Kikuchi disease after SARS-CoV-2 vaccination: A Case Report with immunohistochemical analyses

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Conflict of interest

The authors declare no conflict of interest.

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Ethics approval

This study was approved by the Ethical Review Board of Kinki Central Hospital (Proposal No. 456) and was based on the Declaration of Helsinki of 1975. All procedures were performed in accordance with the guidelines and regulations of the committee. We declared an opt-out policy for this study on the website of Kinki Central Hospital.

Author Contributions

Y.H. designed the study, analyzed the data, drafted the manuscript and figures, and carefully reviewed the manuscript and figures. M.K., H.U., K.H., C.K. and H.A. were primarily involved in specimen processing, and histological sectioning and staining. H.K., T.M., and M.H. reviewed the manuscript from a clinical perspective. S.N. and K.Y. were involved in the pathological diagnosis.

Abstract

SARS-CoV-2 vaccines have been administered in many countries after COVID-19 pandemic. Lymphadenopathy is a side effect of SARS-CoV-2 vaccine. We report a rare case of Kikuchi disease in the cervical lymph nodes after SARS-CoV-2 vaccination. Forty-one-year-old male complained of a swollen neck and fever nine days after the first dose of SARS-CoV-2 mRNA-1273 vaccine. Computed tomography revealed enlarged cervical lymph nodes. Fine needle aspiration and resection were performed, and the clinicopathological diagnosis was consistent with Kikuchi disease. Histologically, the resected lymph nodes lost their polarity, and many histiocytes were aggregated with karyorrhectic nuclear debris and apoptosis. SARS-CoV-2 positive cells were small lymphocytes detected by immunohistochemistry. This is the first report that demonstrated SARS-CoV-2 expression in Kikuchi disease post SARS-CoV-2 vaccination.

Introduction

COVID-19 pandemic occurred in 2019 and more than six million people have died from it globally. SARS-CoV-2 vaccines have been administered in many countries to potentially mitigate disease onset. The representative early side effects of the SARS-CoV-2 vaccine include pain at the injection site, fever, malaise, headache, arthralgia, myalgia, and chills. SARS-CoV-2 vaccine-associated lymphadenopathy is another side effect.

Lymphadenopathy is frequently observed in the axillary, clavicular, and cervical lymph nodes[1].

Kikuchi disease is a reactive lymphocytic disease frequently observed in young Asian adults. The characteristic symptoms are fever and cervical lymphadenopathy. Although the etiology of Kikuchi disease is unclear, it may be related to viral infections or autoimmune diseases[2]. Kikuchi disease associated with SARS-CoV-2 vaccination or infection is relatively rare, and its etiology has not been fully elucidated.

Here, we report a case of cervical lymphadenitis associated with SARS-CoV-2 vaccination including analyses of the cytology and SARS-CoV-2 immunohistochemical expressions.

Case report

Herein, we report the case of a 41-year-old Japanese male with no relevant medical history. The patient noticed swollen cervical lymph nodes nine days after the first dose of SARS-CoV-2 mRNA-1273 vaccine. The patient developed fever 19 days after the first vaccination and was administered loxoprofen. Although the patient's fever and lymphadenopathy were relieved after oral administration of loxoprofen, fever and lymphadenopathy waxed and waned. Night-sweating and contact with animals were not apparent. Body temperature was 37.9 °C 20 days after the first vaccination dose. The

