

Jellyfish anaphylaxis: A wide spectrum of sensitization routes

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ABSTRACT

Background: Recent studies demonstrated that, in the past few years, the number of jellyfish species is increasing worldwide; this increase can be explained by environmental and climatic reasons. Contacts with jellyfish can cause acute and chronic effects, including allergic reactions. Although anaphylaxis caused by jellyfish is a rare event, repetitive stings during bathing as well as marine sports and job activities represent important risk factors that can increase the probability of sensitization. Recently, it was also pointed out the possibility of anaphylaxis caused by jellyfish ingestion. In these cases, the sensitization could also be related to previous stings. In cases in which there is no history of jellyfish contact or ingestion, it has been hypothesized that there is a sensitization to an unknown cross-reactive antigen.

Objective: The purpose of this work was to collect and review published studies and cases of anaphylaxis associated with jellyfish.

Methods: We performed a medical literature data base search, which included English language articles published until September 2019, by using the key words “jellyfish” associated with “anaphylaxis” or “anaphylactic shock.”

Results: The results of our research showed that dangerous reactions can be caused both by contact and ingestion. Moreover, the latest changes in food habits, life style, and globalization could lead to a more frequent exposure to jellyfish both by contact and ingestion, and, consequently, to a higher probability of sensitization.

Conclusion: Prospective studies and well-structured research are needed to better understand all the potential immunologic elements of jellyfish, to clarify its role in sensitization, and to avoid possible dangerous allergic reactions caused by cross-reactivity.

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Jellyfish belong to the phylum Cnidaria, and its distinctive feature is characterized by the presence of the cnida, a noticeable specialized, explosive organelle developed by the Golgi apparatus. Specialized cnidae produce penetrant “stinging cells” called nematoblasts, each one synthesizing a singular nematocyst, which allows the deposition of capsular contents or “poison” for capture of prey and for defense.^{1–3} The venom, composed of a complex mixture of nematocysts, is carried by jellyfish tubules. It is a heterogeneous blend of molecules, including imidazole acetic acid, histamine, and five hydroxytryptamines, which cause skin damage; and tetramine, which induces paralysis.⁴

Acute cutaneous effects are usually painful, linear, urticarial, or papular vesicular reactions.⁵ By contrast, chronic skin effects include localized necrosis, fat atrophy, hyperhidrosis, vasospasm, hyperpigmentation, keloids, lichenification, lymphadenopathy, and scarring.^{6,7} Pain is the first reaction, often perceived during the acute event after the sting and caused by the toxic effect of the nematocysts, in which various proteins, such as congestin, hyaluronidase, collagenase, protease, hypnotoxin, thalassin, nuclease, and phosphatase, can be present.⁴ The effects of the venom components on the skin are still not well understood; however, it is hypothesized that, besides these toxic reactions, the immune response to them is similar to any potential antigen or allergen interaction with immune system cells.⁸ Indeed, in some cases, jellyfish sting can cause allergic responses that can be immediate, delayed, and recurrent.

Thus, the purpose of this work was to collect and review the published studies and cases of anaphylaxis associated with jellyfish. We did a NLM Medline data base search for English language articles published until September 2019 by using the key words “jellyfish” associated with “anaphylaxis” or “anaphylactic shock.” The results of our search showed that dangerous reactions

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Table 1 Jellyfish reactions caused by contact and ingestion

