CASE REPORT

Case Report: Systemic lupus erythematosus associated with thrombotic thrombocytopenic purpura, a diagnostic challenge [version 1; peer review: 1 approved with reservations, 1 not approved]

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Abstract

Thrombotic thrombocytopenic purpura (TTP) is an uncommon microangiopathic disease and often occurs as a complication of systemic lupus erythematosus (SLE). However, this probable causal relationship has not been completely proven. The diagnostic differentiation of both diseases is difficult in the first instance because they share similar characteristics that may overlap. We present a case of a 32-year-old woman with antecedents of epilepsy since she was 12 years old. The patient was admitted to the emergency room with a clinical picture of headaches, fever, paleness in the skin and mucosa, confused state, paresthesia, and transient spasticity of the extremities. The laboratory results revealed Coombs negative direct autoimmune hemolytic anaemia, severe thrombocytopenia, significant elevation of the enzyme lactate dehydrogenase, and presence of schistocytes ++ in the peripheral film. In addition, positive antinuclear antibodies and positive anti-native DNA in titers of 1/320 and 1/160, respectively, were found. Renal function was conserved. We concluded that it was a case of TTP associated with SLE and indicated treatment with plasmapheresis and methylprednisolone pulses, obtaining a satisfactory response (normalization of biomarker levels, health condition) after the second session of plasmapheresis. Diagnosis of both SLE and TTP is often difficult to achieve; however, adequate correlation of clinical manifestations and laboratory tests, along with the help of partial therapeutic interventions, may lead to good clinical response.

Open Peer Review

Approval Status

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version 2 (revision) 25 May 2022		view
version 1 09 Jul 2021	view	view

1. **Katerina Pavenski** , St. Michael's Hospital
 - Unity Health Toronto, Toronto, Canada

2. **Ahmet Emre Eşkan** , Istanbul
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Any reports and responses or comments on the article can be found at the end of the article.

Keywords

Systemic Lupus Erythematosus, Thrombotic Thrombocytopenic Purpura, plasmapheresis, adamts-3 protein, human

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Introduction

Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy (TMA) that can be classified as idiopathic or in association with other pathological processes such as neoplasias, infections, and autoimmune diseases such as systemic lupus erythematosus (SLE).¹ Its classical presentation and characteristics are the pentad composed of: fever, neurological disorder, renal dysfunction, microangiopathic hemolytic anemia, and thrombocytopenia.^{1,2} The occurrence of TTP associated with SLE has an immunological basis related to the formation of antibodies that inhibit or diminish the function of a disintegrin-like and metalloprotease with thrombospondin type 1 motif no. 13 (ADAMTS13), and the increase in serum level of the inhibitor of metalloprotease ADAMTS3. The occurrence of both entities at the same time is a rare presentation; generally, TTP is a complication in patients with SLE.^{2,3}

The clinical picture of both entities is somewhat similar because they share clinical characteristics that can overlap. It is difficult to make the diagnostic differentiation in the first instance, which delays the decision with regards to the correct treatment. This is important because the prognosis is more ominous when both entities appear at the same time, either as an association, or a secondary complication. We present a clinical case of a woman with a clinical presentation of SLE and TTP that was difficult to diagnose.

Case presentation

We report a case of a 32-year-old woman of mixed ancestry and with no specific occupation who was admitted to the hospital as an emergency because she was presenting with a confused state, paresthesia, and transient spasticity of the extremities that lasted for 30 minutes. She also reported she had a fever of 38°C for three days before admission. As important antecedents she reported headaches, dizziness, sporadic ecchymosis on the legs, and oral ulcers since she was a teenager, which she did not consider important. She suffered from epilepsy since she was 12 years old for which she has followed irregular treatment with carbamazepine. She also has an obstetric antecedent of three pre-term labors between 32 and 35 weeks. Among family antecedents we can mention that her mother is epileptic, the grandmother on her mother's side has lupus, and her youngest daughter had convulsions at three months of age.

