

Case Report

Macrophage activation syndrome presenting in a child with concomitant systemic lupus erythematosus and HIV infection: A case report

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Abstract

Macrophage activation syndrome (MAS) is a life threatening complication of several autoimmune diseases. Systemic lupus erythematosus (SLE) is infrequently reported in association with HIV; the incidence of MAS in coexistence of SLE and HIV is extremely rare. Herein, we report a case of SLE coexisting with HIV infection in a child manifesting as MAS. A 13-year-old girl diagnosed with a congenital HIV infection, undetectable viral load, presented with fever and edema for 2 weeks. Physical examination revealed a body temperature of 39.5°C, puffy eyelids and splenomegaly. Her complete blood count showed hemoglobin at 10.8 g/dL, WBC 1,600 /mm³ (absolute neutrophil count 660/mm³) and platelets 57,000/mm³. Further investigations revealed hyperferritinemia (31,132.3 ng/mL), hypofibrinogenemia (130.6 mg/dL), hypertriglyceridemia (537 mg/dL) and increased hemophagocytic activity in bone marrow. Her blood urea nitrogen and creatinine were 61.4 and 2.58 mg/dL, respectively. Autoimmune profiles (ANA and anti-dsDNA) were positive with high titers; hypocomplementemia (C3 and C4) was observed. A kidney biopsy was compatible with lupus glomerulonephritis class IV. She was diagnosed as MAS with SLE and subsequently treated with HLH-2004 treatment protocol consisting of IVIG, dexamethasone and etoposide. She did not respond to treatment and died of multiple organ failure 10 days after initiation of treatment. Macrophage activation syndrome in concomitant systemic lupus erythematosus and HIV infection is serious condition and can be fatal. Physicians taking care of children with HIV infection should be vigilant regarding these conditions, particularly in those presenting with prolonged fever and deterioration of organ function.

Key words: Macrophage activation syndrome, Systemic lupus erythematosus, HIV infection

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Introduction

Macrophage activation syndrome (MAS) is a complication of several autoimmune diseases. It is a life threatening hyperinflammatory syndrome caused by hypercytokinemia. The incidence of MAS associated with systemic lupus erythematosus (SLE) is about 0.9 - 4.6%.¹ The coexistence of human immunodeficiency virus (HIV) infection and SLE is rare, and MAS in coexistence of SLE and HIV is extremely rare. We report a rare concomitant case of SLE and HIV infection in a child, manifesting as MAS, refractory to treatment.

Case report

A 13-year-old Thai girl presented with fever and edema for 2 weeks. She was diagnosed with HIV infection since 3 years of age. She was initially treated with azidothymidine, lamivudine and nevirapine then switched to tenofovir, efavirenz and lamivudine due to anemia. She was considered to have good drug adherence; her viral load was less than 20 copies and CD4 count was 285/mm³. Six months prior to admission, she had periorbital swelling in the morning; tenofovir was changed to stavudine due to proteinuria. Two weeks prior to admission, she developed fever, dyspnea and generalized edema. She was admitted to a provincial hospital for evaluation of fever and dyspnea. She was treated with intravenous ceftriaxone and then given piperacillin-tazobactam and meropenem, respectively. There was no identifiable source of infection. On the eighth day after admission, she developed bilateral pleural effusion and anemia. She was referred to our hospital for further investigation. The clinical examination gave a body temperature of 39.5°C, periorbital edema, decreased breath sound in the left lung, pitting edema at pretibial area and splenomegaly. Hematological investigations revealed hemoglobin at 10.8 g/dL, WBC 1,600/mm³ (absolute neutrophil count 660/mm³), platelets 57,000/mm³ and