Study, y	Type of Reaction	Risk Factors	Previous Contacts	Type of Jellyfish Scyphozoa	Other Class of Jellyfish	Type of Work	Diagnostic Examination	Geographic Area
Contact								
Togias <i>et al.</i> , ²¹ 1985	SS, DR	ND	ND	Pelagia (hypothesized)		Case report	BAT for crysaora	Greece
Kokelj <i>et al.</i> , ¹² 1995	AR, DR	ND	Many times, for several years		<i>Olindias sam-baqueinsis</i> ; Hydrozoa	Case report	Patch test; prick test; scratch-patch test	ND
Veraldi <i>et al.</i> , ¹¹ 2000	DR	ND	Several stings	ND	ND	Case report	ND	Red Sea
Kokelj <i>et al.</i> , ⁶¹ 2002	AR	ND	ND	<i>Rizostoma pulmo</i>		Case report	ND	Trieste Gulf, Italy
Oiso <i>et al.</i> , ¹⁰ 2005	DR	Surf	Several stings		<i>Porpita pacifica</i> (hydrozoa)	Case report	Identified by patient	Chiba prefecture
Uri <i>et al.</i> , ¹⁴ 2005	DR	ND	None	<i>Ropilema nomadica</i>		Case report	Identified by patient	
Tibballs <i>et al.</i> , ⁸ 2011	SS (irukandji syndrome)	ND	ND		<i>Carukia barnesi</i> and <i>Alatina mordens</i>	Review	ND	Australia but also Indopacific and Caribbean
Loredana Aszatalos <i>et al.</i> , ¹³ 2014	DR	ND	Unique contact 1 y earlier			Mini review	Skin biopsy	South Carolina
Rossetto <i>et al.</i> , ³¹ 2015	AR (covered areas of the body); DR	Longer exposure to water and more sensitive skin	ND	<i>Linuche unguiculata</i>		Case report	Clinical diagnosis	Santa Catarina, Brazil
Friedel <i>et al.</i> , ²³ 2016	SS	Surf	Recent and recurrent	<i>Ropilema nomadica</i>		Case report	ND	Mediterranean sea; Tel Aviv
Guevara <i>et al.</i> , ²⁷ 2016	DR after 8 hr and also flu like symptoms	ND	ND	<i>Linuche aquila</i>		Case report	Skin biopsy	Davao Gulf, Philippines

Table 1 Continued

Study, y	Type of Reaction	Risk Factors	Previous Contacts	Type of Jellyfish Scyphozoa	Other Class of Jellyfish	Type of Work	Diagnostic Examination	Geographic Area
Pereira <i>et al.</i> ²⁴ 2017	SS, AR	ND	ND	<i>Chrysaora lactea</i>		Case report	ND	Parana, Brazil
Ingestion								
Imamura <i>et al.</i> ⁴¹ 2013	SS, AR	Surf	Frequently stung in the past	<i>Rhopilema esculentum</i> (salted)		Case report	Prick-to-prick test, immunoblot	Japan
Inomata <i>et al.</i> ⁵³ 2014	SS, AR	Surf	Frequently stung in the past			Case report	Prick test, BAT	ND
Okubo <i>et al.</i> ⁵⁵ 2015	SS	ND	ND	<i>Cephea cephea</i> (salted)		Case report	Prick-to-prick test with C. <i>cephea</i>	ND
Li <i>et al.</i> ⁴² 2017	SS; AR (besides, after ingestion, urticaria on the body area previously stung)	ND	Severely stung (twice) 6 mo earlier	Cooked, salted, preserved jellyfish		Case report	ND	China
Kawakami and Taga, ⁴³ 2018	SS, AR	Job (fisherman)	Frequently stung	<i>Stomolophus meleagris</i> (salad)		Case report	Prick-to-prick test for S. <i>meleagris</i>	Japan
Wakiguchi <i>et al.</i> ⁵⁸ 2018	SS	ND	ND	<i>Lobonemoides robustus</i> (salted)		Case report	Skin-prick test for PGA, prick-to-prick tests with the same jellyfish and natto; oral food challenge test	Japan

SS = Systemic symptom; DR = delayed reaction; ND = no data; BAT = basophil activation test; AR = acute reaction; PGA = poly-gamma-glutamic acid.