On physical examination, a confused state, slight malar erythema, and ecchymosis on the legs and arms were found. The osteomuscular articular system and the cardiovascular and pulmonary systems had no alterations and she was hemodynamically stable. On admission, blood test showed hemoglobin: 7.5 g/dL, reticulocytes: 11.92%, and platelet count: 10,000/mm³; biochemical tests showed lactate dehydrogenase (LDH): 1,741 U/L, total bilirubin: 0.9 mg/dL, C-reactive protein (CRP) level: 0.79 mg/L, globular sedimentation rate (GSR): 77 mg/L, urea: 16 mg/dL (normal range: 11-20 mg/dL), and creatinine: 0.9 mg/dL (normal range: 0.7-1.5 mg/dL). Peripheral blood smear showed positive schistocytes (++) . Brain CT-scan showed no alterations. Because of the hematological and biochemical alterations reported, 300 mL of platelet concentrates were transfused five times, elevating the platelet count to 40,000/mm³ with a rapid decline on the second day. This made us suspect that it was a case of thrombotic microangiopathy (TMA) with hemolytic anemia. We indicated autoantibodies tests in which we found negative antiphospholipid antibodies, positive antinuclear antibodies in titers of 1/320, and positive anti-native DNA in titers of 38.24 IU/mL. On the third day after admission, the platelets decreased to 9,000/mm³ and the patient presented with a sudden neurological disorder with language disturbance, paresthesia in lower extremities, and confused state, totally recovering in few hours; an emergency brain CT-scan was performed, which showed no significant changes. The diagnosis of SLE was confirmed, as well as TTP, based on the two positive results of the systemic autoantibodies, along with severe thrombocytopenia, microangiopathic hemolysis, and the neurological disorder. We began treatment with methylprednisolone pulses of one gram IV every 24 hours for three days; however, three days after the beginning of treatment, the level of platelets and red blood cells decreased to 7,000/mm³ and 6.8 g/dL, respectively, so we decided to begin plasma exchanges (plasmapheresis) using fresh frozen plasma with a volume of 2,000 mL. After the first plasma exchange, a significant increase in the level of platelets was evidenced, together with the reduction of LDH; so, four exchanges were completed, obtaining, five days after the last exchange, a normalization of the platelets and LDH levels: 243,000/mm³ and 374 U/L, respectively (Figure 1). Hemoglobin levels also began to raise to 9.5 g/dL, and there was a normalization of total bilirubin levels (0.28 mg/dL) and CRP (0.18 mg/dL). The patient had no clinical evidence of neurological symptoms, with platelets: 277,000/mm³ (normal range: 150,000-400,000/mm³) and hemoglobin: 12.8 g/dL (normal range: 11.9-13.5 g/dL). She was discharged four weeks after hospitalization with a medical prescription of prednisolone at a dose of 0.5 mg/kg/day PO for four weeks and her usual anticonvulsants (valproic acid: 30 mg/kg/day and carbamazepine: 15 mg/kg/day). There were no significant adverse effects.

Thirteen months after discharge, the patient was in good health, became pregnant, and had a satisfactory delivery with normal levels of platelets and hemoglobin.

Figure 1. Evolution of platelets and LDH with established treatment in a patient with systemic lupus erythematosus and thrombotic thrombocytopenic purpura. LDH: Lactate dehydrogenase.

Discussion

TTP occurs in about 2% of patients with SLE.^{2,3} TTP manifestation after SLE has been more frequent than both appearing simultaneously.⁴ This case report is about a young woman who appears for the first time with SLE associated with TTP.

