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Thrombotic Microangiopathy Associated With Concurrent Gemcitabine and Tacrolimus Exposure in a Patient With Pancreatic Adenocarcinoma and Cardiac Transplant

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Abstract

Drug-induced thrombotic microangiopathy (TMA) is an uncommon but potentially life-threatening condition characterized by microangiopathic hemolytic anemia, thrombocytopenia, and end-organ injury. Diagnosis can be particularly challenging in patients where hallmark features can overlap with known comorbidities. We report a case of severe drug-induced TMA in a 75-year-old man with orthotopic heart transplantation on tacrolimus and pancreatic adenocarcinoma receiving gemcitabine presenting with acute kidney injury associated with acute thrombocytopenia, new tremors, and progressive generalized weakness. Subsequent evaluation revealed elevated serum lactate dehydrogenase (LDH), undetectable serum haptoglobin, and the presence of schistocytes on peripheral smear consistent with microangiopathic hemolytic anemia. Given recent exposure to both gemcitabine and tacrolimus, drug-induced TMA was suspected. Both tacrolimus and gemcitabine were discontinued, and empiric treatment with high-dose steroids and plasma exchange was initiated while awaiting a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) activity level testing. The hospital course was complicated by worsening renal function requiring initiation of hemodialysis and status epilepticus necessitating transfer to the intensive care unit. Following a normal ADAMTS13 activity level that effectively ruled out thrombotic thrombocytopenic purpura (TTP) and a lack of clinical improvement, corticosteroids and plasma exchange were discontinued and eculizumab was initiated. The patient gradually experienced neurologic improvement, hematologic recovery, and sufficient renal recovery to discontinue hemodialysis. This case highlights the diagnostic challenges that drug-induced TMA in medically complex patients present and the importance of early recognition and prompt intervention to limit irreversible end-organ damage.

Categories: Hematology, Transplantation, Internal Medicine
Keywords: calcineurin inhibitors, diagnostic challenge, drug-induced thrombotic microangiopathy, gemcitabine, hemolytic anemia, thrombocytopenia

Introduction

Thrombotic microangiopathy (TMA) represents a heterogeneous group of disorders characterized by microangiopathic hemolytic anemia, thrombocytopenia, and microvascular thrombosis leading to end-organ ischemia and injury [1,2]. These syndromes encompass both primary etiologies, such as thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), and secondary causes, including pregnancy-related complications, infections, medications, malignancy, and autoimmune disease [2]. Drug-induced TMA is an important and increasingly recognized subset, accounting for 20%-30% of secondary TMA cases [3]. We use "drug-induced TMA" throughout this report to refer to TMA with a plausible causal link to a medication, whether through an immune-mediated reaction or a dose-dependent toxic effect [3].

Clinical recognition of TMA can be challenging, particularly in patients with multiple comorbidities or competing etiologies for cytopenias and renal dysfunction. Early manifestations may be subtle or non-specific, and delays in diagnosis can result in significant morbidity, including irreversible renal failure, neurologic complications, and death [4]. Gemcitabine, a chemotherapeutic agent, and tacrolimus, a calcineurin inhibitor commonly used after solid organ transplantation, are among the medications frequently implicated in drug-induced TMA [3-6]. Their concurrent use, such as when a transplant recipient develops a malignancy, may increase the risk of developing TMA, as both are potential triggers [4]. However, other more common side effects of each medication and the patient's comorbidities themselves may offer competing explanations for the common signs and symptoms of TMA, making the diagnosis even more challenging. We present a case of drug-induced TMA in a heart transplant recipient with pancreatic adenocarcinoma receiving both gemcitabine and tacrolimus, highlighting the diagnostic challenges and importance of prompt intervention to limit irreversible end-organ damage.