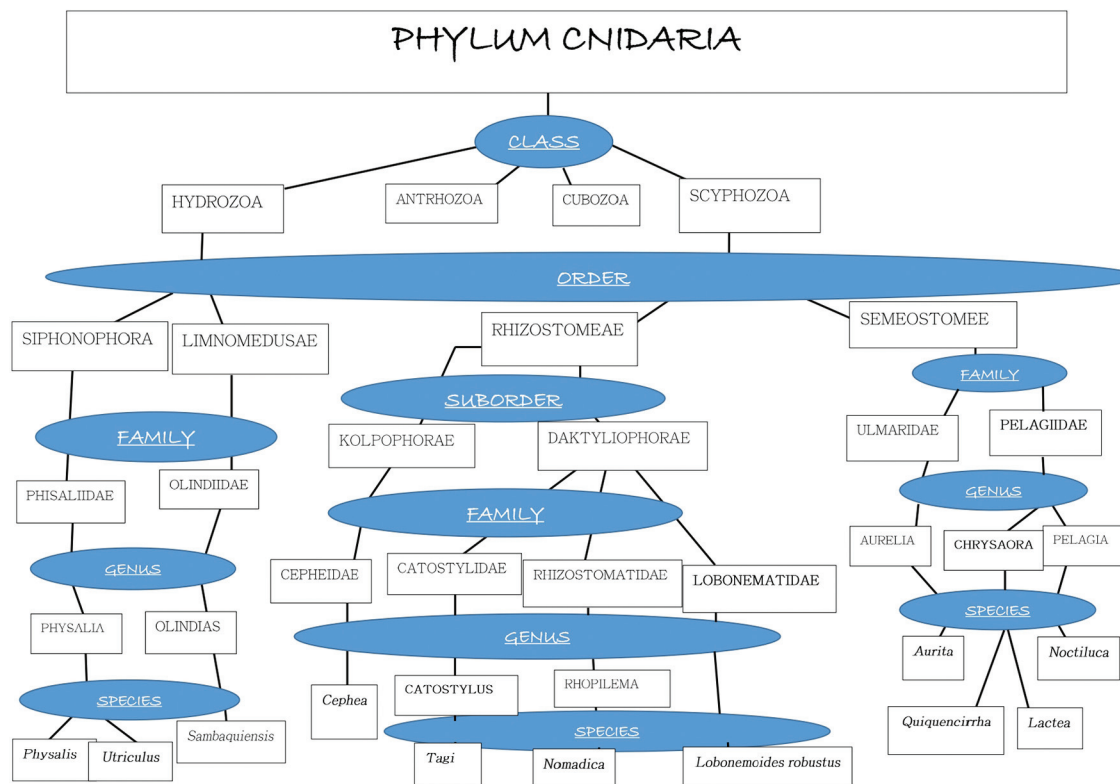


Figure 1. Taxonomy of jellyfish involved in reactions reported in this review.

can be caused by contact as much as by ingestion (Table 1) and the frequency of jellyfish anaphylactic reactions is increasing worldwide for climate and cultural changes.

DISTRIBUTION OF JELLYFISH AND ENVIRONMENTAL FACTORS

There are ~10,000 species of jellyfish, 100 of which are responsible for human poisoning. They are ubiquitous, present not only in temperate and tropical seas but also in cold waters. Analysis of recent data clearly shows that, in the past few years, the number of jellyfish species is increasing worldwide. Changes in water temperature, and sea currents, decrease of salinity and pH can be considered the main factors involved in the increase of jellyfish presence. Particularly, a higher temperature of water caused an increase of jellyfish quantity due to an extension of reproductive periods and a greater presence of flagellate populations on which jellyfish typically fed. Furthermore, the increase of water temperature has led to longer periods of warmer seasons and a change in jellyfish distribution; the result is the presence of invasive jellyfish species, with a greater potential risk of human contact.⁹ For example, in 2005, in the south of Japan, the first case of allergic contact dermatitis caused by *Porpita pacifica*, a typical jellyfish of the northern Japan, was reported.¹⁰ The taxonomy of

jellyfish involved in reactions reported in this review are shown in Figure 1.

