

# **TTP as an Autoimmune Disease**

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# Case

- 43F presents with facial rash, proximal muscle weakness, dysphagia. CK found to be 12000
- EMG and muscle biopsy confirmed myositis; diagnosed with dermatomyositis

# Case

- Treatment consisted of prednisone 1mg/kg and methotrexate 15mg/week
- Clinical improvement over next several days; less dysphagia, improved muscle strength

# Case

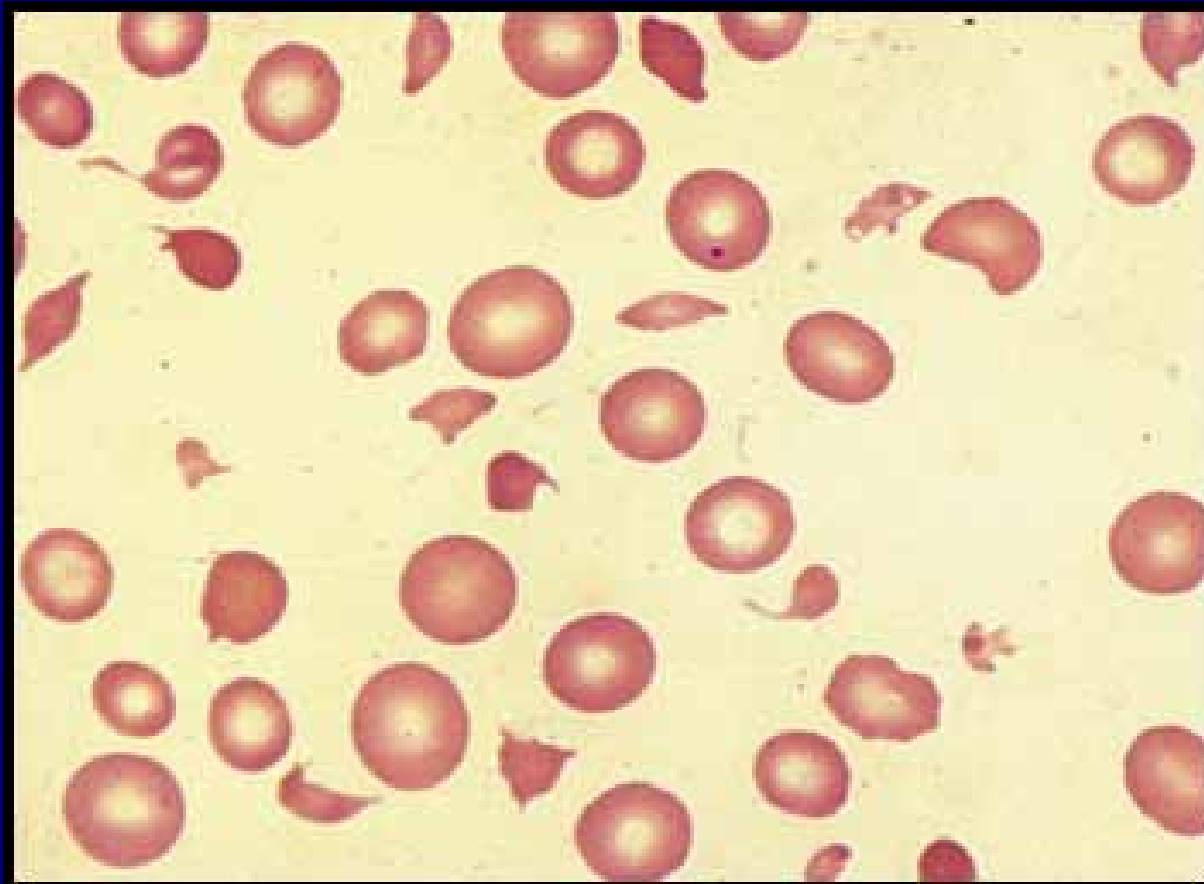
- **However, deterioration in bloodwork:**
  - HGB fell from 110 to 90 over ~72h
  - PLT fell from 165 to 50 over same time period
  - WBC unchanged at ~14
  - Bilirubin 60, mostly unconjugated
  - No change in creatinine, no fever, no mental status changes

