

Juvenile systemic lupus erythematosus and dermatomyositis associated with urticarial vasculitis syndrome: a unique presentation

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Abstract To report a case of triple association of juvenile systemic lupus erythematosus (SLE), juvenile dermatomyositis and urticarial vasculitis as well as a review of the relevant literature. A 12-year-old male patient diagnosed with overlap syndrome between SLE and juvenile dermatomyositis since 2004 evolved with erythematous plaques, which were compatible with an urticarial rash. Clinical, laboratory and histopathological findings indicated a diagnosis of urticarial vasculitis. The patient previously had a C1q deficiency. Using the established treatment with methylprednisolone (1 g/day for 3 days), increasing doses of deflazacort and introduction of a dapsone, as well as mycophenolate mofetil regimen, with the suspension of azathioprine resulted in complete resolution of skin lesions. Urticarial vasculitis can present in various diseases. In SLE, presentation of urticarial vasculitis in children is rarely found. The triple association of juvenile-onset SLE, juvenile dermatomyositis and urticarial vasculitis is unusual, and this is the first case described in literature.

Keywords Systemic lupus erythematosus ·
Dermatomyositis · Urticarial vasculitis ·
McDuffie syndrome

Introduction

Urticarial vasculitis was first described in 1973 by McDuffie et al. [1] as a syndrome in which an urticarial cutaneous manifestation of leukocytoclastic vasculitis exists. Its etiology remains unclear, and most of the presentations are idiopathic. Some cases may be associated with various conditions such as collagen diseases (systemic lupus erythematosus and Sjogren's syndrome), infections (hepatitis B and/or C, infectious mononucleosis and Lyme disease) or medication use (e.g., fluoxetine, paroxetine, propranolol or procainamide) [2].

The main aspect of the disease is the presence of urticarial lesions lasting more than 24 h with a skin biopsy showing vascular inflammatory infiltrate associated with leukocytoclasia figures with or without the presence of fibrinoid necrosis [3]. Systemic symptoms such as fever, arthralgia/arthritis, abdominal pain, nephropathy, or pulmonary or central nervous system involvements can occur and are more common in the hypocomplementemic form of the disease [4]. It corresponds to 11% of all cases of chronic urticaria evaluated by dermatologists and is predominant in adult females [4].

In childhood, urticarial vasculitis is rare as well as has uncertain incidence and prevalence. An association with juvenile-onset SLE has been reported [5], but no association has been described with juvenile dermatomyositis yet. The triple association of juvenile-onset SLE, juvenile dermatomyositis and urticarial vasculitis has never been reported in literature.

Therefore, the purpose of this report is to describe a juvenile patient with an unusual association among juvenile systemic lupus erythematosus, juvenile dermatomyositis and urticarial vasculitis syndrome.

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Case report

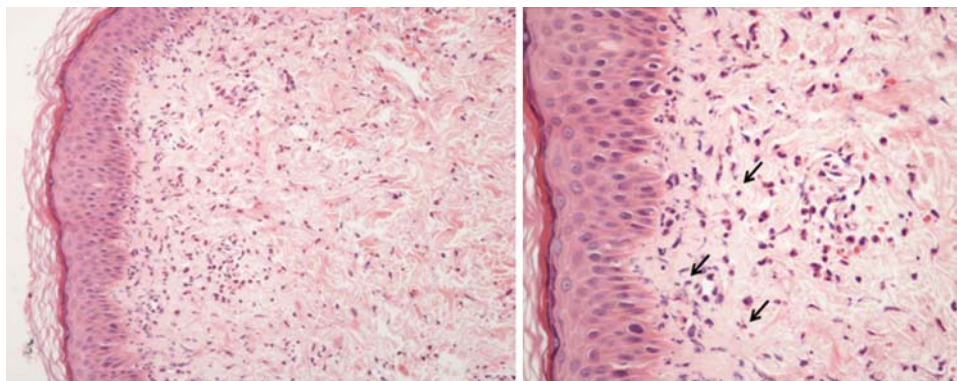
An 8-year-old male child was admitted in February 2004 with complaints of malaise, skin lesions and a photosensitive, erythematous rash on his face and limbs, proximal muscle weakness, psychosis, fever and weight loss. A physical examination showed muscle weakness in the upper and lower limbs, generalized lymphadenopathy, malar rash, heliotrope and Gottron signs. Laboratory tests revealed hemolytic anemia (Hb: 7.0 g/dL, LDH: 700 U/L, indirect bilirubin: 2.1 mg/dL), leukopenia (total leukocytes: 3,400; lymphocytes: 1,400), thrombocytopenia (90,000), and elevated muscle enzymes [CPK: 1,700 U/L (reference: 39–308 U/L) and aldolase: 9.7 U/L (reference: <7.6 U/L)]. The patient had positive antinuclear antibodies (1/320), anti-dsDNA (1/160) and anti-P autoantibodies; the other autoantibodies were negative, and complement levels were low [C3: 12.4 mg/dL (reference: 84–193 mg/dL) and C4: undetectable (reference: 20–40 mg/dL)]. The urinalysis was normal, and a chest X-ray showed bilateral pleural effusion. The diagnosis of overlap syndrome: juvenile systemic lupus erythematosus (ANA, anti-dsDNA, leukopenia, thrombocytopenia, autoimmune hemolytic anemia, psychosis and pleural serositis) and dermatomyositis (heliotrope lesion, Gottron sign, proximal muscle weakness and elevated muscle enzymes) was established. Treatment was started with pulse therapy with

