Non-keratinizing squamous cell carcinoma in a patient with Brenner tumor history - relapse or second cancer?

Carcinom scuamos nekeratinizant la o pacientă cu antecedente de tumoră Brenner – recidivă sau al doilea cancer?

Elvira Brătilă[1], Anca-Maria Manta[2], Cristian Iuliu Mihail Iorga[2], Titus Sorin Pătrășcoiu[3], Monica Mihaela Cîrstoiu[4], Cristina Raluca Iorga[2], Costin Berceanu[5], Diana-Elena Comandașu[1], Victor Dan Eugen Strâmbu[2]

1. "Carol Davila" University of Medicine and Pharmacy, Department of Obstetrics and Gynecology, "St. Pantelimon" Clinical Emergency Hospital, Bucharest, Romania
2. Department of Surgery, Nephrology Clinical Hospital, "Dr. Carol Davila" UMPh, Bucharest, Romania
3. 2nd Surgery Department, "St Mary" Clinical Hospital, Bucharest, Romania
4. "Carol Davila" University of Medicine and Pharmacy, 3rd Obstetrics and Gynecology Clinic, Emergency University Hospital, Bucharest, Romania
5. University of Medicine and Pharmacy of Craiova, 2nd Obstetrics and Gynecology Clinic, Emergency County Hospital, Craiova, Romania

Correspondence:
Anca-Maria Manta
e-mail: anca_manta81@yahoo.com.

Mention:
All authors have equal contribution.

Abstract

Introduction. *Mature teratoma represents one of the most frequent ovarian tumors. Yet, its malignization represents a rarity, the most frequent histological type being the squamous-cell carcinoma. Coexistence with Brenner tumor is very rare.* ***Case report.*** *We present the case of a 59-year-old patient, diagnosed 6 years ago with Brenner tumor coexisting with malignant teratoma. The treatment was total hysterectomy and bilateral annexectomy, lymphadenectomy and omentectomyand adjuvant chemotherapy. Six years postoperatively, the patient presents minimum vaginal bleeding and polakyuria, a pelvic tumor being found, invading the urinary bladder. We practiced infralevator anterior pelvectomy with Briker type urinary derivation and adjuvant radiotherapy.* ***Discussions.*** *Even if the squamous carcinoma represents the most frequent type of malignization of the ovarian malignant teratoma and Brenner tumor, it is not histologically different from other vaginal squamous primary carcinomas. The symptomatology is unspecific, the tumor markers being usually positive. Anatomopathological and immunohistochemical they are similar, p63 positive pleading for epithelial origin. Yet, the free timeframe of the disease in spite of all the paraclinical investigations and periodical oncological consultations negative may plead for a new neoplasia.* ***Conclusions.*** *The correctly directed treatment of an ovarian malign teratoma has led to a good survival of the patient, in spite of the lack of international therapeutic protocols! The accurate treatment of the relapse will determine the prognosis of the the patient, but the main factor is the Brenner tumor's aggressiveness.*

Keywords: *Brenner tumor, non-keratinizing squamous cell carcinoma, relapse*

Rezumat

Introducere. *Teratomul matur reprezintă una dintre cele mai frecvente tumori ovariene. Totuși, malignizarea lui reprezintă o raritate, cel mai frecvent tip histologic fiind reprezentat de carcinomul scuamos. Coexistența cu tumora Brenner este foarte rară.* ***Caz clinic.*** *Vom prezenta cazul unei paciente de 59 de ani, primipară, primigestă, diagnosticată în urmă cu 6 ani cu teratom malign coexistând cu tumoră Brenner. Tratamentul chirurgical a fost de histerectomie totală, cu anexectomie bilaterală, limfadenectomie și omentectomie. La 6 ani postoperator, pacienta prezintă ca simptome dominante sângerare vaginală minimă și polakiure, constatându-se o nouă tumoră pelviană invadantă în vezica urinară. Se practică pelvectomie anterioară infralevatorie, cu derivație urinară de tip Briker și radioterapie adjuvantă.* ***Discuții.*** *Deși carcinomul scuamos reprezintă cel mai frecvent tip de malignizare a teratomului malign ovarian și a tumorii Brenner, el nu este diferit histologic față de alte carcinoame primare scuamoase vaginale. Simptomatologia este nespecifică, markerii tumorali fiind de obicei pozitivi. Din punct de vedere anatomopatologic și imunohistochimic, sunt asemănătoare, p63 pozitiv pledând pentru originea epitelială. Totuși, intervalul liber de boală (6 ani), în ciuda unor investigații paraclinice și consulturi periodice oncologice, poate pleda pentru o nouă neoplazie.* ***Concluzii.*** *Tratamentul corect efectuat al recidivei va determina prognosticul acestei paciente, însă rolul dominant îl deține agresivitatea tumorii Brenner.*