# Case

- Over next 12h, became confused without focal deficits
- No documented temperature  $>38.0$
- Platelets fell to 20
- Biochemical evidence of hemolysis; low haptoglobin, rising bilirubin, LDH  $>1000$ . Normal fibrinogen. Negative DAT
- A diagnostic test was ordered

# Case

- **Peripheral blood film:**



**5% fragments**

# Case

- Clinical diagnosis of TTP made
- Transferred to ICU for monitoring and PLEX
- Intubated for airway protection
- MTX held; prednisone continued
- Daily PLEX x 7d

# Case

- Marked improvement; extubated after 48h
- Neurological status completely normalized
- PLT increased from nadir of 8 to 120
- HGB stabilized; hemolysis parameters improved

# Case

- Transferred to ward
- Continued to receive PLEX (which was subsequently tapered) in addition to steroids, and methotrexate was restarted
- Abdominal ultrasound showed ovarian mass
- Discharged home with rheumatology, hematology, and gynecology follow-up

# Questions

1. Is dermatomyositis known to carry an increased risk of TTP? What about other rheumatologic or autoimmune diseases?
2. How can one differentiate TTP from the other manifestations or complications of rheumatologic disease?
3. Are there differences between the management of isolated TTP and TTP associated with rheumatologic disease?

# Objectives

- Approach to the patient with a rheumatologic disease and thrombocytopenia
- Overview of TTP pathophysiology, diagnosis and management
- TTP as an autoimmune disease
- Differentiation of TTP from diseases associated with thrombotic microangiopathy
- Management considerations

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# Thrombocytopenia in Rheumatic disease

- Challenge because of the wide range of plausible etiologies
- As with many underlying diseases, question of “related or unrelated?” needs to be answered

# “Related”

- Disease process per se (e.g., a criterion for SLE)
- ITP
- TTP
- Drug-induced (marrow suppression or immune-mediated)
- Hematologic malignancy (e.g., lymphoma secondary to Sjogren's, RA)
- Specific disease-associations (e.g., Felty's syndrome with splenomegaly and sequestration, antophospholipid antibody syndrome)

# “Unrelated”

- **Pseudothrombocytopenia- platelet clumping**
- **Decreased production**
  - Viral (HIV, rubella, parvo, HCV, EBV, varicella)
  - Toxins (EtOH, chemotherapy, chemicals)
  - Drugs (sulfa, thiazides)
  - Marrow replacement (granulomatous disease, hematologic malignancy)

# “Unrelated”

- **Destruction**

- Post-transfusion
- DIC
- Other MAHA (e.g., HELLP, HTN)
- HUS
- Drug-induced (e.g., quinine, sulfa, vancomycin, penicillins, HIT)

- **Sequestration**

- Splenomegaly
  - Portal hypertension, many other etiologies

# Basic Workup

- **Detailed history and physical**
- **CBC and blood film**
- **Bone marrow aspiration and biopsy**
  - Generally indicated if severe enough to cause bleeding risk unless patient is <60 with no etiology other than ITP suggested on blood film

Normal to increased megakaryocytes suggests peripheral destruction; decreased or absent is decreased production. May see evidence of malignancy or granulomata

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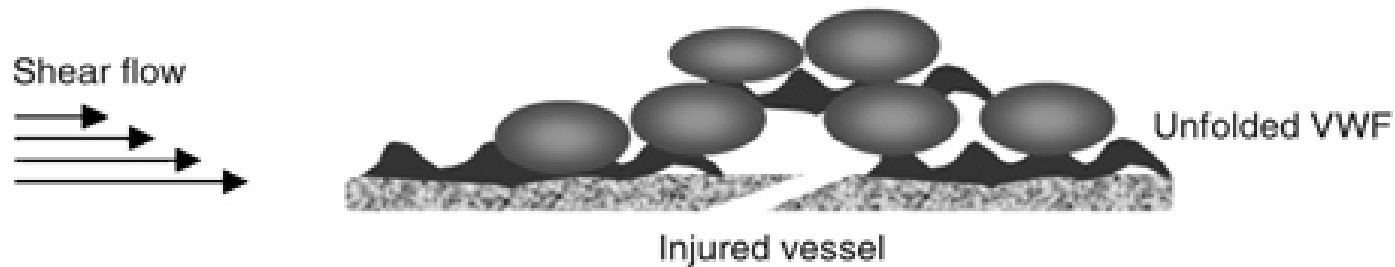
# TTP

