

Risk Factors in Fatal Cases of Anaphylaxis due to Contrast Media: A Forensic Evaluation

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Key Words

Allergic reactions · Contrast media · Anaphylaxis · Postmortem biochemistry · Forensic pathology

Abstract

Background: Fatalities following contrast medium exposure are extremely rare in clinical routine, though they may occur as an exception. Some may fall under the purview of the inquiring authorities and forensic pathologists due to their in-hospital occurrence. The purpose of this study was to assess the risk factors for anaphylaxis due to contrast medium administration that can be identified in fatal cases. **Methods:** Fatalities occurred during the course of clinical investigations with contrast media described in the literature and fatal reactions to contrast agents that had undergone forensic investigations in our medicolegal center were reviewed with respect to patient characteristics, administered contrast medium, performed biochemical investigations and potential risk factors identified based on clinical history and medical records. **Results:** Biochemical investigations into the fatal cases examined in our facility revealed increased mast cell tryptase, total IgE and activated mast cells in all subjects. Data obtained from the literature and our own investigations indicated that in only a minority of the fatal cases had

there been previous exposure to contrast compounds, while most cases of severe anaphylaxis involved patients who apparently reacted on initial exposure. **Conclusions:** Most fatal cases failed to present any identifiable predisposing conditions out of those traditionally considered as risk factors for an anaphylactic reaction to contrast compounds in the medical histories of the patients. Comprehensive clinical histories and thorough reviews of medical data, along with exhaustive forensic investigations, provide information that is relevant in order to better appreciate the interwoven relationships linking all factors potentially involved in the pathogenesis of fatal anaphylaxis to contrast media.

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Introduction

Millions of clinical investigations with administration of contrast compounds are performed each year worldwide [1]. As with all other pharmaceutical agents, contrast media are not completely devoid of risks and adverse side effects can occur. Most of these are generally mild and self-limiting. Nonetheless, fatal reactions may occasionally be observed, with some of these incidences falling under the purview of the inquiring authorities and fo-

rensic pathologists due to their in-hospital occurrences [1–6].

Iodinated radiocontrast media, contrast agents used in magnetic resonance (MR) imaging, microbubbles used as ultrasound contrast agents, blue dyes used to map sentinel nodes during the staging procedures of cancer and other malignancies as well as contrast compounds used in neurosurgery and ophthalmic surgery are all capable of inducing adverse reactions that can be allergic or nonallergic, immediate or delayed [7–9]. Severe reactions reported in the literature mainly result from venous and arterial injection, though rare cases have been observed following other routes of administration due to the absorption of the medium into the circulation [10, 11].

Descriptions of fatal reactions in patients who had not been previously exposed to any contrast compounds have raised the question as to whether immunological IgE-mediated mechanisms are systematically involved in reactions following contrast medium exposure or whether nonimmunological mechanisms or cross-reactivity should be postulated. Additional questions concern the most common risk factors that may predispose individuals to developing contrast agent reactions [12].

The aim of this study was to review the available literature on fatalities following contrast medium exposure as well as the fatal reactions to contrast media that came under medicolegal investigation in our facility. These were considered with respect to occurrence, patient characteristics, administered contrast medium, performed biochemical investigations and potential risk factors identified based on the patients' clinical history and the review of their medical records.

Materials and Methods

Literature Search

We systematically searched the MEDLINE database up to December 2013 to identify all relevant articles pertaining to fatal cases of anaphylaxis following contrast medium administration. The search strategy used the keywords and/or MeSH terms 'anaphylaxis', 'anaphylactic', 'anaphylactoid', 'shock', 'allergy', 'allergic', 'nonallergic', 'non-allergic', 'hypersensitivity', 'immediate', 'reaction(s)', 'adverse drug reaction(s)', 'side effect(s)', 'adverse effect(s)', 'fatal', 'fatality', 'fatalities', 'lethal', 'death', 'forensic', 'medicolegal', 'medico-legal', 'tryptase', 'beta-tryptase', 'β-tryptase', 'mast cell tryptase', 'postmortem', 'post-mortem' or 'autopsy' combined with any combination of the following: 'contrast medium', 'contrast media', 'contrast compound(s)', 'radiocontrast', 'radio-graphic', 'iodine', 'iodinated', 'CT', 'injected', 'angiography', 'magnetic resonance imaging', 'MRI', 'magnetic resonance', 'MR', 'gadolinium', 'gadolinium-based', 'gadopentetate dimeglumine', 'echocardiography', 'echo', 'fluorescein', 'indocyanine green', 'pat-

