Anaphylaxis in Omani Patients: A study from a tertiary care center

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Abstract

Objective: Anaphylaxis is an acute and potentially fatal allergic reaction. To the best of the author's knowledge, no studies have yet been conducted to evaluate the spectrum of anaphylactic reactions among Omani patients. As such, this study aimed to describe the clinical features, causes, investigation, and management of anaphylaxis among patients presenting to a tertiary care center in Oman.

Methods: This retrospective study took place between August 2005 and June 2020 at the allergy and immunology clinic of the Sultan Qaboos University Hospital, Muscat, Oman. All patients diagnosed with anaphylaxis during the study period were included. Data were collected from electronic medical records.

Results: A total of 100 patients were diagnosed with anaphylaxis during the study period. Of these, 52% were male. The mean age was 15.9 ± 16.2 years, with 70% being <18 years old. The eosinophil count ranged from 0–16.9×10^9/L, with a mean of $0.8 \pm 2.2 \times 10^9$/L and a median

1

of 0.30 (IQR: 0.15-0.65) $\times 10^9$/L. Total IgE levels ranged from 25–8,706 kIU/L, with a mean of 935.1 ± 1369.5 kIU/L and a median of 500.4 (IQR: 186.0-972.5) kIU/L. Overall, the majority of patients had a family history of allergies (72%), other concomitant allergic condition (66%) and were all prescribed epinephrine (100%). The most common cause of anaphylaxis was food (65%), the second most frequent trigger was insect venom (32%). The majority of patients had one category cause (81%) however two or more causes were present in 19% of the patients. Clinical symptoms manifested most frequently as cutaneous (92%), and respiratory (85%). The majority of patients (87%) demonstrated involvement of more than one bodily system. Total IgE levels were significantly higher in patients with concomitant presence of other allergic conditions 1193.8 kIU/L compared to patients without another concomitant allergic disease mean 503.6 kIU/L (p=0.03). In addition, concomitant other allergic disease is significantly higher in patients <18 years of age 75.4% compared to patients >18 years of age 45.2% (p= 0.01).

Conclusions: Due to its life-threatening nature, knowledge of the epidemiology and clinical features of anaphylaxis in different populations is necessary in order to deliver rapid treatment. This study found that the clinical features of anaphylactic patients in Oman were similar to those reported elsewhere. Further research is needed to determine the true incidence of anaphylaxis in Oman in order to minimize associated morbidity and mortality.

Keywords: Anaphylaxis; Immediate Hypersensitivity; Immunoglobulin E; Allergens; Symptoms and Signs; Epinephrine; Treatment; Oman.

Introduction

Anaphylaxis is a serious allergic reaction which develops suddenly after exposure to an allergen or trigger and can be life-threatening.[1,2] While it is usually multisystemic, severe involvement of a single system may occur. Various criteria have been developed to help identify and diagnose anaphylaxis.[3,4] The reaction is usually caused by type I immune-mediated hypersensitivity via the production of specific immunoglobulin (Ig) E and mediators released from mast cells and basophils.[5,6] Specific IgE is produced as a result of a Th2-skewed immune response and is important for crosslinking IgE receptors present on the surface of mast cells, the effector cells for type I allergies or immediate hypersensitivity-mediated reactions such as anaphylaxis. Subsequently, the mast cells release mediators responsible for the clinical features of anaphylaxis, primarily histamine, tryptase, leukotrienes, and prostaglandins.[7-9]

In children, the most common causes and triggers of anaphylaxis are foods such as cow milk, egg, fish, soy, wheat, peanut, tree nuts, and seafood; in contrast, the most frequent food triggers in adults are peanuts, tree nuts, and seafood.[10] Other non-food-related anaphylactic triggers include insect venom (i.e. following bites or stings from insects like honeybees, hornets, yellow jacket wasps, and ants), medications such as penicillin, cephalosporin, aspirin, and anesthetics, biological agents, exercise, and latex which can cause anaphylaxis during surgical procedures.[11-13] However, in some cases, the exact cause or trigger of the allergic reaction is unknown; this is referred to as idiopathic anaphylaxis.[14] Patients with anaphylaxis usually present initially to the emergency department, after which they may require further allergy evaluation; alternatively, some patients present directly to allergy or immunology clinics for evaluation and diagnosis following one or more anaphylactic episodes.