- Microangiopathic hemolytic anemia and thrombocytopenia in adults without alternative cause, which may (but does not have to) be associated with neurological or renal abnormalities
- This is the terminology used regardless of possible etiology and regardless of associated conditions

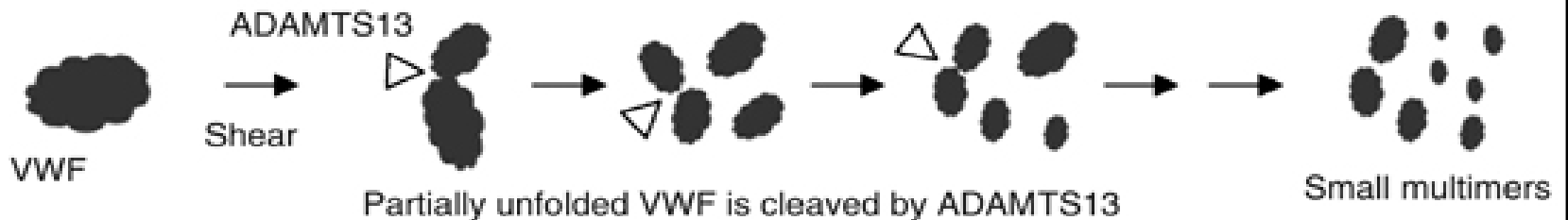
# Pathophysiology

- Congenital (rarely) or acquired deficiency of von Willebrand factor cleaving protease called ADAMTS13 (discovered in 2001)
- Lack of protease causes increased platelet aggregation to vWF multimers, causing microvascular thrombi and consumptive thrombocytopenia
- Acquired ADAMTS13 deficiency is often antibody-mediated

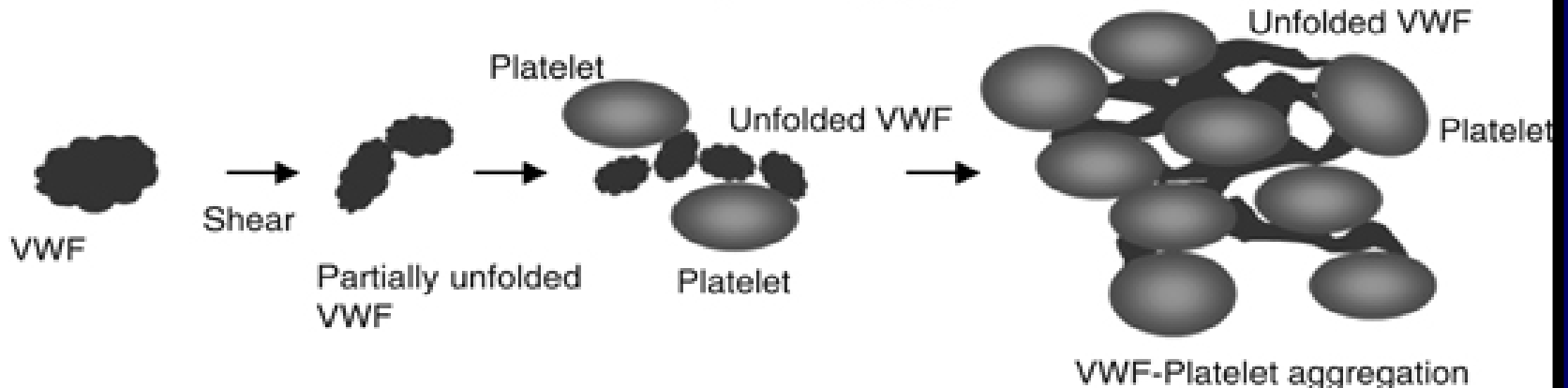
**a** Injury to arterioles or capillaries: VWF attached to the vessel wall quickly unfolds under high shear to provide the substrate for platelet adhesion and aggregation  
 VWF-platelet aggregate



**b** Normal circulation: Multimers become progressively smaller due to cleavage by ADAMTS13



**c** TTP with ADAMTS13 deficiency: Large multimers are unfolded by shear stress, causing intravascular platelet aggregation and thrombosis