patient visited our hospital 23 days after the first vaccination. Physical examination revealed lymphadenopathy on both sides of the neck and swelling on right tonsil. No tonsillar white exudates were observed, and hoarseness was not apparent. Laboratory findings 23 days after the first vaccination were as follows: aspartate aminotransferase 29 U/L, alanine aminotransferase 37 U/L, alkaline phosphatase 314 U/L, lactate dehydrogenase 288 U/L, gamma-glutamyl transpeptidase 55 U/L, total bilirubin 0.4 mg/dL, total protein 7.2 g/dL, albumin 4.4 g/dL, creatine kinase 49 U/L, creatinine 0.83 mg/dL, estimated glomerular filtration rate 82, blood urea nitrogen 14 mg/dL, blood sugar 93 mg/dL, sodium 140 mEq/L, potassium 4.4 mEq/L, chloride 106 mEq/L, C-reactive protein 0.13 mg/dL, procalcitonin 0.02, white blood cell count 3.48 x10^3/μL, red blood cell count 5.31 x10^6/μL, hemoglobin 15.6 g/dL, hematocrit 46.1%, platelet count 245 x10^3/μL, neutrophil 48.5%, lymphocyte 37.4%, monocyte 13.5%, eosinophil 0.3%, basophil 0.3%, interferon gamma release assay (T-SPOT®.TB) negative, soluble interleukin-2 receptor 740 U/mL. Nasopharyngeal swabs tested negative for SARS-CoV-2 during the nicking enzyme amplification reaction. Cervical computed tomography (CT) scan without contrast enhancement showed enlarged lymph nodes scattered around bilateral parotid glands, neck, and supraclavicular fossa. The patient received a second dose of the SARS-CoV-2 mRNA-1273 vaccine 28 days after the first dose. The patient revisited our hospital 30 days after receiving the first dose. The patient experienced fever,

pain, and sweating. Multiple lymph node clusters are observed at the posterior border of the right sternocleidomastoid muscle. A cytological specimen was collected to rule out malignancy, but it could not be determined whether the lesion was malignant or not. Thirty-seven days after the first dose, the patient revisited our hospital, and the neck swelling and fever persisted. Left neck lymph node biopsy was performed 42 days after the first dose. Surgical findings revealed multiple lymph nodes of 5–10 mm diameter on the back of the sternocleidomastoid muscle, three of which were resected.

Histological images of the cervical lymph nodes are shown in Fig. 1. The lymph nodes lost their polarity. Crescent macrophages were focally seen. Neutrophils, eosinophils, necrosis, abscesses, epithelioid granulomas, or multinucleated giant cells were not observed.

Cytological images of the cervical lymph nodes are shown in Fig. 1. An increase in the number of medium-sized lymphocytes was observed; thus, the possibility of a tumor cannot be ruled out.

Immunohistochemical images of the cervical lymph nodes are shown in Fig. 2 and Fig. 3. According to a reported staining protocol[3], positive and negative controls of the SARS-CoV-2 (1A9) (GeneTex Inc., 2456 Alton Pkwy Irvine, CA 92606, USA) monoclonal antibody were set. CD3-positive, CD4-positive, CD5-positive, or CD8-positive T-cells and CD20-positive B-cells were mixed. The Ki-67 labeling index was

approximately 30%. It was unclear whether SARS-CoV-2 (1A9) positive lymphocytes were T-lymphocytes or B-lymphocytes.

The other laboratory tests were as below. Epstein-Barr virus-encoded RNA in situ hybridization (EBER-ISH) was negative. G-banding revealed a karyotype of 46, XY with no chromosomal abnormalities. Flow cytometry (CD45 gating) showed that T- and B-lymphocytes were almost equally observed and that light chain restriction was not apparent. Clonality analysis with polymerase chain reaction (T-cell receptor β chain gene rearrangement) showed no clonal rearrangement of Vβ/Jβ1 and 2, Vβ/Jβ2, and Dβ/Jβ. Clonality analysis with Southern blotting (IGH-JH rearrangement) revealed no clonal IGH-JH rearrangement.

According to these findings, the lymph nodes were compatible with Kikuchi disease and there was no evidence of malignancy. The patient revisited our hospital 63 days after the first dose, and the fever and sweats disappeared. Redness of skin at the neck and lymphadenopathy were less conspicuous. Subsequently, the patient's symptoms completely improved without medication. Based on a clinicopathological conference, the clinical course was compatible with SARS-CoV-2 vaccination-associated lymphadenitis.

Discussion

Lymphadenopathy is a relatively common side effect of the SARS-CoV-2 vaccine.

