

Multiple skin metastases to vulva from carcinoma of the cervical stump

Rak w kikucie szyjki macicy z mnogimi przerzutami do skóry krocza

Grabiec Marek¹, Walentowicz Małgorzata¹, Marszałek Andrzej²

¹ Department of Obstetrics and Gynecology Collegium Medicum in Bydgoszcz Nicolaus Copernicus University in Toruń

² Department of Clinical Pathology Collegium Medicum in Bydgoszcz Nicolaus Copernicus University in Toruń

Summary

Metastases to the skin occur rarely in the cervical carcinoma, even in terminal stage of the disease. The frequency of metastasis is estimated from 0.01% to 2%. The presence of metastasis suggests generalized dissemination of the disease and reflects a rapidly progressive process that appear in the final stage of the disease.

Case: *We present a case of skin metastases in patients with squamous cell carcinoma of the cervical stump after the previous supracervical hysterectomy for benign disease of the uterus. The extensive skin changes on vulva and perineum occurred after radical trachelectomy and external radiation therapy. Patient received HDR brachytherapy for recurrent lesions, but the effect of treatment was poor and she died of progressive disease.*

Conclusion: *As far as we know this is the first case report of squamous cell carcinoma in the cervical stump metastasizing to skin. Palliative brachytherapy has a limited role in controlling symptoms. Skin metastases indicate an aggressive and progressive process.*

Słowa kluczowe: **uterine cervical cancer / cervical stump / neoplasm metastases /**

Streszczenie

Rak szyjki macicy niezwykle rzadko daje przerzuty do skóry nawet w wysokich stopniach zaawansowania klinicznego. Przedstawiono przypadek chorej z rakiem płaskonabłonkowym w kikucie szyjki macicy poddanej radykalnemu leczeniu chirurgicznemu i następnej radioterapii. Po upływie 2 miesięcy od zakończenia terapii u pacjentki stwierdzono obecność przerzutów do skóry sromu i krocza. Chorą leczono brachyterapią HDR nie uzyskując zadowalających efektów. Zgodnie z naszą wiedzą jest to pierwszy opis przerzutów raka w kikucie szyjki macicy do skóry. Zastosowanie brachyterapii ma ograniczone zastosowanie w leczeniu przerzutów do skóry. Obecność przerzutów do skóry wskazuje na agresywny i postępujący przebieg raka szyjki macicy.

Key words: **rak szyjki macicy / kikut pochwy / przerzuty nowotworowe /**

Corresponding author:

Marek Grabiec
Department of Obstetrics and Gynecology Collegium
str. Ujejskiego 75, 85-168 Bydgoszcz, Poland
Phone: 48 52 3655242, Fax 48 52 3655242
e-mail: grabiecm@cm.umk.pl

Otrzymano: 02.02.2009
Zaakceptowano do druku: 15.12.2009

Introduction

Skin metastases of female genital tract malignancies are exceptionally rare, occurring most often in cases of breast and ovarian cancer [1]. Carcinoma of the uterine cervix is a common cancer in females and it metastasizes mainly to the lung, bone and liver [2]. Skin metastases from cervical cancer are extremely rare, even in higher stages of clinical advancement [3]. It seems that in majority of patients they do not occur even in the late stages of the disease [4].

Browstein and Helwig report only four (4) (2%) proved cases of cutaneous metastases of the cervical cancer in their study [1]. However, in the review by Brady et al., only five (5) cervical cancer patients (0.01%) developed skin metastases [5]. Gupta and Naran performed needle puncture of skin changes in sixty (60) women with cancers [6]. These authors found that uterine cervix turned out to be the primary location of carcinoma in only in three (3) women (5%).

Based on a review of the literature, Franciolini et al. report only eleven (11) cases of skin metastases of the uterine cervix carcinoma between 1940 and 1990, while Hayes et al. inform about 22 well-documented cases [4, 7].

To the best of our knowledge, this is the first literature report on multiple skin metastases in patients with squamous cell carcinoma of the cervical stump after previous supracervical hysterectomy for benign uterine diseases.

Case report

A 47-year-old woman with diagnosed squamous cell carcinoma of the cervical stump was referred to the Department of Oncological Gynaecology at Nicolaus Copernicus University on November 7, 2002 in order to receive preoperative brachytherapy.

In 1993 the patient underwent supracervical subtotal hysterectomy due to uterine myoma after previous diagnostic curettage. The result of the postoperative histopathologic examination revealed the presence of a leiomyoma. Regular check-up examinations, along with Pap smear, did not reveal any pathological changes during the years following initial surgery.

