



Medical and pathologic characteristics of fatal anaphylaxis: a Spanish nationwide 17-year series

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Abstract

Forensic series on fatal anaphylaxis are scarce, probably because the diagnosis of anaphylaxis is often complex and the incidence is low. We report on the medicolegal, demographic and histopathological characteristics of a series of sudden deaths which were investigated for anaphylaxis at the Spanish National Institute of Toxicology and Forensic Sciences (INTCF) over a 17-year period (1998–2015). A total of 122 undetermined sudden deaths from a high percentage of Spanish regions (81.5% of the total population) were sent to the INTCF with anaphylaxis as the suspected cause of death for histological, biochemical, and medicolegal investigation. Two certified allergists confirmed that 46 of the 122 cases were fatal anaphylaxis. The results indicated a median age of 51 years (IQR = 29) and a male predominance (76%). The main causes of anaphylaxis were drugs (41%), hymenoptera stings (33%), and food (13%). A previous allergic event had been reported in both food anaphylaxis (67%) and drug anaphylaxis (53%). The deaths occurred in health care settings (37%), at home (22%), and outside the home (26.09%). Histopathology data were available for 40 individuals. The most frequent autopsy findings were angioedema of the upper airways (50%), pulmonary edema (47.5%), atheromatosis of coronary vessels (32.5%), and pulmonary congestion (27.5%). Our findings for fatal anaphylaxis indicated a predominance of men, older age (≥ 50 years) and death in a health care setting (one-third of cases). Previous episodes had occurred in two-thirds of cases of food-induced anaphylaxis and in half of the cases of drug-induced anaphylaxis.

Keywords Anaphylaxis · Deaths · Pathologic · Medicolegal · Demographic · Causes

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Introduction

Anaphylaxis is a life-threatening systemic reaction caused by immediate responses to mediators that originate in mast cells and basophils [1]. In most cases, diagnosis is based on a combination of cutaneous, respiratory and cardiovascular symptoms and signs and a known trigger [2]. Death due to anaphylaxis is a very rare event [3, 4], and cases of fatal anaphylaxis are not commonly recorded in medicolegal practice. Associated knowledge has been accumulated from administrative databases (mainly official state or regional deaths records) [5–12], forensic case series [13–22], and national registries of cases of fatal anaphylaxis developed by research groups interested in this topic [16].

Analysis of administrative data showed the incidence of fatal episodes to be 0.12 to 1.06 deaths per million person-years [3, 4]. It also showed the risk factors to be upright posture, uncontrolled asthma, tree nuts, male sex, drugs, African-American ethnicity, and older age combined with multiple comorbidities [3, 4]. Compared with research based on administrative data, research based on forensic case series of fatal anaphylaxis has enabled us to characterize the unspecific but reproducible histopathologic findings of subjects who die from anaphylaxis (edema and pulmonary congestion, hyperinflation of the lungs and/or mucus plugging, upper airway edema and sinusoidal eosinophilia in the spleen) and provided us with a better knowledge of clinical facts and etiology [13–21].

Forensic cases and cohorts based on administrative data are scarce, probably owing to the low number of cases of fatal anaphylaxis [3, 4]. We report medicolegal and histopathological data from a series of deaths due to anaphylaxis investigated at the Spanish National Institute of Toxicology and Forensic Sciences (INTCF in Spanish) between 1998 and 2015. Our data are based on slightly more than 80% of the Spanish population. Our objective was to describe the medical, demographic and histopathologic characteristics of fatal anaphylaxis to increase medicolegal knowledge of this condition.

Material and methods

Collection of cases

Fatal anaphylaxis can be considered a sudden event [23] that requires forensic assessment owing to doubts about the cause of death in the case of deaths occurring at home or in public settings or when a subject is taken to hospital but dies too quickly for a clinical assessment to be made. In Spain, autopsies of sudden deaths are carried out at the Provincial Institutes of Legal Medicine and Forensic Sciences (IMLCF in Spanish). Further investigation is carried out at the reference

laboratory of the INTCF, based on a request for immunological, biochemical, histopathological and/or toxicological assessment owing to the suspicion of anaphylaxis. A total of 122 of such cases were recorded between 1998 and 2015 from a total sample covering 81.5% of the Spanish population. The series comprised mainly extra-hospital deaths (74.93%).

Research based on several analyses was carried out according to the protocol included in the rules for sending samples to the INTCF (Official Spanish State Gazette, Ministry of Justice, BOE order JUS/1291/2010), including biological (biochemical), toxicological and histopathological studies. A previous macroscopic examination was carried out at the IMLCFs and was followed by a second examination at the INTCF. This second examination covers the assessment of symptoms and/or available clinical data followed by a second macroscopic examination of the organs and microscopic, histological, immunological and toxicological studies. Complete autopsies were performed, although special emphasis was given to the upper and lower airways (larynx, trachea and bronchi), the skin (for examination of insect stings) and the major organs (heart, lungs, liver, spleen, kidneys). Sampling was not complete in all the cases studied. Tissue sections (5–7 µm) from the paraffin blocks were stained with hematoxylin-eosin. Giemsa staining, which is commonly used to study the morphology of hematopoietic cells, was applied because of its metachromatic properties. Calcified samples were immersed in 7% nitric acid before being embedded in paraffin. An immunohistochemical analysis was not performed [24]. Microscopic and macroscopic findings were not investigated in 6 cases (13.04%). In these cases, the histological study was performed elsewhere (hospital, IMLCF). We were unable to trace the findings from these settings. Toxicology screening was carried out using high-resolution liquid chromatography, gas chromatography high-resolution liquid chromatography (HPLC), headspace (HS) gas chromatographic (GC) Flame Ionization Detector (FID) and/or Nitrogen Phosphorus Detector (NPD) and gas chromatography with a mass spectrometer. Serum from the femoral artery, peripheral venous or arterial blood, and cardiac blood was analyzed to investigate the underlying biochemistry of anaphylaxis in each case based on specific IgE, total IgE, and serum tryptase using an immunofluorescent enzyme assay (*ImmunoCAP*, *Thermo Fisher Scientific*®, Sweden). In general, the interval between sampling and processing ranged from a few hours to 72 h.

