Systemic Lupus Erythematosus Progressing to Non-Hodgkin’s Lymphoma Complicated by Fatal Hemophagocytic Syndrome: Case Report

Ivica Jeremić1, Slobodanka Đorđević-Kontić1, Miloš Nikolić2, Mirjana Šefik-Bukilica1, Nada Vujasinović-Stupar1, Branka Bonači-Nikolić3

1Institute of Rheumatology; 2Department of Dermatology; 3Department of Allergy and Clinical Immunology, Clinical Centre of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

SUMMARY Hemophagocytic syndrome (HPS) may be provoked by infections, malignancies and autoimmune diseases. We report on a 56-year-old woman with long-lasting systemic lupus erythematosus (SLE) who presented with malar rash, inflammatory livedo reticularis, fever, weight loss, pancytopenia and mild splenomegaly with cervical lymphadenopathy. She had criteria for SLE flare-up (malar rash, high antinuclear antibody titer, complement consumption, pathological urinary sediment, and retinal vasculitis). Despite high-dose glucocorticoid therapy, pancytopenia and fever worsened. Important elevations of triglycerides and ferritin were also found. Bone marrow aspirate demonstrated hemophagocytosis, which confirmed the coexistence of HPS and SLE. The treatment with glucocorticoids, immunoglobulins, cyclophosphamide, filgrastim and antimicrobial therapy was unsuccessful. After one month, the patient developed Pneumocystis jirovecii pneumonia with fatal outcome. Bone marrow biopsy, taken 5 days before death, showed high grade diffuse large B-cell (CD20+, Ki-67+) non-Hodgkin’s lymphoma (DLBCL). We are the first to report the association of both SLE and non-Hodgkin’s lymphoma complicated by HPS. We showed that, based on clinical and laboratory data, it was difficult to distinguish the early phase of HPS from SLE flare-up and new-onset DLBCL. Therapy of such a complex case of HPS has not been standardized, and opportunistic infections remain a difficult issue.

KEY WORDS: hemophagocytic syndrome, systemic lupus erythematosus, lymphoma

INTRODUCTION

Hemophagocytic syndrome (HPS) is a life-threatening disease caused by high concentrations of inflammatory cytokines (IFN-γ, IL-12, IL-18) (1). The pathogenesis of HPS is not clearly elucidated, but impaired cytotoxic T-lymphocyte functions with low perforin expression play an important role (1). The hallmarks of the syndrome are prolonged fever, splenomegaly and cytopenia. Biochemical characteristics...
of HPS are elevated ferritin and triglycerides with low fibrinogen levels (1). Hemophagocytosis by benign macrophages is most commonly found in the spleen, liver and lymph nodes and, not so frequently, in bone marrow, especially early in the disease.

Primary HPS usually appears in childhood and, if untreated, is fatal (1). Secondary HPS is more common and associated with infections, malignancies and autoimmune disorders (1,2).

A special form of HPS in patients with autoimmune diseases, especially systemic-onset juvenile idiopathic arthritis, adult-onset Still’s disease, and systemic lupus erythematosus (SLE), is known as macrophage activation syndrome (MAS) (1,2).

Lymphoma-associated HPS is more frequently reported in T/natural killer (NK)-cell malignancies, while B-cell lymphoma-triggered HPS seems to be rare (1,3).

A combination of several underlying conditions leading to HPS is very rare in the literature (2). Many features of HPS overlap with characteristics of SLE flare-up and new-onset B-cell lymphoma, which may delay reaching an accurate diagnosis and therapy.

We report on a patient with both active SLE and lymphoma associated with HPS, in whom immunosuppressive therapy was complicated with fatal Pneumocystis jirovecii infection. Although the treatment strategy for HPS triggered by both autoimmune and lymphoproliferative disease is not well established, we discuss the possible favorable effects of pharmacological doses of vitamin D on the course of HPS. To the best of our knowledge, our patient is the first case of associated SLE and new-onset non-Hodgkin’s lymphoma (NHL) complicated by HPS.

**CASE REPORT**

A 56-year-old woman presented in September 2009 with malar rash, livedo reticularis (Fig. 1), fatigue, shortness of breath and fever (up to 39.5 ºC), lasting for two weeks. She reported a 15 kg weight loss during the last two months.

The patient had SLE since 1979 (malar rash, photosensitivity, arthritis, leukopenia, and high antinuclear antibody – ANA) (4). She never had renal or central nervous system manifestations. She was treated with chloroquine and prednisone at maximum 40 mg/day to minimum 5 mg/day.

