Radiology

Delayed Adverse Reaction to Contrast-enhanced CT: A Prospective Single-Center Study Comparison to Control Group without Enhancement[1]

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Purpose: To prospectively assess the incidence of delayed adverse reactions (DARs) in patients undergoing contrast material–enhanced computed tomography (CT) with the low osmolar nonionic contrast agent iohexol and compare with the incidence of DARs in patients undergoing unenhanced CT as control subjects.

Materials and Methods: Institutional review board approval and informed written consent for this prospective study were obtained. The study was HIPAA compliant. Patients undergoing CT for routine indications were enrolled from a random next-available scheduling template by an on-site clinical trials monitor. All subjects received a questionnaire asking them to indicate any DAR occurring later than 1 hour after their examination. Sixteen manifestations were listed and included rash, skin redness, skin swelling, nausea, vomiting, and dizziness, among others. To ensure maximal surveillance, a clinical trials coordinator initiated direct telephone contact for further assessment. Patients suspected of having moderately severe cutaneous reactions were invited to return for a complete dermatologic clinical assessment including skin biopsy, if indicated. Statistical analysis was performed by using a two-sided Wilcoxon-Mann-Whitney test, a logistic regression utilizing a χ^2 test to adjust for sex and age, and a two-sided Fisher exact test.

Results: A total of 539 patients (258 receiving iohexol and 281 not receiving contrast material) were enrolled. DARs were observed in 37 (14.3%) of 258 subjects receiving iohexol and in seven (2.5%) of 281 subjects in the control group ($P < .0001$, χ^2 test) after adjusting for sex and age. Specific manifestations of DARs that were significantly more frequent at contrast-enhanced CT were skin rash ($P = .0311$), skin redness ($P = .0055$), skin swelling ($P = .0117$), and headache ($P = .0246$). DARs involving the skin included generalized rashes of the face, neck, chest, back, and extremities and were often associated with swelling, erythema, and pruritus.

Conclusion: This study substantiates a frequent occurrence of DARs at contrast-enhanced CT compared with that in control subjects. Continued growth in the use of contrast-enhanced CT suggests a need for greater awareness and attention to prevention and management.

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Delayed adverse reactions (DARs) resulting from the parenteral administration of iodinated contrast agents are more common than previously appreciated. The definition of DARs has varied somewhat but usually means adverse events that begin 1 hour or longer after the administration of the contrast agent. The majority occur 6–12 hours after initial contrast material injection. Other than contrast material–induced nephropathy, DARs that are of most frequent concern are cutaneous. The incidence of delayed adverse cutaneous reactions has been reported to range from 0.5% to 9%, of which some are moderate to severe in distribution and associated symptoms (1). These reactions are often not brought to the attention of the radiologist and are ascribed to other causes because contrast agents have a biologic half-time of only about 1½ hours, are too small to function unbound as antigens, and are minimally protein bound. Because many radiologists are unaware that such reactions occur, DARs are often mistakenly thought to be caused by another inciting agent.

There have been a relatively small number of prospective studies that have examined the incidence and characteristics of DARs; the first was by Panto and Davies in 1986 (2), who reported 5% of subjects experiencing a rash and 14% showing a variety of other reactions to high osmolar contrast media. Trying to define the actual occurrence of late reactions has been difficult, and the reported incidence for late reactions to monomeric nonionic low osmolar contrast media varies from 1% to 23% (3). In addition, there is the so-called background noise, whereby anywhere from 3% to 12% of surveyed subjects undergoing unenhanced computed tomography (CT) reported adverse reactions. Indeed, in our survey of the literature, there were only two prospective studies (4,5) that examined DARs and compared patients receiving intravenous contrast material with a similar population undergoing CT examination without contrast material. Interestingly, these studies showed no overall difference between the subjects receiving intravenous contrast material and the control group relative to the occurrence of DARs. Schild et al (5), however, did report that delayed adverse cutaneous events were noted significantly ($P < .05$) more often with a dimeric nonionic agent than with a monomeric nonionic contrast agent.

The purpose of this prospective clinical surveillance study was to assess the incidence of DARs in patients undergoing contrast-enhanced CT with the monomeric nonionic low osmolar contrast material iohexol and to compare these effects with DARs in patients undergoing unenhanced CT as control subjects.