a reticulocyte count of 0.56%. Peripheral blood smear showed some spherocytes. The direct antiglobulin test was positive 2+ and lactate dehydrogenase was 788 U/L. Our biochemical investigation revealed BUN 61.4 mg/dL, creatinine 2.58 mg/dL, serum sodium 131 mmol/L, potassium 4.3 mmol/L, chloride 105 mmol/L, bicarbonate 18.6 mmol/L, calcium 7.2 mg/dL, magnesium 1.3 mg/dL and phosphate 5.1 mg/dL. The liver function test showed total protein 4.7 g/dL, albumin 1.8 g/dL, globulin 2.9 g/dL, total bilirubin 0.37 mg/dL, direct bilirubin 0.26 mg/dL, indirect bilirubin 0.11 mg/dL, AST 59 U/L, ALT 9 U/L, ALP 362 U/L and GGT 517 U/L. Urine analysis revealed protein 3+, erythrocyte 4+, RBC 20-30/HPF; urine protein/creatinine ratio was 12.88.

Further investigations displayed levels of hyperferritinemia (31,132.3 ng/mL), hypofibrinogenemia (130.6 mg/dL), hepartriglyceridemia 537 mg/dL and increased hemophagocytic activity in bone marrow (Figure 1). PT and aPTT were 11.5 and 37.9 seconds, respectively. She was diagnosed with hemophagocytic lymphohistiocytosis (HLH), according to the hemophagocytic lymphohistiocytosis criteria.² The computer tomography of chest and whole abdomen revealed diffuse reticular infiltration in both lungs with bilateral pleural and pericardial effusion, splenomegaly, enlargement of both kidneys, and diffuse edema of bowel wall. Thoracentesis was performed and the pleural fluid analysis was classified as transudate by Light's criteria.³ Additional investigations to identify the infectious causes associated with HLH were done including hemoculture for bacteria and fungus, sputum for acid fast bacilli staining and culture for mycobacteria, and anti-Ebstein-Barr viral capsid antigen IgG and IgM: all were negative. Immunological screening was positive for ANA (Homogenous pattern >1:5,120), anti-dsDNA (>1:640). Serum C3 and C4 complement factors were low, 0.27 g/L and 0.09 g/L, respectively. Renal biopsy was compatible with lupus nephritis class IV (Figure 2 and 3).

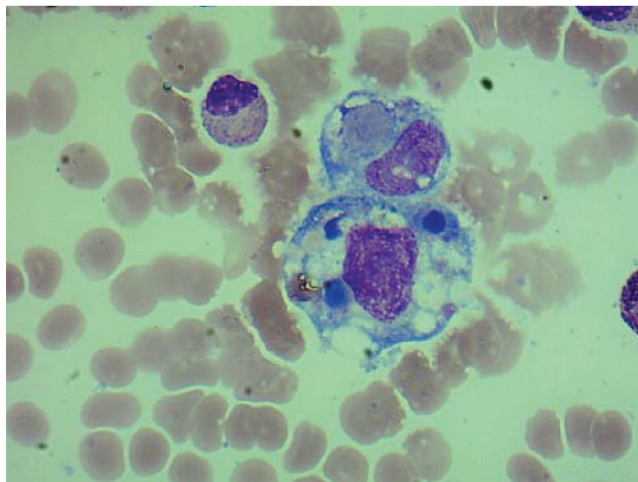


Figure 1 Bone marrow aspiration shows hemophagocytosis consistent with macrophage activation syndrome.

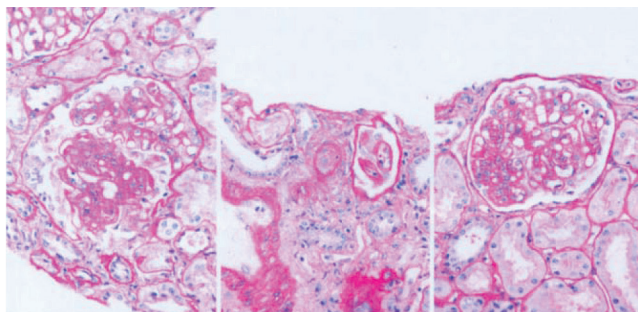


Figure 2 The glomeruli show diffuse segmental endocapillary proliferation with fibrin thrombi.

