Mod Rheumatol (2005) 15:283–285
DOI 10.1007/s10165-005-0399-5

CASE REPORT

Junichi Asakawa · Shigeto Kobayashi · Kazuhiko Kaneda
Hitoshi Ogasawara · Masahiro Sugawara
Masahiko Yasuda · Hiroshi Hashimoto

Reactive arthritis after influenza vaccination: report of a case

Received: March 24, 2004 / Accepted: April 14, 2005

Abstract We describe a patient with reactive arthritis (ReA) induced by influenza vaccination. A healthy 79-year-old Japanese man began suffering from migrating polyarthritis 2 days after receiving influenza vaccine. He proved negative for rheumatoid factor, showing no evidence for microbial infections such as *Streptoccocci*, *Chlamydia*, or Parbovirus B19. Human leukocyte antigen (HLA) typing analysis revealed positive results for HLA-B54 (22), which is one of the cross-reactive antigens to HLA-B27. His arthritis improved with administration of nonsteroidal anti-inflammatory drugs, and recovery was attained within 6 weeks. Reactive arthritis is a rare adverse effect induced by influenza vaccination; however, it is important that it is recognized by all physicians.

Key words Adverse reaction · Influenza vaccine · Reactive arthritis (ReA)

Introduction

Reactive arthritis (ReA) is a clinical entity that is referred to as a sterile inflammatory arthritis occurring secondary to a microbial infection at a distant site in the body.[1,2] It has been ascribed to human leukocyte antigen (HLA)-B27-related arthritides, which are collectively classified into the seronegative spondyloarthropathy (SpA) group, together with Reiter's syndrome and ankylosing spondylitis. In Japan, the occurrence rate of HLA-B27 is less than 1% among the healthy population, in contrast to that of 7%–14% in the United States and Europe, thus HLA-B27-related arthritides are considered to be rare in Japan.[3] Recently, HLA-B27 unrelated ReA, such as poststreptococcal reactive arthritis (PSRA) after pharyngeal infection and acne arthritis, has been reported. Several Japanese cases, including ours, have also been published.[4] Recently we experienced a patient suffering from ReA after influenza vaccination. Although arthritic complaints after influenza vaccination are extremely uncommon, these conditions are worthy of mention especially when we consider the pathogenicity of ReA.

J. Asakawa · S. Kobayashi · K. Kaneda · H. Ogasawara · M. Sugawara · H. Hashimoto
Department of Rheumatology, School of Medicine, Juntendo University, Tokyo, Japan

S. Kobayashi (✉) · H. Hashimoto
Department of Medicine, Juntendo Koshigaya Hospital, 560 Fukuroyama, Koshigaya 343-0032, Japan
Tel. +81-48-975-0321; Fax +81-48-978-7821
e-mail: shigeto@med.juntendo.ac.jp

M. Yasuda
Department of Medicine, Nakaizu Onsen Hospital, Tagatagun, Shizuoka, Japan

Case report

A healthy 79-year-old man had been receiving influenza vaccinations for 30 years, without apparent adverse reactions other than once in 1998. At that time, after receiving a second vaccination within the year, he suffered from right hip joint pain, which improved spontaneously within 4 days. On November 19, 1999, he received an influenza vaccination (inactivated HA Vaccine; Seiken, Tokyo, Japan) without any immediate side effect. Two days later, he began suffering from migrating polyarthritis involving at first the metacarpophalangeal (MCP) joint of the left fourth finger. Subsequently, joint pain moved from shoulder to hip, feet, and fingers day by day and persisted for more than 3 weeks before he sought medical attention at the Department of Rheumatology, Juntendo University School of Medicine on December 15, 1999. On the first visit to our outpatients' clinic, he complained of pain at the MCP joint of his bilateral thumb, both wrist joints, and left ankle on movement. Signs of arthritis were observed such as heat, redness, tenderness, and slight swelling on the suffering joints but no deformity was seen on all the joints examined. Besides joint manifestations no extra-articular abnormal findings, such as conjunctivitis, skin rash, stomatitis, or urethritis, were detected. Laboratory examination revealed a slight increase in