Anaphylaxis usually manifests clinically with cutaneous symptoms such as redness or flushing, urticarial rashes, and angioedema of the lips, face or limbs; moreover, the angioedema

3

may involve the tongue, throat, and larynx, thus putting the patient at risk of upper airway obstruction.[5] Other symptoms of anaphylaxis can involve the lungs, such as wheezing, severe bronchospasms, and the inability to breathe which can lead to respiratory arrest. Gastrointestinal symptoms such as cramps, abdominal pain, and vomiting may also be a sign of anaphylaxis, usually due to bowel edema, while cardiovascular symptoms can include tachycardia, hypotensive shock, and fatal arrhythmias.[5] Certain patients are at increased risk of fatal anaphylaxis because of an underlying chronic disease or risk factor, such as untreated asthma or the use of beta blockers for heart disease.[1,3]

The initial treatment of anaphylaxis consists of ensuring the airway, breathing, and circulation, followed by the administration of injectable epinephrine.[15] Up to 20% of patients develop biphasic anaphylaxis and experience a second anaphylactic episode approximately 4–6 hours after the initial episode due to a secondary allergic response; as such, most patients are usually monitored in the emergency department for 6–8 hours after treatment prior to being discharged.[16] Primary prevention is the best management option for patients at risk of developing anaphylaxis; however, as accidental exposure to allergenic agents does occur and pose a risk, pre-hospital management is recommended.[17] Once diagnosed by an allergy specialist, patients are prescribed self-injectable epinephrine.[18,19] Patients with known allergies should be instructed on the use of these autoinjector devices and carry them on their person at all times.[20] In addition to the risk of mortality, anaphylaxis constitutes a burden to the healthcare system as these patients require emergency management, observations, intensive care and outpatient care.[21]

While the spectrum of anaphylaxis is well-reported in Western countries, very few studies have sought to evaluate the manifestations, triggers, and treatment of this condition in the Middle Eastern region.[22-24] Moreover, to the best of the author's knowledge, no studies on this topic have yet been reported from Oman. As such, the aim of this study was to describe

the clinical features, causes, investigation, and management of anaphylaxis among patients presenting to a tertiary care center in Oman.

Methods

This retrospective observational study included all patients diagnosed with anaphylaxis and seen at the allergy and immunology clinic of the Sultan Qaboos University Hospital (SQUH), Muscat, Oman, between August 2005 and June 2020. The allergy/immunology clinic at SQUH is a subspecialty tertiary care clinic, patients were referred from different institutions all over the country or from the SQUH emergency department for evaluation due to a recent history of allergic reaction including anaphylaxis. During their visit to the clinic, the patients underwent routine history-taking, physical examination, and allergy testing such as the skin prick test or measurement of specific IgE levels to confirm the allergy, if necessary. In all cases, a diagnosis of anaphylaxis was made based on clinical symptoms and the degree of systemic involvement, patients with allergic symptoms and signs involving ≥ two or severe one system involvement are diagnosed with anaphylaxis as per previously published criteria.[3] Patients who did not meet the diagnostic criteria for anaphylaxis were not included in the study.

Data were retrieved from the patients' medical records and prescription history using the hospital information system. Sociodemographic and clinical information was collected, including age, sex, personal history of allergies, presence of other allergic conditions (i.e. asthma, rhinitis, or eczema), family history of allergies, total IgE level, eosinophil count, and whether the patient had been prescribed self-injectable epinephrine. In addition, the body system affected was noted based on clinical symptoms and categorized into cutaneous (urticaria, angioedema, or flushing), respiratory (wheezing, coughing, difficulty in breathing, throat itchiness, or stridor), cardiovascular (palpitations or hypotension/syncope),

gastrointestinal (vomiting, abdominal pain, or diarrhea), and central nervous system (dizziness, unconsciousness or collapse) manifestations. Finally, the cause of the anaphylaxis was classified as either food (cow milk, eggs, fish, peanuts, tree nuts, and seafood), insect venom (from honeybees, wasps, or ants), medications, latex, exercise, contrast media, or blood products. Cases in which the exact cause of anaphylaxis was unknown were considered to indicate idiopathic anaphylaxis.

