EHA-TSH Hematology Tutorial on Immune Hematological Disorders

Self-assessment Case – Acquired Thrombotic Thrombocytopenic Purpura

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Introduction

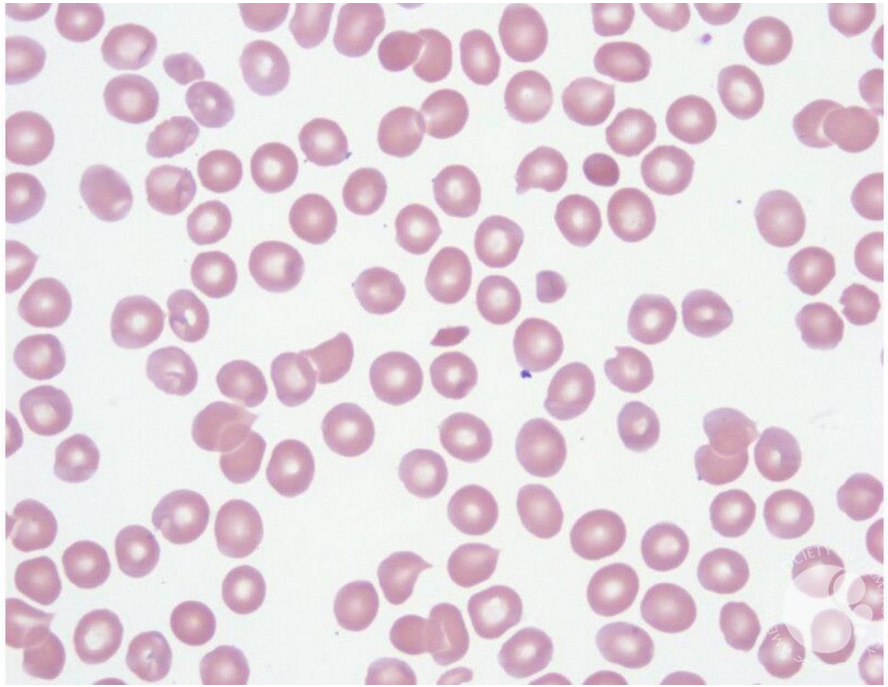
- A 35-year-old woman presented with fatigue, malaise, fever and petechia in her legs.
- Laboratory evaluation showed
  - WBC 5.7 x 10^9/l
  - Hb 84 g/l
  - Hct 0.25
  - MCV 84 fl
  - Platelet count 24 x 10^9/l
  - International Normalized Ratio (INR) 1.4
  - Reticulocyte count 7.4 %
  - Total bilirubin 2.4 mg/dl (0.3–1.0 mg/dL)
  - Lactate dehydrogenase (LDH) 1473 U/L

History

- No history of any known or illicit drug use
- No history of herbal medication
- No history of solid organ or stem cell transplantation
- No history of cancer

Q1) Which of the following is the most appropriate diagnostic test to perform next ?

1. ADAMTS13 activity level
2. Osmotic fragility test
3. Peripheral blood film
4. FLAER (fluorescein-labelled proaerolysin) test
5. Faecal occult blood test



Blood film of a similar patient

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Blood film

- The blood film findings and interpretation
  - Schistocytes (fragmented erythrocytes).
  - Schistocytes are smaller than red blood cells, lack central pallor and have sharp angles and/or straight borders.
  - Schistocytes are likely to be seen in haemolytic anemia, especially microangiopathic haemolytic anemia (MAHA).
  - Breakdown of erythrocytes, which pass through the platelet-fibrin network in the micro-thrombus formed in the capillary and arteriole system, at high blood flow rate.

- According to results, MAHA and thrombocytopenia is confirmed and TTP is suspected.
- Any patient with MAHA and thrombocytopenia should be considered as TTP until proven otherwise.
- ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity and antibody levels ordered.
- More test results:

  Prothrombin time and activated partial thromboplastin time were normal

  Direct antiglobulin test (DAT): negative

Q2) Which of the following is **NOT** a step in the diagnosis of suspected TTP?

1. Assess organ damage
2. Evaluate clinical predictive scoring systems
3. Wait for ADAMTS13 test results
4. Consider differential diagnosis
5. Check B12 level

- TTP is a haematological emergency.
- ADAMTS13 activity levels should not be waited to take action.
- Clinical prediction scores of severe ADAMTS13 deficiency should be evaluated.
- TPE (therapeutic plasma exchange) and corticosteroids should be started according to clinical risk assessment.

Q3) What percent of patients in the Oklahoma TTP HUS registry manifested with classic pentad (thrombocytopenia, microangiopathic haemolytic anaemia, neurological abnormalities, renal failure and fever) ?

1. 10%
2. 20%
3. 30%
4. 40%
5. 50%

- TTP has classically been defined by a pentad of clinicopathological signs and symptoms: thrombocytopenia, microangiopathic haemolytic anaemia, neurological abnormalities, renal failure and fever.
- However, in real life It may be too late to wait for all of these findings.
- In reality, TTP does not often manifest with the “classic pentad,” as only 10% of the Oklahoma TTP-HUS registry presented in this way.

- ***George JN Blood 2010***

- The almost constant signs of TTP remain severe thrombocytopenia (typically <30 x 10^{9}/L) and microangiopathic haemolytic anaemia.
- When evaluating a patient with MAHA and thrombocytopenia, the first step is to distinguish those who are likely to have TTP and would benefit from TPE treatment.
- There are several clinical prediction scores (PLASMIC, French, Bentley)
- Rather than excluding the possibility of TTP or confirming the diagnosis, these scorings are the intended use of clinical prediction scores is to enhance the physician's clinical judgment and guide initial management.