In the histological studies, the researchers looked mainly for data on pulmonary and laryngeal edema, emphysema or pulmonary hyperinflation, bronchial mucus plugs, petechial hemorrhages, visceral congestion and ischemic cardiovascular diseases [18–21].

The 122 cases were subsequently analyzed by 2 allergists (MATA and MMM) who, based on the forensic history and clinical criteria of the NIAID-FAAN Symposium [2], decided whether or not anaphylaxis was the most probable cause of

death. The *kappa* statistic was used to assess inter-rater agreement. In cases of disagreement, the final classification of the case was established by consensus. Finally, logistic regression was applied to show allergists which forensic data were more important when classifying a case as anaphylaxis or not. Tryptase values were not included in the diagnostic post-mortem model because there is no consensus in the literature on the cut-off point in cases of fatal anaphylaxis and the presence of high tryptase values in other causes of death, such as trauma, heart disease, asphyxia, drug overdose (heroin), intracranial hemorrhage and sudden infant death syndrome [25–28].

Consequently, the assessment made by the 2 allergists yielded 46 cases for analysis. Not all tests were performed in each patient, but rather they were selected on a case-by-case basis (thus yielding, for example, 40 pathology studies, 40 total IgE determinations, 34 specific IgE determinations).

The study was approved by the Research Committee and the Clinical Research Ethics Committee of University Hospital Fundación Alcorcón (number 17/103).

Statistics

Receiver operating characteristic (ROC) curves were calculated in cases of INTCF according to the classification made by 2 expert allergists, who established whether a case was anaphylaxis or not. Data are reported as median and interquartile range. Differences between qualitative data were assessed using the χ^2 test; differences between quantitative data were assessed using the Wilcoxon signed rank test and the Kruskal-Wallis test.

Results

Selection of cases

Of the original 122 cases from the INTCF database which were submitted by the forensic doctor with a request for assessment owing to the suspicion of anaphylaxis, 46 were confirmed as being fatal anaphylaxis (37.70%). The rate of agreement was 95.08%, with a kappa index of 0.90 ($p < 0.0001$). The 2 evaluators disagreed on 6 cases.

In the logistic model, the 4 positive predictors in order of strength were as follows: a) usual anaphylaxis trigger, b) positive IgE to the responsible allergen, c) suggestive symptoms and d) previous reaction to the same allergen. The presence of an alternative cause of anaphylaxis was a potent predictor for ruling out death by anaphylaxis (Table 1). The ROC analysis revealed an area under the curve (AUC) of 0.94 (0.89–0.98).

Medical and demographic characteristics

The median age at death was 51 years (IQR = 29 years), and most subjects were males ($n = 35$, 76.09%). The years with the greatest number of cases were 2003 and 2007 with 7 and 5 cases, respectively (Table 2). No cases were recorded in 1997, 2008, 2012 or 2013. The highest percentage of cases was recorded in the third quarter of each year (37.78%) and the lowest in the first quarter (13.33%). The frequency of deaths was higher than 10% in June–October, with a total percentage of cases of 62.22%. In 84.09% of cases, the subject did not live in a city (Table 2).

The most frequent comorbidities were smoking (28.26%), chronic obstructive pulmonary disease (COPD) and asthma (13.04%, each), as well as arterial hypertension and obesity (8.7%) (Table 3).

The main cause of fatal anaphylaxis was drugs (19 cases, 41.30%) and hymenoptera stings (15 cases, 32.61% and 1 additional case where the insect was not identified). Food was the third most common cause (6 cases, 13.04%) (Table 4).

In almost one-third of cases, symptoms began within 5 min, and the highest percentage of deaths occurred within the 4 first hours (52.17%) (Table 5). The deaths occurred mainly in health care facilities (17 cases, 36.96%), outside the home (12 cases, 26.09%), at home (10 cases, 21.74%) and at school (2 cases, 4.35%). Death occurred in hospital in 26.07% of cases (13). Evidence of the trigger was found near the subject in 27 cases (60.01%), as follows: drugs in 16 cases (35.56%) and insect bites in 7 (bite in 2, dead insect in 4, and the sting in 1 case). The episode was observed by witnesses in 37 cases (80.43%). The family witnessed 13 cases, health care staff 4 cases and teachers 2 cases (Table 5).

Table 6 shows the symptoms recorded in the forensic reports. The highest number of symptoms and signs was recorded for the skin and upper and lower respiratory tracts.

Table 1 Logistic regression model analyzing the predictors of anaphylaxis applied to choose the 46 cases of fatal anaphylaxis from the 122 deaths assessed in the INTCF as possible cases of anaphylaxis

Variables related to presence of anaphylaxis	Odds Ratio	P > z	95% Confidence Interval	
Suggestive symptoms	6.27	0.016	1.40	28.05
Usual anaphylaxis trigger	20.03	0.001	3.34	120.06
Positive IgE to allergen	7.02	0.025	1.28	38.47
Presence of alternative cause of anaphylaxis	.021	0.003	.002	.27
Previous reaction to the same allergen	5.15	0.029	1.18	22.52
_cons	.032	0.000	.006	.120

Table 2 Year, month and quarter of fatal anaphylaxis and places of death in the INTCF series. Data were missing in some cases

Country			Year		Month		Quarter	
	Freq.	Percent	Freq.	Percent	Freq.	Percent	Freq.	Percent
Country	37	84.09%	1998	2	4	8.89%	1	13.33%
City	8	18.18%	1999	3	1	2.22%	2	24.44%
Total	44	100.00%	2000	1	3	2.22%	3	37.78%
			2001	1	4	4.44%	4	24.44%
			2002	2	5	8.89%	Total	45
			2003	7	6	11.11%		
			2004	4	7	13.33%		
			2005	4	8	11.11%		
			2006	1	9	13.33%		
			2007	5	10	13.33%		
			2009	2	11	4.44%		
			2010	3	12	6.67%		
			2011	2	Total	45		
			2014	4				
			2015	4				
			Total	45				

Cardiopulmonary resuscitation was carried out in 84.79% of deaths, but not in 6.52% of cases, and it was unknown whether cardiopulmonary resuscitation was performed in the remaining cases. In the forensics reports, the most widely reported drugs used during the anaphylaxis episodes were adrenaline (28.26%), atropine (21.74%) and corticosteroids (15.22%) (Table 7).

