

Letter to the Editor

Sensitization to cross-reactive carbohydrate determinants in 2 patients with Hymenoptera venom allergy and alcoholic cardiomyopathy

To the Editor:

Eberlein et al¹ proposed basophil activation tests with cross-reactive carbohydrate determinants (CCD) and the use of recombinant allergens to solve the problem of double positivity to bee and wasp venom in Hymenoptera venom allergy. The usefulness of this test in confirming allergy in patients with doubtful diagnosis was suggested previously.² However, we recently demonstrated that heavy drinkers with no allergic symptoms and high CCD-IgE values exhibit basophil activation with CCD (MUXF-BSA) and CCD-bearing allergens including bromelain, pollen

extracts, and Hymenoptera venoms, suggesting relevant interference of alcohol intake in the interpretation of these tests.³ The interference of alcohol in allergy would not be restricted to the induction of total and specific IgE by shifting immunity to T_H2, which has been shown in both humans⁴ and experimental animal models,⁵ but would also cause the misinterpretation of clinical symptoms in such patients. Here, we present 2 alcohol abusers with alcoholic cardiomyopathy who experienced what was considered a systemic reaction after Hymenoptera stings, with CCD and Hymenoptera venom sensitization.

Characteristics of the 2 patients are provided in Table I. Both patients were middle-aged male farmers who suffered from long-term alcohol abuse and alcoholic cardiomyopathy (ejection fraction, 17%-20%). Both patients reacted shortly after being

TABLE I. Patient characteristics

	Patient 1	Patient 2
Sex	Male	Male
Age (y)	57	49
Habitat (residence)	Rural	Rural
Occupation	Farmer	Farmer
Beekeeping activities	No	No
Smoking (current)	No	Yes
Alcohol abuse	Yes, >20 y (wine)	Yes, >20 y (wine)
Heart disease	Dilated cardiomyopathy, paroxysmal atrial fibrillation	Dilated cardiomyopathy, ventricular arrhythmia, implanted defibrillator
Additional systemic disease	Sleep apnea syndrome, metabolic syndrome, gout	None
Current therapy	Warfarin, amiodarone, valsartan, atorvastatin, allopurinol	Carvedilol, enalapril, digoxin, spironolactone, furosemide
Hymenoptera venom reaction		
Grade	Mueller grade IV	Mueller grade IV
Number of episodes	1	1
Culprit insect	Wasp vs honeybee	Honeybee
Previous sting reactions	No	No
Additional hypersensitivity disease	NSAID intolerance	None
Intradermal tests		
HBV	Positive at 0.0001 µg/mL	Positive at 0.001 µg/mL
YJV	Positive at 0.0001 µg/mL	Positive at 0.001 µg/mL
PDV	Positive at 0.01 µg/mL	Negative
Total IgE (IU/mL)	1040	607
Specific IgE (CAP Phadia, kU/L)		
HBV	75.4	27.2
YJV	10.3	34.7
PDV	2.12	3.88
MUXF	3.48	16.0
Natural rubber latex	1.55	18.1
<i>Phleum pratense</i>	4.16	19.8
rPh1 p1	ND	0.50
rPh1 p5	ND	0.35
Specific IgE (ADVIA Centaur, kU/L)		
HBV PLA2 (rApi m1)	15.43	5.45
nApi m2	ND	212.0
nVes v1	3.08	0.88
nVes v2	26.67	47.16
rVes v5	23.33	19.04
nPol d1	0.71	0.14
nPol d5	4.73	1.13
Baseline serum tryptase (µg/L)	2.0	6.0
Immunotherapy	Yes (HBV and YJV)	Yes (HBV)

HBV, Honeybee venom; MUXF, the N-glycan from bromelain; n, natural; ND, not determined; NSAID, nonsteroidal anti-inflammatory drug; PDV, *Polistes dominulus* venom; PLA2, phospholipase A; r, recombinant; YJV, yellow jacket venom.

stung by what patient 1 doubtfully identified as a wasp and patient 2 identified as a honeybee. Patient 1 presented with hypotension and loss of consciousness followed by an undefined skin rash, and patient 2 presented with hypotension, chest tightness, feeling of impending doom, and a skin rash. Despite having no other allergic symptoms, the patients had high serum concentrations of total serum IgE and IgE specific to CCD-bearing allergens such as grass pollen and latex and CCD markers such as MUXF3. Moreover, both patients had *in vitro* double reactivity to whole honeybee venom (HBV) and yellow jacket venom (YJV) and displayed IgE specific to venom components. Intradermal test results were positive for both venoms. To identify spurious reactivity induced by CCDs,^{3,6,7} inhibition studies were performed: reactivity to HBV and YJV was inhibited (>50% in patient 1 and 100% in patient 2) by preincubation with an N-glycan (MUXF3) coupled to BSA.^{3,7} Basophil activation tests were not performed because of our experience with heavy drinkers.³ As no definitive results were obtained, patient 1 began HBV and YJV immunotherapy because of the severity of the reaction and the doubtful recognition of the insect and patient 2 was treated with HBV immunotherapy. After 5 years of treatment, patient 1 exhibited a 60% reduction in the levels of specific IgE and patient 2 exhibited a 100% reduction. Interestingly, patient 2 tested negative 2 years after beginning immunotherapy when he also stopped drinking. CCD markers and CCD-bearing allergens were also negative. Determining whether changes in specific IgE were due to immunotherapy, the decrease in alcohol intake, or both is difficult, but one could ask how venom immunotherapy was capable of neutralizing specific IgE to pollens or CCD markers.

In summary, these cases illustrate the difficulties in deciding Hymenoptera venom immunotherapy when several factors influence the reaction. First of all, anamnesis is often less reliable in patients suffering from alcohol abuse. Heart disease and its therapy could be a confounder in the differential diagnosis of arterial hypotension and syncope. Second, double (HBV and YJV) *in vitro* reactivity induced by CCD sensitization⁶⁻⁸ is particularly important in every patient but especially among alcoholics in whom high levels of specific IgE to CCDs are common.^{3,7} Reactivity induced by CCDs extends beyond protein boundaries, and CCD-sensitized patients also have spurious reactivity to many plant allergens,⁶⁻⁸ such as natural rubber latex and grass pollen, as in the cases presented here. This problem can be partly overcome by using nonglycosylated recombinant allergens or naturally nonglycosylated allergens if they are available.^{6,7} The sting challenge test can also be considered in some patients. The presence of cardiomyopathy in the reported cases may be coincidental but presents intriguing questions.

Oral CCD exposure is very common.⁶ Although CCDs are considered devoid of classical *in vivo* activity, they are able to activate basophils in IgE-sensitized individuals.^{3,6} In addition, cardiac mast cells are important effectors in heart disease, including dilated cardiomyopathy. Thus, alcohol-induced experimental cardiomyopathy is more prominent among strains with T_H2-shifted immunity and increased IgE values.⁹ The potential role of T_H2-deviated immunity, increased IgE levels, and CCD sensitization in the development of cardiomyopathy in individuals who abuse alcohol should be tested in further studies.

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