Interstitial lung disease associated with human papillomavirus vaccination

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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.

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 lungs (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 bronchiec- tasis were absent. The radiographic pattern on the HRCT was...
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.

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 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 unanticipated potential adverse events of new vaccines. This probably led to the development of ILD 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].

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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.

Acknowledgement

We are grateful to Naoyuki Miyokawa M.D., Ph.D., Department of Diagnostic Pathology, Asahikawa Medical University Hospital, for making the pathological diagnosis, and Mr. James Stevenson for helping with manuscript preparation.

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