Case Report

Diffuse Intrasinusoidal Hepatic Metastasis From Occult Breast Carcinoma Presenting as Thrombotic Microangiopathy: A Case Report and Literature Review

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Abstract

We report a case of a 37-year-old female presenting with microangiopathic hemolytic anemia (MAHA) and thrombocytopenia. Two years ago, she had left breast ductal carcinoma \textit{in situ} (DCIS) treated with surgical resection and adjuvant radiotherapy. Radiological imaging showed numerous patchy hepatic infiltrating lesions, but no discrete mass lesion. Liver biopsy revealed diffuse intrasinusoidal hepatic metastases (DISH) from a poorly differentiated carcinoma, which stained strongly positive for cerbB2. The patient was treated for metastatic breast carcinoma with improvement in her MAHA and thrombocytopenia. DISH is a rare mode of cancer spread, and is often radiologically occult. Recognition of atypical presentations of metastatic carcinoma in patients who present with clinical features of thrombotic microangiopathy (TMA) is crucial to avoid futile and potentially dangerous interventions. In our patient, prompt liver biopsy yielded a diagnosis of metastatic liver malignancy with secondary TMA within 3 days of admission, and the patient was appropriately started on chemotherapy.

Keywords: Malignancy-associated MAHA; Diffuse intrasinusoidal hepatic metastases; Thrombotic microangiopathy

Introduction

Thrombotic microangiopathy (TMA) is a pathological term that describes vascular injury manifested by microvascular thrombosis and endothelial abnormalities. Although TMA syndromes are heterogeneous, they share similar clinico-pathological features, with microvascular thrombosis leading to clinical features of microangiopathic hemolytic anemia (MAHA) with red cell fragmentation, thrombocytopenia and end-organ injury [1]. Primary TMA syndromes include congenital and acquired deficiencies of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13), also called primary thrombotic thrombocytopenic purpura (TTP), congenital and acquired complement-mediated TMA, Shiga toxin-mediated TMA (ST-HUS) and drug-mediated TMA. These primary TMA syndromes have evidence supporting a probable cause [1]. They should be distinguished from secondary TMA syndromes presenting with MAHA and thrombocytopenia, such as malignancy, disseminated intravascular coagulation (DIC), systemic infection, pregnancy-induced thrombocytopenias, severe hypertension, autoimmune disorders and hematopoietic stem cell or organ transplantation.

It is unusual for TMA to be the first presentation of systemic malignancy [2]. Separate studies have estimated the prevalence of malignancy-related TMA to be 3.5% [3], 5.6% [4] and 7.8% [5] amongst patients initially diagnosed with TTP or atypical hemolytic uremic syndrome (aHUS). Malignancy-related TMA may be a result of the neoplastic process itself [6], or secondary to chemotherapeutic agents such as gemcitabine [7] and mitomycin C [8]. Here, we report a patient with diffuse intrasinusoidal hepatic metastases (DISH) from occult breast carcinoma presenting with TMA.

Case Report

A 37-year-old woman presented to our hospital with a 1-month history of fatigue and sweating. There was no associated weight loss, fever or diarrhea. She was on no medication and did not take any herbal treatment or supplements. Two years ago, she had left breast ductal carcinoma \textit{in situ} (DCIS) treated with local surgical resection and adjuvant radiotherapy, resulting in clinical remission. On examination, she was apyrexial but icteric. She had abdominal distension with ascites, and there was a 4 cm smooth and tender hepatomegaly. She had no palpable lymphadenopathy or splenomegaly; breast and neurological examinations were normal.

Investigations showed a bicytopenia, with Hb 8.9 g/dL and platelets 52 × 10^9/μL. Her absolute reticulocyte count was
834,000/μL, bilirubin 144 μmol/L (direct 63 μmol/L, indirect 81 μmol/L) and lactate dehydrogenase (LDH) 8,603 U/L. Her albumin was 28 g/L, aspartate aminotransferase (AST) 307 U/L, alanine aminotransferase (ALT) 127 U/L and alkaline phosphatase (ALP) 209 U/L. She also had acute kidney injury (AKI), with a creatinine of 138 μmol/L, urea 8.8 mmol/L, sodium 132 mmol/L and potassium 3.1 mmol/L. Direct Coombs’ test was negative. A peripheral blood film showed numerous keratocytes, schistocytes, and polychromasia (Fig. 1). Her prothrombin time was 15.7 s, activated partial thromboplastin time (APTT) 32.4 s and fibrinogen 2.76 g/L. Both CA 15-3 (2,951 U) and CEA (319 U) were elevated. There was no serological evidence of autoimmune disease, Wilson’s disease, hepatitis A, B, C, E, human immunodeficiency virus (HIV) or dengue virus infection.

