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Research Article

AN EXTREMELY RARE CASE OF CONCURRENT THROMBOTIC THROMBOCYTOPENIC PURPURA AND HEMOPHAGOCYTIC LYMPHOHISTOCYTOSIS IN A PATIENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

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ABSTRACT

Cases of Systemic lupus erythematosus complicated by Thrombotic Microangiopathy (TMA) or Hemophagocytic lymphohistiocytosis (HLH) are extremely rare. When concurrent, these diseases delay accurate diagnosis and increase the mortality.

We report a case of 14 years old female with a history of SLE of one month, high grade fever for one week. After admission, the patient rapidly developed headache, declining mental state. Work up revealed platelet count 22×10^9/L, urine RBC 2+, urine protein 1+, blood urea 12.5mmol/l, serum creatinine 122.7 mmol/l, triglyceride 3.34mmol/l, fibrinogen 1.73mg/L, Lactate Dehydrogenase (LDH): 438 IU/L, D-dimer 8.28цg/L, PT 53.4, APPT 61.9 seconds. TMA was suspected because of the presence of fever, anemia, thrombocytopenia, renal involvement and altered mental status. HLH was suspected because of hyperlipidemia, high LDH, low fibrinogen, progressively increasing serum creatinine and splenomegaly. Pulse steroids, broad spectrum antibiotics, iv immunoglobulin were started along with plasma therapy. However, the patient developed multiple organ failure and repeated attempts at resuscitation were unsuccessful.

Conclusion: Lupus patients presenting with TMA and/or HLH might have fatal outcomes despite aggressive treatment. Accurate and timely diagnosis and initiation of treatment is of paramount importance in preserving life in these cases.

Keywords: Systemic lupus erythrematosus, Thrombotic microangiopathy, Hemophagocytic lymphohistiocytosis, plasma therapy

INTRODUCTION

Systemic lupus erythematosus is a multisystem immune associated disorder affecting multiple organs and producing diverse range of symptoms and signs. Patients of SLE are reported to be at a two to three fold higher risk of death than general population [1]. It has been known to present in association with one or more other autoimmune diseases, such as sjrogen's syndrome, etc as a component of an overlap syndrome. Thrombotic microangiopathy(TMA) encompasses two conditions: thrombotic thrombocytopenic purpura (TTP), and hemolytic uremic syndrome(HUS). TTP can be caused by uncontrolled thrombus formation due to an inherited or acquired reduction in activity of Von Willibrand factor (VWf) cleaving protein ADAMS13. The pen-tad for diagnosis of TTP includes fever, thrombocytopenia, Central nervous system (CNS) symptoms, hemolytic anemia and renal dysfunction [2]. TTP rarely occurs simultaneously with SLE; incidence of TTP in cases of SLE being 1-4 % [2], [3]. Onset of TTP can be concurrent with SLE or it can precede or follow its onset [4]. Mortality in TTP is high, approximately 7.5%, even with plasmapharesis [5]. The mortality rate of TTP when occurring in combination with lupus was approximately 34% before 1998, it has since lowered but still remains relatively high at around 12.5% despite aggressive therapy [6]. It is managed by combinations of high dose immunosuppressants such as cyclophosphamide, biological DMARDs such as rituximab, eculizumab,etc steroids and plasma therapy [6],[7],[8].

HLH is a rapidly developing life threatening condition caused by a hyperactive T cell and macrophage activity. It may be familial or acquired. Acquired HLH is triggered by viral infections, hematological malignancies or rheumatic diseases [9]. Macrophage activation syndrome is a subset of HLH caused by severe rheumatological diseases [10]. Clinical presentation includes persistent fever lasting from a week to up to 1 month and poor responsive to antibiotics, organomegaly, serositis, respiratory symptoms, renal disease and central nervous system involvement [11]. Detection of susceptible genes or five of the above given clinical features are required for the diagnosis of HLH [12]. Appropriate treatment of HLH requires immediate application of high dose corticosteroids and cytotoxic agents such as cyclosporin or etoposide [13]. Incidence rates of HLH in the background of SLE ranges is reported to be approximately 9% [14]. Mortality rates in patients with HLH and SLE ranges from 5% to 12% worldwide **[**14], [15].