Q4) Which of the following is **NOT** a component of the PLASMIC score ?

1. Platelet count
2. Serum creatinine level
3. History of solid organ or stem cell transplantation
4. Reticulocyte count
5. D-dimer level

Parameters	Scoring
Platelet count <30 × 10^9/L	+1
Serum creatinine level <2.26 mg/dL	+1
Hemolysis Indirect bilirubin >2 mg/dL or reticulocyte count >2.5% or undetectable haptoglobin	+1
No active cancer in previous year	+1
No history of solid organ or Stem cell transplant	+1
INR < 1.5	+1
MCV < 90 fL	+1

PLASMIC score

- Developed by the Harvard TMA working group in 2017.

- Low risk: 0-4 points,
- Medium risk: 5 points,
- High risk: 6-7 points

- Predicts likelihood of severe ADAMTS13 deficiency (defined as < 10 %)

- 0-4 points: 0%-4%
- 5 point: 5%-24%
- 6-7 points: 62%-82%

Bendapudi KP et. al. Lancet Haematol 2017

- Patient has 7 points according to PLASMIC score; high risk for severe ADAMTS13 deficiency.
- TPE and steroids started immediately.
- The pending results of ADAMTS13 activity and inhibitor results were obtained.
- ADAMTS13 activity 0.2% iu/ml
- ADAMTS13 inhibitor 67.96 ıu/ml

- After seven TPE procedures patient has sustained thrombocyte count ≥150 × 10^9/L
- LDH levels were below 1.5 times upper normal limit.
- There is no clinical evidence of new or progressive ischaemic organ injury

Q5) According to revised outcome definitions of immune TTP (iTTP), in which category does the patient's condition fit?

1. Clinical response
2. Clinical remission
3. Partial ADAMTS13 remission
4. Complete ADAMTS13 remission
5. I am not sure

- Clinical remission: sustained **Clinical Response** with either (a) no TPE and no anti-VWF therapy for ≥30 days or (b) with attainment of **ADAMTS13 Remission** (partial or complete), whichever occurs first.
- Partial ADAMTS13 remission: ADAMTS13 activity ≥20 to <LLN
- Complete ADAMTS13 remission: ADAMTS13 activity ≥LLN
- Clinical response: sustained platelet count ≥150 × 10^9/L and LDH < 1.5 times ULN and no clinical evidence of new or progressive ischaemic organ injury

LLN, lower limit of normal;
ULN, upper limit of normal;
VWF, von Willebrand factor

- ***Adam Cuker et. al. Blood 2021***

- After a clinical response TPE was stopped and steroids tapered.
- Patient has been discharged from hospital and scheduled for weekly visits in the first month and then biweekly visits in the following month.
- Surveillance for ADAMTS13 activity level could not be performed.

Follow-Up

- 3 months after the last TPE, the patient presented with mild anaemia, thrombocytopenia and a mild elevation in LDH
- Hb 104 g/l
- Hct 0.31
- MCV 87 fl
- Platelet count 86 x 10^9/l
- LDH 289 U/L

- Other causes of anaemia and thrombocytopenia were ruled out.
- ADAMTS13 activity level was 5.6%
- Thrombocytopenia and severe ADAMTS13 deficiency were confirmed.
- According to **revised outcome definitions for iTTP**, a clinical relapse was confirmed.

- ***Adam Cuker et. al. Blood 2021***

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Q6) What is the best treatment choice for this patient ?

1. TPE and steroids
2. TPE, rituximab and, if available, caplacizumab
3. N-acetylcysteine
4. Ciclosporin
5. Bortezomib

- According to ISTH guidelines, patients with high risk of iTTP or an ADAMTS13 level <10% should be treated with triple therapy consisting of TPE, caplacizumab and immunosuppressives (e.g., corticosteroids and rituximab).
- However, rituximab and caplacizumab may be withheld or delayed for those with intermediate to low probabilities of iTTP until a positive ADAMTS13 result (e.g., ADAMTS13 activity <10 iu/dL or <10% of normal) is obtained.

- ***X. Long Zheng et. al. Thromb Haemost. 2020***

Feedback

Q1 The first step in evaluating a patient with thrombocytopenia and MAHA is to confirm with a peripheral blood film.

Q2 ADAMTS13 test results should not be waited for in suspected TTP patients.

Q3 Only a minority of patients present with classical pentad of TTP so waiting for these disease features would be too late.

Feedback

Q4 Clinical risk assessment scores and especially PLASMIC score should guide clinicians in the emergency care.

Q5 Clinical response is defined as sustained platelet count ≥150 × 10^9/L and LDH <1.5 times ULN and no clinical evidence of new or progressive ischaemic organ injury

Q6 According to ISTH guidelines, triple therapy with TPE, caplacizumab and immunosuppressives (e.g., corticosteroids and rituximab) should be regarded as first line option if available.

Discussion

- TTP should be suspected in any case with MAHA and thrombocytopenia until proven otherwise.
- Clinical prediction scoring is used in the management of patients with thrombotic microangiopathy.
- Among these scorings, PLASMIC score is the most suitable for daily practice and is used more frequently.
- It would be appropriate to use the PLASMIC score in the initial evaluation of patients in the emergency department.
- Targeted therapies are incorporating into the treatment paradigm for acquired TTP.

References

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