CASE REPORTS

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- Thrombotic microangiopathy (TMA) is a life-threatening syndrome of systemic microvascular occlusions and is characterized by sudden or gradual onset of thrombocytopenia, microangiopathic hemolytic anemia, and renal or other end-organ damage

- TMA has been associated with diverse diseases and syndromes:

- **Systemic infections**,
- **Cancer**
- **Pregnancy** complications [e.g. preeclampsia, eclampsia, HELLP syndrome]
- **Autoimmune** [SLE, systemic sclerosis, antiphospholipid syndrome],
- **Hematopoietic** stemcell or organ transplantation,
- **Severe hypertension**

- The etiologies of TMA also include atypical (aHUS), a rare, progressive, lifethreatening form predominantly caused by dysregulation of the complement alternative pathway

- aHUS can manifest at any age .80 % of patients present with thrombocytopenia, microangiopathic hemolytic anemia, and renal impairment. onset may be more gradual in other patients .Because aHUS can affect multiple vascular beds ,extrarenal manifestations occur in up to 48 % of patients, with frequent neurologic and cardiovascular involvement

- aHUS is a consequence of both
- genetic predisposition to alternative complement dysregulation

- activating complement and/or damaging the endothelium

- Complement-amplifying conditions (CACs):
- Pregnancy complications
- Autoimmune diseases
- Malignant hypertension (MHT)
- may be comorbid with aHUS, unmask
- a previously undiagnosed case, or lead to a misdiagnosis that may precipitate aHUS or occur secondary to aHUS

Case 1

A 33- year-old woman developed abruptio placenta leading to fetal death at 33 weeks of gestation.

She underwent cesarean section and hysterectomy and subsequent laparotomy.

The patient had extensive blood loss and received numerous transfusions.

She developed thrombocytopenia ($39*10^9$) .(normal range at institution 150-350 * 10^9L)

Hemolytic anemia (Hb: 6.7g/dl)

lactat dehydrogenase (LDH)level.2670

Numerous schistocytes on a blood smear

Renal failure (serum cr level: 6 mg/dl)necessitating initiation of hemodialysis.

The fibrinogen level as well as prothrombin and partial thromboplastin times were normal.

ADAMTS13 activity testing was ordered and PE was initiated.

The patient showed minimal improvement in hematologic parameters(Hb level: 7g/dl and platelet count $42*10^9$L)and no improvement in renal function (dialysis dependant)after five daily PEs.

Case 2

A 43- year-0ld woman with a history of migraine headaches since childhood presented with severe headaches and visual impairment lasting for several days.

The examination showed a blood pressure of 300/185 mmHg resulting in immediate hospitalization.

Fundoscopic examination revealed papilledma.and a subsequent cerebral magnetic resonance tomography showed alterations consistent with posterior reversible encephalopathy syndrome.

Lab test: Hb level: 10.8 g/dl, LDH level of 447 U/L (normal range <250 U/L) and schistocytes on a blood smear revealed microangiopathic hemolytic anemia.

The PLT count was normal.

Acute kiney injury (serum Cr level: 3.4mg/dl) proteinuria also was evident.

PE was initiated because thrombotic thrombocytopenic purpura(TTP) could not be ruled out initially,but was discontinued after the ADAMTS13 activity was determined to be 64%.

The patient's HTN was managed with intravenous and oral antihypertensive medications resulting in the resolution of neurological symptoms.

Stool examintaions showed no shiga toxin-producing Escherichia coli .

A kidney biopsy revealed severe obliterative arteriolosclerosis, ischemic glomerular collapses, and extensive acute tubular injury.

Together with typical signs of hypertensive retinopathy and echocardiographic evidence of hypertensive heart disease,the patient was considered to have malignant hypertension.

However,despite adequate blood pressure control and resolution of hemolysis(LDH163 U/L)there was no improvement in anemia (Hb:10.7g/dl) and renal function (serum Cr : 3.3 mg/dl) over approximality 5.5 weeks from presentation.

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Case 3

A 37-year-old female hemodialysis patient with a 14 month history of ESRD due to recurrent pyelonephritis underwent living-related donor kidney transplantation.