The data were entered into an electronic datasheet before being exported to the Statistical Package for the Social Sciences (SPSS), version 23 (IBM Corp., Armonk, NY), for statistical analysis. The results were presented using simple descriptive statistics such as frequencies and percentages. The means and standard deviation between groups and continuous variable were compared using One-way analysis of variance (ANOVA) and the difference between categorial variables were compared using Pearson Chi-Square test. The differences were considered statistically significant if the p-value was <0.05. The study received ethical approval from the Medical Research and Ethics Committee of the College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Oman #1549 dated 8 October 2017.

Results

A total of 100 patients were diagnosed with anaphylaxis during the study period. Of these, 52% were male and 48% were female. The patients ranged in age from three months to 57 years old, with a mean and median of 15.9 ± 16.2 and 10.0 (IQR: 2.9-26.5) years, respectively. Overall, 70% of patients were <18 years of age. A personal history of allergies was reported by 66% of the patients with many patients additionally reporting allergic diseases such as asthma (43%), rhinitis (29%), or eczema (42%). A family history of allergies was positive in 72% of patients.

The eosinophil count ranged from 0–16.9 $\times 10^9$/L, with a mean of $0.8 \pm 2.2 \times 10^9$/L and a median of 0.3 (IQR: 0.15-0.65) $\times 10^9$/L. Total IgE levels ranged from 25–8,706 kIU/L, with a mean of 935.1 ± 1369.5 kIU/L and a median of 500.4 (IQR: 186.0-972.5) kIU/L. Self-injectable epinephrine was prescribed to all the patients [Table 1].

Table 1: Characteristics of Omani patients diagnosed with anaphylaxis (N = 100).

| CHARACTERISTIC	PERCENTAGE
AGE AT DIAGNOSIS (YEARS)	
MEDIAN (RANGE)	10.0 (0.25–57.4)
MEAN	15.9
SEX	
MALE	52%
FEMALE	48%
FAMILY HISTORY OF ALLERGY	
YES	72%
NO	28%
PERSONAL HISTORY OF ALLERGY	
YES	66%
NO	44%
PRESENCE OF OTHER ALLERGIC CONDITIONS	
ASTHMA	43%
RHINITIS	29%
ECZEMA	42%
EOSINOPHIL COUNT ($\times 10^9$/L)	
MEDIAN (RANGE)	0.3 (0–16.9)
MEAN	0.8
TOTAL IGE (KIU/L)	
MEDIAN (RANGE)	500.4 (25–8,706)
MEAN	935.1
PRESCRIBED INJECTABLE EPINEPHRINE	
YES	100%

In terms of clinical symptoms, the most common bodily system involved was the skin (92%), followed by the respiratory system (85%), gastrointestinal system (31%), cardiovascular system (30%), and central nervous system (25%) [Figure 1]. The majority of patients (87%) demonstrated involvement of more than one system. The most frequent cause of anaphylaxis was food (65%), followed by insect venom (32%), medications (5%), and pollen (2%). In addition, there were two cases of exercise-induced anaphylaxis and seven cases of idiopathic anaphylaxis [Figure 2]. Among patients with food-related anaphylaxis, specific

