Tumor Lysis Syndrome Presenting in a Patient with Metastatic Melanoma Treated with Radiation Therapy

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Tumor lysis syndrome is the most common disease-related emergency encountered by physicians caring for children or adults with hematologic cancers. Although it develops most often in patients with non-Hodgkin's lymphoma or acute leukemia, its frequency is increasing among patients who have tumors that were only rarely associated with this complication, such as breast carcinoma, small cell lung carcinoma, germ cell tumor, thymoma, soft tissue sarcomas, ovarian carcinoma, Merkel cell carcinoma, metastatic medulloblastoma, neuroblastoma, vulvar carcinoma, and squamous carcinomas of the head and neck [1]. The tumor lysis syndrome occurs when tumor cells release their contents into the bloodstream, either spontaneously or in response to therapy, leading to the characteristic findings of hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia. These electrolyte and metabolic disturbances can progress to clinical toxic effects, including renal insufficiency, cardiac arrhythmias, seizures, and death due to multi-organ failure [1].

Only a few reports mention the occurrence of TLS in melanoma patients. These cases dealt with the development of TLS either spontaneously or following the commencement of bio- or chemotherapy [2,3]. Historically, melanoma has been considered a relatively radio-resistant tumor. Newer data have challenged this viewpoint, and radiation therapy is now considered a useful component of the therapeutic armamentarium for malignant melanoma, particularly when larger-than-standard doses of radiation are administered in each fraction. Most importantly, it can provide effective palliation for the 40–50% of patients who develop unresectable locally recurrent or metastatic disease that produces bone pain, epidural spinal cord compression, central nervous system dysfunction due to brain involvement, and/or tumor hemorrhage.

The mitogen-activated protein kinase pathway is an important driver in melanoma and comprises several potential targets providing therapeutic options. In this pathway, the activation of RAS proteins (the Ras protein family members belong to a class of protein called small GTPase, which are involved in transmitting intracellular signals) stimulates the RAF kinases (serine/threonine-specific protein kinases that are related to retroviral oncogenes) ARAF, BRAF and RAF1. This process causes the phosphorylation of the cascade of intracellular kinases which, in turn, regulates multiple cellular processes involved in cell division. Therefore, this pathway is a target for modern biological therapeutic interventions.

This report describes TLS in a patient with metastatic melanoma treated with radiation. Clinicians should be aware of the possibility of TLS in patients with solid tumors and should be familiar with the clinical presentation and laboratory tests leading to its diagnosis. To the best of our knowledge, TLS following radiation therapy in metastatic melanoma has not been previously reported.

TLS = tumor lysis syndrome

PATIENT DESCRIPTION

A 65 year old man was diagnosed with melanoma after he noticed a right-sided neck mass; he did not have difficulty swallowing and had no systemic symptoms such as fever, diaphoresis or weight loss. Fine-needle aspiration demonstrated atypical cells from an epithelial malignant source. A computed tomography scan revealed a heterogeneous right-sided neck mass with multiple adjacent small lymph nodes. Resection of the mass and the neck lymph nodes was performed, and the initial pathological finding was of a lesion 22 mm in diameter with a penetration index of Clark 5 (the Clark level refers to how deep the tumor has penetrated into the layers of the skin; level 5 describes invasion into deep subcutaneous tissue).

A positron emission tomography-CT scan revealed the pathologic absorption of FDG in the neck, lungs, mediastinum, liver and skeleton. The patient was not a candidate for local radiation. Since his BRAF status was negative, he was not a candidate for anti-BRAFi biological therapy. Due to his general medical condition chemotherapy in any form was not considered. Palliative radiation therapy of the pelvis and left shoulder was applied for agonizing pain that developed over his spinal cord. Seven days later, after completing five radiation sessions, the patient was hospitalized due to general illness and renal insufficiency. Blood tests demonstrated a sodium level of 137 mEq/L, potassium 5.3 mEq/L, bicarbonate 18.9 mmol/L, creatinine 3.7 mg/dl, phosphorus

7.9 mg/dl, calcium 10.4 mg/dl, uric acid 18.5 mg/dl, and lactate dehydrogenase 2186 IU/L. Upon admission, the patient was aggressively hydrated intravenously. Pharmacologic treatment during admission included allopurinol 200 mg once a day and rasburicase 20 mg intravenously once during the hospitalization with concomitant analgetic drugs. However, his condition progressively deteriorated, and he died due to multi-organ failure 3 weeks after admission.

COMMENT

Tumor lysis syndrome is a catastrophic condition that occurs due to enhanced death of tumor cells, with massive release of cellular breakdown products typically seen following the treatment of malignancies. In the current classification system of Cairo and Bishop, TLS can be classified as laboratory or clinical. Laboratory TLS requires that two or more of the following metabolic abnormalities occur within 3 days before or up to 7 days after the initiation of therapy: hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. Clinical tumor lysis syndrome is present when laboratory TLS is accompanied by an increased creatinine level, seizures, cardiac dysrhythmia, or death [1]. Our patient met the criteria for laboratory TLS when he was hospitalized in our department, and met the criteria for clinical TLS simultaneously when his creatinine level increased to 3.7 mg/dl without any former renal insufficiency.

TLS is a rare complication of cancer therapy for solid tumors, although the reported cases likely underestimate the true incidence. It was found that TLS is most frequently seen in patients with metastatic disease and with tumors highly sensitive to antineoplastic therapy. However, surprisingly, TLS was also reported in patients with relatively insensitive tumor types. It is possible that improvement in the systemic treatment of various solid tumors with increasing response rates is ascribed to the modest increase in the incidence of TLS [3]. Prophylactic treatment to avoid TLS includes allopurinol, hydration prior to treatment, and alkalization of the urine. Urate oxidase (rasburicase) can replace allopurinol as a more effective way of reducing hyperuricemia and, as a result, the risk of TLS [4,5]. Acute kidney injury is associated with high morbidity and mortality, and its prevention requires an awareness of the patient's a priori risk of the tumor lysis syndrome and careful monitoring for early signs of it [1].

The findings in our report further strengthen the possibility of TLS in solid tumors and emphasize the importance of considering TLS in the differential diagnosis of critically ill patients with malignancy and acute renal dysfunction in the setting of characteristic biochemical abnormalities.

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