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In March 2009, she was hospitalized at a department of pulmonology because of dyspnea and fatigue. She had no fever, cytopenia, hepatosplenomegaly, or lymphadenopathy. Erythrocyte sedimentation rate (ESR) was 80 mm/h, ANA titer was 1:640 (fine-speckled), and C3 and C4 were low. Computerized tomography disclosed interstitial infiltrates in the middle and lower lobes of both lungs. Transbronchial lung biopsy showed lupus pneumonitis. SLE flare-up was diagnosed, prednisone dose was elevated to 60 mg/day, and mycophenolate mofetil (MMF), 1000 mg/day, was started.

In September 2009, the patient presented with fever (39.5 ºC), facial pallor, oral ulcerations, increased heart rate (110/minute), tachypnea (23/minute), cervical lymphadenopathy (2 cm) and mild splenomegaly (15 cm). ESR was 96 mm/h and CRP 2.9 mg/L (normal <5 mg/L). Other routine laboratory parameters are shown in Table 1. Direct and indirect Coombs tests were negative.

On HEP-2 cells, ANA (fine-speckled) was 1:640 (Fig. 2). Anti-HIV, HCV, EBV antibodies, and HBsAg were negative. Serum immunoglobulins were normal. Electrophoresis and immunofixation did not show monoclonal immunoglobulins. Anti-SSA was >200 U/mL (normal <25 U/mL), anti-Sm/RNP and anti-dsDNA antibodies were negative. aCL IgG was 77.8 GPLU/mL (normal <10 GPLU/mL), and anti-beta 2 GP I IgG 93.8 U/mL (normal <8 U/mL). C3 was 0.54 g/L (normal 0.9-1.8 g/L) and C4 was 0.15 g/L (normal 0.1-0.4 g/L). International normalized ratio (INR) was 2.29. Urine sediment showed 12-14 WBC and 12-15 RBC per high power field. Other routine analyses were normal. Chest X-rays revealed bilateral infiltrative shadows. Bacteriological and mycological sputum analyses were negative. Urine and blood cultures.
were repeatedly sterile. The patient fulfilled the criteria for SLE flare-up (fever, pancytopenia, complement consumption and pathological urinary sediment). MFM was discontinued (severe leukocytopenia) and prednisone dose was increased to 1 mg/kg. The fever persisted and she was treated with intravenous methylprednisolone pulse therapy (500 mg/day for 3 days). During the next 4 days, she was afebrile, but on day 5 she got fever again and lost vision on her right eye. Ocular fundus examination showed retinal vasculitis. SLE had a high activity index (SLEDAI 28) (5).

On day 10, procalcitonin was 0.1 ng/mL (normal <0.1 ng/mL), β2-microglobulin 12.4 mg/L (normal 1.2-2.8 mg/L) and 25-(OH)-vitamin D₃ was undetectable (normal 34-105 nmol/L). Despite high-dose glucocorticoid therapy, pancytopenia, fever, hepatic lesion and hyperferritinemia worsened in association with hyperferritinemia (Table 1).

Table 1. Routine laboratory analyses

<table>
<thead>
<tr>
<th></th>
<th>At presentation</th>
<th>After 10 days</th>
<th>After 30 days</th>
</tr>
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<tbody>
<tr>
<td>Hgb (n. 119-157 g/L)</td>
<td>86</td>
<td>62</td>
<td>79</td>
</tr>
<tr>
<td>RBC (n. 3.86-5.08x10¹²/L)</td>
<td>2.61</td>
<td>1.87</td>
<td>2.53</td>
</tr>
<tr>
<td>WBC (n. 3.4-9.7x10⁹/L)</td>
<td>1.8*</td>
<td>0.6</td>
<td>8.6</td>
</tr>
<tr>
<td>PLT (n. 150-350x10⁹/L)</td>
<td>50</td>
<td>43</td>
<td>80</td>
</tr>
<tr>
<td>Triglycerides (n. &lt;1.7 mmol/L)</td>
<td>6.3</td>
<td>12.7</td>
<td>13.3</td>
</tr>
<tr>
<td>LDH (n. 220-460 U/L)</td>
<td>598</td>
<td>1,414</td>
<td>1,519</td>
</tr>
<tr>
<td>AST (n. &lt;37 U/L)</td>
<td>32</td>
<td>91</td>
<td>98</td>
</tr>
<tr>
<td>ALT (n. &lt;41U/L)</td>
<td>38</td>
<td>48</td>
<td>66</td>
</tr>
<tr>
<td>Bilirubin (n. &lt;21 μmol/L)</td>
<td>41.8</td>
<td>47</td>
<td>30.2</td>
</tr>
<tr>
<td>Ferritin (n. 5-170 μg/L)</td>
<td>ND</td>
<td>2,770</td>
<td>2,800</td>
</tr>
<tr>
<td>Fibrinogen (n. 2-4 g/L)</td>
<td>2.2</td>
<td>2</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Differential count: neutrophils 51%, lymphocytes 43%, monocytes 5%, eosinophils 1%; ND = not done

