Case Report

Annals of Paediatric Rheumatology

Parvovirus B19 Associated Systemic Lupus Erythematosus in a Child with Sickle Cell Disease; a Diagnostic and Therapeutic Challenge

Marta Cabral[1], Alexandra Dias[2], Clara Abadesso[3], Marta Conde[1], Manuel Ferreira[4], José Melo Gomes[5], Helena Carreiro[6]

Abstract

Although sickle cell disease (SCD) and systemic lupus erythematosus (SLE) are two distinct and relatively common chronic diseases, coexistence of these two conditions in the same patient appears to be rare. The authors report an eight-year-old child with SCD who developed a severe form of parvovirus B19-associated SLE, with secondary severe immune hemolytic anemia related to drugs, Libman-Sacks endocarditis complicated by severe aortic regurgitation, dilated left ventricle with impaired function and myocardial ischemia, with further decompensation culminating in cardiac arrest during an infectious intercurrence, which led to death. This patient displayed a broad spectrum of musculoskeletal, hematologic and cardiovascular complications, which could be associated with either SCD or SLE. Because of a substantial overlap between the clinical manifestations of these two disorders, the diagnosis of SLE in a patient with a previously known diagnosis of SCD may be difficult and is often delayed. Our report illustrates the importance of considering other disease processes, like autoimmune diseases when clinical features or its evolution are atypical of SCD and emphasizes some of the diagnostic difficulties encountered during the diagnosis and management of these patients.

Key words: *Systemic lupus erythematosus, sickle cell disease, child, Libman-Sacks endocarditis, parvovirus B19*

[1]Pediatric Rheumatology Clinics; [2]Pediatric Hematology Clinics; [3]Intensive Care Unit; [6]Department's Director; Department of Pediatrics, Hospital Prof. Doutor Fernando Fonseca E.P.E, Amadora, Portugal: [4]Pediatric Cardiology, Hospital da Cruz Vermelha, Portugal ; [5]Pediatric Rheumatology Unit, Instituto Português de Reumatologia (IPR), Lisbon, Portugal

Corresponding author:
Marta Cabral, Hospital Prof. Doutor Fernando Fonseca E.P.E., Estrada da Venteira, IC19, 2720-276 Amadora, Portugal.
e-mail: *mssr.cabral@gmail.com*

Received: *October 11, 2011*
Accepted: *December 01, 2011*
Ann Paediatr Rheum 2012; 1: 71-76
DOI: 10.5455/apr.120120111141

Introduction

Sickle cell disease (SCD) is a genetic disorder caused by a single amino acid mutation in the hemoglobin gene. Its clinical manifestations range from an asymptomatic state detected only by routine hematologic testing to a chronic triad of recurrent painful vasoocclusive episodes (complicated by progressive organ damage), hemolytic anemia and a predisposition to severe infections [1,2]. Prominent late complications of SCD include avascular necrosis of bone, progressive renal impairment, leg ulcerations, proliferative retinopathy and cerebrovascular accidents[1]. Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with an unpredictable clinical presentation and course [2]. The hallmark of SLE is the multisystem involvement, with prominent cutaneous, musculoskeletal, hematological, renal and neurologic manifestations [1]. The classification of SLE is made when a patient fulfills at least four of the 11 revised criteria established by the American College of Rheumatology (ACR) in 1997. Fever, ar-

thralgia/arthritis and myalgia are common in both conditions [3,4]. Additionally, both diseases commonly affect the renal, cardiovascular and central nervous systems [4]. Although the etiology of this two conditions is different, their coexistence has been rarely reported [1-5].

The authors report a patient with SCD who developed a severe and fatal form of SLE and emphasize some of the diagnostic difficulties encountered during his diagnosis and treatment.

