Case report

Coexisting systemic lupus erythematosus and sickle cell disease: Case report and literature review

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ABSTRACT

Objective: To report a case of coexisting systemic lupus erythematosus (SLE) and sickle cell disease (SCD) with a review of the literature on the topic.

Methodology: Case report and literature review of the association between SLE and SCD through scientific articles in health sciences databases, such as LILACS, MEDLINE/Pubmed and Scielo, until May 2012. Descriptors used: 1. Sickle cell anemia; 2. Sickle cell disease; 3. Systemic lupus erythematosus; 4. Hemoglobinopathies.

Results: The authors describe an association between SLE and SS hemoglobinopathy in an eight-year-old female patient presenting with arthritis, hematologic and neuropsychiatric manifestations during clinical evolution. Forty-five cases of association between SLE and SCD are described in literature, mostly adults (62.2%), women (78%) and with the SS phenotype in 78% of the cases, and diverse clinical manifestations. Compared with our patient, articular, hematologic and neuropsychiatric manifestations were present in 76%, 36% and 27% of the cases, respectively.

Conclusion: SLE and SCD are chronic diseases that have several clinical and laboratory findings in common, meaning difficult diagnosis and difficulty in finding the correct treatment. Although the association between these diseases is not common, it is described in literature, so it is imperative that physicians who treat such diseases be alert to this possibility.

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Coexistência de lúpus eritematoso sistêmico e doença falciforme: relato de caso e revisão da literatura

RESUMO

Objetivo: relatar um caso de coexistência de lúpus eritematoso sistêmico (LES) e doença falciforme (DF) com revisão da literatura sobre o tema.

Metodologia: relato de caso e pesquisa da associação entre LES e DF na literatura, através de artigos científicos nas bases de dados de ciências da saúde, como LILACS, MEDLINE/Pubmed.

Palavras-chave:
Anemia falciforme
Doença falciforme

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Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with an incidence of 1.9 to 5.6 per 100,000 inhabitants, while sickle cell disease (SCD) is one of the most common hereditary diseases, affecting mainly black individuals. SCD is characterized by a mutation in the hemoglobin beta chain with formation of abnormal hemoglobin (HbS), responsible for microcirculation obstruction, ischemia, tissue necrosis and systemic organ dysfunction. The coexistence of SCD and SLE is rarely described in literature, even in predominantly black populations, in which the prevalence of both conditions is higher. Wilson et al. were the first to report this association. Perhaps the defective activation of the alternative complement pathway in sickle cell patients and the increased risk of infections caused by encapsulated bacteria predispose this group to develop an autoimmune disease.

The clinical features of SCD and SLE may show similar manifestations, such as the presence of fever, anemia, articular, renal, neurological and cardiopulmonary involvements and, consequently, diagnostic difficulties. Sickle cell patients showing atypical symptoms or refractory response to conventional treatment should be investigated for the possibility of coexistence of diseases.

In view of the uncommon occurrence of this association, the authors describe an early childhood case and review the previously reported cases until May 2012.

Methodology

Case report and literature review of the association between SLE and SCD through scientific articles in health sciences databases, such as LILACS, MEDLINE/Pubmed and Scielo until May 2012. Descriptors used: 1. Sickle cell anemia; 2. Sickle cell disease; 3. Systemic lupus erythematosus; 4. Hemoglobinopathies.

Case report

Female patient diagnosed with SS hemoglobinopathy since birth, showing recurring, mild painful vaso-occlusive crises responsive to traditional hydration and analgesia. She has never received blood transfusions. At the age of nine, pain symptoms intensified, mainly characterized by repeated crises of acute and asymmetric polyarthritis of the knees, wrists, elbows and ankles, initially attributed to SCD. The clinical picture evolved with the development of photosensitivity, asthenia and intermittent fever, with an episode of generalized tonic-clonic seizure associated with transient left hemiparesis. Laboratory tests: hemoglobin, 7.9 g/dL; hematocrit, 25%; WBC, 12.000/mm³; platelet count, 374.000 mm³ (160-400.000); hemoglobin electrophoresis HbS 98.7% and HbA2 1.26%; positive antinuclear antibody (ANA) 1:320 (homogeneous pattern); positive anti-dsDNA antibody; erythrocyte sedimentation rate, 68 mm (<20); C-reactive protein, 71 units (< 6); rheumatoid factor, anti-Sm, anti-SSA, anti-SSB, were all negative as were viral serology. Serum C₃, C₄ and C₅₉₀ levels were normal as were renal and liverfunctions. Cranial magnetic resonance imaging revealed an area of hypoperfusion in the right temporal lobe. The study of the cerebrospinal fluid was normal. The patient had a sibling with sickle cell anemia who died at the age of two from acute myocardial infarction, and has two maternal aunts diagnosed with cutaneous lupus. She was diagnosed with SLE according to American College of Rheumatology (ACR) criteria, and the possibility of involvement of the central nervous system (CNS) by both diseases (SLE and SCD) was discussed. The patient received prednisone 2 mg/kg/day, hydroxychloroquine 5 mg/kg/day and blood transfusions in order to reduce HbS < 30%. Due to the possibility that the neurological manifestation was secondary to SCD we chose not to associate another immunosuppressive agent. There was significant reduction in joint pain, no progression of the neurological condition and improvement of hematological indices (HbS 60%; Hb 8.5 g/dL). Patient remains asymptomatic, taking hydroxychloroquine and prednisone 5 mg/day.
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<th>Age</th>
<th>Sex</th>
<th>Hb Type</th>
<th>SLE</th>
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<th>Malar rash</th>
<th>Oral ulcer</th>
<th>Photosensitivity</th>
<th>Discoid lupus</th>
<th>Renal involvement</th>
<th>Neuropsychiatric involvement</th>
<th>Serositis</th>
<th>Articular involvement</th>
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Table 1 – Coexisting systemic lupus erythematosus and sickle cell disease – literature review.
Discussion

