

## Short communication

## Subacromial bursitis following human papilloma virus vaccine misinjection

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## ABSTRACT

A patient presented at our clinic with severe subacromial bursitis, which persisted for several months following a third booster injection with Cervarix™. Chronic subacromial bursitis manifested itself in this patient after what appeared to be the misinjection of vaccine in close proximity to the acromion. This bursitis was resistant to conventional physiotherapy and to corticosteroid therapy, but was responsive to arthroscopic surgery. Since such patients may present to an arthroscopic surgeon only months after receiving a vaccine injection, this etiological link may not be fully appreciated by treating clinicians. Further, the accuracy of injection in the deltoid region also appears under appreciated, and this report highlights the importance of accurate injection to the deltoid region or in certain cases, the value of simply changing the injection site to another larger muscle.

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## 1. Introduction

Two types of human papilloma virus (HPV), 16 and 18, have been associated with about 70 percent of invasive cervical cancers. The prophylactic HPV-16/18 vaccine Cervarix™, was developed by GlaxoSmithKline (GSK) Biologicals for the prevention of cervical cancer caused by HPV [1]. To promote a strong and stable antibody response, the Cervarix™ vaccine was formulated with the proprietary Adjuvant System AS04, composed of 3-O-desacyl-4'-monophosphoryl lipid A (MPL) and aluminum hydroxide [2,3]. AS04 injected into the gastrocnemius muscle of mice, transiently induced local NF-κB activity and cytokine production [4]. Vaccines with the AS04 adjuvant are generally accepted to have a favorable safety profile [5–8].

We investigate whether Cervarix™ could have been the cause of a severe form of subacromial bursitis that persisted for many months, resisted conventional treatment, until a successful arthroscopic surgery was performed.

## 2. Case report

A 45-year-old Japanese female presented to our hospital outpatient clinic with left shoulder pain. The pain had an acute onset, three weeks earlier, following a third HPV vaccine injection. There

was no history of allergies or evidence of trauma from her medical history.

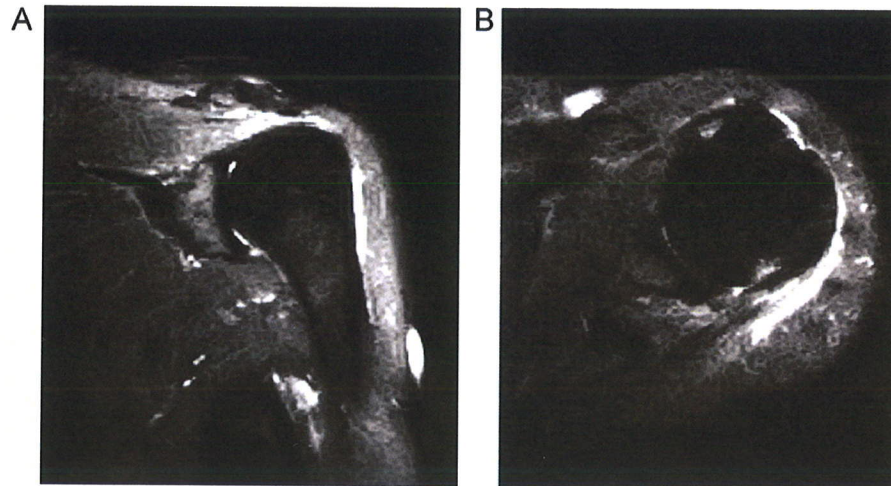
We investigated a possible correlation between the onset of her pain and an earlier Cervarix™ administration. A first injection of Cervarix™ was given on May 06, 2010 at the Department of Gynecology of one of the community hospitals in Kitakyushu city. A second booster injection was given on May 13, 2010. She did not report pain, or other symptoms, after either injection. These injections were given with the sleeves rolled up. The third injection, however, was given at the superior portion of the left deltoid muscle, on October 19, 2010 at the same hospital, with the collar pulled down. Before this third injection, she had no problems with her left shoulder joint and, for example, had no problems playing golf everyday. However, 3 h after the third injection, intense pain was felt throughout the left arm. The pain became worse and progressively impinged on her daily activity level.

