Bullous “Cellulitis” With Eosinophilia: Case Report and Review of Wells’ Syndrome in Childhood

Amy E. Gilliam, MD*; Anna L. Bruckner, MD‡; Renée M. Howard, MD*; Brian P. Lee, MD§; Susan Wu, MD§; and Ilona J. Frieden, MD*||

ABSTRACT. A 1-year-old girl presented with acute onset of edematous erythematous plaques associated with bullae on her extremities and accompanied by peripheral eosinophilia. She was afebrile, and the skin lesions were pruritic but not tender. The patient was treated with intravenously administered antibiotics for presumed cellulitis, without improvement. However, the lesions responded rapidly to systemic steroid therapy. On the basis of lesional morphologic features, peripheral eosinophilia, and cutaneous histopathologic features, a diagnosis of Wells’ syndrome was made. Wells’ syndrome is extremely rare in childhood, with 27 pediatric cases reported in the literature. Because it is seen so infrequently, there are no specific guidelines for evaluation and management of Wells’ syndrome among children. The diagnosis should be considered for children with presumed cellulitis and eosinophilia who fail to respond to antibiotics. Evaluation should include a directed history, physical examination, complete blood count, and stool testing for ova and parasites, to identify potential triggers. Treatment is with systemic steroid therapy unless disease is limited, in which case medium/high-potency topical steroids may be indicated. If systemic features are prominent or disease is chronic (lasting >6 months), then a referral to hematology/oncology should be considered. Pediatrics 2005;116:e149–e155. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-2273; cellulitis, eosinophilia, eosinophilic cellulitis, Wells’ syndrome.

ABBREVIATIONS. CSS, Churg-Strauss syndrome; HES, hyper-eosinophilic syndrome; IL, interleukin.

Wells’ syndrome, or eosinophilic cellulitis, is a rare, recurrent, inflammatory dermatosis of unknown pathogenesis. In 1971, Wells1 described 4 patients with an acute pruritic dermatitis clinically resembling bacterial cellulitis but with histopathologic findings characterized by dermal eosinophilia, phagocytic histiocytes, and the presence of flame figures. He initially called this syndrome recurrent granulomatous dermatitis with eosinophilia but later simplified the name to eosinophilic cellulitis.2

Wells’ syndrome is seen more commonly among adults but has been observed among children. Some hypothesize that this syndrome may represent a hypersensitivity response to a circulating antigen.2 Associated precipitants include insect bites, medication reactions, recent immunization, myeloproliferative disorders, malignancies, and infections. We describe a case of a young child with no identifiable triggering factors, and we review the evidence for evaluation and management of these pediatric cases.

CASE REPORT

A previously healthy, 1-year-old girl presented with acute onset of edematous erythematous plaques, with associated bullae, on her lower extremities and left arm (Fig 1). These lesions were pruritic but not painful, and the patient was afebrile. Her parents denied a history of insect bites, ingestion of medications, trauma, or other intercurrent illness. The patient’s most recent immunizations had been received 3 months earlier. The patient did not have a history of asthma, and there was no family history of asthma or atopic disease.

The patient was admitted with presumed bacterial cellulitis and was treated with intravenously administered oxacillin, without improvement. Her laboratory studies were significant for an elevated white blood cell count of 30 × 10⁶ cells per L, with peripheral eosinophilia of 48%. After the patient failed to respond to systemically administered antibiotics, examination of vesicle fluid was performed and revealed numerous eosinophils. Subsequently, the diagnosis of probable Wells’ syndrome was made. Oral steroid therapy was started at 2 mg/kg, and the patient’s cutaneous symptoms improved within 24 hours, leaving residual erythema and hyperpigmentation (Fig 2). Five days after the initiation of oral steroid therapy, a skin biopsy was performed from

Fig 1. Acute onset of edematous erythematous plaques and bullae on the left arm of a 1-year-old girl.
a persistently indurated area. Histopathologic assessment showed an interstitial infiltrate of histiocytes and waning flame figures, represented by collections of eosinophilic granules surrounded by a palisade of histiocytes (Fig 3).

