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**Title:** Recurrent atrial fibrillation after high-dose methylprednisolone therapy in a girl with lupus-associated hemophagocytic syndrome

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**Running Title:** AF in lupus-associated hemophagocytic syndrome

**Abbreviations:** atrial fibrillation, Af; C-reactive protein, CRP; hemophagocytic syndrome, HPS; interferon, IFN; interleukin, IL; macrophage activation syndrome, MAS; systemic lupus erythematosus, SLE; tumor necrosis factor, TNF.

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**Abstract**

Hemophagocytic syndrome (HPS) is a serious complication of systemic lupus erythematosus (SLE). A 15-year-old female with lupus-nephritis developed HPS. Bone marrow study showed florid thrombophagocytosis. There was no associated infection. High-dose methylprednisolone therapy ameliorated HPS. However, atrial fibrillation (Af) repeated after the infusion and required direct-current cardioversion. No underlying diseases were found in the heart and endocrine system. Chest roentgenogram and echocardiography were normal. Electrocardiogram showed slightly prolonged PR interval in sinus rhythm. Af occurred at high circulating levels of interferon- $\gamma$  and interleukin (IL)-10, but not IL-6, IL-2, tumor necrosis factor- $\alpha$ , C-reactive protein or catecholamines. This is the first observation that high-dose corticosteroid induced Af in case of lupus-HPS. Af is unusual in SLE children without cardiac disease, while conduction defect occurs associated with lupus-myocarditis. Lupus-HPS may be an aggressive SLE subset with cardiac involvement. High-dose corticosteroid infusion controls lupus activity, but could disclose the cardiac stress in lupus-HPS patients.

**Key Words:** atrial fibrillation, systemic lupus erythematosus, high-dose methylprednisolone therapy, hemophagocytic syndrome

## **Introduction**

Hemophagocytic syndrome (HPS) is an immunohematologic emergency characterized by fever, hepatosplenomegaly, cytopenias, disseminated intravascular coagulopathy, and bone marrow hemophagocytosis. Reactive HPS occurs associated with infections, malignancy and rheumatologic diseases such as systemic lupus erythematosus (SLE) and juvenile idiopathic arthritis.<sup>1</sup> HPS arises from uncontrolled lymphohistiocytic activation and hypercytokinemia. Macrophage activation syndrome (MAS) is a prototype of autoimmune-associated HPS involving excessive production of inflammatory cytokines such as interferon (IFN)- $\gamma$ , interleukin (IL)-6 and tumor necrosis factor (TNF)- $\alpha$ . Inflammation has been postulated as a predisposing factor for atrial fibrillation (Af).<sup>2</sup> Sata *et al.*<sup>3</sup> reported that patients with paroxysmal Af had the elevated circulating inflammatory markers of IL-6, TNF- $\alpha$  and C-reactive protein (CRP). Many other reports indicated a significant association between CRP or IL-6 levels and developing Af.<sup>4</sup> Hak *et al.*<sup>5</sup> have recently showed the association between postoperative Af and elevated serum levels of IL-2, IFN- $\gamma$  and IL-10. Histopathological analysis of atrial tissues obtained from patients with lone Af showed inflammatory infiltrates in more than 60% of samples.<sup>6</sup> Nevertheless, arrhythmias are unusual presentation of MAS/HPS or lupus flare-up in children without cardiac involvement.

There is controversy about the risk and benefit of corticosteroids in patients with Af. Low-dose corticosteroid therapy may prevent Af by reducing inflammation.<sup>7</sup> On the other hand, van der Hooft *et al.*<sup>8</sup> reported that high-dose corticosteroid therapy increased the risk of developing Af. The high-dose therapy is the mainstay of controlling SLE and MAS/HPS. Paroxysmal Af after high-dose methylprednisolone therapy were reported in adults,<sup>9-11</sup> but only 2 children with SLE or nephrotic syndrome.<sup>12</sup> There were no reports

warning against arrhythmias in patients with lupus-associated HPS despite the occasions of high-dose corticosteroid therapy.

