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# The Histopathogenesis of the Flame Figure in Wells' Syndrome Based on Five Cases

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Characteristics of Wells' syndrome are recurrent episodes of edema and erythema of sudden onset, often covering large areas of the skin. Microscopy shows marked eosinophilia and the presence of so-called flame figures. The flame figures have been considered to be either secondary to aggregates of expelled eosinophilic granules and disintegrating eosinophils, or foci of necrobiotic collagen. Our study indicates that the flame figure is secondary to disintegration of eosinophils and consists of aggregates of eosinophilic granules and nuclear fragments and not of necrobiotic collagen. We consider Wells' syndrome to be a distinctive clinical and histological reaction, which can be triggered by many different, mostly unknown factors. (Received October 1, 1985.)

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In 1971, Wells described four patients, who had been observed over a period of ten years. They exhibited recurrent, suddenly appearing, distinct skin lesions with a characteristic histopathological pattern, including a rich infiltrate of eosinophils and so-called flame figures in the dermis (1). He called the condition "granulomatous dermatitis with eosinophilia". In 1979, Wells & Smith reported on eight further cases with the same typical clinical and histopathologial features and this time they designated it as "eosinophilic cellulitis" (2). Additional reports on eosinophilic cellulitis or Wells' syndrome, which is now a synonymous term, have been presented during the last few years (3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13).

We report here five additional cases of Wells' syndrome. The clinical features are described and the histopathogenesis of the flame figure and the possible mechanism of the syndrome are discussed.

## CASE REPORTS

*Case 1*

A 60-year-old woman, previously healthy, presented on February 2, 1981, with a severely itching rash. It had been present for a week. The lesions, some of them urticaria-like, showed a swift appearance and disappearance. Several large bullae, yellow crusts and oozing were seen on one elbow. On her back there were urticarial lesions. On March 16 these lesions had disappeared. Instead there were now scattered, rather large erythematous areas with significant infiltration and small vesicles. The patient still complained of severe itching. She was treated topically with corticosteroids. On May 5 all lesions had gone and no new ones had appeared. A biopsy was taken on March 16 from an infiltrated area 25 mm in diameter with small vesicles on one forearm. Examination of this specimen revealed eosinophilia and typical flame figures.

Investigations: ESR, hemoglobin, total white cell count, serum proteins, liver enzymes, complement C3 and C4 were normal. Blood eosinophils were 8%. Polyclonal IgM was slightly increased, as was IgE. Skin test with tuberculin (PPD 2TU) was positive. Skin tests with trichophytin (purified, 0.1 mg/ml, and commercial) were negative.

*Case 2*

A woman, 42 years old, who had mild psoriasis since childhood and had a recently diagnosed anal squamous cell carcinoma, was treated with bleomycin (5 mg/day) intramuscular (i.m.) and local radiation therapy on July 19, 1982. In the afternoon of the same day vesicular lesions appeared. On July 22 there were erythematous areas 5–10 cm in diameter with small vesicles over both shoulders and breasts and the inner sides of her thighs. She was given another injection of bleomycin, which was followed by aggravation with widespread and closely set papulo-vesicular lesions over the upper part of her trunk, arms and legs. She also had slight edema of the eyelids. The bleomycin therapy was interrupted and the patient received 40 mg of triamcinolon i.m. and in addition topical corticosteroids. The radiation therapy was continued. On August 2 the skin condition had deteriorated further, with widespread,confluent, dark red vesicular and partly urticarial infiltrations on the same locations as previously. The patient was hospitalized and the radiation therapy was discontinued. The skin lesions gradually disappeared in the next two weeks and did not recur. One biopsy showing unspecific changes was taken on July 22 from one upper arm, a second biopsy was taken on August 2 from a fresh vesicular lesion on the dorsal aspect of one hand. It revealed eosinophilia and typical flame figures.

Investigations: ESR, hemoglobin, total white cell count, serum proteins and liver enzymes were normal. Blood eosinophils were 6% and haptoglobin was slightly increased. Direct immunofluorescence showed granular $C_3$ deposits along the basement membrane. A tuberculin skin test was positive. Skin tests with trichophytin (purified and commercial) were negative.