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Case Presentation

A 75-year-old male patient with a past medical history significant for orthotopic heart transplant, hypertension, hyperlipidemia, chronic kidney disease stage 3a, and pancreatic adenocarcinoma status post distal pancreatectomy and splenectomy on active chemotherapy was referred from clinic to our emergency department for evaluation of acute kidney injury (AKI), with his serum creatinine level increased to 2.4 mg/dL from a baseline of 1.4 mg/dL. Three months prior to presentation, the patient was started on gemcitabine for his pancreatic adenocarcinoma. One week prior to presentation, he received the third dose of his third cycle of gemcitabine infusion for a total cumulative dose of 13,787 mg/m^2 and subsequently developed progressive generalized weakness and new tremors, particularly in his bilateral upper extremities. He then presented to an outside emergency department and was found to have chronic anemia of 8.8 g/dL and mildly elevated creatinine of 1.93 mg/dL, which were attributed to expected gemcitabine-related myelosuppression and dehydration. He received a unit of packed red blood cells and was discharged.

Upon presentation to our emergency department, initial work-up was notable for an elevated blood pressure of 144/75 mmHg from a baseline of 120 to 130s/70s mmHg prior to admission, acute thrombocytopenia with a platelet count of 45 x 10^3/µL, stable hemoglobin at 8.4 g/dL, and worsened creatinine of 2.9 mg/dL (Table *1*). On physical exam, the patient appeared euvolemic and was noted to have mild bilateral upper extremity tremors. Tacrolimus trough level was 8.8 ng/mL and sirolimus trough level was 8.4 ng/mL, which were above his goal of combined tacrolimus and sirolimus level between 8 and 10 ng/mL (Table *1*). While supratherapeutic levels may have contributed to the AKI, a hemolysis workup was pursued given concurrent acute thrombocytopenia and tremors. This revealed an elevated serum lactate dehydrogenase (LDH) of 618 U/L, an undetectable serum haptoglobin level, and a peripheral smear with greater than 5 schistocytes per high-power field with red blood cell fragments raising concern for a hemolytic process. International normalized ratio (INR), activated partial thromboplastin time (aPTT), and fibrinogen levels were not suggestive of disseminated intravascular coagulation. Direct antiglobulin (Coombs) test was negative (Table *1*). Computed tomography of the abdomen and pelvis demonstrated stable postoperative changes from distal pancreatectomy without evidence of recurrent or metastatic disease (Figure *1*). Blood cultures, respiratory viral pathogen panel, and serum cytomegalovirus DNA polymerase chain reaction (PCR) were negative. Transthoracic echocardiogram showed preserved cardiac allograft function without obvious evidence of rejection (Video *1*), and the single antigen antibody test was negative for both class one and two human leukocyte antigen (HLA class I/II) antibodies (Table *1*).

Laboratory test (unit)	Patient value	Reference range
Hemoglobin (g/dL)	8.4	13.5-17.1
Platelet count (x10³/μL)	45	143-398
Urea nitrogen (mg/dL)	78	7-22
Creatinine (mg/dL)	2.90	0.60-1.30
Total bilirubin (mg/dL)	0.4	0.1-1.2
Activated partial thromboplastin time (seconds)	31.2	24.4-36.2
Prothrombin time (seconds)	16.0	11.5-14.4
International normalized ratio	1.3	N/A
Fibrinogen (mg/dL)	569	235-490
Lactate dehydrogenase (U/L)	618	125-256
Haptoglobin (mg/dL)	<10	21-210
Reticulocyte count (%)	0.64	N/A
Schistocytes	Moderate	N/A
Direct antiglobulin IgG	Negative	N/A
Direct antiglobulin C3	Negative	N/A
Tacrolimus trough (ng/mL)	8.8	N/A
Sirolimus trough (ng/mL)	8.4	N/A
Single antigen antibody, class I/II	Negative	N/A
ADAMTS13 activity (%)	86	≥67
Soluble complement 5b-9 (ng/mL)	311	<250

TABLE 1: Notable laboratory findings

N/A: not applicable; ADAMTS13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13



FIGURE 1: Computed tomography of the abdomen and pelvis without contrast obtained as part of initial workup

Non-contrast computed tomography of the abdomen and pelvis showed stable fluid collection (white arrow) in the operative bed after distal pancreatectomy without evidence of recurrent adenocarcinoma



VIDEO 1: Transthoracic echocardiogram obtained as part of initial workup showing preserved cardiac allograft function in the parasternal long view

View video here: https://youtu.be/trTqWp0oQ7w

Hematology was consulted and suspected TMA given the constellation of hemolytic anemia, acute thrombocytopenia, and end-organ damage with AKI. Drug-induced TMA was considered most likely in the setting of exposure to both gemcitabine and tacrolimus, although TTP could not yet be excluded. A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) activity level was obtained, but the patient was empirically started on high-dose methylprednisolone and plasmapheresis while awaiting results. The patient was also initiated on hemodialysis due to hyperkalemia and uremia from ongoing severe AKI.

