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Case Report

Thrombotic thrombocytopenic purpura and deep vein thrombosis as the presenting manifestations of systemic lupus erythematosus: a case report and review of literature

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Abstract

Systemic lupus erythematosus (SLE), is sometimes complicated by the rare fatal syndrome, Thrombotic thrombocytopenic purpura (TTP), but the occurrence of TTP as the initial manifestation of SLE is very rare. Since they have similarities in some features, the differentiation of TTP from SLE may be missed. SLE patients are also more prone to thrombotic events. Here we report a case with TTP and deep vein thrombosis as the presenting symptoms of SLE.

KEYWORDS: Thrombotic Thrombocytopenic Purpura, Systemic Lupus Erythematosus, Deep Vein Thrombosis.

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Thrombotic thrombocytopenic purpura (TTP) is a rare, but fatal syndrome. It may occur secondary to some diseases such as systemic lupus erythematosus (SLE)[1] and can be presented in up to 0.5-2% of these patients.[2,3] The diagnosis of TTP in the setting of SLE may be difficult, since they share many similar characteristics with each other. But their differentiation and diagnosis is important due to high mortality rate of untreated TTP and their different ways of treatment. TTP as a primary presentation of SLE is very rare and with very high rate of mortality.[2]

On the other hand, SLE patients are at a higher risk for thrombotic events such as deep vein thrombosis (DVT) it occurs in up to 26% of SLE patients.[4] The occurrence of TTP and DVT as the presenting symptom of SLE is also very rare. Here we describe a case of such presentation. The most common autoimmune disease with DVT is SLE.[4]

Case Report

A 33-year-old woman was admitted to our hospital (Ali Ebne Abitaleb Hospital, Zahedan, Iran) due to prolonged fever, neck masses and the swelling of her left lower limb. She complained that fever had been prolonged for 3 months, being persistent during the whole 24 hour, without special pattern during days or nights. She also mentioned that she had spent a short period of productive cough 3 months ago, during which she found some small tender masses on her neck. Her productive coughs improved without medication, but fever and neck masses persisted. Two months later, she visited a surgeon for her persistent neck masses and fever and subsequently underwent an excisional neck mass biopsy. The pathologist reported a lymph node (7mm in diameter) infiltrated by normal shaped lymphocytes, suggestive for Toxoplasma infection and, to a lower probability, viral infections or lympho-

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cyte predominant Hudgkin lymphoma. So the specimen was sent for immuno-histochemistric (IHC) evaluation.

Her fever persisted, but she did not lose appetite or significant weight. She also did not have night sweats but was suffering from fatigue. Two weeks before admission, she noted the gradual swelling of her left lower limb, accompanied by dull pain. She visited a doctor and performed some laboratory tests, including complete blood count (CBC), renal and liver function tests which all showed normal results. She did not continue doing more evaluation for her problem and used no medication. Then, she felt the progression of fatigue as well as slight darkening of her urine, so came to our hospital.

She neither mentioned close contact with a known case of Tuberculosis, nor cats around her living place, but used unpasteurized milk and yoghurt. She was a house-wife and was uneducated. She had 2 children, being delivered by cesarean-section and had no history of abortion. She remembered that she had passed a course of DVT in her left leg after her first delivery, being 4 years ago, for which she had been under treatment for several months, but could not remember the name of her medications. She did not smoke, but her husband was smoker and IV-drug abuser.

On physical examination, she seemed ill, but was oriented. Her blood pressure was 120/80 mmHg. Pulse rate was 108/min and temperature was 39.5 °C (orally). She was pale. Her neck examination showed 5 non-tender, soft and mobile lymph nodes, with maximal diameter of 7-8mm bilaterally, both in anterior and posterior cervical lymph node chains. Her pharynx looked normal, but there were multiple small erosions on her soft palate. The patient was not aware of those erosions and felt no pain. The examination of heart, lungs and breasts were normal. The abdomen was soft, without organomegaly. Her left lower limb seemed edematous. The difference between the circumferential size of her left and right lower limbs were 4cm and 5cm for the legs and the thighs, respectively.

