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An outbreak of joint and cutaneous infections caused by non-tuberculous mycobacteria after corticosteroid injection

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SUMMARY

Objectives: An outbreak of joint and cutaneous infections among patients who had been injected at a single clinic in South Korea was investigated.
Methods: In this retrospective case–control study, 61 cases were diagnosed based on symptoms and signs of septic arthritis or cutaneous infection that developed after injections at the clinic between April and September 2012; 64 controls were investigated by administering questionnaires on risk factors and analyzing the clinic medical records. An environmental investigation was performed, and clinical specimens of the cases were analyzed by pulsed-field gel electrophoresis.
Results: All cases were injected with triamcinolone. A greater number of triamcinolone injections (adjusted odds ratio 4.3, 95% confidence interval 1.5–12.1 for six or more visits, compared with one or two visits) was associated with the development of an infection. In the clinic, only the triamcinolone injection was prepared by mixing with lidocaine and normal saline, and an alcohol swab was prepared using boiled tap water by members of the clinic staff. Although injected medications and environmental cultures were not found to be responsible, a single strain of *Mycobacterium massiliense* was isolated from the affected sites of 16 cases.
Conclusions: Repeated injection of triamcinolone contaminated with NTM from the clinic environment may have caused this post-injection outbreak.

1. Introduction

Non-tuberculous mycobacteria (NTM) are defined as mycobacteria excluding *Mycobacterium tuberculosis* and *Mycobacterium leprae*. NTM are ubiquitous in the environment and there are more than 65 different species, including *Mycobacterium massiliense* and *Mycobacterium abscessus*.[1] They can cause opportunistic infections,[2] and can lead to pulmonary, lymph node, skin and soft tissue, and bone and joint infections. Such infections result from environmental exposure (soil, dust, water), contaminated materials, or invasive procedures (medical devices, multi-dose vials).[3]

Corticosteroid injections are frequently used for the local treatment of musculoskeletal disorders, including osteoarthritis, synovitis, bursitis, tendonitis, back pain, etc.[4–6] Relatively mild adverse effects, including swelling, pain, steroid flare, hot flashes, mild skin discoloration, skin atrophy, and cellulitis, have been reported in prospective and retrospective studies, although there have been a few case reports of atypical Mycobacterium soft tissue infection, tendon rupture, and ischemia.[7]

In October 2012, 27 patients were hospitalized due to septic arthritis caused by a presumed NTM infection, after having been given triamcinolone injections at a single clinic. These cases were reported to the Korea Institute of Drug Safety and Risk Management (KIDS) as a spontaneous adverse drug events report. Since such infections are difficult to diagnose and NTM are difficult to isolate and are resistant to multiple antibiotics,[8] it is important to

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perform prompt investigations in order to detect possible cases and provide appropriate treatment. Therefore, an epidemiological investigation team was assembled, consisting of staff from KIDS, the Korea Food and Drug Administration (KFDA; Ministry of Food and Drug Safety (MFDS) from 2013), the Korea Center for Disease Control and Prevention (KCDC), and the local public health authorities (the community public health center and local city government), supervised by the Ministry of Health and Welfare (MoHW). An epidemiological investigation was performed immediately to identify whether the infection was due to the injected drugs or other factors, and to assess the risk factors for post-injection NTM infection. A case–control study was performed to compare exposure to injections and other environmental factors between patients with NTM infections and healthy subjects.

2. Methods

2.1. Case detection

Initially, 27 cases were reported to KIDS as a spontaneous adverse drug event by the physician at the clinic. During a site visit, the clinic medical charts were investigated to identify other possible cases of infection. Additional cases had to be found from other sources because a medical assistant employed by the clinic intentionally destroyed documents containing patient contact information. At first, the electronic medical chart system was searched and the names and personal identification numbers of eligible patients with orders for any injection at the clinic between April and September 2012 were identified. Every member of the Korean population has his/her own unique personal identification number. Using this information, in collaboration with a police investigation, three postal questionnaire surveys were performed (November 2012, December 2012, May 2013), asking patients whether they had experienced adverse events after the injection at the clinic. Furthermore, two healthcare utilization databases were linked: the Korea Health Insurance Review and Assessment Service (HIRA) and the National Health Insurance Service (NHIS) claims database (December 2011 to June 2013). Using these databases, patients who had visited medical institutions due to suspected infections were identified using the following diagnostic codes: tuberculosis of skin and subcutaneous tissue (ICD-10, A18.4); other mycobacterial infections (A31.8), mycobacterial infection, unspecified (A31.9); cutaneous abscess, furuncle and carbuncle (L02), cellulitis (L03); other specified local infections of skin and subcutaneous tissue (L08.8); pyogenic arthritis, unspecified (M00.9); tuberculous arthritis (M01.1); inflammatory polyarthropathy (M06.4); rheumatoid arthritis, unspecified (M06.9); villonodular synovitis (pigmented) (M12.2); internal derangement of knee, unspecified (M23.9); effusion of joint (M25.4); infection following a procedure, not elsewhere classified (T81.4).