Despite these interventions, the patient developed worsening mental status with new aphasia and intermittent myoclonus in bilateral upper and lower extremities. Neurology was consulted, and the patient was placed on continuous electroencephalographic (EEG) monitoring, which demonstrated seizure activity (Figure *2*). Brain imaging with computed tomography and magnetic resonance imaging showed no acute findings to explain the patient's worsening mental status and seizure activity. The patient was given

intravenous lorazepam and levetiracetam load but remained in status epilepticus and required transfer to the intensive care unit. Given clinical worsening with persistent thrombocytopenia, elevated LDH, and undetectable haptoglobin (Table 2), tacrolimus was discontinued at this time due to concerns it was contributing to progressive TMA and switched to cyclosporine given continued need for immunosuppression and limited alternate options as the patient was already on sirolimus at baseline.

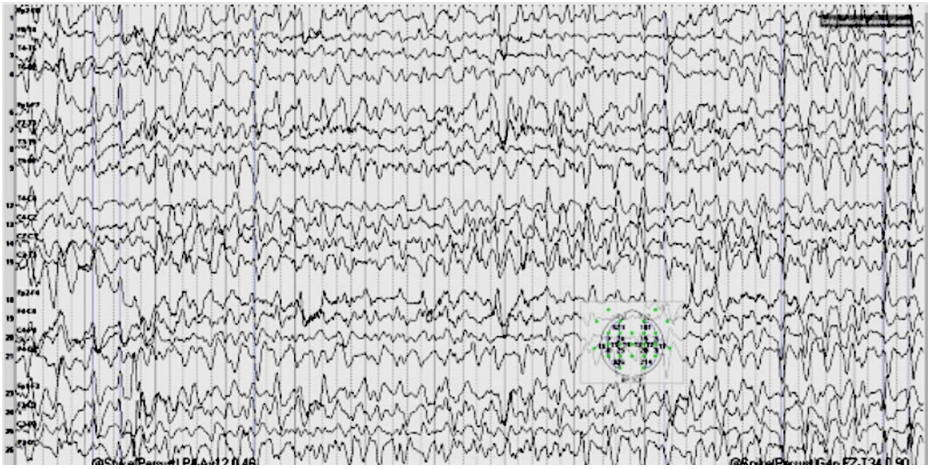


FIGURE 2: Electroencephalographic (EEG) monitor obtained at time of worsening neurologic status showing generalized 3-4 Hz spike waves consistent with active seizure

Laboratory test (unit)	Value on admission	Value upon transfer to intensive care unit after receiving steroids and plasma exchange but before initiation of eculizumab	Value after two doses of eculizumab	Value on discharge	Reference range
Hemoglobin (g/dL)	8.4	7.0	8.3	7.8	13.5-17.1
Platelet count (x10³/μL)	45	71	251	302	143-398
Lactate dehydrogenase (U/L)	618	1,477	902	776	125-256
Haptoglobin (mg/dL)	<10	<10	<10	<10	21-210
Creatinine (mg/dL)	2.90	2.43 (on dialysis)	2.36 (on dialysis)	2.16 (no dialysis required)	0.60-1.30

TABLE 2: Trend of laboratory tests over the course of admission

At this time, ADAMTS13 level returned to normal at 86%, ruling out TTP (Table 1). The patient continued to have evidence of hemolysis requiring blood and platelet transfusions despite receiving high-dose methylprednisolone and plasmapheresis, so both treatments were discontinued, and the patient was instead given two doses of eculizumab 900 mg seven days apart. Following these interventions, the patient demonstrated gradual neurologic improvement, stabilization of hemoglobin and renal function, and normalization of platelet count (Table 2). He no longer required transfusions, hemodialysis was discontinued, and he was ultimately discharged home with close outpatient follow-up. A complement test later showed elevation in soluble complement 5b-9 (sC5b-9) of 311 ng/mL (normal <250 ng/mL) (Table 1).