Case report

An eight-year-old boy from healthy African and non-consanguineous parents, had diagnosis of moderate-to-severe SCD (Hb SS) since 11-month-old, with a long history of multiple painful vasoocclusive crises and severe bacterial infections (osteomyelitis and three episodes of bacterial pneumonia). Anemia had been treated intermittently with red blood cell transfusions. He presented with an acute illness characterized by high fever (>39ºC), fatigue, hepatomegaly and intense low back pain. Further evaluation showed: hemoglobin (Hgb) 4.6g/dl, hematocrit 12.9% and 15,000 reticulocytes/mm^3, 21,900 leukocytes/mm^3, 21,000 platelets/mm^3, C-reactive protein 36.2 mg/dl, alanine aminotransferase 1878u/L, aspartate aminotransferase 767u/L, lactate dehydrogenase 8524u/L, aPTT 40.1 seconds and D-dimers 16418µg/dL. Cardiology evaluation showed global cardiac chambers enlargement, biventricular dysfunction with hypocontractility and mild pericardial effusion, without valve vegetations. He started intravenous (IV) ceftriaxone and required inotropic and oxygen support, multiple red blood cells and platelets transfusions. On day 8, already on clinical stability after septic shock, he had a massive intravascular hemolysis (Hgb 2.8g/dl with hematocrit 3.9%, total bilirubin 8.9mg/dl and direct Coombs test +++ for IgG and C3d) after ceftriaxone infusion. This was interpreted as a severe immune hemolytic anemia, probably related to drugs. Ceftriaxone was suspended and he was treated successfully with high-dose IV methylprednisolone. Despite clinical improvement, the low back pain and intermittent fever persisted for weeks. Further investigation revealed positive parvovirus B19 serology (IgM+IgG+), low C4 (5.6mg/dL), positive antinuclear antibody (ANA) titre 1/320, anticardiolipin (aCL)(total titre: 29.3 u/mL, reference value (RV):<1,1) and anti- B2 glycoproteinI (anti- B2 GPI) antibodies (IgG 24.7 u/mL, RV:<10), while lupus anticoagulant, anti-dsDNA, anti-Sm, anti-RNP, anti-SSA, anti-SSB and anti-neutrophil cytoplasm (ANCA) antibodies were negative. Erythrocyte sedimentation rate (ESR) was >140mm/1st hour. Lumbosacral magnetic resonance imaging showed inflammatory myositis, without purulent defined collections. Drug-induced immune hemolytic anemia study confirmed the coexistence of a high titre of anti-ceftriaxone antibodies. Abdominal ultrasonography and myelogram showed no abnormalities.

After discharge and during one year of follow-up, he developed persistent fatigue, weight loss, intermittent polyarthralgia of the hands, generalized myalgia and anti-dsDNA became positive (18.3 u/mL). Mild pancytopenia (Hgb 7.2g/dl, 139,000 platelets/mm^3, 4,100 leukocytes/mm^3) became persistent, as did high ESR (55-137mm/1st hour) and diagnosis of SLE was established. One year later, after another admission in the context of a lobar pneumonia with bilateral pleural effusion (sterile exudative pleural fluid with 12,409cells/mm^3 and positive ANA (1/640)), recurrent pericardial effusion and persistence of systemic and musculoskeletal symptoms, treatment with hydroxyurea 30 mg/kg/day, regular transfusions and oral prednisolone 0.5mg/kg/day was initiated. There was an extraordinary improvement of the cytopenias, systemic and musculoskeletal symptoms. Direct Coombs test became negative and ESR normalized.

Three months later, suddenly he developed an ejection systolic murmur 5/6 degree. Transthoracic and transesophageal echocardiography showed a mild aortic regurgitation with severe valvular dysfunction, with abnormalities compatible with Libman-Sacks vegetations: valve masses of varying size (>2 mm in diameter), irregular borders and echodensity, firmly attached to the aortic valve surface, exhibiting no independent motion (Figure 1). No vegetations suggestive of bacterial endocarditis were found. Enalapril 5mg/day was started and he remained relatively stable. One year later he developed a sudden onset of chest pain. Electrocardiogram was compatible with myocardial ischemia (Figure 2) and echocardiography showed severe aortic regurgitation with partial occlusion of one of the coronary arteries by an extension of the aortic valve verrucous lesions.

