

Foreign-body granuloma and IgE-pseudolymphoma after multiple bee stings

B.HERMES, N.HAAS, J.GRABBE AND B.M.CZARNETZKI

Department of Dermatology, University Clinics Rudolf Virchow, Free University, Berlin, Germany

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Summary

We report a patient with an unusual combination of an eosinophilic foreign-body granuloma and a pseudolymphoma, with recurrent severe oedema on the forehead, after multiple bee stings. On immunohistology the foreign-body granuloma and lymphoid follicles reacted with monoclonal antibodies against the high- and low-affinity IgE receptors, and against IgE. Prick and intradermal tests with whole-body bee extracts showed positive immediate-type reactions. The eosinophilic granuloma formation and lymphoid follicles may have been induced by a combination of immune complex and cell-mediated hypersensitivity following antigen persistence. Although bee stings are common, as far as we are aware, this complex reaction pattern has not been reported previously.

Case report

A 52-year-old man presented with a 2-year history of a disfiguring swelling above his left eyebrow. The lesion had started to grow after he hit his forehead against a plum tree. Several days later he was stung by bees in the same site as the injury. He had crushed several insects, and his wife subsequently removed one bee sting. During the following months the swelling gradually grew larger, and became studded with pustules and small ulcers, and there was recurrent oedema of the entire area, including the periorbital region. Systemic antibiotic and topical antifungal therapy were ineffective.

On examination there was an erythematous, elevated, indurated, 6 × 2 cm lesion above his left eyebrow, which was studded with pustules and multiple ulcers (Fig. 1).

After a 2-week course of erythromycin the swelling remained unchanged. A biopsy was taken for culture and histological examination. Infection with mycobacteria or fungi was subsequently excluded by smears and cultures.

Histology showed an intense inflammatory infiltrate below a hyperplastic epidermis. The infiltrate extended to a depth of 7 mm, infiltrating subcutaneous fat and muscle. It was composed of plasma cells, numerous eosinophils, neutrophils, lymphoid follicles and foreign-body giant cells. On careful scrutiny, birefringent, intensely yellow foreign bodies of elongated, circular or round shape were noted, some of them with sharp

indentations. They were scattered throughout the tissue, down to the lower border of infiltration just above the muscle layer, as well as in follicular openings. The foreign-bodies did not stain with haematoxylin and eosin, or PAS (Fig. 2).



Figure 1. Foreign-body granuloma on the forehead, with multiple small ulcers.



Figure 2. Histology of the foreign-body granuloma, showing a longitudinal section of a bee sting (haematoxylin and eosin, $\times 40$).

After the diagnosis of a foreign-body granuloma had been established, he was treated with intralesional triamcinolone injections, which resulted in a reduction in the size of the lesion, and allowed a serial excision in two steps. Even after these procedures there were still recurrent episodes of swelling of the supraorbital region and the eyelids, which resolved immediately after oral administration of prednisolone 50 mg/day (Fig. 3). During the following year, new, persistent nodules were excised on three occasions, and these contained additional foreign bodies with surrounding granuloma formation.

Identification of the foreign bodies

The nature of the foreign bodies was not immediately apparent. Initially, it was considered that wood splinters might have penetrated into deeper tissue layers after the injury from the tree. However, sections of the original

