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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