Cuvinte-cheie: *tumoră Brenner, carcinom scuamos nekeratinizant, recidivă*

Introduction

One of the most frequent germinating benign tumors of the ovary is represented by the mature teratoma. It is composed of tissues derived from the three germinating lines (ectoderm, mesoderm and endoderm)[(1)]. But its malignization is very rare (1-2% of the total teratomas)[(2)]. The most frequent histological type of malignization is represented by the squamous-cell carcinoma[(3)]. The prognostic of this disease depends on a series of factors (patient's age, histological grading, stage upon presentation, treatment) but is, in general, unfavorable.

From the point of view of symptomatology and laboratory exams (tumor markers), they are not different from other types of ovarian tumors, but the prognostic is unfavorable as compared to the epithelial ovarian tumors[(1)].

The treatment is multimodal, the surgical intervention having the essential role. The surgical treatment is completed by adjuvant radiotherapy and chemotherapy, but their role in survival remains uncertain.

Taking into account the rarity of these tumors, a standard protocol has not been created yet for an appropriate treatment of this pathology.

Case presentation

We present the case of a 59-year-old patient, primiparous, primigravida, from the urban area, known with high blood pressure under anti-hypertensive chronic treatment and hypothyroidism chronic replacement therapy, admitted for the alteration of her general condition, weakness, diffuse abdominal pain at the level of the lower abdomen, pollakiuria and presentation of a sero-hematic secretion at the vaginal level; these phenomena begun approximately four months before admission.

The patient related a debut of the symptomatology 6 years ago, by abdominal-pelvic pain, variable as intensity and occurrence, progressive abdomen enlargement and urinary phenomena (pollakiuria), developed during several months.

The clinical examination on admission reveals the patient in physiological climax, hemodynamic and respiratory balanced, with teguments and mucous of normal color, with the presence of a tumor formation distinguishable on palpation, situated subumbilical, hard and sensitive on palpation, moderately painful.

The biohumoural exams revealed no abnormal values.

We performed abdominal ultrasound, which raised the suspicion of an abdominal-pelvic tumor formation, with hyperecogenous aspect, well delimited, belonging to the left ovary.

The surgical intervention was decided and we practiced total hysterectomy with bilateral annexectomy, lymphadenectomy and omentectomy after the realization of the extemporaneous anatomic-pathological exam, which reveals the presence of an ovarian Brenner tumor coexisting with malignant teratoma.

The histopathological exam of the part to paraffin revealed cystic transformed ovary with a maximum diameter of 10 cm, with serous content and greenish purulent, revealing solid areas with a structure of mature monodermal malignant teratoma coexisting with malignant Brenner tumor.

Subsequently, the patient undergoes adjuvant chemotherapy treatment with carboplatin andtaxol, 6 cures at 3-week interval.

