

Elevated C-Reactive Protein (CRP) Levels In Patients With Recurrent Urticaria and/or Angioedema

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Citation

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Abstract

Background: Patients with chronic urticaria infrequently have etiologic factors identified despite common laboratory testing. One non-specific gauge of inflammation, C-reactive protein(CRP), has not been routinely used to evaluate such patients.

Objective: To describe a series of patients with recurrent urticaria and/or angioedema and who had elevated(>5 mg/L) C-reactive protein levels.

Methods: Adult patients seen a single office practice with recurrent urticaria and angioedema for a period 6 weeks or greater were identified. Those who had physician observed angioedema or urticaria, and who had an elevated C-reactive protein had their charts reviewed and cases summarized.

Results: Eleven patients were identified for description. The highest CRP levels for each patients ranged from 5.4 to 23.2 mg/L, with a median of 12.6 mg/L. Most patients did not have correspondingly elevated erythrocyte sedimentation rates(ESR's), and there was no concordance between CRP levels and ESR's. Physical factors and thyroid auto-antibodies were noted in some patients. None of the elevated CRP levels were associated with a history of recent infection or overt comorbid inflammatory disease. The pattern of CRP levels appeared to have correspondence with disease activity in several patients.

Conclusions: Modest elevations in C-reactive protein may be observed in some patients with recurrent urticaria and/or angioedema in the apparent absence of infectious or inflammatory comorbidities. It is conceivable that this reflects an acute phase reaction pattern in these patients due to their urticaria/angioedema disease process itself. Further studies are required to confirm if this is a prevalent phenomenon.

INTRODUCTION

Patients with chronic urticaria are often evaluated with a several tests, which usually include erythrocyte sedimentation rates (ESR)₍₁₎. ESR is a non-specific marker of inflammation which may be affected by specimen being measured after 2 hours of phlebotomy, and by erythrocyte abnormalities ₍₂₎. In contrast, C-reactive protein (CRP) is not affected by either of these factors. C-reactive protein has been used to gauge disease activity in several chronic inflammatory and infectious diseases ₍₃₎. However it's utility in evaluating allergic patients has not been widely studied. In this paper, 11 patients with chronic or recurrent urticaria and/or angioedema are described. In all patients, CRP levels were elevated on at least one visit. In some of the patients, the CRP levels appeared to reflect disease activity, while in others persistently high levels seem to suggest ongoing

inflammatory disease.

METHODS

Patients from a single practice in New York City were identified if they had a raised CRP level(>5 mg/L) and a history of recurrent(2 or greater episodes) urticaria and/or angioedema of greater than or equal to 6 weeks duration. Only patients on whom actual urticarial lesions or angioedema were observed by the author or another known physician on at least one occasion were included. Charts were reviewed for historical and laboratory features. Salient features were tabulated and summary statistics were described. All CRP levels were performed using the Dade Behring(Newark DE) CRP nephelometric assay. Actual CRP values below 5 mg/L were determined using the high-sensitivity CRP assay by Dade Behring.

CASE HISTORIES

PATIENT 1

A 33 year old White female was initially seen 8/3/99 for a 9 month history of hives, unresponsive to all medications except methylprednisolone, which she had been taking for the past 4 days in a predetermined dose reducing package. Three months ago, she had blood tests showing HBsAg, rheumatoid factor, and antinuclear antibody all being negative/normal. Her hives were often on her abdomen and thighs and arms, and were recurrent at least twice monthly and consisted of itchy bumps. A biopsy of one of these lesions was reportedly unremarkable. No swelling of the eyes, lips, or tongue were reported. There was no history of asthma or rhinitis. On physical examination she was slightly overweight and had no skin lesions. A CRP was < 3 mg/L and an ESR was 4 mm/hr with a normal complete blood count and differential and a normal TSH level. The IgE level was 33 IU/mL and Radioallergosorbent(RAST) tests to various foods and aeroallergens were normal. The patient returned on 9/17/99 after an outbreak of urticaria and on inspection had urticaria on her arms plus swelling of her cheek and tongue. Cetirizine and albuterol sustained release tablets were prescribed, but the patient continued to have daily urticarial lesions. She returned on 9/21/99 showing hives on her arms, legs, and body. A CRP was 9.8 at this visit, and a tryptase level was 5 ng/L(normal). The dose of cetirizine was increased to 30 mg/d and the patient returned on 10/5/99 having had complete resolution of the urticaria. Antibody to thyroglobulin was < 2 u/mL(normal). A CRP done on 1/10/00, when the patient had no urticaria was < 5 mg/L. The patient continued the medication and did well with occasional mild flares of lesions which were reportedly not raised. The patient was again seen on 3/24/00 without any urticarial lesions noted. A few days prior she claimed a few non raised hives. At that time the CRP was 6.5 mg/L.

