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RESEARCH ARTICLE

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The Ketogenic Diet as Part of Comprehensive Cancer Therapy

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ABSTRACT

Cancer remains a leading cause of death, stimulating the search for metabolic adjuvant approaches, including the ketogenic diet. A clinical case of a patient with metastatic breast cancer is presented. Inclusion of a paleo-ketogenic diet in combination therapy was associated with therapeutic ketosis, regression of neurological symptoms, and a reduction in metastatic lesions while maintaining satisfactory nutritional status. This clinical case suggests that with careful patient selection, monitoring of nutritional status and ketosis levels, and combination with standard chemotherapy and hormone therapy regimens, the ketogenic diet can not only improve metabolic parameters and quality of life but, in some cases, be associated with tumor regression.

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Introduction

Oncology remains one of the key global health issues today: morbidity and mortality from malignant neoplasms continue to rise, and a highly demanded need for high-quality care and patient support significantly outstrips available resources [1].

The situation is further complicated by the "rejuvenation" of cancer, the growing number of long-term patients bearing a heavy burden of suffering alongside with the accumulation of chronic consequences of therapy, it undoubtedly requires a reassessment of oncology being solely considered as a "tumor treatment” but actually rather a comprehensive holistic discipline that goes far beyond this approach.

In recent years, the range of anticancer interventions has expanded significantly: from classical surgery, chemotherapy, and radiotherapy to targeted drugs, immunotherapy, cellular technologies, and combination regimens. Modern approaches include the use of molecular genetic tumor profiling to select individualized treatment regimens, which can improve efficacy and reduce toxicity. Combining immunotherapy with targeted and metabolic interventions, using adaptive therapy aimed at tumor control rather than mandatory eradication, and integrating radiosurgery and minimally invasive technologies are in the list of high-demand promising areas.

However, even the most modern regimens often provide only temporary disease control: tumors acquire drug resistance, form new clonal lines, and evade immune system control, leading to regrowth and metastasis. In real-world clinical practice, the effectiveness of complex regimens leaves much to be desired as it is often lower than in clinical trials due to comorbidity, late diagnosis, limited access to innovative drugs, and treatment interruptions.

Despite rapid progress in oncology, a considerable proportion of patients still do not achieve long-term remission, and the incidence of advanced and metastatic cancer remains high and continues to grow in some areas [2].

The fact that current therapy fails to cure or stabilize the disease in a significant proportion of patients underscores the need for further development of personalized oncology and the search for new targets and combinations.

Despite progress in targeted and immuno-oncological approaches, some patients develop widespread metastatic disease, including involvement of the central nervous system and spinal cord, which significantly worsens prognosis and quality of life. Against this backdrop, interest in adjuvant metabolic strategies is growing, among which the ketogenic diet is considered a potential adjuvant method capable of modifying tumor and systemic metabolism [3,4].

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The Ketogenic Diet in Oncology

The ketogenic diet is currently being considered as a potential adjuvant strategy in oncology, targeting the metabolic characteristics of tumor cells and potentially enhancing the effects of standard therapy [5-7].

The ketogenic diet is a high-fat, moderate-protein, and highly carbohydrate-restricted diet that places the body in a state of ketosis, where fatty acids and ketone bodies become the primary energy source.

The ketogenic diet in cancer affects tumors through metabolic reprogramming (altering energy sources and growth signals) and through the immune-mediated effects of ketone bodies, which influence inflammation and the antitumor immune response [4,5,6,8-10].

The Warburg effect has been described in most solid tumors: even in the presence of oxygen, cancer cells prefer aerobic glycolysis, actively consuming glucose and producing lactate, which ensures the rapid synthesis of ATP and building blocks for proliferation. A ketogenic diet dramatically reduces carbohydrate intake and circulating glucose and insulin levels, putting the body into a state of ketosis, in which fatty acids and ketone bodies become the primary energy substrates. This fundamentally alters the energy landscape of tumor and normal tissue [4,5,8,11].

For many tumor cells, high dependence on glucose and signaling pathways activated by insulin and IGF-1 (PI3K/AKT/mTOR) means that the reduction in glycemia and insulinemia associated with a ketogenic diet leads to the deactivation of proliferative and anti-apoptotic signals. Experimental studies show that the ketogenic metabolic state is accompanied by a decrease in mTOR activity, a decrease in the synthesis of growth proteins, and changes in the expression of glycolytic and lipid metabolism enzymes in tumor cells, which may limit their ability to rapidly divide [6,11,12].

Ketogenic diets also enhance adenosine monophosphate-activated protein kinase (AMPK), which inhibits aerobic glycolysis and suppresses tumor proliferation, invasion, and migration [6]. Mouse models of metastatic cancer show that exogenous ketones themselves have a direct cytotoxic effect on tumor viability [12].

