenance of the lactobacillus microbiota (**Table**).

Case 2

M. B. L., 36 years old, multiparous, histopathology of squamous cell carcinoma. She performed 26 teletherapy cycles of teletherapy, four high dose rate (HDR) brachytherapy and five cisplatin cycles. The cytopathological analysis revealed NILM result, presence of superficial and intermediate squamous epithelial cells with marked reactive changes associated with radiation (polychromasia, cytoplasmic vacuolization, cellular gigantism, nuclear degeneration, nuclear pallor and anisokaryosis), metaplastic cells at various stages of maturation and coccoid microbiota (Table; **Figure 1**).

Case 3

M. M. C., 37 years old, multiparous, histopathological examination with undifferentiated squamous cell carcinoma result. She was subjected to 28 cycles of teletherapy, four of HDR brachytherapy and three of cisplatin. Cytopathologic follow-up revealed atrophy associated with inflammation, NILM, predominance of parabasal squamous epithelial cells with moderate inflammatory alterations (pseudoeosinophilia, polychromasia and nuclear pyknosis) and undetermined microbiology (Table).

TABLE – Histopathological characteristics, treatments and results of cytopathologic follow-up of women with cervical cancer after radiotherapy and/or chemotherapy

	Age	Histopathology	Start of treatment	Chemotherapy	Teletherapy	HDR Brachytherapy	Surgery	Cytopathologic follow-up (conventional technique)	Material cytopathology	Result cytopathology
Case 1	65 years	Undifferentiated squamous cell carcinoma (Nov/2006)	July/2007	Three cycles of cisplatin and 5-fluorouracil (Jul-Aug/2007)	50.4 Gy in 28 fractions (Nov-Dec/2007)	-	Total hysterectomy (Oct/2007)	June/2017	Vaginal vault	NILM Lactobacillus
Case 2	36 years	Squamous cell carcinoma (Nov/2016)	November/2016	Five cycles of cisplatin (Jan/2017)	26 fractions (Nov/2016-Jan/2017)	Four fractions of 700 cGy (Jan/2017)	-	July/2017	Ectocervix/ endocervix	Radiation-associated BRCC NILM
Case 3	37 years	Undifferentiated squamous cell carcinoma (Dec/2015)	December/2015	Three cycles of cisplatin (Jan/2016)	50.4 Gy in 28 fractions (Dec/2015-Feb/2016)	Four fractions of 700 cGy (Mar-Apr/2016)	-	July/2017	Ectocervix/ endocervix	Atrophy with inflammation NILM
Case 4	56 years	Moderately differentiated squamous cell carcinoma (Oct/2015)	November/2015	24 cycles of cisplatin, paclitaxel and carboplatin (Nov/2015-Jun/2016)	45 Gy em 25 fractions (Jan-Feb/2016)	-	Total hysterectomy (Apr/2015)	July/2017	Vaginal	Squamous carcinoma
Case 5	41 years	Squamous cell carcinoma (Aug/2015)	December/2015	Six cycles of cisplatin and paclitaxel (Dec/2015-Feb/2016)	50.4 Gy in 28 fractions (Jan-Feb/2016)	Four fractions of 700 cGy (Mar-Apr/2016)	-	August/2017	Ectocervix/ endocervix	Radiation-associated BRCC NILM
Case 6	66 years	Moderately differentiated squamous cell carcinoma (Aug/2015)	November/2015	-	50.5 Gy in 28 fractions (Nov-Dec/2015)	-	Total hysterectomy (Aug/2015)	September/2017	Vaginal vault	NILM Inflammatory cytology *Gardnerella vaginalis*
Case 7	47 years	Well differentiated squamous cell carcinoma (Sept/2014)	November/2014	Six cycles of cisplatin (Nov-Dec/2014)	50.4 Gy in 28 fractions (Nov-Dec/2014)	Four fractions of 700 cGy (Jan-Feb/2015)	-	September/2017	Ectocervix/ endocervix	Atrophy with inflammation NILM
Case 8	27 years	Undifferentiated squamous cell carcinoma (Dec/2016)	January/2017	Three cycles of cisplatin (Jan/2017)	50.4 Gy in 28 fractions (Jan-Mar/2017)	Four fractions of 700 cGy (Mar/2017)	-	October/2017	Ectocervix/ endocervix	Radiation-associated BRCC NILM

