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Gemcitabine-Induced Thrombotic Microangiopathy with Renal Involvemente: A Case Report

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Abstract

Introduction: Thrombotic microangiopathy (TMA) is characterized by small vessel occlusion, leading to thrombocytopenia, hemolytic anemia, and organ damage. It is increasingly recognized as a complication of chemotherapy, including gemcitabine, which can induce renal disfunction. **Case Report:** A 61-year-old man with undifferentiated giant cell carcinoma of the pancreas developed gemcitabine-induced TMA after two months of treatment and a cumulative dose of approximately 6000 mg/m^2. Laboratory findings revealed thrombocytopenia, hemolytic anemia, elevated LDH, and progressive renal impairment. A renal ultrasound indicated chronic nephropathy. The diagnosis was confirmed with peripheral schistocytes and the absence of haptoglobin and Coombs positivity. Following discontinuation of gemcitabine, renal function and hematological parameters improved. **Discussion:** Gemcitabine-induced TMA is an emerging complication in oncological treatments. Its mechanisms likely involve endothelial injury and immune-mediated responses. Early diagnosis and prompt cessation of gemcitabine can mitigate severe renal consequences. **Conclusion:** Gemcitabine should be considered a potential cause of TMA in cancer patients, especially those with unexplained renal dysfunction, to prevent irreversible kidney damage.

Keywords

Thrombotic Microangiopathy, Gemcitabine, Acute Kidney Injury, Chemotherapy, Nephrotoxicity

1. Introduction

Thrombotic microangiopathy (TMA) constitutes a group of occlusive microvas-

cular disorders characterized by thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and organ dysfunction, particularly renal and neurological dysfunction. The modern classification of TMAs divides them into primary forms, such as thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), and secondary forms, which include drug-induced TMAs [1]-[3].

Gemcitabine, a pyrimidine antimetabolite widely used in treating pancreatic, pulmonary, bladder, and breast adenocarcinomas, as well as lymphomas, is associated with TMA development in approximately 0.015% to 2.2% of cases. However, studies suggest that the actual incidence may be underestimated due to underdiagnosis and variability in clinical presentation [4]-[6].

Gemcitabine-induced TMA (G-TMA) demonstrates specific characteristics that distinguish it from other forms of drug-induced TMA. The median time to G-TMA development varies between 5 - 8 months after treatment initiation, with cumulative doses frequently exceeding 20,000 mg/m^2. Interestingly, late cases have been documented after prolonged exposures of up to 58 months, emphasizing the need for continuous surveillance throughout the entire treatment period [5] [7].

1.1. G-TMA Pathophysiology

The pathophysiological mechanisms underlying G-TMA remain partially elucidated, but evidence suggests multiple pathways of endothelial injury. Three main mechanistic hypotheses have been proposed [2] [3] [8]:

1) Direct Endothelial Toxicity:

Gemcitabine may cause direct endothelial injury, leading to cellular activation and microvascular thrombus formation. This mechanism is supported by the observation that TMA typically develops with cumulative drug exposure [2] [8].

2) Immune-Mediated Mechanism:

Some cases present features suggestive of an immune-mediated response, with circulating antibodies and improvement with immunosuppressive therapy. The detection of complement factors in renal biopsies (C3, IgM, IgA) in 97% of G-TMA cases that underwent immunofluorescence supports this hypothesis. These findings are not specific to G-TMA as they are also seen in other forms of TMA [7].

3) Complement Pathway Dysregulation:

Although specific abnormalities in the alternative complement pathway have not been consistently demonstrated in G-TMA, the presence of membrane attack complexes along glomerular and tubular membranes suggests complement system involvement [7].

1.2. Clinical Presentation and Diagnostic Features

1.2.1. Clinical Manifestations

G-TMA typically presents with the classic triad of thrombocytopenia, microangiopathic hemolytic anemia, and organ dysfunction, with renal involvement being

the most common and severe manifestation. New-onset hypertension or worsening of preexisting hypertension constitutes a frequently observed early sign, preceding other diagnostic markers by 10 - 14 days [9]-[12].