The post-operative and post-chemotherapy evolution was favorable, the patient presenting a free disease interval of approximately 5 years (documented by oncological

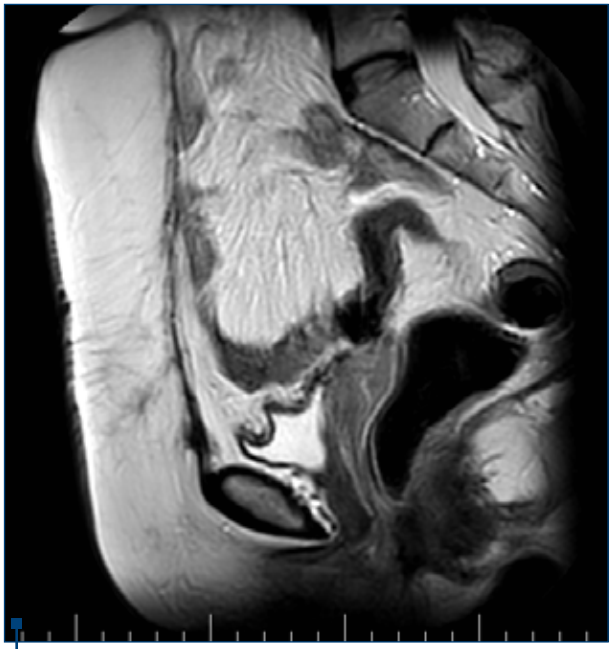

Figure 1. Abdomen and pelvis enhanced with contrast MRI (tumor without delimitation mark with the urinary bladder)

Figure 2. Intraoperative aspect

Figures 3 and 4. Operatory sample including vagina and urinary bladder

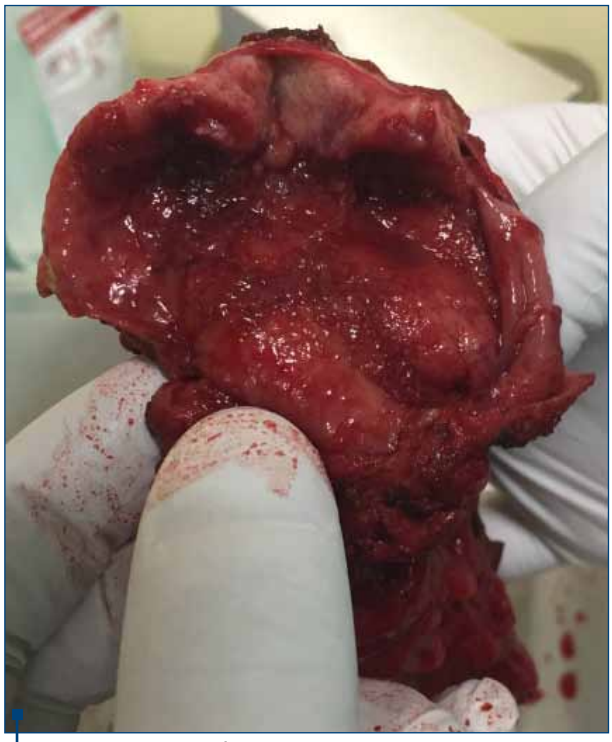

Figure 5. Operatory sample - section

assessment with clinical exams, biohumoral exams, ovarian tumor marker CA 125 and abdominal-pelvic MRI with IVC every 6 months and then annually, which revealed no pathological modifications).

After approximately 6-7 months from the last oncological exam, the patient presented symptomatology relapse, with diffuse abdominal pain, pollakiuria and a vaginal sero-sanguinolent secretion, according to the above mentioned.

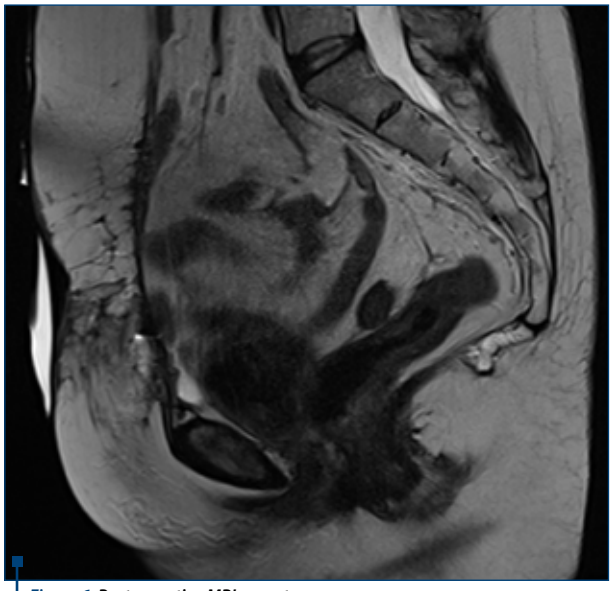

Figure 6. Postoperative MRI aspect

The vaginal tact revealed a tumor formation of approximately 5cm, hard, stationary. The valve examination highlights a vagina with erythematous mucous, filled here and there with vegetative lesions in the upper 2/3 and the presence of a sero-hematic secretion.