Discussion

TMA is defined by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and end-organ ischemia [1]. It may be categorized as primary-including TTP and HUS-or secondary, arising in association

with medications, infections, autoimmune disorders, malignancy, transplantation, and other systemic conditions [2-4].

Drug-induced TMA accounts for approximately 10%-13% of all TMA cases and 20%-30% of secondary TMAs [3]. The underlying mechanisms can be classified into two categories: (1) an immune-mediated reaction, characterized by the sudden onset of severe systemic symptoms within hours of drug exposure, and (2) a dose-dependent toxic effect, which typically manifests as progressive kidney dysfunction with variable thrombocytopenia and/or hemolytic anemia [1,3]. Antimicrobials are the most common causes of immune-mediated disease, whereas chemotherapeutic agents, immunosuppressants, and vascular endothelial growth factor inhibitors are more commonly associated with toxic dose-related drug-induced TMA.

This case highlights two key challenges in drug-induced TMA: recognizing the syndrome when its initial manifestations may be subtle or overlap with more common clinical conditions and initiating timely treatment before irreversible complications develop.

Diagnostic challenges

Diagnosing TMA is particularly challenging in oncology and transplant patients as the hallmark features may resemble expected chemotherapy toxicity or transplant-related complications [5,6]. In our patient, the acute thrombocytopenia and chronic anemia were initially attributed to expected myelosuppression from gemcitabine, a reasonable consideration given his recent chemotherapy exposure. However, the presence of worsening AKI combined with new neurologic symptoms prompted evaluation for hemolysis, which ultimately established the diagnosis of TMA. This clinical course reflects an important diagnostic principle: patients on high-risk medications such as gemcitabine or calcineurin inhibitors with unexplained intrinsic AKI and concurrent cytopenias should prompt evaluation for hemolysis even when a competing explanation exists [5]. New neurologic symptoms, such as weakness or tremors, should further increase suspicion.

Once TMA is identified, determining the underlying etiology is essential because management varies among the different causes. In a patient with malignancy, the differential diagnoses include TTP, Shiga toxin-associated HUS, atypical HUS, cancer-induced TMA, and chemotherapy-associated TMA [7]. TMA has also been seen after solid transplantation, though due to multiple sources of endothelial damage, including transplantation surgery itself, acute rejection, and immunosuppressants [8]. For this patient, Shiga toxin-associated HUS was considered less likely given the absence of recent diarrheal illness. TTP was effectively excluded by an ADAMTS13 activity level greater than 10%. Although malignancy itself is a recognized trigger, interval imaging demonstrated no evidence of recurrent or metastatic disease, making this diagnosis less likely as it typically occurs in advanced or disseminated cancer [7]. TMA due to infection and transplant rejection were similarly considered less likely given a negative infectious work-up and stable allograft function on transthoracic echocardiogram with negative HLA class I/II antibodies, respectively. Although atypical HUS cannot be definitively excluded as there is no single confirmatory test, the temporal association with recent gemcitabine exposure and chronic tacrolimus use favored drug-induced TMA as the most likely etiology [9].

Both gemcitabine and tacrolimus are among the medications most frequently implicated in drug-induced TMA [4]. Gemcitabine-associated TMA is thought to be due to direct endothelial injury [10,11]. Although rare, with an estimated incidence ranging from 0.015% to 1.4%, TMA is a well-described and potentially severe complication of gemcitabine with reported mortality rates up to 40%-90% [11]. Risk of incidence increases with greater cumulative exposure, particularly above 20,000 mg/m² or beyond seven months of treatment [11]. This patient's cumulative dose was approximately 13,000 mg/m², but cases of gemcitabine-associated TMA have been observed at lower cumulative doses in combination with other chemotherapeutic agents [10,11]. In this case, concomitant tacrolimus use may have further increased the risk of TMA. New or worsening hypertension has been reported as an early manifestation of gemcitabine-associated TMA, which was noted in our patient on admission [5,10].