REACTIONS CAUSED BY CONTACT

Delayed and Recurrent Reactions

Together with acute reactions to jellyfish stings, there are several cases that demonstrate a type IV allergic reaction that manifests as delayed or recurrent skin manifestations. Delayed reactions are characterized by cutaneous lesions and histopathologic findings similar to those present in allergic contact dermatitis, which occur several days after the contact with jellyfish.¹¹ In these cases, it is possible to evoke an allergic response through the application of a patch test or a scratch-patch test with jellyfish extract, as reported by Kokelj *et al.*¹²

Recurrent dermatitis is characterized by the reactivation of lesions, which may be due to an intracutaneously sequestered antigen or to a cross-reacting venom.¹³ Uri *et al.*,¹⁴ in 2005, reported a severe delayed skin reaction 2 days after envenomation by a *Rhopilema nomadica* in a patient stung while in the Mediterranean Sea. This can represent another example of the influence of rising temperatures in the Mediterranean waters because *R. nomadica*, known as the nomad jellyfish, is indigenous in tropical warm waters of the Pacific and Indian Oceans.¹⁵ However, in the past decades, it has also been identified in the Mediterranean Sea, probably migrating through the Suez Canal.^{14,16} Loredana

Asztalos *et al.*,¹³ in 2014, reported another case of delayed reaction, unique for the timing of recurrence, because it reappeared more than 18 months after a jellyfish sting.

Because of the persistence of dermatitis, a skin biopsy was performed, which showed superficial and deep dermal lymphocyte and eosinophils infiltrate. The responsible jellyfish was not identified but, through geographic location (South Carolina), it was assumed that it was one of the most common species of this area (jellyfish).¹³ The patient was successfully medicated with intralesional triamcinolone acetonide injections and tacrolimus. In another case, pimecrolimus, in association with oral levocetirizine, contributed to complete resolution of jellyfish recurrent dermatitis after 45 days of treatment.¹⁷

Anaphylaxis with Cross-Reactivity

Although most patients with stings are treated beachside and never demand hospitalization, a small proportion of victims, in particular, children (due to the larger damaged body surface), may develop systemic reactions with intense muscular pain, cardiac arrhythmias, low cardiac output, and, finally, shock. It is important to note that, since 1901, we have known of the concept of anaphylaxis because of the experiments of Paul Portier and Charles Richet on toxicity of jellyfish.¹⁸

In 1968, Gollan¹⁹ reported a case of fast collapse, with unconsciousness, pulselessness, and unreactive dilated pupils after a sting by *Physalia utriculus*. It was considered an allergic phenomenon. In 1980, Hartman *et al.*²⁰ reported elevated immunoglobulin E (IgE) levels against the nematocyst venom of the Chesapeake sea nettle (*C. quinquecirrha*) in two patients. Both patients had unusually severe reactions, but neither of them were believed to have experienced anaphylaxis. The first case of anaphylaxis induced by jellyfish after a single sting was reported in 1985 by Togias *et al.*²¹ in a 59-year-old woman.

After a previous sting, which occurred 6–7 years earlier, the patient developed a large local reaction. The second time, after a single sting on the back of knee, within a few minutes, she experienced systemic symptoms typical of a classic anaphylactic reaction. The researchers proved, by using a radioallergosorbent test, that IgE antibodies to jellyfish venom proteins were present in the patient's serum, but the exact species was not identified. The patient, who was stung while in the Mediterranean Sea, responded *in vitro* to the venom of Chesapeake Bay sea nettle (*Chrysaora quinquecirrha*), a not common jellyfish in those waters. This can be explained by a cross-reactivity between sea nettle and other kinds of jellyfish with a close morphologic resemblance more common in the Mediterranean Sea, such as *Pelagia noctiluca*.²¹ Indeed, previously,

specific cross-reacting IgE and IgG antibodies were demonstrated in 66 patients envenomated by jellyfish, such as the sea nettle and Portuguese man-of-war (*P. physalis*).²²

In 2016, Friedel *et al.*²³ reported another case of anaphylaxis after jellyfish envenomation in the Mediterranean Sea. In this case, the lesion was treated with magnesium and then with intramuscular adrenaline. The severe reaction may be due to the multiple close stings that the patient experienced in a short time during surfing.²³ The culprit jellyfish was *R. nomadica*, whose envenomation usually is mostly mild.