Biohumoural exams were within normal limits.

The abdominal and transvaginal ultrasounds revealed the presence of a tumor formation of vaginal stump invasive in the bladder wall.

The abdominal-pelvic MRI with IVC confirmed the presence of the tumor formation situated at the level of the vaginal stump and raises the suspicion of the rectal invasion, 2nd degree right ureterohydronephrosis, partially obturating adenopathies on the right side (Figure 1).

The lower digestive urethrocystoscopy and endoscopy (up to the caecum level) revealed no modifications.

Intraoperative, we found the presence of the tumor formation, of approximately 5 cm, situated at the level of the vaginal stump, adherent to the upper wall of the urinary bladder. No visible or palpable local-regional adenopathies were found. We practiced infralevator anterior pelvectomy with Briker urinary diversion, splinted 8 Ch (Figure 2).

Postoperative evolution was favorable; the patient did not develop immediate or tardive complications. Adjuvant radiotherapy was performed postoperatively.

The histopathological exam of the operative part established the diagnostic of keratinized squamous-cell carcinoma G2 infiltrative extrinsic at the level of her (own muscular) urinary bladder wall and of the anterior vaginal stump (Figures 3, 4, and 5).

The immunohistochemical exam revealed the presence of CK34 beta E12 positive diffuse in the tumor proliferation, p63 positive diffuse in the tumor proliferation, p16 negative, ki 67 positive in 80% of the tumor cells.

The abdominal-pelvic MRI with IVC performed postoperatively revealed 2nd degree right ureterohydronephrosis, right obturating adenopathies with the maximum diameter of 17/10 mm and inguinal adenopathies with a maximum diameter of 14/6 mm, without a notable progress as compared to the preceding MRI examinations (Figure 6).

Discussions

The ovarian germinating tumors represent a frequent reality in the course of the ovarian pathology, occupying the 3rd place (10-20%) in all the ovarian tumors[4]. Among them, a small number becomes malignant (1-2%). Deriving from the three different histological types (ectoderm, endoderm, mesoderm), the malignization is realized in different histological types, most of the times intricate, the squamous-cell carcinoma being the most frequent[4,5]. This histologic type appears frequently associated with the uterine intraepithelial cervical neoplasia[6].

Primary vaginal carcinoma represents a rare disease, accounting for less than 2% of all gynecologic malignancies. Squamous-cell carcinoma of the vagina represents approximately 80-90% of the primary vaginal cancer[7].

If the mature teratoma appears in young women[5], its malignization appears in women in pre-menopause or menopause, the age varying in different stages between 52 and 62 years[4]. In our patient's case, the diagnostic was established at the age of 53, with a debut of the symptomatology a few months prior to her presentation at the doctor (52-years-old).

Even if in most cases the teratoma is asymptomatic, the appearance of the tumor is suggested by a symptomatology manifested by diffuse abdominal pain, the abdomen's increase in volume, palpable tumor mass at the level of the lower abdomen, urinary phenomena. The symptomatology is not specific to this type of ovarian tumor formation, being the same as for other histological types[4]. Our patient presented initially the abdomen's increase in volume, attributed to her gaining weight, which led to her delayed presentation to the doctor, the unspecific abdominal pains, variable as intensity, appearing a few months after the debut of the symptomatology.

The biohumoral exams are unspecific for this pathology, yet they are frequently associated with the increase of the tumor markers CA-125 and CA 19-9[5]. In our patient's case, CA 19-9 was not dosed, but CA-125 was periodically dosed during the postoperative period since the first intervention and until the second one, remaining all the time within the normal reference range, without presenting significant fluctuations during all these 6 years.