Metabolic reprogramming affects not only the tumor, but also the liver, adipose tissue, and systemic metabolism: the fatty acid–AMPK–MNK–eIF4E axis is activated, which regulates the transcriptome and translation of the gene lipid metabolism and ketogenesis. During a ketogenic diet, increased eIF4E phosphorylation and adaptive translational changes allow normal tissues to efficiently utilize fats and ketones, whereas tumor cells in a number of models are less plastic and more vulnerable to energy stress, especially when combined with MNK/eIF4E inhibitors [9].

Ketone bodies, primarily β-hydroxybutyrate (β-HB), are considered not only as an energy substrate but also as signaling molecules influencing epigenetic mechanisms and immune cells. β-HB can act as an inhibitor of several classes of histone deacetylases, altering the histone acetylation profile and thereby modifying the expression of genes associated with inflammation, stress response, and metabolism, including in immune and tumor cells [4,5,8,11].

At the level of systemic inflammation, ketogenic metabolic therapy in clinical trials for breast cancer was associated with a decrease in the levels of proinflammatory cytokines (TNF-α, CRP) and a relative increase in the concentration of anti-inflammatory IL-10, which may contribute to a reduction in chronic tumor-associated inflammation. Since chronic low-grade inflammation maintains immune dysfunction and tumor progression, its modulation against the background of ketosis can potentially enhance the effectiveness of chemotherapy and hormonal therapy by reducing immune tolerance to the tumor [4-6,10,13,14].

Experimental studies show that ketone bodies can influence the phenotype of T lymphocytes, macrophages, and innate immune cells by altering the balance between pro- and anti-inflammatory subtypes. For example, in models combining a ketogenic diet with immunotherapy or chemotherapy, an increase in the cytotoxic response of CD8+ T cells and a decrease in the functional activity of suppressive subsets have been observed [4-6,10].

β-HB also influences the NLRP3 inflammasome signaling pathway, which plays a key role in the activation of caspases and the secretion of IL-1β and IL-18, important mediators of inflammation and tumor progression. Some models have shown that ketone bodies can inhibit NLRP3 inflammasome activation, thereby reducing excessive inflammatory responses and improving the tumor microenvironment in terms of functional T cell infiltration [4-6,8].

A ketogenic diet induces complex restructuring of cellular signaling networks associated with energy stress and survival, primarily AMPK, mTOR, HIF-1α, and the translation factor eIF4E. AMPK activation during glucose deficiency and elevated fatty acid levels leads to suppression of mTOR-dependent protein synthesis, increased autophagy, and decreased lipid biosynthesis, which in tumor cells can increase sensitivity to cytotoxic drugs and radiation [4,8].

Some reviews highlight that the ketogenic diet can sensitize many tumors to standard therapies by exploiting their altered metabolism and consider it a promising component of future combination regimens [4,6,9].

In terms of radiosensitivity, the reduction in glucose levels and increase in oxidative stress with the use of ketones may enhance the effectiveness of radiation therapy by reducing the tumor's antioxidant defenses and disrupting DNA repair. Some preclinical data suggest a more pronounced radiobiological effect when combining the ketogenic diet with radiation, but the clinical base is still limited and the results are heterogeneous [4,5,8].

Overall, the potential mechanisms of action of the ketogenic diet as part of combination cancer therapy include: decreased availability of glucose and insulin for tumor cells; modification of signaling pathways associated with tumor tissue growth and survival; reduction of systemic inflammation; possible correction of the immune response and the tumor microenvironment; and improving the patient's energy status without additional pharmacological interventions [6,8].

Systematic reviews in recent years have noted that ketogenic diets in oncology are generally safe and can improve metabolic parameters, but their effectiveness in terms of survival and

sustained antitumor effects has not yet reached a convincing level of evidence [10,13].

Case Description

A 43-year-old female patient diagnosed with stage IIB (pT2N1M0) invasive right breast cancer received primary treatment in accordance with the principles of modern oncological practice. The first stage involved radical resection of the right breast. Postoperatively, adjuvant therapy courses were administered, including chemotherapy and hormonal therapy. Taking into account the hormone-dependent nature of the tumor, the patient underwent bilateral oophorectomy.

Despite the standard treatment, disease progression was subsequently noted with the formation of multiple metastatic foci, including spinal cord damage at the Th1 level and multiple metastases in the brain (In the brain (at the level of native CT scanning), areas of low density are detected in the right frontal lobe and left occipital lobe. A hypermetabolic lesion measuring 25 x 43 mm is present in the posterior cranial fossa), indicating the process has progressed to a disseminated stage.

Clinically, the patient developed lower paraparesis and pelvic dysfunction. Systemic therapy, including repeated courses of chemotherapy and hormone therapy, was continued in the hospital. However, at this stage, a ketogenic diet was additionally introduced into the comprehensive sophisticated treatment to achieve therapeutic ketosis.