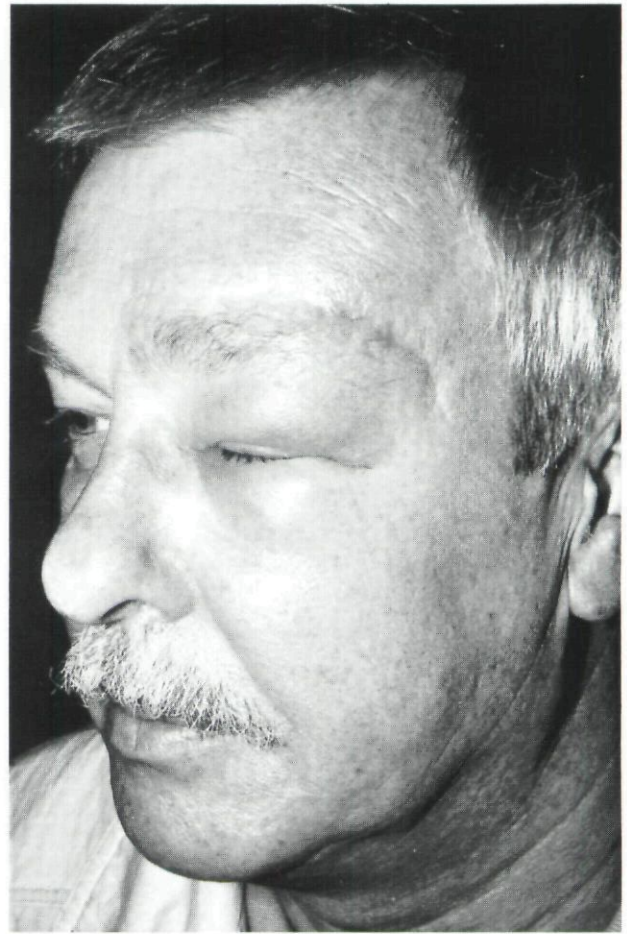


Figure 3. Oedematous swelling of the periorbital region which recurred after excision of the granuloma.

tree bark had a very different appearance from the tissue foreign bodies. Furthermore, wood splinters would not explain the numerous eosinophils present. Subsequent sectioning of a bee sting showed a marked similarity to the foreign bodies. Longitudinal sections of the sting (Fig. 4a) and of a foreign body in the patient's tissue (Fig. 4b) showed identical structures. Cross-sections of the sting (Fig. 5a) and of one of the foreign bodies (Fig. 5b) also demonstrated identical structures.

Bee stings are composed of a dorsal stylet and two ventrolateral barbed lancets enclosing the venom canal. The latter communicates with the poison sac.¹

Immunohistochemical investigations

Biopsy specimens of the original lesion (1990), and of the smaller nodules which developed during the following year (1991), were compared for their reactivity with monoclonal antibodies against T cells (UCHL1 for pan-

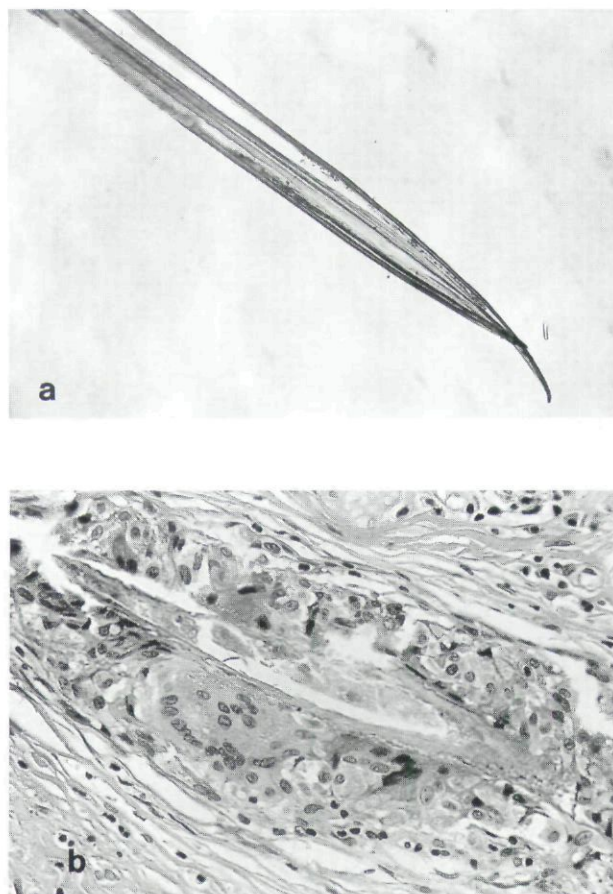


Figure 4. (a) Longitudinal section of a bee sting (unstained, $\times 100$). (b) Longitudinal section of a bee sting in an epithelioid cell granuloma, with giant cells (haematoxylin and eosin, $\times 100$).

