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Urticarial vasculitis in the childhood with C2 hypocomplementenemia: a rare case

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Key words
urticaria; child; urticarial vasculitis; complement

Summary
We report a first case of hypocomplementemic urticarial vasculitis of C2 fraction in a child, with cutaneous manifestation only, with no reports in scientific literature.

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Introduction

Urticarial vasculitis (UV) is defined as recurrent episodes of urticaria persisting for more than 48 hours, with pain and burn sensations that have histopathological characteristics as leukocytoclastic vasculitis (1,2,3). The UV occurs in about 1.8% of the adult population, that corresponds to 5-10% of the chronical urticarias on adults, while the childhood prevalence is unknown (2,3,4,5).

Three types of UV have been described: the normocomplementemic form, responsible for 80% of the cases, self-limited and restricted to the skin (3); the hypocomplementemic form, frequently associated with systemic inflammatory diseases like arthritis (50%), intestinal diseases (20%), asthma and chronical obstructive pulmonary diseases (20%); and the hypocomplementemic vasculitis syndrome, a rare and potentially severe condition, characterized by the urticaria with hypocomplementenemia persisting for at least six months. This form is associated with systemic manifestations such as severe angioedema, laryngeal edema, lung diseases, arthritis, glomerulonephritis and recurrent abdominal pain (6,7,8).

Case report

The patient, a 5 years old male, reached the medical service complaining about recurrent urticarial episodes lasting 48-72 hours, and were relieved with anti-histaminic drugs without any other symptoms. Through the examination were found the presence of urticariform lesions on the trunk (**figure 1a**) and superior limbs, and as well residual hyperchromic lesions were found on proximal limbs and back (**figure 1b**).

The followed laboratorial exams were: complete blood count (CBC), renal function (urea, creatinine), hepatic function (Aspartate transaminase, Alanine transaminase, Gamaglu-

til transferase, alkaline phosphatase, coagulation profile), C reactive protein (CRP), hepatitis B and C serology, cryoglobulins, total and fraction bilirubins, anti-nuclear antibody (ANA), anti-DNA double stranded, Anti-SS-A (Ro), anti-SS-B(La), rheumatoid factor (RF), anti-thyroid antibodies, electrophorese of protein, Glucose-6-phosphate dehydrogenase (G6PD), Perinuclear Anti-Neutrophil Cytoplasmic Antibody (pANCA), Cytoplasmic Anti-Neutrophil Cytoplasmic Antibody (cANCA), C4 and urine-analysis. However, the complement fractions CH50 (50% haemolytic complement) was reduced (75 mg/dL; reference: 150-300 mg/dL) and C3 (89.3 mg/dL; reference: 90-180 mg/dL). C1 esterase dosage was normal, C1 was normal value and C2 fraction was diminished (57% Reference: higher than 67%), characterizing C2 deficiency.

The patient was also submitted to a cutaneous lumbar punch biopsy. This provided evidence of vasculitis of the superficial and profound vascular plexus with eosinophilia, and hystologically compatible with urticarial vasculitis.

To control the urticaria, therapies with anti-histaminic drugs and corticoids were used.

During follow-up, the patient showed diverse hives episodes, with 48-72 hours of duration, worsening when anti-histaminic use was stopped. After 4 years of segment and periodical exams (**table 1** and **figure 1b**) the patient returned with ANA reagent, nuclear fine speckled pattern (1⁄640) which was followed up until April of 2014. During that period, titles of ANA were rising (1⁄1280), nuclear fine speckled pattern, with no development of other diseases, with persistence of the cutaneous manifestation, but with notable improvement.

Discussion

The urticarial vasculitis typically manifests itself through painful hives with prolonged duration and residual hyperpigmentation (9). It affects mainly the trunk and extremities, having an average duration of three years (9) with higher prevalence among females and peaking in the fourth decade of life, being extremely rare in children (1,4,11,12,15). In hypocomplementemic form, which is observed most exclusively in female patients (16), other manifestations may occur such as gastrointestinal symptoms (abdominal pain, nausea, vomiting and diarrhea in approximately 17-30% of cases), musculoskeletal involvement (arthralgia and arthritis in 50-75%), renal involvement (proteinuria and hematuria in 20 to 30% of cases). Chronic obstructive pulmonary disease is present in 20 to 30% of patients while ophthalmic complications were present in less than 10% of patients (10).

The diagnosis of this entity should be considered in the presence of persistent hives with suggestive clinical, serologic or systemic diseases evidences. Histopathologically, as observed in our patient, the UV demonstrates leukocytoclastic vasculitis signals, such as endothelial damage of post-capillary venules, extravasation of red blood cells, fragmentation of leukocytes with nuclear debris, perivascular and infiltrated fibrin deposition with a predominance of neutrophils (3,8-10).