Oral steroid treatment was tapered over 3 weeks, and a topical triamcinolone preparation was applied to residual lesions twice daily until the lesions resolved. At 1 year, the patient has not experienced recurrent disease.

### DISCUSSION

Wells’ syndrome is extremely rare in childhood, with only 27 pediatric cases reported (Table 1). It is characterized by a combination of distinct clinical and histopathologic findings. Classically, patients present with pruritic erythematous plaques, sometimes with associated bullae, that evolve rapidly over 2 to 3 days. These resolve spontaneously over 2 to 8 weeks, leaving residual skin atrophy and hyperpigmentation, resembling morphea.² There is usually no improvement with antimicrobial therapy; instead, a rapid response to oral corticosteroid treatment is observed, as in our case. It is not uncommon for patients to have recurrent disease, with exacerbations and remissions occurring over several years.

The histopathologic findings are quite specific and are characterized by flame figures, which are composed of eosinophilic fasciitis major basic protein deposited on collagen bundles.³ With resolution, there is a granulomatous phase of histiocytes palisading around the flame figures. Vasculitis is absent, and direct immunofluorescence findings are negative.⁴⁻⁵

Associated laboratory findings include an elevated white blood cell count and peripheral eosinophilia, which is found in up to 50% of cases during the active phase of disease.⁵⁻⁶ The erythrocyte sedimentation rate is elevated for some patients, and there are several reports of associated elevated IgE levels.⁷⁻¹⁴ Fever, lymphadenopathy, arthralgias, and other systemic symptoms (such as pulmonary involvement) have been described for Wells’ syndrome, and these findings may be indicative of a more severe or progressive course.⁷

The differential diagnosis of Wells’ syndrome includes bacterial cellulitis, Churg-Strauss syndrome (CSS), eosinophilic fasciitis, and hypereosinophilic syndrome (HES) (Table 2). The skin lesions of Wells’ syndrome are distinguished from those of bacterial cellulitis by the absence of tenderness and the presence of pruritus, which is often the primary symptom of Wells’ syndrome. Lack of warmth, failure to respond to antibiotic therapy, and characteristic histopathologic findings are the other features that differentiate Wells’ syndrome from bacterial cellulitis.

CSS should be considered for patients with persistent peripheral eosinophilia and skin lesions. Although more commonly seen among adults, CSS can present in childhood.¹⁵⁻¹⁷ This syndrome is characterized by asthma, peripheral eosinophilia, and vasculitis and is associated with autoantibodies to perinuclear antineutrophil cytoplasmic antibody, as well as cutaneous and systemic granulomas. Palpable purpura, tender subcutaneous nodules, and cutaneous infarctions are more often the associated skin findings in CSS, whereas patients present with bullae and vesicular lesions in Wells’ syndrome. In both conditions, flame figures can be identified histopathologically, as can peripheral blood and tissue eosinophilia. However, the presence of vasculitis with extensive fibrinoid necrosis of collagen is more suggestive of CSS.²⁻⁹

Eosinophilic fasciitis is another condition that can resemble Wells’ syndrome. Also seen more frequently among adults but reported in children,¹⁸⁻¹⁹ it presents with acute onset of skin inflammation and resolves with hyperpigmentation and scleroderma-like skin changes. Unlike Wells’ syndrome, eosinophilic fasciitis is characterized by arthritis as a prominent symptom, and it follows a more chronic course, with individual lesions requiring months or years to resolve.¹² It is distinguishable from Wells’ syndrome by the depth of inflammation, with eosinophilic invasion into deeper fascial tissues.