Advances in Knowledge

- In this prospective surveillance of subjects undergoing contrast-enhanced CT, we observed a significantly ($P < .0001$) higher rate of delayed adverse reactions (DARs) in subjects receiving nonionic monomeric low osmolar contrast material (14.3% [37 of 258]) than in a CT control group that did not receive contrast material (2.5% [seven of 281]).
- The most commonly observed DARs were cutaneous in nature, may be moderate in severity and duration, and may require treatment.

Implications for Patient Care

- DARs to contrast-enhanced CT occur more often than is generally recognized, may be moderate in severity, and are often ascribed to causes other than contrast media.
- Given the continual and dramatic increase in the utilization of contrast-enhanced CT, the implications are for a substantial occurrence of patient morbidity in need of clinical strategies for treatment.
- Our findings should alert radiologists about the common occurrence of DARs secondary to contrast-enhanced CT and raise the level of awareness of the referring clinicians.

Materials and Methods

Bracco Diagnostics (Princeton, NJ) has provided financial support for this study. The authors had control of the data and information submitted for publication. Our study was approved by the institutional review board, and informed written consent was obtained from each patient participating in the study. The study was Health Insurance Portability and Accountability Act compliant. This prospective surveillance was conducted over the course of 2 years (2006–2008) at a tertiary academic medical center and included patients who were referred for chest, abdominal, pelvic, head, neck, or extremity CT with or without contrast material administration. Patients were excluded if they *(a)* were younger than 18 years old, *(b)* were pregnant or lactating, *(c)* had a prior moderate-to-severe adverse reaction to contrast media, *(d)* had renal dysfunction, *(e)* had previously participated in a similar study, *(f)* were scheduled for CT with injection of a contrast medium other than iohexol (350 mg of iodine per milliliter), and *(g)* anticipated not being available for telephone contact or were unwilling to complete the

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Abbreviation:
DAR = delayed adverse reaction

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See Materials and Methods for pertinent disclosures.

mail-in questionnaire. After a patient was deemed eligible for participation in the study, the study was described in full, and informed written consent was obtained by a clinical trials monitor during regular working hours and during evening hours and weekends by another clinical trials monitor who was employed for 3 months at the midpoint of the study. The patients were randomly included in the study. Each patient was approached sequentially and was invited to participate, with each of the daily imaging sessions having been determined by schedulers unaware of the study and routinely employing a next-available scheduling template.

Patients in whom contrast-enhanced CT was performed received the monomeric nonionic low osmolar contrast agent iohexol (Omnipaque 350; GE Healthcare, Princeton, NJ). The osmolality of iohexol is 844 mOsm/kg, and the iodine content is 350 mg of iodine per milliliter. Subjects in whom intravenous contrast medium administration was not requested for their CT examination served as the control group. Our original protocol had also included a third cohort of subjects receiving iodixanol (Visipaque 320; GE Healthcare), but this was abandoned because our radiology faculty ceased using this agent shortly after the beginning of this study.

CT was performed according to our standard clinical protocols with one of two spiral systems (LightSpeed 16, Discovery ST, or LightSpeed QX/i; GE Medical Systems, Milwaukee, Wis). If intravenous contrast material was clinically indicated, a standard volume of 125 mL was injected at a rate of 4 mL/sec with a power injector. Subjects in the control group did not receive contrast material prior to being scanned. CT was performed in one of two locations: either in the main hospital or at a separate ambulatory center.

All patients were monitored closely for 1 hour following CT. Each patient received a questionnaire (Fig 1) that listed 16 possible reactions and invited any other comments about other types of clinical findings observed by the patient that occurred more than 1 hour to 7 days following CT examination. Patients

Figure 1

CT SCAN QUESTIONNAIRE

Subject Code Number: _____

Type of Exam _____

After the completion of your CT scan, did you experience any of the following symptoms within the next 3 days?

1. rash
2. itching
3. skin redness
4. skin swelling
5. nausea
6. vomiting
7. low blood pressure
8. dizziness or lightheadedness
9. difficulty breathing
10. throat pain
11. throat swelling
12. chest pain
13. palpitations
14. abdominal pain or cramps
15. diarrhea
16. lip swelling
17. other: _____

If you experienced any of the above symptoms, please answer the following questions:

- How soon after the exam did your symptoms start? _____

- How long did your symptoms last? _____

- Did you see a doctor for your symptoms? Yes _____ No _____

- Did you receive any treatment for your symptoms? Yes ____ No _____
  If yes, what was the treatment? _____

If you experienced no symptoms, please check here: _____

Figure 1: CT scanning questionnaire.

were encouraged to contact the clinical trials monitor if they encountered any alarming or persistent signs or symptoms. To ensure maximum compliance, the study coordinator also initiated direct telephone contact with each patient at 3 days following CT. Any patient suspected of having a clinically important cutaneous reaction possibly necessitating treatment was invited for a full dermatologic assessment (S.B., M.A.F.) including skin biopsy, if indicated.