triggers included tree nuts (38%), eggs (25%), peanuts (19%), shrimp (17%), cow milk (14%), and fish (10%). For those with anaphylaxis triggered by venom, the insects responsible were primarily black ants (21%), followed by wasps (9%) and honeybees (6%).
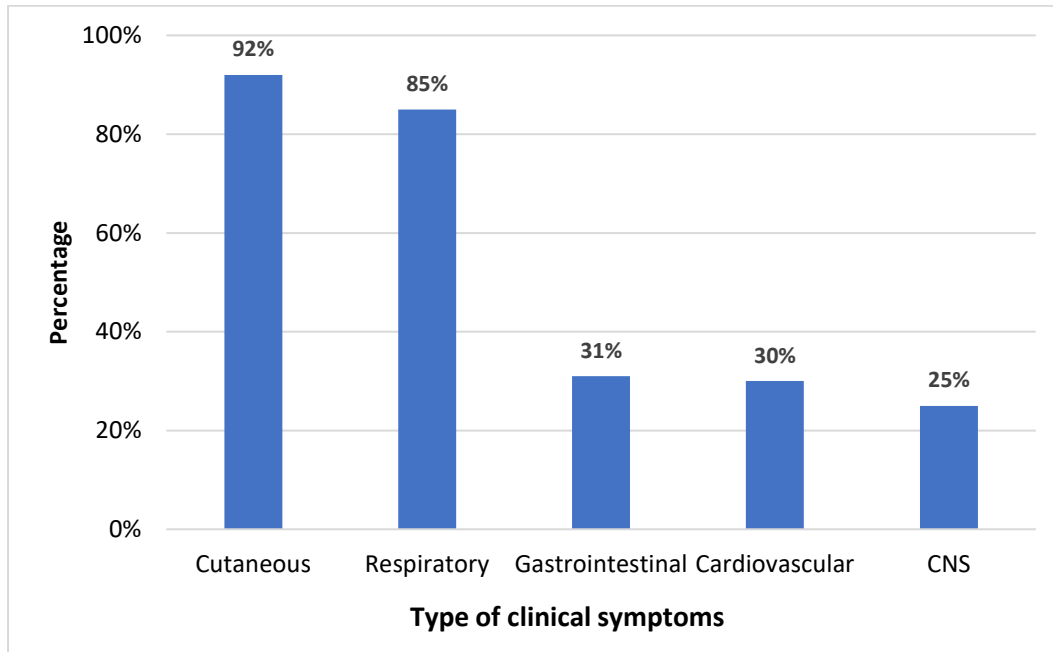
Figure 1: Systemic involvement according to clinical symptoms among Omani patients diagnosed with anaphylaxis (N = 100).

CNS = central nervous system.
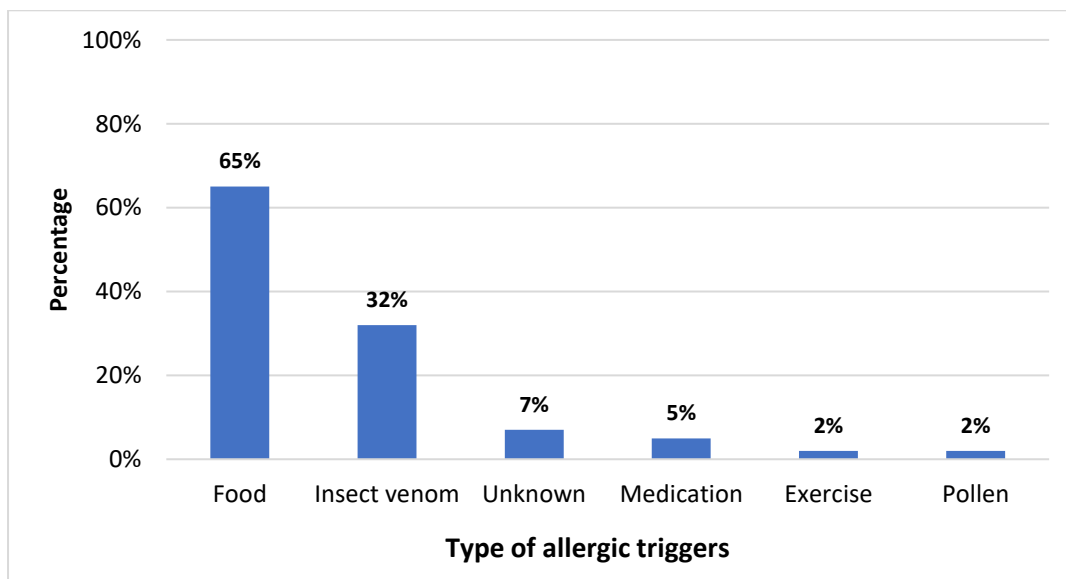
Figure 2: Anaphylactic causes or triggers identified among Omani patients diagnosed with anaphylaxis (N = 100).