During the follow up, autoimmune diseases should be investigated, given the fact that its association with Sjögren's syndrome is 30% and with systemic lupus erythematosus (SLE) is 20% (1,3,8). These diseases were excluded in the diagnostic elucidation of the patient, even though it had progressing ANA titles with fine speckled pattern, once it didn't show any clinical laboratory changes that would close the diagnostic criteria for both conditions.

Figure 1a *- Urticariform lesions on the trunk (abdominal region).*

Figure 1b *- Residual hyperchromic lesions on the back.*

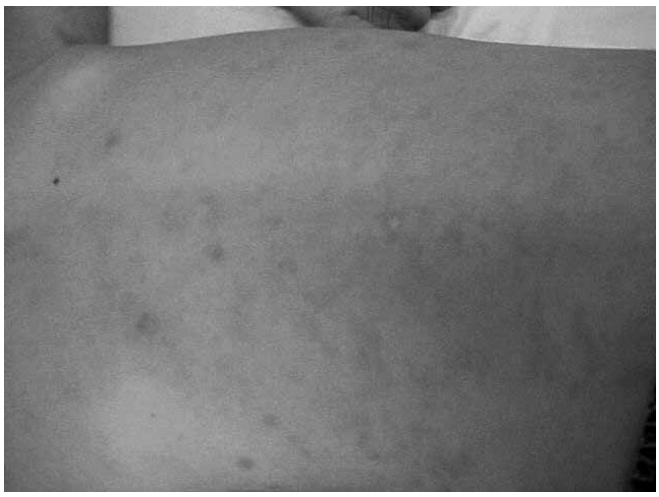

Tabella 1

Patient's data	Mar-06	Jan-07	dec-07	Mar-08	Jul-09	Mar-10	Jul-11	Jan-13	Jan-14
Hb (g/dl)	*	12,3	12,8	13	13,6	12,4	12,8	13,9	13
WBC (10E9/L)	*	5,9	5,8	5,3	6,22	4,9	4,5	5,07	5
Platelets (10E9/L)	*	368	281	313	354	259	294	228	240
CRP (mg/L)	< 5	0,1	0,1	*	< 0,10	< 5	< 5	< 0,3	< 0,3
ANA (1:n)	0	0	0	80	0	0	640	1280	1280
pattern				speckled			speckled	speckled	speckled
CH50 (mg/dL)	75	80,29	*	*	*	160	*	161	160
C2 (%)	57%	57%	58%	57%	56%	55%	55%	56%	55%
C3 (mg/dL)	98	89,3	*	*	108	88	86	98	*
C4 (mg/dL)	14	12,8	*	*	14	10	10	11	*
Urea (mmol/L)	31	22	28	*	*	*	29	*	*
Creatinine (umol/L)	0,4	0,38	*	*	0,5	0,72	0,4	*	*
RF	< 10	7,4	*	*	< 10	*	< 11	< 9,3	*
24 h urine protein (g/dL)	50,5	*	*	*	*	*	*	*	*

*Unknown values / Hb hemoglobin / WBC white blood cell count / CRP C reactive protein / ANA antinuclear antibody / CH50 50% haemolytic complement / RF rheumatoid factor

Elevated erythrocyte sedimentation rate and a drop in levels of complement are frequently observed (10), characterized by activation of the classical pathway with reduced C1, C2, C4, C3 and CH50 (11), and the C1q deficiency is associated to severe autoimmune disease in 95% of cases (13). Even though the complement fall is a sensitive marker for systemic disease (10) and the C2 loss is associated in 40% with autoimmune severe diseases (13), this situation was not observed in this case described of exclusively cutaneous presentation without any systemic manifestation.

It is an unwieldy condition, often guided by the severity of symptoms and the underlying systemic disease. Antihistamines are the first choice drug for the treatment of UV with only cutaneous involvement (e.g. Cinnarizine), even though they don't control inflammation caused by immune complexes, requiring oral corticosteroid, indomethacin, colchicine, dapsone and hydroxychloroquine. In cases of systemic involvement, patients may require treatment with immunosuppressants such as azathioprine or cyclophosphamide, or immunomodulators such as rituximab, or Immunoglobulin G intravenous (1,4,17).

This case illustrates an atypical presentation of urticarial vasculitis Hypocomplementaemic (C2 decrease) in a very young male patient with only cutaneous involvement, and no systemic manifestation until now, such fact not seen in the literature before. The diagnosis of this likely pathology systemic involvement from a cutaneous manifestation stresses the importance of further investigation of vascular lesions of the skin, resulting in early diagnosis that will provide greater care and attention to any systemic change, favoring a better prognosis and disease management.

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