

Spontaneous Tumor Lysis Syndrome and Secondary Thrombotic Thrombocytopenic Purpura in Early Stage Colorectal Cancer

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Introduction

Acute tumor lysis syndrome (ATLS) is a well-described oncological emergency that is usually associated with hematological malignancies complicated by treatment. It is typically related to a high tumor burden, rapidly growing and chemosensitive malignancies. ATLS is characterized by the presence of hyperphosphatemia, hyperuricemia, hyperkalemia, hypocalcemia and acute renal failure^[1,2]. The administration of cytotoxic chemotherapy causes tumor death and tissue necrosis which leads to release of inflammatory mediators precipitating this syndrome^[3,4]. However, it has been rarely reported in hematological malignancies without administration of chemotherapy, and has been referred to as spontaneous tumor lysis syndrome (STLS). STLS is even more infrequent in solid tumors^[5-15].

Secondary thrombotic thrombocytopenic purpura has been rarely described in the literature with all the cases associated with metastatic adenocarcinomas^[16-18]. Herein, we describe the first reported case of limited stage colorectal cancer presenting with STLS and secondary thrombotic thrombocytopenic purpura (TTP).

Case Report

A 60-year old post-menopausal woman with prior history of asthma and diverticulosis presented with a 4-day history of diarrhea with blood clots and left-sided abdominal pain. She had taken albuterol inhalation p.r.n (as needed). Physical examination showed stable vital signs and left-lower quadrant tenderness. Laboratory studies revealed microcytic anemia (10.4 gm/dl, MCV = 64.5 fl), leucocytosis (44,100 cells/mm³, N = 4,000~11,000) and reactive thrombocytosis (619,000 plts/mm³, N = 150,000~400,000). CT scan of the abdomen and pelvis showed massive uterine fibroids (largest around 6.0 cm in size), a sigmoid mass and diffuse colitis suggestive of either ischemic colitis or inflammatory bowel disease (Fig.1). The patient underwent colonoscopy which revealed a fungating mass obstructing the sigmoid colon. The biopsy of the mass displayed well to moderately differentiated adenocarcinoma. On day 4 of admission, the patient's chemistry profile showed acute renal failure, hyperphosphatemia, hyperuricemia, hypocalcemia and hyperkalemia consistent with STLS. At the same time, she developed fever, her hemoglobin and platelet counts plummeted and peripheral blood smear showed a microangiopathic hemolytic picture (Fig.2), low haptoglobin (< 6 mg/dl, N = 16~200) and elevated serum LDH levels (2,435 U/L, N = 100~225), compatible with TTP. Direct or indirect Coomb's tests or Ham's assay were not con-

ducted. Her other lab values were as follows: PT 12.3 (normal 9.1–11.9 s), PTT 30.9 (normal 23–34 s), INR 1.10 (normal 0.86–1.14), TT 17.3 (normal 14.4–17.9 s), fibrinogen 256 (normal 180–462 mg/dl) and d-Dimer 4.05 (normal < 2.78 mg/L). Autoimmune hemolytic anemia and other microangiopathic hemolytic anemia were ruled out. She had no central nervous system symptoms, and no bone marrow biopsy was performed.

The patient was aggressively hydrated and treated with allopurinol. She underwent distal colectomy and histopathologic examination confirmed the initial biopsy results. Focal intraluminal tumor necrosis was seen without angiolymphatic invasion (Fig.3), and 9 perirectal lymph nodes were negative for metastases. The patient was diagnosed with Stage IIA colon cancer. Her renal function and blood counts started to improve on day 9 of admission (Graphs 1, 2 and 3). She was discharged home on day 14 in a clinically stable condition.

Discussion

Acute tumor lysis syndrome (ATLS) is a constellation of serious metabolic complications that typically occurs in the setting of chemotherapy treatment of hematological malignancies such as high grade lymphomas or leukemias that are bulky and chemosensitive^[1–3]. It also has been rarely reported in patients with advanced solid tumors, usually following or during chemotherapy, but also sometimes post-radiotherapy or immunotherapy. Acute spontaneous tumor lysis syndrome (acute STLS), on the other hand, is a phenomenon that has been occasionally reported de novo prior to therapy in high grade hematological malignancies, but very rarely in solid malignancies especially in patients with advanced-stage, bulky, rapidly proliferating and highly chemosensitive tumors^[4–7]. Only a few more than 10 cases of this syndrome have been reported to date. This syndrome results from massive tumor cell death and release of cellular contents in the blood stream such as intracellular ions and metabolic by-products^[8–10]. This in turn

causes severe and rapid metabolic changes manifested by hyperkalemia, hyperuricemia, hyperphosphatemia and hypocalcemia. Sudden electrolyte imbalance can be life threatening and may lead to cardiac arrhythmias, seizures, acute renal failure, coma and death.

