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Tumor Lysis Syndrome after Hepatic Artery Embolization in a Patient with Neuroendocrine Tumor of Unknown Primary

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Abstract While tumor lysis syndrome is a relatively common oncologic emergency that may occur spontaneously or resulting from cancer directed therapy, it is relatively unusual occurrence in solid tumors, especially neuroendocrine tumors. It is also particularly rare after hepatic trans-arterial embolization. We report a case of a 60-year-old man who had hepatic trans-arterial embolization for metastatic neuroendocrine tumor of the liver of unknown primary, who developed tumor lysis along with post-embolization syndrome. He received aggressive intravenous fluid resuscitation, allopurinol and rasburicase for his tumor lysis syndrome but subsequently had acute renal failure for which he underwent renal replacement therapy. The patient responded well to treatment with complete resolution of his post-embolization syndrome, tumor lysis syndrome and acute renal failure. Our case report highlights the need to consider tumor lysis syndrome in solid tumors. It should be readily recognized and treated given the associated high risk of morbidity and mortality.

Keywords: *tumor lysis syndrome, hepatic artery embolization, neuroendocrine tumor*

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1. Introduction

Tumor lysis syndrome (TLS) is a life-threatening complication most commonly seen in hematological malignancies with a high cell turnover rate or large tumor burden such as Burkitt's lymphoma, acute lymphoblastic leukemia, and acute myeloid leukemia [1]. The constellation of hyperuricemia, hyperphosphatemia, hyperkalemia and hypocalcemia occurs when malignant cells rapidly release these intracellular contents into the bloodstream [1,2]. These metabolic disturbances can lead to cardiac arrhythmias, acute kidney injury, seizures or death from multi-organ failure [1,2].

TLS can occur spontaneously or following cancer-directed therapy such as radiation, hormonal therapy and most commonly, chemotherapy [2]. Though uncommon, there has been increasing reports of TLS in solid malignancies such as lung, breast, colorectal, hepatocellular, testicular and extra-testicular cancers, and neuroendocrine tumors [2]. Risk factors include large burden of hepatic metastases, bulky tumors, rapidly dividing tumors, and nephrotoxic drugs [2]. With the advent of newer locally ablative treatment modalities such as transhepatic arterial ablation, reports of TLS post procedure have been emerging in medical literature, warranting early recognition and treatment due to the associated high mortality. Here we present a case of TLS occurring after hepatic trans-arterial embolization (TAE) in a patient with metastatic neuroendocrine tumor of unknown origin.

2. Case Presentation

A 60-year-old male with history of Bronchial Asthma and Gastroesophageal reflux disease (GERD) first presented with an episode of small-volume hemoptysis. He denied history of smoking or carcinogen exposure. He also denies a family history of malignancy. Chest x-ray showed a small nodular density in the right lower zone. Chest CT revealed two benign-appearing sub-centimeter pulmonary nodules and multiple hepatic lesions. Abdominal MRI revealed multiple hypovascular hepatic lesions, largest 3.2 x 1.4cm in the left hepatic lobe. He declined liver biopsy and did not follow up. The patient presented a year later with abdominal pain, early satiety and unintentional weight loss. He denied any other symptoms. Follow-up CT abdomen demonstrated hepatomegaly, diffuse hepatic lesions with near replacement of the left hepatic lobe with metastases and

new lesions in the right lobe (Figure 1). Liver biopsy confirmed metastatic, well-differentiated intermediate grade neuroendocrine tumor. Ki-67 proliferative rate was 5-10%. Immunohistochemistry (IHC) staining was positive for synaptophysin and chromogranin and negative for CDX2 and TTF-1.

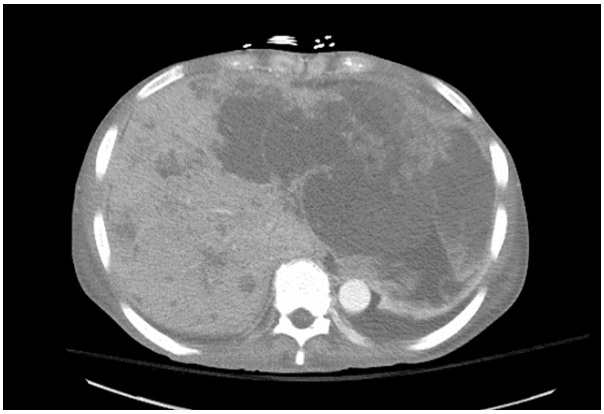

Figure 1. CT abdomen with contrast demonstrates multiple hypovascular hepatic masses (see arrows) with near replacement of the left lob

Due to bulky liver lesions, the patient was referred for left hepatic artery embolization after receiving 2 doses of octreotide. Two days following the procedure, he became disoriented, complained of worsening abdominal pain and vitals revealed tachycardia, hypotension, and fever (100.4^0F). Laboratory studies showed an increase in AST (86 to 1335mg/dl) and ALT (90 to 500 mg/dl), potassium of 6meq/dl, phosphate 5.5mg/dl, uric acid 10.5mg/dl and lactic acidosis. CT abdomen was negative for acute intra-abdominal pathology. Aggressive IVF resuscitation was initiated with allopurinol and rasburicase for TLS prophylaxis and treatment. The patient also received empiric antibiotic coverage with piperacillin/tazobactam, lactulose and rifaximin for presumed hepatic encephalopathy in setting of fulminant hepatitis. Blood cultures remained sterile.

