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ASFA CATEGORY IV BECOMES CATEGORY I: IDIOPATHIC THROMBOTIC THROMBOCYTOPENIC PURPURA IN A PATIENT WITH PRESUMED GEMCITABINE-INDUCED THROMBOTIC MICROANGIOPATHY

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Abstract

In the implementation of American Society for Apheresis national guidelines, the decision for therapeutic plasma exchange may be confounded by a clinical presentation that fits both a category I and IV designation. We report the case of a 45-year-old female who presented with concern for a category IV disorder, gemcitabine-induced thrombotic microangiopathy and was ultimately diagnosed with a category I disorder, idiopathic thrombotic thrombocytopenic purpura. This case highlights the importance of ruling out idiopathic TTP by a thorough evaluation for ADAMTS13 activity and inhibitor, even when an alternate thrombotic microangiopathy diagnosis may be likely.

Keywords

Therapeutic plasma exchange; TTP; TMA; ASFA national guidelines

INTRODUCTION

The American Society for Apheresis (ASFA) national guidelines incorporate evidence from the literature to guide the appropriate use of therapeutic apheresis.¹ A category IV designation clearly defines a disorder for which apheresis is likely to be ineffective or harmful. Nevertheless, in the implementation of ASFA guidelines, the decision for therapeutic plasma exchange (TPE) may be confounded by a clinical presentation that fits both a category I diagnosis and a category IV diagnosis.

Here, we report the case of a patient whose initial clinical presentation was consistent with gemcitabine-induced thrombotic microangiopathy, a category IV disorder for which TPE was held; but was ultimately diagnosed with idiopathic thrombotic thrombocytopenic

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purpura (TTP), a Category I disorder that was successfully treated with therapeutic plasma exchange (TPE).

CASE REPORT

A 45-year-old woman was admitted with exertional chest pain, palpitations, and progressive dyspnea. She had recently been diagnosed with Stage IIB uterine leiomyosarcoma treated with total abdominal hysterectomy and bilateral salpingo-oophorectomy. Three months prior to presentation, she initiated adjuvant chemotherapy with gemcitabine 900 mg/m² (day 1 and 8) and docetaxel 75 mg/m² (day 8), every 21 days. At the time of admission, she was cycle 4, day 13 of therapy (cumulative gemcitabine dose of 14.7g). Following initiation of chemotherapy, she experienced dyspnea with exertion but, by the time of admission, symptoms had progressed to dyspnea after ambulating several feet. In the same time period, she noted progressive lightheadedness, confusion, myalgias, weakness, dark urine, and rare hematochezia, without peripheral edema. The day prior to admission, upon rising from a seated position, she experienced dyspnea, palpitations and acute onset exertional chest pain that resolved after 3-5 minutes of rest.

Initial workup showed new onset hypertension with blood pressure of 149/98 mmHg (baseline normal), sinus tachycardia and normal cardiac markers. She was found to have anemia with hemoglobin 8.4 g/dL (baseline 9.0 at gemcitabine initiation; reference range 12.0 – 15.5) with platelet counts of 176 x10⁹/L (baseline 300s; reference range 150 – 450). On hospital day 2, platelet count had declined to 10 x10⁹/L and hemoglobin to 6.7 g/dL. LDH was elevated at 1144 U/L (reference range 100 – 200). Creatinine, which was initially 0.9 g/dL (baseline 0.7), peaked at 1.3 g/dL. Blood urea nitrogen (BUN), and vitamin B12 levels were normal. Peripheral blood smear showed 3-6 schistocytes/high power field, concerning for thrombotic microangiopathy (TMA). Given the concern for TMA, hematology was consulted. Because of the patient's history of gemcitabine administration, underlying malignancy, and presentation with hypertension and acute renal injury, her case was felt to be consistent with gemcitabine-induced TMA. Since gemcitabine TMA is considered an ASFA category IV diagnosis, TPE was deferred. Nevertheless, due to severe thrombocytopenia and because edema and profound acute kidney injury were absent, ADAMTS13 testing was sent to a referral lab.

The patient received 1 unit of packed red blood cells and was started on prednisone 1mg/kg/day. By hospital day 4, patient's symptoms had moderately improved, but platelets remained low with new petechiae and purpura along the back and the arms. At this point, ADAMTS13 activity levels returned at < 5% and TPE was initiated. She was subsequently found to have an ADAMTS13 inhibitor titer of 4.8 (reference range < 0.4), consistent with a diagnosis of idiopathic TTP. She was treated with single volume exchange with fresh frozen plasma, daily for six days followed by two sessions given every three days, using the Spectra Optia® (Terumo BCT, Lakewood CO) apheresis system. The anticoagulant used was Anticoagulant Citrate Dextrose Solution, Solution A (ACD-A; Citra Labs, Braintree MA) with a ratio of 1:15.

Within 4 days of TPE initiation, dyspnea and lightheadedness resolved and platelet counts recovered to $187 \times 10^9/L$ (Figure). After 8 sessions over 12 days, TPE was held. After one month of remission, prednisone taper was initiated. At 2-month follow-up, patient had not experienced return of symptoms, platelet levels remained within normal range and ADAMTS13 activity had increased to 87%. Thrombocytopenia and/or TTP did not recur; however, 9 months later, the patient died from complications of metastatic leiomyosarcoma.