Pelvic examination before brachytherapy revealed condition after supracervical hysterectomy, uterine adnexa were not palpable. The vaginal part of the cervix was found to be cylindrical, expanded, with crater-like ulceration limited to the cervix, without parametrial extension. Cervical biopsy revealed FIGO stage IB1 invasive squamous cell carcinoma. Ultrasound examination indicated that the size of the uterine cervix was 53x42x45mm. The patient underwent preoperative intracavitary brachytherapy.

Radical trachelectomy with pelvic and aortic lymphadenectomy was performed six weeks after brachytherapy (Piver III). Pathologic examination revealed a cervical tumour, 3.2cm in diameter. Foci of squamous cell carcinoma infiltrating the cervical stump were clearly visible. The lesion was resected with adequate safe margins of healthy tissues. Parametria and lymph nodes were negative for neoplastic invasive metastases.

Afterwards the patient was treated by external radiation therapy with X-rays - 15MeV. Teletherapy was applied using "box" technique in the total dose of 4500cGy (25 fractions of 180cGy/g).

12 weeks after teletherapy, the patient returned to our department due to palpable nodulous lesions at the perineum.

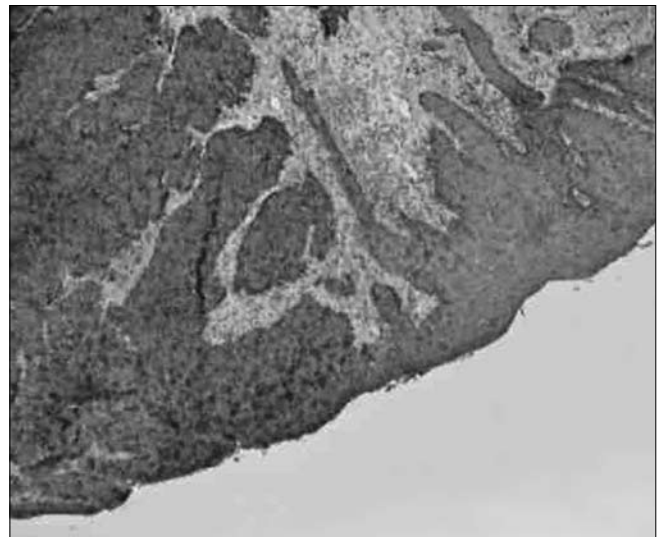


Figure A. Tissue specimen from cervix. The infiltrative moderately differentiated squamous cell carcinoma is present. There is well visible transition from normal (non-neoplastic) squamous epithelium to neoplastic (invasive) one. The brown color corresponds to localisation of cytokeratins with epithelial component in the specimen (immunohistochemistry with AE1/AE3 antibodies). The cell nuclei were highlighted by Meyer's hematoxylin staining. Primary objective mag. 4x



Figure B. Tissue specimen from vulva. There is well visible nest of metastasis. The cancer cells form irregular islands deep within vulvar tissue. The brown color corresponds to localisation of cytokeratins by immunohistochemical procedures with AE1/AE3 antibodies within epithelial component (the top of tissue specimen) and within cancer cells. The cell nuclei were highlighted by Meyer's hematoxylin staining. Original size scan of tissue slide.

The changes were resected for histopathological examination. Skin biopsy confirmed metastatic squamous cell carcinoma, which was histologically identical to the previous carcinoma of the cervix. No other pathological changes were found.

In the first surgically removed material histopathological study revealed invasive nonkeratinized moderately differentiated squamous cell carcinoma of the cervix (according to WHO rules) [8]. A clear-cut connection to the cervical squamous epithelium was visible (Figure A).

The second studied material was surgically removed vulvar specimen. In that sample we observed irregular islands of moderately differentiated squamous cell carcinoma, which were not connected to overlying skin (Figure B). The morphology of neoplasms in cervical and vulvar location was comparable. Further immunohistochemical analyses were performed on both samples to confirm the cervical origin of vulvar metastases.

Multiple skin metastases to vulva from carcinoma of the cervical stump.

In accordance with recommendations published earlier, we used p63 (anti-human p63, clone 4A4, cat. no. N1604, DAKO) as a marker of cervical origin of squamous cell carcinoma [9]. Moreover, we used cytokeratins panel (clone AE1/AE3, cat. no. 1590, DAKO) to confirm epithelial origin of the tumor, as well as to exclude the possibility of the non-epithelial tumor. The results of the aforementioned studies are presented in Figure C.