NILM: *negative for intraepithelial lesion and malignancy;* BRCC: *benign reactive cellular changes; HDR: high dose rate.*

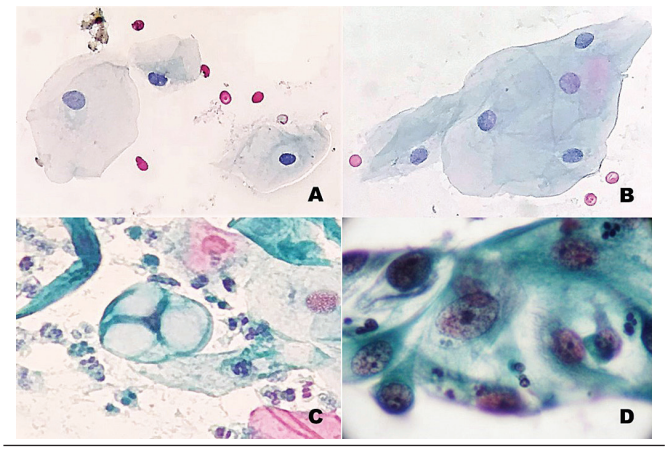

FIGURE 1 – *Benign reactive cellular changes associated with radiation*

A) intermediate squamous epithelial cell with cellular gigantism; B) cellular gigantism and nuclear pallor; C) cytoplasmic vacuolation; D) bizarre effects on metaplastic cells (magnification 400×).

Case 4

M. A. R., 56 years old, multiparous, histopathology of moderately differentiated squamous cell. She performed 24 cycles of cisplatin, paclitaxel and carboplatin, 25 of teletherapy and total hysterectomy. The patient reported abundant vaginal bleeding, also observed on speculum examination. The material for cytopathological collection was vaginal, and the result showed squamous carcinoma, predominance of parabasal squamous epithelial cells with marked nuclear (pleomorphism, hyperchromasia, coarse and irregularly distributed chromatin and anisokaryosis) and cytoplasmic (fusiform and orangeophilic cells) alterations (Table; **Figure 2**).

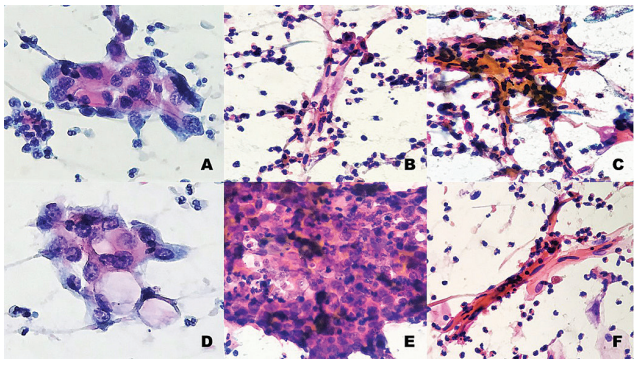

FIGURE 2 – *Squamous cell carcinoma*

A) parabasal squamous epithelial cells with karyomegaly, anisokaryosis, changes in the nuclear shape and contour, coarse and irregularly distributed chromatin; B) pleomorphic, fusiform squamous cells, orangeophilic cytoplasm, hyperchromatic nuclei, coarse and irregularly distributed chromatin; C) spindle cells, orangeophilic and hyperchromatic nuclei; D) parabasal squamous epithelial cells with changes in the nuclear contour and coarse and irregularly distributed chromatin; E) syncytia of parabasal squamous epithelial cells with nuclear dyskaryosis; F) orangeophilic, fusiform cells and hyperchromatic and elongated nuclei (magnification 400×).

