CASE REPORT

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Thrombotic Microangiopathy Associated with Etoposide in Metastatic Lung Cancer: Diagnostic and Therapeutic Challenges

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ABSTRACT

Thrombotic microangiopathy (TMA) is a rare hematologic complication characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and variable involvement of organ systems. Drug-induced TMA (DI-TMA) is most commonly associated with agents such as mitomycin C and gemcitabine. Etoposide, a chemotherapeutic agent frequently used in lung cancer treatment, is rarely implicated. Recognition of DI-TMA is particularly challenging in oncology patients, in whom cytopenias often have multifactorial etiologies. We present a 60-year-old woman with a history of stage IIIC2 endometrial cancer in remission who subsequently developed metastatic large-cell lung carcinoma. She was treated with carboplatin and etoposide. Following the initial two cycles of chemotherapy, the patient developed severe anemia and thrombocytopenia, along with elevated lactate dehydrogenase, indirect hyperbilirubinemia, decreased haptoglobin, and peripheral blood schistocytosis-consistent with MAHA. ADAMTS13 activity was normal, and no renal or neurologic dysfunction was present. A diagnosis of etoposide-induced TMA was established. Etoposide was discontinued, corticosteroid therapy was initiated, and the patient subsequently demonstrated hematological recovery. Chemotherapy was resumed with irinotecan as an alternative agent. This case highlights etoposide as a potential etiologic agent of TMA in patients with lung cancer. Given the non-specific clinical presentation and overlap with chemotherapy-induced cytopenias, early recognition and prompt drug withdrawal are essential for achieving hematologic recovery. Clinicians should consider DI-TMA in oncology patients with new-onset hemolysis and thrombocytopenia-even in the absence of classic TMA organ involvement.

Keywords: Etoposide; lung cancer; hemolytic anemia; thrombocytopenia

INTRODUCTION

Thrombotic microangiopathy (TMA) is a clinical syndrome characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and variable degrees of end-organ damage, most commonly involving the kidneys and central nervous system. Primary forms of TMA include thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), whereas secondary forms may occur in association with malignancies, autoimmune diseases, infections, and certain medications.[1] Drug-induced TMA (DI-TMA) is a rare but potentially life-threatening complication, typically linked to agents such as mitomycin C, gemcitabine, calcineurin inhibitors, and quinine.[2] Etoposide, a topoisomerase II inhibitor used in the treatment of various solid tumors and hematologic malignancies, is rarely associated with TMA; only a few cases have been reported in the literature.[3-5] We report a rare case of etoposide-induced TMA in a patient with metastatic large-cell lung carcinoma, notably presenting without the classic features of renal or neurologic involvement. This case underscores the diagnostic challenges associated with TMA in oncology patients and emphasizes the critical importance of early recognition and intervention.

CASE PRESENTATION

A 60-year-old woman whose medical history was significant only for endometrial adenocarcinoma (International

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Federation of Obstetrics and Gynaecology IIIC2), diagnosed seven years earlier, underwent primary surgical treatment followed by chemotherapy with carboplatin and paclitaxel, as well as pelvic and para-aortic radiotherapy. The patient remained under routine surveillance and showed no disease progression for five years. However, during routine follow-up, thoracic computed tomography (CT) revealed a 2×1-cm solid lesion in the right lower lobe and multiple enlarged mediastinal lymph nodes. Further evaluation with positron emission tomography/CT showed hypermetabolic foci in the right lung, mediastinum, adrenal gland, and skeletal system. A CT-guided lung biopsy confirmed the diagnosis of large-cell carcinoma of the lung. The patient was subsequently started on chemotherapy with carboplatin (area under the curve 5 on day 1) and etoposide (100 mg/m^2 on days 1-3), administered every 21 days.

On day 14 following the second cycle of chemotherapy, she presented with worsening fatigue and pallor. Initial findings revealed a WBC count of 4,980/µL, a hemoglobin level of 3.9 g/dL, a platelet count of 128,000/µL, and a neutrophil count of 2,040/µL. Laboratory evaluation revealed indirect hyperbilirubinemia, elevated lactate dehydrogenase (LDH), decreased haptoglobin, and the presence of schistocytes on peripheral blood smear. Direct and indirect Coombs tests were negative. Prothrombin time, activated partial thromboplastin time, and international normalized ratio were within normal ranges. Renal function tests were within normal limits. Physical examination including a normal neurological assessment, was unremarkable and revealed no clinical evidence of bleeding. ADAMTS13 activity was within the normal range (50-150%). Based on the clinical and laboratory findings, a diagnosis of TMA was established. Initial laboratory findings are presented in Table 1, which summarizes the patient's hematologic and biochemical parameters at presentation.

