



Case report

Interstitial lung disease associated with human papillomavirus vaccination



Yasushi Yamamoto^{*}, Yoshihiro Kazebayashi, Noriko Hirai, Takaaki Sasaki, Yoshinobu Ohsaki

Respiratory Center, Asahikawa Medical University, Asahikawa, Hokkaido, Japan

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ABSTRACT

Vaccinations against the human papillomavirus (HPV) have been recommended for the prevention of cervical cancer. HPV-16/18 AS04-adjuvanted vaccines (Cervarix) are said to have favourable safety profiles. Interstitial lung diseases (ILDs) can occur following exposure to a drug or a biological agent. We report a case of ILD associated with a Cervarix vaccination. A woman in her 40's, with a history of conisation, received three inoculations of Cervarix. Three months later, she presented with a cough and shortness of breath. Findings from a computed tomography of the chest and a transbronchial lung biopsy were consistent with non-specific interstitial pneumonia. Workup eliminated all other causes of the ILD, except for the vaccination. Over the 11 months of the follow-up period, her symptoms resolved without steroid therapy. The onset and spontaneous resolution of the ILD showed a chronological association with the HPV vaccination. The semi-quantitative algorithm revealed that the likelihood of an adverse drug reaction to Cervarix was "Probable". The outcome was relatively good, but more attention should be paid to a potential risk for HPV vaccinations to cause ILDs. Wherever possible, chest radiographic examinations should be performed in order not to overlook any ILDs.

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1. Introduction

Vaccinations against the human papillomavirus (HPV) have been recommended for the prevention of cervical cancer [1]. Large-scale investigations have shown favourable safety profiles regarding HPV-16/18 AS04-adjuvanted vaccines (Cervarix) [2,3]. On the other hand, adverse effects related to Cervarix are being registered on online databases [4]. Interstitial lung diseases (ILDs) can occur following exposure to a drug or a biological agent [5,6]. Vaccines are rarely associated with ILDs, except for some cases of influenza [7,8] or BCG vaccines [9]. We report a case of ILD secondary to the HPV vaccination.

2. Case

2.1. Case presentation

A woman in her 40's presented with a three-month history of a non-productive cough and shortness of breath. She had no past

history of pulmonary diseases and dust inhalation. She had quit smoking 14 years ago, and had not been taking any medication including over-the-counter drugs, Chinese herbs or supplements.

One year earlier, she had undergone a conisation due to cervical intraepithelial neoplasia. A pre-operative chest radiograph (Fig. 1a) and her pulmonary function test results were normal. Two months after the resection, she had received vaccinations with Cervarix at 0, 1, and 6 months. She had no adverse events between the first and third vaccinations. Her symptoms developed three months after the last vaccination.

2.2. Investigations

The physical examination revealed her body temperature to be 37.0 °C and fine crackles in chest auscultation, but no clubbing or skin rashes. Arterial oxy-haemoglobin saturation was 98% with a heart rate of 70 beats per minutes. A chest radiograph showed patchy infiltrations on both lower lung fields (Fig. 1b). High-resolution computed tomography (HRCT) of the chest revealed peribronchial consolidations, subpleural reticular shadows and ground glass opacities, all of which were predominantly seen in both lower lobes (Fig. 2a). Honeycombing and traction bronchiectasis were absent. The radiographic pattern on the HRCT was

^{*} Corresponding author. 2-1-1 Midorigaoka-Higashi, Asahikawa, Hokkaido, 078-8510, Japan.

E-mail address: yasuyama@asahikawa-med.ac.jp (Y. Yamamoto).

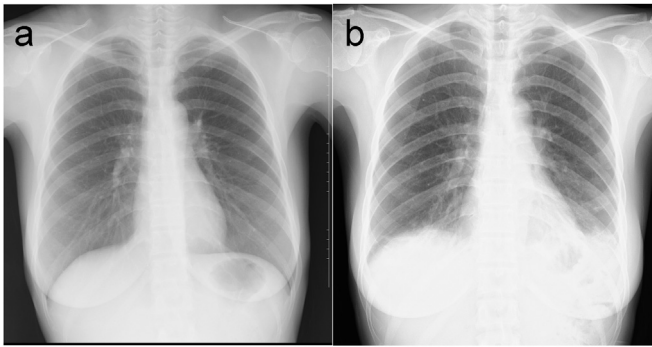


Fig. 1. Chest radiographs before and after HPV vaccinations. The pre-vaccination chest radiograph (a) has no abnormalities. The post-vaccination chest radiograph (b) shows patchy infiltrations on both lower lung fields.

suggestive of non-specific interstitial pneumonia (NSIP). A ^{67}Ga scintigram showed a significant uptake of ^{67}Ga -citrate into the diseased areas.

