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B-hCG and H-hCG levels in patients with gestational trophoblastic neoplasia

Stężenie B-hCG i H-hCG u pacjentek z ciążową neoplazją trofoblastu

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Abstract

Objective: Gestational trophoblastic disease is a term that encompasses a spectrum of disorders all arising from the placenta. Human chorionic gonadotropin (hCG) hormone has an essential role in the diagnosis and management of gestational trophoblastic neoplasia. Measuring beta-hCG (B-hCG) levels is the only standard method of monitoring treatment response in patients on chemotherapy. Serial B-hCG levels are also helpful in defining the suitable approach and the dosage of chemotherapeutic drugs. Unfortunately, this marker may not be helpful in some cases. Therefore, the present study was conducted to determine the results of the ratio of B-hCG and hyperglycosylated human chorionic gonadotropin (H-hCG) in patients with gestational trophoblastic neoplasia. **Materials and methods:** This was a cross-sectional study in 22 patients with gestational trophoblastic neoplasia who were referred to an oncology clinic of an academic hospital of Mashhad University of Medical Sciences in Iran from December 2017 to May 2018. Inclusion criteria were plateau level of B-hCG (during 4 weeks) or persistent low level of hCG. After ruling out other etiologies, H-hCG level was measured and the H-hCG/total hCG ratio was evaluated. If the proportion was more than 20%, active gestational trophoblastic neoplasia was diagnosed, and if it was less than 20%, quiescent gestational trophoblastic neoplasia was diagnosed. In patients with active gestational trophoblastic neoplasia, interventional procedures involved a change in the dose intensity or chemotherapy or proposing a surgery. However, only serial follow-up was recommended in patients with quiescent gestational trophoblastic neoplasia. Then, the patients were followed during the therapy and the condition of patients was followed and recorded. **Results:** The mean age of patients was 31.36 ± 8.01 years. Hydatidiform mole was the most common diagnosis, accounting for approximately 64% (14) of patients. A total of 81% of patients were undergoing chemotherapy. The interval time between the onset of chemotherapy until plateau or persistent low level of hCG was 11.26 ± 4.03 weeks. The mean B-hCG level was 36.6 mIU/mL and the mean H-hCG/total hCG ratio was 6.24%. This proportion was less than 20% in 82% of patients. Among these patients, 14 patients (77.8%) had spontaneously normalized levels of B-hCG during a 6-month follow-up. Two cases underwent chemotherapy due to increased B-hCG. Other patients are still under follow-up without disease progression. Among 4 patients with a H-hCG/total hCG ratio >20%, hysterectomy was recommended to one patient duo to multiparity and the fact that the tumor was localized in the uterus. In the other patients, an increase in the dose of methotrexate or a change of chemotherapy regimen was performed, which caused a decrease in B-hCG level to normal. All patients are still under follow-up without disease progression. **Conclusion:** The data in this study suggests the use of H-hCG as a tumor marker in patients with persistent low level of B-hCG, which is useful to distinguish between quiescence gestational trophoblastic neoplasia, which does not need treatment, from active gestational trophoblastic neoplasia. However, further studies with larger sample size are needed to confirm and generalize the above findings.

Keywords: gestational trophoblastic disease, human chorionic gonadotropin, hyperglycosylated hCG, B-hCG

Streszczenie

Cel pracy: Ciążowa choroba trofoblastyczna to termin obejmujący spektrum zaburzeń wynikających z nieprawidłowego rozwoju łożyska. Ludzka gonadotropina kosmówkowa (*human chorionic gonadotropin*, hCG) odgrywa kluczową rolę w diagnostyce i leczeniu ciążowej neoplazji trofoblastu. Jedyną standardową metodą monitorowania odpowiedzi na leczenie u pacjentek otrzymujących chemioterapię jest pomiar stężenia beta-hCG (B-hCG). W wyborze sposobu leczenia i dawki chemoterapeutyku pomocne są również seryjne oznaczenia B-hCG. Niestety, marker ten może nie być pomocny w niektórych przypadkach. W związku z tym celem niniejszej pracy było określenie stosunku podtypu beta gonadotropiny kosmówkowej (B-hCG) do hiperglikozylowanej ludzkiej gonadotropiny kosmówkowej (H-hCG) u chorych z ciążową neoplazją trofoblastu. **Materiał i metody:** Przeprowadzono przekrojowe badanie z udziałem 22 pacjentek z rozpoznaniem ciążowej neoplazji trofoblastu, skierowanych do kliniki onkologicznej szpitala akademickiego Uniwersytetu Medycznego w Mashhad w Iranie w okresie od grudnia 2017 do maja 2018 roku.

Kryteriami włączenia były stężenie plateau B-hCG (przez 4 tygodnie) lub utrzymujące się niskie stężenie hCG. Po wykluczeniu innych patologii dokonano pomiaru stężenia H-hCG i oceny stosunku H-hCG do całkowitej hCG. Jeśli odsetek ten przekraczał 20%, ustalano rozpoznanie aktywnej postaci ciążowej neoplazji trofoblastu, natomiast jeśli był mniejszy niż 20%, rozpoznawano postać nieaktywną ciążowej neoplazji trofoblastycznej. W przypadku pacjentek z aktywną postacią ciążowej neoplazji trofoblastu procedury interwencyjne obejmowały zmianę intensywności dawki lub chemioterapii, ewentualnie proponowano leczenie operacyjne. Natomiast u pacjentek z nieaktywną postacią choroby zalecano jedynie seryjną obserwację. Przez cały okres leczenia prowadzono obserwację pacjentek, monitorując i rejestrując ich stan zdrowia. **Wyniki:** Średnia wieku badanych wynosiła 31,36 ± 8,01 roku. Najczęstszym rozpoznaniem wśród pacjentek był zaśniad groniasty, występujący u około 64% (14) badanych. Chemioterapię otrzymywało łącznie 81% kobiet. Odstęp czasu od rozpoczęcia chemioterapii do momentu osiągnięcia plateau lub uzyskania utrzymującego się niskiego stężenia hCG wynosił 11,26 ± 4,03 tygodnia. Średnia wartość stężenia B-hCG wynosiła 36,6 mIU/ml, natomiast średnia wartość stosunku H-hCG do całkowitej hCG – 6,24%. U 82% pacjentek odsetek ten wynosił poniżej 20%. U 14 spośród tych pacjentek (77,8%) doszło do samoistnej normalizacji stężenia B-hCG podczas 6-miesięcznej obserwacji. W 2 przypadkach z uwagi na podwyższone stężenie B-hCG zastosowano chemioterapię. Pozostałe pacjentki nadal znajdują się pod obserwacją i nie wykazują oznak progresji choroby. U jednej spośród 4 kobiet ze stosunkiem H-hCG do całkowitej hCG wynoszącym powyżej 20% zalecono zabieg histerektomii z uwagi na liczne porody w wywiadzie i ograniczenie choroby nowotworowej do macicy. U pozostałych pacjentek zwiększano dawkę metotreksatu lub dokonywano zmiany schematu chemioterapii, co skutkowało obniżeniem stężenia B-hCG do poziomu prawidłowego. Wszystkie pacjentki pozostają pod obserwacją i są wolne od progresji choroby. **Wnioski:** Dane zgromadzone w przedstawionym badaniu wskazują na zasadność stosowania H-hCG jako markera nowotworowego u pacjentek z utrzymującym się niskim stężeniem B-hCG, pomocnego w rozróżnieniu między nieaktywną postacią ciążowej neoplazji trofoblastu, w przypadku której nie ma potrzeby stosowania leczenia, a jej postacią aktywną. Niemniej jednak w celu potwierdzenia i uogólnienia wyżej przedstawionych wyników potrzebne są dalsze badania z udziałem większej grupy pacjentek.

Słowa kluczowe: ciążowa choroba trofoblastyczna, ludzki hormon gonadotropiny kosmówkowej, hiperglikozylowana hCG, B-hCG

INTRODUCTION

Human chorionic gonadotropin (hCG) is a hormone that has two subunits of alpha and beta. Hyperglycosylated hCG (H-hCG) is a variant of hCG made by cytotrophoblast cells. H-hCG is not a hormone, but acts as an autocrine on cytotrophoblast cells, thereby causing cell growth, differentiation and invasion. H-hCG is as an invasive signal of cytotrophoblast cells[1]. The invasion may involve a replacement of gestational products or the invasion of choriocarcinoma cells, thereby showing that choriocarcinoma cells are the main source of H-hCG. hCG is involved in many stages of placental and fetal development[2,3]. The ratio of H-hCG to total hCG greater than 20% can stimulate invasion. Indeed, the invasive potential of H-hCG has been proven by a number of studies. However, the exact mechanism of this phenomenon is still unknown. The first study reported by Cole et al. showed that choriocarcinoma cells mainly produce H-hCG, and this is a factor that induces invasion in choriocarcinoma[4]. It seems that H-hCG expresses protease enzymes, thereby facilitating invasion. This invasion can be controlled in a complete molar pregnancy or partial mole, or it may be uncontrolled in GTN[5]. In complete and partial moles, regular hCG is the main form of hCG because the syncytiotrophoblast cells are the main cells in benign moles. However, a small amount of H-hCG is also produced by the extra-villous cytotrophoblasts. In GTN, H-hCG makes up a high percentage of hCG because cytotrophoblastic cells account for a high percentage of cells in these invasive tumors[6]. The hCG tumor marker plays an important role in the diagnosis and treatment of patients with GTN, especially in patients receiving chemotherapy. Unfortunately, beta-hCG (B-hCG) may not be helpful in all cases. H-hCG marker, which allows for distinguishing active GTN from quiescence GTN, is very important in therapeutic planning in these patients[7]. An increase in the percentage of hCG-H indicates the presence of active disease. Physicians usually wait until hCG rises rapidly or until the diagnosis is confirmed by other methods. The purpose of the present study was to help physicians avoid unnecessary treatment of GTN and begin the treatment of patients with neoplasia as soon as possible. Cases of quiescence GTN do not need chemotherapy, while it is necessary to treat active GTN[8]. Since few studies have been conducted in this field worldwide, and no similar study has been conducted in our country (Iran), the present study aimed to investigate B-hCG/H-hCG ratio in GTN patients.

MATERIALS AND METHODS

This was a cross-sectional study in 22 GTN patients who were referred to an oncology clinic of an academic hospital of Mashhad University of Medical Science in Iran between December 2017 and May 2018. Inclusion criteria were plateau level of B-hCG (during 4 weeks) or persistent low level of HCG. After ruling out other etiologies and a history of medical illness (such as liver and kidney diseases and hypertension); patients with no contraindications for chemotherapy were eligible for the study. Exclusion criteria included patient's refusal to continue cooperation after initiation of the study; inability to follow-up the patient; confirmed metastasis or evidence of GTN recurrence in subsequent

studies. H-hCG was measured with Zelbio kit, which is an ELIZA kit (Germany) with reported accuracy of more than 99%[9]; then the ratio of H-hCG/total hCG was evaluated. If the proportion was more than 20%, active GTN was diagnosed, and if it was less than 20%, quiescent GTN was the diagnosis. In patients with active GTN, interventional procedures included a change in dose intensity or chemotherapeutic agents, or a surgery was proposed. Only serial follow-up was recommended in patients with quiescent GTN. Patients' status was followed during therapy and until normal level of hCG was reached. Descriptive statistical methods included central indices, distribution and frequency distribution in appropriate tables and charts, and were analyzed with version 23 of SPSS software.

RESULTS

In this study, 22 GTN patients were evaluated. The mean age of patients was 31.36 ± 8.01 years and the mean body mass index was 20.7 ± 2.1. The most frequent diagnosis was hydatidiform mole, which was reported in 14 (64%) patients, while partial mole was confirmed in 18.2% (4 patients). Placental site trophoblastic tumor accounted for 13.6% (3 patients). The lowest frequency was related to choriocarcinoma, which occurred in only one patient (4.5%). In total, chemotherapy was administered in approximately 18 (82%) patients (Tab. 1). The most common chemotherapy regimen was methotrexate (MTX) – 72% (13 patients), followed by a combination of MTX and Actinomycin (3 patients) – 17%, and methotrexate and EMA-Co (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine/oncovine) in 1.2% (2 patients).