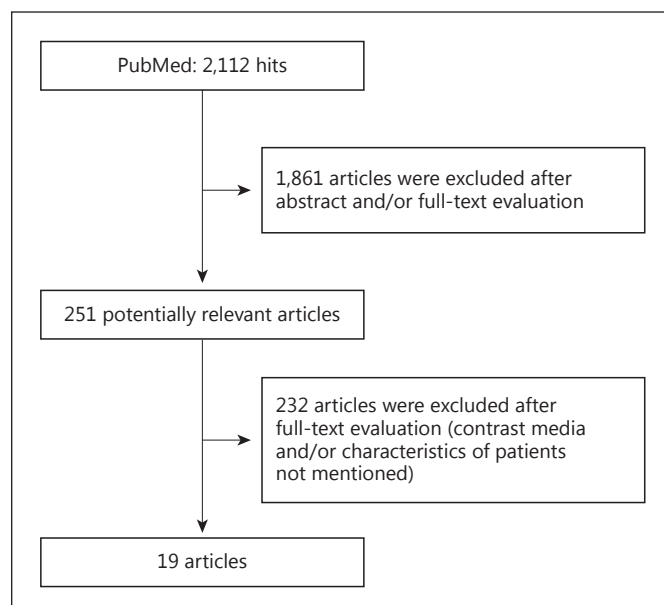


Fig. 1. The results of the search strategy, study selection and inclusion.

ent blue', 'isosulfan blue' and 'blue dye'. The reference lists of these selected articles were then hand-searched for additional potentially relevant articles. In order to be considered significant for the aim of our study, articles had to report fatal reactions following contrast medium administration, patient characteristics (age, gender and medical records) and contrast agent details. The absence of autopsy findings or postmortem biochemical investigation results were not considered exclusion criteria. Published meta-analyses pertaining to fatal reactions to contrast media were included when data concerning individual fatal cases could be obtained. Two reviewers checked all potentially relevant data in order to select pertinent papers, from which full-text papers were retrieved for further checking of inclusion and exclusion criteria. Articles that did not mention the characteristics of patients (i.e. age, gender and medical records) and the type of contrast medium were excluded. Inclusion and exclusion criteria were checked independently by 2 reviewers.

Our initial search resulted in 2,112 articles, 251 of which were related to fatal anaphylaxis to contrast media (after reading the abstracts and/or full texts). Nineteen papers were found to be relevant after reading the full texts. The results of the search strategy are shown in figure 1.

Medicolegal Autopsies in Our Facility

Our study was performed as a retrospective study of forensic data collected from 2002 to 2013. A total of 4,800 medicolegal autopsies were performed during this period. Eight cases of fatal anaphylaxis following administration of contrast media were examined in our medicolegal center. This represented 0.001% of all clinical investigations with contrast media performed in 2002–2013 in all hospitals located in the canton and accounted for 0.16% of all autopsies performed in our medicolegal center over this same pe-

riod. The cases that were fatal concerned 8 patients (6 males and 2 females) who had been admitted to local hospitals where they had undergone diagnostic procedures with administration of contrast medium. No premedication had been administered in any of these cases. In all of these cases, the arterial pressure markedly decreased approximately 3–10 min after the contrast medium was administered, the patients then lost consciousness, became unresponsive, collapsed and were immediately transferred to the intensive care unit. Electromechanical dissociation or cardiac arrest was evident on electrocardiogram and all of the patients died between 45 and 90 min after having lost consciousness despite cardiopulmonary resuscitation attempts. Acute systemic hypersensitivity reactions to contrast compounds were suspected in all of these cases. Levels of mast cell tryptase and total IgE from serum samples prior to the reaction were unavailable. The bodies were transferred from the local hospitals to the medicolegal center upon request by the inquiring authorities (public prosecutor) for postmortem investigations in order to reconstruct the sequence of events leading or contributing to death.