The 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET-CT) showed an enlarged liver with FDG uptake and edema in the intrahepatic biliary ducts along the peripheral parenchyma. However, there was no discrete lesion to suggest a neoplastic deposit. No FDG-avid lesions were seen in the chest, including the contralateral breast. She underwent magnetic resonance imaging (MRI) of the liver with magnetic resonance cholangiopancreatogram (MRCP). This showed hepatomegaly with extensive areas of signal abnormality in both lobes of the liver (Fig. 2).

Despite the lack of discrete nodules on radiological imaging and the fact that DCIS is normally considered to have an excellent prognosis, malignancy-associated TMA had to be considered. A trans-jugular liver biopsy was performed. Histopathology showed intrasinusoidal nests of malignant cells (Fig. 3). These cells had features consistent with metastatic, poorly-differentiated carcinoma (AE1/3 positive, Fig. 3 inset). Hormone receptor studies were negative for estrogen and progesterone receptors, but strongly positive for cerbB2. The
findings in our patient showed radiologically non-specific features consistent with cases reported in the literature [11, 13, 14]. DISH in association with TMA is exceedingly rare. One other case series by Allison et al reported a patient who presented with a TTP-like syndrome, with metastatic breast carcinoma infiltrating the hepatic sinusoids only becoming apparent at autopsy [14]. The authors noted the presence of widespread intravascular tumor emboli to the lungs, gastric mucosa and adrenal cortex, without concurrent parenchymal metastases. TMA may have resulted in this case, as in ours, from shear stress created by numerous metastasizing carcinoma cells. Alternatively, crowding of hepatic sinusoids in itself, or endothelial damage from malignant deposition, could result in shearing forces on circulating erythrocytes and MAHA with thrombocytopenia.

The distinction between malignancy-related TMA and primary TTP as a cause of MAHA and thrombocytopenia had significant implications for the management of our patient. Treatment for primary TTP is plasma exchange, whereas that of malignancy-related TMA is directed at the underlying malignancy [4]. Plasma exchange would not be predicted to be effective in malignancy-related TMA [15], and exposes the patient to unnecessary procedure-related morbidity and mortality, including death due to sepsis from catheter-related bloodstream infections and complications of catheter insertion, such as hemorrhage, pneumothorax and catheter-related thrombosis [16]. This is because, unlike primary TTP, the pathogenesis of malignancy-related TMA is not due to deficiency of the von Willebrand factor (vWF)-cleaving protease, ADAMTS13 [17].

However, distinguishing between malignancy-related MAHA and other forms of TMA can be difficult during the acute presentation, especially in situations where urgent treatment with plasma exchange is required. Although diagnostic confirmation of primary TTP can be made with demonstration of low ADAMTS13 enzyme levels, this assay is not routinely available at a rapid enough turnover to enable decision-making in the first 24 - 48 h. A retrospective analysis of a French TMA registry has found that patients with malignancy-related TMA are more likely to be older, have a history of malignancy and have a longer prodrome consisting of severe weight loss, bone pain, asthenia and/or dyspnea. Neurological involvement was less common in malignancy-related TMA, and renal involvement tended to be less severe. Biochemically, malignancy-related TMA tended to be associated with DIC (lower median fibrinogen levels and persistently raised D-dimers), in contrast with other forms of TMA [6]. However, none of these clinical or laboratory features are specific, and diagnosis of malignancy-associated TMA always requires histological confirmation.

Given the rarity of both DISH and its association with TMA, a high index of suspicion was required to make a diagnosis of malignancy-related TMA, particularly given its radiologically occult findings. In our case, prompt liver biopsy yielded a diagnosis of metastatic liver malignancy within 3 days of admission, and the patient was appropriately started on chemotherapy.

**Conclusion**

Malignancy-associated TMA is well described, but its association with DISH is unusual. The diagnosis of malignancy in our
patient is critical, because primary TTP is treated with plasma exchange while malignancy-related TMA is managed by treating the underlying cancer. Our case highlights the importance of a high index of suspicion in excluding a diagnosis of malignancy-associated TMA, especially when the presentation of metastatic disease is atypical.

References