Recurrent or Secondary HUS after transplantation

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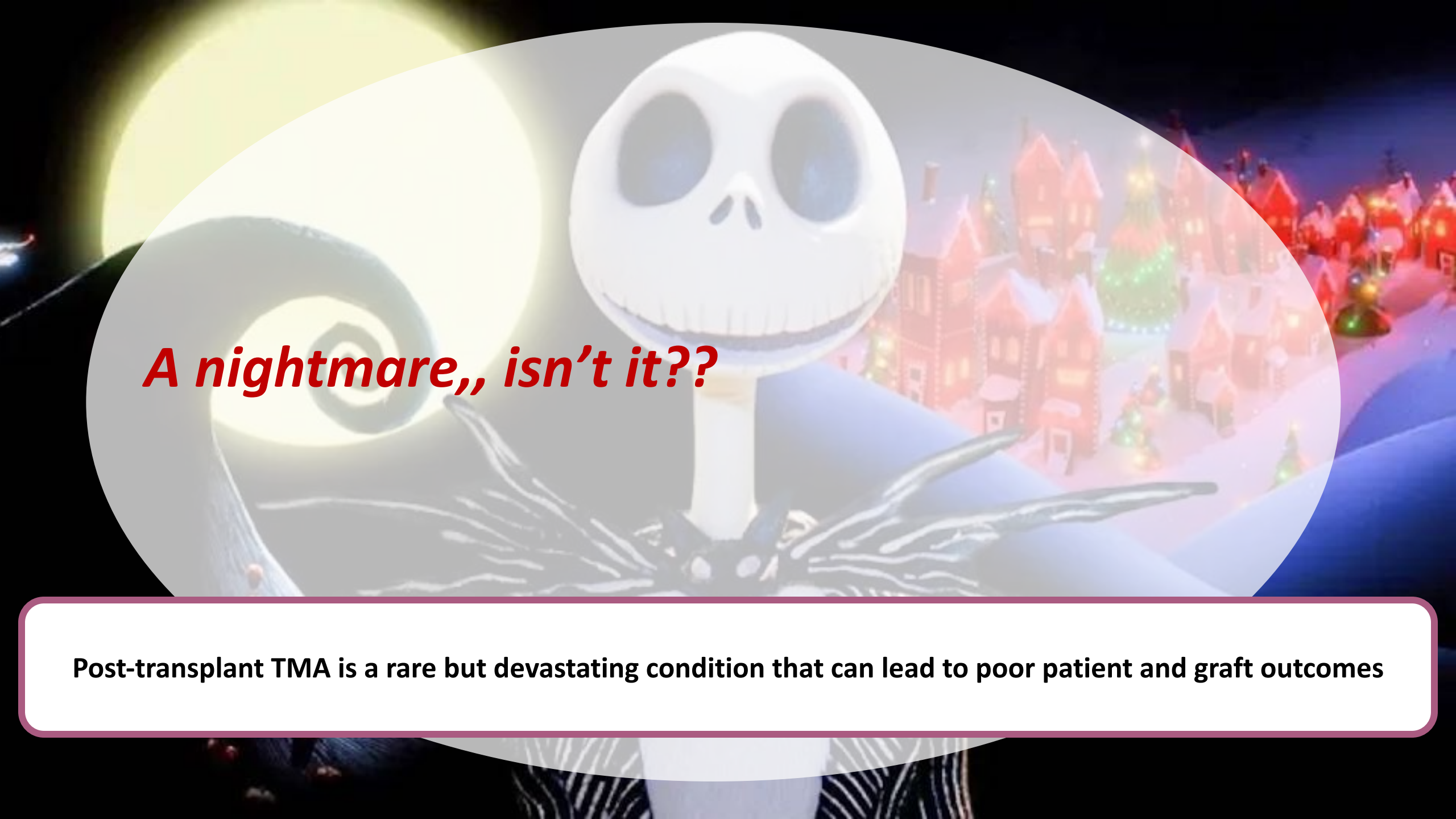
Agenda

1) Causes of PT-TMA
2) Clinical Presentation of PT- TMA
3) Histopathological findings of PT-TMA
4) Management of PT-TMA



Post-transplant TMA is a rare but devastating condition that can lead to poor patient and graft outcomes