Finally, idiopathic HES also should be considered when the diagnosis of Wells’ syndrome is being entertained. This condition is extremely rare in the pediatric age group but has been reported in childhood.²⁰ HES is a lymphoproliferative disorder characterized by overproduction of eosinophils with a predilection to damage specific organs, especially the cardiovascular system. It is defined by sustained eosinophilia (>1.5 × 10⁹ cells per L, lasting for >6 months), with evidence of multiple-organ system involvement, in the absence of parasitic disease, allergic diatheses, or other conditions known to cause eosinophilia. The heart, lungs, central and peripheral nervous systems, kidneys, and gastrointestinal tract can be affected, and the cutaneous findings are similar to those of Wells’ syndrome, including erythematous pruritic papules and nodules, urticaria, and angioedema.⁹⁻²¹⁻²³ Histopathologically, the skin lesions of HES are nonspecific, and the flame figures

![Image](http://pediatrics.aappublications.org/)

**Fig 2.** Appearance of skin lesions after 5 days of oral steroid therapy, showing residual erythema, induration, and hyperpigmentation.
Fig 3. High-power view of a biopsy specimen from a resolving lesion, showing a waning flame figure, represented by collections of eosinophilic granules surrounded by a palisade of histiocytes. (Hematoxylin-eosin; original magnification: ×100.)

and granulomatous infiltrate seen in Wells’ syndrome are absent.21

The pathogenesis of Wells’ syndrome is not well defined. One hypothesis is that it represents a hypersensitivity mechanism triggered by factors such as infections, drugs, or internal disease. However, in approximately one half of reported cases among children, there is no identifiable precipitating factor.24 Reported precipitants have included bites or stings from ticks, bees, and spiders8,9,12,25–28 and infections with mumps, molluscum contagiosum, varicella, and herpes simplex virus.1,24,29,30 There are also several reports of Wells’ syndrome associated with bacterial, parasitic, and fungal infections.5,9,14,31–33 Numerous medications have been implicated as triggers for Wells’ syndrome.1–3,5,9,31–33 Also, several cases of Wells’ syndrome occurred after vaccinations, and it was proposed that the preservative thimerosol was the causative agent in those cases.34 Several cases of Wells’ syndrome among adults have been associated with hematologic disorders,5 lymphoproliferative malignancies,1,34,42 and carcinoma.34,43–45 Zachary et al reported a case of Wells’ syndrome in a 17-year-old girl with nasopharyngeal carcinoma, which is the only pediatric case of Wells’ syndrome associated with malignancy reported in the literature.

One of the key events in disease expression of Wells’ syndrome appears to be aberrant and inadequate eosinophil skin homing. Increased interleukin (IL)-5 levels have been observed in Wells’ syndrome, and IL-5 not only mobilizes eosinophils from the bone marrow but also promotes homing of eosinophils by altering expression of adhesion molecules. In addition, increased levels of IL-5 appear to induce expression of CD25, the a chain of the IL-2 receptor, which enhances eosinophil degranulation and subsequent tissue destruction.46–48

Treatment for Wells’ syndrome is sometimes unnecessary, because cases often resolve spontaneously. If an infection or other treatable precipitating factor can be identified, then there is often improvement with treatment of the underlying condition.14,30,33,44 However, when no treatable underlying factor can be identified, systemic corticosteroid therapy is used frequently for both adults and children. Most cases resolve after a single course of systemic corticosteroid therapy; when recurrences occur, however, alternative treatments should be considered, to avoid the side effects of chronic systemic steroid therapy.36 Topical steroid treatment has also been reported as successful therapy, both alone,2,29,39 and in combination with systemic steroid therapy.5 Specifically, topical steroid therapy alone resolved skin lesions for 2 children, which suggests that topical steroid therapy may be a safe alternative to systemic corticosteroid therapy in the pediatric age group.29,39 Other therapies reported to be successful include various antimicrobial agents,2,5,6,9,10,13,49 colchicine,13 antimalarial drugs, cyclosporine,50 azathioprine,5 interferon-α51 psoralen with ultraviolet A,52 and antihistamines.10,43,53