Case 5

J. M. L., 41 years old, multiparous, histopathology of squamous cell carcinoma. She was subjected to six cycles of cisplatin and paclitaxel, 28 of teletherapy and four of HDR brachytherapy. The cytopathological examination was NILM, evidencing superficial and intermediate squamous epithelial cells with moderate reactive changes associated with radiation (cellular gigantism, cytoplasmic vacuolization, nuclear degeneration, multinucleation and anisokaryosis), typical endocervical glandular cells, besides metaplastic cells in several phases of reactive maturation (Table; **Figure 3**).

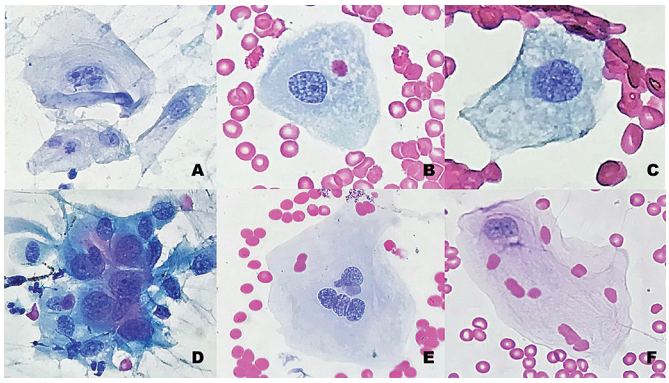

FIGURE 3 – *Benign reactive cellular changes associated with radiation*

A) squamous epithelial cell with cellular gigantism and anisonucleosis; B) cell evidencing nuclear degeneration; C) cell with cytoplasmic vacuolization and nuclear degeneration; D) reactivity in metaplastic cells, with anisokaryosis and nucleoli; E) multinucleated giant cell; F) cellular gigantism and binucleation (magnification 400×).

Case 6

M. I. B. O., 66 years old, multiparous, histopathology showing moderately differentiated squamous cell carcinoma. She performed 28 cycles of teletherapy and underwent total hysterectomy. Cytopathologic follow-up was NILM, but with mild inflammatory changes (pseudoeosinophilia), predominance of intermediate squamous epithelial cells and alterations in the microbiota with a predominance of supracytoplasmic bacilli suggestive of *Gardnerella vaginalis* and/or *Mobiluncus* sp. (Table).

Case 7

L. M. S., 47 years old, histopathology of well differentiated squamous cell carcinoma. She performed 28 cycles of teletherapy, six of cisplatin and four of HDR brachytherapy. The cytopathologic follow-up analysis was atrophy associated with inflammation, NILM, predominance of parabasal squamous epithelial cells, showing moderate inflammatory alterations (pseudoeosinophilia,

polychromasia, cytoplasmic degeneration, karyorrhexis and nuclear pyknosis) and bacillary microbiota (Table; **Figure 4**).

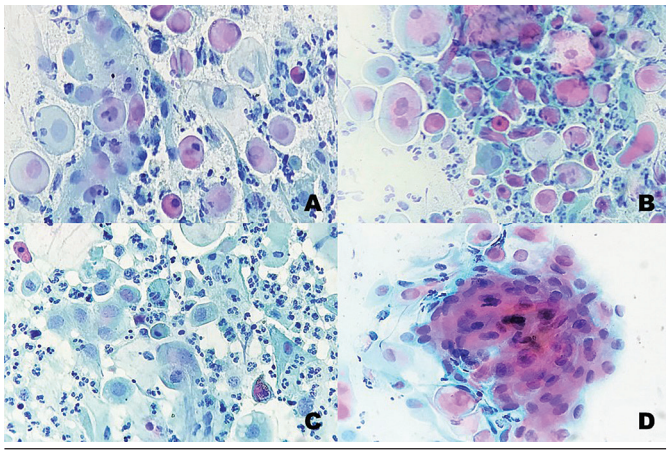

FIGURE 4 – *Atrophy associated with inflammation*

A) parabasal squamous epithelial cells in a cell debris background; B) immature cells with benign reactive changes: nuclear pyknosis, pseudo-eosinophilia and polychromasia; C) predominance of parabasal squamous epithelial cells intermingled with leukocyte infiltrate; D) grouping of parabasal squamous epithelial cells (magnification 400×).