1.2.2. Specific Laboratory Findings

Diagnostic criteria for TMA include [1] [13]:

Hematological Findings:

1) Thrombocytopenia (platelet count < 150,000/μL or ≥25% reduction from baseline).

2) Microangiopathic hemolytic anemia with schistocyte presence (>0.5% - 1% of red blood cells).

3) Lactate dehydrogenase (LDH) elevation > 1.5 times the upper normal limit, approximately >420 IU/L.

4) Undetectable or reduced haptoglobin.

5) Reticulocytosis and indirect hyperbilirubinemia.

6) Negative direct Coombs test.

Renal Involvement:

1) Serum creatinine elevation.

2) Proteinuria (usually non-nephrotic).

3) Microscopic hematuria.

4) Hypertension.

Histopathological Findings

Renal biopsy remains the gold standard for diagnostic confirmation of renal TMA, especially in cases with atypical presentation. Characteristic histopathological findings include [7] [9] [14]:

Glomerular Changes:

1) Glomerular basement membrane reduplication ("double contour" appearance).

2) Endothelial cell swelling and detachment.

3) Capillary lumen narrowing.

4) Fibrin deposition and fragmented red blood cells.

5) Focal mesangiolysis.

Vascular Changes:

1) Arterial and arteriolar thickening.

2) Fibrinoid necrosis.

3) Platelet-rich thrombi in glomerular capillaries.

Immunofluorescence:

1) Complement factor deposits (C3, IgM, IgA) are present in 97% of cases [7].

2) Presence of membrane attack complexes (C5b-9).

2. Case Report

A 61-year-old male patient with undifferentiated giant cell carcinoma of the pancreas (pT2 N0) underwent duodenopancreatectomy (Whipple procedure) with subsequent adjuvant chemotherapy with gemcitabine 1000 mg/m^2 on days 1, 8, and

15 of each 28-day cycle. Initially, the patient had preserved renal function (serum creatinine: 0.9 mg/dL), absence of anemia, and normal platelet count. After two months of treatment (cumulative dose approximately 6000 mg/m^2), he developed hypertension and mild serum creatinine elevation to 1.69 mg/dL.

In subsequent weeks, progressive deterioration of hematological parameters was observed with anemia (hemoglobin: decline from 8.7 g/dL to 6.8 g/dL) and platelet count reduction to 87,000/mm^3. There was also worsening of renal function with serum creatinine elevation to 3.0 mg/dL, development of oliguria, and persistent grade 2 hypertension (systolic pressure between 160 and 179 mmHg and diastolic pressure between 100 and 109 mmHg).

Haptoglobin levels were undetectable, indicating intravascular hemolysis. The direct Coombs test was negative, excluding immune-mediated hemolytic anemia. Examination of the peripheral blood smear revealed the presence of schistocytes, consistent with microangiopathic hemolytic anemia. Renal ultrasonography demonstrated bilaterally increased cortical echogenicity, suggesting chronic nephropathy.

Based on the classic triad of thrombocytopenia, microangiopathic hemolytic anemia, and renal dysfunction, associated with the gemcitabine use context, the diagnosis of gemcitabine-induced TMA was established, and gemcitabine was immediately discontinued. Supportive management with blood pressure control and rigorous monitoring of renal function and hematological parameters was started.

Following gemcitabine discontinuation, gradual improvement of laboratory parameters was observed. At a 6-week follow-up, there was renal function stabilization, presenting a serum creatinine of 1.3 mg/dL and blood count normalization (hemoglobin of 12 g/dL and platelet count of 224,000/mm^3), demonstrating process reversibility when recognized and treated early.