Postmortem Investigations

Complete conventional autopsy, histology, neuropathology, toxicology and postmortem biochemical investigations were performed on all subjects. The medical records and clinical histories of the deceased as well as police reports were consistently reviewed before conclusions were made. Conventional autopsies were performed within 24 h after death and were carried out jointly by 2 forensic pathologists (at least one of whom was board-certified) in accordance with both local standards and international guidelines for medicolegal autopsies. Conventional histology included hematoxylin-eosin stain of the brain, heart, lung, liver, kidney and spleen. Splenic eosinophils and degranulated mast cells were specifically sought out with Pagoda Red stain. All staining was performed after tissue fixation in formaldehyde. Immunohistochemistry using anti-tryptase antibodies was also performed on spleen tissue samples. Toxicology consisted of ethanol determination and general screening for common drugs and illegal substances by gas chromatography-mass spectrometry using commercial mass spectrum libraries, high-performance liquid chromatography with diode-array detection and headspace-gas chromatography flame ionization detection. Toxicology was systematically performed on blood and urine samples collected during autopsy in all cases. Biochemical investigations included measurement of mast cell tryptase and total IgE in the postmortem serum from femoral blood. Mast cell tryptase and total IgE were measured with a commercial fluoroenzyme immunoassay method (Pharmacia and Upjohn, Fisher Scientific, Thermo Fisher Scientific, USA, Pittsburgh, Pa., USA). Biological samples for toxicology and biochemistry were obtained as soon as possible upon arrival of the bodies at the morgue or during postmortem examination. Femoral blood samples were collected by aspiration with a sterile needle and syringe from the femoral vein(s) before autopsy. Blood samples were drawn after clamping the vein(s) at the proximal end and lifting the lower limb(s) for several minutes. They were stored in tubes containing sodium fluoride and preservative-free gel serum separator tubes. These latter were centrifuged immediately after collection at 3,000 g for 15 min. After centrifugation, the separated supernatant (postmortem serum) was collected and stored in preservative-free tubes. No specimens had to be excluded due to an insufficient sample volume. Femoral blood and postmortem se-

rum samples were transferred to the laboratories immediately after collection. When analyses were delayed, samples were stored at -20°C .

Ethics

All relevant ethical issues were identified and discussed with the local ethics committee. All cases collected for this study underwent medicolegal autopsies as requested by the public prosecutor. Postmortem serum from femoral blood and peripheral blood are systematically collected in our facility during autopsy. Toxicology, histology and biochemical investigations are systematically performed when death occurs in the course of medical care. Mast cell tryptase and total IgE measurements were performed as part of the medicolegal investigations. No additional biological samples were needed in order to measure mast cell tryptase and total IgE. All biological samples were anonymized prior to analysis. No further ethical approval was necessary to perform histology and biochemical investigations in the selected cases.

Results

Table 1 displays the articles selected, the age and gender of the deceased, the contrast medium administered, the type of reaction, the results of the biochemical investigation and the risk factors identified, when available. Table 2 shows the cases that underwent medicolegal investigation in our facility and includes the age and gender of the deceased, the cause of death, the contrast medium administered, the type of reaction, the postmortem biochemical investigation results and the risk factors investigated. These risk factors included asthma, allergic rhinitis, atopic dermatitis, a history of multiple allergies, drug allergy, food allergy, any previous clinical investigations with exposure to contrast medium of any type, any previous reactions to contrast medium of any type, beta-blockers or nonsteroidal anti-inflammatory medication intake, preexisting conditions and any cardiovascular, renal, hematologic, autoimmune or metabolic disease. Autopsy, histology, neuropathology and toxicology failed to provide the cause of death in any of the cases included in this group. A significant increase in eosinophils, mast cells and degranulated mast cells in the spleen, the latter mainly located in the spleen sinuses, was systematically detected. Postmortem serum mast cell tryptase and total IgE levels were increased in all cases and ranged from 51 to 979 ng/ml and from 61 to 225 kU/l, respectively. Reference values were chosen according to clinical and forensic literature [6]. Postmortem serum specific IgE, postmortem serum histamine, postmortem serum chymase and urine N-methyl-histamine were not determined due to antemortem biological sample unavailability, prolonged postmortem interval or in-

Table 1. Fatal cases following contrast medium administration available in the literature