PATIENT 2

A 35 year old White female was initially seen on 2/6/98 after being hospitalized 8 days prior, after an apparent reaction to naprosyn, where angioedema of the lip and hands were noted. RAST testing during the hospitalization showed positive results for latex, wheat, and tuna. Nor CRP levels were obtained at that time. The patient had a history of asthma and tonsillectomy as a child but denied seasonal rhinitis symptoms. She had previously had a reaction to sulfa antibiotics consisting of diffuse itching. She was taking sertraline and an oral contraceptive. She admitted having cats as pets. On physical examination she was somewhat

obese, but had no skin lesions. The remainder of the physical examination was unremarkable. Laboratory studies at that time showed an IgE of 1453 IU/mL, and negative RAST tests to various foods and aeroallergens. C4 was 21 mg/dL(normal 14-45).. She was seen again on 4/3/98 without further swelling. Another episode of hives was claimed at the end of the month. On 12/13/99 the patient returned complaining of head, genital, torso, and extremity pruritus and hives. She had been taking bupropion, citalopram, and glucosamine. There was a single hive noted on the right hand. The patient had become more obese. CRP at that time was 23.2, ESR 15 mm/hr, TSH 1.6 mU/L(normal .4-4.2 mU/L), thyroglobulin/thyroid peroxidase antibodies < 2 u/mL(normal < 2 IU/mL), H Pylori antibodies were negative. IgE was 254 IU/mL. CBC was normal. Montelukast, famotidine and fexofenadine were prescribed. The symptoms resolved and a follow-up CRP on 1/8/00 was 8.3 mg/L. The patient was seen again on 2/28/00 without any lesions or complaints, and a repeat CRP at that time was 11 mg/L. The patient was last seen on 3/27/00, where she reported no hives despite taking on fexofenadine

PATIENT 3

A 28 year old White female was first seen on 1/29/1999 for asthma of 5 months duration. She worked in a child care center, and occasional had mice at home. Her mother had thyroid disease. The physical examination was unremarkable. A CBC was normal, with ESR of 5 mm/hr and CRP < 3 mg/L. IgE was 250, with positive RAST to cat and dog dander, mouse urine protein, d. farinae, and grass. The patient was prescribed loratadine, mometasone, and beclomethasone. The patient was next seen 8/24/99 complaining of total body hives during that past 8 months with worsening in the past 2 months. On physical examination hives were noted on the arms and legs. The palms showed petechial like spots. The face was somewhat flushed. On laboratory testing, the TSH was 2.7 mU/L, thyroglobulin and peroxidase antibodies were < 2 u/mL(normal), ESR was 10 mm/hr, CRP 10.7 mg/L and the CBC showed 6.9% eosinophils with a total count of 621/mm³(WBC 9000/mm³). RAST to chicken, cows milk, rice, and wheat were negative. Cetirizine was prescribed and the patient did well until she vacationed a few weeks later in the Caribbeans. There, hives recurred despite taking 20 mg/day of cetirizine but resolved when she returned to New York. She was seen again on 9/21/99, and the physical examination then showed no skin lesions, but an ice cube test was positive. Cryoglobulins, and RPR were negative. The cold agglutinin titer was less than 32, and the CRP was

< 3 mg/L. ESR was 5 mm/hr. The patient was last seen 10/8/99 where no hives were noted and the CRP was < 1.5 mg/L and the ESR was 5 mm/hr. She reported some contact urticaria when touching her recently acquired cat.