Urinalysis and routine blood test results were normal. Serum levels of C-reactive protein, anti-nuclear antibodies and Rheumatoid factor were within normal range. Biomarkers specific to ILDs were elevated in the patient's sera, with Krebs von der Lungen-6 (KL-6) of 2440 U/mL (normal <500 U/mL) and surfactant protein-D (SP-D) of 135 ng/mL (normal <110 ng/mL). Pulmonary function tests revealed neither obstructive nor restrictive ventilatory impairment. Carbon monoxide diffusing capacity fell by 74% from the predicted value. An arterial blood gas analysis while breathing room air was normal.

Transbronchial lung biopsy specimens showed infiltration of inflammatory cells into thickened alveolar septa (Fig. 3). The alveolitis was characterised as having chronological homogeneity. There was no granuloma formation and eosinophil infiltration. These findings were compatible with the histologic pattern of NSIP. Total cell counts in the bronchoalveolar lavage fluid (BALF) increased to 380/ μL , which was composed of 55% lymphocytes, 44% alveolar macrophages, and 1% eosinophils. The ratio of CD4⁺/CD8⁺ T cells was 1.02. No microorganisms including bacteria, fungi, or mycobacterium species were identified from the BALF.

2.3. Diagnosis

Any causes presenting with subacute ILDs had to be excluded. She had no history of inhaling organic dusts, the leading cause of allergic extrinsic alveolitis. Workup eliminated the possibility of respiratory infections, eosinophilic lung diseases, sarcoidosis, or collagen vascular diseases. The ILD was initially diagnosed as idiopathic NSIP.

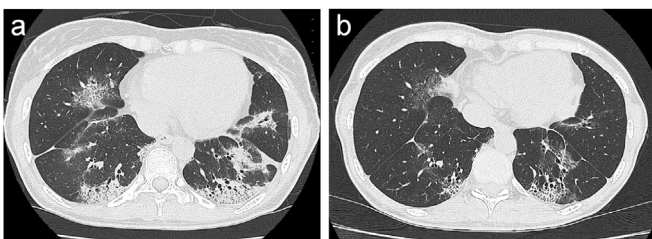


Fig. 2. High-resolution computed tomography scans. Peribronchial consolidations, subpleural reticular shadows, and ground glass opacities were seen in both lower lobes (a). These findings were reduced over 11 month of the observation period (b).

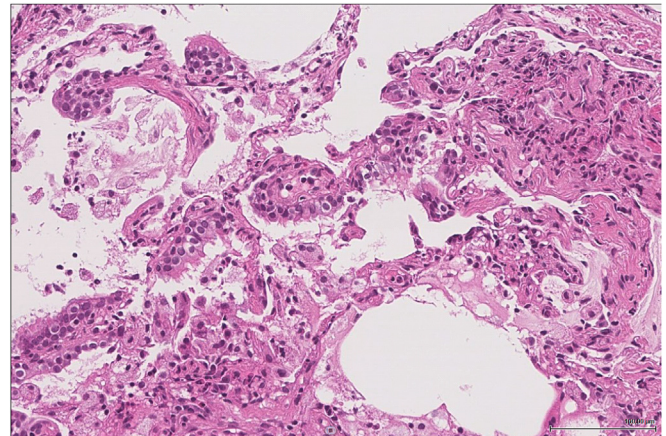


Fig. 3. Transbronchial lung biopsy specimen shows alveolar wall thickness with infiltration of inflammatory cells.

Systemic corticosteroid therapy was scheduled. Unexpectedly, within a few weeks, her symptoms resolved without the need for any treatment. The self-limiting course was likely attributed to the withdrawal of Cervarix. After obtaining her informed consent, we observed the outcome in an attempt to confirm the temporal association with vaccination [6].