TTP shares clinical and laboratory characteristics with SLE, which makes the diagnosis and proper treatment difficult and delayed,⁵ with a resulting elevation of mortality. Mortality due to TTP is greater than 80%, but when the appropriate treatment is followed with plasma exchange, the survival rate is greater than 80%. On the other hand, when TTP is present in patients with SLE, the episode is usually severe and lethal with a mortality rate of 34.1-62.5%.⁶⁻⁸ In this case report, the diagnosis was made by anamnesis and laboratory tests; the patient achieved clinical improvement and survived. The classical clinical pentad in the presentation of TTP: microangiopathic hemolytic anemia (MHA), thrombocytopenia, neurological disorder, renal dysfunction, and fever was not observed in this case; this has been observed previously, but it is not frequent to find this pentad currently.^{7,8} TTP does not usually present alone but is associated with or in concomitance with other pathologies, either autoimmune, neoplastic, or infectious. Sometimes, the treatment of concomitant pathologies in TTP can mitigate or mask some components of the classical clinical pentad. In addition, the poor specificity of the initial clinical manifestations of the TTP such as the neurological deficit associated with ischemia (headaches, consciousness disorders), and fatigue and abdominal pain associated with hemorrhage, make its diagnosis a challenge.^{5,8}

A cohort study that evaluated the clinical characteristics and prognostic factors of 105 cases of TTP associated with SLE found that the occurrence of the neurological disorder alone or accompanied by renal disorder was significantly higher in the group of patients that died than in the ones that survived, suggesting that the neurological and renal deficits could be a possible risk factor for mortality in patients with TTP and SLE.⁷ In this clinical case, the patient presented with sensory disorder and a confused state but recovered immediately and the analysis of images did not show cerebral lesions. The absence of kidney involvement in our patient could be because the clinical presentation of TTP was before or simultaneous to one of SLE, a presentation described as the least frequent in all cases reported to date.^{8,9} The appropriate treatment with plasma exchange and adequate hydroelectrolytic management probably prevented kidney involvement. This is an interesting situation because in most cases in which SLE appeared first, there was kidney involvement accompanying other clinical manifestations of TTP; this could explain the relative resistance to indicated treatments including plasma exchange in the cases reported, which showed a high mortality rate.⁶

Several studies have found that treatment with glucocorticoids and plasma exchange can achieve remission of 65.7% in patients with SLE and TTP^{7,8} and it has been observed that some treatment options such as rituximab are used for refractory cases, achieving a good prognosis.^{3,7,8} In this case, the initial treatment was followed with methylprednisolone

pulses of 1 g/day because it was focused mainly on active SLE complicated with TTP. However, the pulses were not favorable because two consecutive days after having received them, the clinical picture, mainly the neurological one, persisted and the hematological clinical picture with anemia and thrombocytopenia was worse, so plasma exchange was performed. With this management, the platelet figures increased significantly and there was a decrease in serum LDH levels. The response was positive after four plasma exchanges with platelet levels of 243,000/mm³.

The clinical and hematological evolution of the present case, which was favorable and rapid, contrasts with most of the cases reported in which there was a delay in the response and a high mortality rate despite the use of methylprednisolone pulses, plasma exchange, and other options such as the use of rituximab.^{3,7,8} The explanation to this particular situation could be that, excluding the positive serology in this patient (that is, the ANA and anti-native DNA antibody), the presentation of the clinical characteristics was not compatible with SLE but mainly with TTP, which could lead us to assume that SLE, for the moment, would be only serological and that its clinical manifestations could become clear in the future.

Plasma exchange independent of ADAMTS13 activity is important and is recommended until the first platelet counts appear within normal limits for two consecutive days.¹⁰ TTP should always be considered in patients with hemolytic anemia and thrombocytopenia; however, in young women, SLE and TTP can occur simultaneously.

The strength of this case report relies on the uncommon presentation of both SLE and TTP, which adds more information about the clinical picture and possible outcomes. The main limitation was the lack of the ADAMTS13 activity and inhibitor tests, which are not used routinely but may have helped to confirm the diagnosis of TTP. The diagnosis of both conditions was even more challenging considering the differential diagnosis of epilepsy and the irregular use of medication for this neurological disorder.