Demographic information and DARs were first analyzed by using descriptive statistics. The DARs of the iohexol and control groups were then compared by using a two-sided Wilcoxon-Mann-Whitney test. Because age and sex differences were noted between the two treatment groups, a logistic regression was performed to compare the iohexol and control groups for the proportion of patients experiencing any DAR. A two-sided Fisher exact test was then used to compare the proportion of patients experiencing a specific DAR in the iohexol and control groups. All analyses were performed by using software (SAS, version 9.1; SAS Institute, Cary, NC). A P value less than .05 was considered to indicate a statistically significant difference.

Results

Overall, 731 subjects were invited to participate in the study, of which 128 (17.5%) declined. As noted above, the iodixanol cohort, which consisted of just 64 enrolled subjects, was terminated and was not included in the rest of the statistical assessment. Thus, 539 subjects (mean age, 53.05 years ± 14.9 [standard deviation]; age range, 18–94 years) were enrolled in the study, of which 258 comprised the iohexol group and 281 comprised the control group. Of the 539 enrollees, 403 (74.8%) returned

Table 1

Demographic Information in 539 Patients in Iohexol and Control Groups

Parameter	Iohexol Group ($n = 258$)	Control Group ($n = 281$)
Age (y)*	55.6 ± 13.2 (19–94)	52.06 ± 15.9 (18–85)
No. of men	149	132
No. of women	109	149
Age of men (y)*	55.7 ± 12.8 (19–94)	51.9 ± 16.7 (18–84)
Age of women (y)*	55.3 ± 13.7 (22–86)	52.2 ± 15.2 (18–85)
CT type		
Chest CT angiography	17	0
Abdominal and pelvic CT angiography	34	0
Abdominal and pelvic CT	176	0
Head or neck CT	28	0
Extremity CT	3	0
Unenhanced abdominal and pelvic CT	0	94
Unenhanced head CT	0	83
Unenhanced chest CT	0	71
Unenhanced extremity CT	0	33
Subject location		
Inpatient	11	0
Outpatient	247	281

Note.—Unless otherwise indicated, data are numbers of patients. Overall mean age was 53.05 years ± 14.9, with a range of 18–94 years.

* Data are means ± standard deviations, with ranges in parentheses.

the questionnaire. Of the 136 enrollees who had not returned the questionnaire, 72 (52.9%) were contacted by the trials monitor for a total of 475 (88.1%) of 539 follow-ups. The mean age of the 258 subjects in the iohexol group was 55.6 years ± 13.2 (age range, 19–94 years). Similarly, for the control group of 281 subjects, the mean age was 52.06 years ± 15.9 (age range, 18–85 years). There were 149 men (mean age, 55.7 years ± 12.8; age range, 19–94 years) and 109 women (mean age, 55.3 years ± 13.7; age range, 22–86 years) in the iohexol group and 132 men (mean age, 51.9 years ± 16.7; age range, 18–84 years) and 149 women (mean age, 52.2 years ± 15.2; age range, 18–85 years) in the control group (Table 1).

A statistically significant difference was noted between the mean ages in the iohexol and in the control groups ($P = .044$), the latter being slightly younger. There was also a statistically significant difference in terms of sex between the two groups, with the control group having a lower ratio of men to women than the iohexol group ($P = .016$). After adjusting for age and sex, there was a statistically significant difference in the proportion of patients experiencing DARs between the iohexol group and the control group ($P < .0001$). DARs occurred in 14.3% (37 of 258) of subjects receiving iohexol and in 2.5% (seven of 281) of subjects in the control group ($P < .001$). Skin rashes occurred in 2.7% (seven of 258) of subjects receiving iohexol and in 0.36% (one of 281) of subjects not receiving contrast material ($P = .0311$). Other specific DARs that were statistically more frequent in the iohexol group included skin redness ($P = .0055$), skin swelling ($P = .0117$), and headache ($P = .0246$). The constellation of cutaneous DARs, including rash, itching, skin redness, and swelling, also occurred more frequently in the iohexol group, 10.1% (26 of 258), than in the control group, 0.71% (two of 281) ($P < .001$) (Table 2).