In the majority of patients (81%), anaphylaxis was triggered by a single cause. However, in 12% of cases, 2–3 causes of anaphylaxis were identified, whereas the number of causes could not be determined in the remaining 7% of cases. Overall, total IgE levels did not differ considerably between patients according to number of causes of anaphylaxis [Figure 3A], single cause mean 1072.9 (188.0) kIU/L, median 510.7 (IQR: 212.8-1259.3) kIU/L, two or more cause mean 521.6 (106.3) kIU/L, median 597.6 (IQR: 82.4-810.6) kIU/L, and unknown mean 223.9 (81.5) kIU/L, median 171.0 (IQR: 66.5-379.1) kIU/L (all *p*-values >0.05). The highest values were seen in the category of single cause anaphylaxis. Total IgE levels were significantly elevated for the group of patients who also had another allergic disease, such as asthma, rhinitis, or eczema mean 1193.8 (227.1) kIU/L, median 594.4 (IQR: 239.8-1359.2) kIU/L compared to patients without another concomitant allergic disease mean 503.6 (110.0) kIU/L, median 288.6 (IQR: 109.8-615.3) kIU/L, (*p* = 0.03) [Figure 3B]. In addition, concomitant other allergic disease is significantly higher in patients <18 years of age 75.4% compared to patients >18 years of age 45.2% (*p*= 0.01).
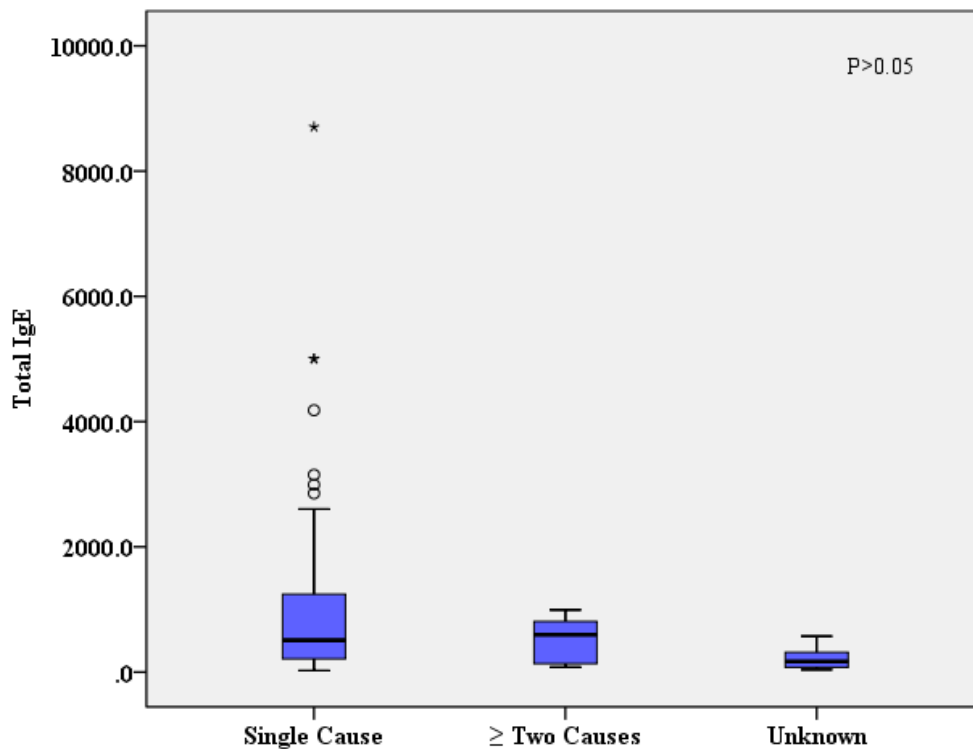
Figure 3A: The relationship between total immunoglobulin E level and number of identified allergic triggers among Omani patients diagnosed with anaphylaxis (N = 100). *Ig = immunoglobulin.*
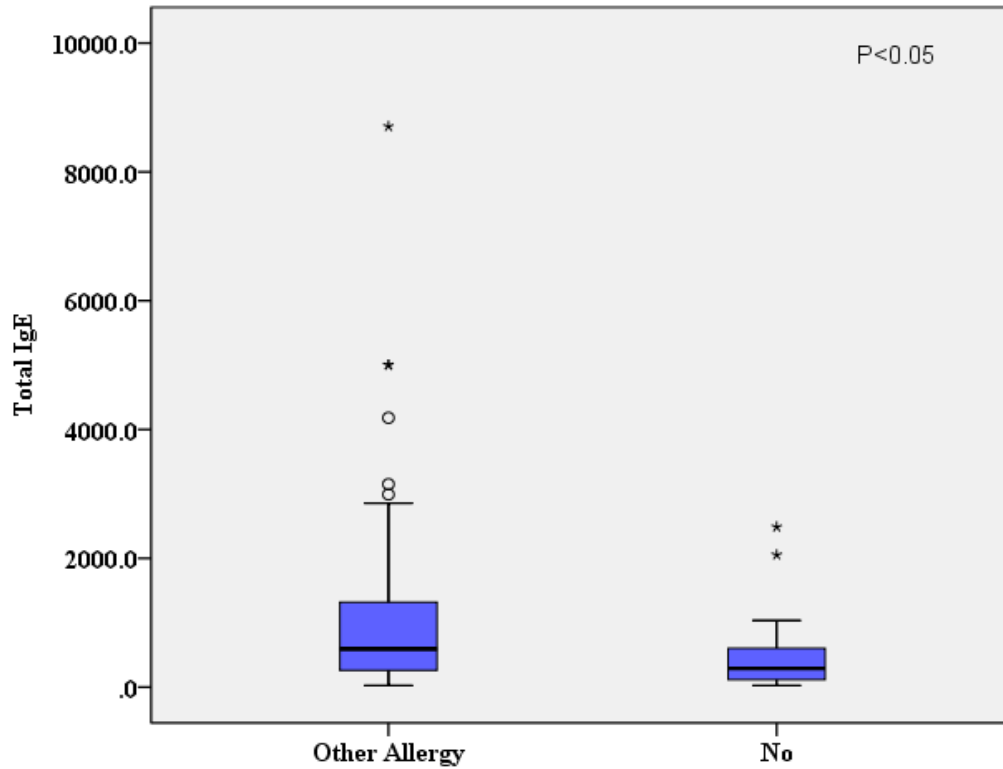
Figure 3B: The relationship between total immunoglobulin E level and the presence of other allergic condition such as eczema, asthma and rhinitis in patients with anaphylaxis (N=100). *Ig = immunoglobulin.*