The small numbers of cases and the fact that most reports are anecdotal make it difficult to draw conclusions regarding whether these therapies are truly effective or these cases resolved spontaneously. However, we think that first-line treatment for children should be systemic corticosteroid therapy, with the addition of topical steroid treatment depending on the extent of disease. A dose of orally administered prednisolone or prednisone of 2 mg/kg per day for 5 to 7 days, with a taper over 2 to 3 weeks, is appropriate. Topical steroid treatment may be used in combination. In cases in which there is limited body surface area involved (15–30%) and an absence of systemic symptoms, it may be prudent to consider medium-potency topical steroid therapy alone, with close follow-up monitoring. This would also be appropriate for recurrent cases of Wells’ syndrome identified early, when disease may be limited. Evaluation should be directed at ruling out other conditions that mimic Wells’ syndrome, as well as evaluating possible triggering factors. We recommend a complete history and review of systems, with specific attention to recent medications, vaccinations, insect bites, infections, or illnesses and associated
<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Gender</th>
<th>Triggering Event(s)</th>
<th>Associated Findings</th>
<th>Treatment and Course of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wells and Smith,2 1979</td>
<td>11 y</td>
<td>M</td>
<td>Mumps, penicillin</td>
<td>Elevated WBC count (16 × 10^9 cells per L), fever</td>
<td>Prednisolone and sulfapyridine, recurrences over 3 y</td>
</tr>
<tr>
<td>Wells and Smith,2 1979</td>
<td>12 y</td>
<td>M</td>
<td>Erysipelas, penicillin</td>
<td>Elevated WBC count (26 × 10^9 cells per L), eosinophilia (44%)</td>
<td>Prednisolone, recurrences over 2–3 y</td>
</tr>
<tr>
<td>Nielsen et al,25 1981</td>
<td>11 y</td>
<td>M</td>
<td>Unknown</td>
<td>Elevated WBC count (42 × 10^9 cells per L), eosinophilia (13%), fever, ANA-positive,</td>
<td>Prednisone, 1 recurrence</td>
</tr>
<tr>
<td>Saulsbury et al,32 1983</td>
<td>7 y</td>
<td>M</td>
<td>Possible insect bites</td>
<td>Elevated WBC count (17 × 10^9 cells per L), eosinophilia (48%), fever, elevated IgE</td>
<td>Ampicillin and antihistamines, spontaneous resolution in 1 wk, with</td>
</tr>
<tr>
<td>Bonvalet et al,4 1983</td>
<td>2 y</td>
<td>M</td>
<td>Unknown</td>
<td>Eosinophilia</td>
<td>recurrences</td>
</tr>
<tr>
<td>Schorr et al,28 1984</td>
<td>3.5 y</td>
<td>M</td>
<td>Flea bite</td>
<td>Fever</td>
<td>No record of treatment, multiple recurrences</td>
</tr>
<tr>
<td>Brehmer-Andersson et al,34</td>
<td>14 y</td>
<td>M</td>
<td>Unknown</td>
<td>None</td>
<td>No treatment, spontaneous resolution in 1 wk, multiple recurrences over 8 y</td>
</tr>
<tr>
<td>Wood, et al,26 1986</td>
<td>18 mo</td>
<td>M</td>
<td>Unknown</td>
<td>None</td>
<td>Systemic steroids, recurrences responsive to steroids</td>
</tr>
<tr>
<td>Wood et al,26 1986</td>
<td>10 y</td>
<td>M</td>
<td>Insect bites</td>
<td>Elevated WBC count (22 × 10^9 cells per L), eosinophilia (16%), fever, elevated IgE level, pericarditis, pulmonary infiltrates with eosinophilic exudates/effusions</td>
<td>Systemic steroids, recurrences responsive to steroids</td>
</tr>
<tr>
<td>Kamani and Lipsitz,7 1987</td>
<td>7 wk</td>
<td>M</td>
<td>Genetic (?), mother and brother with Wells’ syndrome</td>
<td>Elevated WBC count (29 × 10^9 cells per L), eosinophilia (32%), fever, generalized seizure, meningitis, pulmonary infiltrates with eosinophilic cerebrospinal fluid pleocytosis and pleural effusions</td>
<td>Systemic steroids, recurrences responsive to steroids</td>
</tr>
<tr>
<td>Kamani and Lipsitz,7 1987</td>
<td>3 wk</td>
<td>M</td>
<td>Genetic (?), mother and brother with Wells’ syndrome</td>
<td>Elevated WBC count (29 × 10^9 cells per L), eosinophilia (32%), fever, generalized seizure, meningitis, pulmonary infiltrates with eosinophilic cerebrospinal fluid pleocytosis and pleural effusions</td>
<td>Systemic steroids, recurrences responsive to steroids</td>
</tr>
<tr>
<td>Correia and Garcia e Silva,54 1988</td>
<td>12 y</td>
<td>F</td>
<td>Possibly diabetes mellitus</td>
<td>Muscular weakness</td>
<td>No record of treatment in English abstract</td>
</tr>
<tr>
<td>Lindskov et al,31 1988</td>
<td>4 y</td>
<td>F</td>
<td>Unknown</td>
