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...
are several reports of associated elevated IgE lev-
tation rate is elevated for some patients, and there
active phase of disease.5,6 The erythrocyte sedimen-
tation, resembling morphea.2 There is usually no
weeks, leaving residual skin atrophy and hyperpig-
erythematous plaques, some-
ng.4,5
els.7–14 Fever, lymphadenopathy, arthralgias, and
other systemic symptoms (such as pulmonary in-
volvement) have been described for Wells’ syn-
drome, and these findings may be indicative of a
more severe or progressive course.7

The differential diagnosis of Wells’ syndrome in-
cludes 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 pre-
  nce of pruritus, which is often the primary symp-
tom of Wells’ syndrome. Lack of warmth, failure to
respond to antibiotic therapy, and characteristic hist-
ologic findings are the other features that differen-
tiate Wells’ syndrome from bacterial cellulitis.

CSS should be considered for patients with persis-
tent peripheral eosinophilia and skin lesions. Al-
though more commonly seen among adults, CSS can
present in childhood.15–17 This syndrome is charac-
terized by asthma, peripheral eosinophilia, and vas-
culitis and is associated with autoantibodies to pe-
rinuclear antineutrophil cytoplasmic antibody, as
well as cutaneous and systemic granulomas. Palpa-
ble purpura, tender subcutaneous nodules, and cu-
taneous infarctions are more often the associated
skin findings in CSS, whereas patients present with
bulla and vesicular lesions in Wells’ syndrome. In
both conditions, flame figures can be identified his-
topathologically, 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 fre-
cently 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, eosino-
philic fasciitis is characterized by arthritis as a prom-
inent 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 in-
vansion into deeper fascial tissues.

Finally, idiopathic HES also should be considered
when the diagnosis of Wells’ syndrome is being en-
tertained. This condition is extremely rare in the
pediatric age group but has been reported in child-
hood.20 HES is a lymphoproliferative disorder char-
acterized by overproduction of eosinophils with a
predilection to damage specific organs, especially
the cardiovascular system. It is defined by sustained eo-
sinophilia (>1.5 × 10⁹ cells per L, lasting for >6
months), with evidence of multiple-organ system in-
volvement, in the absence of parasitic disease, aller-
gic 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 simi-
lar to those of Wells’ syndrome, including erythem-
atous pruritic papules and nodules, urticaria, and
angioedema.9,21–23 Histopathologically, the skin le-
sions of HES are nonspecific, and the flame figures

**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 erythematosus plaques, some-
times with associated bullae, that evolve rapidly over
2 to 3 days. These resolve spontaneously over 2 to 8
weeks, leaving residual skin atrophy and hyperpig-
malation.10–15

Fig 2. Appearance of skin lesions after 5 days of oral steroid
therapy, showing residual erythema, induration, and hyperpig-
malation.
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.2,9,14,31–33 Numerous medications have been implicated as triggers for Wells’ syndrome.1–3,5,9,34–38 Also, several cases of Wells’ syndrome occurred after vaccinations,39,40 and it was proposed that the preservative thimerosal was the causative agent in those cases.39 Several cases of Wells’ syndrome among adults have been associated with hematologic disorders,1,35,42 and malignancies.1,34,42 and carcinoma.34,43–45 Zachary et al45 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 α 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 condi-