PATIENT 4

A 26 year old White female was initially seen on 3/29/99 with recurrent diffuse hives and angioedema of the lip of several months duration. She has a family history of allergic rhinitis and she claimed allergies to cats. On physical examination she had edema of the inferior turbinates of the nose but no skin lesions. An ice cube test was negative. An epicutaneous allergy skin test was positive to dust mite, but negative to peanuts, shellfish, cow's milk, and mixed fish. Laboratory testing revealed a CRP < 3 mg/L, C4 of 23 mg/dL, and a TSH of 2.7 mU/L. ESR was 14 mm/hr, and the differential leukocyte count was normal. RAST to various tree nuts were negative. An IgE level was 57 IU/mL. Dust mite environmental control measures were advised. The patient was seen 1 month later reporting a few episodes of hive outbreaks. Also she had an episode of lip swelling after taking an aspirin. Loratadine was prescribed and non-steroidal anti-inflammatory drug avoidance was advised. The patient next returned on 10/15/99 complaining of hives x 2 weeks despite taking loratadine and using mite precautions. She had started oral contraceptives 2 months prior. On physical examination hives were noted on her arms and legs. At that time laboratory test showed a CRP of 16.3 mg/L, ESR of 32 mm/hr, elevated thyroglobulin and peroxidase antibodies(49.6 and 228.9 IU/mL respectively). She did not return subsequently.

PATIENT 5

A 31 year old White male was first seen on 5/9/00 with irritation of the nose and eyes as well as hives for several years duration. He had a history of allergic seasonal and cat associated rhinitis and received allergy immunotherapy treatment in the past. He had hives 5 days after starting amoxicillin/clavulanic acid 1.5 years ago. He claimed the hives occurred daily and were precipitated by wind, rain, and exercise. Incomplete relief was observed with fexofenadine 180 mg/day. On physical examination, small almost petechial like erythematous macules were observed on the arms and legs. There was some edema and pallor of the inferior turbinates. There was no dermatographism and an ice cube test was negative. A CRP was 6.1 mg/L, cold agglutinins were normal, and the IgE was 298 IU/mL. The CBC was normal and cryoglobulins were not detected. RAST tests were positive to several pollens and molds as

well as cat dander. Many nasal eosinophils were observed. The patient returned 3 weeks later, claiming no change in the rash, despite continued antihistamine administration. Similar macules were observed on the neck, chest, and arms. On the right arm, a 2 cm macule with central clearing characteristic of an urticarial lesion was observed.

PATIENT 6

A 61 year old Indian male was seen 1/15/99 with recurrent swelling of hands, feet, and face associated with cold exposure for 4-5 years. He claimed no benefit with antihistamines(loratadine). He had a history of allergic seasonal rhinitis. He had a history of a nasal operation the year prior. On physical examination the nose showed edema and pallor. The dorsum and fingers of the left hand had diffuse swelling. montelukast, cetirizine, and sustained release albuterol tablets were prescribed, but the patient's swelling progressed and he was subsequently treated in the emergency department to remove his marriage ring and he was given diphenhydramine parentally. Laboratory tests showed an IgE of 214 IU/mL and positive RAST to d. farinae. The CRP level was 12.6 mg/L, ESR 17 mm/hr, C4 32 mg/dL, TSH 2.1 mU/L. Cryoglobulins and RPR were negative and the cold agglutinin titer was normal. The leukocyte differential count was normal. The patient was seen 2 weeks later with no recurrence of swelling. The physical examination was normal then, and the CRP level was < 3 mg/L. The patient was seen several times since then without any claims of swelling recurrence and without any new skin lesions while taking montelukast and cetirizine only. The last visit was in February 2000 when the CRP level was .7 mg/L.

