CASE REPORT

Thrombotic microangiopathy associated with *Mycoplasma pneumoniae* infection

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SUMMARY

Thrombotic microangiopathy (TMA) comprises a process of sequential endothelial damage, microvascular thrombosis, consumptive thrombocytopenia and microangiopathic haemolytic anaemia that can affect several organs, including the kidney. A 36-year-old woman was presented with a petechial rash 3 weeks after an upper respiratory tract infection. Laboratory results showed normocytic normochromic anaemia, thrombocytopenia and evidence of TMA with decreased haptoglobin, elevated serum lactate dehydrogenase and a peripheral blood smear with numerous schistocytes. Treatment included daily plasmapheresis and prednisolone, with favourable clinical evolution. Antibodies anti-ADAMTS13 were positive, establishing the diagnosis of acquired thrombotic thrombocytopenic purpura. There was also serological evidence of a recent infection by *Mycoplasma pneumoniae*, and therefore the preceding respiratory tract infection by this agent was the most likely trigger for the disease. Due to the high mortality rate and poor outcomes, the prompt diagnostic and treatment are crucial in this rare disease. The identification of triggers related to this pathology can allow new therapeutic targets or preventive strategies.

BACKGROUND

Thrombotic microangiopathy (TMA) comprises a process of sequential endothelial damage, microvascular thrombosis, consumptive thrombocytopenia and microangiopathic haemolytic anaemia.¹ The formation of thrombi in the microcirculation and the swelling of the damaged endothelium cause ischaemia and infarction of several organs, including the kidney, brain, heart, lung, liver and intestine.²

Depending on the prevailing clinical manifestations, renal or cerebral, two different entities were formerly considered: haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP).³ However, according to recent advances in the comprehension of the physiopathological mechanisms, TMA can assume different terminology but represents no more than the final common pathway of endothelial damage and dysfunction.⁴

The formerly called typical HUS is now referred as infection-induced HUS and is caused by shiga toxin-producing bacteria (*Escherichia coli* and *Shigella dysenteriae* type I); *Streptococcus pneumoniae*, influenza A virus, H1N1 and HIV are other identified causes of infection-induced HUS⁵; atypical HUS can be triggered by genetic or acquired

defects in complement system alternative pathway regulators,⁶ as well as by multiple drugs⁷; TTP is caused by reduction of the levels or disruption of the ADAMTS13 protease activity, congenital or immune mediated.^{8,9} De novo post-transplant TMA, cobalamin C defect-HUS and diacylglycerol kinase ϵ mutations-related HUS are additional uncommon causes of TMA.^{10–13}

Complement system hyperactivation causing endothelial inflammation and thrombogenic status induction was highlighted as a main common pathogenic effector or amplifier in the majority of these diseases,¹⁴ allowing new therapeutic options.¹⁵

A high degree of clinical suspicion and a correct differential diagnosis are fundamental to optimally treat these high morbidity-associated and mortality-associated diseases. In this case report, we present a rare and aggressive form of TMA and suggest an interesting possible aetiology.

CASE PRESENTATION

A 36-year-old woman presented to the emergency department after 4 days with increasing oedema and cutaneous rash in both hands and lower limbs. Three weeks earlier, she had undergone an upper respiratory tract infection.

She had a past medical history of hypothyroidism, on levothyroxine and oral contraceptive. No relevant familiar history. She had an high education level, living in a city, without close contact with animals or recent travels to other countries.

On clinical examination, she had no fever and her vital signs were within the normal range. There were scattered monomorphic petechial lesions all over her skin, more predominant in the lower limbs and face. The remaining clinical examination was unremarkable.

After 24 hours, she developed temporospatial disorientation and confusion.

INVESTIGATIONS

Laboratory results showed normocytic normochromic anaemia (Hb 8.8 g/dL) and severe thrombocytopenia ($5 \times 10^9/L$). White cell count and C-reactive protein were both slightly elevated ($15.3 \times 10^9/L$ and 5.6 mg/dL, respectively) but the initial microbiological screening (blood and urine cultures, viral panel including HIV, hepatitis, Epstein-Barr virus and cytomegalovirus) was negative. Coagulation studies were normal (prothrombin time 10.6 s, activated partial thromboplastin time 28.3 s) and the direct and indirect Coombs tests

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were negative. Complement C3 level was normal (92 mg/dL) but C4 was decreased (8 mg/dL), suggestive of complement classic pathway activation. Antinuclear and anti-dsDNA antibodies were negative. Urea and creatinine levels were within the normal range (32 mg/dL and 0.65 mg/dL, respectively) and urinalysis showed no pathological findings. Liver function tests had no significant changes (total bilirubin 1.29 mg/dL, direct bilirubin 0.29 mg/dL, alanine transaminase 10 U/L, aspartate transaminase 46 U/L, gamma-glutamyltransferase <10 U/L and alkaline phosphatase 61 U/L). The immunological pregnancy test was negative.

After 24 hours under observation, a significant decrease in haemoglobin occurred (Hb 6.1 g/dL). An undetectable level of haptoglobin (<7 mg/dL) and an elevated serum lactate dehydrogenase (7432 U/L), alongside a peripheral blood smear showing numerous schistocytes, supported the suspicion of a thrombotic microangiopathy.