Excellent graft function was noted immediately following the surgery. And the serum Cr level decreased to 0.9 mg/dl.

Over the subsequent days, however,urine output gradually decreased and serum Cr levels increased (1.85 mg/dl on day 5 post-surgery).

Humoral rejection was suspected (increasing titer of donor- specific antibodies).

And the patient was treated with high dose corticosteroids and PE.

However, the patient developed anuria. Doppler ultrasound showed near absent graft perfusion.

In addition TMA was suggested by laboratory values including the presence of schistocytes, plt count of $33*10^9$.

Hb level of 11.7 g/dl, LDH of 675U/L . Serum Cr level of 3.5 mg/dl.and heavy proteinuria . (6701 mg/g Cr)

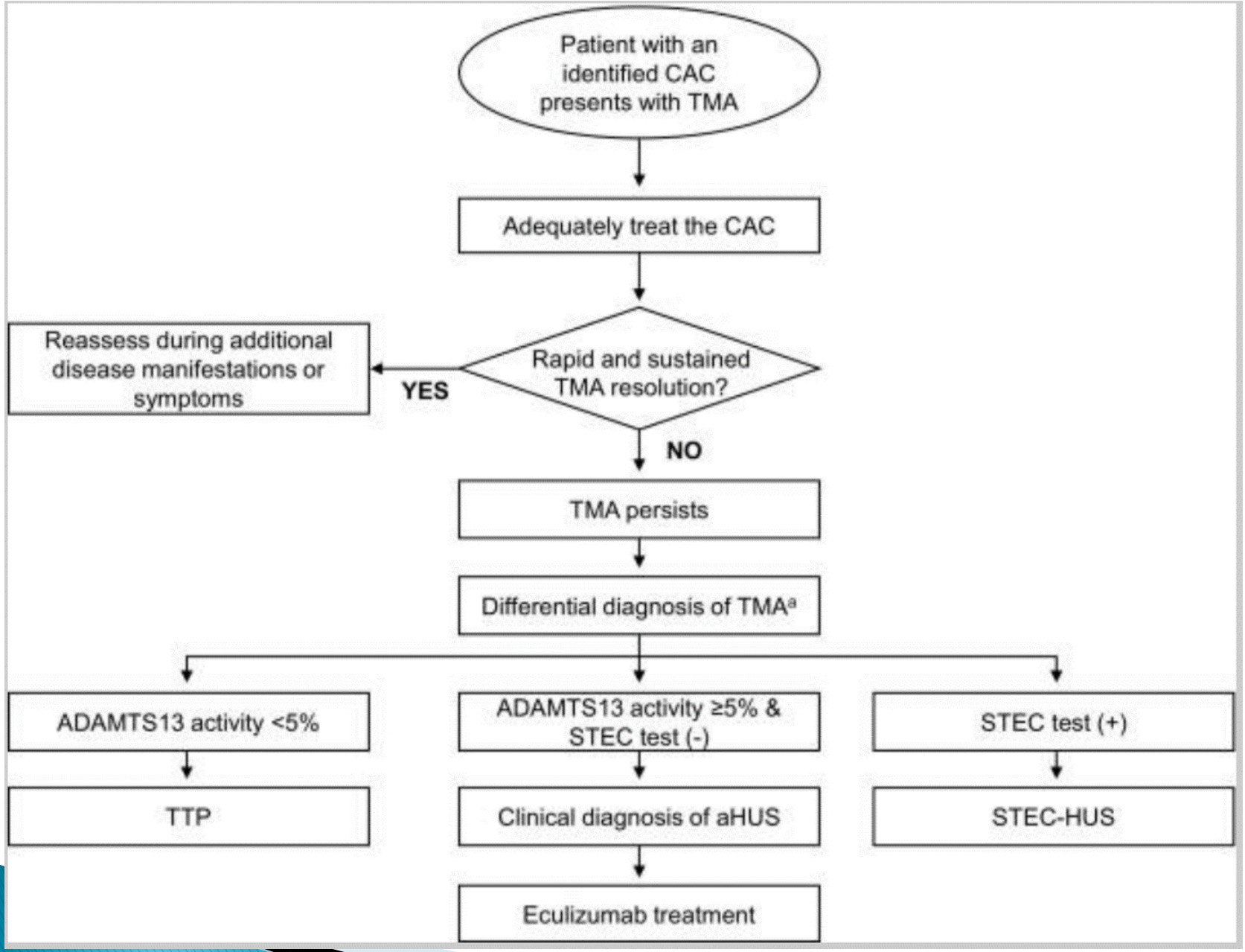
The patient was started on hemodialysis because of volume overload and progressive renal dysfunction.