DISCUSSION

Gemcitabine-induced TMA is a rare but well-categorized entity.² Although the exact mechanism is unclear, as with other drug-induced TMAs, it is thought to be the result of dose- and time-dependent endothelial injury.^{3,4} Gemcitabine TMA risk appears to increase with cumulative dose; however, consistent with our case, it has been reported with doses ranging from 1,250 to 81,000 mg/m², and, in 2 cases, after a single dose.^{4,5} Like TTP/HUS, patients can present with fatigue, thrombocytopenia, anemia, renal dysfunction and/or neurological symptoms.⁴⁻⁶ In particular, most patients present with acute kidney injury, edema, and the onset or worsening of hypertension, a feature seen in about 74% of cases.^{1,4-6}

Gemcitabine TMA does not seem to be associated with ADAMTS13 deficiency, whereas ADAMTS13 deficiency and presence of inhibitor is a defining feature of idiopathic TTP.^{1,4,6} One study of 15 patients with cancer- or chemotherapy-induced TMA showed that 2 patients had severe ADAMTS13 deficiency. Of these 2 patients with ADAMTS13 deficiency, only 1 had inhibitor.⁷ Thus, the presence of both a drug-induced and an idiopathic TTP is unusual, and suggests that, instead of causing direct endothelial injury, gemcitabine or the underlying malignancy may have precipitated autoimmune inhibitor formation.

TPE has not been shown to be effective in treating gemcitabine-induced TMA. In a retrospective cohort of 26 patients with gemcitabine-induced TMA patients, compared to patients who did not receive TPE treatment, recovery in TPE-treated patients was lower (56 vs. 30%).⁸ The mainstay for treatment is cessation of gemcitabine and control of hypertension. Corticosteroids, rituximab and dialysis have also been used.^{1,5} Additionally, recent studies have suggested disease improvement with eculizumab^{9,10} (See Table).

In this case, the condition was initially felt to be most consistent with gemcitabine-induced TMA, a Category IV diagnosis. Therefore, given the Category IV designation and the lower reported recovery for patients treated with TPE and TPE was held out of concern for ineffectiveness. However, the presence of severe ADAMTS13 deficiency with a high titer inhibitor led us to ultimately treat her as having idiopathic TTP. Her symptoms and platelet counts quickly responded to therapy with TPE with durable remission.

This case is a novel example of idiopathic TTP in a patient who met criteria for gemcitabine TMA. It highlights the importance of ruling out idiopathic TTP by a thorough evaluation for ADAMTS13 activity and inhibitor, even when an alternate diagnosis such as Gemcitabine TMA may be likely. In any patient presenting with gemcitabine TMA, an idiopathic TTP diagnosis should be strongly considered.

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Figure 1:
Change in platelet count during hospital course. TPE = Therapeutic Plasma Exchange

Table.

Patient characteristics as compared with gemcitabine TMA case series in the literature

Author, Year N	Age	Sex	Malignancy type	Platelet count [†]	Hypertension Present	Edema Present	Serum Creatinine (g/dL)	Gemcitabine Cumulative dose	Time to TMA* (months)	ADAMTS13
Our patient										
-	45	F	Leiomyosarcoma	176	Yes	No	1.3	14.7g	3	< 5%
Cases in the Literature										
Turner 2016 ⁹ (2)	67 59-75	100% F	Pancreas	53 42-63	1/2 (50%)	1/2 (50%)	3.5 3-3.9	NR	4 3-4	Normal
Grall 2016 ¹⁰ (8)	62 36-69	75% F	Pancreas, ovary, lung	NR	6/8 (75%)	5/8 (63%)	NR	22.8g 9.0-48.0g	5.5 1.7-13	NR
Richmond 2013 ¹¹ (2)	65 55-75	50% F	Pancreas	39 36-41	2/2 (100%)	1/2 (50%)	1.7 (reported for 1 patient only)	13.6 g/m ² 9.1-18 g/m ²	6 5-7	25% (1) Normal (1)
Izzedine 2006 ² (3)	68 30-78	100% F	Breast, lung, ovary	90 64-115	2/3 (67%)	3/3 (100%)	2.5 2-3-2.6	7 g/m ² 2-15 g/m ²	6 5-6	60% (1)
Lewin 2005 ¹² (3)	57	100% F	Ovary	25 20-191	3/3 (100%)	1/3 (33%)	3.2 1.6-3.6	9 g/m ² 6-9.5 g/m ²	6 cycles 5-7	NR
Muller 2005 ¹³ (4)	47 38-61	33% F	Lymphoma, bile duct carcinoma,	26 9-112	2/3 (67%)	2/3 (67%)	1.7 1.2-1.7	19.2g 14-4-28.8g	4 4-6	NR
Humphreys 2004 ¹⁴ (9)	53 33-67	56% F	Pancreas, Sarcoma, Breast, liver, pseudomyxoma peritonei, lymphoma	61 38-237	7/9 (78%)	NR	2.3 1.9-5.1	19.2 g/m ² 9-56 g/m ²	8 3-18	NR
Fung 1999 ¹⁵ (12)	56 37-73	42% F	Pancreas, lung, gastric biliary	NR	7/12 (58%)	2/12 (17%)	NR	18.3 g/m ² 2.5-40.2 g/m ²	6 4-13	NR
Flombaum 1999 ¹⁶ (3)	65 63-67	67% F	Pancreas	119 56-315	2/3 (67%)	1/3 (33%)	2.2 1.9-3.1	NR	13 12-16	NR

F = female; NR = Not reported; TMA = Thrombotic microangiopathy;

[†] At presentation;

* Time from first dose of gemcitabine to development of TMA.