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Case Report: Chemotherapy and PD-1 Inhibitor-Induced Tumor Lysis Syndrome in Primary Hepatic Sarcomatoid Carcinoma

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1. Abstract

Primary Hepatic Sarcomatoid Carcinoma is a rare and highly aggressive tumor with a poor prognosis, primarily diagnosed through meticulous histopathological examination and extensive immunohistochemical analysis. It is characterized by the sarcomatoid transformation of hepatic epithelial cells, resulting in mixed epithelial and mesenchymal features. Tumor lysis syndrome (TLS) is an oncological emergency caused by the rapid tumor cell lysis, causing electrolyte imbalances like hyperkalemia, hyperuricemia, and hyperphosphatemia. Without timely treatment, TLS can lead to acute renal failure and multiple organ damage. In this report, we present a case of advanced sarcomatoid carcinoma that developed TLS following initial chemotherapy and immunotherapy, along with a review of relevant diagnostic and management strategies. This case highlights the complexities of diagnosing sarcomatoid carcinoma, underscores the risks associated with combined systemic therapies, and illustrates the importance of early recognition and intervention for TLS in solid tumors.

2. Introduction

Primary hepatic sarcomatoid carcinoma (PHSC) is an extremely rare yet highly aggressive malignancy, accounting for approximately 1.8% of in surgical liver cancer cases [1, 2]. Histologically, it is characterized by poorly differentiated cells exhibiting both malignant epithelial (either hepatocellular or cholangiolocellular) and sarcomatous or sarcomatoid features. The precise pathogenesis of this disease remains unclear, and it lacks distinctive clinical, serological, or radiological manifestations, rendering histopathological examination the only definitive diagnostic tool. The available evidence on treatment is primarily derived from case reports and retrospective reviews. Even when surgical resection is feasible in the early stages of the tumor, this disease is associated with a high rate of recurrence and metastasis, with a median survival time of approximately 8 to 9 months [3, 4].

Tumor lysis syndrome (TLS) refers to a group of metabolic abnormalities that occur when a large number of tumor cells undergo rapid destruction or lysis, either spontaneously or due to physical or pharmacological interventions. The release of intracellular contents and metabolic byproducts overwhelms the body's homeostatic mechanisms, leading to significant metabolic disturbances[5]. TLS is commonly observed in malignancies such as hematologic cancers and germ cell tumors, especially in cases with a high tumor burden or those highly sensitive to chemotherapy and radiotherapy. The clinical presentation of TLS varies widely in severity and can often be overlooked in clinical settings. If not promptly treated, TLS can lead to renal failure, severe cardiac arrhythmias, or disseminated intravascular coagulation, carrying a high risk of mortality[6].

Given the invasive nature of sarcomatoid carcinoma, it is critical to recognize and understand the potentially life-threatening complications that may arise from its treatment, particularly when utilizing contemporary therapeutic methods. This report highlights a case where TLS occurred in a patient with advanced sarcomatoid carcinoma following combined chemotherapy and immunotherapy, providing insights into the management and implications of such interactions.

3. Case Report

A 74-year-old male patient presented with a 3-month history of abdominal distension and reduced appetite. His medical history is notable for hypertension and diabetes, but he denies any family history of malignancy or prior surgical interventions. Laboratory evaluations revealed hypoalbuminemia (34.9 g/L; reference range: 44-55 g/L) and elevated serum creatinine (114 μmol/L; reference range: 41-73μmol/L), serum uric acid (496 μmol/L; reference range: 155-357 μmol/L), and lactate dehydrogenase (LDH) (425 U/L; reference range: 120-250 U/L). Serological testing for viral hepatitis was positive for HBcAb and HBeAb, with HBV-DNA levels below the detection limit. Tumor marker analysis showed elevated CA125 (297.2 U/mL; reference range: 0-35 U/mL) and a mildly increased PIVKA-II level (43 mAU/mL; reference range: 0-40 mAU/mL). Other blood investigations were within normal limits.

Enhanced computed tomography (CT) revealed multiple, nearly round, and patchy low-density lesions within the liver, the largest of which was located in segment 4 and measured 62.0 mm × 31.0 mm, with post-contrast imaging showing peripheral ringlike enhancement. Additionally, imaging indicated the presence of ascites in the abdominal and pelvic cavities, widespread peritoneal, mesenteric, and omental metastases, as well as tumor infiltration into the gallbladder and intestinal wall. Highresolution pulmonary CT detected multiple solid or ground-glass nodules in both lungs, raising suspicion of malignant tumors (Figure *).