The time interval between the onset of chemotherapy until plateau or persistent low level of hCG was 11.26 ± 4.03 weeks with a range between 4 and 18 weeks. The time interval between the plateau hCG level and testing H-hCG was 5.27 ± 2.76 weeks, with a range between 2 and 13 weeks. The reason for the prolongation of this range was the lack of timely participation in the tests. The mean B-hCG level was 36.6 mIU/mL with a range between 5.20 and 212.00 mIU/mL. The mean H-hCG/total hCG ratio was 6.24%, ranging from 0.6 to 49.30%. This ratio was less than 20% in 82% (n = 18) of cases; the therapeutic process was intended only as continuous follow-up. Among these patients, 14 (77.8%) had spontaneously normalized levels of B-hCG during 6 months of follow-up. Two patients underwent chemotherapy due to an increase in B-hCG. Other patients are still under follow-up without disease progression (Tab. 2). Among 4 patients whose H-hCG/total hCG ratio was more than 20%, hysterectomy was recommended to one patient due to multiparity and disease limited to the uterus. The dose of methotrexate was increased in one patient. In the other 2 patients, chemotherapy regimen was changed to EMA-CO, and a decrease in B-hCG level to normal was observed in all of them.

Variable		Number (%)
Diagnosis	Hydatiform mole	14 (63.6)
	Partial mole	4 (18.2)
	Placental site trophoblastic tumor	3 (13.6)
	Choriocarcinoma	1 (4.5)
Chemotherapy	No	4 (18.2)
	Yes	18 (81.8)

Tab. 1. The clinical features of the study group

DISCUSSION

The purpose of the present study was to help physicians avoid unnecessary treatment in patients suffering from GTN and begin the treatment in patients with neoplasia as soon as possible. The results of this study indicate that H-hCG level can be used to distinguish an active GTN from the quiescence one. Cases of quiescent GTN do not need chemotherapy, while it is necessary to treat the active GTN group. According to studies, the continuous level of hCG begins to change, and hCG rapidly increases within 6 months to 10 years after it reaches the plateau level in 10–25% of patients with quiescence GTN. In many of these patients, the subsequent follow-up confirms the presence of a tumor with pathology of choriocarcinoma or other GTN cases. In fact, quiescence gestational trophoblastic disease is a pre-malignant syndrome which can become malignant in a number of patients. As noted, a single measurement of H-hCG is sufficient to confirm active GTN. This process allows to initiate treatment as early as possible or it may indicate a delay in treatment until hCG-H is present in the blood[7,8]. Previous studies also approve using H-hCG as a diagnostic tool. In his review study, Cole reported that a total of 100% of trophoblastic malignancies produced hyperglycosylated hCG markers in serum and urine and that no benign disease cases are positive for this malignancy promoter. They also indicated that hyperglycosylated hCG and its free β-subunit exist in all human cancers and promote malignancy[10]. Another, more recent study showed that the hCG β-subunit produced by cancers promotes malignancy, enhances cancer cell growth, cancer cell invasion and blockage of apoptosis in cancers. A study of 42 choriocarcinoma cases showed that percentage hyperglycosylated hCG exactly correlates with weekly doubling rate of cancer[11]. Another study was designed to answer the following two questions: Can H-hCG be a reliable marker for the diagnosis of active neoplasia in pregnancy or choriocarcinoma? And can H-hCG help in differentiating quiescent gestational trophoblastic disease from active neoplasia? The study patients were 82 GTN cases; choriocarcinoma, previous hydatidiform mole under chemotherapy and low real positive hCG level. The results of the present study were consistent with the previous study. There was no significant difference in total hCG value between women with quiescence GTN and active cases ($p > 0.05$). However, H-hCG was significantly higher in active cases ($p < 0.000001$). Indeed, hCG was able to differentiate this phenomenon with a 5% false positive ratio, while H-hCG could differentiate 100%

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Patient's code	H-hCG/total hCG ratio	Therapeutic plans	Final situation
001	More than 20%	Follow-up	Monthly follow-up
002	Less than 20%	Follow-up	Zero concentration/ended Follow-up
003	Less than 20%	No referral	–
004	Less than 20%	Follow-up	Zero concentration/monthly Follow-up
005	Less than 20%	Follow-up	Zero concentration/ended Follow-up
006	Less than 20%	Follow-up	Zero concentration/weekly Follow-up
007	Less than 20%	Follow-up	Zero concentration/ended Follow-up
008	More than 20%	Follow-up	Zero concentration/ended Follow-up
009	Less than 20%	Follow-up	Zero concentration/ended Follow-up
010	Less than 20%	Follow-up	Zero concentration/ended Follow-up
011	More than 20%	Follow-up	Zero concentration/ended Follow-up
012	Less than 20%	Follow-up	Zero concentration/ended Follow-up
013	Less than 20%	Follow-up/an increased beta/hysterectomy/ an increased concentration/PET scan	Under follow-up
014	Less than 20%	Follow-up	Zero concentration/monthly Follow-up
015	Less than 20%	Follow-up/an increased concentration	Under chemotherapy
016	More than 20%	Chemotherapy/a decreased concentration	Ended Follow-up
017	Less than 20%	Follow-up	Zero concentration/monthly Follow-up
018	Less than 20%	Follow-up	Zero concentration/monthly Follow-up
019	Less than 20%	Follow-up/an increased concentration/an increased dose of methotrexate/an increased concentration again/a recommended hysterectomy	No referral
020	Less than 20%	Two zero concentrations	Zero concentration/weekly Follow-up
021	Less than 20%	One zero concentration	Zero concentration/weekly Follow-up
022	Less than 20%	Follow-up	Zero concentration/monthly Follow-up

Tab. 2. The results of follow-up in the study group

active GTN with the same false positive ratio[12]. Active disease was diagnosed half to 11 months earlier than the rapid increase in hCG using HCG-H in 23 patients in the present study. In the remaining 11 patients, H-hCG increased during clinical diagnosis of GTN tumor. Consistently, in 2009, Muller and Cole reported their experience of the US hCG Reference Laboratory Service between 1999 and 2009, on 133 cases of quiescent GTN, 35 cases of active disease and 30 cases of low level hCG. All cases of patients with low level of hCG (hCG-H less than 40%) were resistant to chemotherapy. The Center recommends that chemotherapy should not be used in patients with low level of hCG unless the hCG level is above 3,000 IU/mL[5].

All told, hCG and hyperglycosylated hCG free β-subunit promote the production of invasive enzymes collagenases and metalloproteinases, promote cell growth, and block cellular apoptosis, or have all malignancy properties[13].

We hope to make an antibody against hCG-H that would block tumorigenesis to prevent disease progression in GTN patients in the future.

LIMITATIONS

Small sample, which reduces the power of the study to generalize the results, is one of the limitations of our study.

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The limited duration of the study, which makes it unlikely that patients will ultimately be followed for months or years, is also a limitation. Another limitation of this study was the inability to perform long-term follow-up in all patients as they were not residents of Mashhad.

CONCLUSION

The data in this study suggests using H-hCG as a tumor marker in patients with persistent low level of B-hCG, which is useful to distinguish between quiescence gestational trophoblastic neoplasia, which does not need treatment, and active gestational trophoblastic neoplasia. However, further studies with larger sample size are needed to confirm and generalize the above findings. In addition, it is also useful to choose the best treatment option for patients. However, further studies with larger sample size are recommended.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication

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Immunotherapy toxicities in metastatic vulvar and vaginal melanomas: a retrospective cohort study

Toksyczność immunoterapii w przerzutowych czerniakach sromu i pochwy: retrospektywne badanie kohortowe

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Abstract

This retrospective cohort study examined the factors for patients with metastatic vulvar and vaginal melanomas on immune checkpoint inhibitors. The study included all patients over the age of 18 who received either anti-cytotoxic T-lymphocyte-4 (anti-CTLA-4) therapy or anti-programmed cell death protein-1 (anti-PD-1) therapy at the Sunnybrook Hospital from June 2012 to December 2018. There were 11 patients with vulvar or vaginal melanoma on immune checkpoint inhibitor therapy. The main sites of metastasis included the lungs, lymph nodes, soft tissues, and liver. The majority of patients received prior radiation therapy (7/11) and prior surgical therapy (9/11). There were no differences in overall survival for vulvar or vaginal melanomas on anti-PD-1 vs. anti-CTLA-4 therapy ($p > 0.05$). There were no significant differences in overall survival for vulvar and vaginal vs. cutaneous melanoma ($p > 0.5$). There were no significant differences in overall survival in patients with vulvar and vaginal melanoma in the presence vs. absence of immune-related adverse events ($p > 0.05$), yet there was a significant difference in patients with cutaneous melanoma in the presence vs. absence of immune-related adverse events ($p < 0.05$). Knowledge of the presentation and outcome of vulvar and vaginal melanomas is important for clinical practice in gynecology.

Keywords: immune-related adverse events, metastatic melanoma, vulvar and vaginal melanoma, immune checkpoint inhibitors

Streszczenie

W retrospektywnym badaniu kohortowym ocenie poddano pacjentki z przerzutowym czerniakiem sromu i pochwy leczone inhibitorami immunologicznego punktu kontrolnego. Do badania kwalifikowały się pacjentki powyżej 18. roku życia, u których w Sunnybrook Hospital w okresie od czerwca 2012 do grudnia 2018 roku stosowano terapię blokującą antygen-4 cytotoksycznych limfocytów T – CTLA-4 (terapię anty-CTLA-4) lub leczenie przeciwciałami skierowanymi przeciwko receptorowi programowanej śmierci komórki 1 (terapię anty-PD-1). Do badania włączono 11 pacjentek z czerniakiem sromu lub pochwy leczonych inhibitorami immunologicznego punktu kontrolnego. Przerzuty były umiejscowione głównie w płucach, węzłach chłonnych, tkankach miękkich i wątrobie. U większości pacjentek wcześniej stosowano radioterapię (7/11) i leczenie chirurgiczne (9/11). Nie stwierdzono różnic w przeżyciu całkowitym u pacjentek z czerniakami sromu i pochwy otrzymujących terapię anty-PD-1 i terapię anty-CTLA-4 ($p > 0,05$). Nie odnotowano znamiennych różnic pod względem przeżycia całkowitego u pacjentek z czerniakiem sromu i pochwy w porównaniu z czerniakiem skóry ($p > 0,5$). Ponadto nie stwierdzono znamiennych różnic w przeżyciu całkowitym u pacjentek z czerniakiem sromu i pochwy w związku z obecnością/brakiem zdarzeń niepożądanych pochodzenia immunologicznego ($p > 0,05$), jednak znamienną różnicę w zależności od obecności/braku zdarzeń niepożądanych pochodzenia immunologicznego ($p < 0,05$) odnotowano wśród pacjentek z czerniakiem skóry. Wiedza na temat obrazu klinicznego i wyników leczenia czerniaków sromu i pochwy jest istotna dla praktyki klinicznej w obszarze ginekologii.