He was treated with IV pulse methylprednisolone, antibiotics and emergent coronary artery graft bypass surgery with associated aortic valve replacement by a mechanical prosthesis. Simultaneously, low molecular weight heparin was started. Macroscopic intraoperative examination revealed

signs of lupus carditis with poor ventricular function and the presence of bacterial vegetations on the aortic valve. Laboratory evaluation revealed Hgb 6.3 g/dl, 93,000 platelets/mm^3, aPTT 50.3 seconds, positive ANA (1/640) and lupus anticoagulant (105 seconds, RV:<38), troponin 5.5 ng/dl and proBNP>10,000pg/mL. Post-operative echocardiography showed a dilated left ventricle with impaired function (ejection fraction: 15%), mild mitral regurgitation and a moderate peri-prosthetic aortic valve leak.

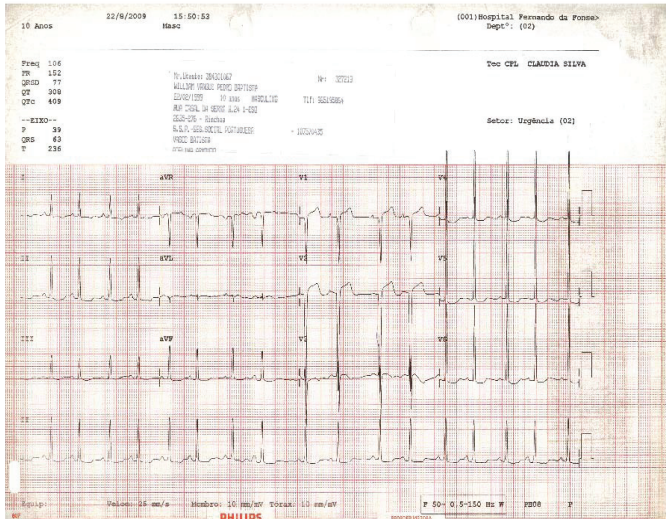


Figure 1. Electrocardiogram performed 3 weeks after surgery, showing persistence of repolarisation abnormalities (ST depression and T-wave changes) compatible with myocardial ischemia.

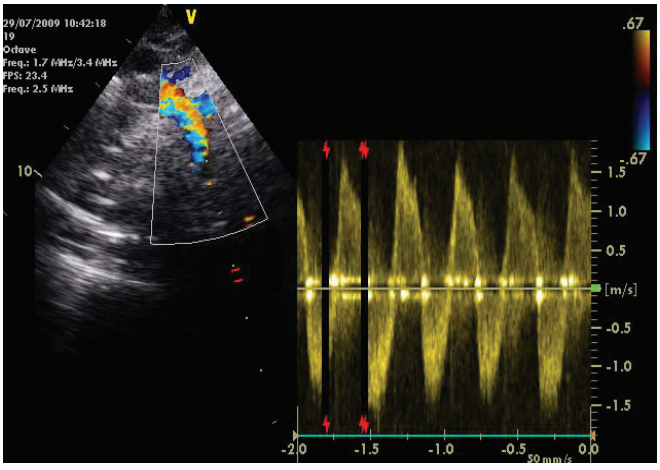


Figure 2. Pre-operative two-dimensional echocardiogram in the parasternal (long/short-axis) view showing diastolic flow reversal in the descending aorta, suggestive of severe aortic regurgitation.

Lupus and drepanocytosis were well controlled with remission of systemic and musculoskeletal symptoms as well as rare painful crises, while taking 30mg/kg/day hydroxyurea, 0,5mg/kg/day prednisolone, warfarin (INR: 2-2,5), folic acid, captopril, furosemide, spironolactone and digoxin.

