



Analysis of clinical characteristics of Kounis syndrome induced by contrast media

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ABSTRACT

Background: Understanding the relationship between contrast agents and Kounis syndrome (KS) is mainly based on case reports. The purpose of this research is to explore the clinical characteristics of contrast media induced KS. **Methods:** We searched for contrast-induced KS case reports through Chinese and English databases from 1991 to October 31, 2021.

Results: A total of 26 patients (19 men and 7 women,) were included, with a median age of 60 years (range 30–83). The contrast agents that cause KS mainly included gadolinium-based contrast agent (7 cases), iodine-containing contrast media (12 cases). KS mainly occurred within 30 min after administration and mainly manifests as chest pain and allergic reactions. Electrocardiogram (ECG) mainly showed ST elevation. Echocardiography mainly revealed normal. Coronary angiography showed normal, coronary vasospasm, stent thrombosis, occlusion and stenosis. After treatment with steroids, antihistamines and anti-ischemic therapy, 24 patients recovered completely and 2 patients died.

Conclusions: KS is a rare adverse reaction of contrast media. Radiologists should recognize this rare but serious disease to ensure rapid diagnosis and proper management.

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1. Introduction

Kounis syndrome (KS) is an acute coronary syndrome caused by an allergic reaction, first described by Kounis and Zavras in 1991, and is also called “allergic angina syndrome” or “allergic myocardial infarction” [1]. A variety of reasons can induce KS, including various drugs, environmental exposures and several conditions [2]. KS can occur at any age and is often missed in clinical diagnosis due to atypical clinical manifestations [3].

Contrast media is a chemical product injected (or taken) into human tissues or organs to enhance the effect of image observation. Adverse reactions of contrast agents can be divided into renal or non-renal. They can be acute (<1 h after contrast medium injection), late (>1 h to <1 week after contrast medium injection), or very late (>1 week after contrast medium injection) [4]. KS is a rare adverse reaction of contrast media. However, the incidence and the clinical features of contrast-induced KS are still unclear. The purpose of this study is to explore the clinical characteristics of contrast-induced KS by collecting relevant case report.

2. Methods

2.1. Search strategy

We searched for contrast-induced KS case reports through Chinese and English databases from 1991 to October 31, 2021. Search using a combination of subject and free words, including Kounis syndrome, contrast media, iodine contrast media, gadolinium contrast media, coronary artery spasm, angina, myocardial infarction, cardiac arrest, hypersensitivity.

2.2. Inclusion and exclusion criteria

Inclusion criteria: We collected case reports and case analyses of contrast-induced KS for inclusion as preliminary studies. **Exclusion criteria:** Reviews, repeated cases, animal studies, mechanism studies, and literatures lacking full texts were excluded.

2.3. Data extraction

Two researchers independently conducted a preliminary screening of the literature according to the inclusion and exclusion criteria, and then the group discussed the literature to be included in the analysis. Use a self-designed data extraction table to extract the following

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information of the patient: nationality, gender, age, primary disease, comorbid diseases, dose and type of contrast agent, route of administration, time of onset, clinical manifestations, laboratory examinations, imaging examinations, treatment and prognosis, etc.

3. Results

3.1. Basic information

A total of 26 patients were included, including 19 men and 7 women, with a median age of 60 years (range 30–83) (Table 1) [5–29]. These patients were mainly from Asia (12 cases), Europe (8 cases), the United States (4 cases), Chile (1 case), Australia (1 case). Twenty-one patients had medical history, including myocardial infarction (5 cases) [5,7,15,17,19], diabetes (5 cases), [8,9,12,18,27] and hypertension (9 cases) [7,9,11,16,18,22,24,26,27]. Two patients had a history of smoking [5,22]. In eight of these 26 cases, KS was associated with coronary arteriography (CAG).