Słowa kluczowe: zdarzenia niepożądane pochodzenia immunologicznego, przerzutowy czerniak, czerniak sromu i pochwy, inhibitory immunologicznego punktu kontrolnego

INTRODUCTION

The use of immunotherapy for the treatment of metastatic melanoma was initially started with the approval of anti-cytotoxic T-lymphocyte-4 (anti-CTLA-4) therapy which was the first therapy to improve overall survival (OS) in patients with metastatic melanoma[1]. Furthermore, anti-programmed cell death protein-1 (anti-PD-1) therapy was approved by the Food and Drug Administration for the management of advanced melanoma upon evidence of their unprecedented response rates of 30–40% in various clinical trials[2]. Anti-CTLA-4 antibodies block the interaction between CTLA-4 (cytotoxic T-lymphocyte-associated protein-4) molecules on the surface of T cells and B7 receptors[3], while anti-PD-1 antibodies block the interaction between PD-1 receptors[4]. Vulvar and vaginal melanomas comprise a subgroup of mucosal melanoma associated with high rates of recurrence and distant metastases. They have a poor prognosis, in part due to the lack of well-established protocols for staging and treatment, as well as difficulties performing full surgical resection for advanced presentations[5]. In view of the rare incidence of these melanomas, data on clinical presentation and treatment outcome for these melanomas is largely available through case reports and small retrospective studies[6]. As there are few comprehensive studies that examine patients metastatic vulvar and vaginal melanomas on anti-PD-1 and anti-CTLA-4 therapies[6,7], we have investigated the clinical presentation, disease management, and clinical outcomes for these immunotherapeutic agents.

MATERIALS AND METHODS

The study inclusion criteria were patients with metastatic melanoma at least 18 years old that received immune checkpoint inhibitors (ICIs) (either anti-PD-1 and/or anti-CTLA-4 therapy) at the Sunnybrook Hospital from June 2012 to December 2018. There were no specific exclusion criteria. Research Ethics Approval was obtained from the Sunnybrook Health Sciences Centre. The primary outcome included the clinical presentation and management of vulvar and vaginal melanomas. The secondary outcomes included the clinical outcome in vulvar and vaginal melanomas treated with ICIs. Descriptive statistics were used to summarize data. Chi-square test was used to determine associations. Kaplan–Meier analysis and log-rank test were used for OS. p-values <0.05 were considered statistically significant.

RESULTS

From 235 patients with metastatic melanoma, 11/235 (4.7%) had vulvar and vaginal melanomas, 173/235 (73.6%) cutaneous melanoma, and the remainder other subtypes. Patients with vulvovaginal melanoma had a median age of 58.0 years (range 29.0–78.0). The clinical features and treatments for vulvar and vaginal melanomas are depicted in Tab. 1. Most patients who received radiation therapy were also treated surgically.

There were no significant associations between types of toxicities and sites of metastasis including lung metastases and pneumonitis (p = 0.2), liver metastases and gastrointestinal toxicity (p = 0.4), central nervous system metastases and nervous system toxicity (p = 0.1), musculoskeletal/connective tissue disease metastases, and soft tissue/other toxicities (p = 0.1). Furthermore, there were no differences in OS for vulvar or vaginal melanomas on anti-PD-1 (46.0 months) vs. anti-CTLA-4 therapy (45.3 months; p > 0.05). There were

Clinical features and treatment data	***n*** **(%)**
Melanoma	
Vaginal	7/11 (63.6%)
Vulvar	4/11 (36.4%)
Mutation status	
NRAS	1/11 (9.1%)
c-*KIT*	1/11 (9.1%)
BRAF	0/11 (0%)
Site of metastasis	
Lung	9/11 (81.8%)
Lymph node	9/11 (81.8%)
Soft tissue	7/11 (63.6%)
Liver	6/11 (54.5%)
Central nervous system	2/11 (18.2%)
Bone	2/11 (18.2%)
irAEs	
Gastrointestinal	2/11 (18.2)
Cutaneous	1/11 (9.1)
Pneumonitis	1/11 (9.1)
Hypothyroidism	1/11 (9.1)
Nervous system disorder	1/11 (9.1)
Renal and urinary disorder	1/11 (9.1)
Musculoskeletal and connective tissue disorder	1/11 (9.1)
Prior treatment	
Adjuvant systemic therapy (paclitaxel/carboplatin)	1/11 (9.1%)
Adjuvant interferon	4/11 (36.4%)
Surgery only	9/11 (81.8)
Radiation therapy only	7/11 (63.6%)
First line ICI therapy for unresectable/metastatic disease	
Anti-PD-1	5/11 (45.5%)
Anti-CTLA-4	5/11 (45.5%)
Treatment outcome	
Progressive disease	6/11 (54.5%)
Response to treatment	1/11 (9.1%)
Missing data	4/11 (36.4)

anti-CTLA-4 – anti-cytotoxic T-lymphocyte-associated protein-4; **anti-PD-1** – anti-programmed cell death protein-1; ***BRAF*** – human gene that encodes the protein B-raf; **c-*KIT*** – human gene that encodes the receptor kinase protein known as tyrosine-protein kinase KIT; **ICI** – immune checkpoint inhibitor; **irAEs** – immune-related adverse events; ***NRAS*** – human gene that encodes the protein N-Ras.

Tab. 1. Clinical features and treatments for vulvar and vaginal melanomas

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no significant differences in OS for vulvar and vaginal vs. cutaneous melanoma ($p > 0.5$). Furthermore, OS was not different in patients with vulvar and vaginal melanomas with and without immune-related adverse events (irAEs) ($p > 0.05$), but was significantly different in cutaneous melanoma with and without irAEs ($p < 0.05$).

DISCUSSION

In summary, our results included 11 patients with vulvar or vaginal melanoma on ICI therapy. These patients developed irAEs and metastases that affected a wide variety of organ systems. The majority of patients received prior radiation therapy and prior surgical treatment. Furthermore, there were no significant differences in OS for vulvar and vaginal vs. cutaneous melanoma. Lastly, there were no significant differences in OS in patients with vulvar and vaginal melanoma in the presence vs. absence of irAEs ($p > 0.05$), yet a significant difference was noted in patients with cutaneous melanoma in the presence vs. absence of irAEs ($p < 0.05$).

Literature findings correlate with ICI-induced irAEs such as colitis, dermatitis and hypophysitis[6,7], alongside additional irAEs such as vulvitis[8]. The ICI therapies were generally well-tolerated, as demonstrated by the low incidence of irAEs, a result that is further supported by other previous studies[6]. Importantly, however, many irAEs can present asymptomatically or with non-specific, mild-grade symptoms, thus necessitating the importance of educating providers about the distinct toxicity profiles of irAEs in this patient population despite unassuming initial clinical presentations[9–11]. The management of ICI-induced-irAEs in patients with vulvar and vaginal melanoma has ranged from the discontinuation of ICI therapy, and the switch from combination therapy to monotherapy, to the provision of steroids[12].

Furthermore, radiation is more commonly used in disease management due to difficulties obtaining clear surgical margins. Recent studies indicate better outcomes in patients treated with surgery or combination therapy, as compared to radiation monotherapy[13], explaining the high number of patients receiving both radiation and surgical therapy prior to ICIs. Of note, complete surgical resection in unattainable in many cases of vulvar and vaginal melanoma due to the advanced disease presentation[5]. In addition, radical surgeries usually require a long recovery period in the vulvar and vaginal region, as well as the associated lymph nodes[14]. Thus, efforts towards earlier diagnosis of vulvar and vaginal melanomas may contribute to a more effective treatment of these melanomas. As clinical management in highly dependent on tumor stage[15,16], and may include other modalities such as chemotherapy and targeted therapy[17], future studies can compare the number of prior radiation vs. surgical therapies in these patients prior to ICI therapy.

While our data showed no significant difference in survival for vulvar and vaginal vs. cutaneous melanoma, other studies suggest a worse prognosis for vulvar and vaginal melanomas[18]. Furthermore, the survival of vaginal melanoma specifically is inferior to that of vulvar melanoma due to histopathological differences[19]. Therefore, the ratio of vulvar to vaginal melanomas may have affected our results.

The ICI-induced-irAEs are postulated to be caused by the systemic activation of cytotoxic lymphocytes that target healthy tissues[20]. Our results showed significant differences in OS in the presence and absence of irAEs for cutaneous melanoma but not vulvar or vaginal melanomas. The finding suggests that while irAEs were historically associated with improved survival in cutaneous melanoma, this survival benefit might not necessarily translate to rare subtypes of mucosal melanoma such as vulvar and vaginal melanomas. Increasing education about the presentation of irAEs and disease outcome could serve as a vital touchpoint for patients with vulvar and vaginal melanomas on ICI therapy. Future studies can examine whether irAE sites and severity affect disease outcome in vulvar and vaginal melanomas. With the increasing use of ICIs for vulvar and vaginal melanomas, knowledge of the presentation and outcomes is important for routine clinical practice in gynecology.

Conflict of interest

Rossanna C. Pezo reports the receipt of honoraria from Pfizer, EMD Serono and Novartis, and research funding from Merck, and serves on advisory boards for Astra Zeneca, Exact Sciences, Lilly, Myriad Genetics, Pfizer and Novartis, all outside the submitted work. The other authors report no conflicts of interest.

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Examining the impact of body mass index on overall survival in vulvar, vaginal and other mucosal melanomas: a retrospective cohort study

Analiza wpływu wskaźnika masy ciała na przeżycie całkowite u pacjentek z czerniakiem sromu, pochwy i innych czerniaków błon śluzowych: retrospektywne badanie kohortowe

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Abstract

Aim of the study: In this retrospective cohort study we have examined differences in survival profiles with respect to the body mass index in patients with mucosal melanoma on immune checkpoint inhibitor therapy. **Materials and methods:** The primary outcome included the association between the body mass index and overall survival in patients with metastatic mucosal melanoma. The secondary outcomes included the clinical presentation and management of vulvar and vaginal melanomas with oral and anorectal mucosal melanomas, as well as the surgical and radiological management of vulvar and vaginal melanomas. Kaplan–Meier analysis and log-rank test were used for the assessment of overall survival. **Results:** The results showed that patients with mucosal melanoma whose body mass index was ≥25 had better overall survival ($p = 0.02$). Overall survival was different between vulvar/vaginal vs. oral mucosal melanoma ($p = 0.02$). Overall survival was not different between vulvar/vaginal vs. anorectal melanoma ($p = 0.77$). Some immune toxicities were specific to patients with vulvar/vaginal melanoma. **Conclusions:** Obesity is associated with improved survival in patients with metastatic mucosal melanoma, although findings can be heterogeneous depending on the subtype of mucosal melanoma.

Keywords: body mass index, vulvar melanoma, vaginal melanoma, immune checkpoint inhibitors

Streszczenie

Cel pracy: W ramach retrospektywnego badania kohortowego oceniano różnice w profilu przeżycia w odniesieniu do wskaźnika masy ciała u pacjentek z czerniakiem błony śluzowej leczonych inhibitorami immunologicznego punktu kontrolnego. **Materiał i metody:** Jako pierwszorzędowy punkt końcowy analizowano zależność między wskaźnikiem masy ciała a przeżyciem całkowitym u pacjentek z przerzutowym czerniakiem błony śluzowej. Drugorzędowe punkty końcowe obejmowały obraz kliniczny i sposób leczenia czerniaków sromu i pochwy w porównaniu z czerniakami błony śluzowej jamy ustnej oraz odbytu i odbytnicy, a także leczenie chirurgiczne i radiologiczne czerniaków sromu i pochwy. Ocenę przeżycia całkowitego przeprowadzono przy wykorzystaniu analizy Kaplana–Meiera i testu *log-rank*. **Wyniki:** W badaniu stwierdzono lepsze przeżycie całkowite ($p = 0,02$) u pacjentek z czerniakiem błony śluzowej, u których wskaźnik masy ciała wynosił ≥25. Odnotowano różnice w przeżyciu całkowitym między czerniakiem sromu/pochwy a czerniakiem błony śluzowej jamy ustnej ($p = 0,02$). Nie wykazano natomiast różnic w przeżyciu całkowitym między czerniakiem sromu/pochwy a czerniakiem odbytu i odbytnicy ($p = 0,77$). Niektóre objawy toksyczności immunologicznej były swoiste dla pacjentek z czerniakiem sromu/pochwy. **Wnioski:** Otyłość wiąże się z lepszym przeżyciem u pacjentek z przerzutowym czerniakiem błony śluzowej, chociaż w zależności od podtypu nowotworu wyniki mogą być zróżnicowane.

