Case Report

# Human papilloma virus vaccine induced Kikuchi-Fujimoto disease: A case report

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## ABSTRACT

Cervical lymphadenopathy can be due to numerous causes. The common causes include reactive and infections conditions in children and malignancy in the elderly. Kikuchi-Fujimoto disease (KFD) is a rare cause of cervical lymphadenopathy. As viral vaccines contain viral antigens, they can trigger the development of KFD. The human papillomavirus (HPV) vaccine can trigger KFD. It is important to elicit a history of prior vaccination to identify the trigger in patients with necrotising histiocytic lymphadenitis suspected of having KFD. We hereby report a case of a 16-year-old female who was diagnosed with HPV vaccine induced KFD. Ours is the first case to be reported from India. Histopathology revealed necrotising histiocytic lymphoid hyperplasia and the absence of neutrophils, eosinophils, plasma cells, vessel wall vasculitis, haematoxylin bodies, and Reed-Sternberg cells, and negative aerobic, MTB cultures, anti-nuclear antibodies, clinched the diagnosis of KFD.

**KEY WORDS:** Cervical lymphadenopathy, histiocytic lymphadenitis, Kikuchi-Fujimoto disease

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## INTRODUCTION

The causes of cervical lymphadenopathy are varied. The causes of cervical lymphadenopathy include infections, malignancy, autoimmune and granulomatous diseases, drug-induced, and miscellaneous causes.[1] Reactive cervical lymphadenopathy is more common in children, while malignancy is more common in the elderly.[2] Accurate diagnosis requires eliciting a proper history and appropriate radiological, serological, histopathological, and microbiological evaluation.

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## CASE REPORT

A 16-year-old female presented with multiple swellings on the right side of her neck, low-grade fever, night sweats, and fatigue for 4 weeks. She took multiple courses of antibiotics with no improvement. She had received two shots of the human papillomavirus (HPV) vaccine, 4 weeks apart, and had received the second dose 2 weeks before the onset of symptoms. There was no history of any boils on the face or on scalp or ulcers in the mouth. There was no



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history of rash over the body, excessive hair loss, multiple large or small joint pains, photosensitivity, recurrent mouth ulcers, recurrent genital ulcers, recurrent red eyes, cyclical colour changes in fingers on exposure to cold, fingertip ulcers, bleeding from the nose, dryness of eyes or mouth, difficulty in combing hair, difficulty in getting up from a sitting position, or difficulty in swallowing. On examination, multiple, tender, enlarged lymph nodes with no overlying draining sinuses were palpated in the right cervical region. Skin, scalp, and oral examination was normal. A Computed Tomogram (CT) of the neck revealed multiple necrotic, discrete, enlarged lymph nodes in the right upper, middle, lower deep cervical, posterior triangle stations, and right supraclavicular region (Level II-V), the largest measuring 1.7 × 1.5 cm in the posterior triangle. It was associated with adjacent fat stranding. There was no mediastinal adenopathy or any significant lung parenchymal lesions on the CT of the thorax. A complete blood count revealed anaemia and leukopenia (Total leucocyte count – 3,670 cells/cmm). A peripheral smear did not show the presence of any atypical lymphocytes. The interferon-gamma release assay (IGRA) (QuantiFERON-TB Gold) was negative. Serum anti-nuclear antibody (ANA) by immunofluorescence was negative. The rheumatoid factor was negative. Serum angiotensin-converting enzyme (ACE) was negative (40 ug/L). HIV by Enzyme-linked immunosorbent assay (ELISA) was negative. Serology for Epstein Barr virus (EBV), Cytomegalovirus (CMV) and Parvo B19 was advised but patient refused for the same due to affordability issues. Ultrasound of the abdomen revealed hepatosplenomegaly. Protein electrophoresis did not reveal any abnormal paraprotein. A Trucut Biopsy from the cervical lymph node revealed reactive lymphoid infiltrate with amorphous necrotic and karyorrhectic debris admixed with foci of large mononuclear cells and histiocytes [Figure 1]. The aerobic culture was negative. On Cartridge based nucleic acid amplification test (CBNAAT), Mycobacterium tuberculosis (MTB) was not detected. Culture for MTB and Non-tubercular mycobacteria (NTM) was negative. The excision biopsy of the cervical lymph node showed architectural distortion with irregularly shaped, pale areas composed of histiocytes, eosinophilic granular material and abundant karyorrhectic debris (nuclear dust) surrounding a central zone of overt necrosis suggestive of necrotising histiocytic lymphadenitis. On immunohistochemistry (IHC), there were predominantly CD3T cells and the CD4:CD8 ratio was preserved. Residual follicles and subcapsular B cells were positive for CD20. Reactive histiocytes were CD68 positive [Figure 2]. BCL 2 was positive in the T zone. Bcl-6 was positive in the residual follicles [Figure 3]. IHC for EBV was not done as patient could not afford the cost of the test. This was consistent with reactive lymphoid hyperplasia (paracortical T zone expansion). Aerobic, MTB and NTM cultures were negative. Hence a diagnosis of KFD secondary to HPV vaccination was made. She was managed conservatively with NSAIDs. Follow-up ultrasound of the neck and abdomen after two weeks showed a decrease in the size of lymph nodes, liver and spleen which completely resolved at 6 weeks' follow-up. Total leucocyte counts also improved to 9900/cmm. The patient has been kept under follow-up to detect recurrence and development of any autoimmune features.