PATIENT 7

A 39 year old White male was first seen 6/5/00 complaining of recurrent swelling of various parts of his body for 8 months. He claimed swelling of his forehead, testicles, shoulder, fingers, feet, tongue and lips. He had been seen on 3 occasions in the emergency department in the past 12 months, and he had been admitted to the intensive care unit 11 months ago for this problem. He also claimed some itching of his arms and hives associated with some of the swelling outbreaks. He denied allergic rhinitis symptoms or asthma, but admitted to taking aspirin or ibuprofen at least twice weekly. He was taking cetirizine, which he felt gave him partial improvement. He also claimed possible exacerbations of swelling due to shellfish, vinegar, and wine. On physical examination, he had swelling of his left forehead consistent with angioedema, and a 2-3 cm hive on

his right posterior shoulder. Laboratory testing revealed normal liver function and complete blood count tests, with a normal differential. ESR was 11 mm/hr, thyroid peroxidase/thyroglobulin antibodies normal, and CRP of 17.6 mg/L. C4 was 31.2 mg/dL, IgE was 167 IU/mL, and RAST tests were positive to d. farinae, negative to shellfish.

PATIENT 8

A 35 year old White female was first seen on 5/22/00 for urticaria and lip swelling of 6 weeks duration. She had either hives on the arms or neck or lip swelling 2-3 times a week. She denied other known atopic diseases. On physical examination, a few urticarial wheals were observed on her right arm. Laboratory testing showed leukocytosis of 12,800/mm³. ESR was 6 mm/hr, thyroglobulin/peroxidase antibodies were normal, CRP was 7.2 mg/L. IgE was 158 IU/mL and RAST tests to d. farinae, cat, shrimp, and wheat were negative. She was seen again on 6/13/00, reporting a decrease in outbreaks of hives and lip swelling. No hives or angioedema were noted on examination.

PATIENT 9

A 56 year old White male was seen on 11/29/99 for hives of 3 years duration. These occurred on the head and extremities especially in the summer time. He had been prescribed cetirizine with complete resolution of the hives. He described his hives as itchy bumps, which had been diagnosed as urticaria by a dermatologist he had seen previously. He also complained of chronic cough and laryngitis. He was taking cortisone and fluoronef since diagnosed as Addison's disease 15 years prior. He had a history of a lung tumor removal 15 years prior. On physical examination, no skin lesions were noted except for extensive vitiligo, and an ice cube test was negative. Laboratory testing showed an IgE level of 6 IU/mL, with negative RAST tests to d. farinae, various molds and foods. The TSH was 1.6, ESR 4 mm/hr, C4 26. mg/dL The CBC and differential were normal. The thyroglobulin antibody was elevated 12.7 but peroxidase was normal. CRP was 22.8 mg/L. Cetirizine 20 mg/day was prescribed. The patient was seen subsequently on 12/13/99, still reporting regular recurrence of hives in the morning, but had only taken 10 mg/day of cetirizine. The CRP level was 19.1 mg/L. The patient was prescribed montelukast. The patient was again seen on 1/10/00 with complaints of only some body itching and improvement in his cough. The CRP levels was 12.4 mg/L at that time.