One year later his clinical course was complicated by an extensive lobar pneumonia with further left ventricular dysfunction. The patient's clinical condition significantly improved after multiple transfusions, inotropics, IV antibiotics and oxygen. However, when he was already hemodynamically stabilized, he developed sudden cardiac arrest secondary to ventricular fibrillation. Cardiac resuscitation was attempted but ineffective, and the patient died.

Discussion

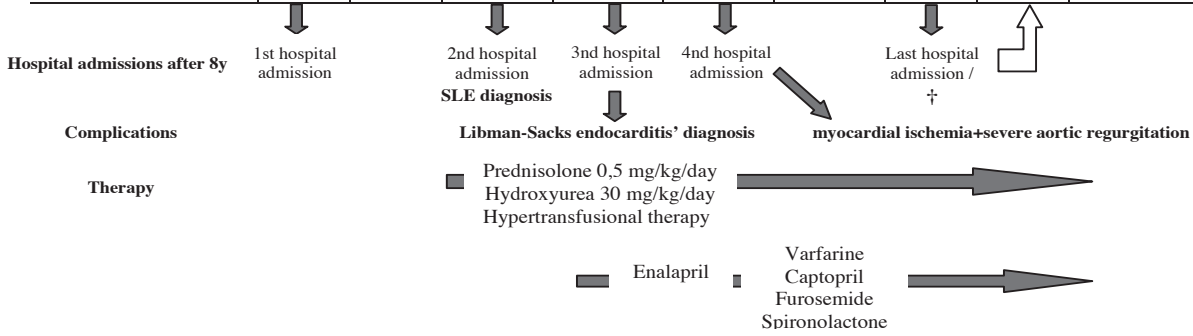
Although SLE and SCD are distinct diseases, both conditions appear to be more prevalent among patients with an African ancestry and effectively, the patient reported supports that epidemiology [6]. Coexistence of SCD and SLE has been previously reported but, because of the limited number of cases from previous reports it is not possible to conclude whether SLE is more or less prevalent in patients with sickle cell hemoglobinopathies [1,3-5]. In fact, a MEDLINE search of the literature, from 1970 to 2004 revealed only 19 cases of coexisting SLE and SCD, from which only 14 fulfilled the 1997 revised criteria of the ACR, which highlights the rarity of the overlap between these entities [1] and since both conditions have a high prevalence in blacks, a protective effect of SCD in preventing SLE has been speculated [1,7]. On the other hand, the defective alternate pathway of the complement system, characteristic of the SCD patients, leading to a failure to eliminate bacterial antigens with subsequent formation of immune complexes, may predispose these patients to the development of autoimmune diseases like SLE, although the data on the latter are conflicting [2,3]. Furthermore, ANA positivity seems to be more common in patients with SCD (23%) than in the general population (10-15% of healthy children) [2]. This may suggest an etiopathological link between these two entities.

The diagnosis of an underlying autoimmune disease may be particularly challenging in patients with SCD. These conditions share a number of common manifestations, like joint involvement, pulmonary, cardiac and renal complications [2]. In our patient four of these main systems were affected: he developed musculoskeletal symptoms (intermittent polyarthralgia and lumbar myositis), bilateral pleural effusion, recurrent pericardial effusion and Libman-Sacks endocarditis reflecting

Table 1. First laboratory investigation for infectious and autoimmune diseases. Clinical and laboratory evolution since the diagnosis of SCD and SLE coexistence.

Infectious disease - first admission's investigation	
Parvovirus B19 serology	**IgM+**(4.0)**IgG+**(5.8) (Positive:>1.2)
Parvovirus B19 PCR (serum and medular blood)	Negative
Other serologic evaluations (*Cytomegalovirus, Epstein-Barr virus, Adenovirus, Mycoplasma pneumoniae, Clamydiapneumoniae, Human immunodeficiency virus* (HIV)1 and 2, *Hepatitis B virus* (HBV), *Hepatitis C virus* (HCV), *Toxoplasma gondii, Brucella*and*Leishmania)*, Huddleson, VDRL, PCR for *Enterovirus* and *Adenovirus* (stool), PCR forLeishmania (medular blood)	Negative
Antistreptolysin O test (ASO) / anti-Dnase B	Normal / <200
Tuberculin test	Anergic
Ziehl-Neelsen and Lowenstein (bronchial secretions and bronchoalveolar lavage), PCR *Mycobacteria tuberculosis* and atypical (medular blood)	Negative
ADA	51 U/L(5-23)
Blood, urine, stool and secretions cultures; Blood culture for Brucella	Sterile