Case 8

A. F. S., 27 years old, histopathological examination of undifferentiated squamous cell carcinoma. She performed three cycles of cisplatin, 28 of teletherapy and 4 of HDR brachytherapy. The cytopathological examination revealed rare superficial and intermediate squamous epithelial cells and numerous parabasal cells, which presented reactive changes associated with radiation (cytoplasmic and nuclear vacuolization, nuclear degeneration and anisokaryosis) and undetermined microbiota (Table; **Figure 5**).

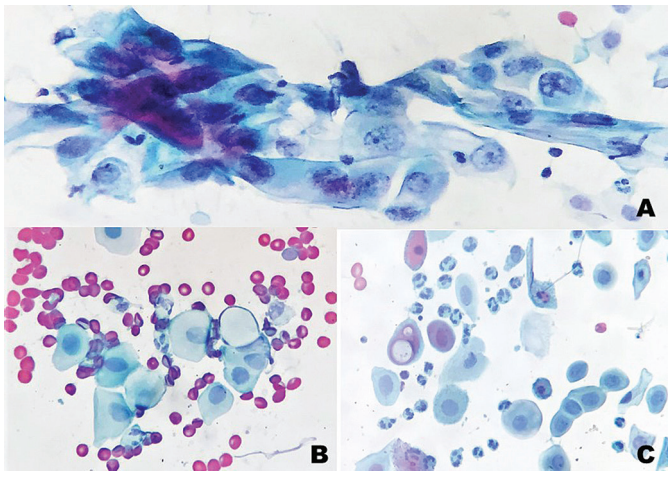

FIGURE 5 – *Benign reactive cellular changes associated with radiation*

A) squamous cells with nuclear degeneration and vacuolization; B) parabasal squamous epithelial cell with cytoplasmic vacuolization; C) benign reactive changes: cytoplasmic vacuolization and polychromasia, in addition to leukocyte infiltrate (magnification 400×).

DISCUSSION

Regarding the profile of the women included in this study, the mean age was 46.87 years [standard deviation (SD) ± 26.87], 100% had a histopathological diagnosis of squamous cell carcinoma, 75% presented three or more pregnancies and 62.5% underwent chemotherapy, teletherapy and concurrent brachytherapy. Regarding the number of pregnancies, the data obtained in this study agree with the literature, which describes multiparity as a possible risk factor for the development of intraepithelial lesions and cervical cancer[6].

Radiation can cause morphological and molecular changes in neoplastic and non-neoplastic cells due to interference in messenger ribonucleic acid (mRNA) synthesis, decrease in protein production, inhibition of deoxyribonucleic acid (DNA) synthesis and mitotic activity, as well as cytochemical changes, with protein denaturation and enzyme release, with the consequent destruction of cytoplasmic organelles[7,8].

In the present study, cytopathologic follow-up ranged from five months to 10 years, and 60.5% presented cellular changes associated with radiation, of which, three cases (37.5%) with squamous cells showing benign reactive morphological changes and two cases (25%) with an inflammatory atrophic pattern, which is described by the literature as a finding induced by ionizing radiation, since it promotes DNA changes, preventing the maturation process[4].

With regard to the cytological findings caused by radiation in the cervicovaginal smears evaluated, in three cases (37.5%) occurred cytoplasmic vacuolization, nuclear degeneration and anisokaryosis, two cases (25%) of cellular gigantism, and only once, but in different cases (12.5%), occurred nuclear pallor, multinucleation and nuclear vacuolization.

Zannoni and Vellone (2008)[9] evaluated the diagnostic accuracy of cytopathology in patients with cervical cancer after radiochemotherapy, finding 46% of smears with benign alterations produced by radiochemotherapy, 20% with atrophy and 9% inflammation. The authors reported that nuclear and cytoplasmic enlargement, multinucleation, cytoplasmic vacuolization, and bizarre cell forms, such as fibroblast, tadpole and anucleate cells type, were among the most radiation-induced cell morphological changes in the smears studied, corroborating much of the morphological changes found in the present study.