On post-transplant day 8,

A renal allograft biopsy revealed TMA consistent with the clinical diagnosis of aHUS.

Immunostaining demonstrated Cd4 staining of peritubular capillaries consistent with humoral rejection.

Immunoabsorption was performed for 3 days followed by two doses of intra venous immunoglobulins.


Patient with an identified CAC presents with TMA
Adequately treat the CAC
Rapid and sustained TMA resolution?
YES
Reassess during additional disease manifestations or symptoms
NO
TMA persists
Differential diagnosis of TMA[a]
ADAMTS13 activity <5%
TTP
ADAMTS13 activity ≥5% & STEC test (-)
Clinical diagnosis of aHUS
Eculizumab treatment
STEC test (+)
STEC-HUS

Case 1

- the ADAMTS13 activity level was 56%.TTP was rule out.shiga toxin was negative.
- Following diagnosis of aHUS PE was discontinused.
- After the discontinuation of PE, the patient was Vaccinated against meningococcus,antibiotic prophylaxis was started, and eculizumab therapy was initiatad.

- 2 weeks later, dialysis was discontinued. Laboratory tests showed a platelet count of .147*109/L

- Hb level (13g/dl) and serum cr level (0.9mg/dl)were normal.
- The patient remains on ongoing eculizumab therapy.

case2

- Therefore, a HUS was diagnosed with MHT as a presenting sign.
- No complement gene mutations were identified

- After meningococcal vaccination and antibiotic prophylaxis, initiation of eculizumab therapy resulted in gradual improvement of renal function after 9 month of therapy.
- The patient's Hb level was 12.2 g/dl and serum Cr level was stable at 2.1 mg/dl.
- After 11 months the Hb and serum Cr levels were 12.9 g/dl and 2 mg/dl,respectively.
- The patient discontinued from eculizumab therapy after 1 year.

case3

- a diagnosis of HUS was made. Eculizumab therapy , along with antibiotic prophylaxis for meningococcal infection,was initiated , leading to gradual resolution of hemolysis and improved renal function.
- eculizumab treatment was continued with improvement in renal function without the need for further renal replacement therapy.

- The patient received meningococcal vaccination following discharge. At a follow up of 6 months,PLT count: stable at 213*109

- Hb level at 11.9 g/dl. LDH level at 273U/L and serum Cr level at 1.7 mg/dl.
- The patient continues to receive eculizumab therapy. Genetic testing did not reveal any complment gene mutations

- These case reports illustrate aHUS in the setting of three CACs:
- pregnancy complications, MHT, and renal transplantation
- the standard management of the individual CAC (i.e. cesarean section and subsequent hysterectomy after pregnancy complications, antihypertensive medications for MHT, and corticosteroid therapy for humoral allograft rejection) did not resolve TMA.
- Each patient had a thorough evaluation for potential underlying causes of TMA.

- The patients with underlying complement dysregulation are particularly prone to develop TMA when experiencing a CAC.

- Chronic complement dysregulation both in aHUS and other disorders predisposed patients to TMA .

- Diagnosis may be challenging.
- Patients may not show classic triad:
- Microangiopathic hemolytic anemia ,thrombocytopenia ,renal impairment
- Particularly thrombocytopenia.

