DOI: https://doi.org/10.17816/aog630125

Simultaneous tumors: ovarian cancer in a patient with multiple myeloma

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ABSTRACT

Multiple myeloma is the second most common hematological malignancy, accounting for approximately 1% and 10–15% of malignant tumors of the hematopoietic and lymphoid systems, respectively. Until recently, the diagnosis of multiple myeloma was inherently associated with unfavorable prognosis of overall survival. On the one hand, advanced diagnosis techniques and the development of new treatment approaches have led to the improved life expectancy and significant reduction of mortality of patients with multiple myeloma. On the other hand, the medical and research communities have encountered a previously unknown issue: the combination of multiple myeloma with other types of cancer. This combination sets a task of multidisciplinary approach in the diagnosis and requires development of patient management strategy and prognostic parameters of the outcome. Some researchers adhere to the theory of independent tumor appearance in patients suffering from multiple myeloma, while other authors suppose that multiple myeloma and secondary cancer virtually represent multiple primary malignant neoplasms. This article presents a clinical case of postmortem verification of ovarian cancer in a patient with recurrent multiple myeloma.

Keywords: simultaneous tumors; multiple myeloma; ovarian cancer; chemotherapy; clinical case.

To cite this article:
Gadaev IYu, Gadaeva IV, Rossolovskaya KA, Bochkarnikova OV, Sokolova IYa. Simultaneous tumors: ovarian cancer in a patient with multiple myeloma. *V.F. Snegirev Archives of Obstetrics and Gynecology.* 2024;11(4):499–506. DOI: https://doi.org/10.17816/aog630125

Received: 08.04.2024 **Accepted:** 25.04.2024 **Published online:** 12.12.2024

DOI: https://doi.org/10.17816/aog630125

Симультантные опухоли: рак яичников у пациентки с множественной миеломой

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АННОТАЦИЯ

Множественная миелома — второе по распространённости гематологическое злокачественное заболевание, на долю которого среди всех злокачественных опухолей приходится примерно 1% и 10–15% опухолей кроветворной и лимфоидной систем соответственно. До недавнего времени сам факт наличия у пациента множественной миеломы ассоциировался с низкой общей выживаемостью. С одной стороны, совершенствование методов диагностики и разработка новых подходов к лечению привели к увеличению продолжительности жизни пациентов и значительному снижению смертности от множественной миеломы, с другой стороны — врачебное и исследовательское сообщества столкнулись с ранее не верифицированной проблемой: сочетание множественной миеломы с раком другого вида, что потребовало поиска решения и междисциплинарного подхода при диагностике и определении тактики ведения пациента и прогностических маркеров исхода. При этом одни исследователи придерживаются теории независимого формирования опухолей как следствия множественной миеломы, другие авторы считают, что множественная миелома и второй рак — это ни что иное как множественный первичный рак. Данная статья посвящена клиническому случаю посмертной верификации рака яичника у пациентки с рецидивирующей множественной миеломой.

Ключевые слова: симультанные опухоли; множественная миелома; рак яичников; химиотерапия; клинический случай.

Как цитировать:
Гадаев И.Ю., Гадаева И.В., Россоловская К.А., Бочкарникова О.В., Соколова И.Я. Симультантные опухоли: рак яичников у пациентки с множественной миеломой // Архив акушерства и гинекологии им. В.Ф. Снегирёва. 2024. Т. 11, № 4. С. 499–506. DOI: https://doi.org/10.17816/aog630125

Рукопись получена: 08.04.2024 **Рукопись одобрена:** 25.04.2024 **Опубликована online:** 12.12.2024

DOI: https://doi.org/10.17816/aog630125

同时性肿瘤：多发性骨髓瘤患者的卵巢癌

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摘要

多发性骨髓瘤是第二常见的血液系统恶性肿瘤，占所有恶性肿瘤的约1%，以及造血和淋巴系统肿瘤的10 – 15%。直到最近，多发性骨髓瘤患者的存在本身就与较低的总体生存率相关。一方面，诊断技术的改进和新治疗方法的开发显著延长了患者的生存时间，并降低了多发性骨髓瘤的死亡率；另一方面，医学界和研究界面临着一种以前未被确诊的问题：多发性骨髓瘤与另一种类型的癌症同时存在。这种情况需要在诊断、患者管理策略以及预后指标方面采取多学科方法。一些研究者认为，这种肿瘤的共存是多发性骨髓瘤的结果，而另一些学者则认为，这种情况实际上是多原发性癌症。本研究讨论了一个临床病例，即一名复发性多发性骨髓瘤患者在死后确诊为卵巢癌。

