Thrombotic Microangiopathy in the Cancer Patient

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Disclosures

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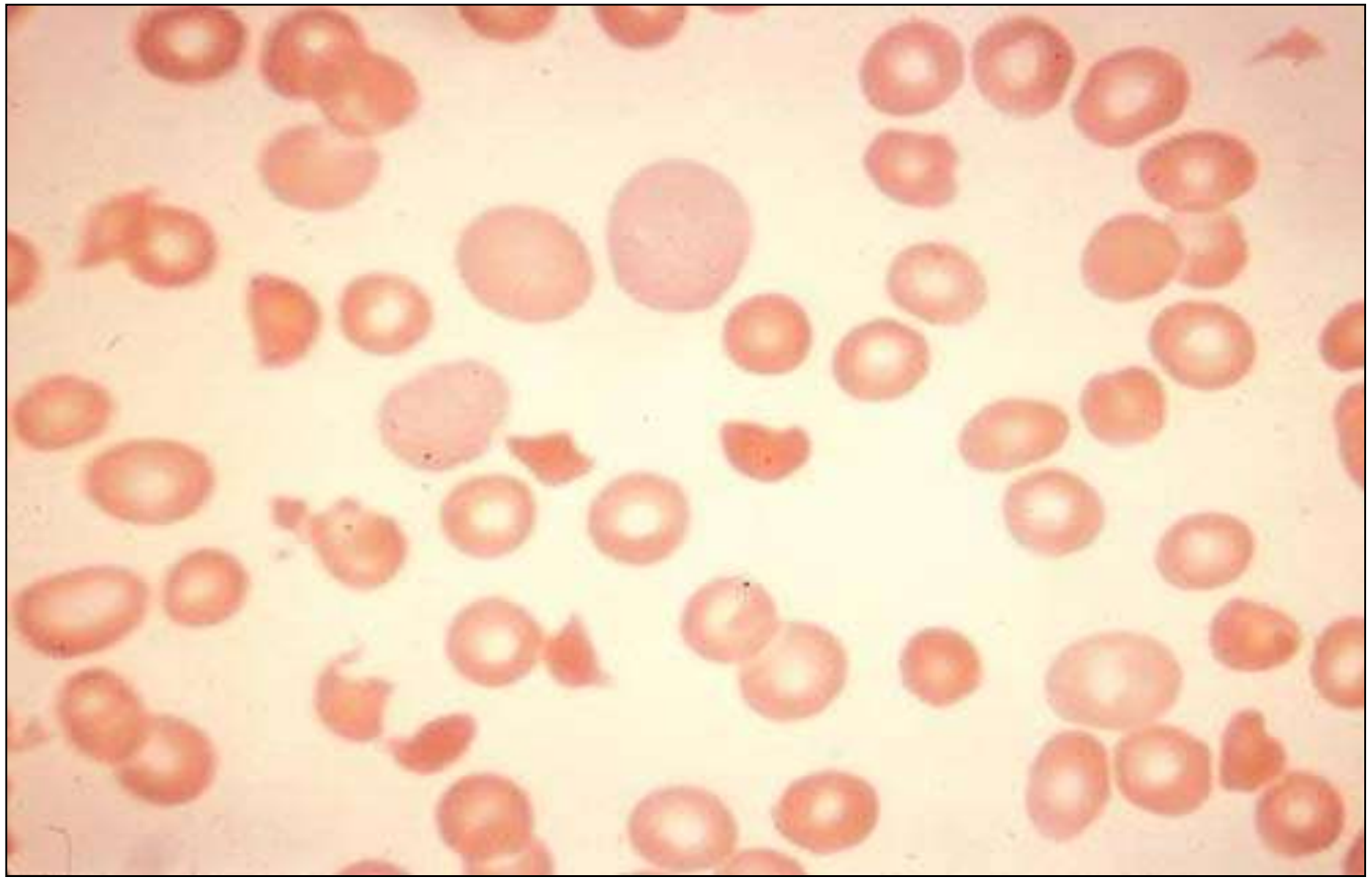
What is Thrombotic Microangiopathy?

Clinical syndrome associated with: thrombocytopenia platelet count < 150K or <25% decrease from baseline

microangiopathic hemolytic anemia

organ damage resulting from endothelial damage



Cancer associated TMA

- Cancer itself has long been associated with both macro and microvascular thrombosis.[1, 2-4]
- Original descriptions in mucinous adenocarcinomas, gastric and ovarian[1]
- Cobalamine deficiency, which may cause a TMA like syndrome, can occur in the setting of gastric cancer and may be a contributing factor.[5]
- Direct activation of the complement system through the lectin pathway involving MASP2, has been described in Adult T cell leukemia and ovarian cancer by galacto-mannose on the tumor cell membrane.[7,8]
- Chemotherapeutic agents have been associated with TMA