Statistical contrast media include gadolinium-based contrast agent (7 cases), iodine-containing contrast media (12 cases), perflutren lipid microsphere (1 case) and sulphur hexafluoride (1 case), and other unreported contrast agents (5 cases). Iodine-containing contrast agents include iopromide (5 cases), iohexol (3 cases), iodixanol (2 cases) and iopamidol (1 case). Gadolinium-based contrast agent mainly include gadoterate meglumine (3 cases), gadobenate dimeglumine (2 cases), gadopentetate dimeglumine (1 case). The route of administration was mainly intraarterial injection (9 cases) and intravenous injection (17

cases). Five patients had ever used iodine contrast agent and all had allergic reactions [6,12,14,19,24], 1 patient received gadolinium-based contrast agent administration without any allergic reactions [29].

According to the current KS classification, 26 cases of contrast-induced KS were mainly divided into type I (8 cases), type II (11 cases), and type III (4 cases).

3.2. Clinical manifestations

The clinical manifestations of these patients mainly included chest pain (10 cases), sweating (8 cases), and dyspnea (4 cases); unconsciousness (9 cases), shock (2 cases), allergic reactions (18 cases), gastrointestinal reactions (4 cases) chest tightness and shortness of breath (6 cases) (Table 2). Allergic reactions mainly manifested as itching (5 cases), urticaria (7 cases), rash (6 cases), erythema (4 cases), flushing (4 cases). Hypotension appeared in 16 patients.

Twenty-five patients developed KS within 30 min, including immediately after the infusion (7 cases), during the infusion (3 cases), within minutes (4 cases), within 10 min after the infusion (6 cases), 15–30 min (5 cases). One patient developed signs of anaphylaxis in an hour after using iodinated contrast media [11]. Sixteen patients experienced hypotension, and six patients experienced cardiac arrest [6,10,14,16,21,23].

3.3. Laboratory examination

The detection of myocardial injury markers was performed in 13 patients, including normal (2 cases), elevated troponin I (8 cases),

Table 1
Basic information of 26 included patients.

Reference	Region	Sex/age	Medical history	Contrast agent	Dosage	Route of administration	Delay	Blood pressure (mmHg)	KS type
5	Greece	48/M	MI	iopromide	50 mL	intravenous	10 min	110/80	III
6	USA	57/M	gout, depression, prostatic hyperplasia, allergic rhinitis	gadobenate dimeglumine	nr	intravenous	2 min	nr	nr
7	Chile	79/M	hypertension, angina pectoris	iodixanol	nr	intraarterial	Immediately	hypotension	II
8	Korea	54/M	DM, CAOD	nr	nr	intraarterial	10 min	40/30	II
9	Turkey	51/M	DM, hypertension	iopromide	30 mL	intraarterial	10 min	nr	II
10	Japan	62/M	pancreatic cancer	iohexol	100 mL	intravenous	During infusion	72/nr	I
11	China	71/M	hypertension	iodinated contrast media	400 U	intraarterial	1 h	50/40	I
12	Croatia	46/F	hypophyseal prolactinoma, DM	gadoterate meglumine	15 mL	intravenous	10 min	120/80	II
13	Netherlands	83/F	hip replacement, TAVR	nr	nr	intravenous	During infusion	50/20	I
14	Korea	74/M	no	iopromide	nr	intravenous	Immediately	nr	I
15	Spain	72/F	MI	sulphur hexafluoride	5 mg	intravenous	Immediately	hypotension	III
16	France	81/M	HC, hypertension, arrhythmia	gadoterate meglumine	20 mL	intravenous	Several min	85/60	II
17	Australia	83/M	MI	iohexol	nr	intraarterial	Immediately	hypotension	II
18	Italy	47/M	hypertension, DM, hyperlipidemia	nr	nr	intraarterial	30 min	80/60	III
19	Japan	60/M	HC, MI	iopamidol	80 mL	intravenous	Immediately	70/nr	II
20	usa	53/F	renal cell carcinoma	GBCA	nr	intravenous	Several min	nr	I
21	Taiwan	81/F	breast cancer	nr	nr	intravenous	15 min	nr	nr
22	Poland	59/F	hypertension, hyperlipidemia	iopromide	nr	intraarterial	Within min	80/40	I
23	usa	76/M	no	perflutren lipid microsphere	nr	intravenous	Within min	hypotension	II
24	Kuwait	60/M	hypertension	nr	nr	intraarterial	20 min	nr	III
25	usa	30/M	no	gadobenate dimeglumine	nr	intravenous	Immediately	nr	I
26	Japan	78/M	hypertension	gadopentetate dimeglumine	5199.6 mg	intravenous	Immediately	72/48	II
27	China	59/M	hypertension, DM, AF	iodixanol	nr	intraarterial	During infusion	70/40	II
28	China	78/M	no	iohexol	80 mL	intravenous	20 min	60/32	II
28	China	72/F	renal cell carcinoma	iopromide	80 mL	intravenous	20 min	60/38	nr
29	Italy	45/M	no	gadoterate meglumine	0.2 mL/kg	intravenous	2 min	no	I