Autoimmune disease									
Patient's age (years-old)	8	8.5	9	9.5	10	11	11.5		Units (reference values)
ANA	**1/320**	**1/640**	**1/640**	**1/640**	**1/640**	**1/160**	1/160	-	
Anti-dsDNAab	Neg	**+(18.3)**	Neg	**+(24.9)**	Neg	Neg	Neg	-	
Anti-SMab	Neg	Neg	Neg	Neg	Neg	Neg	Neg	-	
Anti-RNPab	Neg	Neg	Neg	Neg	Neg	Neg	Neg	-	
Anti-SSA / SSBab	Neg	Neg	Neg	Neg	Neg	Neg	Neg	-	
Anti-nucleossomeab	-	+	**+++**	**+++**	++	-	-	-	
Anti-histone ab	-	-	**+**	Neg	-	-	-	-	
C3	89	**59**	95	88	-	111	-	-	mg/dL (78-140)
C4	**5.6**	**7.6**	15.3	13	-	28.1	-	-	mg/dL (8-44)
CH50	-	35	41	45	-	46.9	-	-	U/mL (23-46)
Lupus anticoagulant	**39.1**	**38.9**	**42.3**	-	**54.9**	35.7	**-**	-	seconds (< 38)
aCPabtotal titre (IgG, IgM, IgA)	**29.3**	4.5	**25.5**	6.5	4.1	0.1	8.9	-	U/mL (Positive: >15)
Anti-β2GPI abIgM IgG	**24.7** 0.1	**31.1** 0.1	5.2 0.1	0.9 0.1	5.5 0.1	**20.1** 0.1	0.6 0.9	-	U/mL (Positive: IgM or IgG>10)
DirectCoombstest	**+++**	**+**	**+**	Neg	Neg	Neg	-	-	
ESR	**>140**	**55**	**83**	8	**45**	13	**-**	-	mm/1st hour
PCR	**36.2**	0.47	17.7	0.89	14.8	0.2	**8.9**	<0.05	mg/dL
Sickle cell disease and hematologic evaluation									
Hemoglobin	**2.8**	**7.2**	**6.0**	8.8	6.3	9.7	10.2	9.9	g/dL
Fetal / S Hbg	/25.4	**-**	2.6/65.9	4.6/85.7	4.8/36.8	13.4/75.1	-	-	%
White blood cell	21.9	**3.1**	2.7	6.3	16.4	**3.5**	**2.1**	2.5	$x10^3/\mu l$
Platelets	**21**	93	156	**78**	**93**	94	**117**	112	$x10^3/\mu l$
Others									
Microalbuminuria	0.62	1.8	0.38	-	-	-	**-**	-	mg/dL(<3.00)
Protein (24hours urine)	-	64	-	-	-	**245.3**	**-**	-	mg/24h (<149.1)
Creatinine	0.4	0.3	0.3	0.5	0.6	0.6	0.6	0.6	mg/dL
Urea	30	17	12	19	27	38	35	26	mg/dL



VDRL: Venereal Disease Research Laboratory; ab: antibody; ESR: Erythrocyte sedimentation rate; PCR: C-reactive protein; Hbg: Hemoglobin

pulmonary and cardiac involvement respectively, and he had one determination of elevated proteinuria (Table 1). Libman-Sacks endocarditis is characterized by non-infective verrucous vegetations that develop mainly on the mitral valve, but also can be seen on other valves (e.g. aortic), as in our patient [8]. Although reported in a significant proportion of patients (30-50%) in autopsy studies, symptomatic valvular disease with hemodynamic implications has been considered rare, but it was one of the severe comorbidities of our patient.