It is well known that uric acid is relatively insoluble in the acidic milieu of urine, and may form uric acid crystals that cause acute obstructive breathy and acute renal failure. Hypercalcemia can cause seizures and muscle cramps. Also, the rapid increase in serum potassium and phosphate level can lead to cardiac arrhythmias and sudden death. Clinically, the most common and serious complications in these patients are acute renal failure and metabolic acidosis. Hence, it is very important to recognize patients at a high risk level for developing this syndrome so that prophylaxis and early institution of appropriate treatment can be initiated.

Traditionally, management of these patients has been mainly supportive and palliative, consisting of allopurinol, intravenous hydration, diuretic therapy and urinary alkalinization^[11]. Recently, Baeksgaard and Sorensen^[10] reported that urate oxidase (rasburicase) is gradually replacing allopurinol because it is a more effective method for reducing hyperuricemia, and there by decreasing the risk for TLS.

Some authors have suggested that elevated LDH, hyperuricemia and azotemia in a patient with malignancy are important warning signs for TLS, and that they should be corrected prior to institution of chemotherapy. Other investigations also revealed new information on uric acid metabolism and its role in this syndrome, such as the urate elimination pathway, and described new generation urate-lowering agents^[8]. Also, a study by Pumo et al.^[11] found that treatment of TLS in elderly patients is often further complicated by renal and heart senescence and the presence of co-morbid conditions and polypharmacy.

Various solid tumors complicated by this syndrome have been reported including small cell carcinoma of the lung, breast carcinoma, gastric carcinoma, ovarian



Fig.1. Photomicrograph of peripheral blood smear showing several schistocytes (erythrocytes fragments), anisocytosis, hypochromasia and microcytes (Wright Giemsa stain, oil/ \times 1,000).

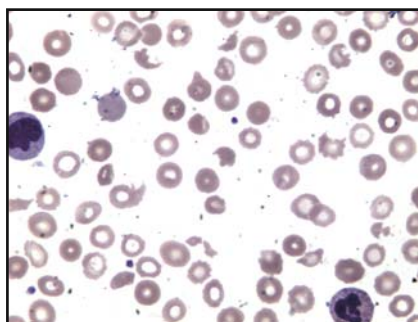


Fig.2. Low power magnification of the sigmoid colon mass showing infiltrating tumor glands and nests into the muscle propriety (H&E stain, \times 4).

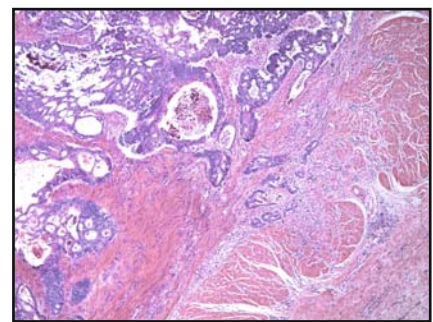
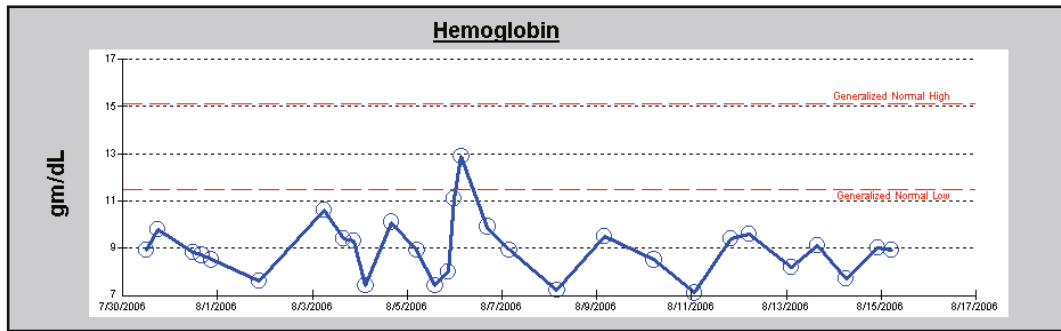
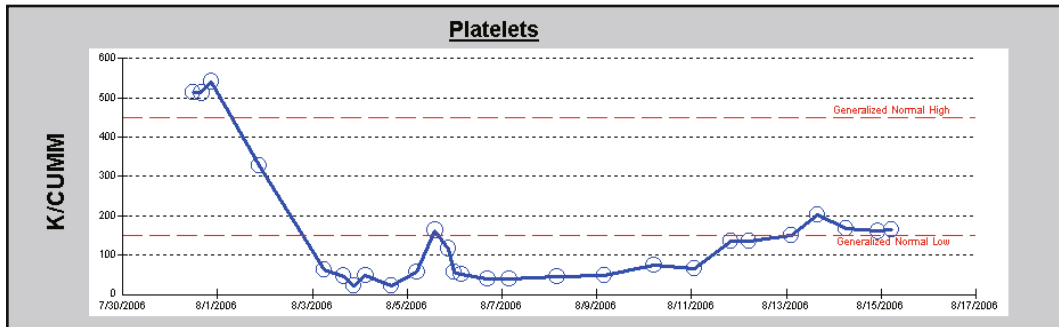