Ultrasound-guided abdominal paracentesis and percutaneous liver biopsy were subsequently performed, with malignant cells identified in the ascitic fluid. The pathological examination of tissue sections indicates significant tumor cell atypia, with numerous spindle-shaped cells arranged in sheets and nests, infiltrating the surrounding liver tissue. The cells exhibit a high nuclear-to-cytoplasmic ratio and prominent eosinophilic cytoplasmic staining. Frequent mitotic figures are observed (>5 per 10 high-power fields), and moderate-sized nucleoli are present. Further immunohistochemistry (IHC) revealed positivity for pan-cytokeratin (CK), CK7, CK19, GLUT-1, Vimentin, WT-1, and tumor protein p53. In contrast, the following markers were negative: CK20, ERG, CDX2, Hepatocyte, Arginase-1, AFP, CD34, CD45, Napsin A, TTF-1, PAX-8, HMB45, SOX-10, and Oct-4. The Ki-67 proliferative index was approximately 30%, and PD-L1 (clone 22C3) showed a diffuse, membranous pattern, with a Combined Positive Score (CPS) of 80 (Figure *). These immunohistochemical findings suggested sarcomatoid carcinoma or malignant mesothelioma. However, in the absence of a homozygous deletion of P16 (CDKN2A)[7], a final diagnosis of sarcomatoid carcinoma of hepatic origin was proposed.

Considering the treatment strategy for pulmonary sarcomatoid carcinoma [8-10] and the strong tumor positivity for PD-L1, the patient was started on a combination regimen of paclitaxel, cisplatin, and pembrolizumab, an immune checkpoint inhibitor. The patient developed hyperkalemia and elevated creatinine levels the day after treatment, yet vital signs remained stable, peripheral extremities were warm, and there were no signs of significant perfusion deficit. Urine output was over 2000 mL/day, and urinary N-acetyl-β-D-glucosaminidase enzyme levels were elevated. Initially, acute kidney injury due to cisplatin or immunotherapy was suspected. However, further laboratory tests revealed hyperuricemia, hyperphosphatemia, hypocalcemia, hypomagnesemia, and metabolic acidosis, and no significant abnormalities were found in the urine routine or specific gravity tests, raising suspicion for tumor lysis syndrome (TLS).

Consequently, all suspected offending medications were immediately discontinued, and a comprehensive treatment strategy was implemented, including aggressive hydration, insulin to reduce potassium levels, cardiac protection measures, urine alkalization, and a trial of corticosteroids to reduce inflammation. These interventions were aimed at accelerating the elimination of toxic substances and preventing further organ damage. After one week of treatment, the patient's renal function and electrolyte levels gradually improved. The patient was successfully discharged home on the tenth day post-treatment.

4. Discussion

PHSC is a rare histological subtype of liver cancer, characterized by the presence of both epithelial and mesenchymal elements. These tumors generally demonstrate poor cellular differentiation, limited resectability, and poor response to chemoradiotherapy. These malignancies are more common in elderly males and often present without early clinical symptoms. Previous studies have shown that PHSC has molecular similarities to conventional carcinomatous counterparts. Additionally, locoregional therapies may exert selection pressure that accelerates the sarcomatoid transformation of carcinomatous elements [3, 11, 12]. The absence of cirrhosis, lack of prior anti-tumor treatment, and normal serum AFP levels, along with the absence of distinct histopathological features to determine tumor lineage, suggest a pathogenesis different from typical hepatocellular carcinoma (HCC). This may indicate that this case of PHSC originated from primary carcinomatous progenitor cells, undergoing progressive morphological and [13, 14].