2.4. Outcome and follow-up

She was restored to full health over 11 months of the follow-up period. The patchy infiltrations in chest radiographs gradually disappeared with increasing lung volume. HRCT of the chest showed a reduction in the consolidations (Fig. 2b). Diffusing capacity also normalised. The likelihood of an adverse drug reaction (ADR) to Cervarix was estimated using the semi-quantitative Naranjo algorithm [10]. The total score was five, which corresponded to the “Probable” ADR. The ILD was not life threatening, and did not result in a persistent disability.

3. Discussion

Drug-induced ILDs are referred to as ADRs, which involve the respiratory system [6]. We identified five cases of ILDs associated with HPV vaccinations (1 Cervarix and 4 Gardasil) in the Vaccine Adverse Event Reporting System database between 1990 and 2014 [4]. In our case, the likelihood of an ADR was graded as “Probable” [10].

The clinical manifestations were compatible with influenza vaccine-induced ILDs, such as lymphocytosis in the BALF, pathologically proven alveolitis and radiographic patterns on HRCT [7,8]. Likewise, biomarkers specific to ILDs (i.e. KL-6 and SP-D) increased [8]. The workup eliminated all other causes of the ILD. NSIP often precedes systemic developments of collagen vascular diseases [11,12]. However, so far she has been free from any signs of the disease. For ethical reasons we refrained from a re-challenge test, the most effective diagnostic procedure for ADRs [6,10]. Therefore, we cannot conclude that the ILD resulted from a “definite” ADR to Cervarix. However, a series of repetitive vaccinations might have acted as a “natural” re-exposure.

The temporal association with a suspected drug is a crucial factor for the diagnosis of drug-induced ILDs [6,8]. Obviously, the ILD developed following a sole exposure to the HPV vaccines. No other drugs were involved in the disease process. If possible, corticosteroid use should be avoided with a view to verifying the

sole effect of drug discontinuation [6]. We followed this policy because the patient was free of respiratory distress. The fact that the ILD improved after the drug was withdrawn possibly suggests an association with Cervarix.

The Cervarix-associated ILD presumably occurred after the last vaccination, and it peaked at the time of diagnosis. In general, exposure to a drug can induce ILDs with various latencies [5,6]. We failed to determine the onset precisely because the HRCT scans had not been checked before and during the vaccination period. Influenza vaccines can induce ILDs with latencies ranging from 1 to 10 days [7,8]. In contrast, the ILD in this case developed three months after the last vaccination. The latency appeared longer than those of influenza vaccines [8]. Possible mechanism(s) may include direct toxic effects, T cell-mediated immune responses, or both [5,6]. Nevertheless, three doses of Cervarix were unlikely to exert persistent cytotoxic effects on the lungs. Instead, the presence of the lymphocytic alveolitis suggested that cell-mediated immunity was attributed to the development of ILDs. BCG vaccines can also cause ILDs through *Mycobacterium bovis* dissemination [9]. This was unlikely because Cervarix is a non-infectious recombinant vaccine [13–15].

The most likely explanation is that repetitive vaccinations might have sensitised the patient's immune system. Unlike influenza and BCG vaccines, Cervarix contains the AS04 adjuvant that exhibits strong immunogenicity [13–15]. The compound itself might have been an offending antigen to the lungs. We speculate that the patient became sensitive to Cervarix during the course of the first two vaccinations. This probably led to the development of ILD after the final vaccination. To date, AS04-adjuvanted vaccines have not been associated with new onset of chronic diseases or autoimmune disorders [2,3,13–15]. Unfortunately, the list of these conditions does not contain any types of ILDs. Further studies are needed to clarify the prevalence of ILDs in vaccinated subjects.

The Cervarix-associated ILD showed a mild clinical manifestation, and did not result in a persistent disability. This was probably because the patient was relatively young and free from comorbidity. In contrast, influenza vaccines can induce ILDs more often in elderly patients [7,8]. Pre-existing lung diseases may increase the risk of developing ILDs [8]. Severe ILDs can develop after pandemic influenza-A vaccinations [8]. However, in most cases, steroid therapy can achieve a good response, leading to a preferable clinical outcome [7,8]. Vaccine-induced ILDs are difficult to recognize because vaccines have rarely been reported as causative agents. Therefore, noticing the probability of ADRs to vaccines is important to make the appropriate intervention.