Eight subjects reported skin rashes during the study, as indicated on their questionnaire. Five (four in the iohexol group and one in the control group) subjects reported having a rash to the clinical coordinator when contacted by telephone. Referrals for dermatologic assessment were offered, and three of these subjects (three in the iohexol group) accepted the referral. The one subject in the control group reporting a rash discussed his reaction to the dermatology department by telephone only. The findings in these patients are described and depicted in more detail in Appendix E1 (online) and Figures 2–4.

Discussion

In our literature search, we found two prospective clinical investigations that assessed DARs and incorporated an unenhanced CT cohort in parallel with a study population receiving intravenous contrast media. These were studies by Munechika et al (4), an extended abstract reported in 1998 from Japan, and Schild et al (5), in 2006, a prospective randomized control trial from Germany. Munechika et al (4) found an incidence rate of DARs of 10.3% with unenhanced CT and 12.4% with contrast-enhanced CT. The authors then reported the true-positive rate for DARs after iohexol, a nonionic monomer, to be 2.1% (12.4% − 10.3% after unenhanced CT; $P = .094$, not significant). Schild et al recruited 895 patients and compared iopromide (Ultravist 300; Schering, Berlin, Germany), a low osmolar contrast material monomer, to iotrolan (Isovist 280; Schering), an iso-osmolar dimer, and a cohort of subjects not receiving contrast material. These authors observed no significant difference between the three groups for DARs, overall. However, in the subset of moderate DARs, these authors reported a higher frequency ($P < .006$) in the dimeric group than in the control group. Delayed cutaneous symptoms (itching or skin rash) were also reported significantly more often ($P = .027$) in the dimeric group (16.4%) than in the monomeric group (9.7%).

In our study, overall, 14.3% of subjects in the iohexol group and 2.5% of subjects in the control group experienced a DAR, with these complications being seen significantly more frequently ($P < .001$) in the iohexol group than in the control group. Other significant findings were the occurrence of rash ($P = .0311$), skin redness ($P = .0055$), skin swelling ($P = .0117$), and headache ($P = .0246$).

Table 2

DARs in Iohexol and Control Groups

Parameter	Iohexol Group ($n = 258$)	Control Group ($n = 281$)	*P* Value
No. of patients with DARs	37 (14.3)	7 (2.5)	<.0001*
No. of patients with itching or rash	13 (5.0)	2 (0.71)	.00273*
No. of patients with cutaneous DARs	26 (10.1)	2 (0.71)	<.0001*
No. of DARs recorded	75	13	
Type of DARs			
Rash	7 (2.7)	1 (0.36)	.0311*
Itching	6	1	.0587
Skin redness	7	0	.0055*
Skin swelling	6	0	.0117*
Nausea	8	2	.0542
Vomiting	3	0	.109
Low blood pressure	0	1	>.99
Dizziness or lightheadedness	9	3	.0785
Difficulty breathing	1	1	>.99
Throat pain	2	1	.6089
Throat swelling	1	0	.4787
Chest pain	4	1	.1987
Palpitations	1	0	.4787
Abdominal pain or cramps	2	1	.6089
Diarrhea	1	0	.4787
Lip swelling	0	0	NA
Other			
Headache	5	0	.0246*
Loss of energy or fatigue	4	0	.0519
Slight burning feeling on lips	1	0	.4787
Dry cough	1	0	.4787
Excess mucous	1	0	.4787
Fever	1	0	.4787
Tingling	1	0	.4787
Head felt hot	0	1	>.99
Metallic taste in mouth	1	0	.4787
Stinging in rib area	1	0	.4787
Bruising due to intravenous placement	1	0	.4787

Note.—Data are numbers of patients, with percentages in parentheses. NA = not available.

* Denotes statistical significance.

Approaching, but not achieving, statistical significance were nausea, loss of energy or fatigue, and dizziness or lightheadedness.

Eight prospective investigations (4–11) have assessed the incidence of DARs, with the intravenous administration of monomeric nonionic low osmolar contrast material. Five (5–9) of these specifically identified the rate of delayed rashes. One of these studies, however, by Bertrand et al in 1995, examined DARs following phlebography by injecting both extremities, utilizing tourniquets, and employing a double dose of contrast material (200 mL) (6). This appears to be an outlier with regard to the overall rate of DARs and the rate of rashes following intravenous administration. These authors described a rash incidence of 18.8% (nine of 48) and an overall rate of DARs of 70.8% (34 of 48) (6). If we omit this single study, we find that the incidence of delayed rash ranges from 2.3% to 5.8% (5, 7–9).

