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About authors:

Minaev Sergey Viktorovich, MD, PhD, Professor, Head of the Department of Pediatric Surgery;
tel.: +79624507653; e-mail: sminaev@yandex.ru; https://orcid.org/0000-0002-8405-6022

Rubanova Maria Fedorovna, postgraduate student;
tel.: +79289232328; e-mail: maryrubanova@mail.ru; https://orcid.org/0000-0001-5168-6004

Gerasimenko Igor Nikolaevich, MD, PhD, Associate Professor, Professor of the Department;
tel.: +79187704217; e-mail: igor9551@yandex.ru; https://orcid.org/0000-0003-3003-612X

Akselrov Mikhail Aleksandrovich, MD, PhD, Associate Professor, Head of the Department of Pediatric Surgery;
tel.: +79292694933; e-mail: akselerov@mail.ru; https://orcid.org/0000-0001-6814-8894

Mishvelov Artem Evgenievich, specialist of the 3D Technology laboratory;
tel.: +79197579330; e-mail: Archi4717@yandex.ru; https://orcid.org/0000-0003-2004-9429

Razin Maxim Petrovich, MD, PhD, Professor, Head of the Department of Pediatric Surgery;
tel.: +79128281527; e-mail: mprazin@yandex.ru; https://orcid.org/0000-0003-3561-3256

Martinez Jennifer, pediatric surgeon,
tel.: +79019067071; e-mail: dra.jcmartinez@gmail.com; https://orcid.org/0009-0005-2221-3992

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CLINICAL CASE OF PRIMARY MULTIPLE METACHRONOUS BRCA-ASSOCIATED CANCER

G. M. Salieva, A. V. Kubyshkin, I. I. Fomochkina, I. E. Braude, A. V. Kamysheva

**Medical Institute named after S. I. Georgievsky
of V. I. Vernadsky Crimean Federal University, Simferopol, Russian Federation**

КЛИНИЧЕСКИЙ СЛУЧАЙ ПЕРВИЧНО-МНОЖЕСТВЕННОГО МЕТАХРОННОГО BRCA-АССОЦИИРОВАННОГО РАКА

Г. М. Салиева, А. В. Кубышкин, И. И. Фомочкина, И. Е. Брауде, А. В. Камышева

**Медицинский институт им. С. И. Георгиевского,
Крымский федеральный университет им. В. И. Вернадского,
Симферополь, Российская Федерация**

The article offers a clinical case presentation involving the treatment of a patient featuring symptoms of primary multiple metachronous cancer affecting the patient's breast, and ovaries, associated with the BRCA1c5382insC mutation. From 2007 to 2023, the patient underwent comprehensive treatment, which included surgical, antitumor, and radiotherapy of various modes and targeted therapy with PARP inhibitors. The obtained data reveal the importance of identifying the genetic reason behind tumor growth when dealing with oncological cases.

Keywords: primary multiple cancer, breast cancer, ovarian cancer, BRCA1, molecular genetic tests, PARP-inhibitors

Представлен клинический случай лечения пациентки с первично-множественным метахронным раком молочной железы и яичников, ассоциированным с мутацией *BRCA1*c5382insC. В период с 2007 по 2023 год больная проходила комплексное лечение, включающее хирургическое, противоопухолевую и радиолучевую терапию в разных режимах, а также таргетную терапию PARP-ингибиторами. Таким образом, представленное наблюдение демонстрирует важность идентификации генетической основы опухолевого роста в введении онкологической пациентки.

Ключевые слова: первично-множественный рак, рак молочной железы, рак яичников, BRCA1, молекулярно-генетическая диагностика, PARP-ингибиторы

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BC – breast cancer
CT – computed tomography
DNA – deoxyribonucleic acid
MNP – malignant neoplasms
OC – ovarian cancer
PARP – poly(adp-ribose) polymerase
PCT – polychemotherapy
PCR – polymerase chain reaction
PMMN – primary multiple malignant neoplasms
ROMA – risk of ovarian malignancy algorithm

Recent years have witnessed cancer incidence dynamics, which points to the growing relevance of primary multiple malignant neoplasms (PMMN). In2022, for instance, the number of identified PMMN cases was unprecedented – 68 thousand, which accounted for 10.9 % within the structure of all the malignant neoplasms detected (2021 – 10.0 %; 2020 – 9.5 %; 2019 – 9.3 %). By the end of the reporting year, the total number of patients diagnosed with PMMN exceeded 258 thousand people (6.4 % of the entire number) [1].

One of the most typical combined MNPs is a combination of tumor lesions affecting the female reproductive system, namely, breasts (breast cancer / BC) and ovaries (ovarian cancer / OC), which is to be explained by standard molecular & genetic, hormonal and metabolic processes involved in the pathogenesis of the said tumors [2].