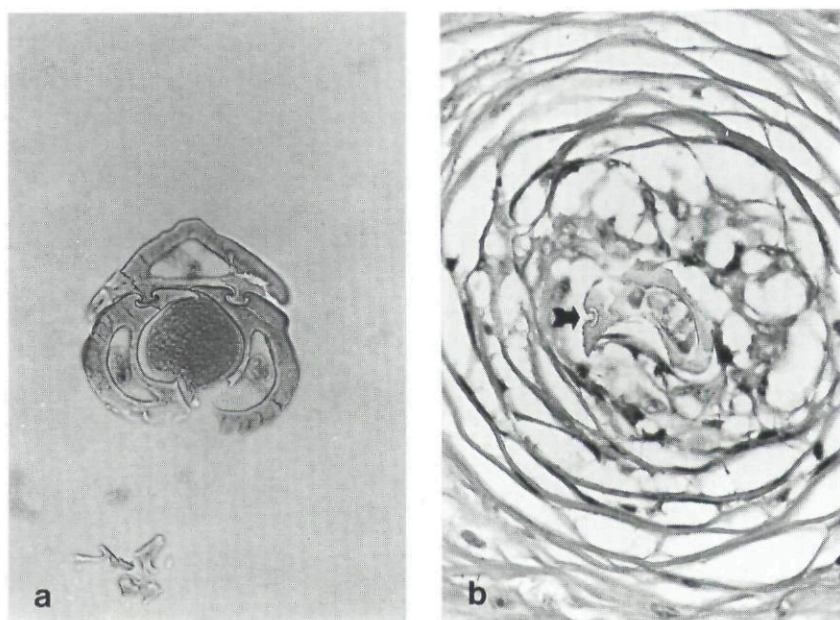


Figure 5. (a) Cross-section of a bee sting showing the venom canal surrounded by three chitin components linked by joint-like structures (unstained, $\times 400$). (b) Cross-section of an epithelioid cell granuloma showing the same joint-like structure (arrow) [haematoxylin and eosin, $\times 400$].

T cells, T4 for T-helper cells, T8 for T-suppressor cells; DAKO, Denmark), B cells (L26; DAKO, Denmark), proliferating cells (PC; DAKO, Denmark), IgE (DAKO, Denmark) and IgE receptors (FC ϵ RI = high-affinity IgE receptor = 29C6, gift from J.Haimi, Hoffmann-La Roche Inc., NJ, U.S.A.; FC ϵ R2 = low-affinity IgE receptor = T $\bar{u}$ 1, gift from A.Ziegler, Freie Universitt, Berlin, Germany) by the APAAP technique on frozen tissue sections (Table 1). Direct immunofluorescence was performed with anti-IgG, anti-IgM, anti-IgA, and anti-C3 (Behring, Germany), also on frozen tissue sections.

In the 1990 sections, the lymphadenoid structures showed strong reactivity with L26 and PC in the centre of follicles, and with T4 and UCHL1 in the perifollicular cuff. In the 1991 sections, there was similar strong reactivity with UCHL1 and T4 in the perifollicular cuff. L26 and PC were distinctly less reactive in the centre of the follicles. In the original sections, the germinal centres stained with anti-IgE, whereas there was no reaction in those from 1991. There was no staining for IgG, IgA or IgM in the germinal centres at any time. In both 1990 and 1991 sections, the germinal centres were markedly positive for FC ϵ R2. FC ϵ RI was expressed by numerous cells of the mixed dermal infiltrate, and by epidermal Langerhans cells.^{2,3} Deposits of IgM and C3 were found in the walls of small venules.

Allergy tests

There was a strong reaction to whole-body extracts of bee (Allergopharma, Reinbek, Germany), and to a lesser

Table 1. Immunohistology of pseudofollicles

	Centre of follicles		Perifollicular cuff		Inflammatory infiltrate	
	1990	1991	1990	1991	1990	1991
UCHL1	+	(+)	++	++	+++	+++
T4	++	+	+++	+++	+++	+++
T8	0	0	+	+	+	+
L26	+++	+	0	++	(+)	+
PC	++	+	(+)	(+)	0	0
29C6	(+)	0	0	0	++	+++
Tü1	++	++	+	+	+	+
IgE	+	0	(+)	0	+	(+)

+++ , ++ , + , (+) , 0; strong to no reaction.

UCHL1, T4, T8 = markers for pan-T cells, T-helper and T-suppressor cells, respectively; L26, B-cell marker; PC, proliferating cell marker; 29C6, high-affinity IgE-receptor marker; Tü1, low-affinity IgE-receptor marker.

Table 2. Allergy tests

	Prick test	Intracutaneous test		Patch test
		Immediate	Delayed	
NaCl	0	0	0	—
Histamine	+++	+++	0	—
Bee, whole-body	++	++	0	—
Wasp, whole-body	+	+	0	—
Bee venom	0	—	—	—
Wasp venom	0	—	—	—
Plum tree bark	—	—	—	0

+++ , ++ , + , 0; strong to no reaction. —; not done.

extent of wasp (Table 2), on prick and intradermal testing. In five control subjects tested, only one showed a positive reaction to the whole-body extract of bee. A patch test with the bark of the plum tree was negative. Specific serum IgE level for bee venom was slightly raised (RAST class 2). In order to investigate the pathogenesis of the granulomatous reaction further, we implanted a bee sting into the skin of the left upper arm of the patient.⁴ No reaction was noted at the site during the following 6 weeks. A biopsy was not performed, as the patient subsequently developed a severe gastrointestinal disease (perforated sigmoid diverticulitis with peritonitis) which required major surgery and high-dose corticosteroids over several weeks whilst he was in the intensive care unit.

