

Occupational Asthma Caused by Inhalable Royal Jelly and Its Cross-reactivity with Honeybee Venom

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Royal jelly is a honeybee nutriment secreted from the glands in the hypopharynx of worker bees essential in the development of queen bees. Ingestion of royal jelly has been reported to trigger rhinitis, asthma, and anaphylaxis,^[1] but occupational asthma occurring after inhalation of volatile royal jelly is rare. Here, we presented a case of occupational asthma induced by royal jelly with coexisting allergy to honeybee venom and investigated the immunoglobulin E (IgE) cross-reactivity between royal jelly and honeybee venom.

A 43-year-old Chinese woman was referred to Department of Allergy, Peking Union Medical College Hospital due to repeated wheezing for 10 years. The patient was a senior manager of a royal jelly processing factory with a work history of 11 years. She developed wheezing within half an hour of entering the processing workshop and gradually recovered following her departure without medical intervention. The patient also complained of edema after ingestion of royal jelly. In addition, the patient presented with a positive 5-year history of honeybee venom allergy. Upon being stung, she would present swelling with a lesion diameter exceeding 10 cm lasting longer than 24 h.

Skin prick test was positive to royal jelly: 11 mm × 9 mm. Intradermal tests for common aeroallergens (dust mites, fungi, pollens, and animal dander) were all negative. The total IgE was 297 kU/L, and specific IgEs were positive to i1 (2.465 kUA/L) and i208 (13.1 kUA/L) (ImmunoCAP, Phadia, Sweden). Baseline spirometry results were normal, and then we performed the workplace challenge test. The patient entered the factory processing workshop with a portable spirometer (eResearch Technology, Philadelphia, Pennsylvania, USA) and salbutamol aerosol. She measured and recorded her forced expiratory volume in 1 s (FEV1)

and peak expiratory flow (PEF) every 30 min. She developed wheezing 1 h later. The spirometer showed that her FEV1 fell 44% (>20%) and PEF fell 56% (>20%) compared to the baseline level in the workshop, where the royal jelly was filtered and packed, indicating the uniquely high level of inhalable volatile royal jelly in the air of the workshop to be the cause of her asthma.

As mentioned above, this patient had allergic reactions to both royal jelly and honeybee venom. To clarify cross-reactivity between royal jelly and honeybee venom, competitive IgE enzyme-linked immunosorbent assay (ELISA) inhibition tests and immunoblotting inhibition assays were performed.

The royal jelly or honeybee venom extract (provided by the royal jelly processing factory where the patient worked) was incubated with a mixture containing the serum of the patient and the honeybee venom or royal jelly as inhibitors. The royal jelly managed to inhibit 82% of the total IgE binding to honeybee venom at 0.1 mg protein, whereas 0.1 mg of honeybee venom was required to inhibit 90% of the total IgE binding to royal jelly.

The sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) results of royal jelly and honeybee venom are shown in Figure 1a and 1b. Immunoblotting analysis of royal jelly extract with the serum of the patient showed one IgE-binding component

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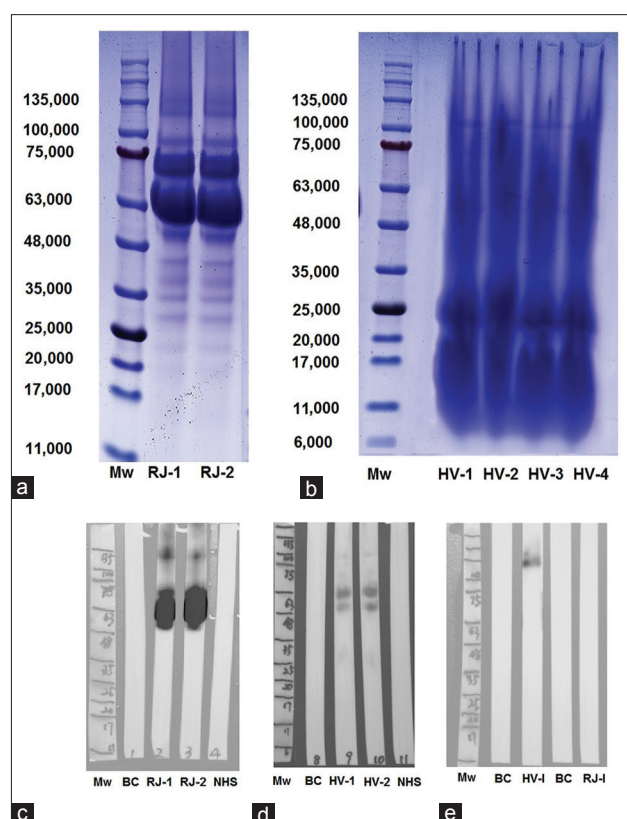