After identifying potential cases from the various sources, cases for this epidemiological investigation were identified through interviews and medical chart review. A case patient was a patient with an abscess, mass, pain, redness, swelling, or a burning sensation, who was diagnosed with a potential NTM infection at a medical institution (either inpatient or outpatient) between April and September 2012 after exposure to any injections at the clinic.

2.2. Selection of controls

Among patients who had been given injections at the clinic between April and September 2012, those without any symptoms or signs of NTM infection were assumed to be potential controls. The absence of NTM infection was assessed by (1) no diagnostic codes for a suspected infection in the HIRA or NHIS claims database, and (2) a response indicating no signs or symptoms in the postal survey or direct contact interview. Those who agreed to the request for enrollment and who completed the questionnaire were included as controls in the case–control study.

2.3. Data collection

To define the patients who had visited the clinic during April to September 2012, the electronic medical charts were reviewed and the exposure status of those who had received any injections was determined. For the case–control study, data were collected by interview using a structured questionnaire during the epidemiological investigation. The questionnaire included information on patient characteristics, risk factors (age, sex, smoking, alcohol consumption, hygiene, and comorbidities), exposures (visit to the clinic, injection procedure, and site of injection), and adverse events for the cases (symptoms of infection, date of onset, medical visits due to infection, and site of infection). For the cases, the medical charts were reviewed for information about the treatment of infections, noting the diagnosis of the signs and symptoms, laboratory tests, synovial fluid examination, surgery modality and location, antibiotic treatment, and NTM species identified. The data from the completed questionnaires and medical records were entered into a computerized database.

2.4. Evaluation of injection practices and environmental/ laboratory investigations

The physician and medical assistants at the clinic were interviewed about their injection procedures. However, it was impossible to investigate the medical assistant who gave the injections, because we were not able to contact him. KFDA staff ascertained the manufacturer and lot numbers of the injections, and performed an evaluation of the microorganisms present in the injection medications and syringes. Environmental specimens were taken, including empty vials, injection needles, alcohol swabs, surfaces, and water to culture for mycobacteria. In addition, the clinical specimens of 18 NTM-positive cases from six hospitals were examined using pulsed-field gel electrophoresis (PFGE) by the KCDC.[9]

2.5. Statistical analysis

Descriptive statistics were used to illustrate the characteristics of the study population. For the cases, the incubation period between the last injection of triamcinolone and symptoms of infection was calculated. The odds ratios (ORs) and their 95% confidence intervals (95% CI) for infection according to exposure to various injections, including triamcinolone, betamethasone, methylprednisolone, hyaluronate, piroxicam (non-steroidal anti-inflammatory), tramadol (analgesic), pridinol (muscle relaxant), Arnica tincture, and Aconitum tincture (combined anti-inflammatory injection), were calculated using logistic regression. The ORs and their 95% CI of factors associated with infection were also calculated. The number of administrations of each injection, the calendar month of last injection, and injections in specific periods were included as factors. The statistical analysis was performed using SAS statistical application software (release 9.3; SAS Institute, Inc., Cary, NC, USA).

2.6. Ethics statements

This study was waived from review by the Institutional Review Board of the Korea Institute of Drug Safety and Risk Management. The collection of patient information using the HIRA and NHIS databases and contacting them via police investigation was endorsed by the Ministry of Security and Public Administration

as an exception to the Personal Information Protection Act. Informed consent was collected from cases and controls who we were able to contact and who responded to an interview.

3. Results

3.1. Characteristics of the study population

Among the 1264 patients who visited the clinic between April and September 2012, 244 were administered one or more injections at the clinic. Among these, 118 patients were excluded from the study population as it was not possible to contact them or they refused to be contacted ($n = 5$ for patients assumed to have symptoms of NTM infection, $n = 113$ for patients assumed to have no symptoms or signs of NTM infection). Another patient who had a history of NTM infection in the previous calendar year was also excluded from the study population. A total of 66 potential cases were identified by spontaneous reports from patients and physicians treating potential cases, the HIRA claims databases, and the postal survey; the response rate to three administrations of the postal survey was 52.7%. However, it was not possible to assess whether five patients fit the case definition because their contact information was unavailable or they refused to participate. Thus, 61 subjects were included in the analysis, among whom 29 were confirmed as NTM-positive in the treatment hospitals and 32 suspected cases had clinical symptoms of NTM infection diagnosed by clinicians. A total of 164 patients were assumed to be without NTM infection according to the HIRA and NHIS databases. However, there were 99 patients who could not be contacted in order to carry out the questionnaire interview, and one patient had a history of NTM infection just before the study period. The final population for the case–control analysis was 61 cases and 64 controls (Figure 1).