“Negative or reactive” florid lymphoid hyperplasia, Kikuchi disease, Langerhans cell hyperplasia, and Rosai-Dorfman-Destombes disease have been histologically reported[1]. There are a few reports of Kikuchi disease associated with SARS-CoV-2 vaccination and our case is one of them. Our patient presented mild leukocytopenia and a relatively long disease duration typical of Kikuchi disease. Necrosis was not apparent; thus, we considered it to be the xanthomatous phase of Kikuchi disease[2]. Differential diagnoses for cervical lymphadenopathy include cat-scratch disease, tularemia, tuberculous lymphadenitis, toxoplasmosis, systemic lupus erythematosus, malignant lymphoma, and metastatic carcinoma. We ruled out malignancy and confirmed immunohistochemical positivity for SARS-CoV-2. The symptoms completely disappeared without medication, and recurrent symptoms did not occur for at least one year. Based on the chronological relationship with SARS-CoV-2 vaccination, we clinically considered Kikuchi disease associated with SARS-CoV-2 vaccination.

Eight cases of Kikuchi disease after SARS-CoV-2 vaccination have been reported[4-10] (Table 1). The eight cases mainly showed axillary and cervical lymphadenopathies. Symptoms appeared three months after vaccination in one case[6]. If the disease is prolonged, Kikuchi disease should be considered. Symptoms disappeared two months after vaccination in one case[10]; therefore, the disease duration of Kikuchi disease may be long. In the present case, symptoms persisted for 63 days. Several case

reports of Kikuchi disease after SARS-CoV-2 infection have also been published, and the histological findings were similar to those of Kikuchi disease after SARS-CoV-2 vaccination[11-15]. Remarkably, several pediatric Kikuchi disease cases following SARS-CoV-2 infection have been reported[11, 12, 14, 15].

In this study, cytological specimens were collected and the immunohistochemical expression of SARS-CoV-2 was analyzed. Previous reports did not include the expression of SARS-CoV-2, so our report is unique. However, there are still limitations regarding the understanding of Kikuchi disease after SARS-CoV-2 vaccination because of the small number of cases reported. Immunohistochemistry using SARS-CoV-2 (1A9) showed less non-specific staining, but might be less sensitive than other anti-nucleocapsid protein antibodies[16]. To further understand the etiology of Kikuchi disease post SARS-CoV-2 vaccination, additional case collection is needed in the future.

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Figure Legends

Fig. 1 Histological and cytological images of cervical lymph nodes. (a) Lymph nodes with paracortical expansion and obscure germinal centers (Hematoxylin and eosin (HE) stain, scale bar = 1 mm). (b) Histiocytes with clear cytoplasm and small lymphocytes together (HE stain, scale bar = 200 μm). (c) Large amount of karyorrhectic nuclear debris and apoptosis images (HE stain, scale bar = 50 μm). (d) Large and small lymphocytes at each maturation stage (Papanicolaou stain, scale bar = 50 μm). (e) Observed histiocytes (Papanicolaou stain, scale bar = 50 μm). (f) Karyorrhectic nuclear debris and apoptosis images (Giemsa stain, scale bar = 50 μm).

Fig. 2 Immunohistochemical images of cervical lymph nodes. (a) Focally aggregated CD68 positive histiocytes (scale bar = 100 μm). (b) Focally aggregated CD163 positive histiocytes (scale bar = 100 μm). (c) Myeloperoxidase expressions in histiocytes (scale bar = 100 μm). (d) Presence of CD123 positive plasmacytoid dendritic cells (scale bar = 100 μm).

Fig. 3 Immunohistochemical images of cervical lymph nodes.

(a) Widely aggregated CD20 positive B-lymphocytes (scale bar = 500 μm). (b) Widely aggregated CD3 positive T-lymphocytes (scale bar = 500 μm). (c) SARS-CoV-2 (1A9)

positive cells focally aggregated (scale bar = 500 μm). (d) SARS-CoV-2 (1A9) positive cells composed of small lymphocytes (scale bar = 50 μm). Cytoplasm and cell membrane of lymphocytes were positive for SARS-CoV-2 (1A9).