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# Effect of Coronavirus Disease 2019 Vaccine-Related Lymphadenopathy on Lung Cancer Treatment



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Smallpox is an infectious disease that has threatened the survival of human beings, and vaccination against it was proven to be extremely effective. The effects of vaccination have long been noted; literature of ancient People's Republic of China and India both report a preventive measure involving the use of scabs from patients with smallpox.<sup>1,2</sup> Nevertheless, it was not until the modern approach to vaccination was developed by Dr. Jenner that the side effects of vaccines reached acceptable levels. Vaccination has since become a powerful countermeasure against smallpox and has been continuously improved on, becoming widespread throughout the world.<sup>2,3</sup> In the 1970s, however, just before the WHO declared the eradication of smallpox, axillary lymphadenopathy was detected as a side effect of the vaccine in approximately 50% of the vaccinated population.<sup>4</sup>

The coronavirus disease 2019 (COVID-19) pandemic, which started at the end of 2019 and continues to plague the population, is the most serious public health issue in the world now, and the acquisition of immunity through a vaccine is regarded as one of the best countermeasures against this infectious disease. Serious adverse events after COVID-19 vaccination are considered rare; ChAdOx1 nCoV-19/AZD1222 and Ad26.COV2.S have been associated with thrombosis with thrombocytopenia, and the mRNA vaccines have been associated with myocarditis/pericarditis.<sup>5-7</sup> In the phase 3 trial leading to emergency use authorization for the Moderna vaccine, adenopathy was reported as an unsolicited event in 1.1% of patients.<sup>8</sup> In the clinical trial leading to emergency use authorization for the Pfizer-BioNTech vaccine, the self-reported rate of adenopathy in patients was 0.3%.<sup>9</sup>

Nishino et al.<sup>10</sup> used prevaccine and postvaccine chest computed tomography data of patients with thoracic malignancies who received two doses of mRNA-based COVID-19 vaccinations. The incidence rate was 9%, with a median time of 1.7 weeks after the second booster shot, and female sex and vaccine type (mRNA-1273 vaccine) were revealed to be predisposing factors.

The median short-axis diameter of the largest node was 7 mm, and the median number of swollen nodes was four. Nevertheless, the study protocol did not clearly specify the timing of the imaging study, so whether or not the maximum diameter of a swollen lymph node (LN) was accurately captured and how long the swelling continued was unclear. This makes it difficult to focus on how to use the findings obtained clinically.

Vaccine-related lymphadenopathy in patients with lung cancer can lead to conflicting situations owing to disease burden. First, in the early stage, axillary lymphadenopathy can confuse staging, resulting in unnecessarily invasive procedures. Second, in the evaluation of neoadjuvant therapy with a marginally substantial disease stage, it becomes difficult to make treatment decisions. Third, in cases of advanced diseases, it can affect the determination of the treatment effect. Finally, new LNs in completely resected patients make it difficult to distinguish the presence of recurrence.

Vaccine-related lymphadenopathy has been evaluated in a variety of modalities. For example, prevalent ultrasound features include oval form, asymmetric cortex with hilum evidence, and central and peripheral vascular signals at superb microvascular imaging, along with elastosonography patterns resembling the surrounding tissue.<sup>11</sup> Positron emission tomography (PET)-computed tomography results of 274 vaccinated cases revealed

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66% positivity and used the maximum standardized uptake value of LN with or without the ipsilateral arm uptake with 55.4% of sensitivity and 83.6% of specificity for the differential diagnosis.<sup>12</sup> Nevertheless, making a differential diagnosis using only diagnostic imaging has limited utility. A similar problem is found in “nodal immune flare” in neoadjuvant immune checkpoint inhibitors.<sup>13</sup>