We herewith report a 15-year-old female with lupus-associated HPS who suffered from recurrent Af following high-dose methylprednisolone therapy. Precipitating factors for developing Af in the pediatric lupus-HPS were discussed.

### **Case report**

A 15-year-old girl was diagnosed as having class IV lupus nephritis in 2007. High-dose methylprednisolone pulse therapy led to a remission of glomerulonephritis. Lupus activity was controlled by oral prednisolone and mizoribine for subsequent two years. Hospital admission was prompted in 2009 because of fever, facial butterfly rash and disseminated intravascular coagulopathy. A course of 3 consecutive daily pulses of intravenous methylprednisolone in a dose of 500 mg failed to control the disease activity. This patient was then transferred to our hospital for the treatment.

Physical examination revealed blood pressure to be 100/50 mmHg, a regular pulse of 88/min, and a body temperature of 37.8 °C. She had moon face, facial erythema, hepatosplenomegaly, but no cardiac murmurs. Laboratory examination revealed that hemoglobin concentration was 11.5 g/dl (reference range [rr]: 12.0-16.0); white blood cell count 5,680/ $\mu$ l (rr: 3,500-9,000); platelet count 46,000/ $\mu$ l (rr: 140,000- 440,000); blood urea nitrogen 13 mg/dl (rr: 8-22); serum creatinine 0.45 mg/dl (rr: 0.40-0.70); sodium 129 mmol/l (rr: 138-146); potassium 4.1 mmol/l (rr: 3.6-4.9); calcium 9.0 mg/dl (rr: 8.7-10.3); CRP 0.01 mg/dl (rr: <0.10); creatinine kinase 18 unit/l (rr: 45-163); lactate dehydrogenase 1,003 unit/l (rr: 119-229); ferritin 9,340 ng/ml (rr: 5.2-138.0); soluble IL-2 receptor 5,286 U/ml (rr: 206.0-713.0); brain-type natriuretic peptide 4.1

pg/ml (rr: <18.4); fibrinogen 68 mg/dl (rr:150-400); prothrombin time-international normalized ratio 0.98 (rr: 0.90-1.10); activated partial thromboplastin time 79.2 seconds (rr: 26.0-41.0); fibrinogen degradation products 29.0 µg/ml (rr: <5.0); and D-dimer 16.7 µg/ml (rr: <1.0). High titers of antinuclear antibody, anti-DNA antibody, anti-SS-A/Ro antibody, but not anti-SS-B/La antibody, along with hypocomplementemia indicated the exacerbation of SLE. Anti-cardiolipin antibody and lupus anticoagulant were not detected. Coombs' test was negative. Platelet-associated immunoglobulin G increased to 141.9 ng/10<sup>7</sup> cells (rr: 5.0-25.0). There was no evidence of infection or thyroid dysfunction. Chest X-ray was normal in 45% of cardiothoracic ratio. Electrocardiogram showed normal sinus rhythm with slight prolongation of PR interval (0.18 sec) and normal QT interval (HR 88 bpm, QT interval 0.32 sec, corrected QT interval 0.39 sec). Echocardiography showed normal cardiac functions (ejection fraction 75.9%; left atrial diameter 21.4mm; E' 12.2cm/s, E/E' 5.9; tricuspid regurgitant pressure gradient 20mmHg). Bone marrow study revealed vacuolated macrophages and florid hemophagocytosis mostly consisting of thrombophagocytes (**Figure 1**). These findings led to the diagnosis of lupus-associated HPS.

The second course of 3 consecutive daily pulses of intravenous methylprednisolone in a dose of 1 gm was started with oral cyclosporine-A. Fresh frozen plasma and furosemide were concomitantly administered for the treatment of coagulopathy. She complained of palpitation 3 hours after completion of the first 1 gm of high-dose methylprednisolone. Her pulsation was irregular with a body temperature of 36.8 °C. An electrocardiogram obtained at this time showed Af with a ventricular rate ranging from 80 to 90 beats per minute (**Figure 2**). She complained of chest discomfort and palpitation. Intravenous administration of pilsicainide failed to terminate Af.