Instances of TMA or HLH occurring simultaneously have been reported uncommonly in published literature. However, a case of HLH and TTP occurring together in a patient of lupus is so rare, it has only been reported once before. This paper reports a case of HLH and TMA occurring simultaneously in a patient of HLH.

Case description:

A 14 years old female diagnosed as SLE one month earlier and under steroid and mycophenolate mofetil presented with fever for one week was admitted as a case of 1. fever under investigation, 2. Systemic lupus erythematosus, 3. lupus nephritis, 4. hematological involvement of lupus. Body temperatures reached 39.8℃and dropped on taking ibuprofen. On examination she was conscious and cooperative but dyspnoic, icteric and ill looking. Body temperature was high (39.8℃), pulse rate was 138bpm, respiratory rate was 24/min. Blood pressure was normal. Physical examination revealed coarse breath sounds but abnormal sounds

were not heard. She was started on methylprednisolone 80mg iv and cefoperazone sulbactam 1.5g q12h. Patient developed headache, and suffered one episode of non-projectile vomiting on the second day of admission; she was conscious but had poor mental status. Signs of meningeal irritations were negative and pathological reflexes were not produced. Diagnostic workup revealed normal leukocyte count, high neutrophil percentage of 88.2%, low lymphocyte of 9%, monocyte 2.8 %, thrombocytopenia: thrombocyte count 22×109/L, anemia: erythrocyte count 3.09×1012/L, Hemoglobin 89g/L; proteinuria 1+, hematuria 1+; high Erythrocyte Sedimentation rate (ESR) of 18mm/hr, Immunoglobulin G (IgG) was high at 8.6g/L, C3 was low at 0.611g/L. Epstein Barr virus, Cytomegalovirus couldn't be detected. G test and gm test were negative. TMA was suspected on the basis of presence of fever, anemia, thrombocytopenia, renal involvement and altered mental status. Patient was started on Pulse steroid therapy at methylprednisolone 500mg iv. and low molecular weight heparin. Intravenous immunoglobulin was administered at a dose of 15mg iv when platelet count plunged to 21×109//L. Patients condition didn't improve even with intensive steroid therapy, so steroid was reduced to methyl prednisolone 80mg iv. Cefoperazone sulbactam was increased to 1.5g q8h. However, fever, headache, abdominal pain and altered mental status persisted. Blood workup showed hyperlipidemia: cholesterol 2.7 mmol/L, triglyceride 3.34 mmol/L, low High Density Lipoprotein (HDL) 0.34 mmol/L, high Lactate Dehydrogenase (LDH): 438 IU/L, low fibrinogen of 1.73g/L, progressively increasing serum creatinine: 122.7 цmol/L. USG abdomen showed enlarged spleen. SLE flare along with TTP and HLH was suspected. Total Plasma Exchange (TPE) was planned and preparations were started immediately. Central venous line was placed. Antibacterial therapy was intensified by switching to imipenem cilastin 1g iv bd, and fluconazole to be started on 6mg/kg bd and later changed to 4mg/kg iv bd. Some other parameters were as follows: high inflammatory markers: high sensitive C-reactive Protein (hsCRP) was 53.2 mg/L, Procalcitonin (PCT) was 5.81 ng/ml. Liver Function test (LFT) and Kidney function test (KFT) were as follows: total protein 51.3g/L, albumin 24.4 g/L, alanine aminotransaminase(ALT) was 42.1 IU/L, aspartate aminotransferase (AST) was 75.20 IU/L, urea was 11.6 mmol/L. Angiotensin Converting Enzyme (ACE) and Creatine Phosphokinase (CPK) were 111.6 U/L, 20.3 IU/L respectively. Coagulation profile revealed Fibrinogen Degradation Products(FDP) of 25.3 mg/dL, D-dimer 8.28 цg/dL, activated Partial Thromboplastin Time (aPTT) 61.9 sec. Cerebrospinal fluid (CSF) examination didn't show any microorganisms including cryptococcus and acid fast bacilli but found IgG to be 55.20mg/L and IgA of 5.67 mg/L. Patient deteriorated rapidly requiring resuscitation; she became comatose, unresponsive to call or painful stimuli, developed tremors, rigidity. Physical examination demonstrated coarse breath sounds with wheezing; facial, periorbital, conjunctival edema. Pupillary reflex was delayed; deep tendon reflexes were heightened. Neck rigidity appeared and babinski's sing turned positive. She was stabilized with sodium valproate and diazepam. Mannitol was added to reduce intracranial pressure and furosemide was added to relieve peripheral edema. Resuscitation was successful but she remained comatose. TPE was started as soon as was possible. Despite all measures employed, patient's condition continued to decline sharply with recurrent fever, respiratory alkalosis, necessitating repeated attempts of resuscitation, the last of which was

