Potential risk factors of adverse reactions to nonionic contrast media in patients with underlying dermatological diseases: An 8-year retrospective survey

Nakauchi, Emi ; Fukumoto, Takeshi ; Takahashi, Satoru ; Horita, Nobuyuki ; Oka, Masahiro ; Nishigori, Chikako

(Citation)
Allergology International,68(4):529-532

(Issue Date)
2019-10

(Resource Type)
journal article

(Version)
Version of Record

(URL)
https://hdl.handle.net/20.500.14094/90007779

Allergology International 68 (2019) 529–532

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Letter to the Editor

Potential risk factors of adverse reactions to nonionic contrast media in patients with underlying dermatological diseases: An 8-year retrospective survey

Dear Editor,

Iopamidol and iohexol were first launched in 1986 and 1987, respectively, as nonionic contrast media (CM) in Japan.[1] Nonionic CM cause fewer adverse reactions (ARs) than do ionic CM.[2–7] A nationwide, large-scale study reported that the incidences of ARs to ionic and nonionic CM were 12.66% and 3.13%, respectively.[2] To our knowledge, no large-scale studies have assessed ARs in patients with underlying dermatological diseases.[1–7] Some studies described late-onset ARs (LARs), occurring >1 h after nonionic CM

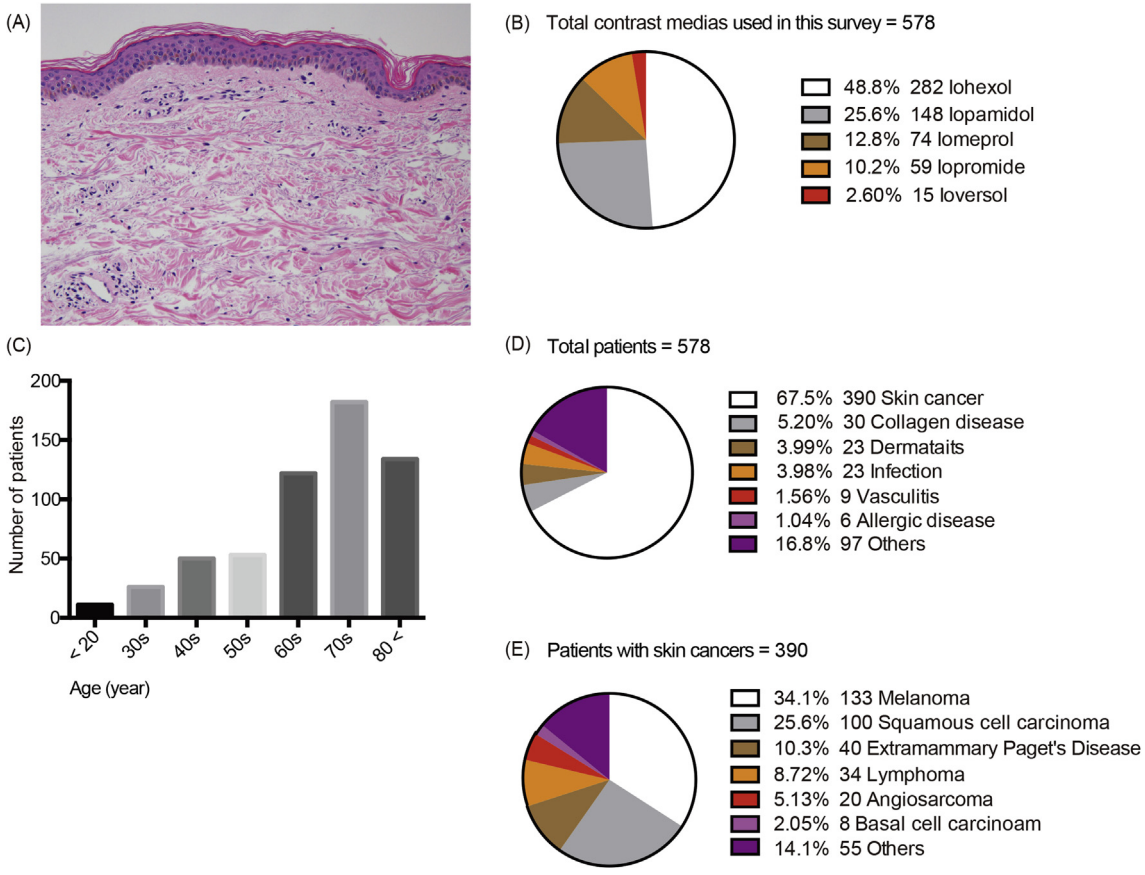

Fig. 1. Histopathological findings of the current patient **(A)**, and histopathological features of 578 patients who were injected with nonionic contrast media (CM) for examination of underlying dermatological diseases **(B–E)**. **(A)** Histological examination of the left upper arm (hematoxylin and eosin staining; 200×). **(B)** Nonionic CMs used in the 578 patients in this survey. **(C)** Age distribution of the 578 patients included in this survey. **(D)** Underlying dermatological diseases in the 578 patients. **(E)** Types of cancers in the 390 patients with underlying skin cancers.