Abbreviation: MI, myocardial infarction; TAVR, transfemoral transcatheter aortic valve replacement; CAOD, coronary artery obstructive disease; DM, diabetes mellitus; AF, atrial fibrillation; GBCA, Gadolinium-based contrast agent; HC, hepatocellular carcinoma.

Table 2

Clinical manifestations, laboratory tests, treatment and prognosis of the 26 included patients.

Reference	Clinical manifestations	ECG	Cardiac Arrest	Revascularization	Troponin I (ng/ml)	Echocardiography	Coronarography	Treatment	Outcome (hospital day)
5	unwell, pale, weak, dizzy, sweating, retrosternal discomfort, pain, numbness, itching	ST elevation	no	PTCA	11.39	nr	CCA intrastent stenosis	steroids, diphenhydramine, ranitidine, nitroglycerin	recovery
6	shortness of breath, warm, erythematous with urticarial lesions, shock	nr	yes	no	nr	normal	nr	steroids, epinephrine, atropine	recovery (35d)
7	rash, papular erythema, chest pain	ST elevation	no	no	nr	nr	cramps	steroids, chlorpheniramine, salbutamol, verapamil, CCB, nitrates, aspirin, statins, loratadine	Recovery (3d)
8	flushing, shortness of breath, chest pain, dyspnea, diaphoresis, facial swelling, pruritic rash	ST elevation	no	PTCA	0.04 ^a	normal	subtotal occlusion of proximal LAD	steroids, chlorpheniramine, cimetidine, morphine, heparin	recovery (4d)
9	chest pain, urticaria, itching, chilling	AMI	no	no	nr	nr	mid-LAD occlusion	steroids, antihistaminic	recovery (5d)
10	nausea, unconsciousness, chest pain	ST elevation	yes	no	normal	hyperkinetic	no	steroids, adrenalin, dopamine	recovery (5d)
11	hyperspasmia, unconsciousness, flushes, sweating, urticaria	ST elevation	no	no	nr	nr	nr	steroids, dopamine, promethazine, glycerin trinitrate, lidocaine	recovery
12	urticaria, angioedema, shock	ST depression	no	no	0.311 ^a	normal	normal	steroids, epinephrine, chlorpheniramine	recovery (10d)
13	rash	ST elevation	no	no	nr	nr	subocclusive spasm	steroids, antihistamine, adrenaline, nitrates	recovery
14	unconsciousness, deep coma	ST elevation	yes	no	normal	nr	normal	steroids, epinephrine, chlorpheniramine	recovery (5d)
15	sweating, dyspnea, rash, chest pain	ST elevation	no	PTCA	nr	nr	stent thrombosis of RCA	steroids	recovery
16	erythema	ST elevation	yes	CAS	1557	normal	coronary vasospasm of LAD	Epinephrine, nitroglycerin	died
17	urticaria	ST elevation	no	CAS	nr	nr	Mid-to-distal RCA vasospasm	steroids, metaraminol, adrenaline	recovery
18	nausea, sweating, chest pain, itch, erythema	ST elevation	no	PTCA	nr	nr	stent thrombosis	steroids, chlorpheniramine, eptifibatide, DAT, statin, beta blocker, ACEI	recovery (3d)
19	numbness of upper limbs, dyspnea, unconsciousness	ST elevation	no	no	elevated	normal	nr	steroids, adrenaline, heparin, nicorandil	recovery
20	chest pain, shortness of breath, unresponsive	ST elevation	no	no	1.12	nr	mild disease of middle RCA	steroids, atropine	recovery
21	unconsciousness, rash	ST elevation	yes	no	nr	normal	nr	steroids, atropine, CPR, dopamine	recovery
22	back pain, unconsciousness	ST elevation	no	no	elevated	LVOT obstruction	normal	steroids, norepinephrine	recovery
23	flushing, diaphoresis, chest pain	ST elevation	yes	PTCA	nr	hypokinesis	coronary vasospasm	steroids, diphenhydramine, DAT, anticoagulation, epinephrine, nitroglycerin	died
24	chest pain	ST elevation	no	CAS	nr	hypokinesis	stent thrombosis of proximal LAD	steroids, antihistamine, DAT, bisoprolol, atorvastatin	ICD (a few days)
25	urticaria, chest tightness, laryngospasm	normal	no	no	6.65	normal	normal	steroids, epinephrine, antihistamines, heparin, aspirin, nitrates	recovery (3d)
26	tingling sensation, throat discomfort, chest discomfort, dry cough, shortness of breath	ST elevation	no	no	nr	normal	nr	steroids, itroglycerine, isosorbide dinitrate, atropine	recovery (9d)
27	rash, itching, chest tightness, nausea	AF	no	no	0.372	nr	coronary vasospasm	steroids, adrenaline, dopamine	recovery
28	chest pain, sweating, unconsciousness	ST elevation	no	no	0.00832 ^a	nr	30% stenosis of distal RCA and middle ADA	steroids, dopamine, epinephrine, promethazine, norepinephrine	recovery (4d)
28	sweating, flushing, abdominal pain, unconsciousness	ST elevation	no	no	no	nr	nr	steroids, dopamine, epinephrine	recovery (4d)