Direct-current cardioversion successfully stopped the arrhythmia. Sinus rhythm continued for 2 days. However, 6 hours after completion of the third 1 gm of methylprednisolone, asymptomatic Af recurred with a rate of 90 beats per minute. It resolved spontaneously in 6 hours of fast sleep. Five days after the end of second course, the third course of daily pulses of methylprednisolone was started in half-dose (500 mg) for further control of macrophage activation with prolonged coagulopathy. No arrhythmia developed during the half-dose therapy.

Serum levels of cytokines and catecholamines were serially measured during the treatment course. Levels of IL-6 and catecholamines, often reported to be associated with Af, were not elevated at the onset of arrhythmias (**Table 1**). CRP showed a subtle rise, and IFN- $\gamma$  and IL-10 levels remained to be high during the convalescent phase of HPS. There was no alternation of sodium (129 mmol/l) and potassium (4.1~4.2 mmol/l) levels. Chest roentgenogram and echocardiogram were unremarkable during the treatment course. Lupus activity was then controlled with no arrhythmias by 20 mg prednisolone and 2 mg tacrolimus orally every day.

## **Discussion**

The diagnosis and treatment of HPS is challenging because of a different pattern of diagnostic findings and a wide range of treatment strategy according to the underlying disease. Reactive HPS occurs as the first manifestation or exacerbation of SLE. Our observation might provide new information in the management of patients with lupus-HPS; a risk of arrhythmias and a unique feature of thrombophagocytosis.

The major concern is the triggers for Af. This is the first report of recurrent Af that occurred in an HPS patient during high-dose methylprednisolone therapy. Previous

reports<sup>9-12</sup> suggested an effect of high-dose steroid on the initiation of Af, but not determined whether it was triggered by the underlying inflammatory conditions. Arrhythmia is not considered a specific manifestation for HPS. Atrioventricular block but not usually Af occurs in SLE patients unless they have cardiac or extra-cardiac predisposition.<sup>13</sup> In the present patient, slightly prolonged PR interval and relatively low ventricular rate at Af might represent a concomitant low degree AV block due to subclinical lupus-myocarditis. At the time of Af, IL-6 and catecholamines were not elevated. Despite the remitting course of HPS, Af recurred several hours after the completion of methylprednisolone pulse. Sustained high levels of IFN- $\gamma$  and IL-10 along with a subtle rise of CRP could precipitate arrhythmias without the elevation of IL-6 and TNF- $\alpha$ .<sup>5</sup> Taken together, it is likely that recurrent Af was triggered by high-dose steroid infusion on the background of subclinical cardiac involvement.

Clinical effects of corticosteroids on Af are varied. **Table 2** summarizes 6 reported patients who developed paroxysmal Af during or after high-dose methylprednisolone therapy. Dernellis and Panaretou<sup>7</sup> demonstrated that low-dose steroid therapy following direct-current cardioversion successfully prevented the Af recurrence, and the treatment effect correlated with a reduction of CRP levels. Halonen *et al.*<sup>14</sup> reported that low-dose hydrocortisone reduced the incidence of Af after cardiac surgery in a randomized multicenter study. On the other hand, van der Hooft *et al.*<sup>8</sup> showed that both oral and parenteral high-dose steroid therapies raised the risk of developing Af in a case control study. High-dose methylprednisolone therapy might contribute to the development of Af in patients with SLE or rheumatoid arthritis (**Table 2**).<sup>9-12,15</sup> Although myocarditis are detected in 3-15% of SLE patients, subclinical cardiac disease could occur more frequently. Lupus-associated HPS may be defined a severe SLE form with frequent



