CASE REPORTS

SEROUS ADENOCARCINOMA DETECTED IN THE CERVICAL SMEAR
– A CASE REPORT

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Summary

Introduction. Cytological smear tests of the cervix are routine diagnostict methods used for detection of precancerous lesions and tumors of the cervix; they are highly sensitive and specific in the detection of precancerous squamous intraepithelial lesions. Glandular lesions are much less frequently found in the cervical smear. The most common glandular lesions detected in the cervical smear are endocervical and endometrial adenocarcinomas. Cervical metastases are rare, although there are case reports in the literature. Case Report. In this case report, we present a 64-year-old woman with an abnormal cervical smear and postmenopausal metrorrhagia. Numerous accumulations, as well as individual atypical epithelial cells, were detected in the cervical smear and a cytological diagnosis of a high-grade squamous intraepithelial lesion was made based on cytomorphicological features suspicious for invasion (Bethesda Classification, 2014) so a cervical biopsy and curettage of the endocervical canal were performed. A high-grade serous adenocarcinoma was diagnosed by histopathological examination of cervical biopsy and cervical canal curettage specimens, after which a transvaginal ultrasound examination was performed, which showed tumors on both ovaries and free fluid in the abdominal cavity. The patient underwent abdominal hysterectomy with bilateral salpingo-oophorectomy. Histological examination confirmed high-grade ovarian papillary serous adenocarcinoma with psammoma bodies. Conclusion. The cytological diagnostic features and criteria for serous adenocarcinoma in Papanicolaou smears are still vague and insufficiently defined in the literature, which is the reason for very common errors in the interpretation, so further research on the pathogenesis, diagnosis and therapy of this tumor is of great importance.

Key words: Adenocarcinoma; Ovarian Neoplasms; Vaginal Smears; Papanicolaou Test; Cervix Uteri; Diagnosis

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SEROZNI ADENOKARCINOM U CERVIKALNOM BRISU – PRIKAZ SLUČAJA

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Sažetak

Uvod. Citološki bris grlića materice je dijagnostička metoda koja se rutinski koristi za otkrivanje prekanceroznih lezija i tumora grlića materice; visoko je senzitivna i specifična metoda za otkrivanje prekanceroznih lezija iz skvamoznog epitelia. Glandularne lezije u cervikalnom brisu se identifikuju znatno red. Najčešća glandularna lezija opisana u brisu grlića materice je endocervikalni adenokarcinom, a potom adenokarcinom endometrijuma. Metastaze u grliću materice se retko javljaju, mada u literaturi postoje prikazi sličnih slučajeva. Prikaz slučaja. Predstavljamo 64-godišnju ženu sa abnor- malnim nalazom cervikalnog brisa i postmenopauzalnom metror- rhagijom. U razmazu brisa svaka su otkrivene brojne nakupine, kao i pojedinačne atipične epitelnene ćelije, te je na osnovu citomorfoloških karakteristika postavljena citološka dijagnoza skvamozne in- traepitelne lezije visokog gradusa – ne može se isključiti invazija (H-SIL ne može se isključiti invazija, Betezda klasifikacija 2014), nakon čega je urađena biopsija grlića materice i kiretaža endocer- vikalnog kanala. Histopatološkim pregledom biopsije grlića materice i kiretaže cervikalnog kanala postavljena je dijagnoza serozno-adi- nokarcinoma visokog gradusa posle čega je urađen transvaginalni ultrazvučni pregled kojim je dokazano prisustvo tumorskih masa na oba jajnika i slobodna tečnost u trbušnoj duplji. Pacijentkinja je pod- vrgnuta abdominolojnoj hysterektomiji sa bilateralnom salpingo-oofor- ekтомijom. Histološkim pregledom potvrđen je papilarni serozni adenokarcinom u Papanikolau razmazu još uvek su u literaturi neprecizno i nedovoljno definisano što je vrlo često razlog grešaka u interpretaciji, pa su dalja istraživanja potre- bna, dijagnoze i terapije ovog tumora od velikog značaja.

Ključne reči: adenokarcinom; tumori jajnika; vaginalni i cervikalni bris; PAPA test; grlić materice; dijagnoza
Serous adenocarcinomas in the Pap smear are characterized by papillary clusters with serrated edges and very often present with cell overlap and formation of three-dimensional clusters. The cells are large, the nuclei of the cells are large, round, they often have prominent nuclei, and the amount of cytoplasm is variable and may contain eccentrically placed vacuoles. Psammoma bodies are rarely present in cytological samples [7]. Most metastatic cancers are characterized by a clean background and absence of tumor diathesis, while the direct spread of the tumor to the cervix is characterized by tumor diathesis. Tumor cells of serous adenocarcinoma express Wilms’ tumor 1 (WT1), p53, and estrogen receptor (ER) immunohistochemical markers.