The imagistic exams used for the diagnostic are the abdominal and transvaginal ultrasound, computed tomography and nuclear magnetic resonance with contrast agents[8,9]. Subsequently, the final diagnostic is confirmed by extemporaneous histopathological exam and by the resection part on paraffin.

In the reported case, the diagnostic was suspicioned by the abdominal ultrasound and subsequently confirmed by the abdominal-pelvic MRI with IVC. In the case of the first intervention, an extemporaneous histopathological exam was also performed, which raised the suspicion of malignant teratoma (germinal tumor). The surgical intervention was thus performed and the diagnostic was subsequently confirmed by paraffin exam, which also revealed the coexistence with Brenner tumor (epithelial ovarian tumor). No immunohistochemical tests have been performed.

The malignization of the ovarian teratoma is a rarity; that is why there are no international therapeutic protocols established. The surgical intervention represents the standard therapy, completed by radiotherapy and adjuvant chemotherapy. Currently, there are no significant proofs in the increase of the survival rate by adjuvant therapy[4]. Although there is no consensus over the type of surgical intervention, the removal of the entire tumor is essential or, when this is not technically possible, the cytoreduction, nevertheless, the complete surgical resection is important for a long-term survival[10]. With regards to the lymphadenectomy, it is arguable, being yet practiced in most of the patients[8,9]. The adjuvant chemotherapy is based on the platinum derivations in various therapeutic combinations[11]. It can be completed with the irradiation of the whole pelvis[11]. Thus, the adjuvant treatment (chemotherapy based on platinum

derivations and radiotherapy) is similar to the squamous cervical carcinoma[12].

Brenner tumor has an epithelial origin, containing transitional cells, whose incidence represents approximately 2-3% of the total ovarian tumors. In case of the coexistence with malignant teratoma, long-term evolution is determined by the aggressiveness of the Brenner tumor.

In our case, the tumor relapse appeared at the age of 59, after a free interval of the disease of approximately 5 years. In the case of the tumor relapse, a urinary symptomatology occurred first, manifested by polakiuria, abdominal pains and the presence of vaginal sanguinolent secretions, which were the alarm symptoms determining an early presentation to the doctor (approximately 6 months from the last oncologic consultation and abdominal-pelvis MRI without any visible signs of disease).

In spite of all imagistic exams initially performed every 6 months for a year and then annually up to 5 years, when there was no imagistic proof of local relapse, the abdominal-pelvic MRI with intravenous contrast performed after the debut of the actual symptomatology approximately 6-7 months after the last radiological and oncological exams, which were negative, shows the presence of a tumor formation of approximately 5 cm at the level of the vaginal stump, raising the suspicion of a posterior invasion into the rectum.

We decided and practiced the investigation of the digestive and lower urinary tract by lower digestive endoscopy and urethrocystoscopy, which presented a negative result.

Yet, intraoperatively, we found the presence of the tumor formation of approximately 5 cm situated at the level of the vaginal stump, adherent to the upper wall of the urinary bladder. When trying to do the vesical tumoral decollation, we found there is no cleavage plan between the two structures and the vesical wall is penetrated. We found the tumor's adherence to the posterior vesical wall up to the level of the vesical trigon. The tumor presents though cleavage plan with the rectal wall, rescinding the suspicion raised by the MRI exam. The local situation shows the limits of the paraclinical investigations performed, both of the magnetic resonance and of the urethrocystoscopy. Taking into account these considerations, we decided and practiced infralevator anterior pelvectomy with Briker urinary diversion, splinted 8 Ch. The histopatologic examination of the operatory part to paraffin revealed the presence of the keratinized squamous-cell carcinoma. Immunohistochemistry exam showed CK 34 beta E12 positive, p16 negative, p63 positive, ki67 positive in 80% of the cells. The association between p63 and CK 34 beta E12 has a high specificity for transitional cells, while p16 is specific for squamous-cell vaginal carcinoma. In our case, the association between CK 34 beta E12 and p63 positive with p16 negative pleads for the diagnosis of Brenner tumor recall.

Conclusion

The malignization of the mature teratoma represents rare cases. In cases of coexistence between malignant teratoma and Brenner tumor, the relapse risk is determined by the Brenner compound.