# Diagnosis

- In the pre-plasma exchange era, mortality was 90% from systemic microvascular thrombosis leading to MI, renal failure, stroke
- Traditionally taught progressive pentad is MAHA, thrombocytopenia, neurological deficit, renal failure, and fever
- More recently, MAHA and thrombocytopenia without alternative explanation are accepted indications for PLEX

# Diagnosis

- Need high index of suspicion to make the diagnosis
- Diverse clinical features because of microvascular thrombi in many organs
- Half of patients have neurological involvement (anything)
- Fever is uncommon
- 1/3 of patients have decreased GFR, but ARF is uncommon

# Diagnosis

- Laboratory data is key to the diagnosis
- Schistocytes are a sine qua non (>1% supports, but mean is ~8%), however although non-specific, becomes more specific with increasing %
- Evidence of hemolysis with negative DAT and IAT supports, but is nonspecific by itself
- The role of measurement of ADAMTS13 is unclear; it is currently a research assay; severe deficiency is present in 33-100% of patients depending on study

# Differential Diagnosis

- Differential diagnosis for this presentation includes sepsis, disseminated cancer, malignant hypertension, HELLP
- The presence of DIC makes TTP less likely and increases the likelihood of cancer and sepsis

# Management

- PLEX is only evidence-based therapy; was significantly better than plasma infusion in 1991 RCT published in NEJM
- 6-month survival was 78% vs. 63% (p=0.04)
- FFP is indicated until PLEX is available
- Thought to work by replacing ADAMTS13 and possibly removing antibodies to it

# Management

- In cases of presumptive acquired ADAMTS13 deficiency, immunosuppressive therapy is often used to induce remission
- There are no randomized trials to guide therapy
- Most commonly used are prednisone 1mg/kg, or methylprednisolone pulse 1g/d x 3
- Other case series have suggested benefit with rituximab, cyclophosphamide, and cyclosporine. Trials are ongoing to determine role of adjuvants to PLEX

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# Autoimmunity and TTP

- “Secondary TTP” is characterized by normal levels of ADAMTS13; this is associated with autoimmune hemolysis, DIC, cancer, pre-eclampsia, malignant hypertension, calcineurin inhibitors
- Although plasma exchange is often used in these cases, its benefit is questioned

# Autoimmunity and TTP

- “Primary” or “idiopathic” TTP refers to cases where extremely low ADAMTS13 level is the primary driver of the disease
- This may be congenital (rarely) and these patients have recurrent TTP
- Many of the remaining idiopathic TTP cases are presumed to have an autoimmune basis

# Autoimmunity and TTP

- In a 2006 French cohort study, 21/33 cases of idiopathic TTP had detectable inhibitory anti-ADAMTS13 antibodies
- Patients with antibodies required significantly longer achieve remission (23d vs. 7d of PLEX)
- Mortality was non-significantly higher (4/21 vs 0/12) in the group with antibodies
- Recurrence rate was not found to be different

# Autoimmunity and TTP

- PLEX has been shown to increase ADAMTS13 levels and decrease inhibitor levels, but this does not always correspond to disease activity or prognosis

# Autoimmunity and TTP

- A 2008 Italian registry study showed that the presence of measurable anti-ADAMTS13 antibodies carried a 3-fold increased risk of relapse (overall 20-50% of patients relapse)
- However, the mortality rate seems to be higher for patients with “secondary” TTP, presumably because of the underlying disorder (e.g., cancer, stem cell transplant, etc)

# Autoimmunity and TTP

- Many cases of 'idiopathic' TTP are therefore autoimmune; the presence of detectable anti-ADAMTS13 antibodies has unclear prognostic value
- PLEX appears to 1) replenish ADAMTS13 and 2) remove inhibitor
- The presence of antibodies may carry a higher risk of recurrent episodes

# Autoimmunity and TTP

- This autoimmune basis probably explains the higher risk of TTP in patients with other autoimmune or rheumatologic conditions, as in the case presented

# TTP in Setting of Known Autoimmune Disease

- Lupus (by far the most common)
- Dermatomyositis
- Polymyositis
- Sjogren's
- Adult-onset Still's disease
- Rheumatoid arthritis
- Myasthenia gravis
- Ulcerative colitis
- Ankylosing spondylitis
- PAN
- Graves' disease
- Autoimmune hepatitis