Case Report

Due to postmenopausal vaginal bleeding, a routine cervical smear was taken from a 64-year-old woman. It was taken with a cervix brush and prepared by the conventional Pap staining method. Numerous cell clusters were detected in the smear, as well as individual atypical epithelial cells. Cell groups were arranged in the form of small clusters and hyperchromatic crowded groups (Figure 1), papillary-like structures (Figure 2), while scattered individual cells were present in rare foci. The cells were mostly polygonal and round in shape, elongated in places, and spindle-shaped (Figure 3). The nuclei of the cells were oval or round with a present pronounced nuclear pleomorphism, coarse-grained chromatin and one to two visible nucleoli. In most cells the cytoplasm was sparse, in rare cells it contained vacuoles, and in some cells it was orangeophilic in appearance, suggesting possible squamous differentiation. Abundant amount of nuclear debris, polymorphonuclear cells, and a lot of fresh erythrocytes in the background of the smear indi-
cated presence of pronounced tumor diathesis. Based on cytomorphological characteristics in the cervical smear, the diagnosis of high-grade squamous intraepithelial lesion suspicious for invasion was made (Bethesda classification, 2014).

Vaginal examination verified a tumor mass on ectocervix with contact bleeding. A biopsy of the cervix and curettage of the endocervical canal were performed. Histopathological examination of cervical biopsy and cervical canal curettage confirmed the presence of high-grade serous adenocarcinoma without clinical data on the primary location of the tumor. The tumor tissue was composed of polygonal epithelial cells with a pronounced degree of pleomorphism, and the cells were almost entirely arranged into solid groups with focally present, poorly formed glandular and sparse papillary formations (Figure 4). An immunohistochemical analysis was performed on the cervical biopsy sample, which confirmed high positivity of ERs in tumor cell nuclei (Figure 5A), low positivity of progesterone receptors, positive expression of WT1 (Figure 5B), and high expression of Ca-125 in the cytoplasm of tumor cells (Figure 5C). Immunohistochemical profile of the tumor indicated a high-grade serous adenocarcinoma.

After the diagnosis of serous adenocarcinoma in the biopsy sample of the cervix and endocervical canal curettage, a transvaginal ultrasound examination was performed. It confirmed the presence of tumor masses on both ovaries and free fluid in the abdominal cavity. The patient underwent laparotomy and abdominal hysterectomy with bilateral salpingo-oophorectomy. Multiple peritoneal biopsies were performed and ascites fluid was sent for cytological analysis. Omentectomy and lymphadenectomy were not performed due to extensive omental infiltration by the tumor. Macroscopically, the tumor mass in the right ovary was 6.8 cm x 4.9 cm x 5.3 cm, and in the left ovary 7.6 x 5.2 x 4.7 cm. Tumor tissue infiltrated the entire fimbriae and ampullary portion of both fallopian tubes. A cross-section revealed a solid tumor, grayish-white, and crumbly. The cervix in all four quadrants was invaded by a 2.3 x 1.8 x 1.3 cm tumor nodule. In cross-section, the tumor tissue in the cervix was grayish-white and crumbly, reaching to the lateral edges of the resection on the anterior lip of the cervix. In the tissue of the ovaries, fallopian tubes and cervix, microscopic examination confirmed a high-grade papillary serous adenocarcinoma with psammoma bodies. Immunohistochemical analysis was performed on ovarian tumor fragments, and the results were identical to those from the biopsy sample of cervical tumors. A simple cystic hyperplasia without atypia was present in the endometrium. The presence of numerous malignant cells originating from the adenocarcinoma was proved in the cytological sample of ascitic fluid.