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.)
<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</td>
<td>11  y</td>
<td>M</td>
<td>Mumps, penicillin</td>
<td>Elevated WBC count (16 x 10⁹ cells per L), fever</td>
<td>Prednisolone and sulpyridine, recurrences over 3 y</td>
</tr>
<tr>
<td>Wells and Smith</td>
<td>12  y</td>
<td>M</td>
<td>Erysipelas, penicillin</td>
<td>Elevated WBC count (26 x 10⁹ cells per L), eosinophilia (44%)</td>
<td>Prednisolone, recurrences over 2-3 y</td>
</tr>
<tr>
<td>Nielsen et al</td>
<td>11  y</td>
<td>M</td>
<td>Unknown</td>
<td>Elevated WBC count (42 x 10⁹ cells per L), eosinophilia (13%), fever, ANA-positive, arthralgia, alopecia</td>
<td>Prednisone, 1 recurrence</td>
</tr>
<tr>
<td>Saulsbury et al</td>
<td>7   y</td>
<td>M</td>
<td>Possible insect bites</td>
<td>Elevated WBC count (17 x 10⁹ cells per L), eosinophilia (48%), fever, elevated IgE level, bone marrow eosinophilia, oculomotor nerve palsy</td>
<td>Ampicillin and antihistamines, spontaneous resolution in 1 wk, with recurrences</td>
</tr>
<tr>
<td>Bonvalet et al</td>
<td>2   y</td>
<td>M</td>
<td>Unknown</td>
<td>Eosinophilia</td>
<td>No treatment, spontaneous resolution in 2 wk with recurrences</td>
</tr>
<tr>
<td>Schorr et al</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</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</td>
<td>18 mo</td>
<td>M</td>
<td>Unknown</td>
<td>Eosinophilia</td>
<td>Systemic steroids, recurrences responsive to steroids</td>
</tr>
<tr>
<td>Wood, et al</td>
<td>10 y</td>
<td>M</td>
<td>Insect bites</td>
<td>Elevated WBC count (22 x 10⁹ 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</td>
<td>7 wk</td>
<td>M</td>
<td>Genetic (?), mother and brother with Wells’ syndrome</td>
<td>Elevated WBC count (29 x 10⁹ 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</td>
<td>3 wk</td>
<td>M</td>
<td>Genetic (?), mother and brother with Wells’ syndrome</td>
<td>Elevated WBC count (29 x 10⁹ 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</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</td>
<td>4   y</td>
<td>F</td>
<td>Unknown</td>
<td>Elevated WBC count (13 x 10⁹ 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</td>
<td>5   y</td>
<td>F</td>
<td>Unknown</td>
<td>Elevated WBC count (47 x 10⁹ cells per L), eosinophilia (55%), fever, ESR of 62 mm/h, anemia, arthralgia, 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</td>
<td>20 mo</td>
<td>M</td>
<td>Unknown</td>
<td>Elevated WBC count (20 x 10⁹ 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>Author(s)</td>
<td>Year</td>
<td>Age</td>
<td>Sex</td>
<td>Clinical Findings</td>
<td>Treatment</td>
</tr>
<tr>
<td>----------</td>
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</tr>
<tr>
<td>Lindskov et al.</td>
<td>1988</td>
<td>9 y</td>
<td>M</td>
<td>Unknown</td>
<td>Elevated WBC (19 x 10^9 cells/L), eosinophilia (13%), fever</td>
</tr>
<tr>
<td>Reichel et al.</td>
<td>1991</td>
<td>6 y</td>
<td>M</td>
<td>Varicella</td>
<td>Eosinophilia (3%), varicella zoster virus titer of 1:32</td>
</tr>
<tr>
<td>Paquet et al.</td>
<td>1992</td>
<td>10 y</td>
<td>M</td>
<td>Unknown</td>
<td>Eosinophilia (13.4%), elevated IgE level</td>
</tr>
<tr>
<td>Anderson et al.</td>
<td>1995</td>
<td>4 y</td>
<td>F</td>
<td>Bee sting</td>
<td>Elevated WBC (45 x 10^9 cells/L), eosinophilia, elevated IgE and septicemia</td>
</tr>
<tr>
<td>Garty et al.</td>
<td>1997</td>
<td>&lt;1 mo</td>
<td>F</td>
<td>Possibly danazol, ingested by mother during pregnancy</td>
<td>Elevated WBC count (15 x 10^9 cells/L), eosinophilia (25%), ESR of 30 mm/h, mild hepatosplenomegaly, lymphadenopathy</td>
</tr>
<tr>
<td>Davis et al.</td>
<td>1998</td>
<td>7 y</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>
</tr>
<tr>
<td>Davis et al.</td>
<td>1998</td>
<td>5 y</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>
</tr>
<tr>
<td>Aroni et al.</td>
<td>1999</td>
<td>12 y</td>
<td>F</td>
<td>Unknown</td>
<td>Eosinophilia</td>
</tr>
<tr>
<td>Kuwahara et al.</td>
<td>2001</td>
<td>Birth</td>
<td>F</td>
<td>Possibly penicillin or danazol ingested by mother during pregnancy</td>
<td>None</td>
</tr>
<tr>
<td>Moossavi and Mehregan</td>
<td>2003</td>
<td>21 mo</td>
<td>F</td>
<td>Unknown</td>
<td>None</td>
</tr>
<tr>
<td>Koh et al.</td>
<td>2003</td>
<td>3.5 y</td>
<td>M</td>
<td>Hepatitis B and DPT vaccination</td>
<td>Slight peripheral eosinophilia</td>
</tr>
<tr>
<td>Stavropoulos et al.</td>
<td>2003</td>
<td>9 y</td>
<td>F</td>
<td>Molluscum contagiosum treated with cryosurgery</td>
<td>Eosinophilia (12%), ESR of 26 mm/h</td>
</tr>
<tr>
<td>Gilliam et al.</td>
<td>2005</td>
<td>1 y</td>
<td>F</td>
<td>Unknown</td>
<td>Elevated WBC count (30 x 10^9 cells/L), eosinophilia (48%)</td>
</tr>
</tbody>
</table>

ANA indicates antinuclear antibody; WBC, white blood cell; ESR, erythrocyte sedimentation rate; DPT, diphtheria-pertussis-tetanus.
TABLE 2. Differential Diagnosis of Wells’ Syndrome

<table>
<thead>
<tr>
<th>Disease</th>
<th>Associated Findings</th>
<th>Standard Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSS</td>
<td>Eosinophilic and granulomatous infiltrate with flame figures, no vasculitis</td>
<td>Oral or intravenous antibiotics</td>
</tr>
<tr>
<td>HES</td>
<td>Eosinophilic fasciitis with early acrual fibrosis</td>
<td>Oral steroids with or without chemotherapy</td>
</tr>
<tr>
<td>WSC</td>
<td>Palmar/planter pustules</td>
<td>Oral steroids with or without methotrexate</td>
</tr>
</tbody>
</table>

WBC indicates white blood cell.

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*Based on anecdotal reports.

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**REFERENCES**

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