PATIENT 10

A 58 year old Hispanic male was initially seen on 11/5/00 complaining of chronic hives since 6/99. He had been treated with cetirizine with some suppression of the hives. He had been evaluated by a dermatologist for this and told of allergies to cat, ragweed, and dust. Laboratory tests done previously showed an ESR of 8 mm/hr, a normal CBC and differential, a normal chemistry profile, negative HBsAg, and a negative stool parasite/ova examination. He claimed the hives when they occurred were on his total body and consisted of itchy bumps. He denied food or drug allergies. On physical examination, he had some edema of the inferior turbinates, but no hives or angioedema. Laboratory tests showed a CRP of 5.4 mg/L, normal thyroglobulin/thyroid peroxidase antibody levels, TSH of 1.8 mU/L. The patient was seen again on 11/8/99 claiming outbreaks of hives while taking cetirizine. No hives were noted. Fexofenadine 180 mg/day was prescribed. A repeat CRP was done on 11/19/99 which was < 5 mg/L. The patient was seen again on 12/17/99 after attempting an elimination diet. He had hives on his left forearm and right abdomen. A sinus x-ray was normal. The CRP level done at that time was 3.5 mg/L. The patient was given cetirizine and montelukast. The patient was next seen on 2/15/00 still with outbreaks of urticaria, and on examination had toenail changes consistent with onychomycosis. Itraconazole was prescribed. A CRP was 4.9 mg/L at that time. The patient returned again on 5/4/00 reporting only one episode of hives since that last visit, which was an improvement from previous months. No hives or angioedema were noted, and no CRP levels were done at that time

PATIENT 11

A 29 year old White male was seen initially on 4/03/00 with a 2 month history of itchy bumps especially in the axillary, waist, and upper leg areas. He had been treated for a cutaneous fungal infection in the fall of 1999, which was followed by the development of rash. After the development of the rash, he was prescribed steroids and cetirizine with resolution of the rash. He was currently taking ketoconazole. On physical examination, there was erythema over the left eyebrow, hives on his legs and upper chest near the axilla. There was mottling of the skin of the palms. He was somewhat overweight. The CRP level was 22.2 mg/L, ESR 17 mm/hr, IgE 50 IU/mL, CBC normal, thyroid antibodies normal, and RAST to d. farinae positive. The patient was instructed to stop the Nizoral and prescribed cetirizine 30 mg/day. The patient returned on 4/10/00 with improvement

but still claimed occasional hives after showering. No hives were noted on examination. Ranitidine and montelukast were prescribed. The patient returned on 5/19/00 reporting no raised rash, while taking medication. However on physical examination small hives on the shoulder/axillary area were observed. A CRP done 5/10/00 was 10.0 mg/L.

STATISTICAL AND OTHER DESCRIPTIVE FEATURES

CRP levels and ESR's did not show any concordance using Pearson (parametric) or Spearman(non-parametric) tests. The mean CRP level was 13.9 mg/L with a standard deviation of 6.8 mg/L. The median value was 12.6 mg/L. 9 out of 11 patients had elevated CRP levels at the time when actual urticaria or angioedema was observed. Case 9 never had lesions observed by the author. Case 10 had a marginally elevated CRP level when no hives were observed.

Figure 1

Table I and 2: Summary of clinical characteristics of the 11 patients with recurrent urticaria and/or angioedema

Patient number	Age/ Sex	highest CRP (mg/L)	number of elevated CRP levels/total CRP determinations	Corresponding ESR	Temperature or weather related factors
1	33/F	9.8	2/4	not done	none
2	35/F	23.2	3/3	15	none
3	28/F	10.7	1/4	10	cold
4	26/F	16.3	1/2	32	none
5	31/M	6.1	1/1	17	wind/rain
6	61/M	12.6	1/3	17	cold
7	39/M	17.6	1/1	11	none
8	35/F	7.2	1/1	6	none
9	56/M	22.8	3/3	4	none
10	58/M	5.4	1/4	not done	none
11	29/M	22.2	2/2	17	none

Patient number	Angioedema (A) and/or urticaria(U)	Thyroid auto-antibodies: TG=thyroglobulin PO=peroxidase	obesity	Possible clinical correlation
1	A & U	no TG, PO not done	+	Exacerbation or outbreak associated with higher [CRP]
2	A & U	none	+	Exacerbation or outbreak associated with higher [CRP]
3	U	none	-	Exacerbation or outbreak associated with higher [CRP]
4	A & U	Both elevated	-	Exacerbation or outbreak associated with higher [CRP]
5	U	none	-	
6	A	Not done	+/-	Initially increased disease activity associated with higher [CRP]
7	A & U	none	-	
8	A & U	none	-	
9	U	elevated TG no PO	-	Initially increased disease activity associated with higher [CRP]
10	U	none	+/-	
11	U	none	-	Initially increased disease activity associated with higher [CRP]