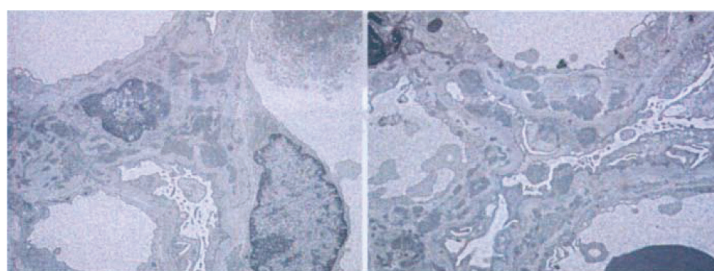


Figure 3 The glomerulus shows electron dense deposits in subepithelium, subendothelium and mesangium.

She was subsequently treated with IVIG, etoposide and pulse methylprednisolone for three days then switched to dexamethasone as per HLH

protocol.² She did not respond to given treatment and died of multiple organ failure 10 days after initiation of treatment.

Discussion

Hemophagocytic lymphohistiocytosis was first described by Farquhar and Claireaux.⁴ HLH is fatal and arduous to diagnose. HLH pathogenesis is when a defect in inflammatory signals occurs, resulting in uncontrollable hypercytokinemia, ultimately leading to end-organ damage.⁵ HLH is classified into primary and secondary HLH. The latter may develop as a complication of infection, malignancy, post-allogeneic hematopoietic stem cell transplantation and autoimmune disease.⁶ Viral pathogens are notoriously known as a cause of infectious associated HLH, especially Epstein-Barr virus (EBV). HIV infection is also found associated with HLH.⁷ The manifestations of HIV-associated HLH are not different from those of other virally associated HLH.⁷ Interestingly, those who developed HIV-associated HLH tend to have higher viral loads, co-commitment opportunistic infections or underlying of malignancies such as lymphoma.⁷

The term macrophage activation syndrome (MAS) is specifically reserved for secondary HLH resulting from autoimmune disease. MAS is commonly associated with juvenile idiopathic arthritis and to a lesser extent with SLE; the incidence of MAS associated with SLE is rare, about 0.9-4.6%.¹ The criteria for diagnosis of MAS is different from that of HLH, i.e. the evidence of hemophagocytosis is not required for MAS diagnosis given that it may delay diagnosis.⁸ There are several signs and symptoms of MAS including high fever, hepatosplenomegaly, mucocutaneous bleeding, and central nervous system dysfunction. Occasionally, renal, pulmonary and cardiac involvement has been reported.⁹ The most common precipitating factor is inter-current viral infection, especially EBV infection.¹⁰ In this case, there was no identifiable infectious organism. However, we cannot exclude other obscure viral pathogens. Although both HIV infection and SLE can cause HLH, SLE appeared to be the culprit since the clinical features revealed active SLE while her HIV infection was well under control.

The incidence of autoimmune disease in those with HIV infection is higher than that in the normal population.¹¹ However, highly active antiretroviral therapy (HAART) seems to be the pivotal factor determining the types of autoimmune disease. HAART lowered the incidence of several types of autoimmune disease including SLE, Sjögren syndrome, psoriasis, rheumatoid arthritis, scleroderma, polymyositis, and Hashimoto's thyroiditis while it increased the incidence of autoimmune haemolytic anaemia.¹¹ The imbalance between CD4+ T and CD8+ T cells and the molecular mimicry between HIV and self-antigens are considered to be the possible mechanism.^{12, 13} In our case, she developed severe SLE despite being treated with HAART; the possible explanation is that she had a congenital HIV infection which might have prolonged immune deregulation versus those with non-congenital infection. Interestingly Strauss et al. also report the case series of glomerular disease in patients with congenital HIV infection.¹⁴ Cumulatively, these may explain why our patient had severe lupus nephritis.