Peer review under responsibility of Japanese Society of Allergology.

https://doi.org/10.1016/j.alit.2019.03.004

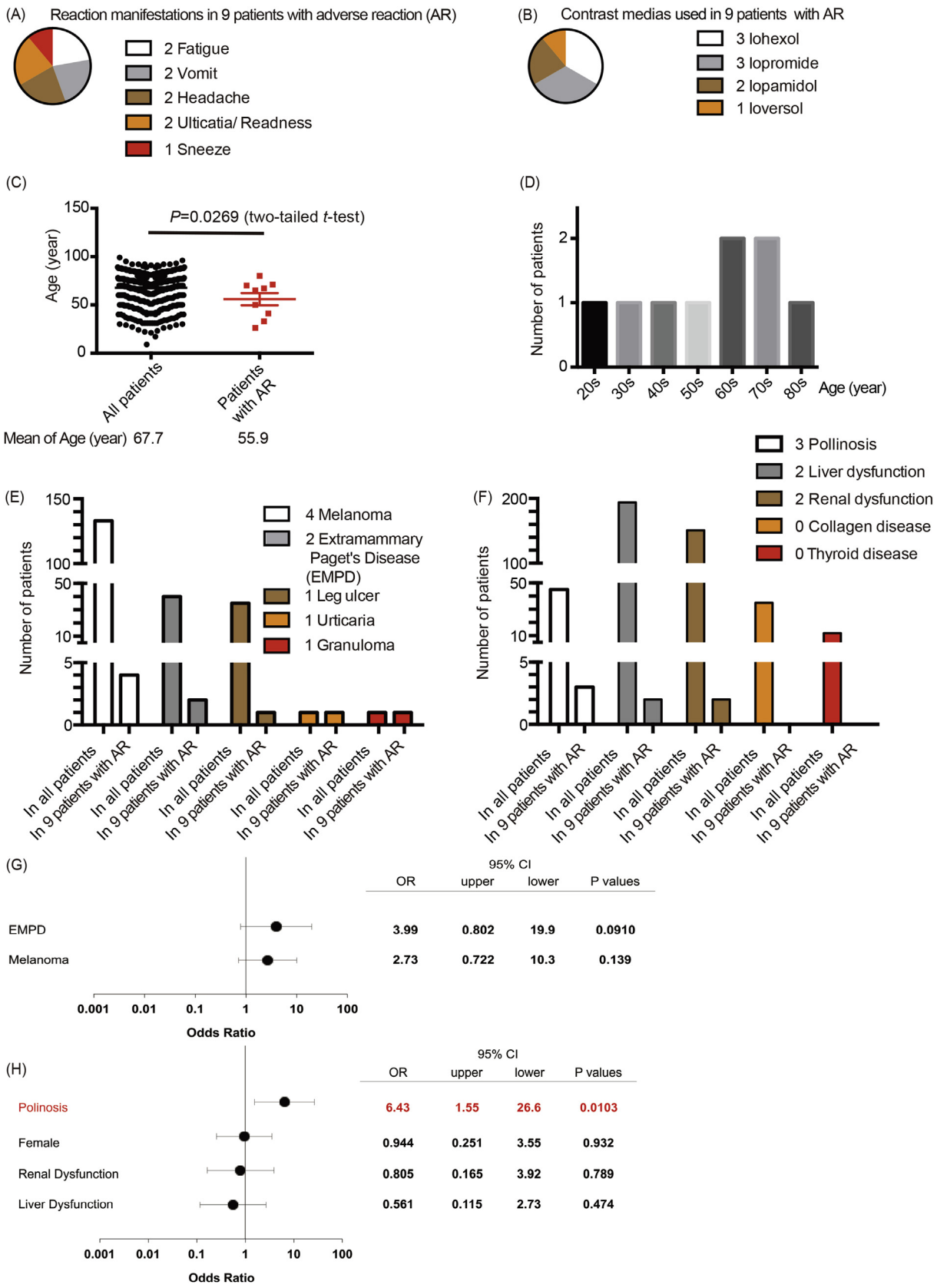

Fig. 2. Retrospective survey of nine adverse reactions (ARs) in response to nonionic contrast media (CM). **(A)** Reaction manifestations in the nine patients with ARs in this survey. **(B)** Nonionic CMs used in the nine patients with ARs. **(C, D)** The mean age of the nine patients with ARs (55.9 years) is lower than that of all patients (66.7 years; $P = .0269$; two-tailed t-test). **(E)** Underlying dermatological diseases in the nine patients with ARs. **(F)** Risk factors other than underlying dermatological diseases in all 578 patients. **(G, H)** Odds ratios of specific risk factors of underlying dermatological diseases **(G)** and of diseases other than dermatological diseases **(H)**.

exposure, but the underlying reason for LARs is unclear.[1,7,8] Here, we report a case of urticaria 6 h after CM exposure. Furthermore, we conducted a retrospective survey of ARs in response to nonionic CM in 578 patients in our institution between March 2008 and October 2016.