Another case of anaphylaxis was reported in 2017 by Pereira *et al.*²⁴ in Brazil, in a 3 year-old girl after contact with a *Chrysaora lactea* species identified on the beach. With regard to the possible molecules involved in jellyfish reaction, Lotan *et al.*¹⁶ purified a new protein from *R. nomadica* tentacles appointed as a phospholipid A2 toxin, which may explain the injurious effect of the venom on the skin as well as the systemic involvement, mainly of lungs and heart. In addition, Gusmani *et al.*²⁵ reported the presence of a hemolytic portion and chymotrypsin-like serine protease activity in the venom of *R. nomadica*.

Seabather's Eruption and Irukandji Syndrome

Special attention should be called to two nosological phenomena characterized by acute reaction and by systemic symptoms, respectively, after a jellyfish sting. One of these is a typical dermatitis called seabather's eruption. The responsible agent could be any of the three free-swimming or larval stages (ephyrae, medusae, planulae) of the "thimble jellyfish" *Linuche unguiculata*.²⁶ Although the contact with jellyfish does not cause pain, a tingling or stinging sensation may be recognized while the victim is in the water. The disease is characterized by this toxic element, followed by an immunologic involvement represented by an urticarial eruption and a dermatitis, which could last from a few days to several weeks.⁸

The larval and adult forms of the cnidarians (*L. unguiculata* and *Linuche aquila*) are caught under the swimwear and release nematocysts under mechanical pressure, which provokes cutaneous manifestations on surfaces covered by swimwear. Discharge from the stinging cells also happens when the victim washes his or her body with fresh water, which causes osmosis of the contents of the nematocysts. These pruritic erythematous papules can appear within 24 hours after exposure to seawater.²⁷ The prognosis is good, and the dermatitis could resolve spontaneously in 1 or 2 weeks, however, a severe envenomation that leads to flu-like symptoms has been reported.²⁸ The treatment could include an association of topical corticosteroids and systemic antihistamines.^{29,30}

Table 2 Trigger allergens and toxic proteins

	PGA, between 100 and 1000 kDa	Minicollagen, 60– 30 kDa	CQ-TXA 45 kDa ⁴⁷	Toxin Protein
Jellyfish class (nematocysts)	S, OC; natto bacteria	OC	OC	S, OC
Category of protein	IgE binding protein	IgG; IgG ₁ binding protein	IgG ₄ binding protein; heat stable	41 Proteins with unknown function; 27 proteins with enzyme activity; 27 structural proteins; 36 proteins associated with cell regulation
Type of reaction	Anaphylaxis	Trigger to anaphylaxis; late-phase allergic reaction	Late-phase reaction	Toxic

PGA= Poly-gamma-glutamic acid; CQ-TXA = *Chiropsalmus quadrigatus* toxin A; S= scyphozoa; OC= other class; IgE = immunoglobulin E.

The diagnosis is purely based on clinical and epidemiologic factors: most of the cases appeared while bathing in the sea; victims were predominantly teenagers, an age in which sports and the exposure time in the water are generally longer than with adults.³¹ This eruption needs to be distinguished from cercarial dermatitis or swimmer's itch, which is caused by *Schistosoma cercariae*, a species found either in fresh water or seawater, with the main symptoms represented by pruritic erythematous papules limited to exposed surfaces of the body.³² Other differential diagnoses include arthropod bites, scabies, *Pseudomonas* folliculitis, and cold and/or aquagenic urticaria.