When comparing cases with NTM infection and controls among those who were exposed to the injections under investigation, the cases did not differ significantly from the control group in terms of age, alcohol consumption, BMI, and frequency of showering and bathing on the date of injection. However, the case group included more females and non-smokers ($p < 0.05$) (Table 1).

The epidemic curve for the 61 cases is shown in Figure 2. The date of onset of signs or symptoms of NTM infection stretched from May 2012 to February 2013. The most frequently reported calendar month was September 2012 ($n = 27$). The dates of injection were distributed from May to September 2012. Because each case was given a triamcinolone injection one or more times (mean 6.1, standard deviation 4.5, range 1–22) during the study period, it was not possible to calculate the time gap between the date of the suspected injection and the date of illness onset. Each case had one or more sites of infection. The location of symptoms among cases was as follows: the knee joint in 50 cases (82.0%), the hip in nine cases (14.8%), the back in eight cases (13.1%), the lumbus in six cases (9.8%), and the shoulder in five cases (8.2%), etc. When the clinical progress of cases was assessed in August 2013, 13 cases (21.3%) had recovered, 46 cases (75.4%) were undergoing outpatient care with antibiotic treatment, and two cases (3.3%) had been hospitalized. Antibiotic susceptibility testing showed that the NTM strains were sensitive to amikacin, clarithromycin, and linezolid.

3.2. Risk of NTM infection

Among the 1264 patients who visited the clinic between April and September 2012, all 61 cases occurred among the 229 patients