关键词：同时性肿瘤；多发性骨髓瘤；卵巢癌；化疗；临床病例。

引用本文:
Gadaev IYu, Gadaeva IV, Rossolovskaya KA, Bochkarnikova OV, Sokolova IYa. 同时性肿瘤：多发性骨髓瘤患者的卵巢癌. *V.F. Snegirev Archives of Obstetrics and Gynecology.* 2024;11(4):499–506. DOI: https://doi.org/10.17816/aog630125

收到: 08.04.2024 **接受:** 25.04.2024 **发布日期** 12.12.2024

BACKGROUND

Multiple myeloma (MM), also known as plasma cell myeloma as revised by the World Health Organization in 2017, is the second most common B-cell blood malignancy. The underlying morphological substrate of this condition is the presence of plasma cells that produce monoclonal immunoglobulin [1, 2]. This disease is associated with multifocal proliferation of neoplastic plasma cells and the secretion of monoclonal immunoglobulin [3].

According to global statistics, 86,000 new cases of MM are documented annually, with a mortality rate that approaches 63,000 cases worldwide [4]. A review of global and Russian literature reveals that MM manifests primarily in the 65-to-70-year age range. However, there are documented cases that it occurs in younger demographics as well [5]. There are no significant gender differences in MM.

Until recently, MM was considered a fatal disease with a poor prognosis, as evidenced by observational results. For instance, a study by Rajkumar demonstrated that the median overall survival of patients with MM is not more than six years, even when treated promptly [6]. However, the advent of advanced diagnostic and therapeutic modalities in the last decade, including transplantation of autologous hematopoietic cells, the use of immunomodulatory agents, targeted monoclonal and biclonal antibodies, and proteasome inhibitors, has yielded substantial success in the treatment of patients with MM [7]. Furthermore, a similar positive trend was observed among both young and elderly patients [8]. This encouraging development, known as the time factor, highlights the challenge posed by secondary tumors, which present significant diagnostic and therapeutic challenges. Clinicians are increasingly confronted with the detection of cancer of other types and locations in conjunction with MM. In patients diagnosed with multiple types of cancer, the development of separate tumors in sequence is frequently observed [9]. The precise mechanisms underlying the development of secondary malignancies remain to be fully elucidated; however, the majority of researchers posit that MM treatment (including cytostatics and immunomodulators) contributes to the development of subsequent cancers. Consequently, a paper dedicated to the treatment of MM states that patients undergoing lenalidomide treatment regimen are advised to undergo screening due to the elevated risk of developing secondary tumors [10]. Several studies have documented the concurrent development of MM and secondary cancer, a phenomenon referred to as multiple primary cancer (MPC) [2]. MPCs are two or more malignant tumors that appear simultaneously and independently, localized in the same or different organs. These tumors are typically diagnosed sequentially and independently of each other, with a period of time between diagnoses ranging from several months to even years. This temporal separation forms the basis for their classification: synchronous tumors, which are detected within six months, and metachronous tumors, which are detected six months afterwards. The pathogenic mechanisms of MPC remain unspecified; however, as in the case of the development of isolated tumors together with MM, these mechanisms may be associated with exposure to anticancer agents or may be related to molecular genetic events.

This paper presents a case report of postmortem detection of ovarian cancer in a patient with recurrent MM who had undergone several courses of polychemotherapy.

CASE DESCRIPTION

In November 2023, patient X, a 74-year-old individual, was admitted to the Ostroumov Hospital Therapy Clinic of Sechenov First Moscow State Medical University. The patient was diagnosed with stage IIA MM according to Durie-Salmon and stage III according to the International Staging System. Furthermore, the patient's immunochemistry revealed a positive for protein phosphatase IgA-λ type.