Causes of Post-transplant Thrombotic microangiopathy

1. Caused by complement protein mutations: atypical hemolytic uremic syndrome
2. *De novo* post-transplant associated TMA or secondary aHUS
   a. Related to the type of donor and the organ procurement
      - Complement activation associated to DBD and CDC
      - Ischemia reperfusion injury
   b. Associated to post-transplant events
   - Drugs
      - Calcineurin inhibitors
      - mTOR inhibitors
   - ABMR
   - Infection
   - Viral: CMV, parvovirus, Nile fever
   - Funghi

   Antiphospholipid syndrome
   c. Other causes of TMA not related to the kidney transplant: malignancies, pregnancy, other drugs (anti VEGF, gemcitabine,…)

At the time of kidney transplantation, the coincidence of several mechanisms that activate the complement system can trigger the recurrence of aHUS in patients with a genetic background or the development of de novo PT-TMA.

PT-TMA can appear at any time in the post-transplant course, but they develop primarily ***in the first 3 months*** *after transplantation in conjunction with the presence of more complement activating events (e.g., ischemia-re-perfusion injury, high immunosuppressive drug levels, higher infectious risk).*

Post-transplant TMA

“0.8-14% of kidney TX”

The risk associated with development of PT-TMA is > in patients with history of aHUS

de novo PT-TMA
(90%)

recurrent aHUS
(10%)