There is little doubt, if any, of the efficacy and safety of HPV vaccines [2,3]. The aim of this case report was not to focus on the negative aspects of Cervarix, but to attract more attention to unexpected complications in the lungs. When those who have been inoculated complain of persisting respiratory symptoms, chest radiographic assessments are required. Moreover, the ILD developed independently of its known risks such as high age and pre-existing pulmonary lesions [5,6]. This is noteworthy because

healthy young women are the most common demographic to receive the HPV vaccination [1,2].

4. Conclusions

Cervarix is an effective and safe vaccine, but may have a risk to cause ILDs. Wherever possible, chest radiographic examinations should be performed in order not to overlook any ILDs.

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References

- [1] International Federation of Gynecology and Obstetrics, FIGO Statement on HPV Vaccination Safety. Secondary FIGO Statement on HPV Vaccination Safety, 2013. <http://www.igo.org/news/igo-statement-hpv-vaccination-safety-0014668>.
- [2] M. Lehtinen, J. Paavonen, C.M. Wheeler, et al., Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial, *Lancet Oncol.* 13 (1) (2012) 89–99.
- [3] S.R. Skinner, A. Szarewski, B. Romanowski, et al., Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomised controlled VIVIANE study, *Lancet* 384 (9961) (2014) 2213–2227.
- [4] Vaccine Adverse Event Reporting System. <https://vaers.hhs.gov/index>.
- [5] P.H. Camus, P. Foucher, P.H. Bonniaud, et al., Drug-induced infiltrative lung disease, *Eur. Respir. J. Suppl.* 32 (2001) 93s–100s.
- [6] K. Kubo, A. Azuma, M. Kanazawa, et al., Consensus statement for the diagnosis and treatment of drug-induced lung injuries, *Respir. Investig.* 51 (4) (2013) 260–277.
- [7] S.D. Johnston, A. Kempston, T.J. Robinson, Pneumonitis secondary to the influenza vaccine, *Postgrad. Med. J.* 74 (875) (1998) 541–542.
- [8] S. Watanabe, Y. Waseda, H. Takato, et al., Influenza vaccine-induced interstitial lung disease, *Eur. Respir. J.* 41 (2) (2013) 474–477.
- [9] V. Delimpoura, K. Samitas, I. Vamvakaris, et al., Concurrent granulomatous hepatitis, pneumonitis and sepsis as a complication of intravesical BCG immunotherapy, *BMJ Case Rep.* (2013 Oct 10), <http://dx.doi.org/10.1136/bcr-2013-200624>, 2013, pii: bcr2013200624.
- [10] M.J. Doherty, Algorithms for assessing the probability of an adverse drug reaction, *Respir. Med. CME* 2 (2) (2009) 63–67.
- [11] I.N. Park, Y. Jegal, D.S. Kim, et al., Clinical course and lung function change of idiopathic nonspecific interstitial pneumonia, *Eur. Respir. J.* 33 (1) (2009) 68–76.
- [12] W.D. Travis, U. Costabel, D.M. Hansell, et al., An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias, *Am. J. Respir. Crit. Care Med.* 188 (6) (2013) 733–748.
- [13] M.G. Angelo, M.P. David, J. Zima, et al., Pooled analysis of large and long-term safety data from the human papillomavirus-16/18-AS04-adjuvanted vaccine clinical trial programme, *Pharmacoepidemiol Drug Saf.* 23 (5) (2014) 466–479.
- [14] T. Verstraeten, D. Descamps, M.P. David, et al., Analysis of adverse events of potential autoimmune aetiology in a large integrated safety database of AS04 adjuvanted vaccines, *Vaccine* 26 (51) (2008) 6630–6638.
- [15] D. Descamps, K. Hardt, B. Spiessens, et al., Safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine for cervical cancer prevention: a pooled analysis of 11 clinical trials, *Hum. Vaccine* 5 (5) (2009) 332–340.