*Case 3*

A 14-year-old boy, who had experienced an otherwise normal adolescence, had suffered from recurrent skin lesions since the age of 5 years, which appeared every year in April, May or June. Occasionally there had also been eruptions in the autumn and in the winter. The skin lesions were few in number and were usually situated on the legs. From time to time they also occurred on the trunk and neck. The initial lesion, which he described as a bright red macula, started with an intense localized itching. The macula turned bluish and became infiltrated on the first day. On the second or third day vesicles or pustules developed, with oozing, and the itching ceased. The lesions could reach the size of a palm. They healed within a week and left no trace. He never had fever or systemic symptoms. No triggering cause was known. In the middle of April, 1983, the patient presented with a bluish plaque measuring 3×2 cm, with petechiae and three vesiculo-papules on the ventral aspect of the left lower leg. The lesion was 3–4 days old. A biopsy was taken on that same day, and showed eosinophilia and typical flame figures.

Investigations: Blood values, including ESR and differential count, were normal. There was no eosinophilia. Liver enzymes were normal, as were IgE, serum complement $C_3$, $C_4$ and $C_{1q}$, and antinuclear antibodies. Culture from the throat and from feces yielded no abnormal growth. Parasitologic investigations gave negative results. Skin tests and inhalation provocation tests with birch, alder and hazel were all negative.

*Case 4*

A 26-year-old man, previously healthy, had noticed recurrent palmar erythema for four years. He was first examined in November 1982, when patchy erythema of the palms was observed. The lesions disappeared spontaneously. In the autumn of 1983 he contracted Chlamydia urethritis. He was treated with tetracyclines and rapidly developed a series of skin lesions. These started with the usual erythema and swelling of the palms. Scattered target lesions and infiltrated urticarial lesions on the trunk, and papules and follicular pustules on the face then followed. There was a tendency to spontaneous regression, but when by accident tetracyclines were given anew, a flare-up occurred. This time the face became very swollen and the lesions described above increased in severity. Spontaneous regression took place within a week after the tetracycline treatment was discontinued. Three biopsies were taken. Two of them were obtained on the same day—one from a fresh pustule on the face and the other from the erythematous palmar area and on examination marked eosinophilia was seen, but no flame figures. The third biopsy was taken later on, when the lesions were mainly in regression, from a small vesicular eruption located on the wrist. This one contained flame figures.

Investigations: ESR, hemoglobin, total white cell count, serum proteins, immunoglobulins and liver enzymes were normal, as were the results of urine analysis. Cultures from the throat, skin, and feces were negative. No immune complexes were found. At repeated differential counts eosinophils were 6%. IgE was slightly elevated. Viral antibodies revealed non-active hepatitis. A tuberculin skin test was positive, and a skin test with trichophytin negative.

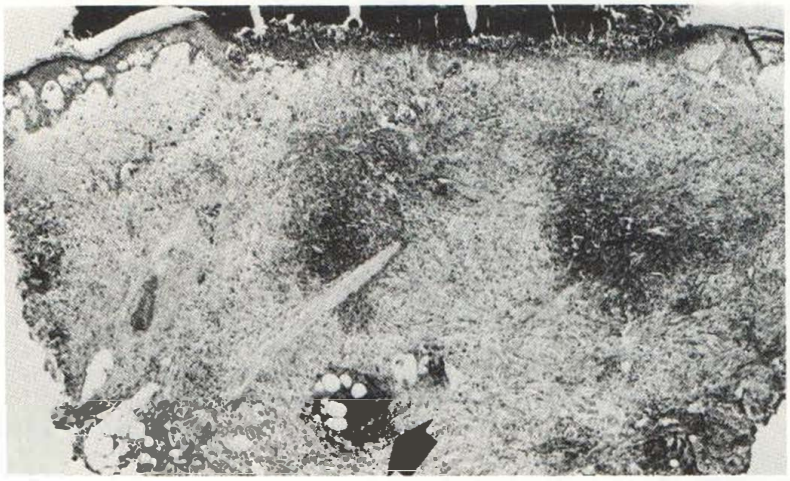

*Fig. 1.* Case 2. In the dermis there are two large foci with disintegrating eosinophils and flame figures. One flame figure is situated mainly in a fat lobule (arrow). Subepidermal edema, several intraepidermal vesicles and central ulceration of the epidermis are seen.

*Case 5*

A 56-year-old woman had suffered as a child from atopic dermatitis and had chronic lymphocytic leukemia since 1976. During 1980 and 1981 she received periodic treatment with chlorambucil. Every year since 1980 she had experienced episodes of severely itching skin lesions during the period May-August. These always started suddenly with shooting pain, erythema and marked edema. After about 24 hours some of the lesions contained vesicles in the center. One or several lesions occurred located on the face, trunk or extremities. They varied in size from a few centimeters to being very large, e.g. covering a large part of the extremity. The lesions usually vanished spontaneously after 2–3 weeks. Treatment with long-acting corticosteroids i.m. shortened the course and lessened the itching. The patient presented at he end of May 1984, with a fresh eruption. A biopsy was taken from an edematous and reddish lesion of a few hours' duration. It showed only edema. Late in June she had a further episode and a biopsy was taken from a 24-hour-old lesion with a crust in the center. This exhibited both eosinophilia and flame figures. In the beginning of July a new outbreak occurred. This time a biopsy was taken from an erythematous area, having the size of a palm, with small vesicles. The lesion was about 24 hours old. Only eosinophilia was found.