Due to its rapid progression, PHSC typically appears as a large,

heterogeneous low-density mass on non-contrast CT scans, often accompanied by adjacent biliary duct dilatation, venous tumor thrombus, intrahepatic metastases, and lymphadenopathy. Necrosis is common, resulting in a characteristic contrast-enhanced imaging pattern with central low density and peripheral rim enhancement indicating viable tumor tissue. These enhancement patterns may vary depending on the tumor size and the proportion of sarcomatoid components. In this case, the large PHSC tumor had predominant sarcomatoid components, displaying imaging features similar to intrahepatic cholangiocarcinoma, characterized by delayed progressive enhancement [15]. When a patient shows multiple enhancement patterns, like nonperipheral washout and delayed enhancement, PHSC should be considered in the differential diagnosis of heterogeneous tumors. Further detailed pathological and molecular testing is recommended to ensure accurate diagnosis and guide effective treatment planning. For pathologists, diagnosing PHSC poses a significant challenge. Although PHSC tumor cells typically exhibit spindle shape, high pleomorphism, and atypia with a haphazard or disorganized arrangement—hallmarks of poorly differentiated malignant tumors—epithelial features can still be identified through immunohistochemical staining or electron microscopy [3, 16, 17]. In well-sampled cases, tumor morphology may show regions with a typical epithelial phenotype, indicating either hepatocellular or cholangiocellular origin. Transitional features between carcinomatous and sarcomatoid components may also be observed. However, when carcinomatous and sarcomatoid components are clearly distinct, and the sarcomatoid component shows heterologous differentiation (e.g., chondrosarcoma, osteosarcoma, or rhabdomyosarcoma), the diagnosis should be classified as carcinosarcoma. On IHC, epithelial components generally express broad-spectrum cytokeratin and EMA. Spindle cells, however, show more complex patterns, sometimes expressing both epithelial and mesenchymal markers. Utilizing a panel of cytokeratins helps in accurately identifying epithelial features and improving diagnostic precision [18]. The tumor cells in this case predominantly exhibit spindle-shaped morphology, with no epithelioid component or extensive necrosis, reflecting a fully sarcomatoid differentiation pattern. IHC revealed positivity for at least one marker in both epithelial components (including CK-pan, CK7, CA19) and mesenchymal components (including Vimentin, Calretinin, WT1). The absence of typical HCC structures in the patient's tissue morphology and the immunohistochemical results suggest two possibilities: first, a mesothelial tumor, with epithelial markers expressed in mixed or heterogeneous regions; second, a mesenchymal transition or sarcomatoid transformation of hepatic epithelial cells, resulting in dual positivity for both epithelial and mesenchymal markers. Ultimately, after further molecular diagnostics, we were inclined to diagnose this case as sarcomatoid carcinoma.

Due to the rarity of this tumor, there are currently no evidence-based treatment guidelines for recurrent or metastatic PHSC. Both palliative and adjuvant chemotherapy options have shown limited efficacy [19, 20]. Similar to advanced HCC, the development of systemic therapies has expanded treatment options for PHSC. Several case reports have shown that anti-angiogenic therapy and/or immunotherapy can effectively control disease in PHSC, and in some cases, even provide opportunities for surgical resection [21-26]. Moreover, high PD-L1 expression is common in PHSC, possibly related to the presence of abundant tumor-infiltrating lymphocytes [27, 28]. The presence of PD-L1 expression in immune cells is associated with more favorable survival outcomes [11]. Further research is needed to explore the relationship between immune marker expression and the efficacy of immunotherapy in PHSC. For our patient, who has a favorable performance status and a high CPS, we chose a treatment regimen combining chemotherapy and immunotherapy.

With the introduction of new and more effective anti-cancer therapies, the incidence of TLS has been increasing. Tumor cell lysis and associated metabolic disturbances can lead to multisystem dysfunction, potentially causing severe complications or even death. This underscores the importance of preventing, recognizing, and promptly treating TLS in solid tumor malignancies [6]. This elderly patient, in the advanced stages of disease, presented with a high tumor burden including liver metastases, baseline hyperuricemia, elevated LDH levels, and mild renal insufficiency, and received cisplatin-containing combination therapy—all of which increased the risk of developing TLS [29-31].

Given the absence of factors such as inadequate blood flow or urinary tract obstruction, the most likely cause of acute renal dysfunction after treatment in this patient is tubular damage. This damage could be attributed to the direct effects of chemotherapy drugs; however, the urinalysis did not reveal hematuria, proteinuria, casts, or low specific gravity. Therefore, tubular obstruction leading to increased intratubular pressure and subsequent mechanical stress and damage to renal tubular cells should be considered. Combined with hyperuricemia and hyperphosphatemia, TLS is a likely diagnosis. Cairo and Bishop established definitions for laboratory TLS and clinical TLS in 2004[32], and our case aligns with these criteria. Additionally, an increase in LDH levels, along with other metabolic abnormalities, also indicates that tumor lysis is occurring.

Once TLS is suspected or diagnosed, the first step is to maintain high urine output through hydration with large volumes of crystalloid fluids and careful monitoring of fluid balance. Supportive treatments, such as correcting electrolyte imbalances and lowering uric acid levels, should be implemented, with hemodialysis considered if necessary. In this case, the patient refused hemodialysis; however, fortunately, with aggressive medical management, the

patient's condition gradually improved. Nevertheless, if irreversible renal damage, severe electrolyte imbalances, or fluid overload unresponsive to diuretics occur, early consideration of renal replacement therapy (RRT) is warranted [33].

5. Conclusion

In conclusion, PHSC is a highly invasive malignant tumor with dismal prognosis. Accurate diagnosis of PHSC, especially from needle biopsy specimens, requires careful consideration, and IHC and molecular analysis can provide valuable diagnostic insights. Furthermore, during the treatment of solid malignancies, TLS should be considered if electrolyte imbalances and acute renal insufficiency are present. Close monitoring and appropriate interventions can help reduce the incidence and mortality of TLS.

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