The diagnosis of MM was first established in March 2021, based on patient complaints of pain in the lumbar region and ribs, as well as laboratory and instrumental diagnostic findings. These included anemia (hemoglobin [Hb] up to 101 g/L), and paraproteinemia (M-gradient up to 58.6 g/L), and diagnostically significant plasmatization of bone marrow (large clusters of plasma cells) in the puncture. MRI showed osteolytic foci in the spine (L3–L5) and pelvis, and no evidence of renal damage. From March to October 2021, six courses of polychemotherapy (PCT) were administered in VCD regimen (cyclophosphamide, bortezomib, and dexamethasone), yielding a highly favorable response that attested to the high chemosensitivity of the tumor. However, the M-gradient remained undetermined. In May 2022, the patient experienced a relapse of MM, characterized by a decline in hemoglobin (Hb) to 86 g/L, the presence of paraproteinemia up to 44.5 g/L, and an erythrocyte sedimentation rate of 110 mm/h. Concurrently, new osteolytic foci were identified, accompanied by signs of consolidated rib fractures. From May to August 2022, the patient received four courses of PCT, administered in accordance with the previously established regimen (VCD). Concurrently, bisphosphonates (zoledronic acid) were administered. However, the previous effect was not achieved due to significantly reduced hematologic and biochemical responses. Consequently, the PCT regimen was changed in October 2022 from VCD to VRD (lenalidomide, bortezomib, and dexamethasone). From October 2022 to June 2023, five courses of PCT according to VRD regimen were performed, resulting in a favorable response, as evidenced by a decrease in M-gradient to 3.1 g/L and an increase in Hb to 105 g/L.

In November 2023, the patient noted an increase in bone pain (ossalgia). Laboratory findings revealed an increase in M-gradient up to 56 g/L and a worsening anemia with a Hb of 89 g/L. Based on the data obtained, a second relapse of MM with the development of double refractoriness to

DOI: https://doi.org/10.17816/aog630125

chemotherapy was diagnosed. The purpose of the present hospitalization of the patient in the Ostroumov Hospital Therapy Clinic was to determine the further strategy for double relapse and refractoriness to PCT. An abdominal computed tomography (CT) scan revealed for the first time omental thickening accompanied by effusion and indications of peritoneal lesions, necessitating further verification. Notably, a prior study employing the same imaging modality in March 2022 did not detect any pathology within the abdominal cavity or pelvic organs. Additionally, ultrasound scans of the abdominal and pelvic regions provided no informative findings. Consequently, contrast-enhanced magnetic resonance imaging (MRI) was performed, which revealed an irregularly enlarged tubular structure measuring up to 55 mm in the projection of the right uterine appendage, exhibiting characteristics suggestive of fluid signaling. In light of the collected data and the patient's condition, a histological examination (core biopsy) of the peritoneum and a cytological evaluation of the ascitic fluid were conducted. These analyses revealed peritoneal carcinomatosis with an undetermined primary origin. Subsequent immunohistochemical analysis of a peritoneal biopsy led to the diagnosis of serous carcinoma of the female genital organs. The patient was subsequently evaluated by a gynecologist specializing in intensive care, and the following oncomarkers were determined: CA-125, HE-4, and ROMA (Risk of Ovarian Malignancy Algorithm) index, all falling within standard reference values. The interdisciplinary council determined that gynecologic pathology (ovarian cancer) cannot be ruled out. The patient's condition exhibited a marked clinical deterioration, characterized by a rapid increase in weakness, abdominal symptoms, and a decline in laboratory parameters, with plasma cells reaching up to 3% in the blood count. In light of the pronounced progression of the disease, a decision was made to initiate a short course of prednisolone, followed by a BP (bendamustine and prednisolone) regimen. A slight clinical improvement was achieved by the beginning of December 2023. However, on December 4, the patient exhibited symptoms of cough and subfebrile fever, with temperature reaching 37.3 °C. Based on the clinical presentation, polymerase chain reaction testing was conducted, which revealed SARS-CoV-2 infection. Despite a sharply increasing coagulopathy (disseminated intravascular coagulation syndrome) and multiorgan failure resulting from the somatic background and coronavirus disease, the patient died.

A pathological and anatomical examination revealed the presence of MM and a cancerous lesion in the right ovary, confirmed through histological analysis as an epithelial serous carcinoma.

DISCUSSION

Since the 1960s, literature on the subject has documented the development of malignant tumors in patients with MM, including an increased incidence of epithelial tumors [11]. In MM, abnormal plasma cells primarily affect the bone marrow, although other organs may also be affected. On average, approximately 13% of patients with MM develop secondary tumors, with 7% detected at initial diagnosis and 6% detected during subsequent follow-up [12]. Secondary neoplasms in these cases have been observed to exhibit more aggressive characteristics associated with myeloma, including elevated lactate dehydrogenase levels, immunoblastic morphology, a high tumor cell doubling index, and complex karyotypic features [13].