1. Moake JL. Thrombotic Microangiopathies. N Engl J Med 2002; 347: 589-606. 2. Brain MC, Azzopardi JG Baker LR, Pineo GF, Roberts PD, Dacie J, Microangiopthic Anemia in Mucin forming adenocarcinoma BJH 1970;18: 183-193. 3. Lohrmann HP, Adam W, Heymer B, Kubanek B, Microangiopathic hemolytic anemia in metastatic carcinoma. Report of eight cases Ann Intern Med, 79 (1973), pp. 368-375. 4.Antman K, Skarin AT, Mayer RJ, Hargerenus HK, Canellos GP Microangiopathic Hemolytic anemia and Cancer. Med Balt 1979; 58 : 377-84. 5Coppola A, Davi G, De Stefano V, Mancini FP, Cerbone AM, Di Minno G. Homocysteine, coagulation, platelet function, and thrombosis. Semin Thromb Hemost 2000;26:243-254. 6. IshidaY, Yamashita K, 7.Sasaki H, Takajou I, Kubuki Y, Morishita K, Tsubouchi H, Okayama A. Activation of complement system in adult T-cell leukemia (ATL) occurs mainly through lectin pathway: a serum proteomic approach using mass spectrometry.Cancer Lett 2008; 271:167. 8. Swierzko, AS Immunotherapy 2014 ;63 (11): 1129-40

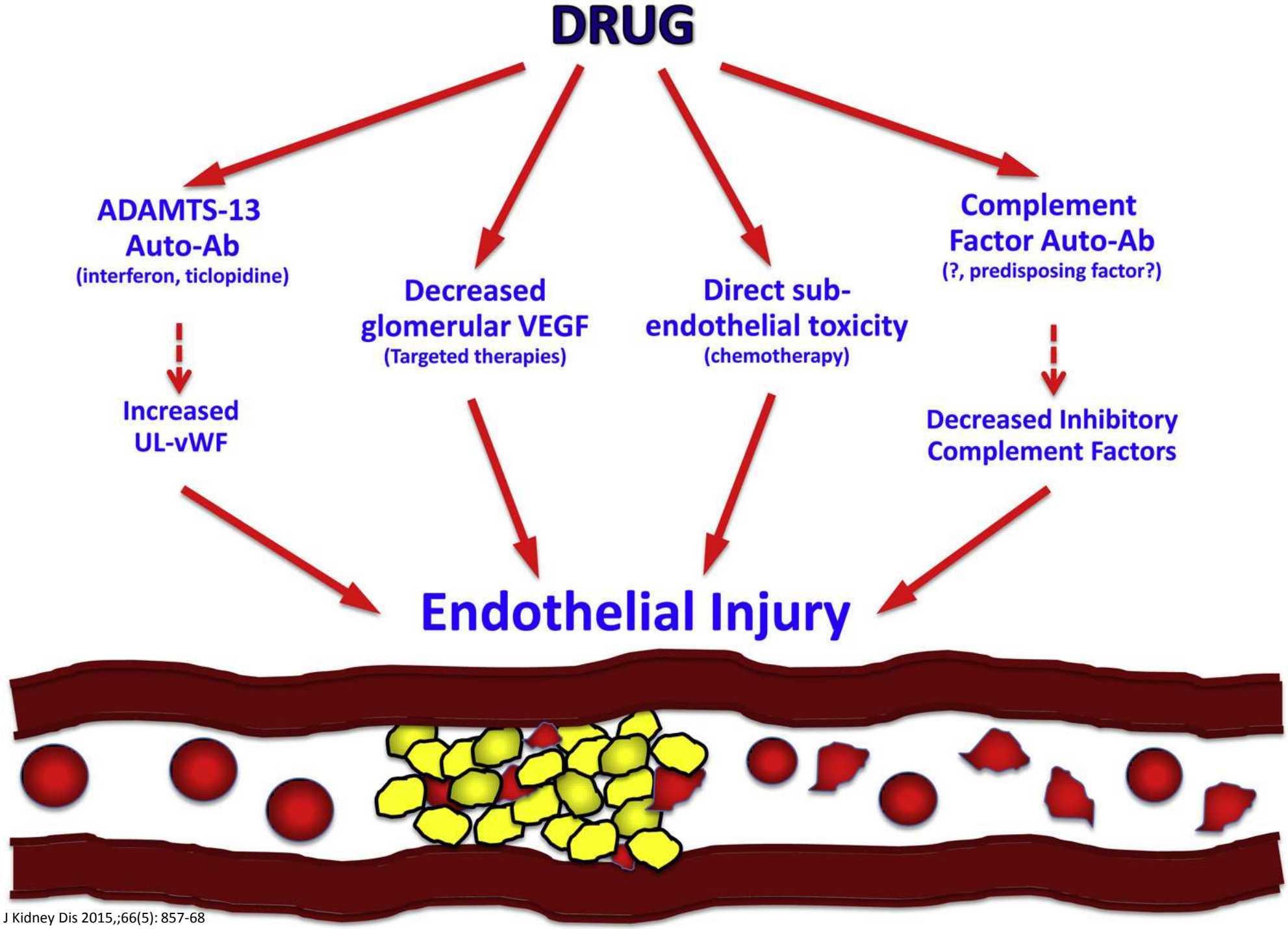
Complement in Cancer Associate TMA

- Upregulation of complement genes have been described in endometriosis associated ovarian cancer (EAOC) compared to benign endometriosis.[1]
- A highly statistically significant upregulation of complement genes was noted on RNA sequencing in lung cancer tissue of patients with thrombosis compared to those patients without thrombosis.[2]
- Studies performed in combined C3 and C5a knock out mice suggest that these complement proteins are critical for the development of cancer neo-vascularization by altering endothelial cell function and vascular endothelial growth factor (VEGF) expression.[3]