Clinical manifestations of PT-TMA

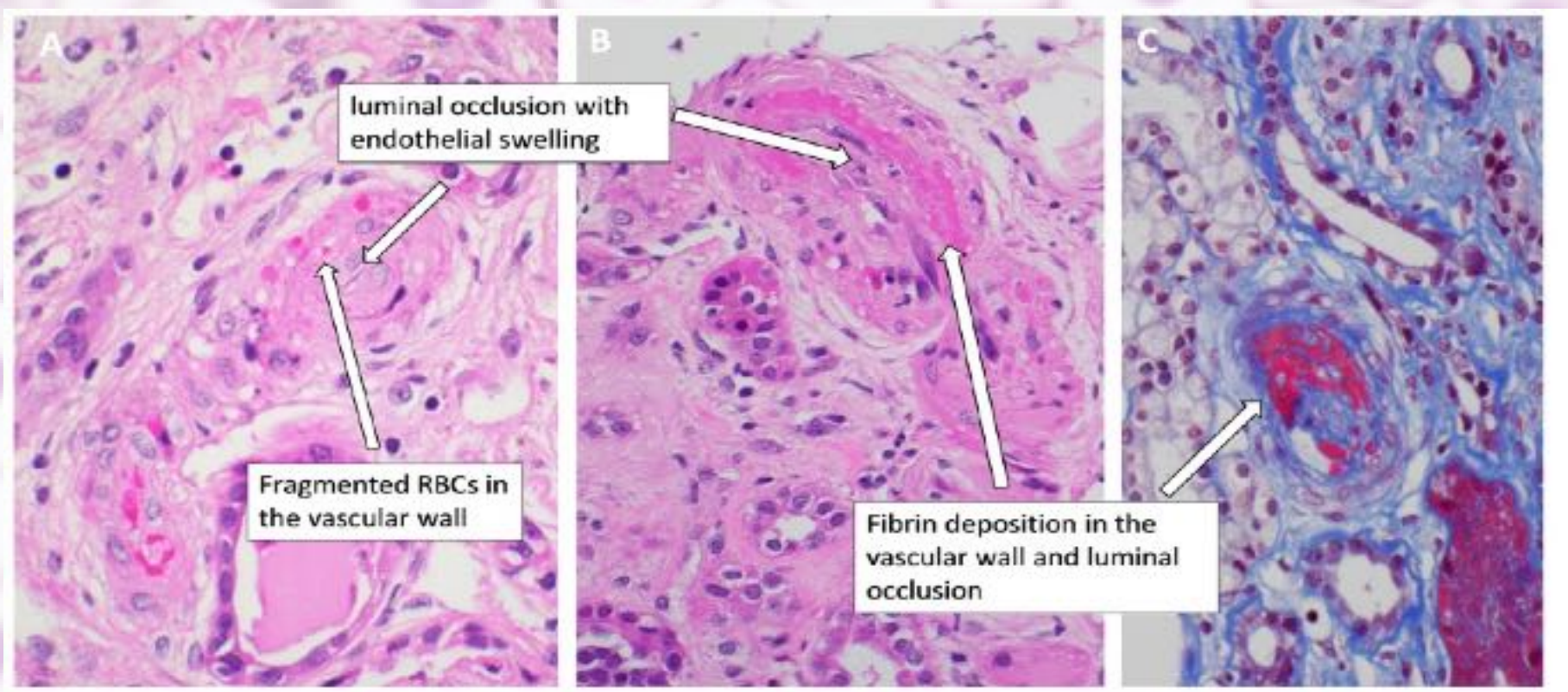
Localized form

- ✓ ***Isolated AKI*** or ***chronic*** form with slowly progressive graft dysfunction, proteinuria or difficult to control arterial HTN
- ✓ Can appear at all stages after transplantation

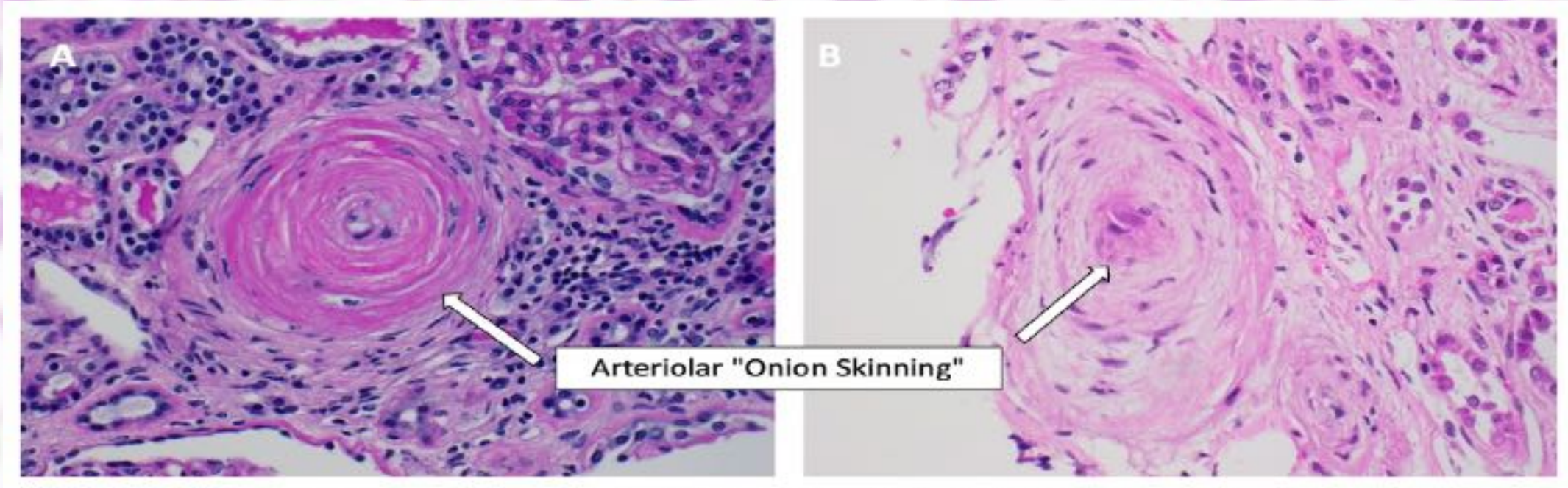
Systemic form

- ✓ ***Extra-renal manifestations*** of aHUS apart from hemolytic anemia are frequent in aHUS recurrence, but they are rarely observed in de novo PT-TMA
- ✓ Usually appears in the early post-transplant period

Histological changes of PT-TMA (active lesions)