The primary laboratory data are shown in table 1. The patient was also tested for Toxoplasma antibody (IgM & IgG), Wright test (due to consumption of unpasteurized dairy products), Purative Protein Derivative test (PPD) (due to the high prevalence of Tuberculosis in the region), and also HBS antigen, HCV antibody and HIV antibody owing to the presence of risk factors in her husband. Color Doppler ultra-sonogragphy showed the presence of thrombus in the left femoral and iliac veins. Heparin infusion and then warfarin (5mg-PO-daily) were started. Abdominal ultrasonography (US) reported a small (4-5mm) hyper-echo lesion in the liver (The sonographist suggested that it must have been a hemangioma). No organomegaly or intra-abdominal lymphadenopathy was detected by US. Renal parenchymal echogenisity was slightly increased, with no hydronephrosis.

At the same day, the patient reported diarrhea (6 times per day with small volume). So stool specimen was sent for evaluation. Due to the presence of Anemia and Thrombocytopenia, the patient's peripheral blood smear (PBS) was observed, showing nucleated RBCs and multiple schistocytes and fragmented RBCs. No malignant or leukemic cell was observed on PBS. Furthermore, white blood cell (WBC) count on PBS was 2,750/ml (with 85% polymorpho-nuclear cells and 10% lymphocytes) and platelet count was 50,000/ml.

According to the presence of micro-angiopathic hemolytic anemia, thrombocytopenia, fever and renal involvement, the diagnosis of TTP was assumed at the 2nd day of admission. Fresh frozen plasma (FFP) was administered (2 units every 8 hour) and the patient became a candidate for plasma exchange with FFP (2 liters daily, according to her weight).

Following the diagnosis of TTP, the presence of anti-nuclear anti-body (ANA), anti double-stranded DNA (anti-dsDNA) were tested. Because of the previous history of DVT, the patient was also tested for anti-phospholipid and anti-cardiolipin antibodies (both IgM and IgG). At the time, the patient

Table 1. Primary laboratory data of the patient on admission

Lab test	Result	Normal range (unit)
White Blood Cell (WBC)	5.2 { Polymorpho-nuclear: 68% Lymphocyte: 26% }	4-10 (×1000/ml)
Red Blood Cell (RBC)	4.05	3.9-5.8 ($\times 10^6$/ml)
Hemoglobin	10.5	12-16 (g/dl)
Mean Corpuscular Volume	78	80-100 (fl)
Platelet	90,000	150-450 (/ml)
Erythrocyte Sedimentation Rate	45	<20 (/1st hour)
Blood Urea Nitrogen	50	8-20 (mg/dl)
Creatinin	4.3	0.6-1.3 (mg/dl)
Sodium	141	135-145 (meq/L)
Potassium	5.8	3.5-5.2 (meq/L)
Calcium	8.3	8.5-10.5 (mg/dl)
Phosphorus	6.1	2.5-5 (mg/dl)
Serum Albumin	3.2	3.5-5.3 (g/dl)
Prothrombin Time	12	11-13 (sec)
Partial Thromboplastin Time	34	30-45 (sec)
Aspartate-amino Transferase	21	0-41(U/L)
Alanine-amino Transferase	11	0-37 (U/L)
Alkaline Phosphatase	183	64-306 (U/L)
Lactate Dehydrogenase (LDH)	823	225-500 (U/L)
Uric Acid	8.3	2.4-7 (mg/dl)
Urinalysis*	Protein 3+ Blood 3+ RBC: many WBC: 10-15	

*The patient was spending her 7th day of menstrual cycle.

was retrospectively asked about photosensitivity and she gave positive answer. The result of stool examination showed Giardia lamblia trophozoites, so metronidazole was started (250mg PO every 8 hour).

At the 3rd day, the patient complained of right knee pain. Her right knee was warmer than the leg surface and the opposite knee. It had mild effusion and was painful during both active and passive movements, but had no tenderness or erythema. Other peripheral joints were normal on examination. The frequency of her defecations had decreased, but she was still febrile and did not seem to be well and even seemed worse and lethargic to some extent. Her blood pressure rose to 160/90 mmHg. Hydrocortisone (200mg IV as a stat dose) and then, dexamethasone (8mg IV every 6 hours) were administered and it got possible to initiate the 1st session of plasma exchange.