A 66-year-old woman presented with wheals on her trunk 6 h after iohexol injection. She had previously undergone annual iomeprol injections for follow-up of idiopathic portal hypertension, and this was her first exposure to iohexol. Olopatadine (10 mg/day) and betamethasone ointment were applied; however, her symptoms worsened. Histological examination revealed edema of the superficial dermis and perivascular lymphocyte infiltration with no eosinophilic infiltration (Fig. 1A). Olopatadine (20 mg/day), hydroxyzine (75 mg/day), montelukast (10 mg/day), and betamethasone ointment were administered on hospitalization. Her symptoms disappeared seven days later. Because annual iomeprol injections might cause cross-reactivity to iohexol, patch and prick tests using both iohexol and iomeprol (as is) were performed,[1,9] which showed negative results according to the International Contact Dermatitis Research Group scoring system. However, she did not provide consent for provocation tests.

LAR incidence ranges from 0.4% to 22%,[8] because detecting the correlation between LARs and CM usage is difficult after time has passed. The most common symptoms of LARs are skin-related.[7,8] Immediate-onset ARs occur within 1 h after injection, some of which are related to histamines and IgE production.[3,7] LARs reportedly contain both delayed-type hypersensitivity mediated by T-cell reactions and non-allergic mechanisms.[1,3,7] Approximately 50% of patients had positive reactions to skin tests of CM or showed cross-reactivity to several CM.[1] Our patient had negative results for all skin tests. Considering the negative skin test results and histopathological examinations, our patient may have developed an AR via a non-allergic mechanism. However, it should be noted that skin tests are not always positive even in patients with allergic AR.[1,9]

Although the precise pathogenesis of LARs caused by CM is controversial, reports have revealed that LAR incidence is higher in Japan than in other countries because of pathogeneses such as deficiency of aldehyde dehydrogenase-2, frequent exposure to CM, or pre-testing with small amounts of CM.[1,7] Further studies might elucidate this relationship. ARs lasting longer than 24 h are rare.[5] Our patient needed hospitalization with administration of antihistamine orally and local steroid ointment for one week. Accumulating data on similar cases remains important to determine appropriate treatments.

Next, we retrospectively surveyed the electronic medical records of 578 patients who received nonionic CM for examination of underlying dermatological diseases over an 8-year period (Fig. 1B–E). This is the largest study of ARs in response to nonionic CM in patients with underlying dermatological diseases. There were nine ARs (incidence: 1.56%) associated with nonionic CM (five men, four women) (Fig. 2A, B). No significant differences based on sex were observed in our study (odds ratio [OR], 0.944; 95% confidence interval [CI], 0.251–3.55; $P = .932$)[4,5,7]. ARs occurred in patients aged 26–80 years, and the mean age of patients with ARs (55.9 years) was lower than that of all patients (67.7 years) ($P = .0269$; two-tailed t-test) (Fig. 2C, D). Although our patient without underlying dermatological disease demonstrated late-onset AR that required medication, the ARs of the nine patients were immediate-onset ARs and resolved spontaneously. Most symptoms of ARs were not cutaneous (Fig. 2A). Four of the 578 patients had a history of ARs before March 2008; however, these four patients were not included among the nine patients with ARs in this survey.[7] Implications of a history of ARs remain obscure.[5,7] ARs occurred mostly in melanoma patients (four patients) and in extramammary Paget disease (EMPD) patients (two patients) (Fig. 2E), consistent with the findings of Jung *et al.* that ARs occurred mostly in patients with malignant neoplasm.[3] However, we found that patients with melanoma formed the largest group of subjects in the present study (Fig. 2E); therefore, we used OR for accurate clarification. Unfortunately, we were unable to detect specific risk factors among underlying dermatological diseases (melanoma: OR, 2.73; 95%CI, 0.722–10.3; $P = .139$; EMPD: OR, 3.99; 95%CI, 0.802–19.9; $P = .0910$) (Fig. 2G). In addition to patients with dermatological diseases, we found that patients with pollinosis, liver dysfunction, and renal dysfunction experienced ARs (Fig. 2F). Pollinosis was a statistically significant risk factor (OR, 6.43; 95%CI, 1.55–26.6; $P = .0103$), but neither sex nor underlying renal/liver dysfunction had a significant influence on ARs (sex: OR, 0.944; 95%CI, 0.251–3.55; $P = .932$; renal dysfunction: OR, 0.805; 95%CI, 0.165–3.92 $P = .789$; liver dysfunction: OR, 0.561; 95%CI, 0.115–2.73; $P = .474$). In contrast, there were no ARs in 11 patients with asthma.[7] We routinely asked several questions before CM administration using screening forms, especially to determine the history of allergies, such as asthma, pollinosis, and atopic dermatitis. Although the association between allergic background and ARs remains unclear, our results support the association between pollinosis and ARs in patients with underlying dermatological diseases (Fig. 2H).[2,6–8] Previous studies have reported that ARs occur more frequently during pollinosis seasons; however, we could not detect a moderate pollinosis season.[7,8] Premedication with steroids and/or antihistamines before nonionic CM administration in patients with a history of multiple allergies may be performed. However, we could not reliably determine whether all our cases with a history of allergies received premedication.[2,3,6,10]