The patient received red blood cell transfusions during periods of severe anemia; however, the response was suboptimal. Despite erythrocyte replacement for low hemoglobin levels, the expected improvement was not observed. She was treated with methylprednisolone 40 mg daily for 5 days, along with supportive care. A marked improvement in hemoglobin was observed beginning on day 3 of steroid therapy. Both hemoglobin levels and platelet counts continued to improve

TABLE 1: Baseline laboratory parameters (female).

Parameter	Value	Hemogram value before CTx	Unit	Normal range (female)
WBC	4,980	8,160	/µL	4,000-11,000
Neutrophil	2,040	5,610	/µL	1,500-8,000
Lymphocyte	2270	1,900	/µL	1,000-4,800
Monocyte	650	460	/µL	200-1,000
Hemoglobin level	3.9	11.7	g/dL	12.0-15.5
Platelet count	128,000	260,000	/µL	150,000-450,000
AST	10.5		U/L	5-35
ALT	5.9		U/L	7-35
LDH	893		U/L	140-280
Total bilirubin	2.27		mg/dL	0.2-1.1
Direct bilirubin	0.92		mg/dL	0.1-0.3
Indirect bilirubin	1.35		mg/dL	<1.0
Urea	19.2		mg/dL	10-50
Creatinine	0.71		mg/dL	0.5-1.1
CRP	16.59		mg/L	<5
Haptoglobin	0.01		g/L	0.3-2.0
ADAMTS13 activity	55.36		%	40-130
Coombs test (direct)	Negative		–	Negative
Coombs test (indirect)	Negative		–	Negative
INR	1.18		Ratio	0.85-1.15
APTT	21.9		Seconds	21-32
PT	13.4		Seconds	10.4-14

INR: International normalized ratio; PR: Prothrombin time; aPTT: Activated partial thromboplastin time; WBC: White blood cells; AST: Aspartate transaminase; ALT: Alanine transaminase; LDH: Lactate dehydrogenase; CRP: C-reactive protein.

thereafter. The patient had previously received a carboplatin-containing regimen without any evidence of hemolysis or thrombocytopenia. At presentation, there were no clinical or laboratory signs of infection. Because her endometrial carcinoma had been diagnosed years earlier and she had not developed a similar clinical picture before receiving etoposide, tumor-associated TMA was considered unlikely. Therefore, etoposide-induced TMA was considered the most probable cause. In light of these findings, etoposide was discontinued, and treatment was switched to irinotecan. The patient completed four cycles of irinotecan; no recurrence of hemolysis, thrombocytopenia, or TMA-related clinical or laboratory abnormalities occurred. Temporal changes in the patient's hemoglobin and platelet counts are illustrated in Figure 1A, B, highlighting the decrease after chemotherapy and the subsequent recovery observed following steroid therapy.

Informed consent was obtained from the patient for the publication of this case report and any accompanying images.

DISCUSSION

TMA encompasses a group of syndromes characterized by endothelial injury leading to MAHA, thrombocytopenia, and potential end-organ damage-most notably to the renal and neurological systems. While primary TMAs such as TTP and HUS have distinct etiopathogenic pathways, secondary or DI-TMAs are increasingly recognized, but remain underdiagnosed due to their non-specific presentations and overlap with chemotherapy-related cytopenias.[1,2] The pathogenesis of TMA involves widespread endothelial damage, which triggers activation of the coagulation cascade and platelet aggregation within the microvasculature. This results in the formation of microthrombi that shear red blood cells, leading to hemolysis, and consume platelets, causing thrombocytopenia. In drug-induced forms, the mechanisms may include direct endothelial toxicity, immune-mediated injury (such as drug-dependent antibodies), or complement activation. The extent and site of vascular involvement determine the severity and nature of organ dysfunction, with renal and central nervous system involvement being the most common.[6,7]

Etoposide, a topoisomerase II inhibitor, is commonly used in combination with platinum-based agents for the treatment of small-cell and large-cell lung cancers, among others. Although DI-TMA has been widely reported with agents such as mitomycin C, gemcitabine, and calcineurin inhibitors, etoposide is rarely implicated. Literature on etoposide-associated TMA is sparse and primarily consists of case reports and observational data.[6,7] The mechanism is presumed to involve dose-dependent direct toxic injury to the vascular endothelium, although immune-mediated pathways have also been postulated. Table 2 summarizes previously reported cases of etoposide-associated TMA, including patient characteristics, underlying malignancy, treatment regimens, and clinical outcomes.

Our patient presented with rapid-onset hemolysis and thrombocytopenia following initiation of etoposide, without any prior history of cytopenias or baseline TMA features. The diagnosis was supported by schistocytes on peripheral smear, elevated LDH, low haptoglobin, and indirect hyperbilirubinemia, which are hallmark features of microangiopathic hemolysis.