(continued on next page)

Table 2 (continued)

Reference	Clinical manifestations	ECG	Cardiac Arrest	Revascularization	Troponin I (ng/ml)	Echocardiography	Coronarography	Treatment	Outcome (hospital day)
29	cough, dyspnea, nausea, desaturation, unconsciousness, urticaria	low progression of R wave	yes	no	elevated	low cardiac output	normal	steroids, adrenaline, salbutamol, antihistamines	recovery (4d)

Abbreviation: ECG, Electrocardiogram; CCA, circumflex coronary artery intrastent stenosis; LAD, Left anterior descending; LVOT, left ventricular outflow tract; AMI anterior myocardial infarction; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; PTCA, Percutaneous transluminal coronary angioplasty; CPR, Cardiopulmonary resuscitation; CAS, coronary artery stenting; DAT, dual antiplatelet therapy.

^a Troponin T.

elevated troponin T (3 cases) (Table 2). Serum tryptase level was markedly elevated in 2 patients [5,17], and creatine kinase-MB (CK-MB) was elevated in 2 patients [26,28].

3.4. Image examination

The imaging examination results were summarized in the Table 2. Electrocardiogram (ECG) mainly showed ST elevation (20 cases), ST depression (1 case), low progression of R wave (1 case), atrial fibrillation (1 case), normal (1 case) and acute myocardial infarction (1 case). Echocardiography in 13 patients revealed normal (8 cases), hyperkinetic wall motion (3 cases), low cardiac output (1 case), left ventricular outflow tract obstruction (1 case). CAG in 19 patients showed normal (5 cases), coronary vasospasm (6 cases), right coronary artery (RCA) stent thrombosis (3 cases), occlusion (2 cases), stenosis (2 cases), mild disease (1 case).

3.5. Treatment

Treatment of these patients included steroids (25 cases), antihistamines (14), nitrates (5 cases), epinephrine (15 cases), dopamine (6 cases), antiplatelet drugs (5 cases), and anticoagulant drugs (5 cases) (Table 2). Eight patients underwent revascularization, including percutaneous transluminal coronary angioplasty (5 cases) [5,8,15,18,23] and coronary artery stenting (3 cases) [16,17,24]. One patient undergoing cardiopulmonary resuscitation [21]. After symptomatic treatment [23], patients recovered completely, two patients died [16,23] and one patient was implanted with an implantable cardioverter defibrillator (ICD) to prevent sudden cardiac death [24].