3. Management Strategies and Treatment

G-TMA management is primarily based on **immediate gemcitabine discontinuation**, which constitutes the most effective intervention to halt the progression of endothelial injury. Supportive treatment includes strict blood pressure control, correction of electrolyte disorders, transfusion support when necessary, and renal function monitoring [15] [16].

Although it is the standard treatment for TTP, plasmapheresis demonstrates limited efficacy in G-TMA with only 42% complete remission rates and no demonstrated survival benefit, as the mechanism involves direct endothelial toxicity rather than ADAMTS13 deficiency. In contrast, plasmapheresis used for TTP shows a 75% - 100% response rate and dramatic survival improvement (from 10% to 79%), as it effectively removes anti-ADAMTS13 antibodies and replaces the deficient enzyme. This difference underscores the importance of matching the underlying pathophysiological mechanism with the specific therapeutic intervention.

Meta-analyses show that only 28% of patients experience complete renal recov-

ery, while 48% present partial recovery or stable function [16] [17].

Eculizumab, an anti-C5 monoclonal antibody, has emerged as a promising therapy for refractory G-TMA [7] [16] [18].

The question of gemcitabine resumption after a G-TMA episode remains controversial. Isolated cases report successful use of prophylactic eculizumab during gemcitabine re-exposure, but data are limited. The decision should be individualized, considering oncological prognosis, availability of therapeutic alternatives, TMA episode severity, and treatment response [7] [16].

G-TMA presents a reserved prognosis, with high morbidity and mortality even after adequate recognition and treatment. There is a 4-month mortality rate of up to 60% - 75% due to underlying oncological disease progression and TMA complications [7] [19]. Early recognition and immediate gemcitabine discontinuation, the absence of pulmonary involvement, and preserved baseline renal function are favorable prognostic factors.

The progression to chronic kidney disease happens in 24% - 26% of cases [7] [18], and the need for dialysis goes up to 70% of patients in the acute phase, and 26% of patients end up needing long-term dialysis [11]. Complete renal recovery happens in 28% of cases [19].

4. Discussion

Suggested Prevention Strategies

To prevent G-TMA, it is important to identify at-risk patients, being those with advanced age, borderline renal function, previous hypertension, and undergoing high cumulative gemcitabine doses.

Intensified monitoring protocols become essential, requiring more frequent laboratory assessments, including complete blood counts, comprehensive metabolic panels, and specific markers of hemolysis such as lactate dehydrogenase and haptoglobin levels. This enhanced surveillance should occur not only before each cycle but also at mid-cycle intervals, enabling prompt detection of subclinical changes that may herald the onset of thrombotic microangiopathy, thereby facilitating early intervention and potentially preventing progression to severe, irreversible complications [4] [8].

Now, there are no prophylactic TMA prevention protocol modifications as the dose reductions are reactive, not prophylactic, meaning there are only applied after toxicity occurs.

Dose adjustments and/or extending the intervals between treatment cycles from standard schedule, particularly in elderly patients, those with borderline renal function, or individuals with preexisting cardiovascular comorbidities, would need to be supported by prospective studies demonstrating efficacy in TMA prevention.

5. Conclusions

Gemcitabine-induced thrombotic microangiopathy represents a severe and poten-

tially fatal complication of oncological chemotherapy. Early recognition through systematic monitoring, immediate gemcitabine discontinuation, and multidisciplinary management constitutes the fundamental pillars of treatment.

The presented case illustrates the importance of continuous clinical surveillance and adequate therapeutic response, resulting in favorable renal function recovery. The growing understanding of pathophysiological mechanisms and the development of new therapeutic strategies, particularly anti-complement therapy, offer promising perspectives for improving clinical outcomes.

The need for prospective multicenter studies remains critical to establish standardized monitoring protocols, prevention strategies, and optimized therapeutic algorithms. The development of predictive biomarkers and the implementation of personalized medicine represent important frontiers to reduce the incidence and severity of this devastating complication.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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