methylprednisolone (30 mg/kg/day) for 3 days followed by 30 mg/day deflazacort, azathioprine (150 mg/day) and hydroxychloroquine (200 mg/day). After treatment, clinical lupus and dermatomyositis manifestations improved, laboratory tests normalized, complement fraction levels increased (C3: 45 mg/dL; C4: 10 mg/dL) and the patient was discharged for outpatient clinic follow-up. After 2 years, using azathioprine (150 mg/day), hydroxychloroquine (200 mg/day) and deflazacort (9 mg/day), he presented with new onset of fatigue, anorexia, weight loss and appearance of erythematous urticarial patches, which were pruritic and lasting over 24 h in the trunk, abdomen, back, and upper and lower limbs (Fig. 1a, b). Laboratory tests revealed low levels of complement (C3: 75 mg/dL; C4: undetectable) and positive anti-dsDNA (1/160) and CK 45U/L. The skin lesion was biopsied and showed an inflammatory infiltrate of predominantly neutrophils and lymphocytes in the papillary dermis, with the presence of leukocytoclasia figures and fibrinoid necrosis in the vessel wall, which are characteristics of urticarial vasculitis (Fig. 2). The patient also presented with C1q deficiency [18 mg/dL (reference: 29–42 mg/dL)]. The established diagnosis was urticarial vasculitis, and a new course of therapy was started with methylprednisolone (1 g/day for 3 days) followed by an increase of deflazacort dose to 30 mg/day. Azathioprine was stopped and dapsone (50 mg/day) and mycophenolate mofetil (MMF) (2 g/day) were

Fig. 1 Urticarial skin lesions on the trunk (a) and upper limb (b)



Fig. 2 Skin biopsy demonstrating the dermis with mixed inflammatory infiltrate with a predominance of neutrophils, leukocytoclasia (arrows) and focal areas of fibrinoid necrosis in the vessel wall (leukocytoclastic vasculitis)



added. The patient progressed well with complete resolution of skin lesions and improvement of systemic complaints. Currently, he is in the outpatient clinic, with stable SLE, dermatomyositis and urticarial vasculitis, using dapsone (50 mg/day), MMF (2 g/day) and deflazacort (8 mg/day).

Discussion

Urticarial vasculitis (UV) is a rare syndrome, especially in children. Its diagnosis is determined by high clinical suspicion and is typically associated with urticarial lesions or purpuric skin lesions, as well as typical skin biopsy histopathology.

Data on the prevalence and incidence of UV are inaccurate due to its rarity, nevertheless it is estimated that 5% of patients with urticaria have UV [6]. In a study involving 675 patients with chronic urticaria, Dincy et al. [4] showed that the prevalence of UV was 11% of the cases analyzed: 8% had normocomplementemic UV and 3% hypocomplementemic UV. The patients were mostly women (57%) in the third or fourth decades of life. Pediatric patients of this review exclusively presented with the normocomplementemic form of the disease. Also, in this study [4], it was shown that the main systemic involvement was arthralgia and fever followed by abdominal pain, cough and involvement of the central nervous system. These data are consistent with other studies in the current literature [7, 8]. Our patient presented manifestations of systemic arthralgia, malaise and anorexia, compatible with a hypocomplementemic disease, and was confirmed by the progressive reduction in the serum complement.

The relationship (or overlapping) with connective tissue diseases remains under investigation. It is known that only 2% of patients with the normocomplementemic form of the disease meet the criteria for SLE, similar to the hypocomplementemic form where up to 50% of patients may have a defined overlapping syndrome [3]. The relationship or overlap with Sjögren's syndrome has also been described, since UV was present in 32% of Sjögren's syndrome [9]. Clinical manifestations such as ocular (scleritis/episcleritis/uveitis), renal (hematuria asymptomatic interstitial nephritis, rapidly progressive membranoproliferative glomerulonephritis), pulmonary (chronic obstructive pulmonary disease, asthma, serositis, pleural or pulmonary capillaritis) or articular are often described. Jaccoud arthropathy is rare, but has been reported and may be a marker of valvular disease [10]. However, only in 2007 a clinical myopathy was related to the presence of hypocomplementemic urticarial vasculitis syndrome [11]. The patient mentioned in that report was 31 years old and had a previous diagnosis of hypocomplementemic UV when he

developed proximal muscle weakness and elevated creatine kinase [11]. Muscle biopsy showing inflammatory myopathy with the presence of vasculitis and mononuclear cells in muscle fibers I and II (also affected) is not exclusive to dermatomyositis or polymyositis diagnoses.