Bone marrow aspirate demonstrated histiocytosis with extensive hemophagocytic activity (Fig. 3).

The diagnosis of HPS was made according to 6/8 criteria: 1) fever, 2) splenomegaly, 3) pancytopenia, 4) hypertriglyceridemia (>3 mmol/L), and 5) high ferritin (>500 μg/L), 6) bone marrow hemophagocytosis (6). High-dose intravenous immunoglobulin (IVig) (400 mg/kg/day) for 5 days, filgrastim (5 μg/kg/day), blood transfusion, antibiotics (piperacillin/tazobactam + metronidazole), and antifungals (fluconazole) were started. Methylprednisolone was replaced with equivalent dose of dexamethasone. Seven days after the introduction of IVig and dexamethasone, she...
still had fever and leukopenia (1.6x10^9/L). Because of MAS, treatment with cyclophosphamide (intravenous pulse 1 g) was introduced, and dexamethasone was increased to the dose equivalent to prednisone 2 mg/kg. At that time, biopsy of anterior iliac crest was performed. Six days later, pancytopenia persisted. In order to correct vitamin D deficiency, therapy with high dose cholecalciferol (15,000 IU/day) was started. Five days afterwards, WBC count was normalized and platelet count was increased (Table 1). During that period, she was afebrile. Suddenly, the patient developed cough, fever and dyspnea. On the second day of the onset of new symptoms, *Pneumocystis jirovecii* was isolated from sputum. Immediately, treatment with cotrimoxazole 120 mg/kg/day was started. On the third day, hemoptysis was noted, dyspnea deteriorated, and she died from adult respiratory distress syndrome (ARDS). Immunohistochemical analysis of bone marrow biopsy (Fig. 4), showed high grade DLBCL with the following characteristics: CD 34-, CD 23+, MPO-, CD 31-, CD 68-, CD 79α+, CD 20+ (high membrane positivity), CD 10−, CD 23+, CD 3−, CD 43−, CD 138−, bcl-2−, bcl-6+/−, CD 30−, MUM-1−, ALK-1+/−, Cyclin D1−. More than 80% of cells were Ki-67 positive (high proliferative activity).

**DISCUSSION**

Autoimmune diseases, lymphomas and infections are well known HPS-associated diseases (1). Regardless of the underlying disease, nonspecific clinical characteristics often delay the diagnosis of HPS. The diagnosis can be made if 5/8 criteria are fulfilled: 1) fever, 2) splenomegaly, 3) bicytopenia/pancytopenia, 4) hypertriglyceridemia and/or hypofibrinogenemia, 5) hyperferritinemia, 6) decreased/absent NK-cell activity, 7) high-soluble interleukin-2-receptor levels (sIL-2R), and 8) hemophagocytosis (6).

Attenuation of hyperinflammation is the aim of therapy, but opportunistic infections in immunosuppressed patients complicate the course of HPS (1). Glucocorticoids, IVlg, cyclosporin A, plasmapheresis and etoposide are used in the treatment of HPS. The mortality rate of HPS is 10%-50% (1).

HPS is an uncommon manifestation in SLE and it occurs with flare of the disease or with associated infections (2). In our patient, acute phase reactants (low procalcitonin and C-reactive protein) and microbiological analyses did not reveal infection as a trigger of HPS. The initial presentation (high fever, pancytopenia, low complement, retinal vasculitis, worsening of urinary sediment) strongly suggested a flare-up of SLE. On the other hand, splenomegaly, pancytopenia, fever, high liver enzymes and LDH are common in both SLE and HPS (1,2). High triglycerides, as a marker of HPS, may also be elevated in SLE patients on glucocorticoid therapy. High serum ferritin level is specific but not pathognomonic for HPS. Erythrophagocytosis may also be a manifestation of autoimmune hemolytic anemia, unrelated to HPS (7). Disseminated intravascular coagulation with low fibrinogen, renal failure and central nervous system dysfunction can complicate both HPS and SLE. It was shown that not only patients with HPS, but also SLE patients might have decreased NK-cell activity (8). Although the diagnostic criteria are well established, it may be difficult to make the differential diagnosis between SLE flare and HPS. In our patient, the initial short-term improvement after glucocorticoid pulses, with short afebrile period, was probably due to the natural course of HPS (1). Clinical presentation and insufficient response to glucocorticoid pulses raised suspicion of HPS, which was finally confirmed by sternal puncture.