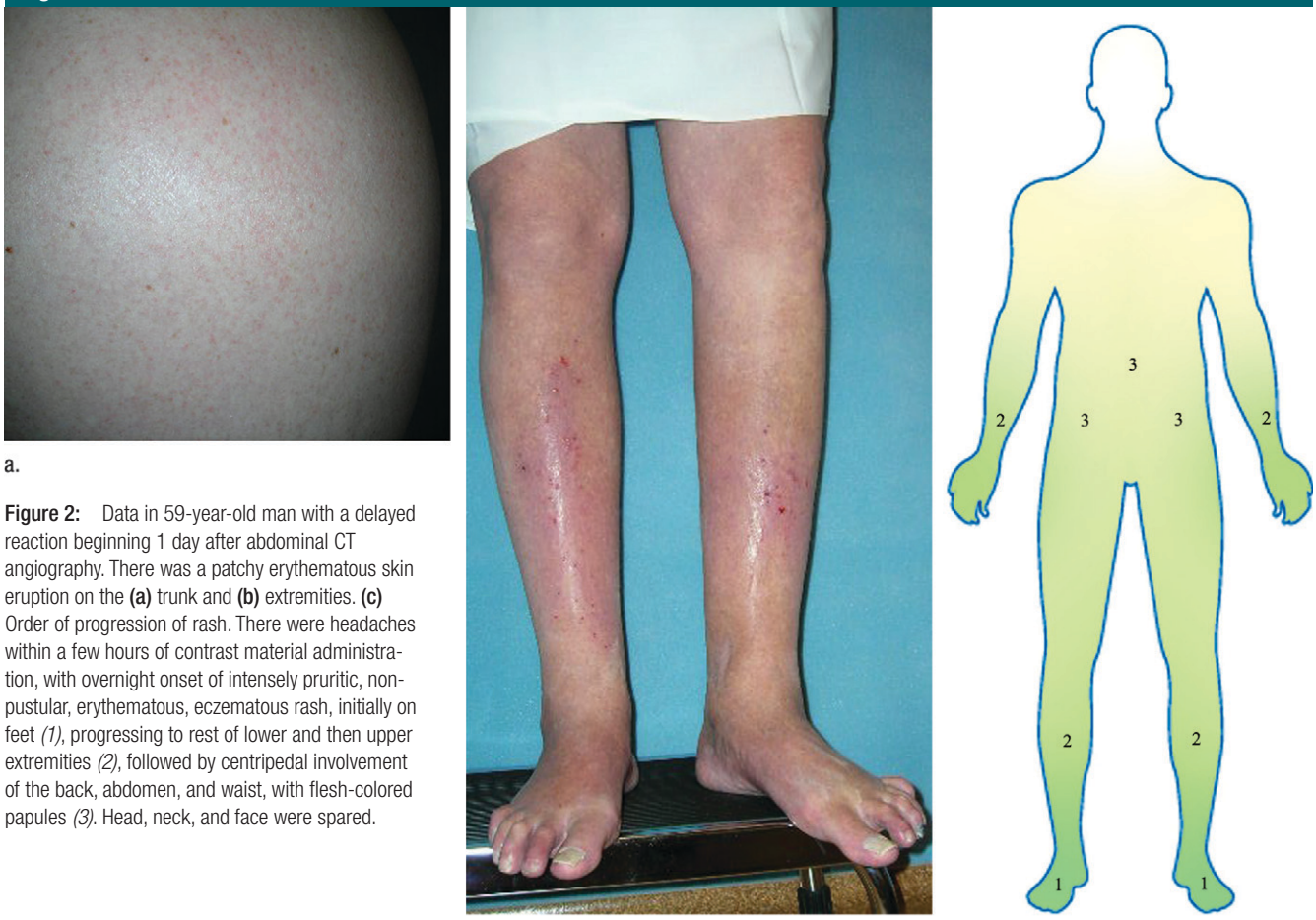
Four prospective studies (12–15) have reported on DARs following the intraarterial administration of monomeric nonionic low osmolar contrast material, with a rate of skin rash ranging from 2.4% to 4.2%.