4. Discussion

The diagnosis of KS is based on clinical symptoms and signs, as well as laboratory, electrocardiogram, echocardiography, and angiography. Three variants of KS have been described [30]. The type I variant refers to patients with normal coronary arteries without any cardiovascular risk factors. The type II variant occurs in patients with existing coronary artery disease. The type III variant occurs in patients with stent thrombosis. Previous allergy, hypertension, smoking, diabetes, and hyperlipidemia are risk factors for the development of KS [31]. Our research showed that 19.2% of patients had a known history of allergies. A careful review of the clinical history of allergic reactions is important for the prevention and treatment of KS.

KS induced by contrast agents was mostly type I and II, which often occurred in elderly male patients. Most modern iodinated contrast media are classified as low-osmolality contrast media (LOCM) and isoosmolar contrast media (IOCM) [32]. Most KS cases were related to LOCM, such as iopromide, iohexol, and iopamidol. Only a few cases were related to IOCM, iodixanol. Gadolinium was divided into two groups based on their chemical structure - linear and macrocyclic. In particular, licences for the linear agents gadodiamide and gadopentetate dimeglumine were suspended due to the risk of nephrogenic systemic fibrosis (NSF) and retention in the brain and other tissues. And macrocyclic chelates are of

lowest risk [33]. Our research found that KS was related to macrocyclic gadolinium-containing contrast agents (GdCAs). In addition, intracoronary injections and intravenous injections of contrast agents can cause any type of KS. Despite its rare incidence, as doctors' awareness of KS increased, it may lead to a further increase in KS-related case reports. Therefore, in our opinion, diagnostic radiologists who routinely use any type of contrast agent should understand KS. Further research is needed to prove whether the risks of KS induced by different contrast agents are the same.

The exact pathophysiological mechanism of KS is still unclear. Mast cells play a central role in the underlying mechanism of KS. Mast cells are abundant in the heart and blood vessels. The degranulation of mast cells leads to the release of allergic inflammatory mediators, including histamine, proteases, leukotrienes, traxane, and platelet activating factor [30]. Serum tryptase levels can provide more information about allergic reactions [34]. Tryptase level as a specific indicator of mast cell degranulation [35].

Currently, there are no standards and guidelines for the treatment of KS. The treatment of KS is challenging because it requires simultaneous resolution of allergic reactions and cardiac symptoms [3]. The prognostic factors that affect KS mainly include the type of KS, complications, allergens, etc. Generally, type I variant had the best prognosis, and type III variant had the worst prognosis. Our research showed that contrast-induced KS can cause serious complications, with a cardiac arrest rate of 23.1% and a mortality rate of 7.7%. In patients with the type I variant, the symptoms can be eliminated by treating allergies alone, such as glucocorticoids, H₁ and H₂ receptor blockers. In patients with the type II variant, treatment should be initiated with an acute coronary event protocol together with corticosteroids and antihistamines. In patients with type III variant the current acute myocardial infarction protocol together with urgent aspiration of intrastent thrombus followed by histological examination of aspirated material. Calcium blockers and nitrates can eliminate coronary artery spasm caused by allergies. Beta-blockers can aggravate coronary artery spasm and should be avoided. Although epinephrine is the drug of choice for the treatment of conventional allergic reactions, it can aggravate myocardial ischemia and cause coronary artery spasm in KS patients [36]. Most patients receive intravenous corticosteroids, diphenhydramine, and epinephrine to abolish allergic symptoms in our study. Coronary arteries have achieved almost complete blood flow restoration by nitrate injections and interventional treatments. Two patients still died of multiple organ failure and recurrent cardiac arrest.

The effective prevention method of KS is unclear. It is still challenging to switch to another type of contrast medium. In particular, CAG/percutaneous coronary intervention (PCI) should be considered for patients with coronary artery spasm/thrombosis progressing to acute myocardial infarction.

5. Conclusion

In summary, contrast-induced KS is a rare adverse reaction. Radiologists should recognize this rare but serious disease to ensure rapid diagnosis and proper management.

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Declaration of Competing Interest

All authors declare that they have no conflict of financial interest.

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