As in the childhood forms, which are low in prevalence, the adult forms of UV are continually being studied. To date, there have been ten studies with reports of childhood forms, totaling about 13 cases. The strong association with systemic lupus erythematosus in children remains similar to the adult population [5, 12, 13]. However, a juvenile inflammatory myopathy associated with UV has not yet been described, and this is the first report.

Juvenile forms of UV syndrome present with a systemic and more severe clinical picture. Hypocomplementemic cases prevail with renal involvement in more than 50% of patients [12, 13]. As in adults, this event is more serious and can lead to early kidney failure [12, 13]. For example, severe pulmonary involvement was described in three brothers who had pulmonary hemorrhage and secondary restrictive lung disease [13].

There are two major criteria for the clinical diagnoses of urticarial vasculitis (urticarial skin lesions and reduction of serum complement fractions) and six minor criteria [venulitis dermal (biopsy), arthralgia or arthritis, glomerulonephritis, uveitis or episcleritis, recurrent abdominal pain and C1q precipitation test positive]. The correct diagnosis is made when one of the two major criteria and at least two of the six minor criteria are present. We emphasize that our patient had two major criteria (urticarial lesions and reduction of serum complement levels) and two minor criteria (arthralgia and positive anti-C1q).

A skin biopsy is an important point of diagnosis because it defines the presence of vascular inflammation that characterizes small vessel vasculitis. Typical findings are neutrophilic inflammatory infiltrate associated with perivascular edema and wall vessel fragmentation with exposure of nuclei of neutrophils (leukocytoclastic findings) and deposition of a fibrinoid exudate [14]. Recently, a study conducted by Lee et al. [7] showed that only 13% of patients had predominant neutrophil infiltration, raising the need for reassessment of current concepts and criteria involving a diagnosis of urticarial vasculitis. This author demonstrated a high prevalence of lymphocytic infiltration (86%) with only 13% of cases with neutrophilic infiltrate. A fibrinoid exudate was seen in 9% of cases, which were all associated with neutrophilic infiltrate. Patients with lymphocytic vascular infiltration exhibit normal complement levels form of the disease as patients with neutrophilic infiltrate, which show a more severe clinical picture that is characterized by the consumption of complement and systemic manifestations.

The treatment of this disease is variable and is usually directed at the symptoms of the syndrome. Antihistamines are useful in controlling itching, but rarely control the appearance of new lesions, especially in those cases with systemic involvement [3]. Systemic corticosteroids are usually necessary for the immediate control of the disease and their dosage depends on the severity of the disease. High doses may be necessary in refractory cutaneous, renal or pulmonary diseases. Dapsone is a drug associated with durable remission of the eruptions, either isolated or associated with systemic manifestations [15]. Because of its low toxicity profile and low cost, it is currently considered the first option for the treatment of this syndrome.

There are also other medications as treatment options. Hydroxychloroquine and colchicine are alternatives for isolated eruptions [14]. Azathioprine has shown success in the treatment of renal and skin involvement [3]. Cyclophosphamide pulse therapy in combination with dexamethasone is an alternative for refractory cases, and mycophenolate mofetil is an option for maintenance therapy [14]. Intravenous immunoglobulin has been used effectively in the case of a child associated with multiple infections [5]. Among the more novel therapeutic agents, rituximab (anti B-cell therapy) has been demonstrated to be effective in treating this syndrome in the adult population [16]. Studies with this medication on children do not so far exist.

UV has a good prognosis. Risk factors for severe disease are the presence of hypocomplementemia and systemic involvement, especially renal and pulmonary [14].

The UV syndrome can be manifested in different ways and with different severities, whether or not it is associated with autoimmune diseases such as systemic lupus erythematosus [10, 12]. The diagnosis is based on the presence of typical lesions and confirmatory pathological findings [3]. The presentation of UV in the adult population has been extensively studied, but cases in children are rare and poorly described [12, 13]. We present a case report associated with juvenile-onset of SLE and dermatomyositis, calling attention to the unprecedented combination of these three diseases and emphasizing the necessity of considering these for the diagnosis of this condition in children, who have a worse prognosis when compared to the adult population [12, 13].

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