For most patients, diagnosis of SCD is established early in life, so another diagnosis is not looked for when they present with common rheumatological manifestations. This may contribute to a delay in the diagnosis of the second disorder, as it happened in our patient, whose definite diagnosis of SLE was established only one year after development of the first symptoms. But effectively, this patient fulfilled five criteria of the classification of SLE: positive ANA, other immunologic abnormalities (hypocomplementemia (C4), positive anti-ds-DNA and antiphospholipid antibodies), serositis (pleural and pericardial effusion), immune hemolytic anemia and mild non-deforming arthritis or polyarthralgia. Moyssakis I. et al reported a significant association between Libman-Sacks endocarditis and aPL syndrome, particularly associated to aCL antibodies. Actually, development of this cardiac complication in our patient occurred concomitantly with the re-appearance of positive lupus anticoagulant; additionally, aCL antibodies were positive at the first presentation of SLE (Table 1).

Hematologic abnormalities are frequent in both SCD and SLE. Anemia is commonly present in both diseases but important differences between them exist with respect to the total white blood cell (WBC) and platelet count. The WBC count is characteristically elevated to 15.000/mm^3 in patients with SCD, and thrombocytosis is also frequent [1]. In contrast, immune-mediated leukopenia and thrombocytopenia are common in SLE. As it was observed in our patient, one should suspect of SLE if there is a reduction in platelet or WBC count, and a positive direct Coombs test can confirm its immune origin. Although rare, this patient presented a drug (ceftriaxone)-induced immune hemolytic anemia. Curiously, Ogunbiyi et al reported a ceftriaxone-adverse reaction in another eight-year-old African patient with SCD and SLE coexistence [7].

We have described a patient whose SLE symptoms began at the onset of an acute parvovirus B19 infection, and who shortly afterwards developed SLE. We could assume that this patient had a recent onset SLE with an intercurrent parvovirus B19 infection or that SLE had been precipitated by the virus. Similarities between their symptoms include the presence of fever, astenia, myalgia, polyarthritis, macular erythema and cytopenia (due to an arregenerative crisis, predominantly in patients with chronic hemolytic anemias such as SCD). Recent research has focused on the role of parvovirus B19 in the etiopathogenesis of SLE. In addition to the clinical similarity, parvovirus infection elicits autoantibodies to antigens commonly found in patients with SLE, including ANA, dsDNA and antiphospholipid antibodies [9]. These symptoms and laboratory abnormalities are transient in some cases, yet persist in others, suggesting that the virus could in fact induce chronic autoimmunity [9]. In addition to our case, Hession et al reported 9 cases in which parvovirus B19 infection produced transient SLE symptoms and 11 other cases in which clinical and serological manifestations persisted at least a year following infection [9]. Additionally, Isa et al reported elevated levels of the Th1 cytokines such as interleukin 12 (IL-12) and IL-15 at the time of the initial peak of parvovirus B19 viral load during acute infection, and some of these patients had a sustained Th1 cytokine response 20 to 130 weeks after acute infection [10]. Moreover, there have been reports showing that Th1-type cytokines might be involved in the development of SLE [11,12]. Thus, there is a possibility that persistently increased IL-12 and IL-15 after parvovirus B19 infection might be involved in chronic SLE autoimmunity [13].

Once SLE is diagnosed, the risk/benefit ratio of each treatment must be carefully considered. Steroids are the main treatment for autoimmune conditions, and in particular for SLE. However, long-term administration of steroids is never free of complications, making patients with SCD more vulnerable to life-threatening vasooclusive episodes and infections, especially if given in combination with immunosuppressive drugs [2,6,14]. The effects of steroids and/or immunosuppressive agents on the progression of SCD remain controversial, and it would be beneficial to know whether SLE diagnosed in SCD patients have specific characteristics and/or a worse outcome, and whether the use of these agents are deleterious in patients with SCD [6]. For optimal management of these patients, rheumatologists and hematologists must work together closely and preventive measures such as chronic transfusions regimen and/or hydroxyurea must be considered before starting therapy [6,14], as was done in our patient.