Discussion

Bee stings occur frequently but, to our knowledge, complications such as those we describe have not been

reported previously. This case raised many questions about the type of trauma, the clinical signs and symptoms, the histological findings, and the possible immunological pathomechanisms involved.

We were initially puzzled by the great depth of penetration of the sting fragments in the histological specimens. There are, however, reports in the literature that stings of wasps and hornets can reach a depth of 4–7 mm. The stings of many insects are withdrawn after stinging, but the sting of honeybees is barbed, and remains in the skin, together with the poison sac and a nerve plexus. It continues to penetrate the skin unless it is removed.^{1,5} In our patient, it is possible that the preceding injury from the plum tree facilitated penetration of parts of the chitin skeleton of the stings. It would appear that the patient was stung by a number of bees, judging from the numerous stings found in the biopsy specimens. When bees are threatened, they are known to summon others to assist them by releasing alarm pheromones.^{1,5}

The clinical picture in our patient was characterized by three striking features: (i) persistent indurated swelling; (ii) transient oedema, and (iii) suppuration. The oedema was particularly annoying for the patient, and it recurred even after surgical removal of the clinically evident granuloma. The recurrent oedema may be similar to the 'weal and flare reaction' described by Baumgarten⁶ at the injection sites of semi-depot extracts during specific hyposensitization. On histological examination, he noted granuloma formation at the injection sites and, even after resolution of the granuloma, reddening, swelling and pruritus recurred when the patient was re-exposed to high doses of antigen. In our patient, mobilized or solubilized antigenic material could have elicited recurrent swelling in a similar way.

Histological examination revealed foreign-body granuloma formation, together with eosinophils and pseudolymphoma. Immunofluorescence showed deposits of IgM and C3 in the walls of small venules. These findings suggest that antigen persistence may have caused an immune complex-mediated reaction, with activation of macrophages leading to the granulomatous inflammation. Phagocytosis of antigenic material by macrophages may have induced antibody production by plasma cells, which in our patient were located in lymphoid follicles in the lesion. These germinal centres may play an important role in sustaining the local immune response.

Because a reaction to a bee sting similar to that which occurred in our patient has not been described previously, we looked for other models of foreign-body reactions in the literature. Schreiber *et al.*⁷ described cactus-spine granulomas of the foreign-body type, and demonstrated positive reactions to cactus antigens on intradermal testing. In 1981, Iwatsuki *et al.*⁸ reported lymphadenoid structures in a hypersensitivity reaction to gold earrings. As in our patient, this model suggests antigen persistence. A combination of granulomatous hypersensitivity and lymphadenoid structures has also been observed after injection of aluminium-adsorbed vaccines or aluminium-adsorbed antigens for hyp sensitization.⁹⁻¹¹ The persisting antigen is thought to elicit development of germinal centres. In a case of histiocytic reaction and pseudolymphoma after hyp sensitization, Klepzig *et al.*¹² noted an immune complex vasculitis.

The positive prick test and intradermal tests to whole-body extract of bee, together with the abundance of plasma cells in the cutaneous infiltrate, support our conjecture of an IgE-mediated reaction as part of the immunological process. The recurrent oedema in our patient may have a clinical equivalent in the type I reaction of Gell and Coombs.

By immunohistology with monoclonal antibodies, we demonstrated nodular masses of B cells in the centre of the lymphoid follicles, and peripheral mantle-zones of T lymphocytes. The low-affinity IgE receptor was expressed in the follicle centres, whereas the high-affinity receptor was expressed by scattered cells in the surrounding mixed infiltrate. IgE, but not IgG, IgA, or

IgM was demonstrated in both the follicle centres and the surrounding infiltrate. The reason why IgE was only expressed in the 1990 and not the 1991 specimen may perhaps be due to the removal of a large amount of the antigen by surgery. To date, exclusive IgE production by pseudolymphomas has not been reported in the literature; usually, there is a heterogeneous pattern of all subtypes of immunoglobulins.¹³

Our findings in this patient suggest the presence of a complex immunological reaction following bee stings where the stings persist. Antigen persistence may promote immune complex vasculitis, granulomatous inflammation with activated macrophages, suppuration, and IgE-producing pseudolymphoma.

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