Authors (year) [Ref.]	Age, years	Gender	Contrast medium	Type of reaction	Mast cell tryptase level (reference values)	IgE level (reference values)	Known allergies and/ or other diseases
Delage and Irely (1972) [37]	40	Male	Meglumine amidotrizoate	–	–	–	–
	77	Male	Sodium diatrizoate	–	–	–	–
	7	Female	Sodium acetrizoate	–	–	–	–
	38	Male	Bromosulphophthalein	–	–	–	–
	35	Male	Bromosulphophthalein	–	–	–	–
Laxenaire et al. (1984) [38]	47	Male	Ioxitalamate meglumine	Immediate	–	–	Beta-adrenergic blocking agent
Feczko et al. (1989) [39]	49	Female	Barium sulfate	Immediate	–	–	Atopic dermatitis, allergic rhinitis, asthma
Curry et al. (1991) [40]	59	Female	IoHexol	Immediate	–	–	No allergy known
	55	Male	IoHexol	Immediate	–	–	No allergy known
	69	Female	IoHexol	Immediate	–	–	Unspecified allergy to sulfa drugs, previous investigations with diatrizoate
Yunginger et al. (1991) [41]	–	–	Hexabrix® (ioxaglate meglumine and ioxaglate sodium)	–	1,038 ng/ml (10 ng/ml)	–	–
Baltaoğlu et al. (1994) [42]	46	Male	Iopromide	Immediate	–	–	No allergy known
Jordan and Mintz (1995) [30]	67	Female	Gadopentetate dimeglumine	Immediate	–	–	No allergy known recent contrast- enhanced CT
	–	–	Gadopentetate dimeglumine	Immediate	–	–	Beta-agonist therapy for asthma
	–	–	Gadopentetate dimeglumine	Immediate	–	–	Terminally ill, received Diprivan 1 h before gadopentetate
Atnaflu (1996) [43]	40	Female	Urografin	Immediate	–	–	No allergy known
Laroche et al. (1998) [10]	53	Male	Ioxitalamate	Immediate	36.5 µg/l (2 µg/l)	–	–
Guharoy et al. (1998) [44]	58	Female	Iothalamate meglumine	Immediate	–	–	No allergy known
Fineschi et al. (1999) [45]	67	Female	Sodium fluorescein	Immediate	194 µg/l (10 µg/l)	–	No allergy known
Brockow et al. (1999) [46]	81	Male	Nonionic radiocontrast medium iopamidol	Immediate	621 µg/l (12 µg/l)	Total IgE 185 kU/l n.i. Specific IgE to timothy grass demonstrated	No allergy known
Hitosugi et al. (2004) [47]	71	Female	Sodium fluorescein	Immediate	33.4 µg/l (9 µg/l)	IgE 8.7 IU/ml n.i.	No allergy known Retinal angiography 13 days earlier
Nishio et al. (2005) [48]	65	Male	–	–	182 µg/l n.i.	–	–
	68	Female	–	–	8 µg/l n.i.	–	–

Table 1 (continued)

Authors (year) [Ref.]	Age, years	Gender	Contrast medium	Type of reaction	Mast cell tryptase level (reference values)	IgE level (reference values)	Known allergies and/ or other diseases
Greenberger et al. (2007) [49]	58	Male	Radiocontrast media	Immediate	–	–	–
	46	Female	Radiocontrast media	Immediate	–	–	–
	66	Male	Radiocontrast media	Immediate	–	–	–
	81	Female	Radiocontrast media	Immediate	–	–	–
	82	Female	Radiocontrast media	Immediate	–	–	–
	36	Male	Radiocontrast media	Immediate	–	–	–
Jansman et al. (2007) [50]	66	Male	Ioversol	Immediate	–	–	No allergy known
Yilmaz et al. (2009) [51]	–	–	Meglumine amidotrizoate	–	–	–	No allergy known
Perkvis and Edston (2007) [52]	55	Male	Radio-opaque dye (X-ray investigation)	Immediate	α- and β-tryptase: 480 µg/l (45 µg/l)	No specific IgE identified	–
Osawa et al. (2008) [53]	56	Male	Iodine-containing contrast agent (ioxaglic acid)	Immediate	182 µg/l (10 µg/l)	59 IU/ml (170 IU/ml)	–
Nagai et al. (2012) [54]	17	Male	Iohexol	Delayed (6 h after administration: headache, vomiting, hyperventilation, respiratory alkalosis, unconsciousness)	–	–	Bronchial asthma (treated) Sclerosing cholangitis and ulcerative colitis (treated) Raynaud's phenomenon
Immediate reactions are reactions occurring within 1 h after exposure. n.i. = Not indicated in the paper.							

sufficient quantities of postmortem serum after the levels of mast cell tryptase and total IgE had been established. The cause of death was determined to be anaphylactic shock following contrast medium administration in all cases. Alternative causes of death were excluded based on the results of all postmortem investigations. Bone marrow histology (vertebral bone marrow) was performed in all 8 cases. The bone marrow was exposed by sawing through the anterior third of the thoracolumbar vertebrae during autopsy. Histology failed to reveal accumulation of pathological mast cells or an increased number of mast cells in all 8 cases. Based on medical records and information provided by the families, only 1 of the patients had undergone 2 previous clinical investigations with gadolinium administration. Allergic bronchial asthma to pollen was reported in 1 case. None of the other investigated risk factors was identified in the subjects studied (tables 1, 2).