Pathology findings

Pathology findings were reported in 40 subjects (86.96%, Table 8). The most frequent findings in the autopsies involved the lower respiratory tract with pulmonary edema (19, 47.5%), pulmonary congestion (11, 27.5%), asthma findings (7, 17.5%) and emphysema (6, 15%). Angioedema affected various parts of the upper respiratory airways (tonsils, oropharynx, glottis, epiglottis, larynx) in 20 cases (50%). Involvement of the cardiovascular system included 14 cases of atheromatosis of non-coronary vessels (35%), 13 cases of

atheromatosis of coronary vessels (32.5%) and 12 cases of cardiac hypertrophy (30%). Five cases of hepatic steatosis (12.5%) and 4 cases of visceral congestion (10%) were also found (Table 8 and Fig. 1). Coronary atheromatosis was severe (stenosis >75%) in 7 out of 13 cases. Five cases out of the 12 with cardiac hypertrophy were characterized by increased heart weight (>500 g).

Laboratory tests

Testing for drugs, toxins and illicit substances was performed in 25 different cases from the INTCF. An average of 1.61 tests per subject (± 0.96 SD) was performed for a total of 47 tests (37 individual drugs).

Specific IgE was measured in 34 cases. A total of 119 specific IgE tests were performed for 25 different allergens, with an average of 4.8 ± 5.35 tests per case. The most frequently tested allergens were vespid (17), *Apis* species (13), amoxicillin (15), penicillin V (8) and penicillin G (9). Specific IgE values were positive (>0.35 kU_A/L) according to the manufacturer's recommendations in 15/35 cases (55.88%). Mean (SD) total IgE in serum was 338.54 ± 524.96 IU/L for 40 cases. The mean tryptase value was 120.62 ± 77.62 µg/L (measured in 41 subjects).

Differences between the main causes of fatal anaphylaxis

Few differences were noted between the 3 main causes of anaphylaxis (food, hymenoptera and drugs). Subjects with food anaphylaxis were younger ($p = 0.0001$) and more often had asthma ($p = 0.019$) than subjects with hymenoptera and drug anaphylaxis, although COPD ($p < 0.001$) was more frequent among individuals with drug anaphylaxis.

Table 3 Atopic and non-atopic comorbidities reported in the 46 cases of fatal anaphylaxis in the INTCF series

Illness	Freq.	Percent
Food allergy	5	10.87%
Asthma	6	13.04%
Drug allergy	12	26.09%
Penicillin allergy	2	4.35%
Allergy to other non-betalactam antibiotics	2	4.35%
NSAID hypersensitivity	3	6.52%
Rhinitis of any cause	2	4.35%
COPD	6	13.04%
Congestive heart failure	1	2.17%
Ischemic heart disease	1	2.17%
Arterial hypertension	4	8.70%
Diabetes	3	6.52%
Hyperlipidemia	1	2.17%
Obesity	4	8.70%
Smoking	13	28.26%

Table 4 Causes of the 46 cases of fatal anaphylaxis in the INTCF series

	Cause of anaphylaxis		Freq.	Percent	
		Drugs	19	41.30%	
		Hymenoptera	15	32.61%	
		Food	6	13.04%	
		Two or more causes	4	8.70%	
		Insect bite	1	2.17%	
		Unknown	1	2.17%	
		Total	46	100.00%	
Culprit drug	Freq	Percent	Culprit food	Freq	Percent
None	25	54.35%	None	41	91.11%
Betalactams	12	26.09%	Hen egg	2	4.44%
Amoxicillin	2	4.35%	Shellfish	1	2.22%
Amoxicillin-clavulanic acid	9	19.57%	Cow milk	1	2.22%
Cefonicid	1	2.17%	Hen egg/cow milk	1	2.22%
Other antibiotics	4	8.70%			
Moxifloxacin	1	2.17%			
Ciprofloxacin	1	2.17%			
Clarithromycin	1	2.17%			
Erythromycin	1	2.17%			
NSAID	6	13.04%			
Ibuprofen	2	4.35%			
Acetylsalicylic acid	1	2.17%			
Metamizole	1	2.17%			
Propyphenazone	1	2.17%			
Paracetamol	1	2.17%			
Diagnostic agents (fluorescein)	1	2.17%			
2 or more drugs involved	5	10.87%			
Aspirin/metamizole	1	2.17%			
Betamethasone/diprophylline	1	2.17%			
Guaifenesin/Dexamethasone					
/Cefonicid					
Amoxicillin-clavulanic acid/ibuprofen	1	2.17%			
Bronchodilators/amoxicillin- clavulanic acid	1	2.17%			
Ciprofloxacin/methylprednisolone/ranitidine/paracetamol	1	2.17%			
Total	46		Total	46	

Pathology findings did not differ between the main causes of anaphylaxis (lower respiratory tract, $p = 0.34$; upper respiratory tract, $p = 0.25$; and cardiovascular system, $p = 0.25$).

A very interesting finding was that in each case of fatal anaphylaxis (food, hymenoptera, drug), the individual had previously experienced allergic episodes related to the same trigger (Table 9).