<td>Elevated WBC count (13 × 10^9 cells per L), eosinophilia (17%), fourfold increase in varicella titer</td>
<td>Oral antibiotics, acyclovir, and prednisone, gradual resolution over 2 mo, recurrence treated with steroids</td>
</tr>
<tr>
<td>Lindskov et al,31 1988</td>
<td>5 y</td>
<td>F</td>
<td>Unknown</td>
<td>Elevated WBC count (47 × 10^9 cells per L), eosinophilia (55%), fever, ESR of 62 mm/h, anemia, arthralgias, lymphadenopathy, bone marrow eosinophilia, and fourfold increase in varicella titer</td>
<td>Oral antibiotics and acyclovir, gradual resolution over 2 mo, no recurrences</td>
</tr>
<tr>
<td>Lindskov et al,31 1988</td>
<td>20 mo</td>
<td>M</td>
<td>Unknown</td>
<td>Elevated WBC count (20 × 10^9 cells per L), eosinophilia (13%), anemia, elevated IgE level</td>
<td>Oral and topical antibiotics, gradual resolution over 2 mo, recurrences over 2 y</td>
</tr>
<tr>
<td>Authors</td>
<td>Age</td>
<td>Gender</td>
<td>Diagnosis</td>
<td>Symptoms</td>
<td>Treatment and Outcomes</td>
</tr>
<tr>
<td>------------------</td>
<td>-----</td>
<td>--------</td>
<td>------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Lindskov et al, 1</td>
<td>9</td>
<td>M</td>
<td>Unknown</td>
<td>Elevated WBC (19 × 10^9 cells per L), eosinophilia (13%), fever</td>
<td>Topical antibiotics, spontaneous resolution over 2 wk with recurrences</td>
</tr>
<tr>
<td>Reichel et al, 29</td>
<td>6</td>
<td>M</td>
<td>Varicella</td>
<td>Eosinophilia (3%), varicella zoster virus titer of 1:32</td>
<td>Spontaneous improvement over 1 mo, topical steroids cleared residua</td>
</tr>
<tr>
<td>Paquet et al, 33</td>
<td>10</td>
<td>M</td>
<td>Unknown</td>
<td>Eosinophilia (13.4%), elevated IgE level</td>
<td>Systemic antibiotics and oral steroids, no recurrences after 9 mo of follow-up monitoring</td>
</tr>
<tr>
<td>Anderson et al, 8</td>
<td>4</td>
<td>F</td>
<td>Bee sting</td>
<td>Elevated WBC (45 × 10^9 cells per L), eosinophilia, elevated IgE and septicemia</td>
<td>Systemic antibiotics and oral steroids, course complicated by systemic infection, improvement over 4 wk with recurrences</td>
</tr>
<tr>
<td>Garty et al, 55</td>
<td>&lt;1</td>
<td>F</td>
<td>Possibly danazol, ingested by mother during pregnancy</td>
<td>Elevated WBC count (15 × 10^9 cells per L), eosinophilia (25%), ESR of 30 mm/h, mild hepatosplenomegaly, lymphadenopathy</td>
<td>Topical steroids, topical antibiotics, and antifungal medications ineffective, spontaneous resolution over months but with recurrences</td>
</tr>
<tr>
<td>Davis et al, 47</td>
<td>7</td>
<td>M</td>
<td>Unknown</td>
<td>Eosinophilia of blood, tissue, and bone marrow, familial case associated with short stature, mental retardation, distinctive habitus</td>
<td>Systemic and topical steroids, frequent recurrences without resolution</td>
</tr>
<tr>
<td>Davis et al, 46</td>
<td>5</td>
<td>F</td>
<td>Unknown</td>
<td>Eosinophilia of peripheral blood and bone marrow and elevated IgA, IgM, and IgG levels, familial case associated with short stature, mental retardation, and distinctive habitus</td>
<td>No treatment, recurrences over years</td>
</tr>
<tr>
<td>Aroni et al, 58</td>
<td>12</td>
<td>F</td>
<td>Unknown</td>
<td>Eosinophilia</td>
<td>Cetirizine, resolved after 4 wk of treatment, recurrence after 18 mo</td>
</tr>
<tr>
<td>Kuwahara et al, 56</td>
<td>Birth</td>
<td>F</td>
<td>Possibly penicillin or danazol ingested by mother during pregnancy</td>
<td>None</td>
<td>None, resolved by the 2-y follow-up visit</td>
</tr>
<tr>
<td>Moossavi and Mehregan, 5</td>
<td>21 mo</td>
<td>F</td>
<td>Unknown</td>
<td>None</td>
<td>Prednisone and topical steroids, resolved without recurrence</td>
</tr>
<tr>
<td>Koh et al, 39</td>
<td>3.5</td>
<td>M</td>
<td>Hepatitis B and DPT vaccination</td>
<td>Slight peripheral eosinophilia</td>
<td>Topical steroids (rapid improvement), recurrences treated with topical steroids</td>
</tr>
<tr>
<td>Stavropoulos et al, 24</td>
<td>9</td>
<td>F</td>
<td>Molluscum contagiosum treated with cryosurgery</td>
<td>Eosinophilia (12%), ESR of 26 mm/h</td>
<td>Oral prednisolone, no recurrences</td>
</tr>
<tr>
<td>Gilliam et al, 2005</td>
<td>1</td>
<td>F</td>
<td>Unknown</td>
<td>Elevated WBC count (30 × 10^9 cells per L), eosinophilia (48%)</td>
<td>Oral prednisolone and topical steroids, no recurrences in 1 y of follow-up monitoring</td>
</tr>
</tbody>
</table>

