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Atypical acute urticaria in children and its relationship with urticarial vasculitis

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Aim: In childhood, urticarial lesions are sometimes associated with purpura. This form might be identified as atypical, and may also be related to urticarial vasculitis (UV). The aim of this study was to assess the clinicopathologic characteristics of UV in children with atypical urticaria.

Materials and methods: Fifteen children with atypical urticaria were evaluated with medical history, physical examination, and laboratory and skin punch biopsy findings.

Results: Infections were detected as possible precipitating factor in 12 patients. Complement levels were normal in all. On histological examination, 6 patients (40%) had neutrophil-predominant infiltrate and 9 (60%) patients had lymphocyte-predominant infiltrate. All the patients with a neutrophil-predominant infiltrate showed leukocytoclastic vasculitis (LCV). None of the 9 patients with perivascular infiltrate of lymphocytes showed LCV. Eosinophil infiltration was present in 8 patients. On direct immunofluorescence examination, 5 of the 6 patients with LCV had deposits of immunoreactants, mainly of Ig G, Ig M, and fibrinogen.

Conclusion: Our findings, in contrast to the literature, suggest that UV is i) not rare in children, ii) generally triggered by infection, iii) normocomplementemic, and iv) self-limited. The biopsy specimens may show neutrophil-predominant infiltrate with LCV or lymphocyte-predominant infiltrate without LCV. These results imply that in children with normocomplementemic UV it may not be necessary to perform a skin biopsy.

Key words: Acute urticaria, biopsy, children, urticarial vasculitis

Çocuklarda atipik akut ürtiker ve ürtikeriyal vaskülitle ilişkisi

Amaç: Çocukluk çağında ürtikeriyal lezyonlar bazen purpura ile birliktedir. Bu ürtiker formu atipik olarak isimlendirilebilir ve ürtikeriyal vaskülitle (ÜV) de ilişkili olabilir. Bu çalışmanın amacı atipik ürtikerli çocuklarda ÜV'in klinikopatolojik özelliklerini saptamaktır.

Yöntem ve gereç: Atipik ürtikeri olan 15 çocuk hikaye, fizik muayene, laboratuvar ve cilt punch biopsi bulgularıyla değerlendirildi.

Bulgular: Enfeksiyonlar 12 hastada olası tetikleyici faktör olarak saptandı. Hastaların tümünde kompleman düzeyleri normaldi. Histolojik incelemede, altı hastada (%40) nötrofil hakim ve dokuz hastada lenfosit hakim infiltrasyon vardı. Nötrofil hakim infiltrasyonu olan hastaların hepsi lökositoklastik vaskülit (LSV) gösterdi. Perivasküler lenfosit infiltrasyonu olan dokuz hastanın hiçbiri LSV göstermedi. Eozinofil infiltrasyonu sekiz hastada vardı. Direkt immunofloresan incelemede LSV'i olan altı hastanın beşinde başlıca IgG, IgM ve fibrinojen olan immunoreaktanların depolanması vardı.

Sonuç: Literatürün tersine bizim bulgularımız ÜV'in I) çocukluk yaş grubunda nadir olmadığını, ii) genellikle enfeksiyon ile tetiklendiği, iii) normokomplementemik olduğunu, ve iv) kendi kendini sınırladığını göstermiştir. Biopsi örnekleri LSV ile birlikte nötrofil hakim veya LSV olmaksızın lenfosit hakim infiltrasyon gösterebilir. Bu sonuçlar normokomplementemik ÜV'li çocuklarda cilt biopsisi yapmaya gerek olmayabileceği anlamına gelmektedir.