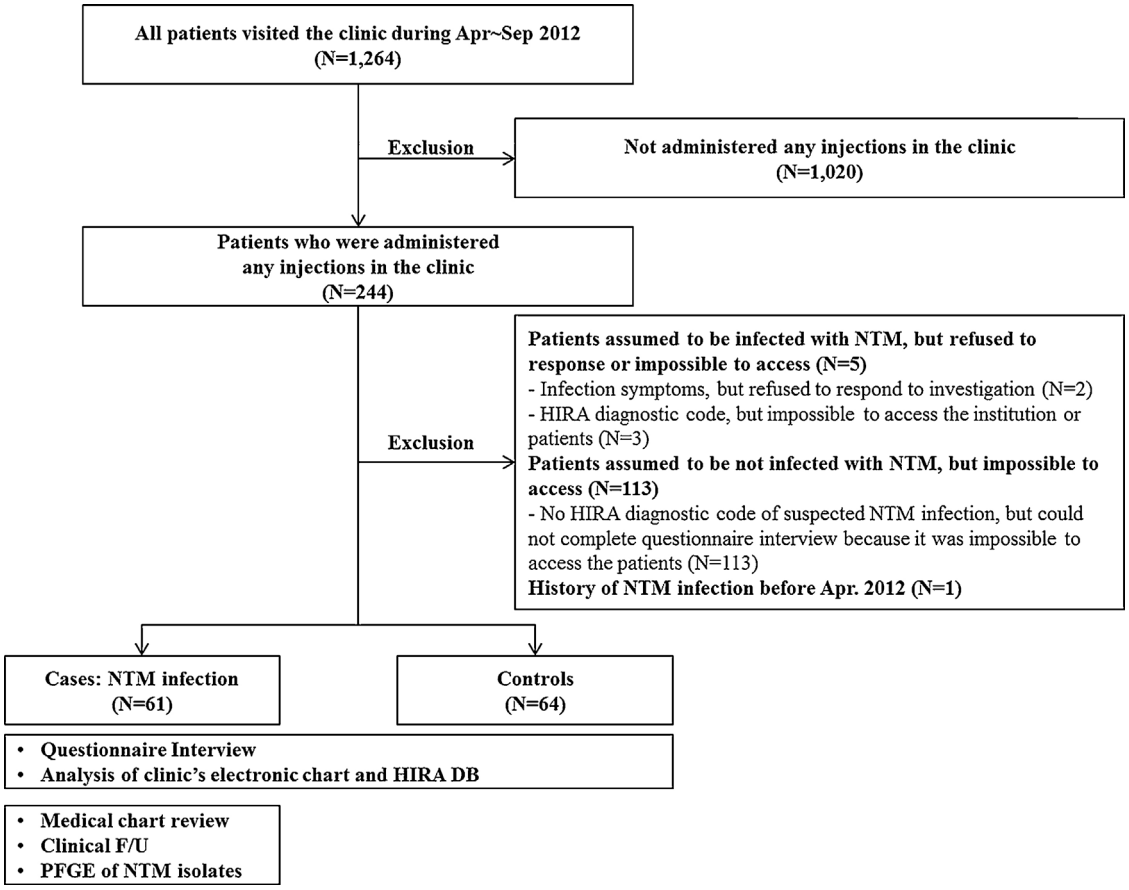


Figure 1. Selection of the case–control study population from patients who visited the clinic. *HIRA: Korea Health Insurance Review and Assessment Service.

Table 1
Characteristics of cases and controls

	Cases (n = 61)		Controls (n = 64)		p-Value[a]
	n	%	n	%	
Sex					
Male	12	19.7	28	43.8	0.004
Female	49	80.3	36	56.2	
Age, years					
Mean ± SD	55.1 ± 9.7		51.6 ± 13.4		0.098
Range	29–75		13–80		
10–19	0	0	2	3.1	0.457
20–29	1	1.6	4	6.3	
30–39	2	3.3	4	6.3	
40–49	13	21.3	13	20.3	
50–59	29	47.6	23	35.9	
60–69	11	18	15	23.4	
70–80	5	8.2	3	4.7	
Smoking					
Current	5	8.2	15	23.4	0.043
Ex	3	4.9	6	9.4	
No smoking	50	82	43	67.2	
Missing	3	4.9	0	0	
Alcohol consumption					
Current	17	27.9	25	39.1	0.199
Ex	6	9.8	2	3.1	
No drinking	35	57.4	37	57.8	
Missing	3	4.9	0	0	
BMI, kg/m^2					
Mean ± SD	23.1 ± 2.5		23.1 ± 2.5		0.953
Range	17.1–28.0		17.8–29.1		
<18.5	3	4.9	4	6.3	0.836
18.5 to <23.0	25	41	28	43.8	
≥23.0	31	50.8	29	45.3	
Missing	2	3.3	3	4.7	
Frequency of shower/bath					
≥1/day	36	59	44	68.8	0.697
2–3 per week	17	27.9	15	23.4	
1 per week	5	8.2	4	6.3	
Missing	3	4.9	1	1.5	
Frequency of changing underwear					
≥1/day	41	67.2	56	87.5	0.011
2–3 per week	12	19.7	7	10.9	
1 per week	5	8.2	0	0	
Missing	3	4.9	1	1.6	
Bath on injection date					
Yes	35	57.4	40	62.5	0.636
No	13	21.3	16	25	
Cannot remember	0	0	2	3.1	
Missing	13	21.3	6	9.4	

SD, standard deviation; BMI, body mass index.
[a] p-Values were calculated by Chi-square test, Fisher's exact test, or the Student's t-test, as appropriate.

who were injected with triamcinolone (attack rate 26.0%); no cases occurred in the absence of exposure to triamcinolone injection.

The results of the case–control analyses are presented in Table 2. After adjusting for potential confounders, a higher number of visits to the clinic for corticosteroid injections showed a significantly increased risk of infection (aOR 4.3, 95% CI 1.5–12.1 for six or more visits, compared with one or two visits). Other injections including hyaluronate, piroxicam, pridinol, tramadol, and arnica tincture did not show a significant association with the infection. Regarding the calendar month of triamcinolone injection, the administration of the last injection in August (aOR 20.4, 95% CI 2.0–206.6) was more associated with the development of the infection compared with April (Table 2).

3.3. Process of preparing and applying injections

Interviews with the physician, cases, and controls indicated that the process of preparing and applying injections was as follows. After administering a massage therapy known as 'Chuna', a medical assistant prepared the injection agent. The triamcinolone injection agent was a mixture of approximately 0.5 ml of triamcinolone from a 1-ml container, 1 ml of normal saline from a 20-ml container, and 1 ml of lidocaine from a 20-ml container. After mixing the agent, the remaining triamcinolone solution was stored in a multidose vial at a normal temperature or in a refrigerator for later use. Other injections were sealed in each ampoule and not mixed with normal saline. The hyaluronate injection was prepared as a pre-filled syringe. The nursing assistant gave the injection at multiple sites, including intra-articular, peri-articular, and others, using a single syringe, without wearing gloves, after cleaning the skin with a cotton ball soaked in 70% alcohol that was diluted with boiled tap water.