Investigations: ESR, hemoglobin, total white cell count, serum proteins, immunoglobulins and liver enzymes, and the results of urine analysis, were normal. Blood eosinophils were 10.0–11.5%. Direct immunofluorescence showed no deposits of immunoglobulin or $C_3$ in a biopsy from an one-day-old skin lesion. A tuberculin skin test was positive. Skin tests with trichophytin (purified and commercial) were negative.

## METHODS

The biopsy specimens in cases 1, 2 and 5 were cut serially, but those from cases 3 and 4 were cut on several levels. Staining was performed with hematoxylin-eosin, van Gieson stain, the Giemsa method and with toluidine blue and PAS.

## HISTOPATHOLOGICAL PATTERN

In all biopsies showing flame figures the whole dermis was involved, and in four of them also the subcutaneous fat tissue. In all specimens there was prominent subepidermal edema, in places giving rise to subepidermal vesicles. In cases 1 and 5 the edema extended into the subcutaneous fat. There were no or only minute deposits of fibrin between the collagen bundles. In addition to dermal edema, two patients had scattered intraepidermal vesicles containing inflammatory cells, some of which were eosinophils. In one case the epidermis was ulcerated (Fig. 1). The most prominent phenomena were a large number of

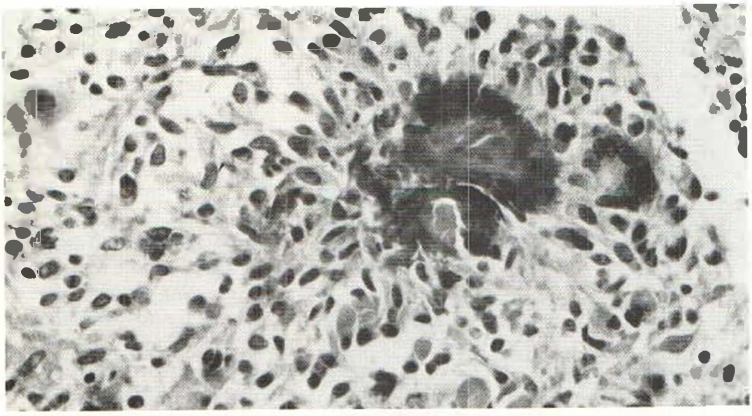

*Fig. 2.* Case 1. A fully developed flame figure. The flame surrounds a large and a small piece of collagen. To the right there is a multinucleated giant cell.

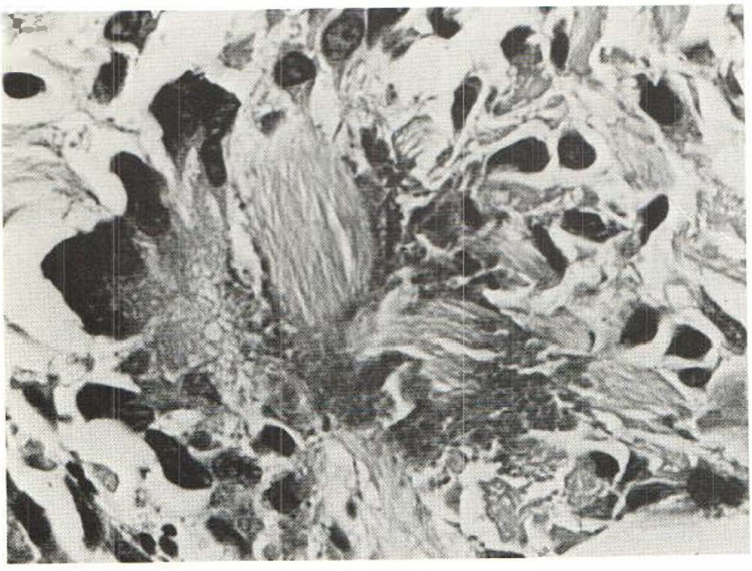

*Fig. 3.* Case 2. A fully developed flame figure with connective tissue in the center. At higher magnification the eosinophilic granules are easily visible. To the left, giant cells.