At the 4th day, fever had subsided; she seemed much better and had no articular complaint. The results of ANA and especially anti-dsDNA (76 E/ml, with normal range being less than 20 E/ml) were positive. Other tests including anti-phospholipid and anti-

cardiolipin antibodies, PPD, Wright, HBs-Ag, HCV-Ab and HIV-Ab had negative results. In addition, IHC evaluation of the lymph node was negative for Hudgkin lymphoma. Additional urinalysis of the patient (3 days after discontinuation of menstrual bleeding) showed persistent proteinuria and hematuria, so urine sediment was observed, showing many RBCs with dysmorphic shapes (60% of total RBCs) as well as RBC casts. The 24-hour examination of the urine showed 14341mg protein and 760mg creatinine in 1700cc urine volume. Therefore, presence of 7 of 11 American College of Rheumatology (ACR) criteria (oral ulcers + photosensitivity + renal involvement + positive ANA and anti-dsDNA tests + hematologic abnormalities including leukopenia, lymphopenia and thrombocytopenia + arthritis) allowed the diagnosis of SLE.

After 5 plasma exchange treatment procedures, serum creatinine decreased to 1.6 mg/dl, platelet count was 100,000 /ml and LDH was 582 U/l. Additional observation of the PBS showed significant decrease in fragmented RBC or schistocyte counts. Fever did not recur and the patient had the feeling of complete well-being, so that she did not accept remaining hospitalized and was self-discharged at the 8th day of admission, despite frequent explanation to the patient about the necessity for completing the plasma exchange treatment course and the need for more evaluation of her renal function status and her DVT. So dexamethasone was changed to prednisolone (50 mg PO daily) and she was advised not to change the dose or discontinue the drug without her physician consult. Warfarin (5mg daily) was continued and the patient was advised to check her International Normalized Ratio (INR) every week. She was also advised to visit a nephrologist, a rheumatologist and a hematologist during the coming week and of course, was advised to come back to the hospital as soon as possible, if not feeling well.

One week later, the patient returned to the hospital due to severe edema, headache, mild dyspnea (orthopnea) and delusion. She seemed ill and puffy. On examination, her blood pressure was 180/90 mmHg, respiratory rate was 18/min and body temperature was normal. Normal vesicular sound could not be heard on the base of her right lung and was dull on percussion. Heart sounds seemed normal with no bruits. Both upper and lower limbs were edematous. She was still taking prednisolone (50mg daily) and warfarin (5mg daily). Laboratory data are shown in table 2.

There were many fragmented RBCs on PBS. Her chest X-ray showed right sided blunting of costophrenic angle. Her electrocardiogram showed low voltage complexes in all precordial parts. She went under echocardiography, but it was negative for pericardial effusion.

Plasma exchange with FFP was started again and 3 methyl prednisolone pulse (1g IV daily, repeated for 3 days) and then a cyclophosphamide pulse (1g IV) was administered. The diuretic furosemide and captopril were

Table 2. Laboratory data of the patient on her 2nd admission

Lab test	Result	Normal range (unit)
Hemoglobin	9.3	12-16 (g/dl)
Platelet	90,000	150-450 (/ml)
Blood Urea Nitrogen	40	8-20 (mg/dl)
Creatinin	1.5	0.6-1.3 (mg/dl)
Serum Albumin	2.7	3.5-5.3 (g/dl)
Lactate Dehydrogenase (LDH)	878	225-500 (U/L)
Urinalysis	Protein 4+ Blood 3+ RBC: many, with dysmorphic shapes WBC: moderately increased	

also started to control her blood pressure and to lower her edema. She became also a candidate for renal biopsy, so it was decided to stop warfarin for 1 week and to start heparin infusion during this period. After 6 courses of plasma exchange, the platelet count was 131,000 /ml and LDH was 505 U/l, so plasma exchange was tapered in volume and the interval durations got longer. She seemed well, her edema was decreased and her blood pressure was 140/80 mmHg and she did not complain of dyspnea anymore. Here, the patient refused renal biopsy.

Finally, she was discharged home after 11 plasma exchange courses. She was advised to continue warfarin and check INR every other week and to take prednisolone 50mg daily for the following 2 weeks, then being tapered by a rheumatologist. She was also advised to receive cyclophosphamide pulses every month for 6 months, under the observation of a nephrologist. It must be mentioned that, we noted no delusions during her hospitalization course.