Discussion

The revised nomenclature for allergies classifies hypersensitivity reactions to drugs as either allergic or non-allergic. The former are mediated by immunologic mechanisms, either antibodies (IgE-mediated or non-IgE-mediated) or cells. All other nonimmunologic reactions should be referred to as nonallergic hypersensitivity reactions [13–15].

The mechanisms responsible for immediate and delayed reactions to contrast media have been a matter of speculation for decades. With regard to radiocontrast agents, it is generally agreed that these may provoke both allergic and nonallergic reactions. Nonallergic immediate reactions, occurring within 1 h after exposure, are thought to be associated with nonspecific histamine release from basophils and mast cells due to (1) a direct membrane effect possibly related to the osmolality of the contrast medium solution or the chemical structure of the contrast

Table 2. Fatal cases following contrast medium administration that underwent medicolegal investigations in our facility

Case	Age, years	Gender	Contrast medium	Type of reaction	Mast cell tryptase (ref. 13.5 ng/ml)	IgE level (ref. 5-50 kU/l)	Known allergies and/or preexisting diseases	Cause of death
1	63	Male	Iomeprol	Immediate	181	120	Hepatocellular carcinoma No allergy known	Anaphylactic shock
2	53	Female	Iomeprol	Immediate	146	91	Abdominal aortic aneurysm No allergy known	Anaphylactic shock
3	74	Male	Iohexol	Immediate	170	135	Renal carcinoma No allergy known	Anaphylactic shock
4	79	Male	Iomeprol	Immediate	979	225	Prostatic adenocarcinoma No allergy known	Anaphylactic shock
5	54	Male	Iohexol	Immediate	282	151	Urothelial carcinoma No allergy known	Anaphylactic shock
6	65	Male	Iomeprol	Immediate	151	144	Hepatocellular carcinoma No allergy known	Anaphylactic shock
7	50	Male	Gadolinium-based	Immediate	136	61	Subcutaneous nodule (thigh) 2 previous MR investigations (6 and 5 years previously) with administration of gadolinium, but with no clinical manifestations. No allergy known	Anaphylactic shock
8	66	Female	Gadolinium-based	Immediate	51	89	Breast cancer Allergy to pollen (bronchial asthma)	Anaphylactic shock

medium molecule, (2) nonspecific binding of contrast molecules to membrane receptors, (3) activation of the complement system and, in turn, complement-related activation of mast cells and/or basophils due to the expression of complement receptors for C3a and C5a, and (4) mast cell activation by the kinin system.

It must be emphasized, however, that an immunologic, IgE-mediated mechanism has been postulated, especially in cases of severe and fatal reactions. This was hypothesized on the basis of positive skin test results and serum-specific IgE assays in a fraction of patients as well as based on evidence of extensive mast cell activation in vivo associated with clinical symptoms and high plasma mast cell tryptase levels in connection with severe or fatal cases after contrast medium exposure. Nonmediated reactions to radiocontrast media, occurring >1 h after administration, mainly consist of skin manifestations. Most of these appear to be allergic reactions mediated by T cells, demonstrated by (1) the frequently reported positive patch tests and delayed intradermal tests to the culprit contrast medium in previous reactors, (2) the presence of dermal infiltrates of T cells in the affected skin

areas, (3) the reappearance of the eruption after provocation testing, and (4) the ability of the contrast medium to stimulate the proliferation of peripheral T cells from patients with contrast medium-induced skin eruptions [8–10, 13, 16–20].

The possibility that cross-reactivity may account for some cases of immediate and delayed reactions to radiocontrast media has also been raised. From a general point of view, cross-reactivity may be due to both immunologic (IgE-mediated or T cell-mediated) and nonimmunologic mechanisms. Most cases of immunologic cross-reactivity are thought to be provoked by an IgE-mediated mechanism. T cell cross-reactivity among various iodinated contrast media has been described in some patients who experienced delayed reactions. Nonimmunologic cross-reactivity derives from a nonspecific activation of mast cells or basophils [13, 21–23].