In conclusion, although more detailed prospective trials are needed for more accurate analyses, our study suggests that pollinosis patients with underlying dermatological diseases are at high risk for ARs during examinations using nonionic CM. Therefore, to avoid ARs, it might be important to confirm the history of pollinosis before using CM in patients with underlying dermatological diseases.

Conflict of interest

The authors have no conflict of interest to declare.

Emi Nakauchi [a], Takeshi Fukumoto [a,b,*], Satoru Takahashi [c], Nobuyuki Horita [d], Masahiro Oka [e], Chikako Nishigori [a]

[a] *Division of Dermatology, Department of Internal Related, Kobe University Graduate School of Medicine, Kobe, Japan*
[b] *Gene Expression and Regulation Program, The Wistar Institute, Philadelphia, PA, USA*
[c] *Department of Radiology, Kobe University Hospital, Kobe, Japan*
[d] *Department of Pulmonology, Yokohama City University Graduate School of Medicine, Yokohama, Japan*
[e] *Department of Dermatology, Kita-Harima Medical Center, Ono, Japan*

* Corresponding author. Division of Dermatology, Department of Internal Related, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan.
E-mail address: fuku@med.kobe-u.ac.jp (T. Fukumoto).

References

1. Nakada T, Akiyama M, Iijima M, Kato A, Maibach HI. Drug eruptions to contrast media in Japan. *Clin Exp Dermatol* 2006;**31**:361–4.
2. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the safety of contrast media. *Radiology* 1990;**175**:621–8.
3. Jung KE, Chung J, Park BC, Jee KN, Jee YK, Kim MH. A clinical study of cutaneous adverse reactions to nonionic contrast media in Korea. *Ann Dermatol* 2012;**24**:22–5.

4. Mortele KJ, Oliva MR, Ondategui S, Ros PR, Silverman SG. Universal use of nonionic iodinated contrast medium for CT: evaluation of safety in a large urban teaching hospital. *AJR Am J Roentgenol* 2005;**184**:31–4.
5. Wang CL, Cohan RH, Ellis JH, Caoili EM, Wang G, Francis IR. Frequency, outcome, and appropriateness of treatment of nonionic iodinated contrast media reactions. *AJR Am J Roentgenol* 2008;**191**:409–15.
6. Callahan MJ, Poznauskis L, Zurakowski D, Taylor GA. Nonionic iodinated intravenous contrast material-related reactions: incidence in large urban children's hospital–retrospective analysis of data in 12,494 patients. *Radiology* 2009;**250**:674–81.
7. Christiansen C, Pichler WJ, Skotland T. Delayed allergy-like reactions to X-ray contrast media: mechanistic considerations. *Eur Radiol* 2000;**10**:1965–75.
8. Munechika H, Hiramatsu Y, Kudo S, Sugimura K, Hamada C, Yamaguchi K, et al. A prospective survey of delayed adverse reactions to iohexol in urography and computed tomography. *Eur Radiol* 2003;**13**:185–94.
9. Delgado-Jimenez Y, Perez-Gala S, Aragues M, Sanchez-Perez J, Garcia-Diez A. Late skin reaction to iodixanol (Visipaque): clinical manifestations, patch test study, and histopathological evaluation. *Contact Dermatitis* 2006;**55**:348–53.
10. Lasser EC, Berry CC, Mishkin MM, Williamson B, Zheutlin N, Silverman JM. Pretreatment with corticosteroids to prevent adverse reactions to nonionic contrast media. *AJR Am J Roentgenol* 1994;**162**:523–6.

Received 1 February 2019
Received in revised form 3 March 2019
Accepted 6 March 2019
Available online 4 April 2019