Słowa kluczowe: wskaźnik masy ciała, czerniak sromu, czerniak pochwy, inhibitory immunologicznego punktu kontrolnego

INTRODUCTION

Despite being a negative prognostic factor in a majority of cancers, body mass index (BMI) is associated with favorable outcome in metastatic melanoma treated with immune checkpoint inhibitors (ICIs)[1,2]. However, these favorable outcomes have largely been observed in patients with metastatic melanoma or cutaneous melanoma, and few studies to date have examined this association in patients with mucosal melanoma. Furthermore, ICIs such as anti-cytotoxic T-lymphocyte-4 (anti-CTLA-4) and anti-programmed cell death protein-1 (anti-PD-1) have been of recent interest for metastatic vulvar and vaginal melanoma. Multiple clinical trials are currently examining the role of ICIs for treating this rare, aggressive disease with poor long-term clinical outcomes[3]. In this retrospective cohort study, we have examined differences in survival profiles in patients with mucosal melanoma with respect to the BMI. We have further performed a subgroup analysis of the survival and toxicity profiles of vulvar and vaginal melanoma vs. oral and anorectal mucosal melanoma on ICI therapy.

MATERIALS AND METHODS

This retrospective chart review involved patients with metastatic melanoma who were at least 18 years of age and received ≥1 dose of ICIs (either PD-1 and/or CTLA-4 inhibitors) at our institution from June 2012 to December 2018. Research Ethics Approval was obtained from the Sunnybrook Health Sciences Centre. The primary outcome included the association between the BMI and overall survival (OS) in patients with metastatic mucosal melanoma. The secondary outcomes included the comparison of clinical presentation and management of vulvar and vaginal melanomas with oral and anorectal mucosal melanomas, as well as surgical and radiological management of vulvar and vaginal melanomas. Kaplan–Meier analysis and log-rank test were used for OS.

RESULTS

A total of 235 patients with metastatic melanoma were examined, including 11/235 (4.7%) with vulvar and vaginal mucosal melanoma, 7/235 (3.0%) with oral mucosal melanoma, 4/235 (1.7%) with anorectal mucosal melanoma, and the remainder melanomas of cutaneous, desmoplastic, and unknown subtypes. The mutation status, prior therapies, toxicities, treatment outcomes for vulvar and vaginal melanoma vs. oral mucosal melanoma and anorectal mucosal melanoma are compared in Tab. 1. The total number of reported immune-related adverse events (irAEs) was 9 in patients with vulvar and vaginal melanoma, 4 in patients with oral mucosal melanoma, and 1 in anorectal mucosal melanoma. Importantly, some irAEs such as hypothyroidism, renal and urinary disorders, as well as musculoskeletal and connective tissue disorders were reported in patients with vulvar and vaginal melanoma, but not in patients with oral or anorectal mucosal melanoma.

Amongst the patients with mucosal melanoma, overweight and obese patients with the BMI greater than or equal to 25 had a significantly higher OS (52.5 years) compared to patients whose BMI was <25 (47.6 years; $p = 0.02$, chi-square statistics = 5.05, degrees of freedom = 1). Furthermore, the subgroup analysis resulted in a statistically significant difference in OS between vulvar and vaginal melanoma vs. oral mucosal melanoma ($p = 0.02$, chi-square statistic = 5.63, degrees of freedom = 1), though without a significant difference in OS between vulvar and vaginal vs. anorectal melanoma ($p = 0.77$, chi-square statistic = 0.08, degrees of freedom = 1).

	Vulvar and vaginal melanoma; frequency (%)	Oral mucosal melanoma; frequency (%)	Anorectal mucosal melanoma; frequency (%)
Mutation status			
NRAS	1/11 (9.1)	0	1/4 (25.0)
c-KIT	1/11 (9.1)	1/7 (14.3)	0
BRAF	1/11 (9.1)	1/7 (14.3)	0
Total	3/11 (27.3)	2/7 (28.6)	1/4 (25.0)
Prior therapy			
Surgery	9/11 (81.8)	4/7 (57.1)	3/4 (75.0)
Radiation therapy	7/11 (63.6)	3/7 (42.9)	1/4 (25.0)
irAEs			
Gastrointestinal	2/9 (22.2)	1/4 (25)	0
Cutaneous	1/9 (11.1)	1/4 (25)	0
Pneumonitis	1/9 (11.1)	1/4 (25)	0
Hypothyroidism	1/9 (11.1)	0	0
Nervous system disorder	1/9 (11.1)	0	0
Renal and urinary disorder	1/9 (11.1)	1/4 (25)	0
Musculoskeletal and connective tissue disorder	1/9 (11.1)	0	0
Pneumonitis	0	0	1/1 (100)
Unknown	1/9 (11.1)	0	0
Total reported	9/9 (100)	4/4 (100)	1/1 (100)
Treatment outcome			
Response to treatment	1/11 (9.1)	0	0
Progressive disease	6/11 (54.5)	4/7 (57.1)	2 (50.0)
Death	0	1/7 (14.3)	1 (25.0)
Unknown	4/11 (36.4)	2/7 (28.6)	1/4 (25.0)
Total	11/11 (100)	7/7 (100)	4/4 (100)

BRAF – human gene that encodes the protein B-raf; ***c-KIT*** – human gene that encodes the receptor kinase protein known as tyrosine-protein kinase KIT; **irAEs** – immune-related adverse events; ***NRAS*** – human gene that encodes the protein N-Ras.

Tab. 1. Comparison of mutation status, prior therapy, irAEs, and treatment outcomes for vulvar and vaginal, oral and anorectal mucosal melanoma

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DISCUSSION

Our results illustrate a favorable relationship between increased BMI values and OS in patients with mucosal melanoma on ICI therapy. The mechanism underlying the association between the BMI and survival in not well-understood, though some sources note that obesity may promote leptin-mediated T-cell dysfunction, which is reversed by the blockade of the PD-1[4]. Furthermore, a recent review on melanoma patients illustrates that the factors that induce an immunosuppressive microenvironment could in turn make these patients more susceptible to ICI therapy[1]. A retrospective study of 423 patients with metastatic melanoma showed a significant survival benefit in overweight and obese patients receiving combination immunotherapy but heterogeneous trends for other treatment types[5]. As our results focus more specifically on patients with mucosal melanoma, our findings shed light on potential contributors to such heterogeneous trends, such as the melanoma subtype. In addition, a body composition analysis on melanoma patients identifies inferior clinical outcomes in patients with sarcopenic obesity ($p = 0.04$), as well as high total adipose tissue index ($p = 0.02$), a difference that was particularly strong in women compared to men[2]. These findings merit further investigation of the association between body composition and survival in patients with mucosal melanoma on ICI therapy.

A greater percentage of patients with vulvar and vaginal melanoma received surgical or radiation therapy prior to ICI therapy, compared to patients with oral mucosal melanoma. Of note, radiation is more commonly used in the management of anorectal melanoma as well as vulvar and vaginal melanoma compared with oral mucosal melanoma, which is related to difficulties obtaining clear surgical margins for the former subtypes[6]. Recent studies indicate better outcomes in patients treated with surgery or a combination of surgery and radiotherapy, compared to radiation monotherapy[7]. The complex nature of vulvovaginectomies, as well as the associated complications and morbidity, could explain the rare prevalence of these procedures despite favorable treatment outcomes[7].

Other studies support the presence of a KIT mutation which encodes a transmembrane receptor tyrosine kinase in both mucosal melanomas as well as other cancers such as gastrointestinal stromal tumors[8]. Similarly, the *BRAF* gene encodes the B-raf protein and has a much lower incidence in mucosal melanoma compared to cutaneous melanoma[8]. Despite the low incidence of targetable *KIT* and *BRAF* mutations, it is essential that mutational analysis is carried out in all cases of metastatic vulvar and vaginal melanoma in order to identify further options for systemic therapy. Furthermore, these findings support the use of targeted therapies such as imatinib for *KIT* mutations in mucosal melanomas[9].

While literature sources demonstrate a more aggressive behavior and poorer prognosis in mucosal melanoma compared to cutaneous melanoma[10], our results indicate that there is wide heterogeneity within some subtypes of mucosal melanoma, as demonstrated by the significant difference in OS between vulvar/vaginal melanoma and oral melanoma, but not anorectal melanoma.

CONCLUSIONS

With the increasing use of ICIs in the management of mucosal melanomas, and vulvar and vaginal melanomas in particular, a greater understanding of the clinical outcomes is imperative for the gynecologists who may treat these patients in routine clinical practice.

Conflict of interest

Rossanna C. Pezo reports the receipt of honoraria from Pfizer, EMD Serono and Novartis, and research funding from Merck, and serves on advisory boards for Astra Zeneca, Exact Sciences, Lilly, Myriad Genetics, Pfizer and Novartis, all outside the submitted work. The other authors report no conflicts of interest.

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The role of long non-coding RNA (lncRNA) in the development of ovarian cancer

Rola długich niekodujących RNA (lncRNA) w raku jajnika

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Abstract

The aim of this study was to review research on the role of long non-coding RNA (lncRNA) in ovarian cancer. This article analyses studies on the effect of increased lncRNA expression on the size of ovarian cancer and the incidence of metastasis. The review covers a period from October 15, 2018 to August 22, 2020, and comprises 23 studies in which a total of 1,580 women with ovarian cancer participated, and an undetermined number of control groups where healthy tissue samples were collected. A review of the studies indicates that increased lncRNA expression is associated with elevated ovarian cancer size and metastatic risk. The most studied lncRNA include *HOTAIR*, *CCAT2*, *GAS5*, *MALAT-1*, *UCA1*. Studies assessing the expression levels of *HOTAIR* lncRNA and *CCAT2* in normal and cancer tissue showed varying levels of expression in studies of different authors, which indicates that the expression of the same lncRNA may vary individually or is a result of study errors.

Keywords: lncRNA, ovarian cancer, expression, FIGO

Streszczenie

Celem pracy był przegląd badań dotyczących oceny roli długiego, niekodującego RNA (*long non-coding RNA*, lncRNA) w raku jajnika. W artykule dokonano przeglądu badań dotyczących wpływu zwiększonej ekspresji lncRNA na rozmiar raka jajnika i występowanie przerzutów. Przeglądu badań dokonano w okresie od 15 października 2018 do 22 sierpnia 2020 roku. W przeglądzie uwzględniono 23 badania, w których łącznie wzięło udział 1580 kobiet z rakiem jajnika oraz nieokreślona liczba osób z grup kontrolnych, od których pobrano zdrowe tkanki. Przegląd badań wskazuje, że zwiększona ekspresja lncRNA jest związana ze zwiększonym rozmiarem raka jajnika oraz przerzutami. Najczęściej badane lncRNA to: *HOTAIR*, *CCAT2*, *GAS5*, *MALAT-1*, *UCA1*. Badania, które oceniły poziom ekspresji lncRNA *HOTAIR* oraz *CCAT2* w tkance zdrowej i nowotworowej, wykazały różne poziomy ekspresji u różnych autorów, co świadczy o tym, że ekspresja tego samego lncRNA może być zmienna osobniczo lub jest wynikiem błędów w przeprowadzonym badaniu.