Most hereditary BC and OC cases are associated with highly penetrant mutations in the BRCA1 and BRCA2 double-stranded DNA break repair system genes. The detection of mutations in the mentioned genes are of significant diagnostic and prognostic value and is taken into account when selecting a treatment strategy for MNPs. In treating cases of BRCA-associated tumors, for instance, drugs belonging to the PARP inhibitors group have proven to be effective [3–5].

Speaking about this category of patients, it should be noted that molecular genetic tests aimed at identifying mutations associated with BC and OC carcinogenesis should become a mandatory diagnostic step.

Clinical case presentation. Patient M., 1960; contact a local GP in July 2023, reporting issues like some pain in the left iliac area, persistent constipation, and bowel movement possible after taking laxatives only. The clinical test results showed reduced hemoglobin levels (down to 95 g/l) and thrombocytosis ($410x10^9$/l), with no specific change registered otherwise.

To complete the outpatient examination, the patient was given a referral for a video colonoscopy test, which showed a sigmoid diverticulum with diverticulitis and abscess. A biopsy sample of the sigmoid colon mucous membrane was used for a histological examination, and the following conclusion was issued: carcinoma of the sigmoid colon.

The CT scans of the chest, abdominal cavity, and pelvis with intravenous enhancement done in August 2023 concluded the following: altered sigmoid colon wall typical of malignant neoplasms, with no other focal changes detected in the examined parts.

The medical history stated that the patient had been registered with an oncologist since 2007, the diagnosis being that of breast cancer pT2N1M0, Stage II, condition following left-sided mastectomy, six courses of PCT (doxorubicin + cyclophosphamide), radiotherapy.

In October 2021, the patient's complaints went on to include growing significant weakness, increased abdominal size, and pain in the right iliac area. A comprehensive examination revealed an increase in the concentration of biochemical markers of CA125–76.1 U/l; Ne4 – 165.5 pmol/l; there was a calculation performed for the individual risk of developing breast cancer relying on the ROMA index: 59.3%, which is indicative of high risk of epithelial ovarian cancer for postmenopausal women.

In January 2022, the patient underwent surgery: extirpation of the uterus with appendages, omentectomy, appendectomy, and peritoneum multifocal biopsy. The conclusion offered for the intravital histological study of the surgical samples stated the following: high malignancy serous cancer, left and right ovaries, High Grade (G3), with vascular invasion and implantation metastases affecting the right fallopian tube, appendix, and pelvis peritoneum.

Given the medical history, a recommendation of undergoing a molecular genetic study was offered; the patient had a DNA sample taken from her blood as well as mutations detected through real-time PCR and a set of HRR screening agents. The test revealed a BRCA1c5382insC mutation; the diagnosis set waspT3aN1M0 OC, Stage IIIA with verification of breast and ovary primary multiple metachronous malignant neoplasms associated with a BRCA1 mutation.

Subject to the respective clinical recommendations, from January through May 2022, the patient received six courses of drug antitumor therapy according to the following scheme: Paclitaxel, 175 mg/m^2 on 1 days + Carboplatin AUC 5 on 1 days; Cycle – 21 days.

The therapy mentioned above came along with positive dynamics of the patient's overall status. The complications entailed by the treatment were anemia, neutropenia, and polyneuropathy. In May 2022, considering the BRCA1 mutation, supportive targeted therapy was administered with a drug belonging to the group of PARP inhibitors (Olaparib).

In September 2023, the patient had sigmoid colon resection with an extended lymphadenectomy. The intravital histological conclusion based on the surgical material examination was poorly differentiated carcinoma, High Grade (G3). An immunohistochemical study has been recommended to clarify the tumor immune phenotype (Table).

Table

Protocol of immunohistochemical examination

Marker and clone	Reaction description
CK7	Positive reaction in tumor cells
CK20	Negative reaction in tumor cells
ER	Positive nuclear reaction in tumor cells. Allred Score 5+3=8
CDX2	Negative reaction in tumor cells
GATA3	Negative reaction in tumor cells
PAX8	Positive nuclear reaction in tumor cells
WT1	Positive reaction
p53	Nuclear uneven expression, Wild type
Conclusion	Immune phenotype of tumor tissue matches High Grade serous ovarian adenocarcinoma

The table above shows that the first recurrent platinum-sensitive ovarian cancer has been identified. The platinum-free interval, in the meantime, was 18 months. Second-line PCT courses have been administered: Gemcitabine, 750–1000 mg/m^2 on 1 days, 8 days + Carboplatin AUC 3–6 on 1 or 2 days; Cycle – 21 days. The treatment was accompanied by lowering hemoglobin concentrations (down to 85 g/l), severe leukopenia, and neutropenia to 0.7 x10^9/l). The complications were stopped by administering iron-based medications and colony-stimulating factors (Filgrastim).