DISCUSSION

This report describes several patients with recurrent angioedema/urticaria who had modestly elevated CRP levels in the absence of historical infection or inflammatory comorbid disease. There appeared to be some correlation between disease activity and CRP levels in several patients. Cases 1, 2, 3, 4, 6, 9, and 11 either showed increases with flares and/or decreases with less frequent disease activity. Three cases had only 1 determination, and thus disease activity correlation could not be ascertained.

There has been considerable interest in CRP levels in gauging cardiovascular risk (4). A recent large study showed that increasing quartiles of CRP levels correspond with higher cardiovascular risks. Based on that study a value < 5 mg/L may be considered as being in a high risk quartile. This older conventional definition of normal levels (<5 mg/L) probably relates to the primary clinical utility of CRP determinations in assessing grossly inflammatory diseases, such as Crohn's disease(5), or in monitoring bacterial infection, such as osteomyelitis(6). In the patients described in this report, only modest elevations of CRP levels were described, with a median value of 12.6 mg/L. In some studies examining viral versus bacterial infections, cut-off points of 20-40 mg/L have been suggested(7,8). None of the patients in this study had values greater than 30. This suggests that if underlying inflammation characterizes the atopic disorder in these patients, the level of inflammation is probably less than that observed with systemic bacterial infections.

It is conceivable that some of the patients who were studied had sub-clinical infections. However, other markers of infection such as leukocytosis and elevated ESR were found only in 1 and 1 patient respectively. No patients claimed upper respiratory infection symptoms such as sore throat or fever. One paper describes elevations in CRP levels in patients with urticaria and attributes these to infection, which caused the urticaria(9). Some patients with infectious urticaria have been described, but those patients all had febrile illnesses(10).

Obesity has also been described as being associated with elevated CRP levels.(11) Prominent obesity was only found in 2 of our patients however(Cases 1 and 2). One of these patients(Case 1) had normalization of CRP levels with lessened disease activity. This speaks against her CRP levels being elevated on the basis of obesity. The other patient(Case 3) had persistently elevated CRP levels with

decreased disease activity, but the levels were less than half of the level found when she had a disease flare. It is conceivable that her baseline CRP level is higher on the basis of her obesity, but the increase seems to have related to urticarial disease flare-up.

It is interesting that 3 patients (Cases 3, 5, and 6) had some weather related factors. Although these patients may be classified differently from patients with idiopathic urticaria/angioedema, it is conceivable that an acute phase response also occurs in flare-ups secondary to temperature/weather related stimuli. Similarly the 2 patients with thyroid auto-antibodies (Cases 4 and 9) had increases of CRP levels which were higher when disease activity was present compared to when disease activity were more quiescent. This speaks against the inflammatory response being solely due to a non-dermal auto-immune process in the 2 patients.

In patients with acute allergic reactions, elevations of serum interleukin 6 (IL6), a cytokine felt to be key in promoting CRP elevations⁽³⁾; have been described⁽¹²⁾. These IL6 elevations occur later than elevations in blood histamine or tryptase levels. Since many studies of IL6 have shown that CRP and IL6 are correlated in disease and in normal humans, it suggests the possibility that acute phase responses may also occur in systemic immediate hypersensitivity reactions. Although it is possible that some of the patients described herein had subclinical or minimally symptomatic minor viral infections which caused the CRP levels to be increased, it would be interesting to speculate that the CRP elevations in some patients with recurrent urticaria and angioedema relate to some degree of immediate hypersensitivity or systemic mast cell activation⁽¹³⁾. Further studies on such patients will be required to explore this hypothesis and to determine the prevalence of CRP elevations in this clinical setting.

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