Słowa kluczowe: lncRNA, rak jajnika, ekspresja, FIGO

INTRODUCTION

An important achievement of biology in the second half of the twentieth century was the understanding of the molecular processes underlying the expression of genetic information. Information created at that time seemed to be precise and completely describe the scheme of living organisms. The information was mainly focused on deoxyribonucleic acid (DNA) as an information carrier and proteins, i.e. the final product. Ribonucleic acid (RNA) molecules were attributed with the secondary role as an intermediary in protein biosynthesis. RNA is a polymer consisting of nucleotides composed of ribose, a phosphate residue, and one of four nitrogen bases: adenine, guanine, cytosine or uracil. Today, the knowledge about the functioning of RNA is much wider. It is known that RNA is not only a skeleton that binds proteins or an adapter that enables translation. The current state of knowledge warrants the conclusion that RNA is directly involved in the synthesis of proteins, and is a cofactor involved in many biochemical processes or affecting the structure of the genome[1]. Biology textbooks divide RNA into messenger (mRNA) and non-coding RNA (ncRNA). Among ncRNA, housekeeping RNA and regulatory RNA are distinguished. Housekeeping RNA includes rRNA, tRNA, snoRNA. Regulatory RNA is divided into short ncRNA (<200 base pairs), long ncRNA (lncRNA) (>200 base pairs), and very long ncRNA (>100,000 base pairs). Short-coding RNA includes miRNA, siRNA, piRNA, tsRNA (Fig. 1)[2]. The amount of lncRNA outweighs the amount of short ncRNA. Most lncRNA is present in the nucleus and cytoplasm[3]. Recent research results indicate that lncRNA may be involved in the development of ovarian cancer. An increased level of lncRNA expression is associated with increased tumor size[4] as well as lower predicted survival outcomes[5]. Studies reveal that the level of lncRNA expression is not dependent on the histological type[6]. The World Health Organization (2014) distinguishes the following histological types of ovarian cancer: serous cancer, mucous carcinoma, endometrioid cancer, clear cell carcinoma, transitional cell carcinoma, Brenner tumor, squamous cell carcinoma, mixed cancer, undifferentiated cancer, sarcoma carcinoma, and granulomatosis[7].

ETIOLOGY OF OVARIAN CANCER

Over 95% of malignant ovarian tumors have epithelial origin. The most important risk factors include *BRCA1* and *BRCA2* mutation carriers, hereditary ovarian cancer syndromes, childlessness, hereditary ovarian and breast cancer syndromes, hereditary ovarian cancer, and familial

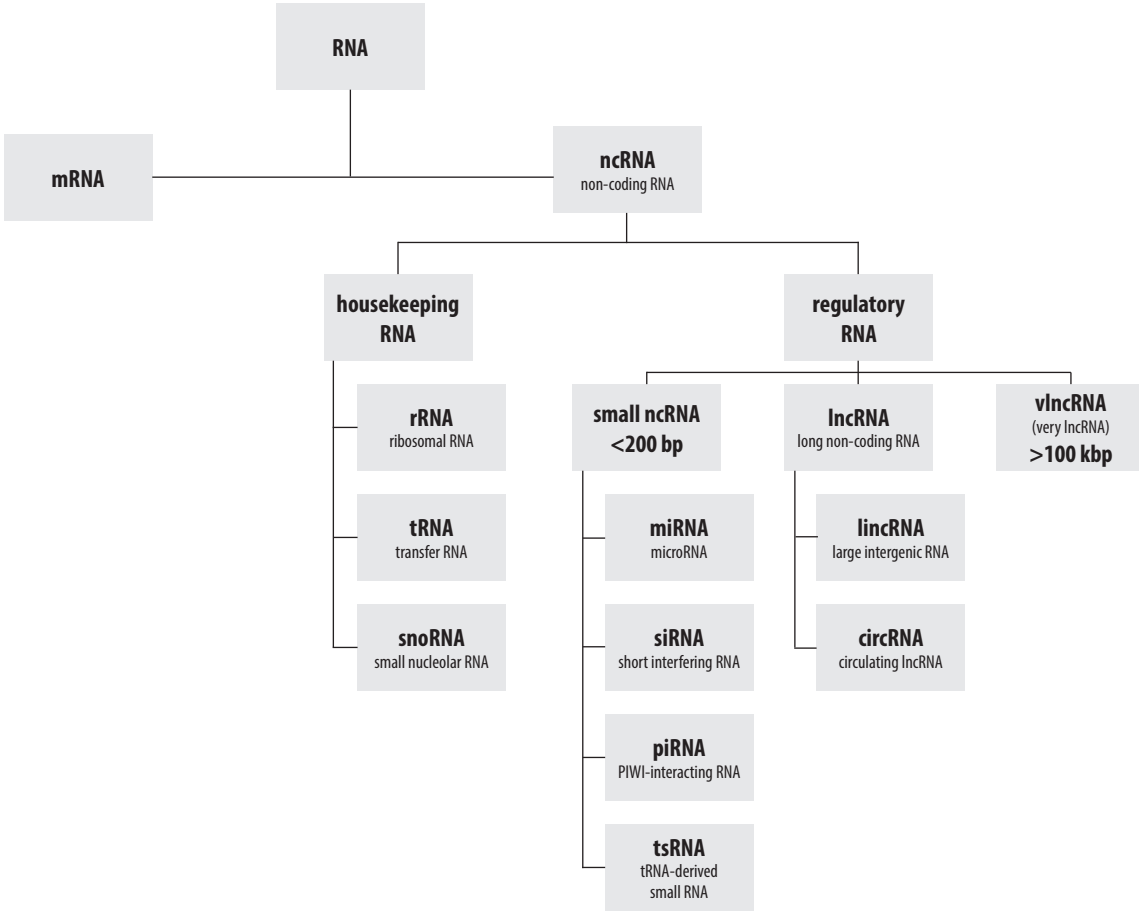

Fig. 1. RNA division[2]

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occurrence of non-globular colorectal cancer. Factors that reduce the risk of ovarian cancer include hormonal contraception, fallopian tube occlusion, uterus excision, and breastfeeding[8].

HISTOLOGICAL TYPES OF OVARIAN CANCER AND THEIR CHARACTERISTICS

Nowak-Markwitz and Spaczyński divide ovarian cancer into two types. Type I is characterized by a diagnosis at a less advanced stage, slow growth and low sensitivity to chemotherapy, and good prognosis. Type I comprises serous, endometrial, mucosal, clear cell carcinomas and Brenner cancers. Type II of ovarian cancer is diagnosed at stages III and IV. Type II is characterized by rapid growth and high sensitivity to chemotherapy, and poor prognosis. Type II comprises serous, endometrial, undifferentiated and sarcoma carcinomas[9] (Tab. 1).

EFFECT OF LNCRNA EXPRESSION ON THE SURVIVAL OF PATIENTS WITH OVARIAN CANCER

LncRNA does not have the translation potential due to the presence of multiple stop codons in mature transcripts[13]. However, the lack of protein coding and the absence of translation potential does not mean that lncRNA does not carry any information or perform any function[1]. The available literature does not contain precise information on the role of lncRNA in the process of protein biosynthesis and their exact function in the cancerous process. Studies conducted so far have focused on associations between increased expression of lncRNA and tumor development and its increased size or involvement in the proliferation and migration of tumor cells[14]. siRNA potentially contributes to lower expression of lncRNA *NONRATT021972* as with other epigenetic mechanisms. Liu et al. (2016) observed that as a result of siRNA activity, the expression may be lowered by 0.5 in relation to the expression in which siRNA transfection was not applied[15]. In the majority of studies conducted to date, the exact impact of siRNA on the level of lncRNA expression has not been assessed, and the moment at which it is joined is not known. According to the literature data, some of them may have a prognostic value. Ning et al. (2018) conducted a meta-analysis to determine the impact of lncRNA expression on the survival of patients. A total of 15 studies evaluating 1,333 patients were included in the analysis. The results of the study predict a higher risk of death for patients with its increased level ($p > 0.05$). Another meta-analysis evaluated the effect of lncRNA expression on the survival time of patients based on its exact formula. A total of 14 studies were included in the study, with 1,276 participating patients. The results predict a higher risk of death in patients with its increased level ($p > 0.05$). The presented studies included the work of Xia et al. (2017) with the Kaplan–Meier curve, which presents the prognosis of survival of people at low and high level of lncRNA *ZFAS1* over consecutive months. The Kaplan–Meier curve predicts that a high level of lncRNA may be associated with the death of 35% of patients 60 months after surgery ($p < 0.05$), and in the case of women with its low level, 40% of patients may die after approximately 65 months. Similar data was reported in the paper by Cheng et al. (2015). According to their results, 55% of patients with a high level of lncRNA *AB073614* are expected to die after ca. 35 months ($p < 0.05$), and in the case of its low level, 50% of patients after 50 months are expected to die. The results obtained by Li et al. (2017) suggest a statistically significant difference between the predicted survival time of patients with low and high levels of lncRNA *SPRY 4-IT1* expression. The death of 25% of patients with high levels of expression is expected after ca. 50 months, and approximately 55% with low levels after ca. 50 months[5,16–21]. The results reported in the paper by Ning et al. (2018) indicate a very poor survival prognosis of patients who participated in the studies included in the meta-analysis.

Histological type of ovarian cancer	Characteristics	Accompanying molecular changes
Serous cancer	The glandular epithelium differentiates towards the phenotype of oviduct epithelial cells. In serous adenocarcinoma, a variety of glandular weaving is found depending on the stage of cancer.	Mutations in the *KRAS* gene (protooncogene Kristen rat sarcoma viral oncogene homolog) or *BRAF* (protooncogene B-Raf proto-oncogene)
Endometrioid cancer	The group of endometrioid ovarian tumors includes phenotypically equivalent proliferations of all types of cancer that may develop in the endometrial mucosa. In order to make an endometrial tumor diagnosis, no histological diagnosis of endometriosis is necessary.	Mutations of the *PTEN* gene (phosphatase, suppressor protein), *PIK3CA* (gene coding the PI3K kinase catalytic subunit), *CTNNB1* (gene coding β-catenin)
Mucosal tumor	They have glandular epithelium in their woven cells, containing neutral glucosamine (mucins) in the cytoplasm. Glandular epithelial cells are phenotypically similar to cells of different mature epithelia producing mucus (intestinal, glandular cells of the pylorus of the pyloric part).	Mutations in the *KRAS* gene and *HER2* overexpression (superficial growth factor receptor)
Clear cell carcinoma	Dispatch through epithelium, cells which have a clear cytoplasm or sometimes take on the hobnail appearance.	Mutations in the *TGF-β RII* gene (transforming the growth factor, receptor β II)
Sarcoma	Non-epithelial origin derived from connective tissue	Mutations in *TP53*
Undifferentiated ovarian cancer	-	-

Tab. 1. Characteristics of different histological types of ovarian cancer[10–12]

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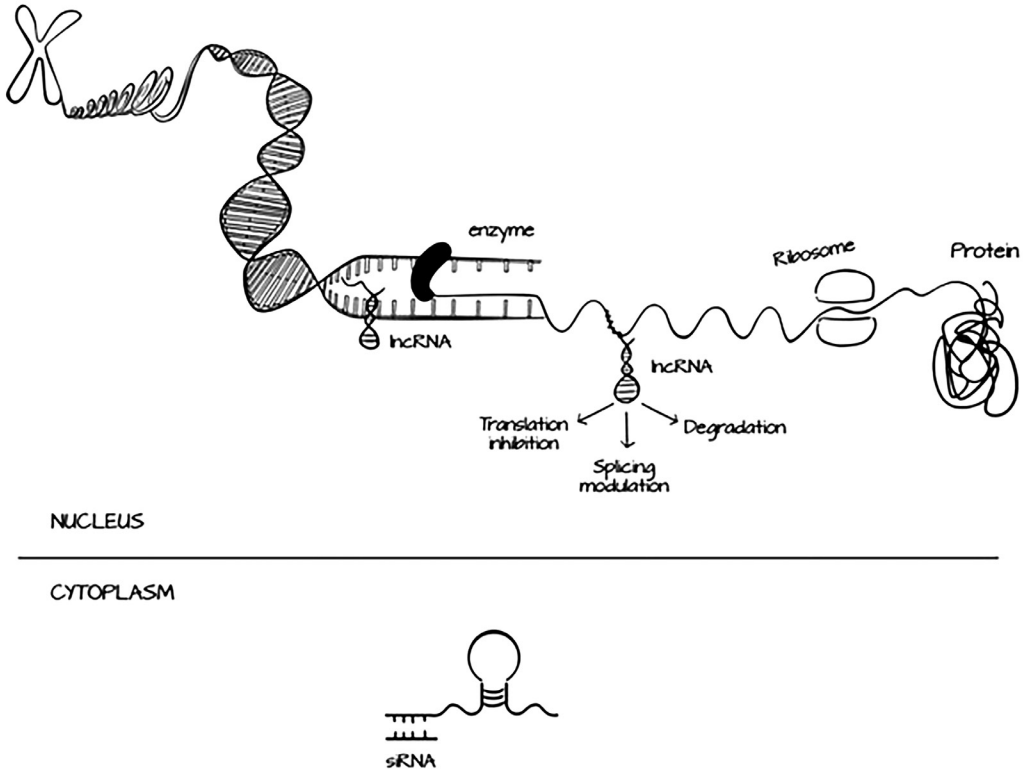

Fig. 2. Molecular function of lncRNA[26,27]

On the basis of only predicted values, it cannot be determined whether and to what extent an increased expression of lncRNA affects the survival time of patients[5]. Worku et al. (2017) in their study compiled 20 lncRNA and attributed the role they play in the cancer process. The analysis compared studies involving humans and animals, demonstrating that increased or decreased expression of ovarian cancer in lncRNA contributes to increased cell proliferation and migration, but there is no description of the underlying mechanism that is responsible for this observation[20].