TMA attributed to calcineurin inhibitors is also a rare complication with a reported prevalence ranging from 1% to 4.7% and occurs more frequently with tacrolimus than cyclosporine [6,12]. The exact mechanism remains incompletely understood, but proposed mechanisms include direct cytotoxicity, effects on synthesis of prostaglandins, and increased von Willebrand factor resulting in endothelial injury [6,13]. Clinical presentation is highly variable and may include generalized weakness, dyspnea, necrotic skin ulcerations, and impaired renal function, the latter being the most consistently reported feature [12,14,15].

When multiple implicated drugs are present, identifying a single causative agent may not be possible. However, this should not delay management, as the cornerstone of treatment is the prompt discontinuation of all suspected offending agents.

Importance of early diagnosis and treatment

Drug-induced TMA complications can be severe and include dialysis-dependent renal failure, cardiovascular events, neurologic sequelae, and death [4]. This patient's development of status epilepticus and renal failure requiring hemodialysis despite receiving high-dose methylprednisolone and plasmapheresis reflects the

progression of disease that can occur before diagnosis is established and treatment is initiated.

Management prioritizes prompt discontinuation of the offending agent and supportive care. Empiric corticosteroids and plasma exchange are often initiated when TTP has not yet been excluded given its high mortality, although there is limited evidence of their benefit in secondary TMA [1,16,17]. Increasing evidence suggests that complement activation may contribute to the pathogenesis of gemcitabine-induced TMA, as complement deposition has been seen on renal pathology of affected patients [10,17]. This has led to the use of eculizumab, an anti-C5 complement inhibitor that is approved for treatment of atypical HUS, with case reports noting improved hematologic and renal outcomes in severe or refractory cases for both gemcitabine- and tacrolimus-induced TMA [15,17-19].

In this case, gemcitabine was discontinued, and the patient was switched from tacrolimus to cyclosporine. Although both agents are calcineurin inhibitors and have been implicated in TMA, there appears to be a lower incidence with cyclosporine than tacrolimus, and case reports have described resolution of tacrolimus-associated TMA following the switch to cyclosporine [12]. The patient was also empirically started on high-dose corticosteroids and plasma exchange until a normal ADAMTS13 activity level excluded TTP. Given progression to status epilepticus and renal failure requiring hemodialysis, he was given two doses of eculizumab seven days apart. The patient's subsequent improvement and moderate renal recovery with these interventions illustrate that even severe complicated TMA can be reversible with early recognition of diagnosis and timely escalation to appropriate therapy.

Conclusions

This case highlights the diagnostic and therapeutic challenges of drug-induced TMA in a patient receiving both gemcitabine and tacrolimus. Because early features such as anemia and thrombocytopenia can easily be misattributed to chemotherapy-related myelosuppression, the diagnosis can be delayed until significant end-organ injury has already occurred. Clinicians should maintain a high index of suspicion for TMA in patients who develop unexplained AKI associated with cytopenias, particularly when accompanied by neurologic symptoms and/or new or worsened hypertension. Prompt removal of the offending agent remains the cornerstone of management. Although there remains limited evidence, eculizumab may be considered as well, especially in severe or refractory cases. The complications observed here-prolonged status epilepticus and dialysis-dependent renal failure-reflect the consequences of delayed TMA recognition, while the patient's recovery affirms that prompt intervention can achieve positive outcomes even in severe cases.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Wen-Ching Tran, Melanie Ramirez, Kevin Kim-Hak

Drafting of the manuscript: Wen-Ching Tran, Melanie Ramirez

Critical review of the manuscript for important intellectual content: Wen-Ching Tran, Kevin Kim-Hak

Supervision: Wen-Ching Tran

Disclosures

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References

1. George JN, Nester CM: Syndromes of thrombotic microangiopathy. N Engl J Med. 2014, 371:654-66. 10.1056/NEJMra1312353
2. Arnold DM, Patriquin CJ, Nazy I: Thrombotic microangiopathies: a general approach to diagnosis and management. CMAJ. 2017, 189:E153-9. 10.1503/cmaj.160142
3. Mazzierli T, Allegretta F, Maffini E, Allinovi M: Drug-induced thrombotic microangiopathy: an updated review of causative drugs, pathophysiology, and management. Front Pharmacol. 2022, 13:1088031. 10.3389/fphar.2022.1088031

