e - ISSN - 2349 - 8005

INTERNATIONAL JOURNAL OF ADVANCES IN CASE REPORTS

Journal homepage: www.mcmed.us/journal/ijacr

HYPOCOMPLEMENTEMIC URTICARIAL VASCULITIS SYNDROME IN AN ADOLESCENT

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Article Info
Received 15/01/2016
Revised 27/02/2016
Accepted 12/03/2016

Key words:
hypocomplementemia, Urticarial vasculitis.

ABSTRACT
Hypocomplementemic urticarial vasculitis syndrome (HUVS) is a rare autoimmune disease characterized by recurrent or persistent urticaria and low C1q, C2,C3 and C4 complement levels, along with multiorgan involvement. We describe a 17-year-old boy who presented with fever, recurrent urticarial rash and arthralgia of the hip joints. His clinical course was complicated by the development of an acute nephritic syndrome. Renal biopsy revealed mesangiocapillary glomerulonephritis. Complement C3 and C4 levels were markedly depressed. The patient was initially thought to have an infectious process with acute post-infectious glomerulonephritis. HUVS was established as the correct diagnosis only after a skin biopsy revealed leucocytoclastic vasculitis. HUVS should be included in the differential diagnosis of a child who presents with urticaria, arthralgia/arthritis and coexistent glomerulonephritis and/or pulmonary disease.

INTRODUCTION

Hypocomplementemic urticarial vasculitis syndrome (HUVS) is a rare autoimmune disease first described by McDuffie et al. in 1973 [1]. It is characterized by recurrent or persistent urticaria and low complement levels, specifically C1q, C2, C3 and C4 along with multiorgan involvement. Urticaria and hypocomplementemia have been designated as the major diagnostic criteria with at least two of the following minor criteria required for diagnosis: leucocytoclastic vasculitis, arthralgias and /or arthritis, ocular inflammation, abdominal pain, glomerulonephritis and positive C1q antibodies [2]. The syndrome is very uncommon in the pediatric population.

Patient description

A 17-year-old, otherwise healthy, male, was admitted due to fever, rash and arthralgia of the hip joints. Past history was notable for the fact that six months prior to the current admission, he experienced an urticarial rash that resolved spontaneously. The patient is the first born child of non-consanguineous parents of Muslim Arabic origin. Apart from a distant relative diagnosed with Bechet's disease, there is no other family history of rheumatologic, autoimmune or renal disease. The patient's symptoms began several days before admission. The rash was originally described as non-pruritic urticaria.

On physical examination, weight was 69.5 kg, height 1.79 m, temperature 38°C, and blood pressure 137/51 mmHg. An elevated maculopapular rash, involving the upper and lower extremities and sparing the trunk, face and hands, was evident. Conjunctival injection was seen in both eyes. Inguinal lymph nodes were palpable bilaterally. Pain was easily elicited on movement of the hips.

Laboratory data were ESR 60 mm/h, Hb 13.0 g/dl (decreased to 10.6 g/dl on rehydration), WBC 13,000/mcl (89% neutrophils), platelets 121,000/mcl, serum creatinine peaked at 1.2 mg/dl (basal 0.8), and urea 59 mg/dl. C-reactive protein (CRP) was initially 9 mg/dl and increased

to 23 mg/dl (range 0.0-0.5 mg/dl). C3 level was 30 (range 90-180 mg/dl) and C4 was 1.6 mg/dl (range 10-40 mg/dl). Anti-neutrophil antibodies, anti-cytoplasmic neutrophil antibodies, rheumatoid factor and cryoglobulins were all negative or within normal limits. Serology tests for mycoplasma, brucella, leptospira, rickettsia, legionella, hepatitis A, B and C, and toxoplasma were negative. EBV and CMV immunoglobulins were indicative of past infection. Repeated blood cultures yielded no growth. Abdominal ultrasound, EKG, chest x-ray and echocardiogram were all normal.

Dipstick urinalysis showed protein 30-100 mg/dl and RBC 200/mcl. Urine microscopy revealed numerous RBC/HPF with no casts. A 24 h urine collection for protein measured 350 mg. Renal ultrasound demonstrated both kidneys to be of normal size and texture. Percutaneous renal biopsy was performed and showed changes compatible with mesangiocapillary glomerulonephritis.