ROLE OF lncRNA IN THE TRANSCRIPTION AND TRANSLATION PROCESS

According to high school textbooks, the process of protein biosynthesis begins with the attachment of polymerase to the gene promoter and dehydration of the DNA double helix. RNA polymerase moves along the DNA strand and unravels it, adding subsequent nucleotides to the mRNA strand[2,21]. In the next step of protein biosynthesis (translation), at first the ribosomal subunit attaches to the end of 5' mRNA, and the START (AUG) codon is attached with tRNA (transporting RNA). During the elongation and termination step, tRNA is carried by consecutive codons until the STOP codon is provided (at the termination stage) by tRNA to terminate the production of the polypeptide chain. In the biosynthesis process, miRNA proteins are responsible for regulating gene expression by joining this 6 nucleotide strand to mRNA and matching their nucleotides, as in the case to tRNA and mRNA, provided that the degradation of the mRNA strand is an effect of miRNA attachment to mRNA. When the complementarity is incomplete, the process of protein biosynthesis is blocked. siRNA is also responsible for the silencing of gene expression. siRNA at the time of connection with the complementary strand of mRNA contributes to the fact that the mRNA strands are cleaved, which prevents the formation of coded protein[21,22]. At the time when the splicing of intronic regions takes place in the transcription process, after it ends there may be degradation of genetic material by the enzyme or protein that has been synthesized. The RNA types mentioned in school textbooks include ribosomal RNA (rRNA), whose molecules are a component of ribosomes – structures where proteins are synthesized, and small nuclear RNA (snRNA), which are involved in the pre-mRNA assembly process the main stage of maturation – transforming the primary transcript of genes encoding mRNA proteins. School textbooks do not describe the exact mechanism of ribosome formation from rRNA, and how it goes into their construction. According to the data reported by de la Cruz et al. (1999) DNA, as a result of rRNA transcription, leads to the formation of mRNA of which the polypeptide chain is biosynthesized, from which ribosomes are then biosynthesized[23]. The literature data indicates that the mechanism of protein biosynthesis is in fact more complicated, and more types of RNA are involved in it. Numerous studies were published, attempting to describe the functions of lncRNA in this process. Osielska and Jagodziński (2018)

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indicate that the epigenetic mechanism of lncRNA action depends on its potential attachment to tRNA in the translation process, however, their study shows that the attachment of lncRNA occurs when tRNA is connected to three ribosomes[2]. Usually, one ribosome is involved in the translation process[21]. Carpenter (2016) argues that lncRNA may play a role in the transcription process. The author does not discuss whether lncRNA is transcribed into mRNA and is a non-coding fragment of an exon that is included in the process of translation into protein biosynthesis or is an intron not transmitted to mRNA and under the influence of polymerase the lncRNA section is separated from the mRNA fragment, and lncRNA thus created participates in epigenetic mechanisms[24]. mRNA may be reverse-transcribed, resulting in the re-formation of DNA that can be stored in the form of chromosomes by wrapping into histones. Despite the lack of accurate information on whether lncRNA is prescribed for mRNA and is subject to the transcription and translation process like the other genes, or the translation process takes place, lncRNA is an intron and is excreted in the transcription process. Based on the information contained in the gene bank, it can be assumed that lncRNA ultimately undergoes reverse transcription and is found on one of the chromosomes[24,25] (Fig. 2).

CHARACTERISTICS OF lncRNA IN OVARIAN CANCER

HOTAIR is located on chromosome 12. According to the Gene Bank database, even though it is a non-coding region, no protein products are attributed to it, and the effect of increased *HOTAIR* lncRNA expression is the binding of lysine demethylase (LSD 1) and repulsive complex 2 Polycomb (*PRC2*) and it serves as scaffolding to connect these regulators to the *HOXD* gene cluster. The available literature lacks data on the method of binding of the above-mentioned compounds.

MALAT is located on chromosome 11. According to Gene Bank, it controls the transcription process and is stored in the nucleus, where it forms a framework for ribonucleoprotein complexes (which include miRNA), which are responsible for blocking the translation process. It can be assumed that this segment is subject to the process of splicing before the translation process, due to the formation of ribonucleoprotein complexes. The available literature lacks a description of the exact mechanism that leads to the incorporation of lncRNA *MALAT* into these complexes.

GAS5 is located on chromosome 6, and the product of this gene is lncRNA. According to Gen Cards, the component of this lncRNA is snoRNA.

HOXA11 according to Gene Bank, is located on chromosome 6 and the result of its action is the impact on the rate of expression of other chromosome 6 genes, the product of which is a protein. According to the Gen Cards data *HOXA11* encodes a protein, but there are no literature reports that would address the product of its expression. There is no data about the functions of some lncRNA in the Gene Bank, including *ANRIL*, *UCA1*, *CCAT2*, *BC200*, *TUG1*, *LNCRSR*, *RAD51-AS1*, *DARS-AS1*, *LSINCT5*, *AFAP-1AS1*, *lncSOX4*, *SNHG20*[28] (tab. 2).

METHODOLOGY

The PubMed database was systematically searched to identify studies that assessed the role of lncRNA in ovarian cancer. The effect of lncRNA expression on tumor size was evaluated. The following phrases were searched: ovarian cancer lncRNA (350 publications), lncRNA ovarian cancer review (36 publications), lncRNA ovarian cancer meta-analysis (11 publications), *MALAT* lncRNA ovarian cancer (4 publications), lncRNA ovarian cancer *H19* (32 publications), lncRNA ovarian cancer *HOTAIR* (23 publications), lncRNA ovarian cancer *HOST2* (2 publications), lncRNA ovarian cancer *UCA1* (15 publications), lncRNA ovarian cancer *PVT1* (1 publication), lncRNA *SNHG20* ovarian cancer (3 publication), and lncRNA *RAD51-AS1* ovarian cancer (1 publication), covering a period from October 15, 2018 to 22 August, 2020. The review included studies conducted among women with ovarian cancer that included information about the size of the study and control groups, which consisted of tissue samples collected from women with cancer involving sites that were not covered by the disease process, and the level of lncRNA expression in cancer tissue and healthy tissue. The review excluded studies conducted on animals and humans which provided no information about the size of the study group and the level of lncRNA expression. Also, the review did not include studies in which the control group consisted of women with benign ovarian cancer or the study group comprised patients with varying degrees of sensitivity to cisplatin.

SUMMARY

Previously conducted reviews of studies and meta-analyses concerned with the assessment of the role of lncRNA in ovarian cancer did not comprise all studies, and there are no exact data on the impact of different lncRNA on tumor size. The most frequently studied lncRNA included *HOTAIR*, *CCAT2*, *GAS5*, *MALAT*, *MALAT-1*, *UCA1*. In the studies carried out to date, the differences in lncRNA expression in healthy and cancerous tissue were typically evaluated without assessing the difference between lncRNA expression in the healthy and cancerous tissues with varying FIGO (International Federation of Gynecology and Obstetrics) stages. The results of eleven studies indicate that increased expression of lncRNA contributes to tumor growth ($p < 0.05$), and the findings obtained in eight studies indicate that increased lncRNA expression is related to metastases. Research carried out to date lacks accurate data that would indicate to what extent increased or decreased expression of lncRNA increases the size of the tumor. Studies evaluating the expression level in the *HOTAIR* or *CCAT2* lncRNA gene in

Author	Type of lncRNA	Population	Age [years]	Type of cancer and size of tumor	Treatment method	Level of lncRNA expression	Results
Zhang et al. (2016)[4]	*HOTAIR*	Study group: $n = 30$ Control group: $n = 30$***	45.8 ± 10.5	No data	Surgical treatment	Healthy tissue: 1.00** Ovarian cancer tissue: 3.00–9.00** <5 cm: 2.00** >5 cm: 4.00–13.00**	A statistically significant difference was observed in the level of *HOTAIR* lncRNA expression in the healthy tissue in relation to ovarian cancer tissue ($p < 0.05$) A statistically significant difference was observed in the level of *HOTAIR* lncRNA expression of the ovarian cancer size <5 cm in relation to ovarian cancer >5 cm ($p < 0.05$)
Qiu et al. (2015)[29]	*HOTAIR*	Study group: $n = 68$ Control group: $n = 30$	<50: $n = 26$ ≥50: $n = 42$	FIGO classification: • FIGO I/II: $n = 19$ • FIGO III/IV: $n = 49$ Tumor size: • <1 cm: $n = 46$ • ≥1 cm: $n = 22$	Surgical treatment	Healthy tissue: 0.000–0.001** Ovarian cancer tissue: 0.000–0.005**	Statistically significant difference in the level of *HOTAIR* lncRNA expression in the healthy tissue in relation to ovarian cancer tissue ($p < 0.05$)
Chang et al. (2018)[30]	*HOTAIR* *CCND1* *CCND2*	Study group: $n = 92$ Control group: $n = 92$***	≤55: $n = 41$ >55: $n = 51$	FIGO classification: • I + II: $n = 60$ • III + IV: $n = 32$ Histological type: • well: $n = 27$ • moderate: $n = 48$ • poor: $n = 17$	Surgical treatment	*HOTAIR*: • healthy tissue: 0.1–3.9** • cancer tissue: 0.3–7.2** *CCND1*: • healthy tissue: w0.1–1.5** • cancer tissue: 0.6–2.0** *CCND2*: • healthy tissue 0.1–2.3** • cancer tissue: 1.0–6.0**	Statistically significant difference in *HOTAIR* lncRNA expression, *CCND1* and *CCND2* between the healthy and cancerous tissue ($p < 0.05$) Relationship between *HOTAIR* lncRNA and *CCND1* expression ($r = 0.6784$, $p < 0.001$) Relationship between *HOTAIR* lncRNA and *CCND2* expression ($r = 0.4884$, $p < 0.001$)
Huang et al. (2016)[19]	*CCAT2*	Study group: $n = 109$ Control group: $n = 45$	<55: $n = 50$ ≥55: $n = 59$	FIGO classification: • I/II: $n = 33$ • III/IV: $n = 76$ Histological type: • serous cancer: $n = 78$ • mucinous: $n = 7$ • endodermal cancer: $n = 8$ • clear cell: $n = 9$ • others: $n = 7$ Tumor size: • ≤10 cm: $n = 62$ • >10 cm: $n = 47$	Surgical treatment and chemotherapy paclitaxel (135 mg/m^2) and cisplatin (75 mg/m^2) or paclitaxel (175 mg/m^2) and carboplatin (AUC 6) administered for 3 weeks in 6 cycles	Healthy tissue: 0.0–1.0** Ovarian cancer tissue: 0.0–4.8**	No statistically significant difference in *CCAT* lncRNA expression between groups of different histological types ($p > 0.05$) Statistically significant difference in the level of *CCAT* lncRNA expression between groups with different FIGO classification ($p < 0.05$)
Hua et al. (2018)[31]	*CCAT2*	Study group: $n = 31$ Control group: $n = 31$***	No data	No data	Surgical treatment	Healthy tissue: 0.01–0.09** Ovarian cancer tissue: 0.03–0.13**	Statistically significant difference in the level of *CCAT2* lncRNA expression in the healthy and cancerous tissue ($p < 0.05$)
Yim et al. (2017)[32]	*HOXA11*	Study group: $n = 129$ Control group: $n = 38$	Low expression: average of 54.7 years High expression: average of 54.6 years	FIGO classification: • I: $n = 6$ • II: $n = 5$ • III: $n = 87$ • IV: $n = 31$ Tumor size: • ≤1 cm: $n = 108$ • >1 cm: $n = 21$	Surgical treatment. Exclusion from the study group of patients who received surgical chemotherapy	Healthy tissue: 0** Cancer tissue: 0–800**	*HOXA11* lncRNA expression in cancerous tissue was 77 times higher than in the healthy tissue ($p < 0.05$)