He was admitted to the intensive care unit (ICU) for management of TLS and post embolization syndrome. His course was further complicated by oliguric renal failure requiring continuous renal replacement therapy and sterile ascites. The patient's mental status gradually returned to baseline and by day 18 of admission, the TLS, post embolization syndrome and renal failure resolved with normalization of laboratory parameters. He was eventually discharged to subacute rehabilation and continued follow-up with primary oncologist.

3. Discussion

Neuroendocrine tumors of unknown primary are a rare group of malignancies arising from the enterochromaffin cells with a diverse clinical presentation depending on the tumor differentiation or grade [3]. Well-differentiated neuroendocrine tumors are graded G1, G2, G3 based on the Ki-67 labeling index (<3, 3-20% and >20%, respectively) and mitotic rate [4]. Neuroendocrine cancers are considered high-grade or poorly differentiated [4]. Neuroendocrine tumors are generally slow growing except the poorly differentiated subtypes which tend to be aggressive [4]. The gastrointestinal tract is the most common site of origin (70%) followed by the lungs (25%). Other less common sites include kidneys, thymus and larynx [5]. Neuroendocrine tumors have a proclivity for hepatic metastasis, with up 90% of patients having hepatic involvement at the time of diagnosis [6]. The presence of hepatic metastases is a poor prognostic factor with a median survival of 2-4 years. By extension, significant burden of hepatic metastases portends for increased morbidity due to symptoms from mechanical compression from the lesions, hepatic synthetic dysfunction as the liver is gradually replaced by tumor or hypersecretion of hormones which may lead to episodic flushing, cardiac failure from valvular damage, profuse diarrhea and bronchospasm (carcinoid syndrome) [5,6,7,8].

Treatment options include surgical resection, chemotherapy, biotherapy, liver transplantation and local ablation by way of hepatic trans-arterial embolization (TAE) or trans-arterial chemoembolization (TACE) [8]. Systemic chemotherapy has not shown promising results for metastatic neuroendocrine liver tumors and biotherapy has limited long term effects in that the disease can become refractory to it [9]. Somatostatin analogs, such as octreotide, work by and may be effective in controlling symptoms but the result is often short-lived. Surgical resection remains gold standard due to its survival benefits, however, tumors that are large and or abutting the hilum, multiple or bi-lobar are often not amenable to surgery [8,9]. In such cases, TAE or TACE may be a suitable option.

Neuroendocrine liver metastases are highly vascular lesions, deriving their blood supply predominantly (>90%) from the hepatic artery while liver paranchyma receives 75-80% of its blood supply from the portal vein. Ischemia through embolization of the hepatic artery branches supplying the tumor underpins the TAE technique. Commonly used embolic agents include lipidol, gel foam particles, polyvinyl alcohol particles and microspheres. In the case of TACE, the same principle applies with the addition of chemotherapeutic agents to the embolization therapy for synergistic effect. TAE and TACE palliate symptoms in 64-93% of patients over 1 to 18 months and 53 and 95% between 10 and 55 months respectively (10,11). Both techniques have proven effective in tumor response and progression free survival which was found to be an average 36 months by Fiore et al. However, TAE seemingly has a better safety profile than TACE. A review by Del Prete et al. made mention of only a few readily treatable complications with death occurring mostly as an adverse effect of chemotherapeutic agents in TACE [12]. Post embolization syndrome characterized by fever and transient increases in liver enzymes is the most common adverse event associated with trans-arterial therapy but is seen more so in TACE than TAE 41% vs 61% respectively [13]. TLS after TAE/TACE is a rare complication but has been cited in a few case reports in the literature. The underlying mechanism is not clearly elucidated but is believed to be the result of rapid tumor destruction that leads to necrosis and cell death [14,15]. Large tumor burden (>5cm) plays a key role in the development of TLS but other risk factors include chemosensitive tumors, large area of tumor necrosis, and pretreatment renal dysfunction [15].

4. Conclusion

Although post-embolization syndrome and fulminant hepatic failure are expected post procedural concerns, TLS is an unusual manifestation in solid tumors and even less common after TAE. Risk factors for TLS post TAE include large burden of hepatic metastases, rapidly dividing tumors and nephrotoxic drugs. TLS in solid tumors must be recognized promptly even more so now given the increased use of palliative or non-invasive local ablative treatment modalities in neuroendocrine tumor and other solid tumors. Given the associated risks of acute liver failure, post embolization syndrome and TLS after intra-arterial liver directed therapies, we suggest proposing a defined algorithm to guide house staff in managing such patients in high volume centers.

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