Her pain became so severe that she eventually presented to her family physician's clinic. An orthopedic physician pointed out that the site of the third injection was the superior portion of the left deltoid muscle, in close proximity to the acromion. Radiographs showed no definitive evidence of osteoarthritis or abnormal bone (data not shown). But the pain continued to be a problem of increasing severity for her. Thus, a T1-weighted magnetic resonance image (MRI: TR4100/TE30) was done, which revealed a high intensity area at the subacromial bursa, suggestive of acute subacromial bursitis (Fig. 1A and B). Laboratory data showed that the erythrocyte sedimentation rate (ESR) was 32 mm in the first hour (range, 0–15 mm in the first hour) and the C-reactive protein (CRP) level was 1.0 mg/dL (range, 0.0–0.2 mg/dL) suggesting no evidence of serious systematic inflammation.

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**Fig. 1.** MRI of shoulder: (A) coronal view of T1-weighted magnetic resonance image (MRI) (TR4100/TE30) showing a high intensity region at the subacromial bursal space (arrow), indicative of subacromial bursitis; (B) axial view showing a high intensity region at the subacromial bursal space (arrow), separate from deltoid muscle.

In an attempt to relieve what appeared to be an acute inflammation, several corticosteroid injections, directly into the subacromial bursa, were given. Although her pain did decrease somewhat, other symptoms such as irritation, limited range of motion and signs of impingement remained. Thus, she presented to our orthopedic clinic with pain throughout the left shoulder region.

Our clinic determined that, three weeks after that third Cervarix<sup>TM</sup> injection, her shoulder range of motion was still severely limited to 80° flexion and 60° abduction. We decided to continue with several more rounds of corticosteroid injections into the subacromial bursa to maintain pain relief, and physiotherapy was performed in an attempt to improve her range of motion. However, six months after the onset of symptoms, she still had moderate pain with a limited range of motion. She showed no neurological abnormalities such as muscle weakness or sensory disturbance suggestive of brachial plexus neuritis [9].

To treat what now appeared to be a chronic problem, arthroscopic surgery was performed. The surgery was performed in the beach-chair position, under general anesthesia. Four portals (posterior, anterior, posterolateral, anterolateral) were established. Synovitis surrounding the superior labrum was observed in the glenohumeral joint (Fig. 2A). An arthroscopic evaluation of the subacromial bursa revealed the presence of adhesive and inflammatory tissue. Several small particles were observed inside the subacromial bursa, at the alleged site of the third injection (Fig. 2B).

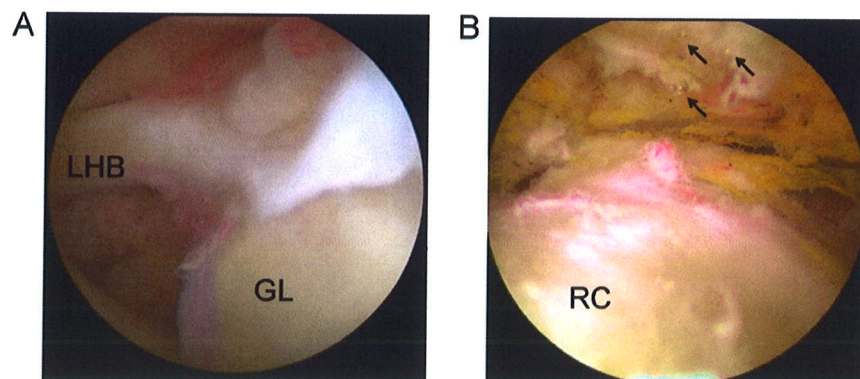
Arthroscopic synovectomy and subacromial decompression were carried out using a shaver and a radiofrequency probe.

Histological analysis of the removed synovial tissue from the subacromial bursa was consistent with a diagnosis of chronic bursitis. We observed abnormal papillary projections of the synovial membrane; mild acute and chronic inflammatory infiltrate and granulation tissue; and mild fibrosis, without evidence of crystalloid structures (Fig. 3).

After the surgery, the patient appeared to make a complete recovery. One week later, the pain dramatically diminished. Six months later, the patient was able to play golf again. One year later, she had no pain and a complete range of motion.

### 3. Discussion

A third booster shot of Cervarix<sup>TM</sup>, injected at the superior portion of the deltoid, near the acromion, had such severe and persistent adverse effects that they could only effectively be treated with arthroscopic surgery. Arthroscopic analysis revealed that the area of the third injection was the superior portion of the deltoid muscle, adjacent to the subacromial bursa, where small white particles were still present. In fact, seven months after the onset of pain, at the time of surgery, the pathological findings revealed evidence of chronic inflammation. Arthroscopic surgical treatment did finally relieve the pain and improve the function.