flares, cardiac involvement, and the need for prolonged immunosuppression.<sup>16</sup> In animal studies, high-dose methylprednisolone has significant effects on cardiovascular physiology that may be mediated both by direct action on the myocardial cell membrane and via alterations in cardiovascular sensitivity to catecholamines.<sup>17</sup> In humans, intravenous methylprednisolone alters the stimulation threshold of myocardial cells and, when given in pulse doses, alters serum potassium and the urinary excretion of both potassium and sodium, particularly if used concomitantly with furosemide. These changes might alter electrolyte shifts across myocardial cell membranes, resulting in cardiac arrhythmias.<sup>18</sup> In the present patient, no arrhythmias occurred during the first high-dose therapy at the onset of SLE. The half-dose infusion induced no Af during the convalescent phase of HPS. Cellular electrolyte shifts in the use of diuretics might also affect the developing arrhythmias. High-dose steroid infusion reduced the lupus activity, but could concurrently disclose cardiac stress in the patient with lupus-HPS.

Numerous thrombo-phagocytosing macrophages were unique in the patient. This phenomenon may be associated with platelet production. However, the platelet-specific hemophagocytosis was more prominent than seen in patients with juvenile idiopathic arthritis- or Kawasaki disease-associated HPS. Kobayashi *et al.*<sup>19</sup> reported a boy with juvenile dermatomyositis who showed marked thrombophagocytosis, and suggested that platelet-specific antibody facilitated selective phagocytosis by activated macrophages in the bone marrow. In our patient, high levels of circulating IFN- $\gamma$  and platelet-associated immunoglobulin G could accelerate thrombophagocytosis by the enhanced expression of Fc $\gamma$ R on macrophages and the eat-me signal on platelets, respectively.

Early diagnosis and treatment is critical for patients with lupus-HPS. Pulse infusion of high-dose methylprednisolone and/or cyclophosphamide is the first line of treatment

for severe SLE or lupus-HPS.<sup>20</sup> To reduce the risk of cardiotoxicity, rituximab therapy can be an alternative choice for refractory cases. In conclusion, thrombophagocytosis and arrhythmias should be paid more attention in the clinical management of lupus-HPS.

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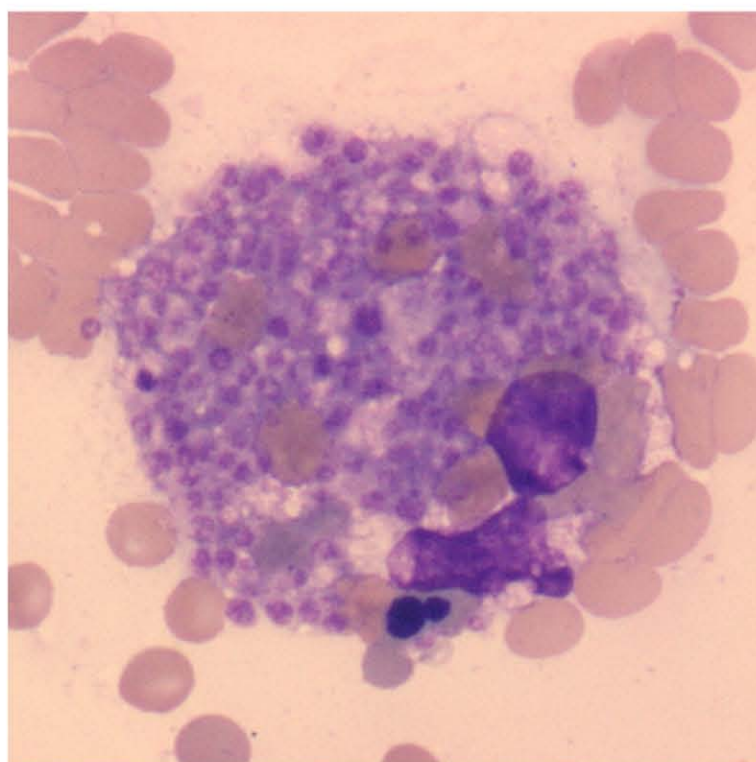
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**Figure legends**