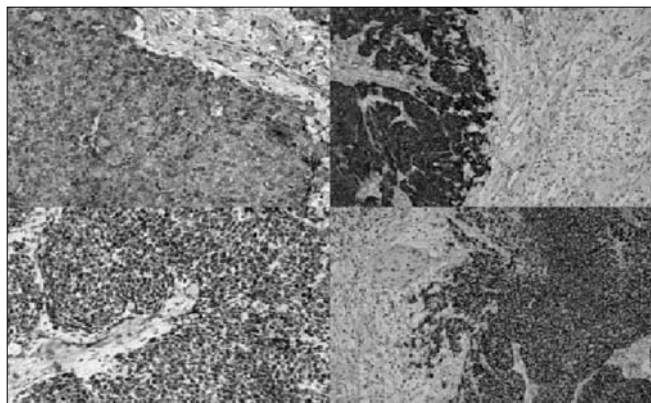


Figure C. Immunohistochemical localization of cytokeratins (antibody clone AE1/AE3) and p63 within squamous cell carcinoma within cervix and vulval metastases. Morphological picture as well as this set of staining confirms a common origin (from cervix) neoplastic cells. The cell nuclei were highlighted by Meyer's hematoxylin staining. Primary objective mag.



Picture 1.

During the next 4 weeks the patient was treated with brachytherapy -3000cGy Ir-192 was applied with the use of 3-6 needle-shaped bars No 16. Due to visible progression of the changes during the subsequent stays in hospital, the last, sixth, scheduled fraction was cancelled. Wide-spread metastatic vulval and perineum changes were found during the examination (Picture 1).

The patient was examined again after two months. The surroundings of the vulva, perineum and rectum were oedematic and covered with nodules of 1.0-1.5cm diameter (intensively infiltrated skin).

The patient was disqualified from further treatment as she had already received her lifetime dosage of radiation (preoperative brachytherapy, postoperative teletherapy, brachytherapy HDR in the area of the metastases). Considering the advancement of the change and its fast progression, chemotherapy was not initiated and the patient was transferred to a local palliative care unit. The patient died of progressive disease seven weeks later.

Discussion

Skin metastases of the cervical carcinoma are extremely rare, even in advanced stages of the disease [4, 10]. It is estimated that they appear only in about 0,1-2% of patients with this carcinoma.

Amit et al. [11] report that until the year 2001, there have been only twenty two (22) well-documented cases of cervical cancer with skin metastases. Metastases are most often located close to the primary site of the cancer, what suggests expansion of the carcinoma process through lymphatic vessels pattern of spread [12].

Macroscopically, the changes can have various clinical presentation. Lesions may appear as plaques nodules or inflammatory telangiectatic areas. When specified as nodular, about half of lesions were solitary and the rest multiple [7]. In our case numerous nodular changes embracing the vulva and perineum were observed.

Imachi et al. found skin metastases in fifteen (15) out of 1190 analysed patients (1,3%) with cervical cancer [2]. At the same time, these authors did not demonstrate any relevant differences between the degree of clinical advancement and the frequency of the metastases. The authors observed nodular pattern of skin metastases in thirteen (13) of fifteen (15) patients (86,7%), of which 66,7% had numerous skin changes. However, only four (4) patients had neither local recurrence nor other distant metastases at the time of the skin metastases diagnosis. It confirms that the extensive skin metastases observed by us in the patient in FIGO stage I were a very rare form of tumor metastasizing.

The mechanisms leading to the intensive skin metastases in patients with cervical cancer, which are resistant to chemo- and radiotherapy treatment, remain as yet unexplained. Theories on the pathophysiology of skin metastases include direct extension of the tumour, hematogenous, lymphatic and neoplastic implants [3, 13, 14].

Some authors focus on rapid progression of neoplastic process in HIV patients [11, 15]. Since HIV infection was excluded in our case, it is difficult to explain both the appearance of wide-spread vulval skin metastases in such a short time and the refraction to radiotherapy and local brachytherapy with Ir-192. Local intradermal brachytherapy is used as an alternative method of treatment in cases of recurrent or metastatic changes. Some studies show that using interstitial implants improves the local state and the rate of survival in patients with advanced cervical cancer [6].

Up to now there have been no standardized operative treatment methods in patients with benign disease of the uterus, particularly in case of uterine myoma. Some authors suggest routine hysterectomy in order to avoid cancer in the left cervical stump, while others are in favour of subtotal supracervical hysterectomy to preserve sexual function [16, 17-20].

The frequency of cervical cancer in patients after subtotal hysterectomy is estimated between 0.3% to 3% [17, 21].

Out of 6635 cases of uterine cancer observed by Hellstrom et al., 145 patients were treated for infiltrating carcinoma of the cervical stump (2.2%) [21].