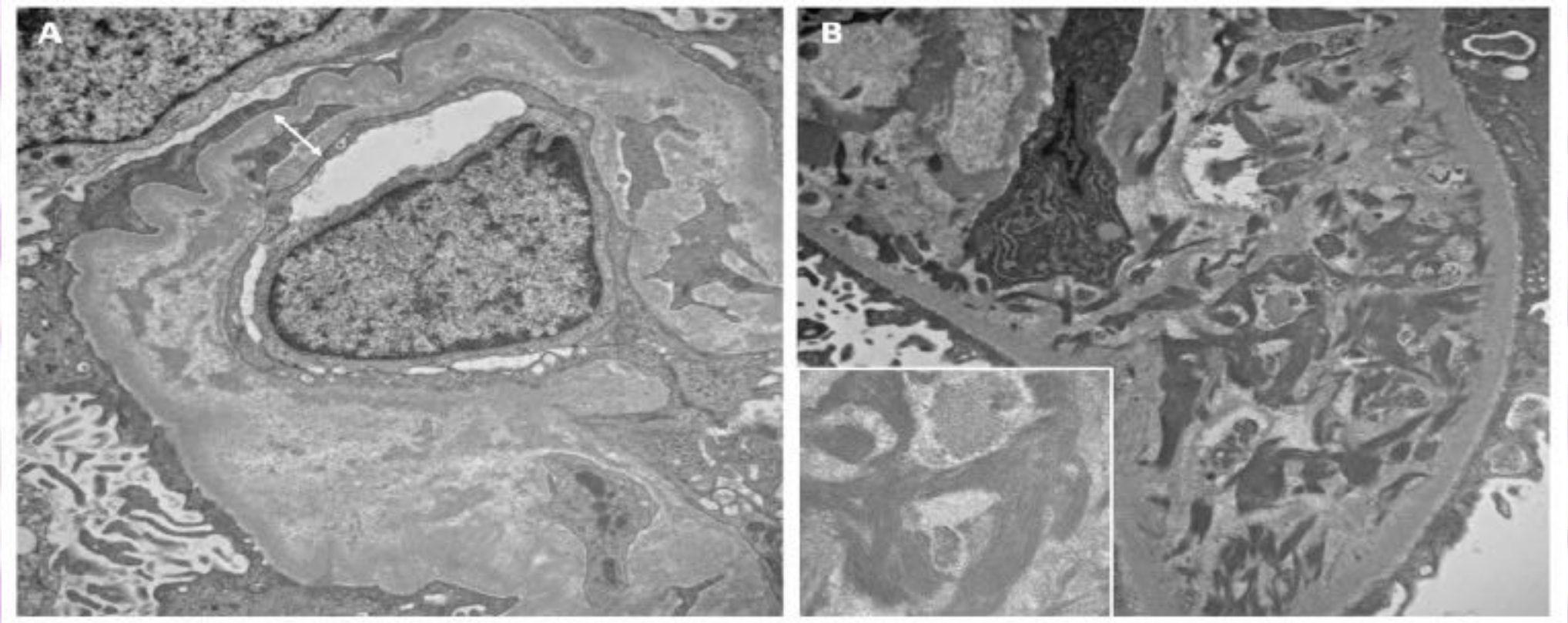


Histological changes of PT-TMA



In the chronic phase, the characteristic lesions are double contour formation in peripheral walls with hyaline deposits in arterioles and fibrous intimal thickening with concentric lamination (onion skin)

Histological changes of PT-TMA



Electron microscopy:

Chronic TMA:" GBM duplication with capillary lumen occluded with fibrin thrombi"

Histological changes of PT-TMA

- ✓ The biopsy does not allow the identification of the etiology, although some changes might suggest certain etiologies, such as C4d deposition, peritubular capillaritis, and glomerulitis in antibody mediated rejection (ABMR) or intimal thickening, reduplication of the elastic lamina, and hyaline degeneration in arterial hypertension.

After the diagnosis of TMA, the etiology of the native kidney ESRD should be investigated to rule out previously missed aHUS

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Recurrence risk of a HUS after kidney transplantation in the pre-eculizumab era

High (RR 80–90%)	- Previous recurrence - Pathogenic mutations in CFH - CFH/CFHR1 hybrid genes. >80 of recurrence rate. High graft loss risk (45, 114) - CFB > 80% of recurrence risk - TBHD = 80% (46, 47)
Moderate (RR 40–75%)	- Isolated CFI mutations. 40–60% recurrence risk (11, 39, 41, 44) - C3. 30–70%* - Detectable circulating Anti–CFH antibodies (48–50) - Two at risk CFH haplotypes (39) - Negative complement genetic study 30% (11) - Complement gene mutation of unknown significance
Low (RR <20%)	- Isolated MCP mutation+(41) - DGKε mutation (13) - Negative Anti–CFH antibodies at the time of transplantation (48–50)