Tab. 2. Summary of tests included in the review

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Wu et al. (2016)[33]	*BC200*	Study group: $n = 22$ Control group: $n = 10$	No data	Histological type: • serous cancer: $n = 8$ • endometrial cancer: $n = 2$ • mucosal cancer: $n = 2$	No data	Healthy tissue: 0.01–2.50** Cancer tissue: 0.00–0.02**	The expression level *BC200* lncRNA is reduced in ovarian cancer tissue
Li et al. (2016)[34]	*GAS5*	Study group: $n = 63$ Control group: $n = 63$	≤55: $n = 29$ >55: $n = 34$	FIGO classification: • I: $n = 8$ • II: $n = 22$ • III: $n = 27$ • IV: $n = 6$ Tumor size: • <5 cm: $n = 33$ • ≥5 cm: $n = 21$	Surgical treatment. No data about the use of chemotherapy	Healthy tissue: 0.5–3.0** Cancer tissue: 0.0–2.0**	Statistically significant difference in the level of *GAS5* lncRNA expression in the healthy and cancerous tissue ($p < 0.05$)
Li et al. (2018)[35]	*GAS5*	Study group: $n = 20$ Control group: $n = 20$***	No data	No data	Surgical treatment	Healthy tissue: 0.5–3.2** Cancer tissue: 0.2–2.3**	Statistically significant difference in the level of *GAS5* lncRNA expression in the healthy and cancerous tissue ($p < 0.05$)
Ma et al. (2018)[36]	*GAS5* *SPRY2*	Study group: $n = 53$ Control group: $n = 53$***	Average of 58.3 years: 37–69 <55: $n = 22$ ≥55: $n = 31$	FIGO classification: • I–II: $n = 32$ • III–IV: $n = 21$ Histological type: • well/moderate: $n = 38$ • poor: $n = 15$	Surgical treatment	GAS5: • healthy tissue: 0.1–5.8** • cancer tissue: 0.0–3.0** SPRY2: • healthy tissue: 0.5–12.0** • cancer tissue: 0.0–7.00**	Statistically significant difference in the level of *GAS5* lncRNA expression in the healthy and cancerous tissue ($p < 0.05$) Statistically significant difference in the level of *SPRY2* lncRNA expression in the healthy and cancerous tissue ($p < 0.05$)
Zou et al. (2016)[37]	*MALAT*	Study group: $n = 20$ Control group: $n = 20$	27–69	No data	Surgical treatment. No use of chemotherapy	Healthy tissue: 0.8–1.3** Cancer tissue: 1.6–2.8**	Statistically significant difference in the level of *MALAT-1* lncRNA expression between the healthy and cancerous tissue ($p < 0.05$) Significant relationship between the level of *MALAT* lncRNA expression and the tumor size (in cm) ($r^2 = 0.78$; $p < 0.05$)
Jin et al. (2017)[38]	*MALAT*	Study group: $n = 64$ Exclusion of women with borderline ovarian cancer who have two or more tumors Control group: $n = 30$	No data	No data	Surgical treatment. Patients were given hormone therapy, radiotherapy or chemotherapy before surgery	Healthy tissue: 5–18** Ovarian cancer tissue: 10–27**	Statistically significant difference in the level of *MALAT-1* lncRNA expression between the healthy and cancerous tissue ($p < 0.05$)
Lei et al. (2017)[39]	*MALAT-1*	Study group: $n = 30$ Control group: $n = 30$***	No data	No data	Surgical treatment	Healthy tissue: 0.1–4.0** Cancer tissue: 4.3–13.0**	Statistically significant difference in the level of *MALAT-1* lncRNA expression between the healthy and cancerous tissue ($p < 0.05$)
Zhou et al. (2016)[6]	*MALAT-1*	Study group: $n = 45$ Control group: $n = 37$	<50: $n = 19$ >50: $n = 26$	Histological type: • serum: $n = 21$ • mucous: $n = 24$ FIGO classification: • I/II: $n = 21$ • III/IV: $n = 24$	Surgical treatment	Cancer tissue: • FIGO I/II: 1.009 • FIGO III/IV: 7.189 • serous cancer: 5.537 • mucous cancer: 3.227 Healthy tissue: 0.0–6.0** Cancer tissue: 0.0–100**	Statistically significant difference between *MALAT-1* lncRNA expression in tumor tissue, which was classified to different sizes according to the FIGO classification ($p < 0.05$) No statistically significant difference between *MALAT-1* lncRNA expression in cancer tissue that has been classified to various histological types (serous or mucosal) ($p > 0.05$) Statistically significant difference in the level of *MALAT-1* lncRNA expression in the healthy and cancerous tissue ($p < 0.05$)

Tab. 2. Summary of tests included in the review (cont.)

DOI: 10.15557/CGO.2020.0010

Qiu et al. (2016)[40]	*ANRIL*	Study group: $n = 102$ Group with low *ANRIL* expression: $n = 51$ Group with high *ANRIL* expression: $n = 51$ Control group: $n = 30$	Group with low *ANRIL* expression <50: $n = 18$ ≥50: $n = 33$ Group with high *ANRIL* expression <50: $n = 23$ ≥50: $n = 28$	FIGO classification: • I–II: ◦ low *ANRIL* expression: $n = 25$ ◦ high *ANRIL* expression: $n = 8$ • III–IV: ◦ low *ANRIL* expression: $n = 26$ ◦ high *ANRIL* expression: $n = 43$ Tumor size: • <1 cm: ◦ low *ANRIL* expression: $n = 24$ ◦ high *ANRIL* expression: $n = 18$ • ≥1 cm: ◦ low *ANRIL* expression: $n = 27$ ◦ high *ANRIL* expression: $n = 33$ Type of cancer: • serous cancer: ◦ low *ANRIL* expression: $n = 31$ ◦ high *ANRIL* expression: $n = 37$ • other cancer: ◦ low *ANRIL* expression: $n = 20$ ◦ high *ANRIL* expression: $n = 14$	Surgical treatment	Healthy tissue: 0.000–0.001** Cancer tissue: 0.000–0.009**	Statistically significant difference in *ANRIL* lncRNA expression in the healthy and cancerous tissue ($p < 0.05$)
Yang et al. (2016)[41]	*UCA1*	Study group: $n = 53$ Control group: $n = 29$	<50: $n = 24$ ≥50: $n = 29$	FIGO classification: • I–II: $n = 21$ • III–IV: $n = 32$ Tumor size: • <8 cm: $n = 28$ • ≥8 cm: $n = 25$ Histological type: • mucous: $n = 21$ • other: $n = 32$	Surgical treatment	Healthy tissue: 0.0–0.25** Cancer tissue: 0.0–0.45**	Statistically significant difference in the level of *UCA1* lncRNA expression between healthy and cancerous tissue ($p < 0.05$)
Zhang et al. (2016)[42]	*UCA1*	Study group: $n = 117$ Control group: $n = 117$***	≤60: $n = 43$ >60: $n = 74$	Tumor size: • <3 cm: $n = 57$ • ≥3 cm: $n = 46$ Histological type: • serous: $n = 60$ • other: $n = 52$	Surgical treatment. Before the surgery, chemotherapy, immunotherapy, radiotherapy treatment were not used	Healthy tissue: 0.0–0.5** Ovarian cancer tissue: 0.0–5.8** FIGO classification: • I + II: 0.0–4.5** • III + IV: 0.0–6.5** No metastases to lymph nodes: 0.0–5.5** Metastases to lymph nodes: 0.0–7.5**	Statistically significant difference in the level of *UCA1* lncRNA expression between healthy tissue and ovarian cancer tissue ($p < 0.05$) Statistically significant difference in the level of *UCA1* lncRNA expression between women who had metastases to lymph nodes and women in whom they were not observed ($p < 0.05$) Statistically significant difference in the level of *UCA1* lncRNA expression between women diagnosed with ovarian cancer classified as FIGO I + II and FIGO III + IV ($p < 0.05$)
Yang et al. (2016)[43]	*AFAP-1AS1*	Study group: $n = 130$ Control group: $n = 65$	≤60: $n = 48$ >60: $n = 82$	Tumor size: • <3 cm: $n = 70$ • ≥3 cm: $n = 60$ FIGO classification: • I + II: $n = 64$ • III + IV: $n = 66$ Histological type: • serous: $n = 86$ • other: $n = 44$	Surgical treatment. No treatment with chemotherapy and radiotherapy before surgical treatment	Healthy tissue: 0.0–1.5** Ovarian cancer tissue: 0.0–7.8**	Statistically significant difference between *AFAP-1AS1* lncRNA expression in the cancerous tissue and tissue of ovarian cancer ($p < 0.05$)

Tab. 2. Summary of tests included in the review (cont.)

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Liu et al. (2018)[44]	*lncSOX4*	Study group: $n = 30$ Control group: $n = 18$	46.2 ± 12.4 ≤55: $n = 17$ >55: $n = 13$	FIGO classification: • I–II: $n = 14$ • III–IV: $n = 16$ Tumor size: • <5 cm: $n = 14$ • ≥5 cm: $n = 16$	Surgical treatment	Healthy tissue: 0.15–2.3** Cancer tissue: 3.5–5.0**	Statistically significant difference in the level of *lncSOX4* lncRNA expression between the healthy tissue and cancerous tissue ($p < 0.05$)
He et al. (2018)[45]	*SNHG20*	Study group: $n = 30$ Control group: $n = 30$***	No data	No data	Surgical treatment	Healthy tissue: 0.3–1.2** Cancer tissue: 0.6–2.3**	Statistically significant difference between the level of *SNHG20* lncRNA expression in the healthy tissue and cancerous tissue ($p < 0.05$)
Kuang et al. (2016)[46]	*TUG1*	Study group: $n = 62$ Control group: $n = 62$***	≤51: $n = 20$ >51: $n = 42$	FIGO classification: • I/II: $n = 25$ • III/IV: $n = 37$ Tumor size: • ≤2 cm: $n = 45$ • >2 cm: $n = 17$	Surgical treatment	Healthy tissue: 0.0–22.0** Cancer tissue: 0.0–35.0**	Statistically significant difference in the level of expression lncRNA *TUG1* in the healthy and cancerous tissue ($p < 0.05$)
Zhang et al. (2017)[47]	*RAD51-AS1*	Study group: $n = 163$	No data	FIGO classification: • I/II: $n = 67$ • III/IV: $n = 62$	Surgical treatment	FIGO classification: • I: 0.7–4.0** • II: 0.7–4.0** • III: 1.8–4.0** • IV: 2.2–4.0**	Statistically significant difference in the level of *RAD51-AS1* lncRNA expression in the healthy and cancerous tissue ($p < 0.05$)
Long et al. (2018)[48]	*LSINCT5*	Study group: $n = 40$ Control group: $n = 30$	≤50: $n = 17$ ≥50: $n = 23$	FIGO classification: • I–II: $n = 17$ • III–IV: $n = 23$ Tumor size: • <1 cm: $n = 28$ • ≥1 cm: $n = 12$	Surgical treatment	Healthy tissue: 0.00–40** Cancer tissue: 1.00–80.00**	Statistically significant difference in the level of *LSINCT5* lncRNA expression in the healthy and cancerous tissue ($p < 0.05$)

FIGO – International Federation of Gynecology and Obstetrics;
n – group size;
p – statistical significance level ($p < 0.05$ – statistically significant difference, $p > 0.05$ – no statistical significance).