Epidemiology of SLE and SCD

The coexistence of SCD and SLE is rarely described in the literature, probably due to the small number of cases. Because of the overlapping of symptoms of both diseases, particularly those related to the CNS, establishing a differential diagnosis between the diseases is unquestionably difficult. Until April 2012, 45 patients with SCD and SLE had been reported in the MEDLINE database (Table 1). Thirty-five (78%) of these patients were female, while 10 (22%) were male. The majority of patients are adults (62.2%), with a mean age of 23 years-old at diagnosis (variation: 4 to 63). This resembles the age group of SLE patients proposed by Manzi, in which the disease developed during the ages of 15 to 45. SLE developed in patients aged ≤16 in only 37.7% of the cases described. Among patients with SCD and SLE, 33 (78%) had the SS phenotype. Due to the coexistence of severe complications, life expectancy of these individuals can potentially be reduced when compared to that of individuals who are diagnosed with one of the diseases. Treatment has also become a great challenge, since there are no controlled and randomized trials (that address the impact of SCD) of immunosuppressive drugs often used in SLE.

Probable etiology for coexistence of SCD and SLE

The infectious complications of SCD patients have a multifactorial etiology: splenic atrophy, reduced phagocytic capacity, defective opsonization, reduced production of antibodies and alternative complement pathway components. Some authors have proposed that the deficiency of factors of the alternative pathway complement and recurring infections caused by encapsulated bacteria could be the link between the immune complex disease and hemoglobin S. However, there had been no reduction of alternative complement pathway components in this report or in others described in the literature.

Articular manifestations

Articular disease were present in 35 patients (76%) with SLE and SCD, corresponding to the most common manifestation. The difficulty in diagnosing the coexistence of these two diseases is due to the fact both have articular manifestations. Hence, SCD patients’ joint complaints are interpreted as vaso-occlusive crises, delaying the diagnosis of SLE. In this study, the patient presented with a clinical picture of an asymmetric, additive, non-deforming polyarthritis unresponsive to analgesia and with prolonged evolution. Such characteristics diverge from standard SCD arthritis, which is usually short-term, monoarticular, acute and recurrent. Thus, general practitioners, pediatricians, hematologists and rheumatologists should be alert to the SCD patients with unsatisfactory response to hydration, analgesia and articular involvement pattern change in relation to the initial picture, and consider the possibility of association with other diseases, including SLE.
Hematological manifestations

Hematological disorders are common in both SCD and SLE. Table 1 shows patients with anemia, leukopenia or thrombocytopenia. In this review, 16 patients (36%) met at least one of these criteria. Hemolytic anemia is only found in 13% of the cases. On the other hand, the decreased hemoglobin in SCD is more important, reaching levels that range from 6 g to 9 g/dL, particularly in cases of sickle cell anemia (HbSS). Therefore, patients suffering from both diseases may show more severe anemia due to the overlapping of pathophysiological disorders.

Leukopenia is identified in 20% to 40% of cases of isolate SLE, including granulocytopenia and lymphopenia. These findings are caused by autoantibodies and by the systemic involvement of the disease. In SCD, predominantly leukocytosis and thrombocytosis are observed due to functional asplenia around the age of five.

Neuropsychiatric manifestations

Cerebral infarction, intracranial hemorrhage, cognitive dysfunction and seizures are neuropsychiatric disorders common to both SLE and SCD. The prevalence of neurological disorders in SLE patients is estimated to be 50%, with large variation among studies, while in SCD it occurs in 25% of patients. In SLE, hemorrhage, thrombosis associated with antiphospholipid antibodies, hypertension and thrombocytopenia relate to cerebrovascular accident, while in SCD the formation of aneurysms and the accumulation of deoxyanephrines in brain vessels promote increased adhesion, intimal hyperplasia and limited endoluminal flow. In Table 1, one can see that 12 patients (27%) with SLE and SCD had neuropsychiatric disorders, including seizures, psychosis, cognitive disorders and cerebrovascular accident, and only two patients did not have the SS phenotype. Presumably, individuals with both diseases, particularly of SS phenotype, are more likely to develop cerebrovascular disease. However, identifying its etiology is imperative for an effective treatment. Additional tests are critical for this differentiation. Transcranial Doppler ultrasonography is a valuable tool for assessing cerebral blood flow dynamic. The presence of antiphospholipid antibodies associated with the increase of inflammatory markers may suggest lupus etiology, requiring high doses of corticosteroids and additional immunosuppressive agents.