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Complement Activation Related to the Donor and Procurement Process

- ✓ Activation of the complement system can be observed from earlier stages of transplant. This activation can be related to the type of donor. Increase in expression of complement factors, such as C1, C3, and CFB, in renal allograft pre-implantation and after transplantation biopsies in DBD compared with living donor (LD) biopsies

- ✓ Ischemia reperfusion damage has been associated with early injury of the renal allograft, through activating the **lectin pathway** then the alternative pathway that could amplify the injury through the release of C3, C5 & MAC.

- ✓ The damage to endothelial glycocalyx secondary to ischemia would reduce the union of factor H to the endothelial cells.

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Drug-Induced TMA

- ✓ It is suspected when there is a sudden onset acute kidney injury, usually within hours or a few days after drug exposure, and resolution can be observed when the drug is stopped or reduced.
- ✓ CNIs and de novo PT-TMA has been well documented in the literature, with the risk higher with **cyclosporine** than with tacrolimus.
- ✓ The loss of normal equilibrium between vasoactive peptides, with an increase in vasoconstrictor substances, such as angiotensin II, thromboxane A2…,
- ✓ Cyclosporine causes endothelial cells to release microparticles that activate the alternate complement pathway
- ✓ The diagnosis of CNI-related TMA is found in the early post-transplant period when the levels of these drugs are high.

Drug-Induced TMA

- It was thought that mTORi could be a good alternative to CNIs for patients with aHUS.

- Inhibition of mTOR inhibition leads to the death of endothelial progenitor cells and the decrease in renal expression of vascular endothelial growth factor (VEGF), which also would lead to a reduction in Factor H synthesis. Other factors, such as an increased procoagulant and a reduced fibrinolytic state, are also believed to contribute to the pathogenesis of TMA in patients taking mTORis.

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Antibody-Mediated Rejection-Associated TMA

- ✓ The complement system plays an important role in ABMR. The donor-specific antibodies bind to human leukocyte antigens on the allograft endothelium and activate the **classical complement pathway** through C1q, leading to activation of C4 and C3.
- ✓ The deposit of C3b on the membrane of endothelial cells triggers the activation of the **alternate complement pathway** with the generation of the MAC.
- ✓ The histological finding of TMA in patients with ABMR has wide variability, between 4 and 46%, most likely as a consequence of the focal presentation of the disease.

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Infection-Related TMA

- ✓ Viral infections can trigger PT-TMA due to the endothelial trophism of the virus, which induces the expression of adhesion molecules and the release of von Willebrand factor, causing platelet adhesion and microvascular thrombosis.
- ✓ CMV is the most frequently involved virus.
- ✓ Parvovirus , hepatitis C virus, and its treatment and fungal infections such as histoplasmosis PT-TMA have also been described.

Others

- ✓ APS can cause ESRD due to large and small kidney vessel thrombosis and TMA.

PT-TMA Prognosis is quite poor for both "the allograft & for the patient":

- ❑ Graft loss rate of 33–40% in the first 2 years
- ❑ Patient survival of 50% at 3 years after TMA diagnosis

Although **poorer** short-term graft survival had been described in patients with the **systemic form of PT-TMA**, reflecting a more severe disease with a higher incidence of dialysis-dependent AKI and plasma exchange (PE) needs, the prognosis ***in the long term*** is similar in both forms.

The prognosis is also similar in **early** (< 3 months) & **late** (> 3 months after transplantation).

Post transplant TMA Prevention

Genetics: Whom to test??

- ❑ Evaluate for genetic mutations that are associated with complement mediated TMA all patients with ESRD 2ry to HUS, TTP or other TMA, unless the disorder was clearly associated with shiga toxin-producing E.coli or other infection.

- ❑ Don’t retest those who are already evaluated (at time of diagnosis) & found to have +ve mutation.

- ❑ Re-evaluate for newly identified mutations and variants those patients previously evaluated and not found to have a mutation, prior to transplant (particularly if the initial evaluation was performed several years earlier).