Several risk factors associated with immediate hypersensitivity reactions to radiocontrast media have been reported in the literature. These are both contrast medium-related, concerning the type, dose and route of administration, and patient-related, pertaining to age, gender,

previous exposure to contrast compounds, previous adverse reactions to contrast media, some medications and allergic (asthma, allergic rhinitis, atopic dermatitis, a history of multiple allergies, drug allergy and food allergy) and nonallergic (cardiovascular, renal, hematologic, autoimmune and metabolic conditions) diseases [1, 12, 16, 19, 23–26].

General adverse reactions may be seen following the injection of gadolinium-containing contrast media with a much lower frequency than that observed with iodinated contrast media. However, reports of cases with severe anaphylaxis have increased, and fatal cases, though rare, have been described. The frequency of adverse reactions to gadolinium-based contrast agents has been reported to be about 8 times higher in patients who have had previous reactions to gadolinium-based contrast agents and 4 times higher in patients with a history of reactions to iodinated contrast media. Subjects with asthma and various allergies would also be at greater risk of adverse reactions. The pathophysiologic mechanisms for this are largely unknown. Based on positive skin reactions to the contrast agent that caused the clinical manifestations, some researchers have suggested a role of IgE-mediated reactions in MR contrast media-related hypersensitivity. However, it is still unclear whether polysensitization and cross-reaction exist among similar molecules. Another report suggesting an immunologic mechanism emphasized that the risk of immediate hypersensitivity reactions was up to 8 times higher in patients with a history of hypersensitivity to MR contrast media, the second reaction tending to be more severe than the first. However, it has been demonstrated that ionic and nonionic preparations of MR contrast agents are capable of directly inducing mast cell degranulation *in vitro*, which would suggest that one of the mechanisms responsible for mast cell degranulation after MR contrast medium exposure might belong to the group of nonimmunologic reactions [8, 27–36].

Based on the medical information provided by the patients themselves, general practitioners, local hospitals and family members, only 1 of the fatal cases observed in our facility (a reaction to gadolinium-based contrast medium) had been exposed to the same drug during former clinical investigations carried out 5 and 6 years previously, with no clinical manifestation in either situation (table 1). These data would suggest that most of these patients apparently reacted to contrast media on their first exposure. Moreover, among the other investigated risk factors, allergic bronchial asthma to pollen was identified exclusively in 1 subject. Postmortem investigations carried out in all 8 cases revealed increased total IgE and mast

cell tryptase levels as well as mast cell and eosinophil accumulation in the spleen. However, since mast cells can be activated by immunologic (IgE-mediated) and nonimmunologic mechanisms (directly, by complement activation or through specific receptors), the current hypotheses supporting IgE-mediated anaphylaxis as playing a major pathogenetic role in cases of severe and fatal reactions to contrast media cannot be confirmed or disproved based on the results of our investigations.

The data we obtained from the literature (table 2) lack systematic autopsy, histology and biochemical investigation results. However, though incomplete, the collected findings appear to suggest results similar to those shown by our own investigations, with most subjects not having experienced any previous exposure or reaction to any contrast medium nor presenting any identifiable risk factors.

The limitations of our study must be acknowledged. A classification bias could have been introduced by inaccuracies in the recording of data and the collection of medical information that physicians may have considered pertinent. This potential classification bias could have led to an underestimation of the number of cases. It must be emphasized, however, that the data were obtained from the selected articles by 2 reviewers who independently checked medical information and laboratory results. Additionally, a selection bias might have resulted from the fact that some fatal cases might not have been referred to our medicolegal center. This potential selection bias may have been responsible for an underestimation in the number of fatal cases following contrast medium administration. Nevertheless, it must be highlighted that there are no other referral centers for fatalities following contrast medium administration in our geographic area.

In conclusion, fatal reactions to contrast media are extremely rare. When they do occur, postmortem investigations should focus not only on establishing the cause of death through complete autopsy, histology, toxicology and laboratory investigations, but also on identifying potential risk factors and predisposing disorders as well as concomitant allergic and nonallergic diseases. Even though risk factors for adverse reactions to contrast media seem to be present only in a minority of fatalities, it is nonetheless the duty of the forensic pathologist to obtain comprehensive clinical histories and review all medical records, especially concerning previous clinical investigations using contrast media. Indeed, this information may provide valuable data in order to better understand the interactions and interrelationships linking the different factors potentially involved in the pathogenesis of fatal cases.

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