ANA indicates antinuclear antibody; WBC, white blood cell; ESR, erythrocyte sedimentation rate; DPT, diphtheria-pertussis-tetanus.
medications such as asthma. A thorough physical examination should be performed, with attention to the liver, spleen, and lymph nodes. Stool samples should be sent for ova and parasite testing, and a complete blood count with differential evaluation should be performed. If there is uncertainty regarding the diagnosis, then a biopsy should be performed to distinguish between Wells’ syndrome and other conditions that mimic it. We do not recommend a complete hematologic evaluation in all cases, because it is rare to see cases of either HES or Wells’ syndrome triggered by hematologic or oncologic disorders in childhood. However, if a child presents with either systemic features, such as fevers, arthralgias, or other organ system involvement, or a chronic course, defined as >6 months of peripheral eosinophilia or recurrences of clinical disease, then a referral to hematologic/oncology should be considered.

REFERENCES

Bullous "Cellulitis" With Eosinophilia: Case Report and Review of Wells' Syndrome in Childhood
Amy E. Gilliam, Anna L. Bruckner, Renée M. Howard, Brian P. Lee, Susan Wu and Ilona J. Frieden

Pediatrics 2005;116:e149
DOI: 10.1542/peds.2004-2273
Bullous "Cellulitis" With Eosinophilia: Case Report and Review of Wells' Syndrome in Childhood
Amy E. Gilliam, Anna L. Bruckner, Renée M. Howard, Brian P. Lee, Susan Wu and Ilona J. Frieden
*Pediatrics* 2005;116:e149
DOI: 10.1542/peds.2004-2273

The online version of this article, along with updated information and services, is located on the World Wide Web at: http://pediatrics.aappublications.org/content/116/1/e149