Post transplant TMA Prevention

If Genetic testing is not feasible !!

- ***Prophylactic eculizumab will be kept for patients with:***

  * Well documented clinical presentation consistent with complement mediated TMA.
  * A known family history of complement mediated TMA.

Post transplant TMA Prevention

How to select kidney Donor??

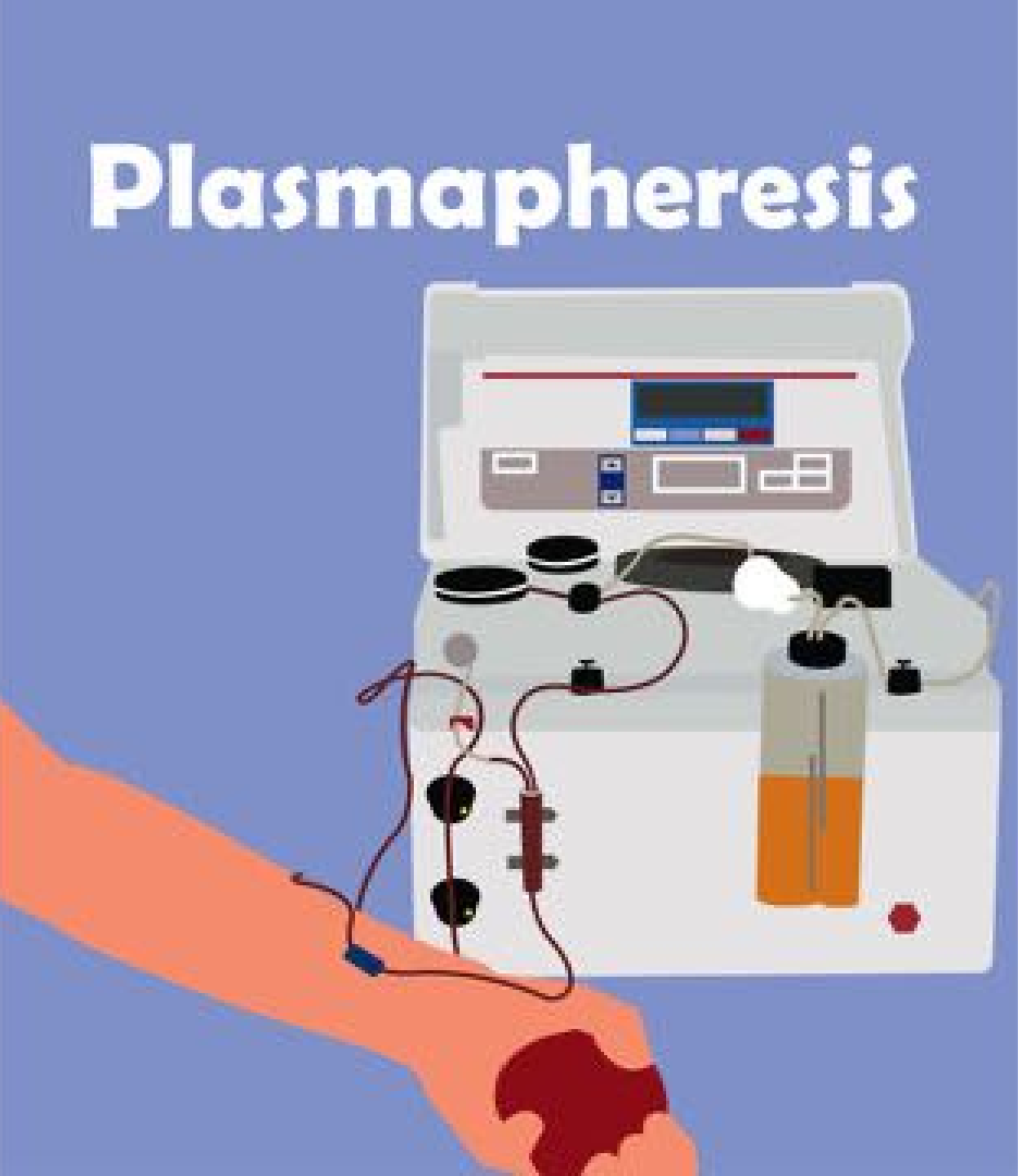
- Using a living-related donor kidney for patients with TMA attributed to a genetic mutation is avoided.
- A negative mutational analysis of a potential living-related donor does not guarantee freedom from mutations. some patients have more than one mutation, and approximately one third of patients with TMA have complement mutations presently unidentified.
- Nephrectomy may trigger complement-mediated TMA in the genetically susceptible donor.
- Living-related donors may be considered in patients with factor H-autoantibody complement mediated TMA as well as those with TMA attributed to a nongenetic