Two prospective studies (12,13) have reported outcomes following the intraarterial utilization of the nonionic dimer iodixinol (Visipaque 320; Nycomed, Birmingham, England). There was a significantly higher rate of rash with the dimer than with either the monomer iopamidol (Niopam 300; Bracco Diagnostics) or the ionic dimer ioxaglate (Hexabrix; Mallinckrodt, Alton, England) and a higher overall rate of DAR. The occurrence of rash was 12.2% and 10.4% for the dimer versus 4.2% and 2.7% for the nonionic monomer in the two prospective studies.

Although DARs are generally considered to be mild and non–life threatening, some can be moderate to severe. Review of some prospective clinical trials performed in the early to mid-1990s with the clinical testing of the then new nonionic dimers reveals potentially substantial side effect observations. Palmers et al (16) in 1993, in a clinical trial of cerebral angiography, reported two (5%) of 40 cases of delayed moderate skin reactions, one lasting 37 hours and the other lasting 5 days. Conroy et al (17) in 1994, in a study on intravenous urography, described a case of severe angioneurotic edema and rash, requiring antihistamines for 1 week, in one of 117 subjects. Fishbach et al (18) in 1995, in a clinical trial of intravenous digital subtraction angiography, reported three (5%) of 60 cases of DARs, including one case of moderate laryngeal edema, facial edema, and conjunctivitis (treated with antihistamine and steroids); one case of severe pruritis; and one case of generalized urticaria. Manninen et al (19) in 1995, in a clinical trial of cardioangiography, described a vasovagal reaction of severe intensity, however, with uncertain relationship to the contrast material itself. Finally, Skehan et al (20) in 1998, in a study on intravenous urography, noted three of 196 cases of DARs, including one patient with facial swelling and skin rash and two other patients with skin rashes.

The clinical appearance of DARs appears to be distinctive enough that certain patterns have been recognized and classified in studies by Sutton and coworkers (12,13). Group A reactions

Figure 2



a. b. c.

Figure 2: Data in 59-year-old man with a delayed reaction beginning 1 day after abdominal CT angiography. There was a patchy erythematous skin eruption on the **(a)** trunk and **(b)** extremities. **(c)** Order of progression of rash. There were headaches within a few hours of contrast material administration, with overnight onset of intensely pruritic, nonpustular, erythematous, eczematous rash, initially on feet *(1)*, progressing to rest of lower and then upper extremities *(2)*, followed by centripedal involvement of the back, abdomen, and waist, with flesh-colored papules *(3)*. Head, neck, and face were spared.

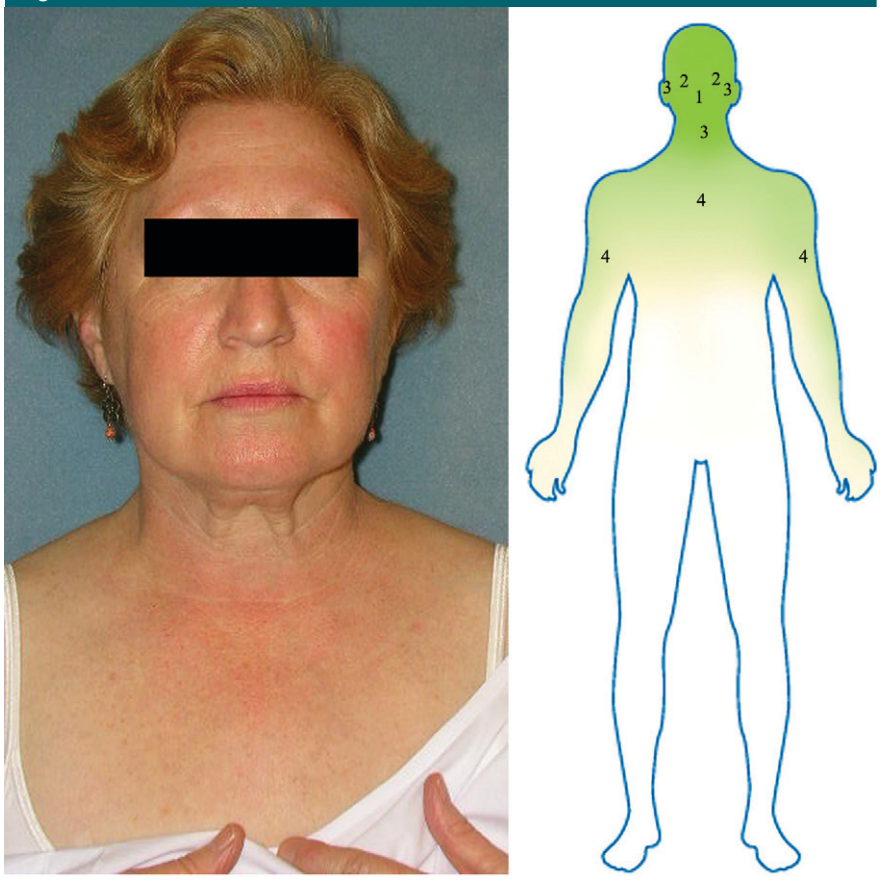
were characterized by a generalized pruritic macular rash. Group B reactions were characterized by localized reaction, most commonly involving palmoplantar surfaces or the face (group B1) or relatively mild involvement of the trunk or extremities (group B2). However, the overlapping features demonstrated in our case histories suggest these groups are not mutually exclusive.