Treatment of HLH is based on the HLH 2004 protocol consisting of IVIG, cyclosporin, dexamethasone and etoposide. The mortality rate of SLE-associated MAS is high, ranging from 5-12.5%.^{8, 9} despite treatment. With our patient, she did not receive cyclosporine due to severe acute kidney injury. On top of that, the immune deregulation due to her perinatal HIV infection may have potentiated her disease activity ultimately resulting in a fatal outcome.

Conclusion

In conclusion, physicians taking care of patients with HIV infection should be vigilant regarding the increased incidence of autoimmune disease. MAS should be suspected in those who have underlying autoimmune disease and subsequently develop fever and deterioration of organ function. Urgent treatment is required in those suspected MAS cases.

Conflict of Interest Declaration

All authors declare no personal or professional conflicts of interest and no financial support from the companies that produce and/or distribute the drugs described in this report.

References

1. Granata G, Didona D, Stifano G, Feola A, Granata M. Macrophage activation syndrome as onset of systemic lupus erythematosus: a case report and a review of the literature. *Case reports in medicine*. 2015;2015:1-4.
2. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48:124-31.
3. Tarn AC, Lapworth R. Biochemical analysis of pleural fluid: what should we measure?. *Annals of clinical biochemistry*. 2001;38:311-22.
4. Farquhar JW, Claireaux AE. Familial haemophagocytic reticulosis. *Arch Dis Child*. 1952;27:519-25.
5. Rosado FG, Kim AS. Hemophagocytic Lymphohistiocytosis An Update on Diagnosis and Pathogenesis. *Am J Clin Pathol*. 2013;139:713-27.
6. Morimoto A, Nakazawa Y, Ishii E. Hemophagocytic lymphohistiocytosis: pathogenesis, diagnosis, and management. *Pediatr Int*. 2016;58:817-25.
7. Fardet L, Lambotte O, Meynard JL, Kamouh W, Galicier L, Marzac C, et al. Reactive haemophagocytic syndrome in 58 HIV-1-infected patients: clinical features, underlying diseases and prognosis. *AIDS*. 2010;24:1299-306.
8. Borgia RE, Gerstein M, Levy DM, Silverman ED, Hiraki LT. Features, Treatment and Outcomes of Macrophage Activation Syndrome in Childhood-onset Systemic Lupus Erythematosus. *Arthritis Rheumatol*. 2018;70:616-24.
9. Ravelli A. Macrophage activation syndrome. *Curr Opin Rheumatol*. 2002;14:548-52.
10. Liu AC, Yang Y, Li MT, Jia Y, Chen S, Ye S, et al. Macrophage activation syndrome in systemic lupus erythematosus: a multicenter, case-control study in China. *Clin rheumatol*. 2018;37:93-100.
11. Yen YF, Chuang PH, Jen IA, Chen M, Lan YC, Liu YL, et al. Incidence of autoimmune diseases in a nationwide HIV/AIDS patient cohort in Taiwan, 2000–2012. *Ann Rheum Dis*. 2017;76:661-5.
12. Fife DJ, Waller JM, Jeffes EW, Koo JY. Unraveling the paradoxes of HIV-associated psoriasis: a review of T-cell subsets and cytokine profiles. *Dermatol Online J*. 2007;13:4.
13. Russo S, Lopalco L. Is autoimmunity a component of natural immunity to HIV? *Curr HIV Res*. 2006;4:177-90.
14. Strauss J, Abitbol C, Zilleruelo G, Scott G, Paredes A, Malaga S, et al. Renal disease in children with the acquired immunodeficiency syndrome. *N Engl J Med*. 1989;321:625-30.