Anahtar sözcükler: Akut ürtiker, biopsi, çocuklar, ürtikeriyal vaskülit

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Introduction

In childhood, acute urticaria is characterized by pruritic, red circular or irregularly shaped migratory eruptions on any part of the body, and frequently related to medication and food (1). Urticarial lesions usually resolve in 24 h, and leave no residual pigmentation. Sometimes lesions starting as acute urticaria may exceed this duration, associated with purpura, resolving with dusky changes and residual hyperpigmentation, and may or may not be pruritic. This form might be identified as atypical, and may be related to urticarial vasculitis (UV). Urticarial vasculitis is a clinicopathologic entity frequently reported in adults, but rarely in children (2). Urticarial vasculitis can be a local process or the presenting manifestation of a systemic disease such as malignancy or infectious and connective tissue diseases (3). Based on accompanying systemic findings and complement levels, UV is classified as normocomplementemic urticarial vasculitis (NUV), hypocomplementemic urticarial vasculitis (HUV), and hypocomplementemic urticarial vasculitic syndrome (HUVS). The aim of this study was to assess the clinical and histologic features of the patients who presented with atypical acute urticaria.

Materials and methods

In this prospective study conducted between January and May 2007, the findings of 15 children (13 males, 2 females) with atypical acute urticaria with an age distribution of 5 to 120 months (mean age: 41.8 months) were examined. The patients whose urticarial lesions last longer than 24 h, and resolve with hyperpigmentation, and/or associated with purpura or dusky changes were included in the study. They were interviewed for detailed allergic history, associated systemic symptoms, and possible precipitating events as prior infection and drug ingestion. A careful physical examination was performed to identify any clues of systemic disease. Complete blood cell counts, erythrocyte sedimentation rate (ESR), biochemical parameters, C3 and C4 complement levels, antinuclear antibodies, and hepatitis serology were studied. Skin punch biopsies of lesions that developed within 18-24 h were obtained for histological examination and direct immunofluorescence (DIF). On histology, the type of infiltrate and its distribution, endothelial cell swelling, presence of nuclear debris, red blood cell extravasation, fibrin exudation, and epidermal changes were evaluated. A predominant cell type was described when it made up 50% or more. Written informed consent of the parents was obtained before participation in the study.

Results

Clinically, all the patients had urticarial lesions persisting longer than 24 h and resolving with residual hyperpigmentation. While 11 patients had diffuse skin lesions, 4 had lesions confined to the limbs. Nine patients had purpura associated with urticarial lesions. Angioedema was detected in 3 patients. History of infection as a possible precipitating factor was detected in 12 patients. None of the patients had elevated ESR or CRP, and had no systemic involvement. Other laboratory investigations including urinalysis, C3 and C4 complement levels, and antinuclear antibodies were normal in all the patients. In addition, hepatitis B and C serology was negative (Tables 1 and 2).

All the patients underwent a skin punch biopsy. On histological examination, 6 patients (40%) had neutrophil-predominant infiltrate, and 9 patients (60%) had lymphocyte-predominant infiltrate. All the patients with a neutrophil-predominant infiltrate showed leukocytoclastic vasculitis (LCV).

There were endothelial cell swelling in 4 patients, fragmentation of leukocytes with nuclear debris in 5, erythrocyte extravasation in 3, fibrin exudation from vessel walls in 4, and eosinophilic infiltration in 2 (Table 3). None of the 9 patients with perivascular infiltrate of lymphocytes showed fibrin exudation or nuclear dust, and only 1 showed erythrocyte extravasation. Furthermore, eosinophilic infiltration was present in 6 patients (Table 4).

On DIF examination, 5 patients with LCV had deposits of immunoreactants, which were mainly of Ig G, Ig M and fibrinogen, and rarely of Ig A and C3 within dermal vessel walls. All the patients with lymphocyte-predominant infiltrate, and only 1 patient with LCV had negative DIF findings.

Table 1. Clinical characteristics of the patients with neutrophilic vasculitis.