Discussion

Our patient showed TTP and DVT as the primary manifestations of SLE. TTP is rare, but fatal. Our patient was diagnosed to have TTP according to the presence of thrombocytopenia, micro-angiopathic hemolytic anemia, fever and renal involvement. The presence of DVT was confirmed by using color Doppler US. SLE was diagnosed according to the presence of 7 ACR criteria, including oral ulcers, photosensitivity, renal involvement, positive ANA and anti-dsDNA tests, hematologic abnormalities and arthritis. On her 2nd admission, serositis (pleural effusion) was also added to these criteria.

It must be mentioned that the patient's articular manifestations were subsided after high dose corticosteroid administration, so we could not judge about the number and the course of articular involvement. The patient's delusion did not recur during her hospitalization course, so that it was attributed to the consumption of high dose corticosteroid.

The relationship between TTP and SLE is not well understood, but some studies have suggested that ADAMTS-13 (a disintegrin and metalloprotease with thrombospondin motifs) deficiency and its auto anti-bodies are involved in the pathogenesis of both TTP and SLE to varying degrees and the two diseases may be more closely associated.[5] In 1993, Porta et al. reported a 3.8% incidence of TTP in SLE patients during a 20 year follow up period.[6]

TTP and SLE share many characteristics with each other, including thrombocytopenia, anemia, renal and central nervous system involvements and fever. Therefore the occurrence of TTP in SLE patients may be underestimated, but the occurrence of TTP as the initial manifestation of SLE is rare. Hamasaki et al. found that the cumulative reports of coexisting SLE and TTP had been 56 cases and the simultaneous occurrence of SLE and TTP at their initial presentations, had been reported just in 12 cases in English literature.[7] They also reported that the mortality of TTP patients complicated by SLE was relatively higher.[7] Hunt et al. reported that most SLE related TTPs had occurred after the diagnosis of SLE. In 13-15%, TTP occurred before the diagnosis of SLE and 12-26% were diagnosed simultaneously.[8]

SLE patients have a high risk for thrombotic events.[4] According to the report of Ekdahal et al., in SLE patients, sustained systemic activation of platelets leads to extracellular phosphorylation of plasma proteins such as fibrinogen, factor C3 and vitronectin.[9] Fibrinogen phosphorylation results in lower plasmin-mediated degradation of formed fibrin clots[10] and so, increases the risk of thromboses in SLE patients. On the other hand, platelet-mediated phosphorylation of factor XI increases its susceptibility to activation by both factor XIIa and thrombin.[11] Brey et al., suggested that immune complexes, formed in SLE, preactivate the platelets and thereby lower the threshold for platelet activation.[12] Romero-Diaz et al. showed that all the 30 SLE patients being observed in their study, particularly those with

thrombosis, had high levels of β-thromboglobulin, activated factor XI-antithrombin complex and fibrinogen bound phosphate. They concluded that thrombotic events in SLE patients are related to the persistent systemic platelet activation that may lower the threshold for thrombosis.[4]

In SLE patients, higher levels of anti-phospholipid antibody and, to a lesser extent, anti-cardiolipin antibody are associated with thrombosis.[4] In our patient, these two antibodies were negative. So the occurrence of thrombosis might have been related to other mechanisms being involved in SLE or to a different mechanism including deficiencies or lower levels of protein-C, protein-S or factor V Leiden, for which the patient was not evaluated.

Simultaneous occurrence of DVT and TTP as the initial manifestation of SLE is very rare and the reports are lacking. In a report from India, Wadhwa presented a 47 year old woman with 18 years history of rheumatoid arthritis, who had been newly presented with TTP and DVT and positive ANA and anti-dsDNA test results. The patient was then diagnosed as having overlap syndrome.[13] Cesar et al. reported a case of Behcet's disease presenting with TTP and DVT.[14] Other study and case report described the association between TTP and SLE and the primary presentation was anemia (microangiopathic) and thrombocytopenia and after 2 weeks of initial treatment with plasmapheresis articular manifestation developed.[15]

Conclusion

it must be mentioned that, since TTP has multiple similarities with SLE in its clinical or paraclinical features, the diagnosis may be complicated or missed, but accurate and early diagnosis is very important due to the differences between their treatments and fatal course of untreated TTP. In addition, since thrombotic events have a great share in SLE-related mortalities,[1] so keeping a close eye is imperative for lupus patients. It seems that further investigations are essential for determining the common mechanisms involved in the pathogenesis of simultaneous occurrence of these syndromes with each other.

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Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

MAM and ZB carried out the study; prepared and wrote the manuscript. All authors have read and approved the content of the manuscript.

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