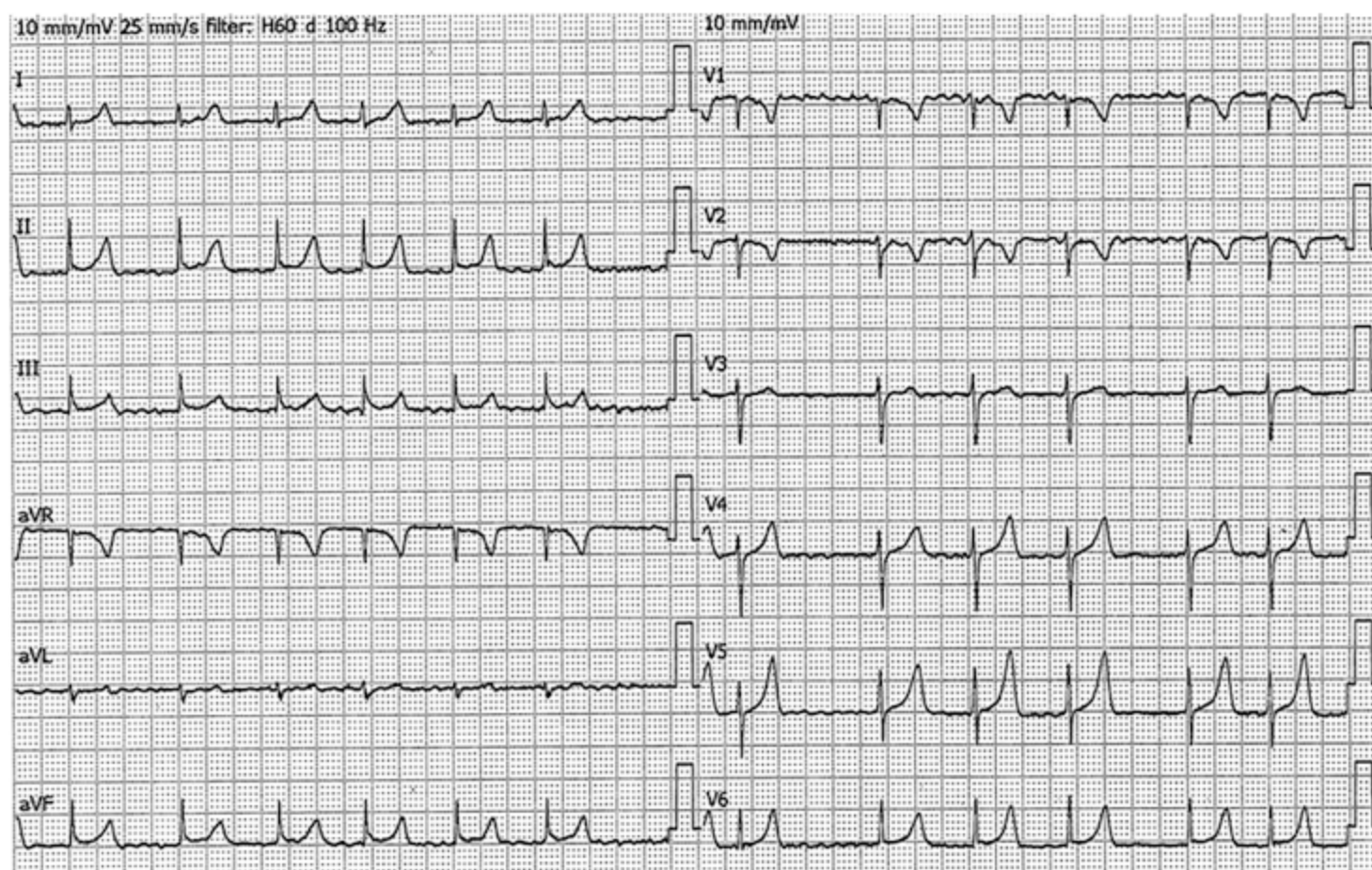
**Figure 1** Bone marrow aspiration revealed marked increase of hemo (thrombo-) phagocytosing macrophages.