Table 5 Temporal characteristics, place of death and witnesses of the 46 cases of fatal anaphylaxis in the INTCF series

Time of onset of symptoms	N	%	Time to death after onset of episode	N	%
< 5 min	15	32.61%	<1 h	7	15.22%
16–30 min	1	2.17%	1–4 h	15	32.61%
31–60 min	3	6.52%	24 h	1	2.17%
1–2 h	5	10.87%	360 h	1	2.17%
Several hours (undetermined)	5	10.87%	Not reported	15	32.61%
Not reported	17	36.96%	Total	46	100.00%
Total	46				
Place of death	Freq.	Percent	Evidence found close to the subject	Freq.	Percent
Health care setting	17	36.96%	Drugs	16	35.56%
Hospital	12	26.07%	Insects	7	15.56%
Non-hospital	5	10.86%	Food	4	8.89%
Home	10	21.74%	Not reported	19	41.30%
School	2	4.35%	Total	46	100.00%
Not at home	12	26.09%			
Not reported	5	10.87%			
Total	46	100.00%			
Witness	Freq.	Percent			
Family	11	23.91%			
Family and health professionals	2	4.35%			
None	2	4.35%			
Not reported	7	15.22%			
Health professionals	2	4.35%			
Teachers	2	4.35%			
Other	20	43.48%			
Total	46	100%			

Table 6 Symptoms and signs of the 46 cases of fatal anaphylaxis in the INTCF series

Muco-cutaneous symptoms and signs			Cardio-vascular symptoms and signs		
	Freq.	Percent		Freq.	Percent
Tongue angioedema	2	4.35%	Bradycardia	2	4.35%
Angioedema	7	15.22%	Not reported	34	73.91%
Mucosal angioedema	4	8.70%			
Cyanosis	13	28.26%			
Petechiae	5	10.87%			
Pruritus	2	4.35%			
Bites	5	10.87%			
Total	36	78.26%			
Not reported	15	32.61%			
Lower airway symptoms and signs			Upper airway symptoms and signs		
	Freq.	Percent		Freq.	Percent
Dyspnea	11	23.91%	Dyspnea	3	6.52%
Wheezing	5	10.87%	Stridor	2	4.35%
Pulmonary edema	8	17.39%	Secretions	5	10.87%
Apnea	3	6.52%	Blood	3	6.52%
Total	26	56.52%	Total	13	28.26%
Not reported	19	41.30%	Not reported	30	65.22%
Digestive symptoms and signs			Neurologic symptoms and signs		
	Freq.	Percent		Freq.	Percent
Food in digestive tract	2	4.35%	Syncope	9	19.57%
Stomach pain	1	2.17%	Seizures	2	4.35%
Vomiting	3	6.52%	Total	11	23.91%
Nausea	1	2.17%	Not reported	35	76.09%
Diarrhea	1	2.17%			
Total	12	26.09%			
Not reported	26	56.52%			
Total cases	46				

No differences were found between the 3 causes in terms of gender, duration of episodes, diseases related to cardiovascular risk, ischemic heart disease and the remaining autopsy findings (Table 9). However, significant differences with respect to age were found for food versus hymenoptera ($p < 0.001$) and food versus drugs ($p < 0.001$). Even though the analysis of variance did not reveal statistical differences in post-mortem serum tryptase levels, values for tryptase in deaths due to hymenoptera or drugs were more than double those of deaths due to food.

Discussion

Post-mortem findings

The post-mortem findings for fatal anaphylaxis are non-specific and vary considerably, although many or all of them are reported in published series (Table 10). In almost all studies, pulmonary edema and congestion are the most frequent histological findings (50–70%), followed by upper airway edema (30–70%). Pulmonary edema and congestion also appear in other types of

Table 7 Treatments used in the 46 cases of fatal anaphylaxis in the INTCF series

Cardio-pulmonary resuscitation			Treatment		
	Freq.	Percent		Freq.	Percent
Basic	32	69.57%	Adrenaline	13	28.26%
Advanced	7	15.22%	Atropine	10	21.74%
Unknown	2	4.35%	Corticosteroids	7	15.22%
None	3	6.52%	6-Methylprednisolone	5	10.87%
Not reported	2	4.35%	Bicarbonate	3	6.52%
Total	46	100.00%	Amiodarone	2	4.35%
			Salbutamol	2	4.35%
			Tracheostomy	2	4.35%
			Vasoactive drugs	2	4.35%
			Cardioversion	1	2.17%
			Plasma expanders	1	2.17%
			Lidocaine	1	2.17%
			Liquids	1	2.17%
			Muscle relaxants	1	2.17%
			Omeprazole	1	2.17%
			Other general anesthetics	1	2.17%
			Physiologic saline	1	2.17%
			Total treatments	54	
			Total cases	46	

Table 8 Pathology findings for 40 cases of fatal anaphylaxis in the INTCF series. Only findings with a frequency of >5% are reported

	N	%		N	%
Lower airway			Upper airway		
Pulmonary edema	19	47,50%	Not reported in 46 subjects	21	52,50%
Pulmonary congestion	11	27,50%	Angioedema affecting upper airways	20	50,00%
Asthma	7	17,50%	Angioedema of the glottis	14	35,00%
Emphysema	6	15,00%	Congestion affecting several sites in the upper airways	8	20,00%
Not reported	6	15,00%	Angioedema of the epiglottis	7	17,50%
Bronchial mucus plugs	5	12,50%	Laryngeal angioedema	5	12,50%
Chronic bronchitis	5	12,50%	Upper airway secretions	5	12,50%
Anthraxis	4	10,00%	Pharyngeal angioedema	4	10,00%
Eosinophils in the bronchial mucus	4	10,00%	Subglottic angioedema	4	10,00%
Eosinophils in bronchial wall	3	7,50%	Blood in the upper airways	3	7,50%
Food aspiration in the lungs or bronchi	3	7,50%	Total subjects	40	100,00%
Hyperplasia of goblet cells	3	7,50%			
Lymphocytic infiltrate	3	7,50%	Cardiovascular system		
Smoker's macrophages	3	7,50%	Not reported	15	37,50%
Pleural adhesions and bilateral calcified pachypleuritis	3	7,50%	Atheromatosis of non-coronary vessels	14	35,00%
Basal membrane thickening	3	7,50%	Atheromatosis of coronary vessels	13	32,50%
Tracheal congestion	3	7,50%	Cardiac hypertrophy	12	30,00%
Total	40	100,00%	Ischemic heart disease (necrosis)	4	10,00%
			Total	40	100,00%
Brain			Digestive system		
Not reported	22	55,00%	Not reported	28	70%
Total for all neurologic findings	6	15,00%	Hepatic steatosis	5	12,5%
Cerebral edema	3	7,50%	Visceral congestion	4	10%
Cranial and cervical congestion	1	2,50%	Food in the digestive tract	2	5%
Encephalopathy	1	2,50%	Blood (various sites)	2	5%
Previous cerebral infarct	1	2,50%	Total	40	100,00%
Cortical atrophy	1	2,50%			
Total	40	100,00%			