Figure 1: Sodium dodecyl sulfate-polyacrylamide gel electrophoresis and immunoblot images. (a and b) Sodium dodecyl sulfate-polyacrylamide gel electrophoresis profiles of royal jelly and honeybee venom extracts. (c and d) Immunoblot of royal jelly and honeybee venom extracts. (e) Immunoglobulin E immunoblot inhibition tests between royal jelly and honeybee venom extracts. Mw: Molecular weight markers; RJ: Royal jelly; HV: Honeybee venom; BC: Blank control (without any serum as a probe); NHS: Probed with pooled normal human sera; HV-I: Honeybee venom used as inhibitor; RJ-I: Royal jelly used as inhibitor.

of 135,000 and several components between 50,000 and 70,000 [Figure 1c]. In the same way, immunoblotting with honeybee venom revealed two IgE-binding components of 52,000 and 63,000 [Figure 1d]. In the immunoblotting inhibition assays, royal jelly extract showed complete inhibition of specific IgE reactivity to honeybee venom, whereas most of the IgE-binding components of royal jelly were also inhibited by honeybee venom extract, with only one protein band of 135,000 left, indicating the presence of many cross-reactive allergen components [Figure 1e].

Since the initial visit, this patient has stayed away from the processing workshop for 6 months and has not experienced any more asthma attack, without the use of any medical intervention. Recent spirometry results were normal.

It was reported that the workplace was responsible for the development of up to 16% of adult-onset asthma, and 10% of occupational asthma was induced by volatile foods.^[2] Bees and honey had also been reported to be

associated with occupational asthma, but royal jelly had not been mentioned in the literature before 2016.^[3] Only in July 2016, Gómez Torrijos *et al.*^[4] reported the first two cases of occupational asthma due to royal jelly. Our patient developed typical asthma symptoms each time she entered the workshop processing royal jelly and recovered once she left there. Her skin prick test was positive to royal jelly, and the workplace challenge test showed a dramatic decline of FEV1 and PEF after she entered the workshop, indicating definite diagnosis of occupational asthma caused by royal jelly. As mentioned above, Gómez Torrijos *et al.*^[4] reported similar cases of occupational asthma due to volatile royal jelly, but those two patients did not present with coexisting bee venom allergy, which might explain the inconsistency of immunoblot analysis among the three cases. Our patient was a Chinese woman and had allergic reactions to both royal jelly and honeybee venom, whereas the two cases in the literature were from Spain and they only reported allergy to royal jelly.

As we know, royal jelly and honeybee venom are both produced by honeybees. Their homology makes it possible that they share similar allergenic components. In this case, ELISA inhibition tests indicated the presence of cross-reactive IgE antibodies that bound to royal jelly extract and inhibited their binding to honeybee venom. Immunoblotting inhibition also demonstrated that except the band of 135,000, the majority of allergen components were shared between royal jelly and honeybee venom. Based on the patient's clinical history and results of immunoinhibition tests, we could see clear allergenic cross-reactivity between royal jelly and honeybee venom. However, further studies are required to confirm the risk of royal jelly allergy in the patients who have honeybee venom allergy, especially for those patients in processing bee products.

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Conflicts of interest

There are no conflicts of interest.

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