# TTP and SLE

- Although the incidence of TTP is higher in SLE than the general population incidence of 4-10/million, exact incidence is unclear
- A retrospective review identified SLE-associated TTP patients to be younger, presented more subacutely, and had higher mortality than other idiopathic TTP
- Interestingly, 50% of patients with TTP but not SLE had positive ANA

# TTP and SLE

- Another single-centre study identified 26/1203 patients with SLE admitted had TTP
- Independent risk factors for TTP vs. other reasons for admission of SLE patients were higher disease activity (SLEDAI) and coexisting nephritis
- Mortality among SLE patients admitted with TTP was 46%

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# Diagnostic Challenge of TTP in SLE

- Microangiopathic change and multiorgan involvement in SLE raises many possibilities, which may be difficult to differentiate
- Antiphospholipid antibody syndrome, catastrophic antiphospholipid antibody syndrome, SLE flare with hemolytic anemia, small-vessel vasculitis, and malignant hypertension can all have similar features

# Features of TTP vs. SLE

Laboratory or clinical characteristic	Thrombotic thrombocytopenic purpura	Malignant hypertension	Antiphospholipid syndrome	Systemic lupus erythematosus
Thrombocytopenia	Consumptive	Consumptive	Immune-mediated	Immune-mediated
Hemolytic anemia	Microangiopathic	Microangiopathic	Immune-mediated	Immune-mediated
Thrombotic microangiopathy	Diffuse	Diffuse	Renal, not diffuse	Renal, not diffuse
Schistocytes	Present <sup>a</sup>	Present <sup>a</sup>	Absent	Rare (spherocytes more likely, from antibodies to red blood cells and spleen)
Direct Coombs' test	Negative	Negative	Positive or negative	Positive or negative
Complement	Normal	Normal	Normal	Low
Fever	Present <sup>a</sup>	Absent	Absent	Present <sup>a</sup>
Renal abnormalities	Present <sup>a</sup> (platelet-rich thrombi)	Present <sup>a</sup> (arteriolar fibrinoid necrosis, onion-skin lesions)	Present <sup>a</sup> (arteriosclerosis, fibrous intimal hyperplasia, arterial occlusions, thrombotic microangiopathy, organizing thrombosis)	Present <sup>a</sup> (both thrombotic microangiopathy and nephritis on biopsy)
Central nervous system symptoms	Present <sup>a</sup> (delirium, seizures, hemiparesis, aphasia, visual-field defects)	Present <sup>a</sup> (papilledema, headache, visual disturbance, transient ischemic attack, seizures)	Present <sup>a</sup> (transient ischemic attack or cerebrovascular accident)	Present <sup>a</sup> (cerebritis, cerebrovascular accident, myelitis, seizures)

# Distinguishing Among Microangiopathies

- Initial BP (esp. dBP > 130, prior significant HTN)
- Antiphospholipid antibodies
- Extent of fragmentation on blood film (expected to be higher in TTP, but may be present in APLA, esp. if catastrophic)
- ADAMTS13 level may be helpful here, but remains a research tool

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# Management of SLE-Associated TTP

- All patients with suspected TTP should be treated with PLEX (recall 90% pre-PLEX mortality)
- Because TTP is associated with high SLE activity, specific immunosuppressive therapy for both is usually used after PLEX

# Management of SLE-Associated TTP

- There are many case reports and series of success of rituximab in treating patients with SLE-associated TTP
- A randomized clinical trial is underway in Canada to evaluate the benefit of adding rituximab to PLEX in all patients with TTP
- Research into ADAMTS13 assay as a prognostic tool may identify a group more likely to respond to rituximab

# Summary

- Recent research has elucidated the pathophysiology of TTP, and many (possibly the majority) of cases have an autoimmune basis
- This probably explains the many case series and reports of TTP coexisting with many autoimmune diseases, most prominently SLE
- There is considerable overlap between TTP and other microangiopathies that can be seen in SLE and other autoimmune diseases

# Summary

- Some clinical and laboratory features can be useful differentiators
- When TTP seriously considered, PLEX is indicated, and is a life-saving therapy
- Immunosuppressive therapy post-PLEX is commonly used, but there is little evidence to guide clinicians
- Rituximab shows promise as an adjunct to PLEX, especially in the autoimmune disease-associated population