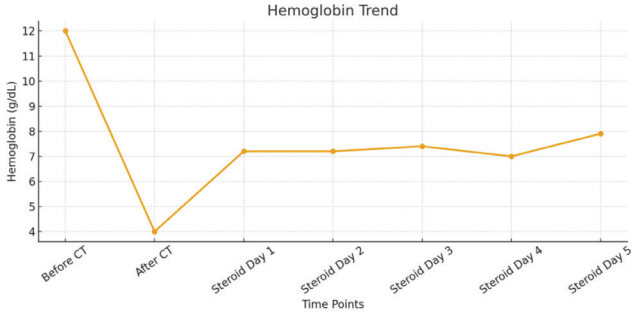

FIGURE 1A: Temporal changes in hemoglobin concentration following steroid administration.

On day 14 after chemotherapy, with worsening fatigue and pallor (after computed tomography). Supportive care and steroid treatment were initiated on day 16 post-chemotherapy (steroid day 1). A 2-day interval followed, during which transfusional replacement was administered. The subsequent gradual rise in hemoglobin levels is likely attributable to both transfusional support and the therapeutic effect of corticosteroids.

CT: Computed tomography.

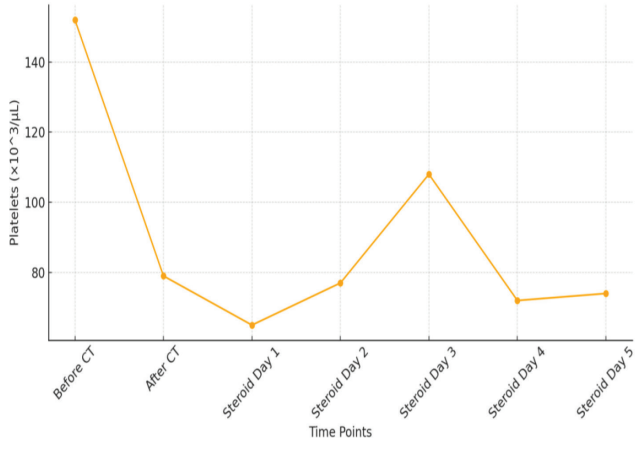

FIGURE 1B: Temporal dynamics of platelet counts in response to corticosteroid therapy.

Supportive care and steroid treatment were initiated on day 16 post-chemotherapy (steroid day 1), with a 2-day interval in between, during which transfusional replacement was administered.

CT: Computed tomography.

TABLE 2: Reported cases of etoposide-associated thrombotic microangiopathy (TMA).				
Author/year	**Indication for etoposide**	**Onset of TMA**	**Key findings**	**Outcome**
Ogunleye et al.[3] 2010	Endodermal sinus tumor	After chemotherapy	Hemolytic uremic syndrome, renal failure	Supportive therapy, clinical improvement
Jodele et al.[10] 2017	Autologous transplant	After chemotherapy	TMA with organ injury	Supportive care
Lee et al.[4] 2014	Malignant ovarian germ cell tumor	After adjuvant chemotherapy	Thrombocytopenia, hemolysis	Plasma exchange+supportive care, improved
Rizvi et al.[5] 2018	Testicular cancer	After BEP cycles	Renal limited TMA, AKI, schistocytes	Supportive care recovery
Our case	Endometrial carcinoma	After 2nd cycle	Hemolysis, thrombocytopenia, schistocytosis	Steroids and supportive care, recovery

TMA: Thrombotic microangiopathy; MAHA: Microangiopathic hemolytic anemia.

Importantly, ADAMTS13 activity was preserved, effectively excluding TTP.[8] In addition, the absence of significant renal or neurological dysfunction differentiates this case from typical presentations of aHUS and TTP, aligning more closely with drug-induced secondary TMA.

Several distinguishing features of this case emphasize its clinical relevance: Temporal association with etoposide use, lack of organ dysfunction, favorable response to drug withdrawal and to corticosteroids, and the diagnostic challenge in oncology patients in whom cytopenias are multifactorial. The Naranjo Adverse Drug Reaction Probability scale would likely categorize this case as "probable" based on timing, exclusion of other causes, and dechallenge response.[9]

There is currently no standardized treatment for DI-TMA, and management focuses on discontinuation of the suspected agent, supportive care, and consideration of plasma exchange only in severe cases or in cases of diagnostic uncertainty.[10] Our patient responded favorably to etoposide withdrawal and corticosteroid therapy, reinforcing the importance of early recognition.

CONCLUSION

This case underscores the need for heightened clinical vigilance when new cytopenias occur in oncology patients. TMA should be considered early in the differential, even in the absence of renal or neurologic findings. Further research is required to elucidate the pathogenesis and define optimal management strategies for etoposide-associated TMA.

Ethics

Informed Consent: Informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.S.G., N.S.D., Concept: S.S.G., Ö.A., Design: S.S.G., N.S.D., Ö.A., Data Collection or Processing: S.S.G., Z.K.Ç., O.K., N.S.D., Analysis or Interpretation: S.S.G., Z.K.Ç., Literature Search: S.S.G., H.B.Ç., Ö.A., Writing: S.S.G., Ö.A.

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