1. Suryawanshi S, Huang X, Elishaev Raluca E A, Budiu A, Zhang L, Kim SH, et al. Complement Pathway Is Frequently Altered in Endometriosis and Endometriosis-Associated Ovarian Cancer. Clinical Cancer Research, 2014; 20(23):6163-74.
2. Sussman, T, Abazeed M, McCrae K, Khorana AA, RNA Sequencing Approaches to Identifying Novel Biomarkers for Thromboembolism (VTE) in Lung Cancer. American Society of Hematology abstr # 554, Dec 2017
3. Nunez-Cruz S, Gimotty PA, Guerra MW, Connolly DC, Wu YQ, DeAngelis RA, Lambris JD, Coukos G, Scholler N. Genetic and pharmacologic inhibition of complement impairs endothelial cell function and ablates ovarian cancer neovascularization. Neoplasia. 201214(11):994-1004.

Typical distinctive features between cancer-associated or chemotherapy-associated thrombotic microangiopathies.

	Cancer-associated thrombotic microangiopathy	**Chemotherapy-associated thrombotic microangiopathy**
Disseminated cancer	Yes	No
Renal involvement	Mild/absent	Mild/severe
Disseminated intravascular coagulopathy	Present	Absent
Circulating erythroblasts	Present	Absent
Clinical presentation	Thrombotic thrombocytopenic purpura-like disease	Hemolytic-uremic syndrome-like disease
Treatment	Chemotherapy	Stop chemotherapy Supportive care Specific treatments – Complement Inhibition



Izzedine H, Perazella, Am J Kidney Dis 2015,;66(5): 857-68

Table 1. Antineoplastic agents associated with thrombotic microangiopathies.

Chemotherapy	Anti-VEGF therapy	Other targeted therapies
Mitomycin C **Gemcitabine** **Platinum salts** **Pegylated liposomal doxorubicin** **Bleomycin**	**Ligands** Bevacizumab Afilbercept **Tyrosine kinase inhibitors** Sunitinib Sorafenib Cediranib Brivanib Pazopranib Lucitanib	Other tyrosine kinase inhibitors Imatinib mesylate Dasatinib Immunotoxins Targeting typically CD22 or IL-2 Other immunotherapies Apolizumab

VEGF: vascular endothelial growth factor; IL-2: interleukin-2.

Characteristics of Types I and II Cancer Drug–Induced TMA

	Type I Cancer Drug–Induced TMA	Type II Cancer Drug–Induced TMA
	Chemotherapy regimen	Anti-VEGF therapy
Characteristic agent	Mitomycin C and/or gemcitabine	Bevacizumab
Onset	Delayed; usually 6-12 mo after starting therapy	Occurs any time after the initiation of treatment and may be involved after prolonged treatment (1 dose to 29 mo)
Dose effect	Cumulative, dose related	Not dose related
Clinical	Appears to be permanent and irreversible; hematologic manifestations usually present; hypertension, acute renal failure, pulmonary edema, and ARDS are common	High likelihood of recovery after interruption (reversible); hematologic manifestations only in half of pts; hypertension, and varying degrees of proteinuria usually without kidney failure
Effect of rechallenge	High probability of recurrent dysfunction that is progressive; may result in intractable kidney failure	Some evidence for the relative safety of rechallenge (additional data needed)
Pathologic	Arteriolar and glomerular capillary thrombosis	Exclusive glomerular capillary thrombosis
Therapy and prognosis	High incidence of acute mortality (4-month mortality up to 75%) and chronic kidney disease requiring dialysis despite drug discontinuation, steroids, or plasma exchange before rituximab and eculizumab use	Patient and kidney survival rates are excellent after stopping drug in association with antihypertensive drugs

Abbreviations: ARDS, acute respiratory distress syndrome; pts, patients; TMA, thrombotic microangiopathy; VEGF, vascular endothelial growth factor.

Izzedina H, Perazella, MG Am J Kidney Disease 2015; 66(5): 857-68

TMA Induced by Targeted Cancer Agents

Targeted Agents	No. of Cases	Biopsy-Proven Diagnosis	Time to Onset	References
Immunotoxins				
CAT-3888 (BL22)	5	0	2-3 cycles	88-90
Moxetumomab pasudotox (CAT-8015 or HA22)	2	0	3-5 cycles	91
Combotox	2	0	3-5 d	92
$DAB_{486}IL$- 2	3	0	Not reported	93, 94
Immunotherapy				
Apolizumab	≥3	0	11 doses	95, 96
Alemtuzumab	1	0	2 doses	97
Anti-VEGF therapy				
Ligands (bevacizumab, afilbercept)	97	86	1-29 doses	7, 104[a]
Tyrosine kinase inhibitors (sunitinib, sorafenib, cediranib, brivanib, pazopanib)	39	38	2 wk-7 mo	7, 98-100, 104[a]
Bevacizumab + sunitinib	8	0	Not reported	101
Lucitanib	11	3	Not reported	105
Imatinib	1	1	5 doses	102

Abbreviations: TMA, thrombotic microangiopathy; VEGF, vascular endothelial growth factor.