** Approximate value read from the graph.
*** No data on the exact size of the control group.

Tab. 2. Summary of tests included in the review (cont.)

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ovarian cancer tissue and healthy tissue showed varying levels of expression in papers published by different authors, indicating that the expression of the same lncRNA can be variable individually or is attributable to study errors. Currently, there is no cytotoxic drug with an effect on lncRNA available on the market.

Conflict of interest

The author declares no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Foam cell formation associated with a borderline ovarian tumor: a case report

Powstawanie komórek piankowatych w przebiegu guza granicznego jajnika: opis przypadku

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Abstract

Foam cell formation is a very common pathologic finding in atherosclerosis, often found in some major organs. However, the involvement of the retroperitoneal organs is very rare and foam cell formation associated with borderline ovarian tumor has not been reported. Borderline ovarian tumors are epithelial ovarian tumors with a low growth rate, low potential to invade or metastasize, and excellent prognosis. Still, a rapidly growing borderline ovarian tumor can exert pressure on the retroperitoneal organs. It may cause retroperitoneal irritation and inflammation, and form a mass lesion in adjacent organs. We report the case of a 41-year-old woman with a borderline ovarian tumor and foam cell infiltration.

Keywords: foam cell, borderline ovarian tumor, retroperitoneum

Streszczenie

Powstawanie komórek piankowatych jest powszechnym zjawiskiem patologicznym w przebiegu miażdżycy naczyń krwionośnych, często obserwowanym w niektórych głównych narządach. Jednak do zajęcia narządów zaotrzewnowych dochodzi bardzo rzadko, a w literaturze nie ma doniesień opisujących tworzenie się komórek piankowatych w związku z guzem granicznym jajnika. Guzy graniczne jajnika należą do nowotworów nabłonkowych tego narządu. Odznaczają się niskim tempem wzrostu, niewielką inwazyjnością i zdolnością przerzutowania, a także doskonałym rokowaniem. Jednak szybko rosnący guz graniczny jajnika może uciskać narządy zaotrzewnowe, powodując podrażnienie i stan zapalny w przestrzeni zaotrzewnowej oraz powstanie zmiany o charakterze masy w sąsiednich narządach. W pracy opisujemy przypadek 41-letniej kobiety z granicznym guzem jajnika i naciekiem z komórek piankowatych.

Słowa kluczowe: komórka piankowata, guz graniczny jajnika, przestrzeń zaotrzewnowa

INTRODUCTION

Foam cells are lipid-laden macrophages which are present in all stages of atherosclerosis. Foam cells play a critical role in the occurrence and development of atherosclerosis. The generation of these cells is associated with the imbalance of cholesterol influx and esterification efflux. When the inflow and esterification of cholesterol increase, and the outflow decreases, the macrophages are transferred into lipid-laden foam cells, the protypical cells in the atherosclerotic plaque[1–3]. But foam cell formation associated with a borderline ovarian tumor (BOT) has not been reported.

Herein, we report the case of a patient who presented with a foam cell formation associated with a BOT in retroperitoneum.

CASE REPORT

A 41-year-old nulliparous woman visited the emergency room because of abdominal distention, voiding difficulty, and 3 kg weight loss over the past three months. She did not have any significant medical or surgical history. On physical examination, there was a large mass in her abdomen. In laboratory tests, the serum cancer antigen (CA) 19-9 level was more than 1,200 U/mL (normal range, 0–37), and the serum CA-125 level was 219.2 U/mL (normal range, 0–35). Other laboratory findings were within the normal range. Chest computed tomography (CT) and abdomen–pelvis CT revealed a cystic mass measuring 37.5 × 33.4 × 24.2 cm (Fig. 1).

Under ovarian tumor impression, we performed an exploratory operation. After approximately 18,000 mL aspiration at the right ovary, a right salpingo-oophorectomy and frozen section biopsy were performed, and the pathological findings confirmed adenocarcinoma. We planned to conduct a staging operation (hysterectomy, left salpingo-oophorectomy, pelvic and paraaortic lymphadenectomy). During the hysterectomy, rice-figured mass lesions suspected of malignancy ranged from the bladder to the right ureter. A frozen section biopsy was performed at the mass, and the result revealed no malignant cells. We consulted with an urologist regarding partial bladder resection.

However, the final pathologic diagnosis revealed a mucinous BOT with stromal microinvasion (Fig. 2A), and the bladder wall and bladder peritoneum showed chronic inflammatory cell infiltrations with foam cells (Fig. 2B). The aspiration fluid contents comprised multiple atypical necrotic cells without tumor cells. The patient was discharged without complications postoperatively. After six months, she is experiencing no abdominal discomfort or voiding difficulty. The follow-up tumor markers were within the normal range, and the abdomen–pelvis CT showed no evidence of recurrence or any remarkable lesions.

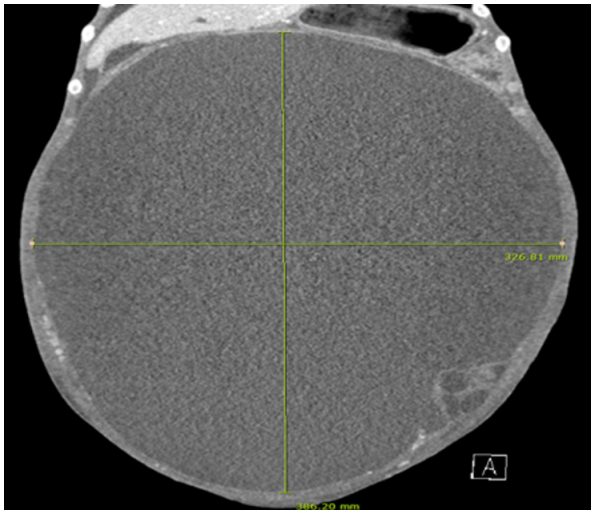

Fig. 1. Abdomen–pelvis CT. Large cystic mass with mural multiseptated cystic portion in the abdominopelvic cavity

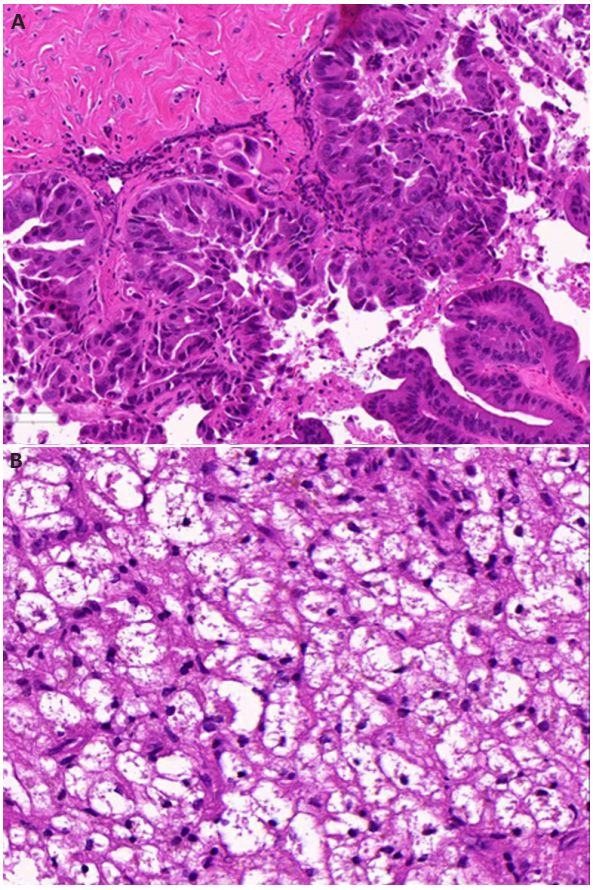

Fig. 2 ***A.*** *Microscopic findings of the ovarian cyst (A, H&E, ×200) and bladder peritoneum (B, H&E, ×200) – the cyst chambers were lined by a layer or stratified mucinous cells. In areas, stratification, villous papillae lined by atypical tumor cells were observed, and small foci of stromal invasion.* ***B.*** *Bladder peritoneum clinically suspected metastasis, showed no cancer but the lesion was of chronic inflammation with predominant infiltration of foamy histiocytes and fibrosis. Tissue from the bladder wall shows chronic inflammatory cell infiltration with foam cells and multinucleated giant cells without any cancer cells*

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DISCUSSION

Mucinous BOTs account for approximately 10% of all primary mucinous ovarian neoplasms. They constitute 30–50% of BOTs in Western and Middle-Eastern populations, where they are the second most common type of BOT after serous tumors. The converse is true in Asia, where mucinous BOTs account for approximately 70% of all BOTs[4,5]. Mucinous BOTs can occur at any age, but are most likely to develop during the fourth through fifth decades of life[6]. Patients typically present with abdominal distension and/or a pelvic mass. Tumors vary greatly in size, and can measure up to 50 cm in the largest dimension[7].

The lipid surrounded by macrophages has a "foamy" appearance, so these cells are referred to as foam cells because of their characteristic visual properties[1,8]. To the best of our knowledge, this is the first reported case of foam cell formation associated with a BOT.

Low-density lipoprotein and cholesterol homeostasis are maintained by macrophages[2,9]. The uncontrolled uptake of oxidized low-density lipoprotein, excessive cholesterol esterification, and impaired cholesterol release result in the accumulation of the cholesterol ester stored as cytoplasmic lipid droplets, and subsequently trigger the formation of foam cells[1]. Foam cells are present in all stages of atherosclerosis, a chronic inflammatory disorder in the arterial wall, and participate in inflammatory responses and tissue remodeling[9]. Foam cells facilitate the bridging of the innate and adaptive immune response to atherosclerosis, and also accumulate to generate fatty streaks. Foam cells may be detected in some major organs such as the brain, liver, and connective tissue, but are extremely uncommon in retroperitoneal organs[9].

We supposed that a large, rapidly growing BOT might exert pressure on the retroperitoneal organs. It may cause peritoneal cavity irritation wherein continuous chronic inflammatory reactions occur and form a granulated mass lesion in the adjacent organs. When lipid inflammation and congestion occur in the limited retroperitoneal space, it can become a congested mass lesion. As the BOT grows, the infiltrated mass can enlarge continually. The exact pathogenesis has not been clearly explained, and the clinical features are uncertain because of the rarity of the condition. Our patient's foam cell lesion ranged from the bladder to the right ureter. If our surgical treatment has been delayed, the mass lesion might have become large and there would have been severe infiltration in the bladder and ureter.

In the peritoneal cavity, there are many lipid sources such as the omentum, peritoneum, and a limited space for the BOT to enlarge. As the BOT grows, lipid-laden macrophage irritation and inflammation may occur in the limited space, and form an infiltrated lesion on the adjacent retroperitoneal organs.

This is the first reported case of a BOT with characteristics found on the surface shape and balloon-like swelling of the retroperitoneum. This is attributable to the BOT in which the underlying cause is the accumulation of foam cells in the bladder peritoneum

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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