3.4. Environmental/ laboratory investigations

An investigation of the injection medication and syringe found no microorganisms. Although the clinic environment, including the method of preparing injections and the site of the procedure, was found not to be appropriately sterilized, no NTM were identified in any environmental specimen. However, the following species of NTM were identified in the specimens from 29 of the 61 cases: *M. massiliense* (n = 21), *M. abscessus* (n = 6), and not specified (n = 2). Molecular typing (PFGE) of the 18 *M. massiliense* strains from six hospitals showed identical results (100%) for 16 isolates and similar results for two isolates (97.9% and 96.0%, respectively) (Figure 3). The presence of identical *M. massiliense* isolates in patients admitted to various hospitals implies a high possibility of a common source of infection.

4. Discussion

Although identical NTM isolates from the cases implied exposure to a common infection source, the environmental samples gave negative culture results and the exact infection source was not determined. However, the epidemiological evidence led us to suppose that the infections were linked to contaminated injections, occurring in the storage of the injection agents, in the process of mixing the injection agents, or in the injection procedure. Furthermore, considering the mean incubation period of 18.3 days estimated in the present population, and the fact that the date of occurrence of the adverse events in the cases was spread widely from May 2012 to February 2013, it is likely that the infection was caused by continuous exposure to certain environmental sources.

The infection showed a specific association with triamcinolone injection at a specific clinic. All the cases were exposed to triamcinolone injections. However, there was no report of infection among other patients who were treated with triamcinolone from the same lot at other medical institutions. In addition, a laboratory test of the triamcinolone gave a negative result. If the outbreak had been due to contaminated drugs, the infection would have occurred in a number of different medical institutions. For example, in 2012, contaminated glucocorticoid medication from a single compounding pharmacy caused a multistate outbreak of fungal infection in the USA; over 700 cases of infection were identified in 20 states.[10]

Regarding the source of infection, the rapidly growing mycobacteria could have been present in air or tap water[3] and likely contaminated cotton balls, the injection agent, or other devices. Based on the interviews with the clinic physician and assistant, as well as an environmental investigation, it was apparent that the staff prepared the alcohol for use as a disinfectant themselves, which included the use of boiled tap water (not normal saline) and mixing this with 99% ethanol. In

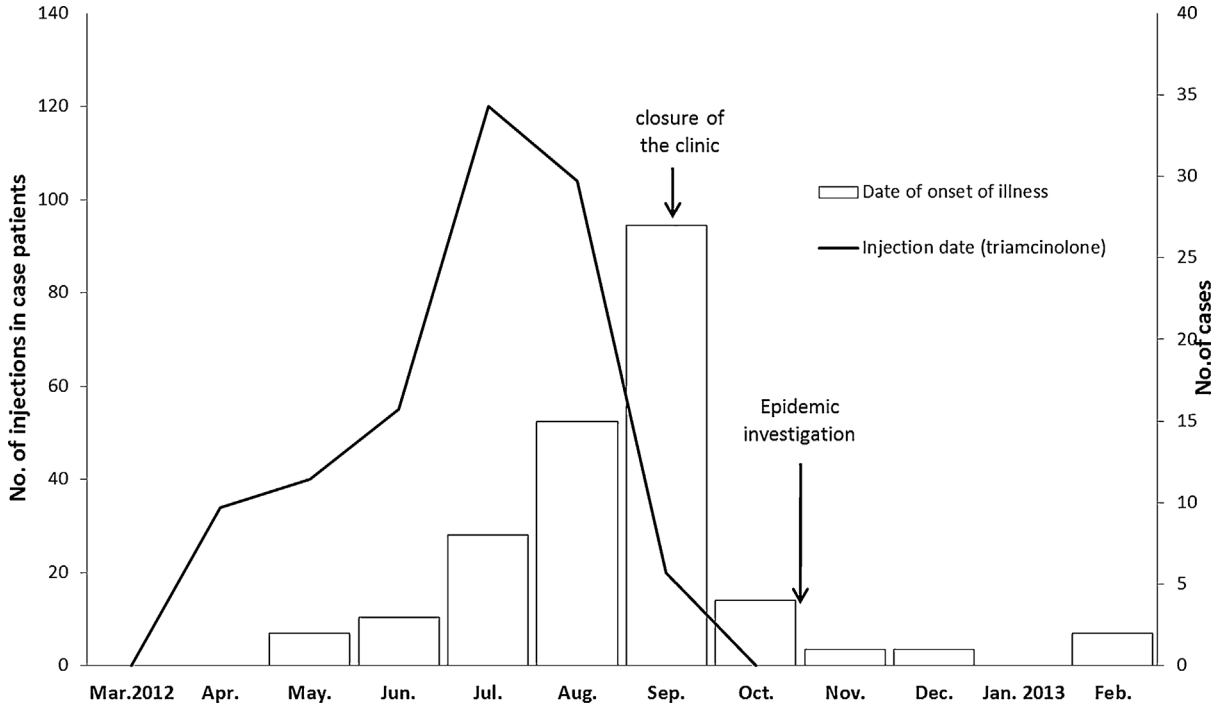


Figure 2. Epidemic curve and longitudinal distribution of date of triamcinolone injection and onset of illness for 61 cases. *Each case had one or more triamcinolone injections (mean ± SD = 6.1 ± 4.5; median (range) = 5 (1–22)).