- 16% of patients did not have thrombocytopenia at disease onset*

*Fremeaux-Bacchi V et al 2013.Am soc Nephrol

Review of CACs

- **Pregnancy complication**:
- TMA occurs in approximately 1 per 25,000 pregnancies*

- Complement activation may be augmented during pregnancy and postpartum due to fetal cell in mother circulation , infection and hemorrhage.
- general signs and symptoms of P-aHUS may include fatigue, headache,nausea, and vomiting also as typical symptom.
- More recent case studies also documented the efficacy of eculizumab in the treatment of P-aHUS, including normalization of hematologic parameters and renal function.

*Dashe JS, Ramin SM, (1998) Obstet Gynecol

- **Malignant hypertension**:
- Many patients with aHUS first present with hypertension, potentially with high severity and/or MHT.
- TMA may occur following fluid shear stress on endothelial cells and subsequent vascular injury (i.e. fibrinoid necrosis, thrombosis, and luminal narrowing), leading to red blood cell fragmentation and platelet consumption. Aldosterone has been implicated as a potential mediator of vascular endothelial damage in hypertension.

- Patients with MHT may present with microangiopathic hemolytic anemia, renal impairment, and thrombocytopenia although the latter may be modest and/or resolve quickly.
- Prior history of hypertension and/or relatively high arterial pressure, signs of hypertensive heart disease,relatively high platelet count, and retinopathy are suggestiveof MHT-associated TMA.

- It has been proposed that a diagnosis of aHUS should be suspected in patients with difficult-to-control MHT who demonstrate persistent TMA.
- In such patients, treatment with eculizumab should be considered

- **Renal transplantation**
- A large series of 22 patients demonstrated that eculizumab therapy was effective in preventing and treating aHUS recurrence post-transplant*
- Expert groups recommend that patients, especially with moderate or high risk for disease recurrence following renal transplantation, receive prophylactic eculizumab**

- *Zuber J, et al (2012) Am J Transplant
- **Campistol JMet al (2015) Nefrologia

- **Autoimmune diseases:**
- Dysregulation of the terminal complement activation has been implicated in the pathogenesis and prognosis of SLE and lupus nephritis
- Complement gene mutations have been identified in patients with SLE and are associated with disease susceptibility*

- *Zhao J, et al (2011). PLoS Genet

- Several cases of scleroderma-related aHUS have been reported in the literature Overall, outcomes were poor, including death within months of onset in one case.
- The effects of eculizumab have not been documented in scleroderma-related aHUS.

- **Drug-induced TMA**
- Nine medications account for 76 % of TMA cases: quinine, tacrolimus,cyclosporine, interferons, gemcitabine, mitomycin,clopidogrel estrogen/progesterone, and ticlopidine.

- The pathogenesis of drug-induced TMA involves two distinct mechanisms: **immune mediated** and **direct toxicity.**

- quinine-, ticlopidine-, and clopidogrel-induced TMAs occur via an immune-mediated reaction, which is typically characterized by severe systemic manifestations including anuric acute kidney injury.

- TMA caused by cyclosporine, gemcitabine, and mitomycin occurs through a toxicity-mediated mechanism that is dose dependent and may also lead to renal impairment.

drug avoidance and supportive care may be the only beneficial options

- However, the role for PE/PI is unclear
- More studies are necessary to determine a potential role for eculizumab in drug-induced TMA.

- **Infection-induced TMA**

- Infections, particularly of the respiratory and gastrointestinal tract, precede aHUS in approximately half of cases*

- *Noris M, et al (2010. Clin J Am Soc Nephrol 5:1844-1859

Diagnosis and management of TMA in patients with CACs

- All patients with TMA should have a thorough evaluation for underlying causes.
- STECHUS can be ruled out with a negative stool test for STEC.
- ADAMTS13 activity <5 % (depending on the assay used) indicates TTP
- Complement gene mutations or factor
- H autoantibodies are identified in approximately 50–70 % of patients with aHUS

- Overall…

- clinicians should have a strong suspicion for aHUS in patients with ADAMTS13 activity ≥5 %, negative STEC test, and persistent TMA despite treatment

of the CAC .

Once aHUS is diagnosed, eculizumab

should be initiated promptly to halt target organ injury and improve outcomes related to TMA.