บทคัดย่อ

ภาวะ macrophage activation syndrome ในผู้ป่วยเด็กโรค systemic lupus erythematosus ที่มีการติดเชื้อ HIV
ร่วมด้วย: รายงานกรณีศึกษาผู้ป่วย

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ผู้ให้ติดต่อ: ผู้ช่วยศาสตราจารย์ แพทย์หญิงผกาทิพย์ ศิลปมงคลกุล คณะแพทยศาสตร์ มหาวิทยาลัยธรรมศาสตร์ ๙๕ หมู่ ๘ ถนนพหลโยธิน อำเภอคลองหลวง จังหวัดปทุมธานี ๑๒๑๒๑

Macrophage activation syndrome (MAS) เป็นภาวะแทรกซ้อนที่รุนแรงมีอันตรายถึงชีวิตได้ของโรคในกลุ่มภูมิคุ้มกันทำงานทำร้ายตัวเอง (autoimmune disease) มีรายงานพบน้อยกว่าโรค systemic lupus erythematosus (SLE) มีความสัมพันธ์กับการติดเชื้อเอชไอวี เช่นเดียวกับการเกิด MAS ในผู้ป่วยที่เป็นโรค SLE และมีการติดเชื้อเอชไอวีร่วมกันก็มีการรายงานการเกิดน้อยมากในที่นี้เราขอจึงนำเสนอตัวอย่างผู้ป่วยเด็ก ๑ รายที่มีโรค SLE ร่วมกับการติดเชื้อเอชไอวีและเกิดภาวะ MAS ขึ้น เด็กหญิงอายุ ๑๓ ปี ซึ่งเดิมได้รับการวินิจฉัยว่ามีการติดเชื้อเอชไอวีแต่กำเนิดและมีระดับไวรัสในเลือดต่ำมากมีอาการไข้และบวมเป็นเวลา ๒ สัปดาห์ ตรวจร่างกายพบว่ามีไข้ ๓๙.๕ องศาเซลเซียส เปลือกตาบวม (puffy eyelids) และม้ามโต ผลการตรวจทางห้องปฏิบัติการพบระดับฮีโมโกลบิน ๑๐.๘ กรัม/ดล., จำนวนเม็ดเลือดขาว ๑,๖๐๐ /ลบ.มม. (จำนวนเม็ดเลือดขาวชนิด neutrophil ๖๖๐ /ลบ.มม.), จำนวนเกล็ดเลือด ๕๗,๐๐๐ /ลบ.มม., ferritin ๓๑,๑๓๒.๓ นาโนกรัม/มล., fibrinogen ๑๓๐.๖ มก./ดล., triglyceridemia ๕๓๗ มก./ดล. และมีการทำงานของ hemophagocytic histiocytes เพิ่มขึ้นในไขกระดูก นอกจากนี้ผู้ป่วยได้ตรวจการทำงานของไตพบ BUN ๖๑.๔, Cr ๒.๕๘ มก./ดล. ผลการตรวจทางภูมิคุ้มกันพบผลบวกต่อ ANA และ anti-ds DNA ในระดับสูงและมีระดับ C3, C4 ต่ำ ตรวจชิ้นเนื้อไตทางพยาธิวิทยาผลเข้าได้กับ lupus glomerulonephritis class IV ผู้ป่วยได้รับการวินิจฉัยว่าเป็น MAS ร่วมกับ SLE และได้รับการรักษาด้วยสูตรยาตาม HLH - 2004 ซึ่งมียาประกอบด้วย IVIG, dexamethasone และ etoposide ซึ่งผู้ป่วยไม่ตอบสนองต่อการรักษาและเสียชีวิตจากการทำงานของอวัยวะหลายระบบในร่างกายล้มเหลวเมื่อ ๑๐ วันหลังจากเริ่มการรักษา ภาวะ MAS ในผู้ป่วย SLE ที่มีการติดเชื้อเอชไอวีมีความรุนแรงและอันตรายถึงชีวิตได้ แพทย์ผู้ดูแลเด็กที่ติดเชื้อเอชไอวีควรตระหนักถึงภาวะดังกล่าวด้วย โดยเฉพาะผู้ป่วยที่มีอาการไข้ติดต่อกันเป็นเวลานานและมีการทำงานของอวัยวะต่างๆ ที่ผิดปกติอย่างมาก

คำสำคัญ: Macrophage activation syndrome, Systemic lupus erythematosus, การติดเชื้อ HIV