Neurological status on the day of initiation of the ketogenic diet: Consciousness is clear. The patient is seated in a wheelchair. There are no meningeal symptoms. Vision is normal. Eye movements are fully functional. There are no sensory disturbances in the face. Moderate smoothing of the left nasolabial fold can be observed. Hearing is normal. No nystagmus. The glottal reflex is normal. The patient does not choke. Her voice is normal. The tongue is in the midline. Arm strength is normal, and reflexes are symmetrical. Flaccid lower paraparesis score is 3.5 points. The knee and ankle reflexes are symmetrically decreased on both sides. No pathological reflexes are detected. The finger-to-nose test shows moderate bilateral misses. Tension symptoms are moderate.

ab tests on the day of initiating the ketogenic diet: total protein, bilirubin, urea, and creatinine are normal. Total cholesterol is normal. Atherogenic index is normal. Serum glucose is normal.

The ketogenic diet was initiated in the paleo-ketogenic diet format, which involves the complete elimination of carbohydrate sources from the food ration. Dietary parameters are the following ones: 1800 kcal/day, 70 grams of protein per day, 170 grams of fat per day. The diet consisted of meat, fish, organ meats, and animal fats.

While on the ketogenic diet, ketone levels increased on day 3, from a baseline of 0.5 mmol/L to 2 mmol/L, reaching 4 mmol/L by day 6. Subsequently, ketone levels remained stable in the range of 2.5 to 5 mmol/L, with a minimum in the morning and a maximum in the evening.

While being on the diet, frequent and poorly digested stools were observed. Stool normalization was observed with the addition of enzymes (Pancreatin 25,000 ME) to each meal and choleretic agents (Allochol, 1 tablet per meal). Nausea and bloating were not observed while on the diet.

No exacerbations of the underlying disease or clinically significant adverse reactions were reported during the diet's introduction, consistent with data from randomized trials on the safety of ketogenic diets in cancer patients [13-17].

Twelve days after starting the ketogenic diet, strength in the legs was noted: the patient began to move independently, without the aid of a wheelchair or cane. Neurological status showed a decrease in the severity of paresis to 4.5 points. Tendon reflexes in the lower extremities returned to normal ones. Pain and tension symptoms in the lower extremities were not detected. The patient reported regaining control over pelvic function and the reappearance of spontaneous bowel movements.

At the follow-up visit a month later, ketone body levels were 3-5 mmol/L. Dyspeptic disorders, including constipation, were not detected. Laboratory tests revealed an increase in total cholesterol to 6 mmol/L with normal triglyceride levels and atherogenic index. Total protein, bilirubin, urea, creatinine, and uric acid levels were normal.

A follow-up MRI two months after the start of ketoracion compliance demonstrated a reduction in the secondary Th1 intramedullary lesion and the absence of perilesional edema compared to previous results.

Given the achieved lesion regression and clinical improvement, a decision to discontinue hormonal therapy while maintaining a ketogenic diet was taken. A follow-up PET/CT scan three months later revealed no pathological accumulation of 18F-FDG, characteristic of a neoplastic process, which was interpreted as the absence of metabolically active tumor foci. At the time of observation, the patient continues to adhere to a ketogenic diet, maintains a stable level of therapeutic ketosis, and reports satisfactory general well-being, without significant nutritional status disturbances.

Discussion

The presented clinical case demonstrates a scenario in which, in a patient with metastatic lesions in the spinal cord and brain, while undergoing long-term standard therapy, the introduction of a ketogenic diet is associated with clinical and radiological improvement, including the disappearance of metabolically active tumor lesions according to PET/CT data. The observed positive dynamics of neurological symptoms (regression of paraparesis, restoration of pelvic function control) and a reduction in the intramedullary mass in the spinal cord MRI findings are consistent with the hypothesis of possible synergy between metabolic therapy and systemic drug therapy [5,13-15].

An important methodological issue is assessing the impact of the ketogenic diet on the nutritional status of cancer patients, as significant weight and fat loss in metastatic disease can worsen sarcopenia and reduce the tolerability of anticancer therapy [13-15,18].

In this case, the patient maintained satisfactory general well-being and showed no signs of clinically significant nutritional deficiency.

Due to the systemic nature of metastatic breast cancer and the complex multicomponent treatment structure, the ketogenic diet should be considered an adjunctive treatment, used strictly as part of comprehensive therapy and under the supervision of a multidisciplinary team.

Conclusion

With the rising incidence of cancer and the increasing number of patients with widespread metastatic disease, the search for additional therapeutic approaches is becoming an absolutely indisputable priority in modern oncology. The ketogenic diet, with its systemic effects on metabolism, inflammation, and possibly| highly likely the immune response, can be reckoned a promising adjunctive method in combination therapy [4,5,13-15,17].

A significant advantage of this approach is its systemic effect on the patient's metabolic and immune status without additional pharmacological intervention.

In clinical practice, the use of the ketogenic diet should be carried out within the framework of controlled protocols or clinical trials, with mandatory participation of a nutritionist, monitoring of laboratory parameters, assessment of tolerance, and preparedness to adjust or discontinue the diet if adverse events occur.

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