Having a reduced incidence, there is no consensus with regards to the therapeutic sequence. Yet, the surgical treatment is basic, appropriate to staging, completed by radiotherapy or adjuvant chemotherapy.

In case of the appearance of a squamous-cell carcinoma in the pelvis after a free disease period, the differential diagnosis between Brenner tumor and a second primary cancer is made through the immunohistochemistry analysis. Association between the immunohistochemistry expression of CK 34 beta E 12 and p63 positive pleads for transitional cells tumor.

With regards to the presented case, even if we know the possible provenience of the squamous carcinoma as a histological type from vaginal epithelium, p16 negative excludes a primary vaginal cancer. ■

Consent:

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interests:

The authors declare there is no conflict of interests regarding the publication of this paper.

References

1. Kikkawa F.,Nawa A., Tamakoshi K., Ishikawa H., Kuzuya K., Suganuma N., Hattori S., Furui K., Kawai M., Arii Y., "Diagnosis of Squamous Cell Carcinoma Arising from Mature Cystic Teratoma of the Ovary", Cancer 1998/ Volume 82 / Number11, 2249-2255.
2. Avci S., Selcukbiricik F., Bilici A., Ozkan G., Ozagari A. A., Borlu F., "Squamous Cell Carcinoma Arising in a Mature Cystic Teratoma", Case Reports in Obstetrics and Gynecology, Volume 2012, Article ID 314535.
3. Santos L. Dos, Mok E., Iasonos A., Park K., Soslow R.A., Barakat R.R., Abu-Rustum N.R., "Squamous-cell carcinoma arising in mature cystic teratoma ofthe ovary: a case series and review of the literature", Gynecologic Oncology, Volume 105, Isuue 2, May 2007, 321-324.
4. Zakkouri .F.A., Ouaouch S., Boutayeb S., Rimani M., Gamra L., Mrabti H. and Errihani H., "Squamous cell carcinoma in situ arising in mature cystic teratoma of the ovary: a case report", Journal of Ovarian Research 2011, 4:5, http://www.ovarianresearch.com/content/4/1/5.
5. Madaan M., Puri M., Sharma R., Kaur H., Trivedi S.S., "Unusually High Levels of CA 19-9 Associeted with Mature Cystic Teratoma of the Ovary", Case Reports in Obstretics and Gynecology, Volume 2014 (2014), Article ID 187910,http://dx.doi.org/10.1155/2014/187910
6. Baughn M.,Plaxe S.C., Weidner N., "Primary squamous carcinoma of the ovary likely arising from a monodermal cystic mucinous teratoma- case report", Annals of Diagnostic Pathology, volume 15, issue 6, 2011, 446-4496.
7. Gadducci, A., Fabrini, M. G., Lanfredini, N., & Sergiampietri, C. (2015). Squamous cell carcinoma of the vagina: natural history, treatment modalities and prognostic factors. Critical reviews in oncology/hematology, 93(3), 211-224.
8. Gershenson D.M., "Treatment of malignant germ cell tumors of the ovary", www.uptodate.com 2015.
9. Gershenson D.M., "Ovarian germ cell tumors: Pathology, clinical manifestations, and diagnosis", www.uptodate.com 2015.
10. Park J.Y., Kim D.Y, Kim Y.M., Kim Y.T., Nam J.H., "Malignant transformation of mature cystic teratoma of the ovary: Experience at a single institution", European Journal of Obstetrics & Gynecology and Reproductive Biology, Volume 141, Issue 2, December 2008, 173-178.
11. Ford T.C., Timmins P.F., "Successful Treatment of Metastatic Squamous Cell Carcinoma Of the Ovary Arising Within a Mature Cystic Teratoma-case report", Clinical Ovarian Cancer, Volume 4, Issue 1, June 2011, 44-46.
12. Andreas H., Doerthe B., Bohlmann M.K., Franke F.E., Hans-Rudolf, MunstedK., "Squamous-cell carcinoma in mature cystic teratoma of the ovary: systematic review and analysis of published data", Lancet Oncology, Volume 2008, Issue 9, 1173-11809.