MABs for TMAs: When Plasma Exchange Is Not Enough

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INTRODUCTION

Thrombotic microangiopathies (TMA) consist of syndromes with microangiopathic hemolytic anemia (MAHA) with shistocytes, thrombocytopenia, and microvascular thrombi.

TMA can have multiple etiologies including thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome (HUS) which can be typical (*E. coli*-associated), secondary (malignancy, hypertension, drugs, autoimmune diseases), or complement-mediated.

Therapeutic plasma exchange (TPE) is often an early intervention while its ability can be limited in some cases.

This case series highlights the life-saving potential of various monoclonal antibody (mAb)-based therapies therapies in two different cases of TMA at our institution.

CASE 1

A 32-year-old woman presented with hematuria.

Thrombocytopenia with 5,000 platelets, anemic with hemoglobin of 8.3 g/dL along with frequent shistocytes on smear (Fig. 2a).

TPE was initiated and diagnosis of thrombotic thrombocytopenic purpura (TTP) made when ADAMTS13 returned <5%.

She appeared refractory after TPE, steroids, and rituximab (Fig. 3). Rituximab was continued weekly while addition of Caplacizumab led to resolution of MAHA and normal ADAMTS13 activity in 4 days.

She was continued on daily caplacizumab until one month after her last TPE date and remained without TTP recurrences at time of annual follow-up.

CASE 2

A 28-year-old woman presented with hypertensive emergency and transient stroke-like symptoms of right-sided weakness and expressive aphasia.

She was found to have microangiopathic hemolytic anemia with platelet nadir of 56,000. Few shistocytes were found on smear (Fig 2b).

A creatinine of 2.32 at presentation reached plateau of 4.20 mg/dL during her admission. Renal biopsy revealed evidence of thrombotic microangiopathy. Renal function was unchanged after two days of TPE.

Diagnosis of complement-mediated hemolytic uremic syndrome (atypical HUS) was suggested when other causes such as TTP and scleroderma were deemed unlikely. She received 2 days of TPE.

Eculizumab was administered and then continued as gene testing further supported aHUS (Fig 4). Functional and inhibitor complement studies were unremarkable.

Following six treatments, creatinine improved to 1.59 mg/dL, with plan to continue therapy using the long-acting ravulizumab.

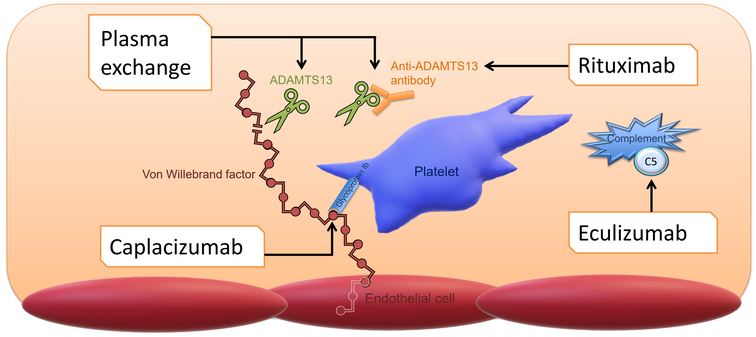

Figure 1. Sites of action of several treatment modalities as it relates to pathophysiology of TTP and CM-TMA

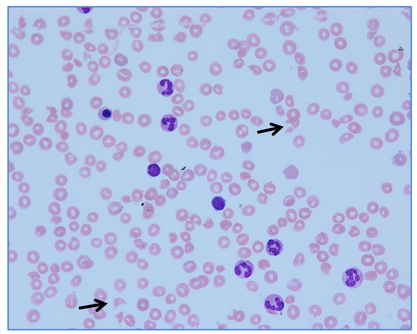

Figure 2a. Case 1 peripheral smear, noting frequent shistocytes/fragments among polychromatic and nucleated red blood cell forms.

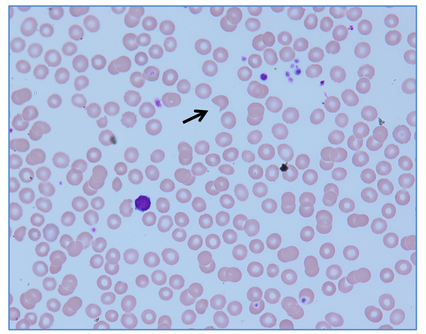

Figure 2b. Case 2 peripheral smear, noting few shistocytes

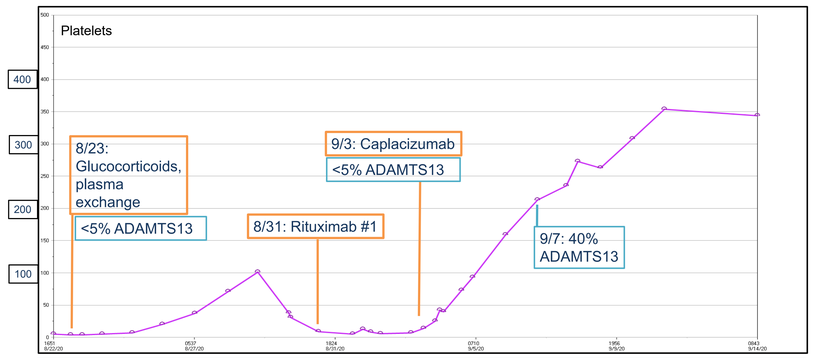

Figure 3. Platelet counts in relation to therapy and ADAMTS13 activity in Case 1

- Heterozygous missense exon 20 CFH (c.3143G>T, p.Cys1048Phe)
- Heterozygous missense exon 20 CFH (c.3004G>C, p.Gly1002Arg)
- Heterozygous missense exon 6 MASP2 (c.881C>T, p.Thr294Met)
- Heterozygous missense exon 7 CFHR5 (c.1067G>A, p.Arg356His)
- 3 polymorphisms in CFH
- 5 polymorphisms MCP/CD46 gene

Figure 4. The complement genetic findings for case 2

DISCUSSION

Therapeutic plasma exchange (TPE)

- TPE continues to have a role in the treatment of TTP, but limited in other causes such as complement-mediated (CM-)TMA[1]
- Even with TTP, patients can prove refractory to TPE as seen in case 1

Case 1 demonstrates successful and life-saving use of **rituximab** and **caplacizumab** for TTP

- When given early for an initial episode of TTP, rituximab has been found to reduce ICU stay by 7 days.[2]
- Caplacizumab lowered recurrence rate by 67% compared to placebo in the HERCULES trial.[3]
- The 2020 TTP guidelines by the International Society on Thrombosis and Hemostasis gives rituximab and caplacizumab a conditional (rather than strong) recommendation for use in first episode of TTP based on available evidence and cost of the medications. Caplacizumab can amount to $270,000 for an acute case of TTP.
- Most experts recommend early use of rituximab while reserving caplacizumab for high-risk TTP (based on PLASMIC score).[4]

Case 2 shows utility of **eculizumab** to improve and maintain renal function for CM-TMA

- Most patients with CM-TMA have been found to respond to eculizumab use, altering the historical 60-70% development of end-stage renal disease to 10%.
- Discontinuation of C5 complement inhibiting agents led to recurrence in about 50% in one of the larger studies.[1]
- Complement genetics may be utilized to identify those at higher risk for recurrence of CM-TMA, where variants of CFH and MCP had highest risk in one study (50%).[5] Given her higher risk, the patient in case 2 was transitioned to ravulizumab with long-term therapy plan.

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