shock and reflect the hypoxia associated with the anaphylaxis episode [14]. Mucus plugs and areas of emphysema or hyperinflation have also been described, although at lower percentages (11.7–28.6%) [12–21, 23]. Coronary atheromatosis has been reported in a significant percentage of cases (4–41%), probably because of the high number of older subjects dying of anaphylaxis [12, 21]. In addition to other factors, this helps to explain the severity of anaphylaxis episodes. Cerebral edema has also been described (6.5%–25%) [23] as a proxy of cerebral ischemia and petechial hemorrhage as a manifestation of asphyxia as the cause of death (8.33–26.1%) [12–21, 23].

In our study, the most frequent manifestations were upper airway edema (50%), pulmonary edema (47.5%) and arteriosclerotic coronary findings (32.5%). Percentages for the remaining manifestations were similar to the intermediate values reported in the literature.

According to Pumphrey and Roberts [16], the post-mortem examination did not reveal macroscopic findings of anaphylaxis in up to 50% of fatal cases. The authors even stated that the real proportion of fatal anaphylaxis with negative findings at necropsy is likely higher, because the probability of identifying deaths as anaphylactic is greater when recognizable features are present.

Demographic and medical investigation

The mean age of the subjects in our series (51.88 years) was similar to that reported in other studies, where the mean or median age was above 50 years [15–17, 19]. However, we found that age was surprisingly low in some studies: Yilmaz et al. [20] in Turkey and Shen et al. [21] in China found the mean age to be 26.7 and 31 years, respectively. These differences can be explained by the higher proportions of young people in the countries where the studies were performed.

In our series, three-quarters of fatal anaphylaxis cases involved men. Similarly, in the study of Ma et al. [12], fatal anaphylaxis more commonly affected males. In other studies [8, 28], increased risk is restricted to specific causes of anaphylaxis. However, elsewhere, this relationship was not observed [9]. Simon and Mulla [8] and Jerschow et al. [29] found an increased risk for insect-induced anaphylaxis, since men are more frequently involved in outdoor activities and are therefore more exposed to hymenoptera. In other cases, these deaths can be attributed to more marked comorbidity in men than in women.

In line with other series, we found the 3 most frequent causes to be drugs (28% to 57%), hymenoptera (22% to 33%) and food (11% to 35.3%). The presence of drugs and hymenoptera as the main causes of fatal anaphylaxis can be