It was observed that the cases in which radiation-induced morphological cellular alterations were revealed, the period

between the end of the treatment and the cytopathologic follow-up ranged from five to 16 months, with mean of nine months. The acute effects of radiation tend to decline gradually and, in most cases, the morphological changes disappear from the cervicovaginal smears within 3-6 months after treatment. However, bizarre and enlarged cells may continue to appear on cytological smears for a period of years after the treatment[10].

The literature reports that the late effects of ionizing radiation in the cervix and vagina promote the appearance of benign squamous epithelial cells, uncommon in cytopathologic smears, such as cells with repair characteristics, large nucleus and macronucleus, multinucleated giant cells, and highly vacuolated cells[10].

It was verified that all the cases in which the women underwent HDR brachytherapy were also evidenced post-radiation reactive cellular changes in the cytopathologic follow-up, justified by the extensive tissue injuries resulting from the insertion of applicators and probes, as well as the damages caused by the radiation itself, which is used at high dose rate within the tumor[11].

The differential diagnosis of the morphological characteristics associated to radiation include the repair processes, squamous intraepithelial lesions (SIL) and squamous carcinoma[4]. In this study, cases 2 and 5 presented cellular changes that could be misinterpreted with those related to lesions and atypia, due to karyomegaly, mild nuclear hyperchromasia and "clear spaces" caused by nuclear degeneration, mimicking irregular chromatin distribution. However, nuclear changes are always important for the diagnostic definition and, in such cases, they are not sufficient for the diagnosis of SIL, since no substantial increases in the core/cytoplasm ratio were observed and the nuclei were pale and degenerate, without changes in shape and contour[12].

In our series, a case of dyskaryosis by cytopathology in cellular vaginal material, revealed locoregional recurrence. The clinical staging [International Federation of Gynecology and Obstetrics (FIGO) as the acronym of its French name Fédération Internationale de Gynécologie et d'Obstétrique], at diagnosis was IV A, since the carcinoma involved the bladder mucosa, justifying the recurrence found in this study[13]. Some authors have shown that post-radiotherapy recurrence rates increase according to tumor staging, and those with stage III and IV show greater likelihood and may have an incidence of 60%-80%[14, 15].

Shield *et al.* (1991)[16], evaluated the action of cytopathology for the detection of recurrent cervical carcinoma after radiotherapy, they revealed that the cytopathologic diagnosis of carcinoma was present in 32.8% (23/70) of cases with histologically confirmed recurrence, in a mean of 14.5 months after completion of radiotherapy, indicating that although the cervicovaginal cytopathologic of follow-up is not highly sensitive, it is a reliable method for the detection of recurrence and locoregional recurrence, providing an early diagnosis of tumor recurrence or persistence before the onset of clinical signs and symptoms.

In the study reported here, it was not possible to calculate the degree of sensitivity of the cytopathologic follow-up, since in the oncology service where the research was performed, follow-up biopsy is not routinely used, and cytopathology is used as the method of choice, as well as the agreed recommendations of several authors of literature[3, 4, 8, 17].

RESUMO

A citopatologia, além de seu papel nos programas de rastreio do câncer cervical, é uma importante ferramenta para o controle da eficácia do tratamento em mulheres com câncer de colo do útero, monitorando e detectando precocemente neoplasias residuais, recorrentes ou alterações reacionais benignas. Neste trabalho, relatamos oito casos de citopatologia de seguimento em mulheres com câncer de colo do útero após tratamento radioterápico, assistidas por um centro de oncologia pernambucano. Os principais achados citológicos pós-tratamento foram descritos, assim como as características histopatológicas ao diagnóstico e os tratamentos realizados.

Unitermos: *radioterapia; neoplasias do colo do útero; efeitos de radiação.*

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