Discussion

To the best of the author's knowledge, this is the first study from Oman to evaluate and describe the clinical spectrum and management of anaphylaxis. Overall, most of the patients were children or adolescents below 18 years of age and there were a similar number of male and female patients. Moreover, it would seem that the patients were highly atopic, given that the majority had a positive family history of allergies in addition to a personal history of other

allergic conditions, such as asthma, rhinitis, and eczema. These findings are to be expected given the natural history or progression of allergic diseases (i.e. atopic march).[25] Moreover, while both the mean and median eosinophil count was below the upper limit of normal, total IgE levels were elevated more so in patients who also have another concomitant allergic disease, the presence of other allergic disease is more significant in children compared to adults; this is consistent with the notion that atopy predisposes patients to allergy and anaphylaxis and the atopic march.[26]

In the current study, the commonest clinical manifestations of anaphylaxis were cutaneous symptoms in the form of urticaria or angioedema, followed by respiratory and gastrointestinal symptoms. This is in line with findings published for other populations, both in the Middle East and elsewhere around the world.[22,27,28] Nevertheless, a small proportion of our patients (8%) did not manifest cutaneous symptoms. This finding is important as a severe allergic reaction or anaphylaxis may not be suspected in the absence of cutaneous symptoms, thus delaying treatment and potentially resulting in the patient going into hypotensive shock. Indeed, up to 10% of anaphylactic patients do not show cutaneous symptoms, or may manifest such symptoms only after a delayed onset.[29] On the other hand, cutaneous, mucosal, or gastrointestinal symptoms alone are sometimes not considered sufficient for a diagnosis of anaphylaxis in the absence of other signs like respiratory compromise or cardiovascular symptoms.[4,29] A diagnosis of anaphylaxis is mainly based on clinical symptoms and associations with a known trigger; however, specific allergy testing may be required in doubtful cases, such as skin prick testing, evaluation of specific IgE levels or serum tryptase, and challenge procedures in controlled settings.[4]

Food triggers represented the most frequent cause of anaphylaxis, with specific allergens being tree nuts, eggs, peanuts, shrimp, cow milk, and fish. Similar causes of food-induced anaphylaxis have been reported elsewhere.[28] The prevalence of food allergies and

specific food triggers of anaphylaxis may vary from one country or region to another, depending on cultural variations in popular foods.[5] In general, food allergies are more common in children compared to adults, as many individuals outgrow their allergies as they get older.[30] Insect venom was the second most common causative factor of anaphylaxis in the present study; of the affected cases, black ants were the most frequent culprit. Black ants have been reported to cause significant allergy-related morbidity in other studies from the Middle East, causing both systemic and local reactions.[3,4,31] Insect bites or stings require special attention as the resulting allergies are known to be severe or even fatal, particularly as emergency services may not arrive in time before the patient goes into hypotensive shock.[3] Appropriate diagnosis and rapid intervention is therefore essential to reduce morbidity and mortality secondary to insect-related systemic allergies.