Conclusion

TTP associated with SLE is not a common presentation. It represents a challenge for diagnosis and treatment because it can be fatal if it is not treated on time. The peculiarity of this case is that the clinical presentation was almost exclusively one of TTP because it had only the neurological manifestations and positive serologic findings of ANA and anti-DNA that are present in cases of SLE. Plasma exchange and corticosteroids can be used successfully and the patients can achieve remission with treatment; in cases resistant to treatment, modulators of monoclonal antibodies like rituximab are frequently used. Our patient with SLE and TTP had a good response to the platelet replacement and methylprednisolone and her evolution has been favorable.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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Version 1

Reviewer Report 11 January 2022

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Ahmet Emre Eşkazan

Division of Hematology, Department of Internal Medicine, Cerrahpaşa Faculty of Medicine, Istanbul University-Cerrahpaşa, İstanbul, Turkey

I have reviewed the manuscript. Although relatively rare, SLE and TTP may occur in the same patient, and although the case was well-presented, I do not think that this case does add anything new to what we have already known on this subject. As the authors stated, there are no ADAMTS13 activity, antigen, and antibody results. This, especially the anti-ADAMTS13 antibody result, is really important to distinguish hereditary TTP from immune-mediated TTP. In addition, the direct antiglobulin test is also lacking. In the longer-term follow-up, the patient did not receive any treatment for SLE, which is quite interesting.

Is the background of the case's history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: TTP, Hematology

I confirm that I have read this submission and believe that I have an appropriate level of

expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 15 November 2021

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Katerina Pavenski

Department of Medicine and Laboratory Medicine, St. Michael's Hospital - Unity Health Toronto, Toronto, Canada

This is a case report of a 32yo female with a new diagnosis of presumably immune TTP. The case is not unique but still may have value to the readers with appropriate revisions. I summarize my feedback below:

Title

Based on reading this case report, I am not convinced that your patient fulfils the diagnostic criteria for SLE. She clearly has positive autoimmune serology but does not appear to have any clinical features of SLE. Finding of positive autoimmune serology is not uncommon in patients with iTTP, and some of these patients eventually develop SLE and some of them will not.

Abstract

1. Suggest to change "TTP often occurs as a complication of SLE" to "TTP sometimes is associated with SLE". The latter statement is more accurate.
2. Re-word "direct Coombs negative hemolytic anemia". You surely do not mean "autoimmune" hemolytic anemia which is associated with spherocytes on film and RBC autoantibodies.
3. What is "conserved" renal function? Do you mean her renal function was at baseline on the basis of measuring her serum creatinine, or serum creatinine was in normal range? Was urinalysis done?
4. Was troponin done to rule out cardiac involvement?
5. ADAMTS13 activity and inhibitor were not done in this case but are required to confirm diagnosis. Please discuss this limitation and way to mitigate it (i.e. in resource constrained circumstance, can use a prediction score - such as PLASMIC) to predict chance of having low ADAMTS13.

Introduction

1. The classical pentad occurs in under 10% of cases of TTP. It is therefore important to question TTP when there is MAHA, thrombocytopenia and no obvious explanation and not

wait for the pentad.

2. Completely disagree with statement "generally, TTP is a complication in patients with SLE". In most patients, iTTP is not associated with SLE or any other disorder. Indeed, to see SLE and TTP is not common at all.

Case presentation

1. What is meant by mixed ancestry?
2. Does "irregular treatment" with carbamazepine mean inconsistent compliance?
3. Was there any history of obstetrical complications? Were antecedent births live and healthy? Were there any pregnancy losses?
4. Why were platelets transfused and repeatedly - 5 times? Based on lab work provided, very high chance of this being TTP (for e.g., if use PLASMIC score) and platelet transfusions are considered contra-indicated in patients with TTP (risk of worsening thrombosis) unless there is a life-threatening bleed. Was she seriously bleeding?
5. Why was plasma exchange not started right away or only after worsening of clinical and labs? Based on presenting labs, very high index of suspicion that this was TTP...why PEX was stopped after 4 treatments? Standard of care is usually daily PEX until platelets are normal for at least 2 consecutive days.