Prophylactic eculizumab In patients with complement-mediated TMA related to a genetic mutation

- In patients who are receiving a living-unrelated donor kidney, eculizumab is administrated at 900 mg intravenously 24 hours **prior to transplantation** and on **days 7, 14, and 21** following transplantation, followed by 1200 mg **every two weeks**.

- Supplemental doses (900 mg or 1200 mg) may need to be administered in settings where complement activation is known to occur, such as following surgery or when there is infection.

The duration of eculizumab therapy after transplantation is unclear. It could be discontinued with subsequent reinstitution among disease recurrence patients.



Is therapeutic plasma exchange an option??

Post transplant TMA Prevention

Combined kidney-liver transplantation??

- Carries significant potential morbidity and mortality.
- Additionally, uncontrolled complement activation precipitated by the stress of surgery has led to widespread perioperative vascular thrombosis and graft loss as the liver allograft may not function initially to produce sufficient amounts of the complement protein.
- Success has improved with the use of intensive plasmapheresis in the pre- and perioperative time to restore levels of the complement protein.
- Despite improvements in the results of simultaneous kidney-liver transplantation, this approach is not commonly used given the effectiveness of prophylactic complement inhibition.

Post transplant TMA Management

- Treatment of de novo TMA
- Treatment of recurrent TMA

Post transplant TMA Management

Treatment of de novo Post-transplant TMA

- Exclude potentially reversible causes of TMA
- Do genetic testing for those who hasn't been evaluated
- Reduce CNI dose if level is elevated or stop if markedly elevated (Tacrolimus over 15 ng/ml or cyclosporin > 400 ng/ml)
- Switching from cyclosporine to tacrolimus or vise versa is an alternative option once the acute episode of TMA resolves
- Exclude infections including cytomegalovirus (CMV), BK virus, parvovirus, and HIV. If testing for any of these infections is positive and eculizumab has not yet been initiated, infection should be treated before starting eculizumab. However, if the signs and symptoms of TMA persist or there is clinical deterioration despite treatment of an infectious agent, initiate eculizumab and continue until the infection is controlled

Post transplant TMA Management

Treatment of de novo Post-transplant TMA

- For patients with D+ve HUS & positive stool culture for shiga toxin……..Eculizumab is given until diarrhea resolves and & patient's genetic status is known.

- ADAMTS 13 is needed to exclude TTP:

If ADAMTS 13 result < 10% + "Negative genetic testing for complement mediated TMA…….Discontinue eculizumab & initiate TPE

Post transplant TMA Management

Treatment of de recurrent TMA = Eculizumab

Nearly all patients who develop recurrent TMA are assumed to have complement mediated process. However, other potential precipitating factors for TMA should be excluded

But

Exclusion of these factors for TMA shouldn't delay the initiation of eculizumab therapy

Post transplant TMA Management

Re-transplanatation

- Potential option in selected patients with recurrent or de novo TMA after transplant
- Considered in patients with graft loss due to complement mediated TMA prior to availability of eculizumab & in those with de novo TMA related to infection or medications.
- Prophylactic eculizumab is warranted in those with genetic risk but may not be necessary for those with infectious or medication related cause of TMA.
- Should be closely monitored for TMA recurrence with initiation of eculizumab if clinically indicated.

Take Home messages

- PT-TMA complicates 0.8-14% of kidney TX.
- At the time of kidney transplantation, the coincidence of several mechanisms that activate the complement system can trigger the recurrence of aHUS in patients with a genetic background or the development of de novo PT-TMA.
- Presents as localized or as systemic form.
- Proper preventive and treatment strategies should be used to protect the graft from PT-TMA


Thank You