Patient no.	Age (months)	Gender	Possible trigger	Distribution of lesions	Purpura	Angioedema	Complement levels	Therapy
1	16	F	URI	G	+	–	N	AH
2	54	M	URI	G	+	+	N	AH+CS
3	30	M	URI	G	–	+	N	AH+CS
4	60	M	–	LE	–	–	UA	AH+CS
5	18	M	URI	LE	+	–	N	AH
6	18	M	AGE	LE	+	–	N	AH+CS

M, Male: F, Female: URI, Upper respiratory tract infection: AGE, Acute gastroenteritis: G, Generalized: LE, Lower extremities: N, Normal: UA, Unavailable: AH, Antihistamines: CS, Corticosteroid

Table 2. Clinical characteristics of the patients with lymphocytic vasculitis.

Patient no.	Age (months)	Gender	Possible trigger	Distribution of lesions	Purpura	Angioedema	Complement levels	Therapy
1	120	M	URI	G	+	–	N	AH+CS
2	24	M	AGE	LE	+	–	N	AH
3	108	M	URI	G	–	–	UA	AH
4	5	M	URI	G	+	–	N	AH+CS
5	12	M	URI	G	+	–	N	AH
6	18	M	AGE	G	–	+	N	AH+CS
7	60	F	–	G	+	–	N	AH+CS
8	12	M	URI	G	–	–	N	AH+CS
9	36	M	–	G	–	–	N	AH

M, Male; F, Female; URI, upper respiratory infection; AGE, Acute gastroenteritis; G, Generalized; LE, Lower extremities; N, Normal; UA, Unavailable; AH, Antihistamines; CS, Corticosteroid

Table 3. Histopathological findings of the patients with neutrophilic vasculitis.

Patient no.	Endothelial swelling	Nuclear debris	Red cell extravasation	Dominant cell	Immunoflourescein
1	+	+	–	N	IgG, Fibrinogen, C3
2	–	+	+	N	IgG
3	–	–	–	N	IgG, A, M, Fibrinogen, C3
4	+	+	–	N	IgG, Fibrinogen
5	+	+	+	N	IgG, A, M, Fibrinogen, C3
6	+	+	+	N	UA

N, Neutrophil ; Ig, Immunoglobulin ; UA, unavailable

Table 4. Histopathological findings of the patients with lymphocytic vasculitis.

Patient no.	Endothelial swelling	Nuclear debris	Red cell extravasation	Dominant cell	Immunoflourescein
1	+	–	–	L	Negative
2	–	+	+	L + Eo	Negative
3	–	–	–	L + Eo	UA
4	–	–	–	L + Eo	Negative
5	–	–	+	L	Negative
6	–	–	+	L + Eo	Negative
7	–	–	–	L	Negative
8	–	–	–	L + Eo	Negative
9	–	–	–	L + Eo	Negative

L, Lymphocyte; N, Eo, Eosinophil

All the patients were given antihistamines. Four patients with LCV and 5 patients without vasculitic findings were also given oral prednisolone (1 mg/kg per day for only a week). All the patients responded dramatically to the treatment and no recurrence developed in the follow-up period of nearly 1 year.

Discussion

Although urticarial vasculitis has been reported in a large number of female adult patients, only a few pediatric cases have been reported (2). In this study, 15 patients with clinical features of UV were presented. To our knowledge this study is the largest series of children with UV in the literature.

Most cases of UV are idiopathic; sometimes it is associated with infections, malignancy and/or connective tissue diseases (3). Although none of our patients had symptoms and findings of systemic diseases, the majority had a history of upper respiratory infection (URI) or acute gastroenteritis (AGE). Therefore, there was accumulation of Ig G, M, and C3 in biopsy specimens, which may suggest alternative complement pathway activation secondary to a prior infection.

None of the patients that participated in our study had low complement levels; however, the frequency of hypocomplementemia in UV has varied, ranging from 18% to 40% in other studies (4-6). To illustrate, in a study by Lee et al. (7), only 2 patients had hypocomplementemia and LCV, with 1 having clinical features of connective tissue disease.