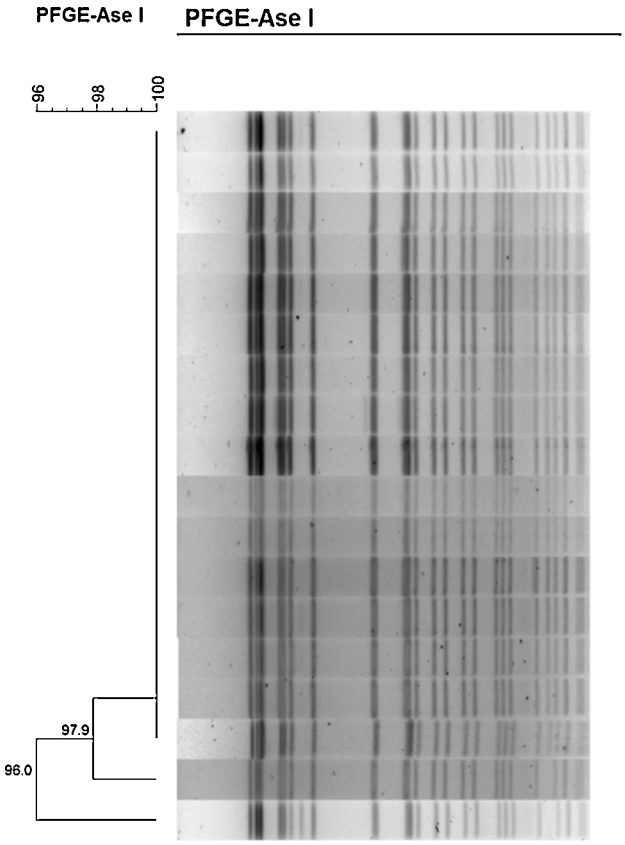
addition, the injection agent was prepared by mixing triamcinolone with normal saline and lidocaine, and some of the remaining agent. After being administered to a patient, the mixed agent was stored at normal temperature or in a refrigerator until its next use.

All cases were given a Chuna massage by a medical assistant. Chuna is a manual therapy widely used in Korean traditional medicine practice for the treatment of musculoskeletal pain; it uses techniques including thrust, mobilization, distraction of joints, and soft tissue release.[11] The massage does not include any

Table 2
Numbers and months of triamcinolone injections, injections with other agents, and the risk of NTM infection: case–control analysis

	Cases (n = 61)		Controls (n = 64)		Crude		Adjusted	
	n	(%)	n	(%)	OR	(95% CI)	OR[a]	(95% CI)
No. of triamcinolone injections[b]								
1–2	13	(21.3)	32	(50.0)	1		1	
3–5	23	(37.7)	21	(32.8)	2.70	(1.12–6.47)	2.91	(1.07–7.85)
≥6	25	(41.0)	11	(17.2)	5.60	(2.17–14.59)	4.25	(1.49–12.13)
Hyaluronate injection	23	(37.7)	11	(17.2)	2.92	(1.27–6.69)	1.27	(0.45–3.63)
Piroxicam injection	58	(95.1)	55	(85.9)	3.16	(0.81–12.30)	3.38	(0.52–21.86)
Pridinol injection	58	(95.1)	59	(92.2)	1.64	(0.37–7.17)	5.17	(0.52–51.06)
Tramadol injection	26	(42.6)	28	(43.7)	0.96	(0.47–1.94)	1.03	(0.38–2.77)
Arnica tincture injection	10	(16.4)	2	(3.1)	6.08	(1.27–29.00)	4.28	(0.66–27.90)
Aconitum tincture injection	2	(3.3)	0	(0.0)	-		-	
Betamethasone injection	1	(1.6)	1	(1.6)	1.05	(0.06–17.17)	-	
Methylprednisolone injection	1	(1.6)	0	(0.0)	-		-	
Last injection date of triamcinolone								
April	1	(1.6)	8	(12.5)	1		1	
May	3	(4.9)	19	(29.7)	1.26	(0.11–14.05)	0.93	(0.08–11.37)
June	3	(4.9)	11	(17.2)	2.18	(0.19–25.02)	1.66	(0.13–20.96)
July	7	(11.5)	9	(14.1)	6.22	(0.62–62.16)	2.53	(0.22–28.87)
August	30	(49.2)	7	(10.9)	34.29	(3.67–320.68)	20.36	(2.01–206.58)
September	17	(27.9)	10	(15.6)	13.6	(1.48–125.31)	8.47	(0.81–88.09)
Triamcinolone injection in specific period								
Apr–May	4	(6.6)	27	(42.2)	1		1	
Jun–Jul	6	(9.7)	5	(7.8)	8.1	(1.66–39.51)	3.79	(0.68–21.3)
Apr–May, Jun–Jul	4	(6.6)	15	(23.4)	1.8	(0.39–8.25)	1.61	(0.33–7.89)
Aug–Sep	12	(19.7)	7	(7.9)	11.57	(2.84–47.12)	12.23	(2.65–56.52)
Apr–May, Aug–Sep	4	(6.6)	1	(1.6)	27	(2.38–306.66)	19.45	(1.36–278.96)
Jun–Jul, Aug–Sep	19	(31.1)	5	(7.8)	25.65	(6.08–108.24)	17.76	(3.83–82.32)
Apr–May, Jun–Jul, Aug–Sep	12	(19.7)	4	(6.3)	20.25	(4.33–94.81)	13.69	(2.61–71.89)