Vaccine-related lymphadenopathy is also a longstanding problem.<sup>14</sup> Histologic evaluations are essential for a definitive diagnosis, and the histologic features described in some reports have included an increased number of reticular lymphoblasts imparting a mottled appearance to the lymphoid tissue; diffuse, follicular, or combined diffuse and follicular hyperplasia; vascular and sinusoidal changes; and a mixed cellular response. Regarding the COVID-19 vaccine specifically, reported features include a florid, reactive lymphadenopathy pattern characterized by a mixed lymphoid population with lymphocytes at different stages of maturation, including many centroblasts admixed with numerous tingible body macrophages<sup>15</sup> and enlarged germinal center with interfollicular expansion by small lymphocytes, prominent germinal center with tingible body macrophages, and reactive germinal center with expansion of interfollicular regions by small lymphocytes and focally prominent endothelial cells.<sup>16</sup> These changes may reflect the immune response to mRNA vaccination. In brief, the presence of tangible macrophages suggests that cells that have taken up the mRNA may have been processed by phagocytic cells, and the proliferation of follicles and lymphocytes at different stages suggests that memory B cells may have been created. In other words, vaccine-related lymphadenopathy may be a surrogate marker of the effective uptake of the vaccine component.

Accurate noninvasive identification of vaccine-related lymphadenopathy and metastatic LN swelling is challenging, even with modern technologies. The current management strategy is guided by clinical context; accurate records of vaccination information, including dates administered, injection sites, and type of vaccine, and imaging findings within 5 days after vaccination and 6 weeks or more after vaccination and vaccine administration on the contralateral side to the cancer.<sup>16–18</sup> Because metabolic activity is often observed on <sup>18</sup>F-fluorodeoxyglucose (FDG)-PET in a considerable number of cases of vaccine adenopathy, a correct diagnosis can be obtained only by follow-up imaging to ensure shrinkage or by a histopathologic evaluation.

Emerging technologies may help manage this situation. FDG, which captures metabolic activity, has excellent sensitivity for identifying lesions but is not useful for differentiating malignant from benign lesions. Radiolabeled amino acids are well-established agents for

PET-based tumor imaging because of their correlation with cellular proliferation with high sensitivity and specificity. Carbon-11(<sup>11</sup>C)-methionine (MET) has been extensively investigated and may reduce the number of false-positive findings in inflammatory lung disorders. Kubota et al.<sup>19</sup> and Hsieh et al.<sup>20</sup> reported that MET is more specific and sensitive than FDG. A major disadvantage, however, is the need for on-site cyclotron, as <sup>11</sup>C is a short half-life isotope (20 min). Besides <sup>11</sup>C-MET, the efficacy of new PET tracers is being investigated as a diagnostic tool for distinguishing between malignancies and inflammatory diseases.<sup>21–23</sup> On the vaccination side, alternate administration methods from the intramuscular approach are also being developed. Compared with intramuscular injection, mucosal administration is less likely to cause adverse reactions because it is not directly administered into the blood. ChAdOx1 nCoV-19 (AZD1222) is an approved adenovirus-based vaccine for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and van Doremalen et al.<sup>24</sup> reported that intranasal vaccination with ChAdOx1 nCoV-19 (AZD1222) reduced virus concentrations in nasal swabs in two different SARS-CoV-2 animal models and reduced viral loads in bronchoalveolar lavage and lower respiratory tract tissue. Other oral or intranasal vaccines are currently under development and may contribute to satisfying the clinical need for SARS-CoV-2 vaccines.<sup>25,26</sup> Regarding the estimation of the tumor volume, circulating tumor DNA (ctDNA) or circulating tumor cells may be useful molecular markers. Among the various liquid biopsy methods, plasma ctDNA is the most extensively studied and is widely used in clinical practice.<sup>27,28</sup> In early stage NSCLC, ctDNA detected after curative surgical resection may be informative in identifying patients at a high risk for recurrence.<sup>29</sup> In advanced-stage NSCLC, the quantitation and dynamic change in ctDNA levels after the initiation of treatment helps clinicians predict the efficacy of immune checkpoint blockade therapy before radiographic changes occur.<sup>30</sup>

Considering the timing and duration of lymphadenopathy in daily clinical practice, as revealed in this study, will provide a very useful light for the strategy of the differential diagnosis of COVID-19 mRNA vaccine-related lymphadenopathy, which has been a longstanding problem.

## CRediT Authorship Contribution Statement

**Katsuhiko Masago, Shiro Fujita:** Writing - original draft.

**Shiro Fujita:** Supervision.

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