Antibodies anti-ADAMTS13 were present in a high titer (>102.7 U/mL) confirming TTP diagnosis. In the serological screening for infectious diseases performed at hospital admission, we found a remarkable positivity for *Mycoplasma pneumoniae* IgM and IgG antibodies (>100 UA/mL and 160 UA/mL, respectively).

The plasma ADAMTS13 enzyme activity test was not available in our institution at the beginning of this clinical case. It was performed later, 1 month after clinical resolution, and its normal result supported the diagnosis of acquired, and not congenital, TTP.

DIFFERENTIAL DIAGNOSIS

A normal coagulation study precluded the hypothesis of disseminated intravascular coagulation and the negative Coombs tests ruled out the hypothesis of Evans syndrome.

Considering the evidence of TMA without systemic lupus erythematosus criteria, pregnancy, severe hypertension or active infection, the main differential diagnoses were non-infectious causes of HUS and acquired TTP. The absence of renal failure and the neurological presentation was more characteristic of TTP, but the ultimate distinction between these two entities is only assured by the result of ADAMTS13 activity.

TREATMENT

Daily plasmapheresis with 1.5 volume exchange with plasma and prednisolone 60 mg/day were immediately prescribed, even before the anti-ADAMTS 13 assay result was available.^{16 17}

OUTCOME AND FOLLOW-UP

On the 19th day of treatment, after four consecutive days with sustained normal platelet count, normal lactate dehydrogenase and stable haemoglobin, plasmapheresis was suspended. Two days later, thrombocytopenia relapsed, so the apheresis was reinitiated and maintained for an additional 15 days. Prednisolone was gradually reduced in the following 6 months and then stopped. There were no relapses at 24 months of follow-up.

DISCUSSION

TTP is a rare and aggressive form of thrombotic microangiopathy, with an annual incidence of approximately four cases per million people.³ Mortality remains high (15%–20%) despite treatment with plasmapheresis.¹⁸

We present a case report of a *M. pneumoniae* infection preceding an acute episode of immune-mediated or acquired

Learning points

- ▶ Thrombotic microangiopathy should be part of the differential diagnosis of anaemia and thrombocytopenia.
- ▶ It is fundamental to have a high index of suspicion in order to diagnose and promptly treat this life-threatening pathology.
- ▶ With the improved knowledge of the thrombocytopenic purpura pathogenic mechanisms, new therapeutic approaches like the monoclonal antibody against CD20, rituximab, are now available and novel targets are under investigation.
- ▶ Since the aetiology is not routinely investigated during the approach of this pathology, the association with *Mycoplasma pneumoniae* may indeed be underestimated.

TTP. We found only four previous case reports of this unusual association.^{19–22}

Diagnosis of TTP should be suspected when thrombocytopenia coexists with microangiopathic haemolytic anaemia without a recognised cause.¹ The aetiological feature that definitely distinguishes TTP from the other causes of TMA is a severely decreased activity of the metalloprotease ADAMTS13, the protease responsible by cleaving the highly thrombogenic ultralarge von Willebrand factor (ULvWF) multimers into smaller fragments.²³ Accumulation of intact ULvWF multimers results in platelet aggregation and thrombus formation, mostly at arterioles and capillaries, where the elevated shear stress promotes platelet aggregation.²⁴

TTP can be congenital (Upshaw-Schulman syndrome) when caused by mutations in the *ADAMTS13* gene,⁸ leading to impaired secretion of the protease from the endothelial cells or compromised catalytic activity.²⁵ However, in the majority of the cases, TTP is entitled acquired and is the result of an autoantibody-mediated ADAMTS13 dysfunction. In its turn, acquired TTP is classified as secondary if a cause is identified (pregnancy, autoimmune diseases, HIV infection, metastatic cancer).

The laboratorial diagnosis of TTP relies on the demonstration of plasma ADAMTS13 enzyme activity below 10%. After this result, autoantibodies directed against ADAMTS13 should be assessed in order to distinguish acquired from congenital TTP.²⁶ Antibody titers are directly correlated with disease severity and probability of relapse.^{27–29}

It has been suggested that autoantibodies formation, in acquired TTP, can be induced by exposure to exogenous antigens presenting molecular mimicry with ADAMTS13.²⁵ T cell presentation of pathogen-associated molecular patterns (PAMPs) homologues to the ADAMTS13-derived peptides was shown to be a potentially trigger of this autoimmune reactivity.³⁰

The possible association between a *M. pneumoniae* infection and TTP described in this case report insinuates the existence of a molecular mimicry between *M. pneumoniae*'s PAMPs and some domain of the ADAMTS13 molecule, promoting this cross-reacting autoimmune response.^{19–21}

Distinguishing congenital from acquired TTP is essential for the treatment selection.³¹ In the congenital TTP, the treatment consists exclusively of replacement of the protease with plasma infusion. In acquired TTP, considering the more complex pathophysiology, a multiple approach is required, with removal of autoantibodies and replacement of functional protease through plasma exchange, associated with immunosuppression to stop new antibodies formation. However, considering the elevated mortality, plasma exchange should be promptly initiated while

pursuing with further investigation to differentiate between the subtypes of TTP. The humanized anti-CD20 monoclonal antibody, Rituximab, is currently an option in the treatment of the acquired TTP, specially in refractory or relapsing cases.³²

In secondary-acquired TTP, the response to plasma exchange is more unpredictable, so treating the suspected cause is recommended.³³

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Competing interests None declared.

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