[a]Minimal change nephropathy/collapsing focal glomerulosclerosis are more often associated with tyrosine kinase inhibitors, whereas microangiopathic hemolysis is rare.

Izzedina H, Perazella, MG Am J Kidney Disease 2015; 66(5): 857-68

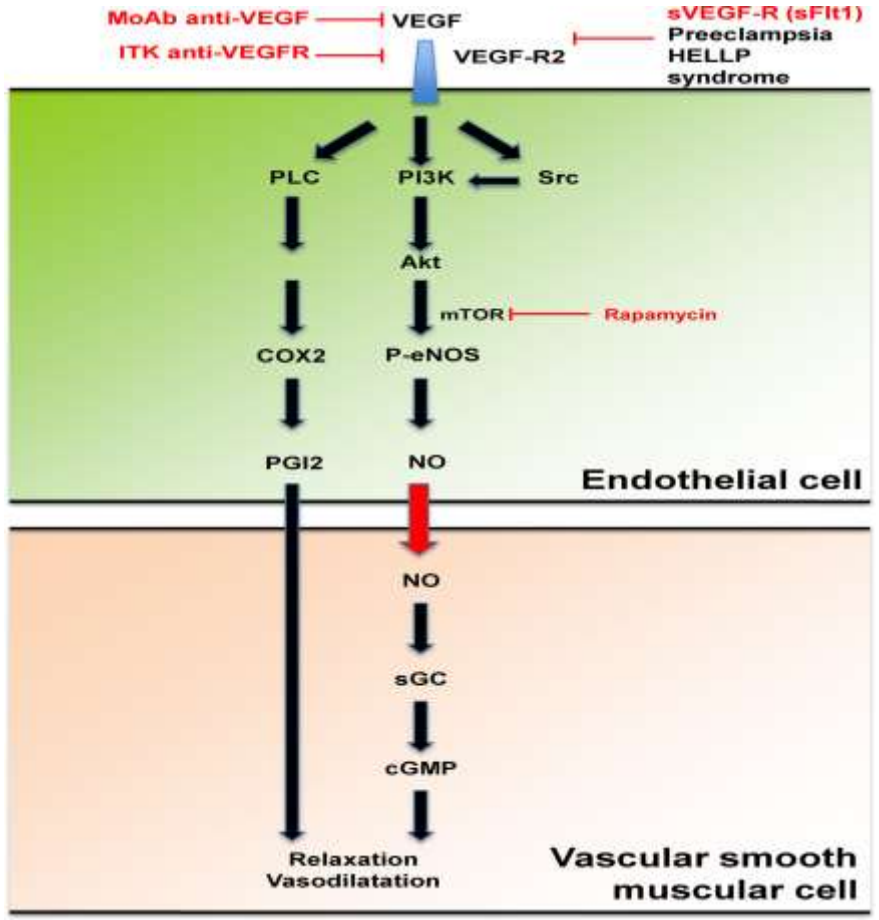
Chemotherapy Associated TMA

- An TMA event in a cancer patient may be due to a direct toxic effect of the chemotherapy on endothelium, antibodies to VEGF or immune complex mediated damage to endothelium
- Decreased endothelial prostacyclin production as has been reported in human endothelial cell cultures in response to mitomycin as well as anti-VEGF treatments.[19,30-
- Prostacyclin is an important physiologic inhibitor of platelet aggregation and its deficiency would enhance platelet aggregation.
- Plasma levels of thrombomodulin, a marker of endothelial activation, tissue plasminogen activator and plasminogen activator inhibitor-1 are elevated in patients with mitomycin C induced TMA, similar to that seen with aHUS.
- Discontinuation of the chemotherapeutic agent does not result in improvement of the TMA

CHEMO INDUCED AHUS ENDOTHELIAL DAMAGE

Role of VEGF/VEGFR pathway in vascular relaxation and involvement of VEGF/VEGFR blockers in thrombotic microangiopathy pathophysiology.

Inhibition of VEGF in the glomerular microvasculature prevents the formation and maintenance of healthy, fenestrated endothelium. Without active VEGF signaling, the endothelium is compromised, along with the filtration barrier of the glomerulus in the kidney



Gange S, Coppo P, Thrombotic microangiopathies and antineoplastic agents. Nephrologie & Therapeutique 2017; 13 (S1) S109-113).

Mitomycin C - associated TMA

- Usually occurs 4 to 8 weeks after the last dose, with most cases occurring after 6 to 12 months of chemotherapy after a cumulative dose of 40 to 60 mg. [1]
- Plasma levels of thrombomodulin, tissue plasminogen activator and plasminogen activator inhibitor-1 are elevated in patients with mitomycin C-induced TMA[1]
- The seminal presentation of Mitomycin C induced TMA is the acute development of non-cardiogenic pulmonary edema and Adult Respiratory Distress Syndrome (ARDS), a finding *not* described in TTP or with other chemotherapeutic agents.[1]
- Hypertension, acute renal failure, pulmonary edema and acute respiratory distress syndrome are common. Microthrombi involve both glomerular capillaries and arterioles. Clinical features are typically permanent and irreversible, and respond poorly to therapeutic plasma exchange.[2]

1. Lesesne B, Rothschild N, Erickson B, Korec S, Sisk R, J Keller J, *et al.*Cancer-associated hemolytic-uremic syndrome: analysis of 85 cases from a national registry. J Clin Onc 1989; 7: 781-789.