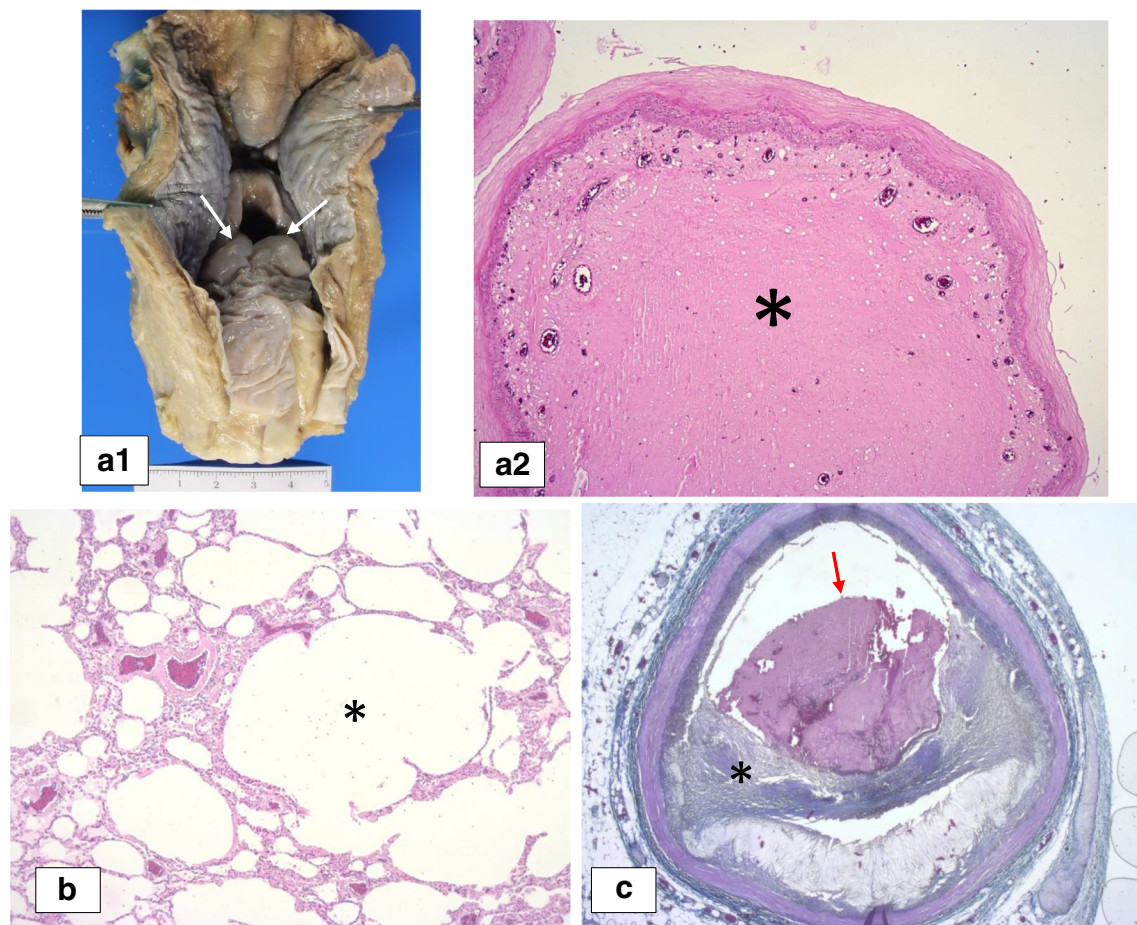


Fig. 1 **a** Macroscopic view (A1) and microscopic view (A2) of edema of the glottis (**white arrows**) from a 54-year-old man with rapid fatal anaphylaxis after being stung by multiple wasps. **A2**: Microscopic detail of the aryepiglottic fold, with abundant acidophilic substance (**asterisk**) in the lamina propria (H&E, $\times 50$). **b** Foci of overinflation in the lung (**asterisk**) of a 47-year-old man who experienced 2

hymenoptera/insect stings over a 2-week period (H&E, $\times 50$). **c** Micrograph of acute thrombosis (**red arrow**) over fibroatheroma plaque (estimated 70% stenosis) (**asterisk**) as an example of allergic acute coronary type-II Kounis syndrome (same case as B) (Masson's Trichrome $\times 25$)

explained by the fact that both causes are more common in older subjects. Drugs in particular have been associated with severity of anaphylaxis [30–32].

Mechanisms of death were reported in 6 studies. Shock was the mechanism in almost 50% of cases of fatal anaphylaxis in several series [14–20], and cardiovascular syncope was the cause in 17.9% of deaths due to drugs and 30% of deaths due to venom in the series of Mullins et al. [10]. Respiratory causes were reported in 15.5%–81.2% of deaths [16–18]. In the series of Greenberger et al. [16], respiratory distress was present at the beginning of the anaphylaxis episode in 68% of individuals and circulatory collapse in 56%. In the series of Low and Stables [19] and Yilmaz et al. [20] the deaths did not occur immediately (16.7% and 13.9%, respectively), and the mechanism was ischemic brain injury. In other words, shock is a very relevant mechanism in deaths due to hymenoptera anaphylaxis and drug anaphylaxis. In the series of Pumphrey and Gowland [7], the predominant mechanism

in deaths due to food was respiratory events. This information was not collected in the INTCF database.

In contrast with cases of anaphylaxis where subjects survive, the percentage of subjects with skin symptoms is low. The most frequent signs are angioedema (3.85%–5.5%) [17, 20] and generalized skin involvement (17.65%) [21]. In our study, the forensic doctors reported cyanosis in 28.26% of cases and cutaneous angioedema in 15.22%.

Circulatory collapse has been recorded in 7.7% [17] to 56% of cases in several series [8, 12, 16]. In our series, syncope was reported in 19.57% of cases. Asphyxia was reported in 7.1–7.7% of cases by Mosbech [17] and Shen et al. [21]. The signs we observed were upper dyspnea (6.52%), secretions (10.87%) and inspiratory stridor (4.35%). Mosbech [17] reported cough and chest pain in 3.8% of cases, while Greenberger et al. [18] reported respiratory distress in 68% of cases. Shen et al. [21] reported dyspnea in 53.6% of cases.

Table 9 Clinical and demographic differences in the 46 cases of fatal anaphylaxis in the INTCF series

Demographic data	Food		Hymenoptera		Drugs		p (chi2)
	N	%	N	%	N	%	
Males	5	83.33	12	80	12	70.59	0.747
Age	Mean	Std- Dev	Mean	Std- Dev	Mean	Std- Dev	ANOVA
Differences (p) between groups (Scheffe)	19	24	55	15	58	15	0.0001
Tryptase	Food-hymenoptera	<0.001	Food-drugs	<0.001	Drugs-hymenoptera	0.898	0.14
	53.20	84.03	131.98	72.44	11.-05	74.28	
	Food-hymenoptera	<0.14	Food-drugs	<0.31	Drugs-hymenoptera	0.79	
Comorbidities	Food		Hymenoptera		Drugs		p (chi2)
	N	%	N	%	N	%	
COPD	0	0	0	0	6	35.29	<0.001
Asthma	3	50	0	0	0	0	0.019
Diabetes	0	0	1	6.67	2	11.76	0.174
Cerebral stroke	0	0	0	0	0	0	
Arterial hypertension	0	0	1	6.67	2	11.76	0.174
Obesity	0	0	2	13.33	2	11.76	0.169
Smoking	0	0	5	33.33	6	35.29	0.164
Hyperlipidemia	0	0	1	6.67	0	0	0.092
Previous allergic diseases	Food		Hymenoptera		Drugs		p (chi2)
	N	%	N	%	N	%	
Hymenoptera	0	0	4	26.67	0	0	0.032
Asthma	3	50	0	0	0	0	0.019
Rhinitis	2	33.33	0	9	1	5.88	0.019
Previous anaphylaxis	1	16.67	0	0	0	0	0.018
Drug allergy	0	0	0	0	9	52.94	<0.001
Food allergy	4	66.67	0	0	0	0	<0.001

The values we recorded were lower: dyspnea in 22% of cases, wheezing in 11.1% and pulmonary edema in 17.39%.