Discussion

1. I disagree with "TTP does not usually present alone". In fact, in majority of cases, TTP presents alone, with no other diseases.
2. I understand that there was a diagnostic uncertainty about her initial diagnosis: SLE vs TTP. And that treatment of SLE was appropriately steroid pulse. However, based on her presenting picture (fragmentation hemolysis and thrombocytopenia and evidence of target organ damage - neurological) TTP could not be ruled out and as such (SLE or not) she should have received PEX or risk mortality or further organ damage. For every day delay in starting TPE, risk of death increases (Van de Louw *et al.*, 2021¹). This should be the message of this case report.
3. I also would encourage the authors to include the statement about importance of getting ADAMTS13 activity test. If APLA, other autoimmune sophisticated serology could be done by the lab, so could be ADAMTS13. And this test is very important precisely because it is so difficult to differentiate TTP from other diseases, especially if more than one disease is present.
4. Re sentence, "TTP should always be considered...however in young women SLE and TTP can occur simultaneously": This is not the reason to delay TTP treatment. TTP is most likely in young women and so is SLE. TTP should always be considered and treatment should be started, whether SLE is also suspected and especially in young women.

Conclusion

Really, conclusion should be that SLE and TTP can occur together (albeit not frequently) and this makes diagnosis more difficult. However, considering the severe consequences of leaving TTP untreated (death, major organ damage), patient should be treated expediently as TTP with PEX

and steroids while diagnosis is being sorted out.

Please consider my suggestions and good luck.

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Is the background of the case's history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Partly

Is the case presented with sufficient detail to be useful for other practitioners?

Partly

Competing Interests: Not relevant to this paper. I have received honoraria and participated in industry trials in iTTP for Ablynx/Sanofi and Shire/Takeda.

Reviewer Expertise: TTP and other thrombotic microangiopathies, therapeutic apheresis and transfusion medicine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 21 May 2022

Virgilio E Failoc-Rojas, Universidad San Ignacio de Loyola, Lima, Peru

Title

Based on reading this case report, I am not convinced that your patient fulfils the diagnostic criteria for SLE. She clearly has positive autoimmune serology but does not appear to have any clinical features of SLE. Finding of positive autoimmune serology is not uncommon in patients with iTTP, and some of these patients eventually develop SLE and some of them will not.

Author Response: In fact, the patient met the criteria for SLE, but we did not detail the clinical manifestations. The patient had a history of epileptic seizures and oral ulcer, and on

admission presented with malar erythema. Given the initial suspicion of SLE, subsequent immunological tests confirmed the diagnosis (positive antinuclear antibodies in titers of 1/320, and positive antinuclear DNA in titers of 38.24 IU/mL). We have sought to clarify the diagnostic process of SLE in the text.

Abstract

1. Suggest to change "TTP often occurs as a complication of SLE" to "TTP sometimes is associated with SLE". The latter statement is more accurate.

Author Response: Thank you. We have changed the statement.

2. Re-word "direct Coombs negative hemolytic anemia". You surely do not mean "autoimmune" hemolytic anemia which is associated with spherocytes on film and RBC autoantibodies.

Author Response: We have re-worded the phrase.

3. What is "conserved" renal function? Do you mean her renal function was at baseline on the basis of measuring her serum creatinine, or serum creatinine was in normal range? Was urinalysis done?

Author Response: We clarified this term. Yes, urinalysis was done and showed that serum creatinine was in the normal range.

4. Was troponin done to rule out cardiac involvement?

Author Response: Yes, troponin was done and ruled out cardiac involvement.

5. ADAMTS13 activity and inhibitor were not done in this case but are required to confirm diagnosis. Please discuss this limitation and way to mitigate it (i.e. in resource constrained circumstance, can use a prediction score - such as PLASMIC) to predict chance of having low ADAMTS13.

Author Response: Thank you, this limitation was discussed briefly.

Introduction

1. The classical pentad occurs in under 10% of cases of TTP. It is therefore important to question TTP when there is MAHA, thrombocytopenia and no obvious explanation and not wait for the pentad.

Author Response: Thank you for your comment. We agreed with this idea; this was pointed out in the text.

2. Completely disagree with statement "generally, TTP is a complication in patients with SLE". In most patients, iTTP is not associated with SLE or any other disorder. Indeed, to see

SLE and TTP is not common at all.

Author Response: Thank you. We clarified this statement, as the message was to explain that TTP might occur after SLE as a complication, in the context of the rare presentation of both entities.