2. Gange S, Coppo P, Thrombotic microangiopathies and antineoplastic agents. Nephrologie & Therapeutique2017; 13 (S1) S109-113).

Gemcitabine associated TMA

- Results from in a cumulative toxicity usually presenting after 6-8 months of treatment with a cumulative dose of 22.5 mg/dl (+/- 14). [1,2]
- Unlike Mitomycin C, *renal insufficiency* is the hallmark presentation. Two-thirds of patients present with proteinuria, microscopic hematuria and the onset of or worsening of systemic hypertension. [2,30]
- Renal biopsy demonstrates C3 deposition in addition to thickening of capillary walls, fibrin thrombi, necrotic endothelial cells, and granular deposits[2]

1. Lesesne B, Rothschild N, Erickson B, Korec S, Sisk R, J Keller J, *et al.*Cancer-associated hemolytic-uremic syndrome: analysis of 85 cases from a national registry. J Clin Onc 1989; 7: 781-789.
2. Izzedine, H, Isnard-Bagnis C, V Launay-Vacher V, Mercadal L, I Tostivint I, Rixe O, et al. Gemcitabine-induced thrombotic microangiopathy: a systematic review. Nephrol Dial Transplantation, 2006; 21: 3038-45.
3. Gange S, Coppo P, Thrombotic microangiopathies and antineoplastic agents. Nephrologie & Therapeutique 2017; 13 (S1) S109-113).

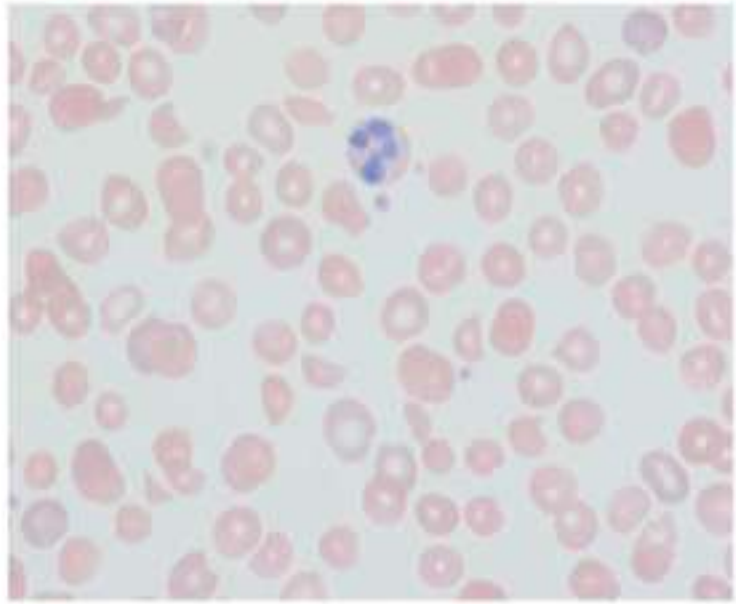
Chemotherapy Associated aHUS: Effect of complement inhibition

Table I. Cases treated.

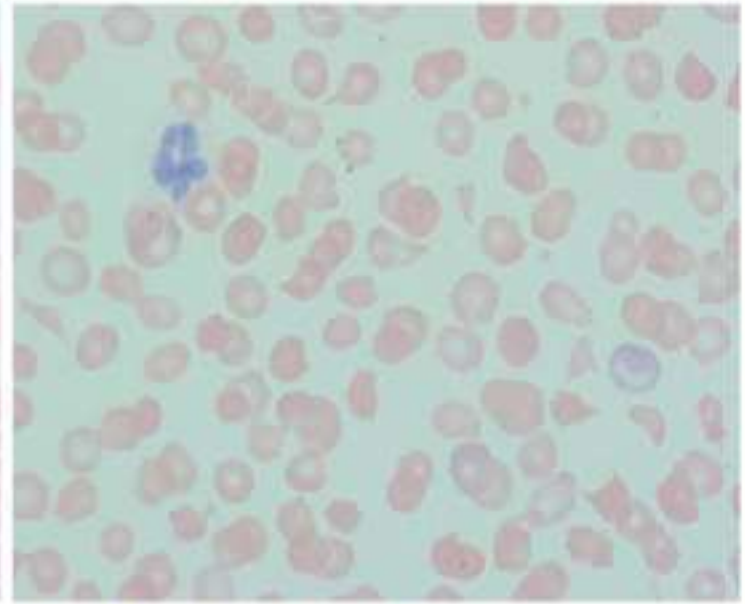
Patient	Age (years) Sex	Drug	ADAMTS13 activity (%)	Platelet count ($\times 10^9$/l)	Tumour	Eculizumab treatment duration (weeks)	Outcome
1	27 Female	Dasatinib*	NA	60	Fibrolamellar hepatocarcinoma	12	CR No dHUS recurrence Died of cancer 6 months later
2	42 Female	Bevacizumab*	68%	50	Ovarian	16	CR No dHUS recurrences Died of cancer 9 months later
3	66 Male	Gemcitabine*	NA	161†	Pancreatic	18	CR No dHUS recurrences in 2 years
4	61 Female	Gemcitabine*	101%	56	Unknown Origin	24	CR No HUS recurrence
5	66 Female	Gemcitabine*	NA	150‡	Lung	16	CR No dHUS recurrence
6	57 Male	Gemcitabine*	NA	150‡	Urothelial	2	CR No dHUS recurrence
7	22 Female	Bleomycin*	NA	57	Hodgkin Lymphoma	Ongoing	CR Still on chemotherapy