The presence of tumors in conjunction with MM is detected as solitary masses, localizing in the upper respiratory tract, lungs, stomach, intestines, lymph nodes, skin, kidneys, breast, testes, or ovaries. Lesions of the organs of the female reproductive system were observed in a variety of hematologic neoplasms, although such cases are rather sporadic [14, 15]. A study by the European Society for Blood and Marrow Transplantation in 2018 found that ovarian involvement in MM occurs in 5.3% of cases [16]. Furthermore, in the context of malignant lymphoproliferative diseases, ovaries are the most frequently affected organ in the female reproductive system [6].

In the clinical case presented, ovarian cancer was confirmed postmortem in a patient with verified MM. This confirmation was made using clinical, laboratory, and instrumental investigation methods. It is challenging to determine with certainty whether ovarian cancer is a concomitant process with progressive MM, an independent entity that cannot be detected due to indistinct clinical presentation, or a consequence of MM treatment.

Ovarian cancer is characterized by its ability to remain asymptomatic in the early stages, often manifesting only when it has already spread to other systems and organs. Given the patient's active ongoing MM process, prominent clinical symptoms, and substantial laboratory abnormalities, the likelihood of ovarian cancer was low. Consequently, instrumental diagnostic methods, particularly ultrasound imaging, CT, and MRI, were the primary tools used due to their accessibility and minimal invasiveness. In this case, none of the imaging modalities except MRI could detect the pathology, which may be due to its small size but rapid transcelomic spread leading to visualization of peritoneal carcinomatosis on CT. This finding supports our theory of MM-independent ovarian cancer. This prompts further inquiry into the potential shared etiopathogenesis of MM and ovarian cancer, the challenges in diagnosing ovarian cancer, and the exploration of approaches to verify ovarian cancer using molecular, genetic, and biochemical markers. Although MM and ovarian cancer exhibit distinct biological characteristics, both are characterized by their reliance on adhesion to the extracellular matrix and interaction with other cells [17]. Research has identified mutations in the RAS family of oncogenes *(KRAS, NRAS), BRAF, PI3K, and P53,* among others, in patients with both MM and cancerous neoplasms [18].

Conversely, there are very few data in the literature describing isolated cases of MM presenting as ovarian plasmacytoma secondary to MM metastasis [19]. This situation was also considered in the diagnostic concept of our patient.

According to the National Cancer Institute database, cancer survivors have a 14% increased risk of developing subsequent malignancies compared to the general population [20]. According to other studies, MM alone and independent of drug exposure increases the risk of secondary tumors [10].

Remarkably, despite a similar histologic pattern, MM exhibits a broad molecular spectrum with unique gene expression profiles that correlate with clinical characteristics and patient survival, possibly accounting for the formation of secondary cancers in not every patient with this diagnosis. Moreover, MM progression and treatment lead to additional molecular events, including epigenetic changes and activation of molecular pathways [21].

Several studies claim that treatment-related factors are important in the pathogenesis of secondary malignancies after plasmacytoma [22]. However, the lack of molecular markers specific for therapy-induced cancer prevents the determination of the effect of prior therapy on the development of secondary malignancies. For example, there are reports of an increased risk of secondary malignancies in MM patients compared to the general population when taking lenalidomide in particular [10, 23].

In view of the aforementioned evidence, it is reasonable to consider the possibility that the pathogenesis of secondary malignancies may reflect a combination of influences, including factors related to MM itself, drug exposure and treatment outcomes, patient comorbid background, environmental conditions, and lifestyle [24].

CONCLUSION

Currently, the etiology of cancer in patients with MM remains unclear. Despite numerous etiopathogenetic hypotheses, further comprehensive studies are necessary to investigate the background of MM and secondary cancers. The elucidation of molecular genetic features in such tumor combinations is promising for predicting their future occurrence and identifying effective therapeutic approaches.

ADDITIONAL INFO

Authors' contributions. I.Yu. Gadaev, I.V. Gadaeva, K.A. Rossolovskaya developed the concept and design of the study; I.Yu. Gadaev, I.V. Gadaeva, K.A. Rossolovskaya, I.Ya. Sokolova, O.V. Bochkarnikova collected and processed the data; I.Yu. Gadaev, I.V. Gadaeva, K.A. Rossolovskaya wrote the text; I.Yu. Gadaev, I.V. Gadaeva, K.A. Rossolovskaya edited the manuscript. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work).

Funding source. This study was not supported by any external sources of funding.

Competing interests. The authors declares that there are no obvious and potential conflicts of interest associated with the publication of this article.

Consent for publication. Written consent was obtained from the patient for publication of relevant medical information and all of accompanying images within the manuscript.

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