Our case of carcinoma in the left cervical stump with numerous vulval and perineum skin metastases in a patient regularly examined could speak in favour of the total hysterectomy for benign disease of the uterus, particularly in patients over the age of 45.

In conclusion, it should be emphasized that prognosis in patients with skin metastases is usually poor. It seems that skin metastases are the sign of generalized dissemination of the disease and reflect rapidly progressive process [2, 3]. The average period of survival is estimated for 3-4 months since the skin metastases diagnosis [7, 14]. The case presented here is consistent with these reports. It is the first case report of squamous cell carcinoma in the cervical stump metastasizing to skin.

References

1. Browstein M, Helwig E. Metastatic tumors of the skin. *Cancer*. 1972, 29, 1298-1307.
2. Imachi M, Tsukamoto N, Kinoshita S, [et al.]. Skin metastasis from carcinoma of the uterine cervix. *Gynecol Oncol*. 1993, 48, 349-354.
3. Behtash N, Mehrdad N, Shamsirsaz A, [et al.]. Umbilical metastasis in cervical cancer. *Arch Gynecol Obstet*. 2008, 278, 489-491.
4. Franciolini G, Momoli G, Minelli L, [et al.]. Cutaneous metastases from carcinoma of the cervix. *Tumori*. 1990, 76, 410-412.
5. Brady L, O'Neill E, Farber S. Unusual sites of metastases. *Semin Oncol*. 1977, 4, 59-64.
6. Gupta R, Naran S. Fine needle aspiration cytology of cutaneous and subcutaneous metastatic deposits from epithelial malignancies. An analysis 146 cases. *Acta Cytol*. 1999, 43, 126-130.
7. Hayes A, Berry AD3rd. Cutaneous metastasis from squamous cell carcinoma of the cervix. *J Am Acad Dermatol*. 1992, 26, 846-850.
8. Tavassoli F, Devilee P. WHO classification of tumors. Pathology and genetics of tumors of breast and female genital tract. Lyon: *IARC Press*, 2003.
9. Wang T, Chen B, Yang Y, [et al.]. Histologic and immunophenotypic classification of cervical carcinomas by expression of the p53 homologue p63: a study of 250 cases. *Hum Pathol*. 2001, 32, 479-486.
10. Liro M, Kobierski J, Brzóska B. Nietypowa lokalizacja przerzutów raka płaskonabłonkowego szyjki macicy do powłok brzusznych opis przypadku. *Ginekol Pol*. 2002, 73, 704-708.
11. Amit A, Edwards C, Athey P, [et al.]. Extensive subcutaneous metastases from squamous cell carcinoma of the cervix in patient with HIV. *Int J Gynecol Cancer*. 2001, 11, 78-80.
12. Kim H, Park N, Kang S. Rare metastases of recurrent cervical cancer to the pericardium and abdominal muscle. *Arch Gynecol Obstet*. 2008, 278, 479-482.
13. Palaia I, Angioli R, Cutillo G, [et al.]. Skin relapse from cervical cancer. *Gynecol Oncol*. 2002, 87, 155-156.
14. Pertzborn S, Buekers T, Sood A. Hematogenous skin metastases from cervical cancer at primary presentation. *Gynecol Oncol*. 2000, 76, 416-417.
15. Joseph B, Chiramana H. Extensive subcutaneous metastasis from squamous cell carcinoma of the cervix in patient with HIV. *Int J Gynecol Cancer*. 2004, 14, 176-177.
16. Eicher W. Total and subtotal hysterectomy-psychosexual aspects. *Arch Gynecol Obstet*. 1994, 255, Suppl 2, 359-366.
17. Silva C, Cardoso C, Menegaz R, [et al.]. Cervical stump cancer: a study of 14 cases. *Arch Gynecol Obstet*. 2004, 270, 126-128.
18. Wydra D, Ciach K, Sawicki S, [i wsp.]. Porównanie życia seksualnego po nadszyjkowym i całkowitym wycięciu macicy. *Ginekol Pol*. 2004, 75, 274-280.
19. Markowska J, Markowska A. Całkowite czy nadszyjkowe wycięcie macicy. *Ginekol Pol*. 2000, 71, 34-38.
20. Gorlero F, Lijoi D, Biamonti M, [et al.]. Hysterectomy and women satisfaction: total versus subtotal technique. *Arch Gynecol Obstet*. 2008, 278, 405-410.
21. Hellstrom A, Sigurjonson T, Pettersson F. Carcinoma of the cervical stump. The radiumhemmet series 1959-1987. Treatment and prognosis. *Acta Obstet Gynecol Scand*. 2001, 80, 152-157.