**Figure 2** Twelve-lead electrocardiogram at the onset of atrial fibrillation which occurred three hours after completion of the first 1 gm of high-dose methylprednisolone. Electrocardiogram 10 mm/mV, 25 mm/s.

Figure 1



**Figure 2**





**Table 1** Changing levels of CRP, cytokines and catecholamines during the treatment course

	normal range	day 0 <i>admission</i>	day 1 <i>Af</i>	day 8	day 43
CRP* (mg/dl)	<0.10	0.01	0.05	0.01	0.01
IL-6* (pg/ml)	<3.0	UD	UD	UD	UD
TNF- $\alpha$ * (pg/ml)	<2.8	UD	UD	UD	UD
IFN- $\gamma$ * (pg/ml)	<7.1	506	39.6	UD	UD
IL-10* (pg/ml)	<2.8	194.1	92.7	UD	UD
IL-2*, IL-4 (pg/ml)	<2.6	UD	UD	UD	UD
adrenaline (pg/ml)	<100	16	18	24	9
noradrenaline (pg/ml)	100-450	128	232	95	240
dopamine (pg/ml)	<20	15	12	17	12

Serum concentrations of cytokines were determined by cytometric bead array (Becton Dickinson, San Jose, CA) and flow cytometric analysis. Each detection limit was 2.6 pg/ml for interleukin (IL)-2, 2.6 pg/ml for IL-4, 3.0 pg/ml for IL-6, 2.8 pg/ml for IL-10, 2.8 pg/ml for tumor necrosis factor (TNF)- $\alpha$ , or 7.1 pg/ml for interferon (IFN)- $\gamma$ .

Af: atrial fibrillation, CRP: C-reactive protein, UD: under detectable limit.

\* These inflammatory markers were reported to be associated with developing Af.

**Table 2** Reported cases of paroxysmal atrial fibrillation during or after high-dose methylprednisolone therapy

Pt	Sex	Age (yrs)	<u>High-dose steroid therapy<sup>a</sup></u>		<u>Predisposing factors for arrhythmia<sup>b</sup></u>		<u>Af</u>			Reference
			Underlying disease, Dose		Cardiac	Extra-cardiac	Episode	Treatment	Outcome	
1	F	12	SLE, NS	1g x 3days	no	no	singleton	PCV	success	[12]
2	M	16	NS	1g x 3days	no	no	singleton sp,	PCV	success	[12]
3	F	46	RA	500mg x 3days	no	no	singleton	PCV	success	[15]
4	M	22	MS	1g x 3days	no	no	recurrent	PCV	success	[10]
5	M	59	MS	1g x 3days	no	no	recurrent	PCV	success	[11]
6	F	37	SLE	120mg /day	myocarditis	no	singleton	sp	success	[9]
7	F	15	SLE-HPS	1g x 3days	no	no	recurrent	sp, PCV, ECV	success	Ours

Af: atrial fibrillation, ECV: electronic cardioversion, F: female, HPS: hemophagocytic syndrome, M: male, MS: multiple sclerosis, NS: nephrotic syndrome, PCV: pharmacological cardioversion, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, sp: spontaneous remission.

<sup>a</sup>All but one patient received intravenous administration. Patient 6 were received daily oral therapy.

<sup>b</sup>Congenital heart diseases, pericarditis, endocarditis, myocarditis, pancarditis, and conduction defects were examined by blood pressures, echocardiography, electrocardiogram and chest roentgenogram. Non-cardiac conditions included electrolytes imbalance, hypertension, and endocrinological abnormality.