The Irukandji syndrome, another envenomation syndrome, is characterized by discomfort, sweating, muscle spasm, serious hypertension, and, potentially, late hypotension and cardiac failure. Because of the involvement of some systemic symptoms, it must be differentiated from anaphylaxis. This syndrome has been referred to certain species of smaller, four-tentacled box jellyfish,³³ including also the carybdeid species *Carukia barnesi*.³⁴

The Irukandji sting area is usually characterized by minimal local reaction, and, after 20–30 minutes, systemic symptoms become evident, with the evolution of the syndrome over hours and/or days. Current comprehension of the underlying pathophysiology is limited. Clinically, some features of Irukandji syndrome can be caused by catecholamine excess and can be similar to the ones seen in pheochromocytoma.³⁵ The most successful therapy for Irukandji syndrome seems to be an intravenous infusion of magnesium,³⁶ which reduces both hypertension and pain.³⁷ The success of this therapy is based on the *in vivo* evidence of parasympathetic and sympathetic involvement and on catecholamine excess.³⁸

REACTIONS CAUSED BY INGESTION

Jellyfish that belong to the Scyphozoa class, are divided into four orders, of which, only the rhizostomae in the mature stage (designated as medusa) are considered edible.³⁹ The edible part is the umbrella after the digestive and reproductive tracts and edges have been removed.⁴⁰ There are reports in the literature of some cases of anaphylaxis after jellyfish intake in subjects sensitized by repeated stings.^{41–43} Surfing or any other seawater sport could represent the glaring risk factor for this kind of anaphylaxis.

The jellyfish edibility was tested by Raposo *et al*⁴⁴ through trial snacks composed of jellyfish umbrella products. These snacks were dispensed to 20 subjects with allergy (with previous systemic reaction due to crustacean, fish, and/or cephalopods sensitization) and to 21 volunteers without allergy.⁴⁴ All of them had no reaction after previous skin-prick-to-prick test with raw and boiled umbrella and, consequently, after ingestion of increasing doses of trial snacks.⁴⁴ Hypothetically, the absence of a reaction in people who were previously stung, in the Authors' opinion, could be explained because the venomous part of jellyfish is in the nematocyst, which was not present in their trial's snacks, which were mainly composed of the edible umbrella.⁴⁴ In 2018 Amaral *et al*.⁴⁵ also asserted that ingestion of the *Catostylus tagi* umbrella was safe in individuals with seafood allergy and evaluated that all the patients tolerated all the jellyfish trial pastes.

The compounds involved in seafood allergy are heat-stable high-molecular proteins represented by tropomyosin as the major allergen and by collagen type I, which is suspected of anaphylaxis and has been considered, in Japan, as a panallergen.^{46,47} This type of collagen seems not to be present in jellyfish, which,

therefore, justifies the total absence of allergic reaction to the *C. tagi* snack in patients with seafood allergy.^{48,49} In the study by Tibbals *et al.*,³⁸ an immunologic component is also attributed to the edible part of the jellyfish *Nemopilema nomurai*: the collagen extracted from the exumbrella of this jellyfish amplified IgG, IgM, interferon, and tumor necrosis factor levels by human lymphocytes.^{50,51} This type of collagen also promoted inflammatory cytokine secretion, antibody secretion, and population changes in immune cells.⁵²

The differences of the types of collagen present in these two kinds of jellyfish can be explained by the fact that they belong to different families of the same phylum of Cnidaria. For this reason, the Authors suppose that the increase of IgM, IgG, interferon, and tumor necrosis factor could be attributed only to species of *N. nomurai* and that the species of *C. tagi*, used in the preparation of trial snacks, could be free from this reaction.⁴⁵

Imamura *et al.*⁴¹ reported in 2013, a case of anaphylaxis after jellyfish ingestion in a female surfer, probably previously sensitized by skin contact. The prick-to-prick test with the same kind of salted jellyfish produced a positive reaction. The immunoblotting demonstrated that the trigger protein was a 200 kDa unknown jellyfish protein, present in an extract from tentacle and umbrella of living jellyfish and in an extract from the salted jellyfish. Another 25 kDa protein was present only in an extract from living jellyfish.⁴¹