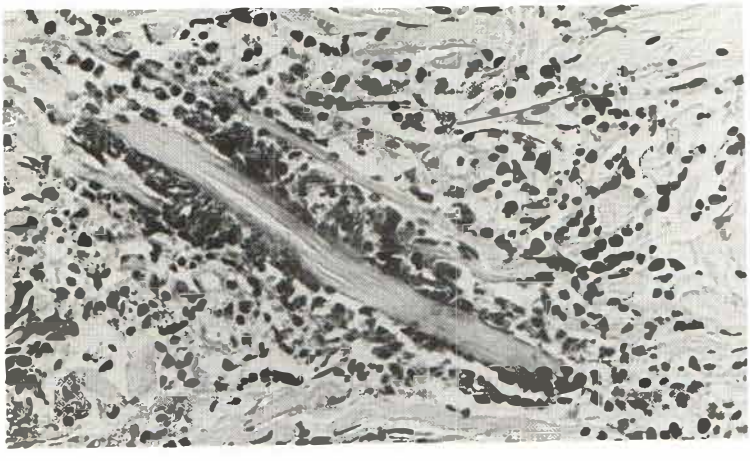

*Fig. 4.* Case 1. One incompletely developed flame figure. Rather loose aggregates of eosinophilic granules are surrounding a collagen bundle. There is no ring of fibroblasts or histiocytes.

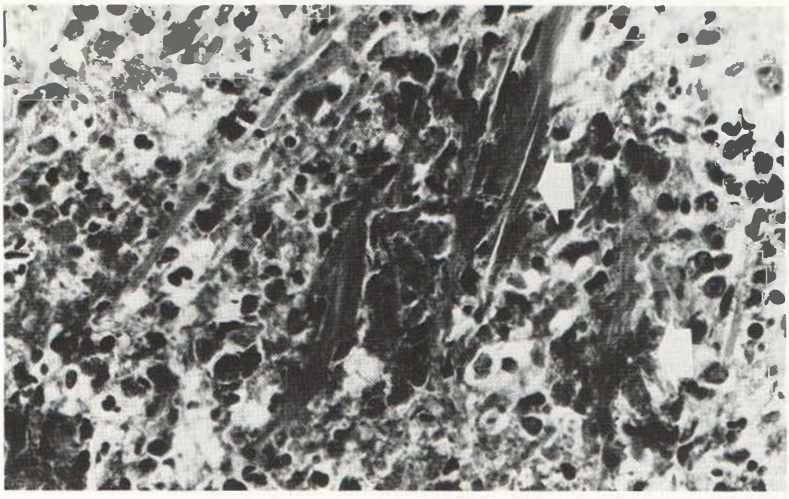

*Fig. 5.* Case 1. A focus with large numbers of eosinophils, nuclear fragments and expelled eosinophilic granules. The arrows indicate incompletely developed flame figures.

eosinophils, an abundance of extruded eosinophilic granules, nuclear fragments and flame figures. In general the eosinophils were diffusely disseminated, but in some places they were aggregated, mostly without any connection with blood vessels. The flame figures were scattered throughout the dermis and were also observed in subcutaneous fat (Fig. 1). They seemed to be of different ages. A fully developed flame figure consisted of dense aggregates of eosinophilic granules, which were adherent to one or both sides of a collagen bundle, surrounding a part of a bundle or covering it completely. Outside the collagen core and the granules there was a ring of fibroblasts and histiocytes, often together with a few multinucleated giant cells of the foreign body type (Figs. 2 and 3). Some, possibly younger flame figures lacked the ring of fibroblasts and histiocytes (Fig. 4). Cases 1 and 5 presented the most pronounced lesions. In these cases the dermis contained several foci, which appeared as if they had suffered the impact of a bomb. In the center of such a focus there were aggregates of disintegrating eosinophils, extruded eosinophilic granules, and basophilic nuclear fragments and dust. At the periphery of the focus there was a border of small, incompletely developed flame figures. The collagen bundles were dispersed but not necrotic (Figs. 1 and 5). In addition to eosinophils, all patients displayed infiltrates of mononuclear cells, mostly lymphocytes but also some histiocytes and a few mast cells. There were only a few neutrophils.

Vasculitis in the strict sense was not observed, but some small thin-walled vessels were dilated and seemed disrupted. Some dilated vessels were densely filled with eosinophils. Extravasation of erythrocytes was a prominent phenomenon in all cases but one. In biopsies containing eosinophils but no flame figures, many eosinophils were disintegrating and an abundance of expelled eosinophilic granules were seen.