Immediately after the diagnosis of SLE and HPS, daily methylprednisolone was replaced with dexamethasone (penetrates the blood-brain and blood-ocular barrier better than methylprednisolone) and IVlg was started. The combination of glucocorticoids, IVlg and cyclophosphamide was previously reported as successful therapy in patients with SLE complicated with HPS, but it proved ineffective in lymphoma-associated HPS (1,2,9).

The mechanism(s) leading to the development of lymphoma in patients with SLE are not fully elucidated, but a sustained autoantigen-driven B-cell proliferation may increase the risk of B lymphocyte malignant transformation. SLE patients develop NHL threefold more frequently than the general population. Also, in patients with SLE, DLBCL is more aggressive and often complicates prolonged course of the
disease, as was the case in our patient (3). Before the presentation of DLBCL, our patient had lupus pneumonitis and leukopenia, which both increase the risk of lymphoma (3). Antiphospholipid antibodies, found in our case, are common serologic markers both in patients with SLE and NHL (10). Differentiation of B-cells, autoantibody production and suppression of B-cell apoptosis are controlled by B lymphocyte stimulator (BlyS). Apart from being one of the key cytokines in SLE, BlyS increases B-cell proliferation in patients with NHL (11).

High concentrations of α-chain of sIL-2R and β2-microglobulin, produced by activated lymphocytes, characterize both HPS and NHL (1). It is obvious that prolonged fever, progressive pancytopenia, hepatosplenomegaly, peripheral lymphadenopathy, elevated sIL-2R and β2-microglobulin might be presenting manifestations of both NHL and HPS (1). Bone marrow biopsy and immunostaining is essential for the diagnosis, identification of lymphoma subtype and appropriate therapy.

Our patient with SLE and NHL-triggered HPS became for the first time afebrile, normalized leukocyte counts and increased platelet counts for five days after the introduction of high dose vitamin D3 therapy, given to correct the undetectable levels of vitamin D3. We assumed that the effects on WBC and platelets might be the result of synergistic effects of glucocorticoids and high doses of vitamin D3. It is well known that HPS is a Th1-driven disease, with elevated levels of IFN-γ, IL-12 and IL-18 (1). IFN-γ is a major mediator of macrophage activation and, together with soluble Fas ligand, may contribute to tissue damage in HPS. Vitamin D decreases IFN-γ and IL-2 synthesis, and increases IL-4, IL-5 and IL-10 synthesis (12). Decreasing of IFN-γ levels attenuates macrophage activity and, by increasing IL-10, enhances negative feedback on Th1 cytokine production. In addition, vitamin D decreases antigen presenting activity and maturation of dendritic cells. Antitumor activity of vitamin D3 on lymphoma cells is further enhanced by induction of transforming growth factor β synthesis (13). Moreover, some vitamin D analogues showed efficacy in patients with follicular small-cleaved cell lymphoma (14). The importance of immunomodulatory effects of relatively non-toxic vitamin D, added early to standard regimen, remains to be elucidated.

Unfortunately, opportunistic infections, very frequent in lymphoma patients, further complicated the course of HPS in our patient. ARDS, triggered by Pneumocystis jirovecii, may be the cause of death in severe immunocompromised patients with lymphoma and HPS (15).

Our case represents the previously unpublished association of SLE flare-up with new-onset DLBCL complicated by HPS. We showed that, based on clinical and laboratory data, it was difficult to distinguish the early phase of HPS from SLE flare and new-onset DLBCL. Although HPS is a well described complication of SLE, we demonstrated that progression of SLE to DLBCL should always be borne in mind, especially in patients unresponsive to standard treatment. R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) as a treatment for SLE complicated with DLBCL has not been investigated in patients with concomitant HPS. Therapy of such a complex case of HPS has not been standardized, and opportunistic infections remain a difficult issue.

Acknowledgment

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References


16. Elida ideal soap; year 1937. (from the collection of Mr. Zlatko Puntijar)