Idiopathic anaphylaxis was observed in 7% of the present cohort. Other studies have revealed that this type of anaphylaxis affects up to 20% of patients.[3,4] Idiopathic anaphylaxis represents a challenge for both the affected patient and the allergist as the causative trigger of the allergic response cannot be identified. Unfortunately, a diagnosis of idiopathic anaphylaxis precludes avoidance of the trigger; therefore, such patients need to rely solely on self-injectable epinephrine. Other types of allergic triggers were observed in fewer patients in the current study, including medications, exercise, and pollen. Medication allergies can constitute a significant diagnostic obstacle for the allergist as standardized diagnostic testing materials are seldom available, with the exception of penicillin.[32] Moreover, in the absence of a safer alternative, desensitization is the only acceptable intervention if the reaction is mediated through an IgE mechanism.[7,8]

In the present study, more than one cause of anaphylaxis was identified in certain patients, such as both food and insect venom. This is probably related to the tendency of certain patients to develop allergic diseases; indeed, while total IgE levels were similar between

patients with different causes of anaphylaxis, they were more elevated in the group of patients who also had other allergic diseases, such as asthma, rhinitis, and eczema and the highest values were seen in latest group and patient with single cause of anaphylaxis. It is well established that total IgE is widely variable among patients with allergic diseases particularly in patients with polysensitization.[33] Overall, the ideal management of allergic disease and anaphylaxis is strict avoidance of the trigger, if known; hence, an attempt should always be made to identify the culprit, particularly in difficult cases or patients with a history of allergic episodes. However, even when triggers are known, accidental exposure to the allergen can occur for various reasons, such as accidental cross-contamination in food allergies or unavoidable contact with flying insects. As such, international guidelines recommend self-injectable epinephrine as a first-line treatment or secondary prevention measure for all patients with a history of anaphylaxis.[20] In the current study, all the patients were prescribed and instructed to keep autoinjector devices with them at all times, after receiving a demonstration on how to use the device in an emergency situation.

Delays in the administration of epinephrine are associated with increased morbidity and mortality in anaphylactic patients.[34,35] As such, the use of self-injectable epinephrine as a form of pre-hospital management gives affected patients sufficient time to reach an emergency department where further management and repeated doses can be administered, alongside adjunctive therapy such as antihistamines and glucocorticosteroids.[17,34] Epinephrine decreases airway edema and smooth muscle spasms; in addition, it has inotropic and chronotropic effects which counter the effects of hypotension and shock and decreases rates of hospitalization and fatality.[34] In cases of anaphylaxis, there is no absolute contraindication to use epinephrine due to the risk to the patient's life; however, the pharmacological effect of the drug is similar to those seen with the 'fight or flight' physiological response, including tremors, anxiety, transient pallor, and palpitations.[17-19]

This study is conducted in a controlled setting where patients are highly atopic with allergy manifestation and receiving specialized diagnostic services. Furthermore the patients were referred from different governates in the country possibility reflecting the situation at large. The limitation of this study was its retrospective nature and single center; furthermore possibly not all patients presenting at primary and secondary healthcare institutions were referred.

Further research is recommended to determine the true incidence and prevalence of anaphylaxis in Oman in order to better understand the burden of the condition and to help establish initiatives to minimize associated morbidity and mortality. To this end, a multicenter study of patients presenting to emergency services would allow a better picture of the impact of anaphylaxis on the national healthcare system, while a population-based study would more accurately reflect the incidence and prevalence of this condition within the community as some patients may not present to a healthcare facility.

Conclusion

Anaphylaxis represents a life-threatening emergency for the affected patient; therefore, awareness of the epidemiological patterns and clinical features of this condition in specific populations is important to in order to establish appropriate management strategies and ensure rapid treatment. This study is the first in Oman to describe anaphylaxis in a group of patients seen at a tertiary care hospital. While the clinical features and results of the cohort were similar to those reported elsewhere in the literature, these findings establish an important baseline for future studies.

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