## DISCUSSION

Since 1971, when Wells described the first four patients with the syndrome which now bears his name, between 20 and 30 cases have been reported. The skin lesions appeared episodically on different parts of the body and often recurred several times over months or years. In severe cases among those reported the symptoms developed suddenly, covering large aras of the trunk or an entire limb. In most patients distinct erythema and edema occurred. More than half of them displayed circinate erythematous plaques with infiltrated

margins, enlarging towards the periphery. In some cases there were vesicles or bullae. The lesions were often accompanied by severe itching and sometimes by a burning sensation or even pain. Eventually the condition subsided without any residues, often after 4-8 weeks. In most cases the general condition was unaffected, but a few patients suffered from malaise and had an elevated ESR. Blood eosinophilia of mild to moderate degree was usually present. No common cause of the syndrome has been discovered. In his original study Wells proposed a hypersensitivity mechanism triggered by factors such as infections, drugs or internal diseases. In most cases no trigger had been discovered. In a few patients, however, the symptoms developed in association with infections and antibiotic treatment, and five cases of proved arthropod bites associated with clinical and histopathological features of Wells' syndrome have recently been described.

Our five patients displayed fairly clear characteristics of Wells' syndrome. In three of them, however, the skin lesions appeared and disappeared on different places within a rather short time. Thus lesions of different ages could be present simultaneously and fresh lesions could be found during the same episode several weeks after the onset of the symptoms. In three of the cases there was no obvious trigger. In one patient the only eruption appeared in connection with bleomycin therapy and radiation of a squamous cell carcinoma. In another patient the eruptions were proved to be caused by treatment with tetracyclines.

Histologically the most conspicuous phenomenon is the appearance of flame figures. Wells & Smith proposed that the flame figures were secondary to the massive infiltrates of eosinophils and expelled eosinophilic granules seen in the very early phase of the disease. They considered the palisade of histiocytes and foreign body giant cells to represent a phagocytic response to the products of disintegrating eosinophils. Since that time other authors have interpreted the flame figures as being due to focal necrobiosis of collagen, with microgranulomas and associated eosinophilia (3, 5, 6, 9). Some investigators believe that the necrobiosis is due to a cytotoxic effect of eosinophilic granules or of their component of major basic protein on the collagen fibers (6, 9).

Our findings strongly support the interpretation proposed by Wells & Smith. By obtaining biopsies from lesions of different ages in the same patients, both very early lesions with edema, massive infiltrates of partly disintegrating eosinophils and abundant extruded eosinophilic granules, and somewhat later lesions with flame figures of different ages were observed. It was clearly evident that in early flame figures the flame (the bright red brim around the collagen bundle) consisted of granules (Fig. 4). Also in fully developed flame figures, eosinophilic granules often could be easily distinguished (Fig. 3). When stained according to the van Gieson method, both the flames and the intracellular eosinophilic granules assume a dusky yellow hue. Our findings are in accordance with those of Peters et al. (9), who investigated flame figures with an immunofluorescence technique with antihuman major basic protein. They observed strong fluorescence of the flame figures and eosinophils (basic major protein constitutes 50% of the eosinophilic granule). Furthermore, like Peters et al. we found a consumption of eosinophils, i.e. in possibly somewhat older lesions there were fewer eosinophils in the dermis and the flame figures were not surrounded by these cells.

In spite of the pronounced edema in some specimens, the deposition of fibrin between collagen bundles was only very slight or absent. Necrobiosis of collagen was not observed. Moreover the collagen located in the middle of many of the flame figures (Figs. 2 and 3) stained normally with hematoxylin-eosin and with the van Gieson stain. Vasculitis in the strict sense was not seen but findings of dilatation and disruption of the walls of small vessels, marked edema and numerous extravasated erythrocytes strongly suggest some kind of vessel damage. Just as in leukocytoclastic vasculitis, there was a large number of

nuclear fragments in several of our specimens (Fig. 5). However, only a few neutrophils were observed, strongly indicating that the nuclear fragments mainly derived from eosinophils.

We consider Wells' syndrome to be a distinctive clinical and histological reaction which, like leukocytoclastic vasculitis and erythema multiforme, can be triggered by different agents. The main event in Wells' syndrome is presumably an immune complex mediated reaction which attracts and destroys eosinophils in large numbers, and gives rise to some kind of vessel damage resulting in leakage of fluid and erythrocytes. It is concluded that the flame figures occur secondarily to the expulsion of large amounts of eosinophilic granules and disintegration of eosinophils. The eosinophilic granules contain a poorly soluble component (14, 15). We consider that the foreign body reaction around the flame is provoked by this component, and not by necrobiotic collagen. Fully developed flame figures were observed in a skin lesion only 24 hours old.

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