In our series, asthma and COPD were each present in 13.04% of cases of fatal anaphylaxis; 28.26% of subjects were smokers, and 8.7% had arterial hypertension. Mosbech et al. [17] reported previous cardiovascular diseases in 19.2%, arterial hypertension in 7.7% and asthma in 3.84%. Greenberger et al. [18] found the percentage of comorbidities to be higher, with ischemic heart disease in 44% of cases, congestive heart failure in 16%, arterial hypertension in 8% and COPD in 25%. However, the previous presence of atopic diseases or previous hypersensitivity to the fatal allergen is more frequently reported; the frequency of asthma ranges from 3.6% to 85% of cases [13, 14, 16, 18, 21]. It seems that the lowest percentage of atopic comorbidity appears in series where anaphylaxis is not related to atopy (for instance drugs and hymenoptera), while percentages higher than 10% appear in series with anaphylaxis related and not related to atopy. In the study of Pumphrey and Roberts [15], a relevant percentage of asthma was not controlled.

In our series, 36.96% of deaths were in a health care setting and 12 cases in a hospital, while 21.74% of deaths were at home. Most cases were in a rural environment (81.8%). In other series, the frequency of hospital deaths ranged from 44% to 50% [14, 18], that of deaths in a health care setting was 83.35% [14, 19] and that of deaths in a private residence ranged from 22.7% to 48% [18, 19]. Finally, Mullins et al.

[10] reported fatal anaphylaxis due to stings occurring at home in 18.2% of cases and on a farm in 21.2%, whereas food anaphylaxis occurred at home in 20.8% of cases and outside the home in 68.1%. Drug anaphylaxis occurred more in health care facilities than at home (70.24% vs 15.48%). Therefore, many cases of anaphylaxis were in a health care setting (35% to 83.3%), probably because of the more frequent administration of drugs and the fact that people attended in these settings are in poor health. Deaths due to stings are expected to occur in rural settings, as confirmed by the percentages reported. Finally, Mullins et al. [10] reported how fatal anaphylaxis caused by food was 3 times more common outside the home than at home. The findings of a Brazilian series showed that hospital cases were 3-fold more frequent than forensic cases [11]. Consequently, at least in some countries, many deaths due to anaphylaxis in the hospital system did not undergo forensic or legal assessment.

Differences between the main causes of fatal anaphylaxis

Consistent with Mullins et al. [10], we found a predominance of males in drug and food anaphylaxis. However, in other studies, females were predominant in food and drug anaphylaxis [7, 19]. In all studies, deaths due to venom-induced anaphylaxis were more frequent in males.

Table 10 Pathologic findings in the different published series. ICD-8, International Classification of Diseases 8th edition

Author	Criteria for death due to anaphylaxis	Upper airway edema	Pulmonary congestion	Pulmonary edema	Pulmonary hyperinflation and mucus plugging
Delage [14] 1972	Clinical and pathologic records	Laryngeal edema 37.5%	90%	50%	Emphysema 5%
Mosbech [17] 1983	ICD-8 codes, records of hospital admissions, general practitioners, police		11.54%	15.38%	Areas of emphysema and collapse 11.75%
Pumphrey [16] 2000	Text strings in the clinical records, tryptase tests of reference laboratory, pathology records, police, anonymous, several people		73%	Hyperinflation/Mucus plugging 26.79%	Hyperinflation/Mucus plugging 26.79%
Greenberger [18] 2007	Algorithm with different combinations of clinical and pathology findings		78%		Hyperinflation 13.64%
Low [19] 2006	Algorithm with different combinations of clinical and laboratory findings and lack of alternative cause of death	Laryngeal edema 40%	72%		
Yilmaz [20] 2009	Algorithm with combination of clinical findings, known trigger and lack of alternative cause of death	28.2%	80.5%		Hyperinflation 13.64%
Shen [21] USA 2009	Algorithm with combination of clinical and pathology findings, known trigger and lack of alternative cause of death	Pharyngeal edema 29.41%	100%		Emphysema 28.57%
Shen [21] China 2009	Algorithm with combination of clinical and pathology findings, known trigger and lack of alternative cause of death	Pharyngeal edema 81.81%	100%		50%
Xu [23] 2014	Criteria of forensic scientists and researchers not provided	Upper airway edema (46%),	Pulmonary congestion and/or edema (60%),		Mucus plugging of bronchi and/or hyperinflation (17%),
Mullins [10] 2016	Assessment of 3 allergists	Pharyngeal edema 11.56			Emphysema and hyperinflation 13.04%
Martínez-Fernández 2019	Assessment of 2 allergists using criteria of NIAID-FAAD [2]		13.04%	32.61%	
Author	Mucus plugging	Arteriosclerotic vascular disease	Brain edema	Eosinophilic infiltration	Skin
Delage [14] 1972				Splenic 22.5%	
Mosbech [17] 1983		Coronary atheromatosis 3.85%			Facial edema 3.85%
Pumphrey [16] 2000	Plugging 4.35%				Petechial hemorrhage 26.09%
Greenberger [18] 2007					
Low [19] 2006					
Yilmaz [20] 2009	Plugging 5.88			Gastro-intestinal tract 29.4%	Cutaneous edema 5.5%
Shen [21] USA 2009	Plugging 90.91%			Respiratory tract 58.82%	Petechial hemorrhage 8.33%
Shen [21] China 2009				Gastro-intestinal tract 27.7%	Erythema skin rash 17.65%
Xu [23] 2014		Brain edema (15%)		respiratory tract 90.9%	
Mullins [10] 2016	Mucus 10.87%		Brain Edema 6.42%	Petechial hemorrhage (14%),	
Martínez-Fernández 2019				Acute myocardial infarct 13.6%	
				In the spleen (2.17%)	Cutaneous angioedema (15.22%)

A review of series of fatal anaphylaxis reveals that younger people died more often because of food anaphylaxis. The difference between this group and persons aged 35–40 years was considerable, except for the study of Low and Stables [19], where the age difference was very similar, even for food anaphylaxis. The cause of food anaphylaxis in this study was seafood. These findings are common and can be explained by the higher presence of food anaphylaxis in the first 2 or 3 decades of life.