unsuccessful. Later on, NK cells activity and CD25 cells and ADAMS-13 levels was found to be 13.92%, 42395 pg/ml and 18.7% respectively.

DISCUSSION

Thrombotic angiopathy (TMA) and Hemophagocytic lymphohistiocytosis (HLH) both are rare and grave conditions which when occurring with SLE worsen the prognosis. SLE shares multiple clinical manifestations with TTP as well as HLH including, thrombocytopenia, hemolytic anemia, fever, renovascular thrombotic microangiopathy, neurological symptoms, serositis, respiratory symptoms, etc. which makes diagnosis of TTP and/ or HLH as a separate clinical entity concurrent with SLE difficult. Distinguishing TTP or HLH in the background of SLE is critical, as the therapeutic approaches targeting these conditions are different. Delay in diagnosis defers initiation of effective treatment modalities and therefore increases risk of fatality. A comparison study conducted by Pagalavan letchumanan et al in 2009 found that diagnosis of TTP in lupus patients was delayed (approx 7.7 days from the onset of first symptom) when compared with those without lupus [16]. This was also evident in present case where the clinical presentation closely mimicked that of lupus flare confounding the diagnosis of TTP and HLS. Diagnosis was delayed to 9 days after the onset of symptoms and contributed to a fatal outcome. A single center study conducted in south Korea by Kwok et al. with 1206 SLE patients found that high SLEDAI scores and nephritis were independent risk factors for development of TTP in lupus patients. Further more they the study also found infection to be a risk factor for mortality in cases of SLE and TTP [17]. Interestingly, a retrospective study conducted by Cui et al. in 2013 found coexisting renal damage to be associated with more severe disease in SLE-TTP patients [18]. In our case, the patient ran a high fever, her blood picture indicated infection and her inflammatory markers were high, but site of infection couldn't be localized and fever failed to subside in spite of broad spectrum antibiotics. Hence it is likely that uncontrolled infection was an important contributor to mortality. Also, our patient presented with renal involvement which rapidly advanced to renal failure, this could have been a key factor leading to fatal outcome. Similarly, high ferritin was found to be a good predictor of hemophagocytosis patients with SLE **[19]**. In another study conducted by *Aytaç* et al. noted that delay at the time of diagnosis, hepatomegaly, need for plasmapheresis were found to be more common in patients of HLH and SLE with fatal outcomes than those who survived [20]. Hence, special notice should be paid to cardinal signs, symptoms and lab indicators of HLH or TTP presenting in a case of lupus, especially organomegaly, renal involvement, high ferritin levels, infections must be distinguished promptly for timely diagnosis.

A similar case of HLH and TTP overlapping lupus was reported by Yamada et al. from Japan in December 2006 in which the patient improved upon initiation of plasma therapy [21]. Another case of TTP exacerbating lupus which improved on administration of rituximab but advanced to flare of HLH was reported by Kamiya et al. From Japan in 2010. [22]. However, in that case onset of HLH and TTP were temporally asynchronous; where HLH emerged after TTP had started resolving.

CONCLUSION

Presence of a myriad of overlapping manifestations in SLE, HLH AND TMA can confound diagnosis, and defer timely institution of effective therapy increasing chances of mortality. Appearance of certain key features, such as, persistent high grade fever, poor unresponsive to immunosuppressants and steroids, rapid disease progression, renal disease, etc in a patient of lupus should raise suspicion of coexisting TTP/TMA or HLH. Therefore high level of alertness must be maintained while managing SLE patients for timely diagnosis and initiation of life saving intervention.

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