Figure 3. Cervical smear of atypical epithelial cells of polygonal and spindle shape with tumor background (Papanicolaou staining x 400)

Slika 3. Cervikalni bris atipičnih epitenih ćelija poligonalnog i vretenastog oblika sa tumorskom pozadinom (Papanikolau bojenje x 400)

Figure 4. Solid groups and papillary structures of serous adenocarcinoma in a cervical biopsy sample (hematoxylin/eosin staining, x 200)

Slika 4. Solidne grupe i papilarne strukture seroznog adenokarcinoma u bioptičkom uzorku grlića materice (hematoksilin/eozin bojenje, x 200)

Figure 5. A - Positive ER in a cervical biopsy sample (IHH, x 100); B - Positive WT1 in a cervical biopsy sample (IHH, x 100); C- Positive Ca125 in a cervical biopsy sample (IHH, x 200)

Slika 5. A – pozitivni ER u bioptičkom uzorku grlića materice (IHH, x 100); B – pozitivan WT1 u bioptičkom uzorku grlića materice (IHH, x 100); C – pozitivan CA 125 u bioptičkom uzorku grlića materice (IHH x x 200)

Legend: ER – estrogen receptor; WT1 – Wilms’ tumor 1; Ca 125 - Cancer antigen 125; IHH - immunohistochemistry
Discussion

Cervical carcinoma is one of the most common carcinomas in the female population [8]. Serous adenocarcinoma of the female genital tract is a type of tumor that is rarely diagnosed in the cervical smear [3]. The Pap test is not a sensitive test for the detection of serous adenocarcinoma, regardless of the primary site of this histological type of tumor [3].

The description of cytological characteristics and criteria for the diagnosis of serous adenocarcinoma in Pap smear are still inaccurate and insufficiently defined in the literature, which is the reason for very common errors in interpretation. The cytological diagnosis of papillary serous adenocarcinoma should be considered when the cervicovaginal smear contains short, three-dimensional papillary clusters of large atypical cells with prominent nucleoli, individual malignant cells, or naked nuclei with blood or necrosis in the background [9].

Tumor cells of primary adenocarcinoma of the endometrium, ovaries and fallopian tubes in cervicovaginal smears are identical to those in papillary serous adenocarcinoma of the uterus, but the background is clear (without tumor diathesis) unless it is a direct infiltration of the cervix [10].

Primary serous cervical carcinomas are the least frequently detected in the cervical smear because this histological variant of primary cervical adenocarcinoma is rather rare.

Serous adenocarcinomas of primary endometrial origin are most commonly found in Pap smears and serous adenocarcinoma tumor cells whose primary sites of origin are the ovaries, fallopian tubes, and peritoneum, are rarely found in cytological samples [11]. It is not possible to differentiate the primary place of origin of this type of tumor only based on the morphology in the cytological sample [10]. The differential diagnosis of primary serous cervical cancer includes primary serous carcinoma of the endometrium, ovaries, fallopian tubes, and peritoneum with spread to the cervix, with direct infiltration or metastasis, and it requires clinical correlation. If fractional curettage of the endometrium and endocervix does not prove cancer, it is necessary to exclude or confirm the existence of tumors of adnexal and peritoneal origin. The presence of ovarian and fallopian tube adenocarcinoma cells in the cervicovaginal smear varies from 6% to 36% [12]. The cytology of papillary serous adenocarcinoma may be difficult to distinguish from the cytology of primary endocervical carcinoma. Elongated overlapping nuclei, serrated edges of the nuclei ("feathered edges") in clusters are cytological characteristics that indicate endocervical adenocarcinoma [3].

The differential diagnosis of serous adenocarcinoma in the cervical smear includes squamous lesions (either invasive carcinoma or high-grade squamous intraepithelial lesion) because squamous cells occur individually or in clusters with tumor diathesis in the background [13]. Differential diagnosis can sometimes be very difficult if squamous intraepithelial neoplasia involves the endocervical glands. Squamous cells show hyperchromatic nuclei and condensed cytoplasm.

Endocervical adenosquamous carcinoma may be another diagnostic problem. Cervical adenosquamous carcinoma cytologically presents with syncytiun-like cell arrangements and occasionally, as glandular structures consisting of large pleomorphic cells with abundant, dense cytoplasm and macronucleoli. Papillae and psammoma bodies are not a prominent feature of adenosquamous carcinoma [14].

The identification of this poor prognostic variant of female genital tract cancer may be clinically important and a preoperative Pap test may be useful in making a decision in the choice of treatment.

Conclusion

In this case report, poor differentiation of serous adenocarcinoma and technically poor cytological Papanicolaou smear resulted in misdiagnosis of a neoplasm of squamous epithelial origin. Immunohistochemical analysis of tumor tissue from a biopsy sample contributed to the accurate diagnosis of serous adenocarcinoma, that is not often found in the cervix, which is why it is much less often present in the cervical smear.

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