**Fig. 2.** Arthroscopy: (A) arthroscopic view from the posterior portal in the left shoulder showing proliferating synovitis surrounding the superior portion of the glenohumeral joint; (B) arthroscopic view from the posterior portal in the left subacromial bursa showing hypertrophic synovitis (arrows). LHB, long head of biceps; GL, glenoid; RC, rotator cuff.

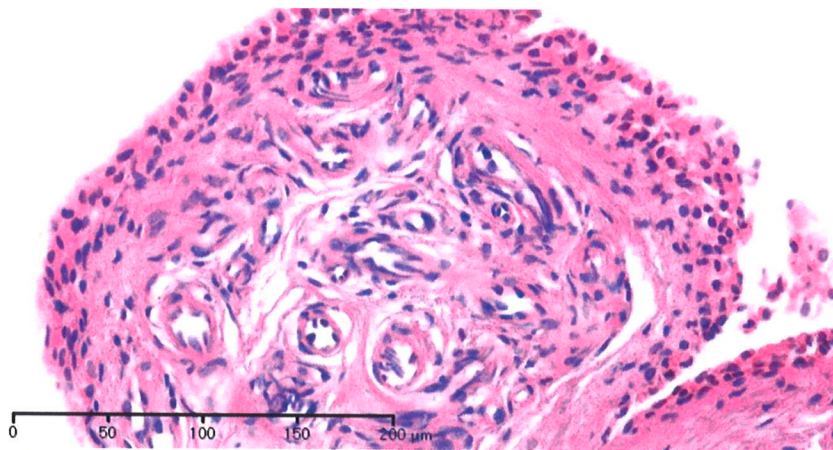


Fig. 3. Histological examination showing inflammatory infiltrate and granulation tissue with mild fibrosis, suggestive of chronic bursitis.

The prevalence of subacromial bursitis following vaccination is not known. A search of the published literature revealed several similar cases of rapid onset shoulder pain with limited range of motion following administration of different vaccines; these were classified as likely acute subacromial bursitis or shoulder arthritis [10,11]. Other studies report that the prevalence of arthralgia related adverse effects are less than 1% [12,13]. It has been suggested that improper injection could cause acute subacromial bursitis [11].

By making the connection to a simple and avoidable human error, which occurred several months earlier, our case report illustrates what could possibly be a more common chronic occurrence. We report that it is in fact plausible that misinjection of HPV vaccine near the subacromial bursa, with a vaccine formulation that includes a strong adjuvant, could actually induce such a severe and chronic inflammatory reaction that it will resist conventional treatment. Further, we show that it may none the less still be possible to successfully treat such a chronic condition with arthroscopic surgery, even several months later.

The manufacturer recommends that the administration of Cervarix™ should be via intramuscular injection to the deltoid region of the upper arm. The mean distance from the midpoint of the acromion to the subdeltoid bursal reflexion was reported as 4.0 cm [14,15]. The size of the deltoid muscle in Asian (including Japanese) women is generally smaller than in Caucasian women. Thus, to safely inject into the deltoid muscle, and to avoid the subacromial bursa, the injection should both be more than 4 cm from the acromion, and within a narrow depth range that is dependent on an individual's muscle size.

The risk of observing this type of complication is probably related to the injection site, to the strength of the particular adjuvant, to the number of booster shots and to possible epitope cross-reactivity. There appears to be a growing trend in the pharmaceutical industry toward increasing the longevity of a vaccine's effectiveness by using stronger adjuvants designed to increase local reactogenicity, as a key part of their competitive strategy [8,16]. However, there is a dearth of knowledge regarding how such strong adjuvants could affect intra-articular tissue such as synovium and cartilage. Further, the consequences of improper injection technique into wrong tissues such as subcutaneous or intrabursal tissues are also not known. The biopsy tissue we obtained seven months after pain onset cannot provide this type of conclusive etiological evidence.

What should be obvious now however, irrespective of etiology, is that the risk of complications could be reduced by using a proper injection procedure, since the accuracy of injection may be more

important than at first believed. Therefore, despite our awareness of these possible chronic complications and the availability of arthroscopic treatment, to simply avoid this type of risk altogether, it may be advisable to administer the vaccine to a larger hip muscle instead (at least for smaller sized individuals).

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