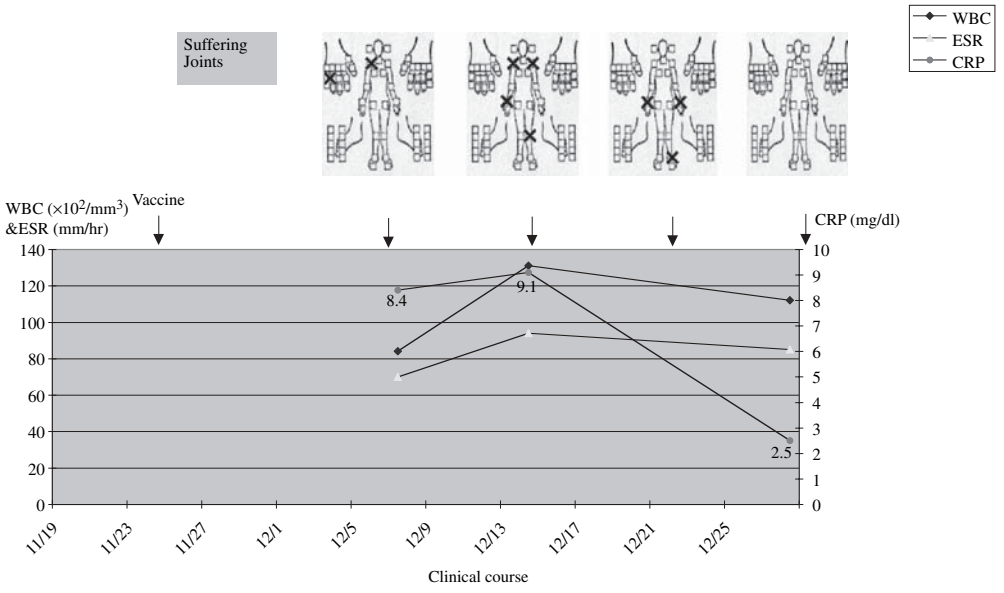

Fig. 1. Clinical course of the patient. *Diamonds*, white blood cell (*WBC*) count ($\times 10^2/mm^3$); *circles*, C-reactive protein (*CRP*) (mg/dl); *triangles*, erythrocyte sedimentation rate (*ESR*) (mm/h)

leukocyte count (white blood cells 13100/mm^3; neutrophils 78.5%, lymphocytes 13%, eosinophils 1%, and basophils 1%). Signs of inflammation were indicated by a C-reactive protein (CRP) content of 9.1 mg/dl and an erythrocyte sedimentation rate of 94 mm/h. Antistreptolysin O and antibodies to streptokinase titers were within normal limits. Serum IgA was 525 mg/dl and complement activity (CH_{50}) was 60.7 U/ml. Antinuclear antibody (ANA) was positive at 1:80 (homogeneous 1:80, speckled 1:80). Rheumatoid factors (evaluated with both RA test and RAPA test) were negative, and antibody titers against *Chlamydia trachomatis* or Parbovirus B19 (in IgM class) were also negative. He had no allergy of drugs and foods, including eggs. Human leukocyte antigen typing analysis revealed positive for HLA A11, A26, B54 (22), and Cw11, respectively. Although HLA B27 was negative, HLA B54 (22) is one of haplotypes known to cross-react with HLA B27, among others such as HLA B7, B39, B40, B42, and B60. Based on these findings, a diagnosis of ReA after influenza vaccination was made. Administration of 400 mg/day of etodolac was commenced. At the last visit on December 28, the patient was free from any arthritis /arthralgia upon examination, although a slight elevation of CRP still persisted. His clinical course is summarized in Fig. 1.