The pathophysiology of cutaneous DARs is speculative but likely represents a spectrum of T cell–mediated delayed hypersensitivity. Recognition of a broad clinical spectrum of DARs and a greater understanding of T cell subsets, functions, and interactions suggest that traditional classification as a type IV delayed hypersensitivity reaction is simplistic (21). A more recent classification of drug hypersensitivity proposes four subsets (IVa–IVd) of delayed drug hypersensitivity reactions reflected by distinct T cell subsets and cytokine and chemokine activation profiles (21). Type IVa reactions are characterized by Th1-mediated monocyte or macrophage activation and contact dermatitis, while Type IVb reactions result from Th2-mediated eosinophil activation and maculopapular or bullous eruptions. Type IVc reactions result from cytotoxic T cell activation resulting in maculopapular, pustular, or bullous eruptions. Type IVd reactions are characterized by neutrophilic infiltrates such as acute generalized exanthematous pustulosis, and possibly, our case of biopsy-proved suppurative folliculitis (Fig 4b).

Specific characteristics of the contrast medium molecule related to the pathophysiology of DARs are unknown. However, it does appear that nonionic dimers have higher rates. Interestingly, Speck et al (22) in 1998, in a rat model, showed unusually long dwell times of the nonionic dimers versus nonionic monomers in the skin and organs known to be involved in immune responses for 3 days after intravenous injection. It is also interesting that the other class of contrast material Speck et al showed as having prolonged dwell time was gadolinium based, of course now linked with nephrogenic systemic fibrosis.

The American College of Radiology has recently highlighted the potential importance of DARs in the Manual on Contrast Media, version 6.0, because they occur more often than is generally recognized, may recur, may have serious sequellae, and importantly, are often ascribed to causes other than contrast media (1). This will be of ever-growing concern because there has been a continual and dramatic increase in the

Figure 3



a. b.

Figure 3: Data in 54-year-old woman with a delayed reaction beginning 4 hours after abdominal contrast-enhanced CT. **(a)** At 96 hours after exposure, this eruption was resolving, with residual mottled patchy erythema on the upper arm, face and neck, and upper back. **(b)** Order of progression of the rash. The rash first started in the perioral region *(1)*, spreading 4 hours later over the remainder of the face *(2)*. It continued to the ears, neck, and upper chest *(3)*, eventually progressing to the remainder of the chest and upper extremities *(4)*.

utilization of CT with contrast media over the course of the past 2 decades. In the United States, approximately 68 700 000 CT scans were performed in 2007 (23). If we presume 50% of these examinations are performed with contrast media and a 2.7% rate of skin rashes, this equates to 927 450 cases of skin rash in the United States alone, which is a major public concern. Our institution is a moderate-sized academic medical center with a level I trauma center and just more than 500 hospital beds. We performed 3127 contrast-enhanced CT examinations on average per month over the period of this surveillance (2007–2008), which equates to 20 cases of skin rashes per week.