Weitz, IC , Deloughery, T BJH 2017

(A)

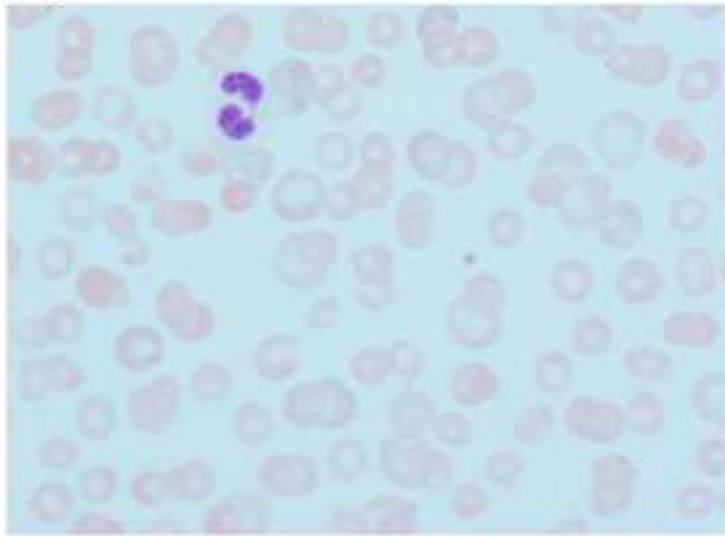


Pre-plasma exchange

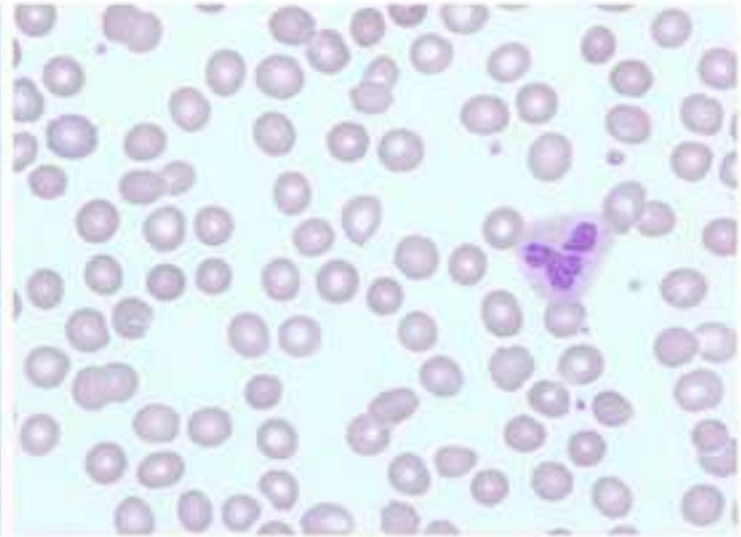


Post 30 days of plasma exchange

(B)



12 weeks of eculizumab



20 weeks post-eculizumab

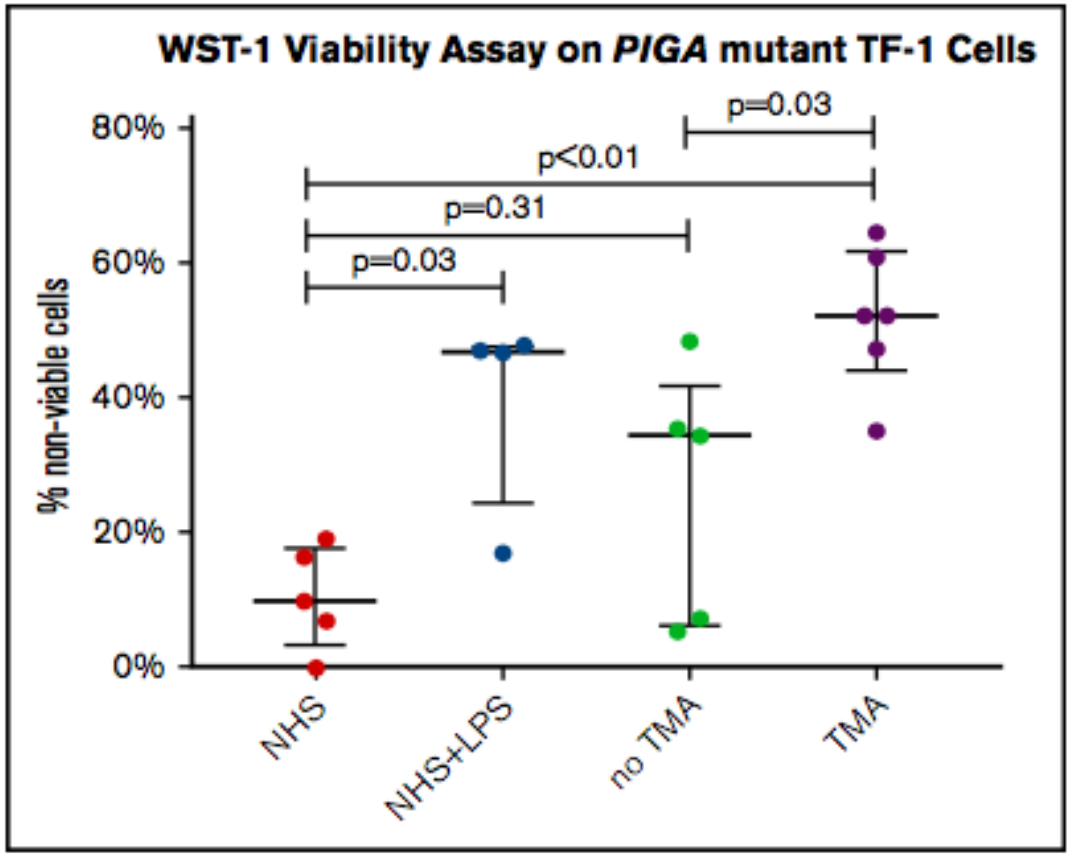
TMA in association with Bone marrow transplantation