4. Bayer G, von Tokarski F, Thoreau B, et al.: Etiology and outcomes of thrombotic microangiopathies. Clin J Am Soc Nephrol. 2019, 14:557-66. 10.2215/CJN.11470918
5. Humphreys BD, Sharman JP, Henderson JM, et al.: Gemcitabine-associated thrombotic microangiopathy. Cancer. 2004, 100:2664-70. 10.1002/cncr.20290
6. Pham PT, Peng A, Wilkinson AH, Gritsch HA, Lassman C, Pham PC, Danovitch GM: Cyclosporine and tacrolimus-associated thrombotic microangiopathy. Am J Kidney Dis. 2000, 36:844-50. 10.1053/ajkd.2000.17690
7. Morton JM, George JN: Microangiopathic hemolytic anemia and thrombocytopenia in patients with cancer . J Oncol Pract. 2016, 12:523-30. 10.1200/JOP.2016.012096
8. Verbiest A, Pirenne J, Dierickx D: De novo thrombotic microangiopathy after non-renal solid organ transplantation. Blood Rev. 2014, 28:269-79. 10.1016/j.blre.2014.09.001
9. Alyamany R, Moyer AM, Willrich MA, Sridharan M: Complement-mediated HUS revisited: evolving insights into pathophysiology, diagnosis, and treatment. Front Immunol. 2025, 16:1621317. 10.3389/fimmu.2025.1621317
10. Zupancic M, Shah PC, Shah-Khan F, Negendra S: Gemcitabine-associated thrombotic thrombocytopenic purpura. Lancet Oncol. 2007, 8:634-41. 10.1016/S1470-2045(07)70203-6
11. Saif MW, Xyla V, Makrilia N, Bliziotis I, Syrigos K: Thrombotic microangiopathy associated with gemcitabine: rare but real. Expert Opin Drug Saf. 2009, 8:257-60. 10.1517/14740330902942299
12. Yu X, Zhang Y, An Z, Feng X, Yang H: Thrombotic microangiopathy associated with calcineurin inhibitors: a real-world analysis of postmarketing surveillance data. Clin Ther. 2025, 47:117-22. 10.1016/j.clinthera.2024.11.017
13. Munjal RS, Sharma J, Polishetti S, et al.: Beyond immunosuppression: the intricate relationship between tacrolimus and microangiopathy. Cureus. 2023, 15:e49351. 10.7759/cureus.49351
14. Massad F, Calcagno T, Issa R, et al.: Tacrolimus-induced thrombotic microangiopathy in orthotopic heart transplant patients: a case series and review of literature. JACC Case Rep. 2025, 30:103790. 10.1016/j.jaccas.2025.103790
15. Gabr JB, Bilal H, Mirchia K, Perl A: The use of eculizumab in tacrolimus-induced thrombotic microangiopathy. J Investig Med High Impact Case Rep. 2020, 8:2324709620947266. 10.1177/2324709620947266
16. Kaname S, Ong ML, Mathias J, Gatta F, Law L, Wang Y: Outcomes in patients with thrombotic microangiopathy associated with a trigger following plasma exchange: a systematic literature review. Transfus Apher Sci. 2025, 64:104048. 10.1016/j.transci.2024.104048
17. Daviet F, Rouby F, Poullin P, et al.: Thrombotic microangiopathy associated with gemcitabine use: presentation and outcome in a national French retrospective cohort. Br J Clin Pharmacol. 2019, 85:403-12. 10.1111/bcp.13808
18. Grall M, Daviet F, Chiche NJ, et al.: Eculizumab in gemcitabine-induced thrombotic microangiopathy: experience of the French thrombotic microangiopathies reference centre. BMC Nephrol. 2021, 22:267. 10.1186/s12882-021-02470-3
19. Burns ST, Damon L, Akagi N, Laszik Z, Ko AH: Rapid improvement in gemcitabine-associated thrombotic microangiopathy after a single dose of eculizumab: case report and review of the literature. Anticancer Res. 2020, 40:3995-4000. 10.21873/anticanres.14393