Conventionally, the diagnosis of UV is made when clinically urticarial lesions last longer than 24 h and histologically show features of LCV with evidence of endothelial cell damage, fibrin deposition, perivascular neutrophil infiltration, and fragmentation of leukocytes with nuclear debris (3). However, our study showed histopathological heterogeneity of the clinical diagnosis of UV in children. Only 6 patients (40%) with neutrophil-predominant infiltrate displayed the findings of LCV while 9 patients (60%) clinically compatible with UV showed predominantly lymphocytic infiltration without LCV. In a similar study concerning adults, 19 patients (86.4%) had a lymphocyte-predominant infiltrate, and only 3 patients had LCV with neutrophils (7). Although the results of the Lee et al.'s study and our study were similar, they were in contrast to other studies of UV where LCV with neutrophil-predominant infiltrate was seen in most of the patients (4,5,8-10). However, the majority of past studies on this subject were mainly based on retrospective analysis of the patients with LCV diagnosed histologically.

The lymphocyte-predominant group is characterized by perivascular lymphocyte and eosinophil infiltration, sometimes erythrocyte extravasation and endothelial cell swelling, but without nuclear debris and fibrin exudation. In our study, of 9 patients with perivascular infiltrate of lymphocytes, none showed fibrin exudation or nuclear debris, and only 1 patient showed erythrocyte extravasation. Infiltration of eosinophils was present in 6 patients. Although a perivascular lymphocyte and eosinophil infiltration, and erythrocyte extravasation, which is named by some dermatopathologists (11) dermal hypersensitivity reaction, may be seen in papular urticaria, urticarial dermatitis, arthropod bite reactions, and systemic malignancies; these diseases were excluded due to the absence of epidermal histological changes, insect bite history and systemic disease, and presence of purpura and hyperpigmentation in our patients. Lee et al. (7) have suggested that the "lymphocytic vasculitis" term may be used for this group due to the presence of the clinical features of inflammation of blood vessels or vasculitis as prolonged urticaria, purpura, dusky changes, and hyperpigmentation. In a retrospective study of 143 biopsy specimens showing dermal hypersensitivity reaction, 23 patients were diagnosed with LCV or UV clinically (11). Many authors state that predominantly lmphocytic infiltrate involving or surrounding the walls of dermal vessels, associated with endothelial cell swelling, erythrocyte extravasation, with or without nuclear debris or fibrin exudation is sufficient for the diagnosis of lymphocytic vasculitis (7,9).

In our study, while 5 patients with LCV had deposits of immunoreactants within and around dermal vessel walls on DIF, the patients with lymphocyte-predominant infiltrate had negative DIF findings. In the study by Lee et al. (7), 26.3% of patients with lymphocyte-predominant infiltrate had deposits of immunoreactants, compared with 67% of patients with neutrophil-predominant infiltrate. The low frequency of positive DIF findings in lymphocytic vasculitis may be related with its cell-mediated pathogenesis in contrast to LCV, which is immune-complex mediated (12).

All the study patients responded dramatically and positively to the treatment with antihistamines and/or oral prednisolone at low doses for only a week, and developed no recurrence in the follow-up period. Such a rapid and good result may imply that NUV secondary to prior infection in children is generally thought to be self-limited. Therefore, NUV associated with infection should be treated differently than classical UV of adults. Nevertheless, in pediatric patients associated with HUV, other possible pathologies should be evaluated as in adults, and systemic diseases such as connective tissue diseases should be excluded. In addition, these patients may need combined immunosuppressive treatment.

In conclusion, our findings, in contrast to the literature, suggest that UV is i) not rare in the pediatric age group, ii) generally triggered by a prior infection, iii) normocomplementemic, and iv) self-limited. It exhibits a different pattern in children than in adults. Biopsy specimens of lesions may reveal not only neutrophil-predominant histology with LCV findings but also lymphocyte-predominant histology without LCV findings. Accordingly, in pediatric patients with NUV triggered by a prior infection it may not be necessary to perform a skin biopsy and apply rigorous severe immunosuppressive therapy. On the other hand, we emphasize the continued need for a diagnostic work-up in children with UV despite the 4 points made.

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