- Previously considered to be TTP
- Thought to be due to calcinuric inhibitors or Mtor inhibitors such as sirolimus.[1,2]
- Poorly responsive to discontinuation of treatment.
- Harbinger may be the development of hypertension[3]

- Associated with increased complement activation[4]

1. Sartelet H, et.al Am J Transplantation 2005;5: 2441-7. 2. Eremina V, et.al NEJM 2008;358:1129-393. Jodele, S etal, Blood September 19, 2013 vol. 122 no. 12 2003-2007
4. Rotz SJ, et.al Blood Advances 2017; 1(20): 1632-4

Complement activation in Transplant Associated TMA



ure 1. **WST-1 viability assay on *PIGA*-mutant TF-1 cells.** Percentage of

. Rotz SJ, et.al Blood Advances 2017; 1(20): 1632-4

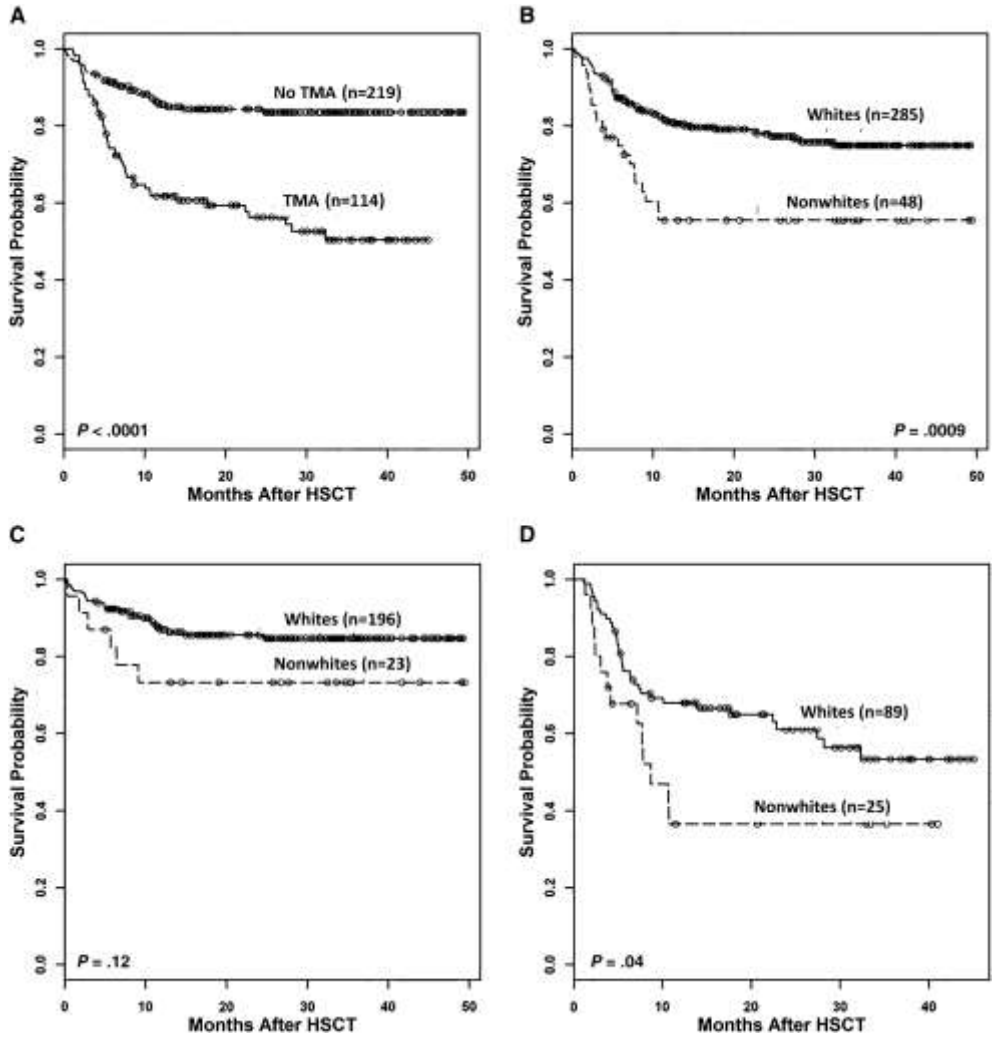
Complement system analysis in patients with HSCT-TMA CFR, complement factor H-related gene 5.