In summary, in patients with coexisting SCD and SLE the recognition of the second is difficult and often delayed, but clinicians should be on the alert if the clinical behavior of the patient has changed, particularly with the appearance of pancytopenia, serositis or progressive neurological, renal or cardiac manifestations that are not consistent with classical SCD clinical profile or are unresponsive to the conventional treatment, as it was described in this report [1]. Early recognition of SLE in patients with SCD is important for beginning of appropriate therapy and eventual prevention of complications caused by their coexistence.

Competing interests: The authors declare that they have no conflict of interest.
Funding: None.
Provenance and peer review: Not commissioned; externally peer reviewed.

References

1. Khalidi N, Ajmani H, Varga J. Coexisting Systemic Lupus Erythematosus and Sickle Cell Disease – a diagnostic and therapeutic challenge. J Clin Rheumatol 2005;11:86-92.
2. Alkindi S, Al-Maini M, Pathare A. Clinical and laboratory characteristics of patients with sickle cell and autoimmune/connective tissue diseases. Rheumatol int 2012;32:373-378.
3. Appenzeller S, Fattori A, Saad S, Costallat L. Systemic lupus erythematosus in patients with sickle cell disease. Clin Rheumatol 2008;27:359-364.
4. Eissa MM, Lawrence JM, McKenzie L, Little FM, Mankad VN, Yang YM. Systemic lupus erythematosus in a child with sickle cell disease. Southern Medical Journal 1995;88:1176-1178.
5. Saxena V, Mina R, Moallem H, Rao Sreedhar, Miller S. Systemic lupus erythematosus in children with sickle cell disease. Journal of Pediatric Hematology/Oncology 2003;25:668-671.
6. Michel M, Habibi A, Godeau B, Bachir D, Lahary A, Galacteros F et al. Characteristics and Outcome of connective tissue diseases in patients with sickle cell disease: report of 30 cases. Semin Arthritis Rheum 2008;38:228-240.
7. Ogunbiyi A.O, George A.O, Brown O, Okafor B.O. Diagnostic and treatment difficulties in systemic lupus erythematosus coexisting with sickle cell disease. WAJM 2007; 26:152-155.
8. Moyssakis I, Tektonidou M, Vasilliou V, Samarkos M, Votteas V, Moutsopoulos H. Libman-Sacks Endocarditis in Systemic Lupus Erythematosus: Prevalence, Associations, and Evolution. Am J Med 2007;120:636-642.
9. Hession M, Au S, Gottlieb A. Parvovirus B19-associated systemic lupus erythematosus: clinical mimicry or autoimmune induction? J Rheumatol 2010;37:2430-2432
10. Isa A, Lundqvist A, Lindblom A, Tolfvenstam T, Broliden K. Cytokine responses in acute and persistent human parvovirus B19 infection. Clin Exp Immunol 2007;147:419-425.
11. Tokano Y, Morimoto S, Kaneko H, Amano H, Nozawa K, Takasaki Y, et al. Levels of IL-12 in the sera of patients with systemic lupus erythematosus (SLE) — relation to Th1- and Th2-derived cytokines. Clin Exp Immunol 1999;116:169-173.
12. Aringer M, Stummvoll GH, Steiner G, Köller M, Steiner CW, Höfler E, et al. Serum interleukin-15 is elevated is elevated in systemic lupuserythematosus. Rheumatology 2001;40:876-881.
13. Park S, Kim J, Ha T and Shin J. Association of Parvovirus B19 Infection with Systemic Lupus Erythematosus: Role of Th1 Predominance. J Rheumatol 2011;38:1221.
14. Couillard S, Benkerrou M, Girot R, Brousse V, Ferster A, Bader-Meunier B. Steroid treatment in children with sickle-cell disease. Haematologica 2007;92:425-426.