NTM, non-tuberculous mycobacteria; OR, odds ratio; CI, confidence interval.
[a] ORs were estimated using a logistic regression model, adjusting for age, sex, smoking status, and frequency of changing underwear.
[b] The p-value for trend calculated by likelihood test for trend was 0.435.



Hospital	Case	Hsp65 genotype	Subspecies
H1	Case01	type II-1	M. massiliense
H1	Case02	type II-1	M. massiliense
H3	Case04	type II-1	M. massiliense
H3	Case05	type II-1	M. massiliense
H3	Case06	type II-1	M. massiliense
H3	Case07	type II-1	M. massiliense
H3	Case08	type II-1	M. massiliense
H3	Case09	type II-1	M. massiliense
H3	Case10	type II-1	M. massiliense
H4	Case11	type II-1	M. massiliense
H5	Case13	type II-1	M. massiliense
H5	Case14	type II-1	M. massiliense
H5	Case15	type II-1	M. massiliense
H5	Case16	type II-1	M. massiliense
H5	Case17	type II-1	M. massiliense
H6	Case18	type II-1	M. massiliense
H5	Case12	type II-1	M. massiliense
H2	Case03	type II-1	M. massiliense

Figure 3. Molecular strain typing of isolates from 18 cases, by pulsed-field gel electrophoresis (PFGE).

products, such as oils, powders, or solutions, that could act as a culture medium for *M. massiliense*. Inadequate sterilization of the needles or the puncture site was also suspected as a route of transmission. After the Chuna massage, the injection site was sterilized with a cotton ball soaked in diluted ethanol, and then the drugs were injected at multiple sites using a single syringe with one needle, without the use of gloves. The process of preparing the cotton balls soaked in alcohol may also have been a source of infection. In an outbreak of *M. abscessus* infection after trigger point injections and epidural blocks at a clinic in Korea in 2009, inadequate sterilization of the injection sites, inadequate equipment sterilization using the autoclave, and improper preparation of the injection drugs and septic techniques were hypothesized as possible sources of the outbreak.[12] Tiwari et al. (2003) reported an outbreak of post-injection infection that was caused by diluted benzalkonium chloride, which was used as the disinfectant although this antiseptic agent was not effective against *M. abscessus*.[13]

Although it was also difficult to identify the exact source of infection and mode of transmission in these previous outbreak investigations, most previously reported NTM infections were presumed to be due to extrinsic contamination. In the case of an outbreak of *M. abscessus* infection after intramuscular injection in China, contamination occurred due to the inappropriate reuse of needles in the rubber septum of 100-ml multiple-dose normal saline bottles, which were initially assumed to be contaminated via tap water.[14] In addition, in an outbreak of *M. massiliense* after intramuscular injections in Icheon, Korea in 2004, contaminated multidose normal saline from an unknown extrinsic source was suggested as the causative agent.[15]