Inomata *et al.*,⁵³ in 2014, presented a case of anaphylaxis after jellyfish ingestion in a subject allergic to fermented soybeans (natto), crab, and shrimp. This patient experienced two episodes of anaphylactic reaction 2 hours after a dinner that included jellyfish salad, which he consumed infrequently. A skin-prick test result was positive for desalted jellyfish as well as for natto and poly-gamma-glutamic acid (PGA).⁵³ PGA, a protein with a high molecular weight between 100 to >1000 kDa, is known to be a major allergen of natto, and it is also present in cnidaria nematocyst capsules.⁵⁴ Therefore, the unknown 200 kDa protein reported by Imamura⁴¹ could be the same PGA.⁵⁵ Because the patient was a surfer and had been frequently stung by jellyfish, the researchers hypothesized a sensitization to PGA through the contact.⁵⁶

Another case of anaphylactic shock by jellyfish ingestion caused by sensitization through repetitive jellyfish stings was reported by Li *et al.*⁴² in 2018. In this case, the culprit agent was a cooked, salted, preserved jellyfish.⁴² Therefore, it could be conceivable that some jellyfish allergens are heat stable. Trigger allergens and toxic proteins of jellyfish are reported in Table 2.

Another risk factor, besides marine sports, can be represented by marine job activities. In 2018, Kawakami⁴³

reported a case of anaphylaxis after ingestion of jellyfish salad in a fisherman with a history of repetitive jellyfish stings. Two more cases of anaphylaxis were reported after ingestion of two different types of dried and salted jellyfish: *Cephea cephea*⁵⁵ and *Lobonemoides robustus stiansnj*,⁵⁷ which occurred without a previous jellyfish contact or sting. In both cases, the results of prick by prick in association with an oral challenge test, performed with the offender jellyfish, were positive. Natto and PGA skin-prick test was performed only in the case of the patient in Wakiguchi *et al.*⁵⁸ and the result was negative. Therefore, these findings suggest an involvement of other allergens than PGA. Moreover, nowadays, it is known that anaphylaxis from ingestion may also occur without contact, supposing other influences and other widely used elements implicated in the adverse reactions, such as cosmetics, drug vehicles, and soft drinks.

CONCLUSION

Although the anaphylactic reactions to jellyfish are not frequent, the number of cases reported in the past years has been increasing due to various factors. In fact, during the past decades, global warming and the consequent rise in sea temperature led to an increase in jellyfish quantity and to a change in the distribution of several jellyfish species. Consequently, the greater risk of repeated stings during bathing as well as marine sports and job activities can increase the probability of sensitization and, therefore, anaphylaxis.

Moreover, recently it was also pointed out the possibility of anaphylaxis caused by jellyfish ingestion.^{41–43,53,55,58} Although jellyfish consumption has been part of the Chinese culture for centuries,³⁹ this practice has spread through the Asian continent, and it is starting to be found in Western markets. In these cases, the sensitization could also be related to previous stings; however, in the cases without a history of jellyfish contact or ingestion, it has been hypothesized that sensitization due to an unknown cross-reactive antigen, such as natto, or to nonedible substances as drugs or cosmetics.⁵⁹

Furthermore, unconscious ingestion of jellyfish, due to food contamination, may represent another risk factor for sensitization. An Italian study, identified by polymerase chain reaction five edible jellyfish species that could not be traceable in Chinese seafood products sold on Italian market without a clear labeling.⁶⁰ Nowadays changes in food habits, life style, and globalization could contribute to an increased exposure to jellyfish both by contact and ingestion, and, consequently, to a higher probability of sensitization.

Therefore, prospective studies and well-structured research are needed to better know all the potential immunologic elements of jellyfish, to clarify their role

in sensitization, and to avoid possible dangerous allergic reactions caused by cross-reactivity. As well, in beachside of jellyfish endemic areas should be useful and necessary to highlight the heightened awareness, the necessity of advanced life-support measures, and, in particular, physicians and allergists should be aware of a potential anaphylaxis caused by jellyfish.

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