In our study, the prevalence of asthma (50%) and rhinitis (33.3%) was higher in fatal food anaphylaxis than in the remaining causes, probably because of the greater presence of other atopic diseases in subjects with food allergy. However, COPD was more frequent in drug allergy (35.29%) than other causes. In 6/7 cases of COPD (85.71%), the drugs involved were antibiotics, thus potentially reflecting the increased use of antibiotics in these subjects. Findings for ischemic heart disease were reported in the series of Low and Stables [19] and in ours. However, despite the fact that we found differences to be non-significant between the 3 main causes, more subjects who died from drug anaphylaxis had ischemic heart disease, probably because of more frequent use of drugs and comorbidities in older subjects with cardiovascular disease.

Previous allergic diseases have been studied in several series. We found that all the main causes of anaphylaxis involved previous episodes of allergic reactions with the same triggers (venom, 26.7%; drugs, 52.94%; food, 66.7%). The frequency of a previous reaction to the trigger that induced fatal anaphylaxis ranged in other publications from 50% [17–19] to 63% [13] and 100% [12, 16, 19]. The percentage of subjects with a previous allergy to the same food ranged from 50% [18, 20, 22] to 90–100% [12, 16, 19], although with a very low number of cases (2 to 6), except in the studies of Mullins et al. [10], Pumphrey and Roberts [16] and Xu [22]. In our study, 66.67% of subjects who died from food anaphylaxis had previously experienced a food allergy event, although, again, the number of cases was small [8]. Delage and Irely [14] reported on the presence of prior exposure or generalized reactions to the drug that triggered fatal anaphylaxis: in 69% of deaths caused by penicillin, the subject had previously been exposed to the drug, and in 22.7% of cases the subject had had a previous reaction to penicillin. Mullins et al. [10] reported the presence of previous allergy to penicillin or cephalosporins in 5.9% and 4.8% of all cases of anaphylaxis due to drugs. Pumphrey and Gowland [7] reported a history of drug allergy in 100% of cases, mainly with antibiotics (50% antibiotics, 62.5% general anesthetics/inducers). Other authors reported lower percentages: Greenberger et al. [18] reported 28.6% (penicillin, radiocontrast agent) and Shen et al. [21] 17.7%. In our study, a previous history of drug allergy was identified in 52.94% of deaths due to drugs.

This percentage is one of the highest recorded for cases of previous drug allergy. The differences between studies may be due to differences in the prevalence of triggers or in the methodologies used to collect information. The presence of prior hymenoptera allergy has been reported in several studies [17–19] and Mullins et al. [10] reported values ranging from 7%–14% to 75%, although the number of cases was very low. In our study, prior hymenoptera allergy was not collected in the reports of the forensic doctors. In other series of clinical-administrative data from admitted subjects [9], the peaks of incidence of each major cause of anaphylaxis were observed in 1 or more years before the peaks of the deaths due to anaphylaxis by the same causes. In summary, the data show that in cases where significant proportions of subjects died from anaphylaxis, these subjects had had previous allergic reactions to the fatal trigger.

Diagnosis: a difficult task

A possible limitation of our study is the lack of specifically designed medicolegal criteria for the diagnosis of fatal anaphylaxis. Similarly, to our knowledge, such criteria neither have not been applied elsewhere [10] or were based on non-validated clinical criteria for fatal anaphylaxis [14, 16–21]. Our approach to establishing a diagnosis of fatal anaphylaxis was based on the overall results, medical data, history of the event and application of widely accepted diagnostic criteria [2]. The criteria of the 2 allergists were similar to those used elsewhere [10]. In addition, diagnostic assessment of anaphylaxis by 2 experienced allergists has been used to validate the most frequently applied algorithm for anaphylaxis in the international literature [2, 33]. Thus, cooperation between an expert allergist and the forensic team should be mandatory and would confirm the forensic diagnosis of fatal anaphylaxis [15]. Our study uses a probabilistic approach to show the most important characteristics used by the 2 allergists to confirm that the INTCF cases were due to anaphylaxis and are concordant with the medical criteria used in other articles about the same topic (Table 10).

In conclusion, many deaths occurred in older age groups (≥ 50 years), and 35.6% of deaths occurred in health care settings. The most frequent manifestations were pulmonary and upper airway edema followed by coronary atherosclerosis. Our data on fatal anaphylaxis over such a long period confirm the need for a multidisciplinary approach in order to make an accurate diagnosis of an episode. Histology and laboratory findings were a necessary part of the analysis and essential for a comparison with clinical data, as were other data on the event itself. Such information would enable us to rule out non-anaphylactic episodes. However, consistent with the literature, our findings were not specific.

Key points

1. Forensic series on fatal anaphylaxis are scarce, probably because the diagnosis of anaphylaxis is often complex and incidence is low.
2. We report on the medicolegal, demographic and histopathological characteristics of a series of 46 fatal anaphylaxis cases which were investigated at a referral center from a high percentage of Spanish regions (81.5% of the total population) over a 17-year period.
3. Our findings for fatal anaphylaxis indicated a predominance of men, older age (≥ 50 years) and death in a health care setting (one-third of cases).
4. The most frequent autopsy findings were angioedema of the upper airways (50%), pulmonary edema (47.5%), atheromatosis of coronary vessels (32.5%), and pulmonary congestion (27.5%).
5. Previous episodes had occurred in two-thirds of cases of food-induced anaphylaxis and in half of the cases of drug-induced anaphylaxis.

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Data Availability The datasets generated and/or analyzed during the current study are not publicly available for legal reasons of privacy. An official LIMS dataset intranet at the INTCF, which is the property of the Ministry of Justice, has been available since 2009.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

The study was approved by the Research Committee and the Clinical Research Ethics Committee of University Hospital Fundación Alcorcón (number 17/103).

Informed Consent Given the retrospective design of the study, formal consent was not required.

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