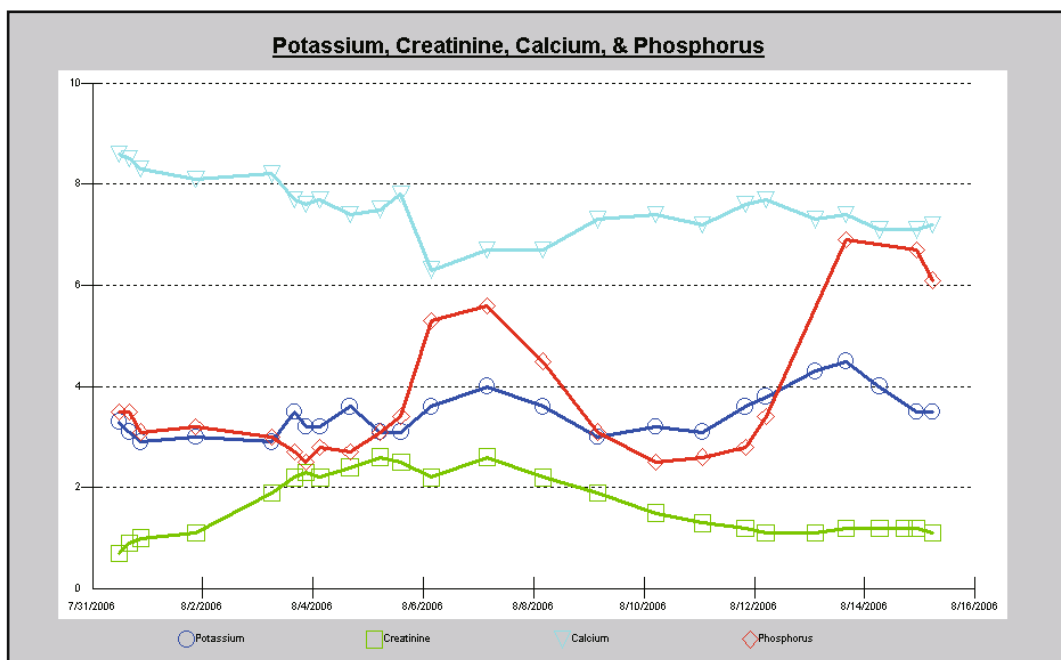
Fig.3. Medium power magnification showing colon carcinoma with invasive irregular glands surrounded by desmoplastic stroma (H&E stain, \times 10).



Graph 1. Trend of hemoglobin levels during hospitalization.



Graph 2. Trend of platelet counts during hospitalization.



Graph 3. Trend of chemistry profile during hospitalization.

carcinoma, melanoma, neuroblastoma and leiomyosarcoma^[6,12,13]. After extensive review of the English medical literature on Medline search, only one case of TLS in colon cancer occurring after chemotherapy was found^[14]. Another case was reported following radiofrequency thermal ablation^[15]. However, no cases of spontaneous TLS occurring in a colon cancer patient prior to chemo or radiation therapy was found. Thus, our described case represents the first report of STLS in colon cancer.

TTP is a disseminated form of thrombotic microangiopathy usually occurring in terminal-stage cancer patients, and rarely in early stage low tumor-burden malignancies. Other etiologies of secondary TTP include infections, drugs, connective tissue diseases, and pregnancy. On review of the English literature, we found 10 reported cases of secondary TTP associated with metastatic adenocarcinoma in the absence of chemotherapy^[16,17]. Unlike the pathogenesis of idiopathic

TTP, which is related to the deficiency of ADAMTS13, the etiology of secondary TTP in cancer is poorly understood^[17]. It may be related to tumor emboli causing endothelial damage and platelet aggregation, or to formation of immune complexes possessing platelet-aggregation properties. Such patients have not benefited from plasma exchange transfusions and only treatment of the underlying malignancy by surgery or chemotherapy can lead to resolution of secondary TTP as was observed in our case^[18–21]. We found only 3 reports of secondary TTP associated with colon cancer^[18,19,22]. One case manifested following hemicolectomy^[19] and two cases were the first presentation of colon cancer^[18,22].

Our case depicts two highly unexpected events that made the management of this patient a challenging process. Our patient had only Stage IIA disease which suggests that these phenomena can potentially, albeit rarely, occur with early stage low tumor-burden malignancies. We report this case to alert physicians to consider STLS and secondary TTP in patients with early stage solid malignancies such as colon cancer.

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