Discussion

Influenza epidemics lead to increased mortality, principally among elderly persons and others at high risk, and in most developed countries influenza-control efforts focus on the vaccination of this group.[5,6] Several large population-based retrospective studies have shown that vaccination is effective in reducing not only the rate of hospitalization due to pneumonia but also mortality from all causes during epidemic periods in the winter.[7,8] In contrast to most developed countries, policy and regulation in Japan was created to control influenza through the vaccination of schoolchildren from 1962 to 1987. Reichert et al.[9] analyzed the monthly rates of death from pneumonia and influenza together with the rates of influenza vaccination both in Japan and in the United States from 1949 through 1998, and drew the conclusion that vaccinating schoolchildren against influenza provides protection and reduces mortality from influenza among older persons as well. Vaccination side effects are usually uncommon, ranging from 5% to 35%, and involve local reaction at the injection site and rare systemic manifestations like anaphylactic reactions, Guillain–Barre syndrome, or small-vessel vasculitis. Recently, De Serres et al.[10] and others reported on oculorespiratory syndrome as a unique adverse reaction after influenza vaccination. From a Medline database search we found only one case report in the last 20 years of reactive arthritis after influenza vaccination by Biasi et al.[11] They reported on an HLA-B27 positive subject (a 32-year-old man) who presented a typical onset of a reactive arthritis 2 weeks after an influenza vaccination. On opening the focus a little wider though, there are some reports in the literature showing that autoimmune reactions including arthritis can occur after vaccination (and not solely influenza). Shoenfeld et al.[12] reported that arthritis can be induced by various vaccines such as tetanus, typhoid, paratyphoid, polio, mumps, diphtheria, rubella, smallpox, hepatitis B, and BCG. Previously, we reported an HLA-B27-positive patient with ankylosing spinal hyperostosis developed reactive arthritis after hepatitis B vaccination.[13]

Another controversial issue is on the immunogenicity and safety of influenza vaccination in patients with rheumatoid arthritis (RA). To consider the causal mechanisms of reactive arthritis, it is important to clarify which molecule of vaccine is arthrogenic for persons who suffer reactive arthritis. Generally speaking, the notion that arthritis can be induced as an adverse reaction to the influenza vaccina-

tion is not documented well enough. It is important to recognize that reactive arthritis can be induced as one of the adverse reactions of influenza vaccination, especially under the circumstances in which the practice of prophylactic use of influenza vaccination is becoming more common in Japan.

References

1. Fan PT, Yu DTY. Reiter's syndrome. In: Kelly WN, Harris ED Jr, Ruddy S, Sledge CB, editors. The textbook of rheumatology. 4th ed. Philadelphia: Saunders; 1993. p. 961–73.
2. Cush JJ, Lipsky PE. Reiter's syndrome and reactive arthritis. In: McCarty DJ, Koopman WJ, editors. Arthritis and allied conditions. 12th ed. Malvern: Lea and Febiger; 1993. p. 1061–78.
3. Kobayashi S. Reactive arthritis (in Japanese). Riumachi 1997;37: 504–13.
4. Asakawa J, Torikoe Y, Kondo I, Yasuda M, Kobayashi S, Hashimoto H. Reactive arthritis after pharyngeal infection: report of two siblings. Mod Rheumatol 2002;12:182–5.
5. Glenzen WP, Payne AA, Snyder DN, Downs TD. Mortality and influenza. J Infect Dis 1982;146:313–21.
6. Simonsen L, Clarke MJ, Williamson DG, Stroup DF, Aeden NH, Schonberger LB. The impact of influenza epidemics on mortality: introducing a severity index. Am J Publ Health 1997;87:1944–50.
7. Nichol KL, Margolis KF, Wuorenma J, Von Sternberg T. The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. N Engl J Med 1994;33:778–84.
8. Nochol KL, Wuorenma J, Von Sternberg T. Benefits of influenza vaccination for low-, intermediate-, and high-risk senior citizens. Arch Intern Med 1998;158:1769–76.
9. Reichert T, Sugaya N, Fedson DS, Glezen WP, Simonsen L, Tashiro M. The Japanese experience with vaccinating schoolchildren against influenza. N Engl J Med 2001;344:889–96.
10. De Serres G, Boulianne N, Duval B, Rochette L, Grenier JL, Roussel R, et al. Oculo-respiratory syndrome following influenza vaccination: evidence for occurrence with more than one influenza vaccine. Vaccine 2003;21:2346–53.
11. Biasi D, Carletto A, Caramaschi P, Tonoli M, Bambara LM. A case of reactive arthritis after influenza vaccination. Clin Rheumatol 1994;13:645.
12. Shoenfeld Y, Maor AA. Vaccination and autoimmunity – "Vaccinosis": a dangerous liaison? J Autoimmun 2000;14:1–10.
13. Ando S, Kobayashi S, Takasaki Y, Hashimoto H. A case of HLA-B27 positive and ankylosing spinal hyperostosis associated with reactive arthritis and palmar erythema after hepatitis B vaccination. Clin Rheumatol 1996;8:194–6.