Patient	Transplant type	*CFI,CFH,MCP,CFB,CFR5* (direct sequence analysis)	Recipient *CFH-CFHR5* (MLPA)	Donor *CFH-CFHR5* (MLPA)	CFH antibody (ELISA)	CFHR1 protein analysis (western blot)
1	autologous	normal alleles	*del(CFHR3-CFHR1)	n/a	absent	present
2	autologous	normal alleles	*del(CFHR3-CFHR1)	n/a	absent	present
3	autologous	normal alleles	*del(CFHR1-CFHR4)	n/a	absent	present
4	allogeneic	normal alleles	*del(CFHR3-CFHR1)	normal allele	present	present
5	allogeneic	normal alleles	*del(CFHR3-CFHR1)	*del(CFHR3-CFHR1)	present	present
6	allogeneic	normal alleles	normal allele	normal allele	present	present

* *del* refers to heterozygous deletions

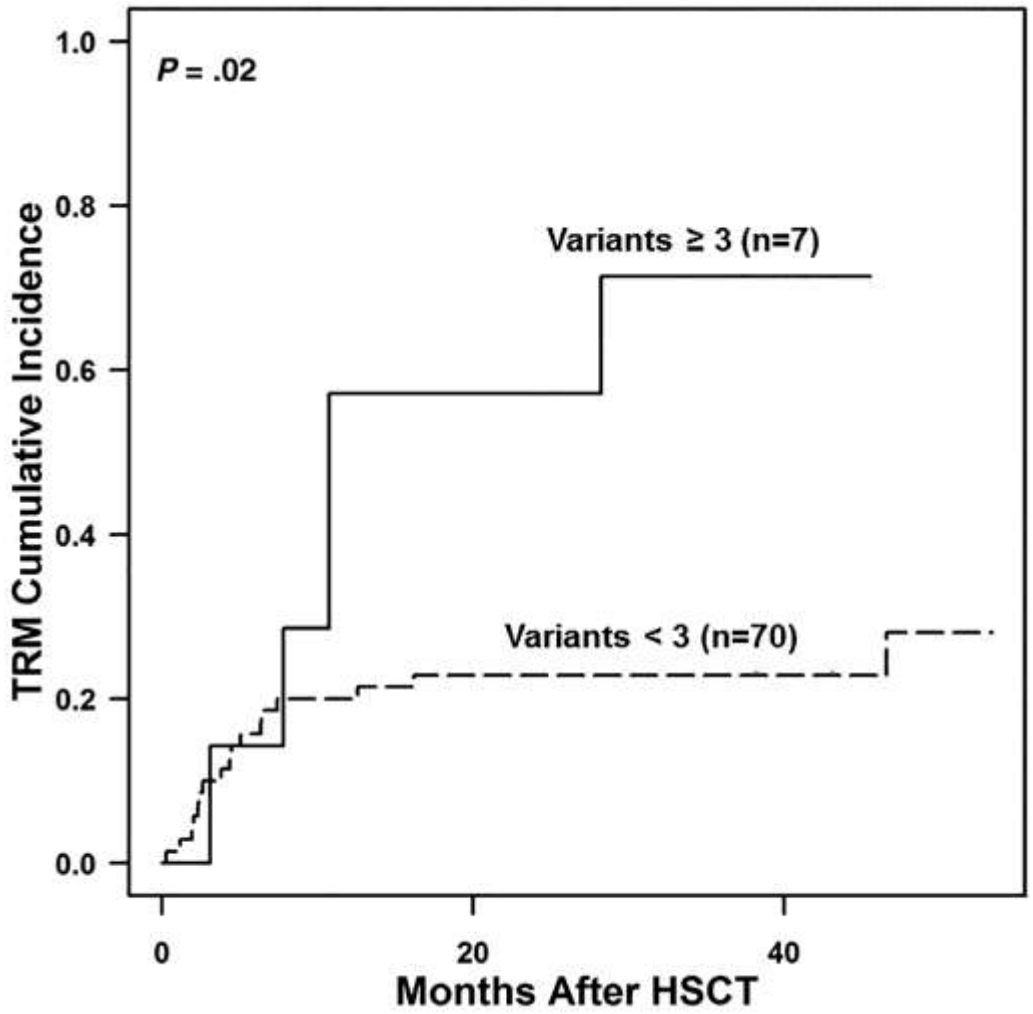
Jodele, S etal, Blood September 19, 2013 vol. 122 no. 12 2003-2007

TMA and race effect on survival among patients who received a transplant.



Jodele, S et al. Blood 2016;127:989-996

Transplant-related mortality (TRM) in relation to gene variant number identified.



Jodele, S et al. Blood 2016;127:989-996

Cancer associated TMA

- May be due to the primary tumor itself. Treatment is tumor specific chemo/targeted therapy.

- May be due to chemotherapeutic or targeted treatments. In addition to drug discontinuation, treatment of choice is complement inhibition.

- Transplantation associated TMA presents with hypertension, often associated with underlying complement regulatory protein mutations, has a worse outcome with multiple mutations and in the African American population, but is responsive to complement inhibition

- *Thank you for your attention!*