Case presentation

1. What is meant by mixed ancestry?

Author Response: This was a term referred to as mestizo. We changed this term for sake of clarity.

2. Does "irregular treatment" with carbamazepine mean inconsistent compliance?

Author Response: Yes, it does. To clarify the term, we changed it to "has been treated inconsistently with carbamazepine".

3. Was there any history of obstetrical complications? Were antecedent births live and healthy? Were there any pregnancy losses?

Author Response: The patient had three preterm delivery events. All births were live and healthy and there were no pregnancy losses. This was added in the text.

4. Why were platelets transfused and repeatedly - 5 times? Based on lab work provided, very high chance of this being TTP (for e.g., if use PLASMIC score) and platelet transfusions are considered contra-indicated in patients with TTP (risk of worsening thrombosis) unless there is a life-threatening bleed. Was she seriously bleeding?

Author Response: Treatment was defined after consultation with experts based on clinical and platelet levels. We agree that this treatment is not the most appropriate but in the limited circumstances of the hospital it was the most accepted option.

5. Why was plasma exchange not started right away or only after worsening of clinical and labs? Based on presenting labs, very high index of suspicion that this was TTP...why PEX was stopped after 4 treatments? Standard of care is usually daily PEX until platelets are normal for at least 2 consecutive days.

Author Response: The reason immediate treatment with plasma exchange was not performed was that TTP was not initially suspected, and the availability of treatment was not immediate to provide timely care. In addition, treatment with PEX was momentarily suspended after four treatments because, by expert consensus, the patient showed a favorable pattern in which the platelet level was increasing, and the DHL concentration was decreasing. Finally, upon seeing a consistent improvement, it was decided not to restart the plasma exchange. This response was also added to the text.

Discussion

1. I disagree with "TTP does not usually present alone". In fact, in majority of cases, TTP presents alone, with no other diseases.

Author Response: Thank you for your comment. We agree with this statement and have therefore revised the term in the text.

2. I understand that there was a diagnostic uncertainty about her initial diagnosis: SLE vs TTP. And that treatment of SLE was appropriately steroid pulse. However, based on her presenting picture (fragmentation hemolysis and thrombocytopenia and evidence of target organ damage - neurological) TTP could not be ruled out and as such (SLE or not) she should have received PEX or risk mortality or further organ damage. For every day delay in starting TPE, risk of death increases (Van de Louw *et al.*, 2021¹). This should be the message of this case report.

Author Response: Thank you for this insightful comment. We recognize that this was a limitation and agree that PTT should have been appropriately ruled out regardless of the diagnosis of SLE. We have added this message in the text.

3. I also would encourage the authors to include the statement about importance of getting ADAMTS13 activity test. If APLA, other autoimmune sophisticated serology could be done by the lab, so could be ADAMTS13. And this test is very important precisely because it is so difficult to differentiate TTP from other diseases, especially if more than one disease is present.

Author Response: Thank you for your kind suggestion. Indeed, ADAMTS13 activity testing is a critical step in the diagnosis of TTP. However, many hospitals in Peru lack these and other sophisticated tests due to cost. With this in mind, we have added a statement on the importance of ADAMTS13 so that it may benefit the proper clinical management of PTT in future events.

4. Re sentence, "TTP should always be considered...however in young women SLE and TTP can occur simultaneously": This is not the reason to delay TTP treatment. TTP is most likely in young women and so is SLE. TTP should always be considered and treatment should be started, whether SLE is also suspected and especially in young women.

Author Response: Thank you. The sentence was modified. We agree that in young women with these characteristics, one should think about TTP regardless of concomitant disease, and in the face of this suspicion act in a timely manner.

Conclusion

Really, conclusion should be that SLE and TTP can occur together (albeit not frequently) and this makes diagnosis more difficult. However, considering the severe consequences of leaving TTP untreated (death, major organ damage), patient should be treated expediently as TTP with PEX and steroids while diagnosis is being sorted out.

Author Response: Thank you for your suggestion. We have modified this section to convey a more precise conclusion.

Competing Interests: We don't have any competing interests

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