Renal manifestations

Both SCD and SLE can cause progressive renal failure, particularly juvenile SLE. Lupus nephritis is reported in 29% to 80% of juvenile cases, depending on the specialty of the researchers, if rheumatologists or nephrologists. The diagnosis of SLE in sickle cell individuals could be neglected due to the overlapping of signals that suggest renal disorder. Proteinuria, hematuria, hyperfiltration, glomerulopathy, nephrotic syndrome and chronic renal failure occur in both diseases. However, nephrotic syndrome is particularly interesting since it occurs much more often in SLE than in SCD. In Table 1, 21 patients (47%) developed renal disease attributed to the development of the SLE. Sickle cell nephropathy has a broad spectrum of pathologic presentations. Glomerular hyperfiltration, hemosiderin deposits, papillary necrosis, cortical infarction, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis with or without deposition of immune complexes, tubular atrophy and interstitial fibrosis may occur. Due to the wide renal involvement variety in SCD, renal biopsy becomes a useful diagnostic method for sickle cell patients with suspected coexistence of SLE. Lupus renal involvement targets glomeruli in most cases, with subendothelial immune deposits and proliferation of mesangial cells. The definition of the etiology of the renal involvement in patients with both SCD and SLE has different implication with regard to morbidity, mortality and treatment options.

Immunologic manifestations

Both SCD and SLE show important immunologic manifestations. Such involvement is mentioned in all case reports of coexistence of both diseases. The ANA may be present in the two diseases, being positive in almost 100% of SLE patients. Approximately 20% of SCD patients have positive ANA with titers greater than 1:160, however, mechanisms related to the development of antibodies in such patients remain unknown. Nonetheless, in the case of the association of both diseases, more specific autoantibodies, e.g. anti-dsDNA, anti-SM, anti-SSA and anti-SSB, should be ordered to support the diagnosis. Testing for antiphospholipid antibodies and lupus anticoagulant are also suggested, although these are also more commonly found in SLE than in SDC patients. Our patient presented with a positive ANA and anti-dsDNA. Anti-Sm, anti-SSA, anti-SSB were negative and C3, C4 and CH50 were within normal levels.

Serositis

Serositis is a clinical manifestation observed in both SCD (as a consequence of vaso-occlusive crises) and SLE patients, present in 18 patients (42.8%) of this review. The clinical similarities of these two diseases may delay the diagnosis of an underlying connective tissue disorder; pericarditis in sickle cell patients is a possible evidence of an active systemic autoimmune disease and/or an infectious process.

Skin manifestations

Cutaneous involvement is reported in 50% to 80% of SLE patients at diagnosis and in 85% of patients during the course of the disease. Skin manifestations may include malar rash, photosensitivity, vascular skin lesions with nodules and ulceration, palmar/plantar erythema, Raynaud’s phenomenon, annular erythema, alopecia and, less often, discoid lupus or lupus profundus. The characteristic cutaneous manifestation in SCD is the presence of lower-limb ulceration. The
most common manifestation in patients with both SLE and SCD has not been reported yet.

The following cutaneous manifestations are described in Table 1: malar rash (26%), discoid lesions (21%), photosensitivity (9.3%) and oral ulcers (6.9%). These features are uncommon in SCD patients and may facilitate the diagnosis of association of the two diseases.3

Conclusion
There is consensus among authors that physicians may face diagnostic difficulties when treating a SCD patient who develops SLE. These are different diseases, both with greater prevalence among blacks and sharing similar clinical manifestations during the course of the disease, delaying the diagnosis of a systemic autoimmune disease in these patients. Another confounding factor is that approximately 20% of SCD patients have a positive ANA at higher titers.32

Due to microvascular occlusion and hemolytic anemia at variable levels, SCD patients will have clinical manifestations, such as severe localized or diffuse pain that may be associated with edema and erythema, as well as chest pain, pulmonary infiltrates, cardiomegaly, congestive heart failure, abdominal pain and other vaso-occlusive manifestations.2

The limited number of cases published in the literature on the coexistence of SLE and SCD in the same individual does not allow stating if SCD patients are more likely to develop SLE.

According to the findings shown in this review, the presence of certain clinical features in SCD should alert pediatricians, hematologists and rheumatologists to the possibility of SLE diagnosis, particularly articular manifestations unresponsive to usual supportive measures, recurrent and refractory neuropsychiatric manifestations (especially if associated to the presence of antiphospholipid antibodies), presence of nephrotic proteinuria and, also, presence of leukopenia and/or thrombocytopenia. Renal biopsy and assessment of the specific antibodies for SLE could be very useful in these cases, just as positivity for other clinical manifestations, such as malar rash, photosensitivity, oral ulcers, alopecia and discoid lupus.

Prospective studies are required to clarify which mechanisms lead SCD individuals to develop SLE or if the coexistence of these two diseases is a mere coincidence.

Conflicts of interest
The authors declare no conflicts of interest.

REFERENCES