The patient's closest family was recommended molecular genetic tests to identify the BRCA1c5382insC mutation carrier. If detected, more intense dynamic monitoring should be carried out along with preventive measures.

Conclusion. Nowadays, the value of molecular genetic research in diagnosing and treating MNP can hardly be overestimated. The timely detection of the BRCA1 gene mutation in the case mentioned above might have explained the need for a set of preventive measures to be taken to prevent the development of metachronous ovarian issues. The administered targeted therapy with PARP inhibitors helped maintain remission for 18 months, which is another proof of the importance of identifying the genetics-bound reason behind tumor growth.

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About authors:

Salieva Guzel Mustafaevna, postgraduate student;
tel.: +79787339953; e-mail: gyuzelsalieva@gmail.com; https://orcid.org/0000-0001-9224-4464

Kubyshkin Anatoliy Vladimirovich, MD, PhD, Professor, Head of the Department of General and Clinical Pathophysiology;
tel.: +79780280111; e-mail: kubyshkin_av@mail.ru; https://orcid.org/0000-0002-1309-4005

Fomochkina Irina Ivanovna, MD, PhD, Professor;
tel.: +79787316780; e-mail: fomochkina_i@mail.ru; https://orcid.org/0000-0003-3065-5748

Braude Irina Evgenievna, PhD, Associate Professor of the Department of Obstetrics and Gynecology № 2;
tel.: +79788104829; e-mail: irina.braude@mail.ru

Kamysheva Anastasia Vladimirovna, junior researcher at the Engineering Center;
tel.: +79785065853; e-mail: anastasiia.maiakovska@gmail.com; https://orcid.org/0000-0003-0157-0550

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BONE METABOLISM STATUS IN CHILDREN WITH CHRONIC RESPIRATORY DISEASES

S. V. Dolbnya [1, 2], V. R. Ponamareva [1], I. N. Zakharova [3], L. Ya. Klimov [1], A. A. Tolkunova [1, 2], N. V. Zarytovskaya [1], V. D. Lugovsky [1], D. A. Pentegova [1]

[1] Stavropol State Medical University, Russian Federation
[2] Regional Child Clinical Hospital, Stavropol, Russian Federation
[3] Russian Medical Academy for Continuous Professional Education, Moscow, Russian Federation

СОСТОЯНИЕ КОСТНОГО МЕТАБОЛИЗМА У ДЕТЕЙ С ХРОНИЧЕСКИМИ ЗАБОЛЕВАНИЯМИ ОРГАНОВ ДЫХАНИЯ

С. В. Долбня [1, 2], В. Р. Понамарева [1], И. Н. Захарова [3], Л. Я. Климов [1], А. А. Толкунова [1, 2], Н. В. Зарытовская [1], В. Д. Луговский [1], Д. А. Пентегова [1]

[1] Ставропольский государственный медицинский университет, Российская Федерация
[2] Краевая детская клиническая больница, Ставрополь, Российская Федерация
[3] Российская медицинская академия непрерывного профессионального образования, Москва, Российская Федерация

This review focuses on the specific issues of bone metabolism in children with chronic respiratory diseases, namely, cystic fibrosis and bronchial asthma. The results of numerous studies show that patients with chronic bronchial and lung issues tend to develop a premature imbalance of bone remodeling, the clinical manifestations of which include osteopenia, osteoporosis and low-impact fractures. There is also a discussion offered around factors that have a certain effect on the bone metabolism status at the physiological level, as well as around the role of various pathogenetic mechanisms and medication therapy in affecting bone mineral density in pediatric patients suffering from cystic fibrosis and bronchial asthma.

Keywords: cystic fibrosis, bronchial asthma, osteopenia, osteoporosis, bone metabolism

Обзор посвящен особенностям костного метаболизма у детей с хроническими заболеваниями органов дыхания, а именно муковисцидозом и бронхиальной астмой. Согласно результатам многочисленных исследований, пациенты с хроническими заболеваниями бронхов и лёгких подвержены преждевременному развитию дисбаланса костного ремоделирования, что клинически проявляется в форме остеопении, остеопороза и низкоэнергетических переломов. Обсуждаются факторы, оказывающие влияние на состояние костного обмена на физиологическом уровне, а также роль различных патогенетических механизмов и лекарственной терапии в снижении минеральной плотности кости у пациентов детского возраста с муковисцидозом и бронхиальной астмой.

Ключевые слова: муковисцидоз, бронхиальная астма, остеопения, остеопороз, костный метаболизм