There have been prior reports of NTM infection after medical procedures. Two outbreaks of *M. abscessus* after acupuncture have been reported in Korea. In the first outbreak in Seoul in 2001, the exact source of infection was not determined.[16] However, in the second outbreak in Ansan in 2008, the contaminated diluted glutaraldehyde solution that was used to disinfect the physical therapy devices was identified as the source of infection.[17] *M. massiliense* infection after arthroscopic and laparoscopic procedures,[18] *M. massiliense* and *Mycobacterium bolletii* infection after laparoscopic surgeries and cosmetic procedures,[19] and *M. massiliense* infection after video-assisted surgery[20] have been reported in Brazil. A report of pedicure-associated infection due to the *Mycobacterium chelonae/abscessus* group was reported in the USA in 2011.[21] NTM infection can even occur in a non-invasive environment. Cutaneous *M. massiliense* infection among seven day-spa workers, without any preceding invasive procedure, has been reported in Japan.[22]

Even though the infection is assumed to have originated from an environmental source, not all of the patients who were given injections were affected. The increased risk of infection when the triamcinolone injection was administered in August suggests that the high temperature and humidity may have amplified the possibility of infection from the contaminated environment. Risk factors for septic arthritis such as advanced age, rheumatoid arthritis, osteoarthritis, immunosuppressive therapies, and diabetes mellitus may have impacted the incidence of NTM infection among patients treated in the clinic.[23]

Multiple cases of septic arthritis due to *M. massiliense* infection were identified in this outbreak. Several patients had experienced the irreversible loss of joint function and had undergone joint replacement surgeries. A study performed on septic arthritis across all hospitals in Iceland from 1990 to 2002 reported that an increased number of intra-articular steroids and joint-viscous supplements increased the incidence

of septic arthritis, and 41.8% of all cases of septic arthritis in adults were iatrogenic.[24]

In the present investigation, patients who were injected with triamcinolone multiple times showed an increased risk of infection. Most patients were told to visit the clinic every week, and were given triamcinolone injections. This pattern of frequently repeated injections may have made the patients prone to infection; even administered into the intra-articular space, the glucocorticoid can be absorbed systemically, with deleterious effects on the hypothalamic–pituitary–adrenal (HPA) axis, resulting in adrenal suppression.[25] The risk of infection was increased when hyaluronate injections were co-administered (data not shown). Concomitant injection may have increased the chance of exposure to sources of infection. In addition, patients who were administered hyaluronate, which is used for viscosupplementation in arthritis of the knee in order to restore viscosity and elasticity of the synovial fluid,[26] may have had a more severe disease status, carrying a higher risk of infection. Thus, confounding by severity of disease remains a possibility.

There were several limitations in identifying the exact contamination source. Due to the delay in the launch of the investigation after the adverse event occurrence and report, the environment of the clinic had been altered, and our ability to acquire specimens was limited. It was not possible to contact many patients who were treated in the clinic because of the intentional destruction of documents containing patient information at the clinic, and we were not able to link the clinic patient list to other databases containing contact information due to the strict Personal Information Protection Act in Korea. We were not able to contact the medical assistant who administered the injections. Therefore the medical assistant's specimen was not included in the environmental investigation and information on his living conditions or socioeconomic status was not collected. In addition, we were not able to collect all clinical specimens from the NTM-positive cases because of delayed contact with the hospitals. Based on the results of each hospital's isolation of NTM species, the majority of NTM cases were identified as *M. massiliense*, but some were identified as *M. abscessus*. *M. abscessus sensu stricto* (also called *M. abscessus*), *M. massiliense*, and *M. bolletii* are very closely related and cause a similar spectrum of human infections; these three species are commonly called the *M. abscessus* complex.[27,28] Since *M. massiliense* is genetically close to *M. abscessus*, some isolates may have been misclassified. In spite of the recommendation to identify isolates of *M. abscessus* to the subspecies level,[29] some clinical laboratories may not have fully identified the *M. abscessus* subspecies *massiliense*. Finally, information bias regarding the injection procedures at the clinic was a possibility because the participants of this investigation had already heard about the outbreak of infection through the news media; however, survey answers on the injection procedure did not differ between cases and controls.

A recent whole-genome sequencing and epidemiological study revealed that the *M. abscessus* subsp. *massiliense* strains from distant epidemics are genotypically highly related, which suggests patient-to-patient transmission.[30,31] However, in the present investigation, we were not able to clarify the possibility of direct patient-to-patient transmission because of the lack of evidence from laboratory tests.

Despite the reports of the possibility of NTM infection from extrinsic contamination, outbreaks of NTM infection in healthcare settings occur regularly. In order to prevent epidemics of NTM infection after injections, it is necessary to educate clinicians on the safe use of intra-articular steroid injections, to observe infection control standards when mixing agents with normal saline, to sterilize the injection site adequately, and to avoid using single vials of injection agents on multiple patients.[32,33]

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2015.05.018.

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