Due to suspicion of an acute bacterial infection, the patient was empirically started on ceftriaxone and doxycycline with no improvement in symptomatology. In particular, he continued to complain of arthralgia of the hips and other joints. Ultrasound of the hip joints detected fluid in the right joint. The rash was persistent and was aggravated by elevations in temperature. He, therefore, underwent a skin biopsy which revealed perivascular lymphocytic infiltration in the middle and superficial dermis.

Over the ensuing week of hospitalization, the patient's condition improved without resort to any specific treatment such as steroids. The fever abated, arthralgias disappeared and blood pressure normalized. The rash faded leaving spots of hyperpigmentation. Serum creatinine returned to its basal value. C3 levels increased to 100 mg/dl. C4 levels remained below normal at 8-9 mg/dl.

DISCUSSION

Our patient fulfilled the diagnostic criteria of HUVS as set forth by Schwartz *et al*. [2]. These included the two major criteria, that is, recurrent urticaria over a 6 month period and hypocomplementemia and four minor criteria (at least two are required), namely, arthralgias/arthritis, glomerulonephritis, ocular inflammation and leucocytoclastic vasculitis. However, diagnosis was only established after the finding of skin vasculitis. Due to its possible protean presentations across a wide variety of medical subspecialties, the diagnosis of HUVS is often considerably delayed. It requires an astute physician to be thinking "outside the box.

HUVS is characterized by marked depression of complement levels (factors C1q, C2, C3 and C4). The decrease of these particular factors indicates activation of the classical complement pathway. C1q antibodies are found in 100% of HUVS cases [3] and are considered a diagnostic marker. There is an ongoing controversy as to whether HUVS is part of the spectrum of systemic lupus erythematosus (SLE). While some authorities consider this to be the case, the absence of classic anti-extractable nuclear antigens (ANA, anti-dsDNA) suggests that HUVS is a separate entity.

Urticaria or hives are commonly encountered in pediatrics. Typical urticaria usually manifest as pruritic wheals which disappear within 8-24 hours leaving no trace of their occurrence. In contrast, the lesions of urticarial vasculitis, as seen in our patient, persist for at least 24 hours and resolve into pupura and eventual hyperpigmentation of the involved dermis [4]. The incidence of vasculitis in apparent urticaria is 5% to 20%.

Extracutaneous manifestations of HUVS include constitutional symptoms (fever, malaise, and fatigue); musculoskeletal symptoms; ocular inflammation such as conjunctivitis, episcleritis, and uveitis; serositis; obstructive lung disease; Raynaud's phenomenon; renal disease; gastrointestinal symptoms; cardiac involvement; and various neurologic problems. Arthralgias are migratory and transient, mainly affecting the hands, elbows, feet, ankles, and knees. Arthritis is seen in up to 50% of cases.

Pulmonary manifestations include cough, dyspnea, hemoptysis, pleuritis, pleural effusions, tracheal stenosis and acute laryngeal edema. These can progress to moderate to severe chronic obstructive pulmonary disease (COPD) and asthma, (seen in 20% to 50% of patients) causing significant morbidity and mortality.

Renal involvement occurs in up to 50% of cases of HUVS. It is usually manifested by proteinuria and microscopic hematuria and follows a benign course. Renal biopsy findings have included mesangial proliferative, focal proliferative, mesangiocapillary, membranous and minimal change glomerulopathies. Very rarely, crescentic glomerulonephritis leading to end stage renal disease has been described [5].

Treatment of HUVS should be tailored to the severity of the disease and the presence of systemic involvement. For mild cutaneous disease, antihistamines may be sufficient. For more severe symptomatology and in particular renal and/or pulmonary involvement, glucocorticoids with cytotoxic agents may be required. Immunomodulatory agents such as hydroxychloroquine and dapsone have also been used to some effect. Notably, our patient's clinical status resolved spontaneously without recourse to immunosuppressive therapy. Nine months after admission, he remains in complete remission on no treatment.

CONCLUSION

The present case serves to increase physician awareness of HUVS in adolescents, an entity rarely encountered in the pediatric population. HUVS should be included in the differential diagnosis of a child who presents with urticaria, arthralgia/arthritis and concomitant with glomerulonephritis and/or pulmonary disease.

ACKNOWLEDGEMENT: None

DECLARATION OF INTEREST

The authors have no conflicts of interest to declare.

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