Our study had several limitations. One limitation was the use of a questionnaire. However, this was the only prospective study in which every attempt was made to make telephone contact with all enrolled subjects at 3 days following CT. In addition, all subjects were enrolled with their agreement for this type of follow-up. Four hundred and three (74.8%) of the 539 patients enrolled returned the questionnaire. However, additional contact by the trials monitor allowed a follow-up rate of 88.1%. Another limitation was that the composition of our control group did not exactly match that of the iohexol group. The ideal randomized comparison of identical examinations with and those without contrast agents is probably impossible. The demographic data were very close, and there does not appear to be any identifiable factor biasing our results. An additional limitation was that only a single agent, iohexol, was studied. Unfortunately, we could not complete enrollment for our iodixanol cohort but are currently collaborating with other institutions that do use iodixanol to complete a multicenter prospective comparison between monomeric nonionic iohexol, dimeric nonionic iodixanol, and a control group. Despite this limitation, the results of our study remain generalizable to other monomeric nonionic low osmolar contrast media.

In summary, we reported a prospective clinical surveillance study that evaluates the incidence of DAR events after CT in patients who received either a monomeric contrast agent or no contrast material at all. We found that patients who received the contrast agent had a significantly higher incidence of DARs compared with those who did not receive contrast material. DARs, including rash, skin redness, skin swelling, and others, were each more frequently seen in the contrast media group than in the control group. Our results support a cause-and-effect relationship from contrast material administration. Greater awareness is needed by the radiologic community, especially with increasing and more common use of contrast-enhanced CT in clinical diagnosis.

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Figure 4

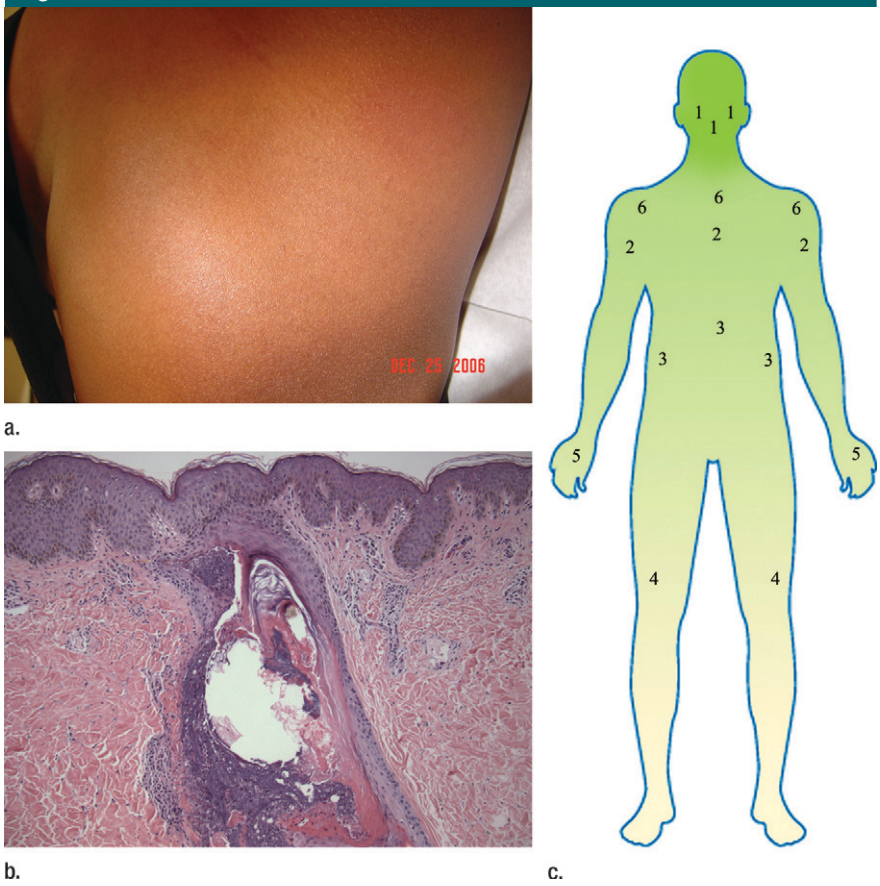

Figure 4: Data in 22-year-old woman with a delayed reaction beginning 2 hours after CT angiography. **(a)** Rare tiny pustules on the trunk. **(b)** Biopsy result showed suppurative folliculitis. **(c)** Order of progression of the rash over 72 hours. An intensely pruritic, burning sensation on the cheeks and jaw *(1)* was followed by an eruption progressing to the upper extremities and chest *(2)*, abdomen and sides *(3)*, lower extremities *(4)*, and finally the back (not shown). While initially, intertriginous areas were involved and the palms and soles *(5)* were spared, by 72 hours, the latter parts became involved, along with generalized xerosis, as well as pustules on a nonerythematous base scattered on the upper trunk and proximal upper extremities *(6)*.

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