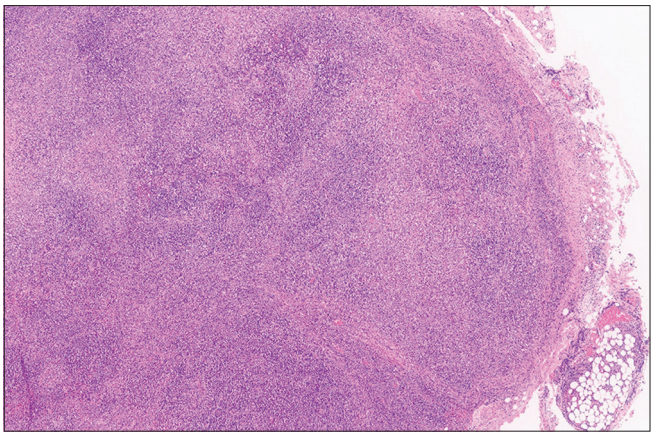

**Figure 1:** Haematoxylin and Eosin-stained slide showing viable area with reactive lymphoid background

## DISCUSSION

KFD also called Kikuchi disease, or Kikuchi histiocytic necrotizing lymphadenitis was first described by Japanese pathologists Kikuchi and Fujimoto in 1972.[3,4] It is a rare, benign, self-limiting immune-mediated/inflammatory sub-acute necrotising histiocytic lymphadenitis. It most commonly involves cervical lymph nodes [posterior triangle of the neck]. The pathogenesis is not yet known. The role of exaggerated/aberrant T-cell immune response to viruses and bacteria in genetically susceptible individuals and autoimmune predisposition has been proposed. The viruses which have been implicated include HPV, Human herpesvirus 6 and 8 (HHV- 6, 8), Human immunodeficiency virus (HIV), Parvovirus B19, and Epstein Barr virus. The bacteria which have been implicated include Chlamydia psittaci and Yersinia enterocolitica.[5] KFD has been found to be associated and may precede or coexist with autoimmune disorders like systemic lupus erythematosus, Sjogren's syndrome, antiphospholipid syndrome, Hashimoto's thyroiditis.[6-8] As viral vaccines contain viral antigens, they can trigger the development of KFD. Cases of KFD following Influenza, Japanese encephalitis, COVID-19 and HPV vaccine have been reported.[5] Five cases of KFD following HPV vaccination have been reported, three from Japan and two from Europe. Three were following vaccination with Cervarix and two following Gardasil. All the cases required hospitalization except one.[9] The case reported from Japan was a 14-year-old girl who developed cervical lymphadenopathy three days after receiving HPV and Japanese encephalitis virus vaccine.[10] However, there was a history of prior Japanese encephalitis virus vaccine receipt without any adverse event. Ours is the first case to be reported from India, to the best of our knowledge.

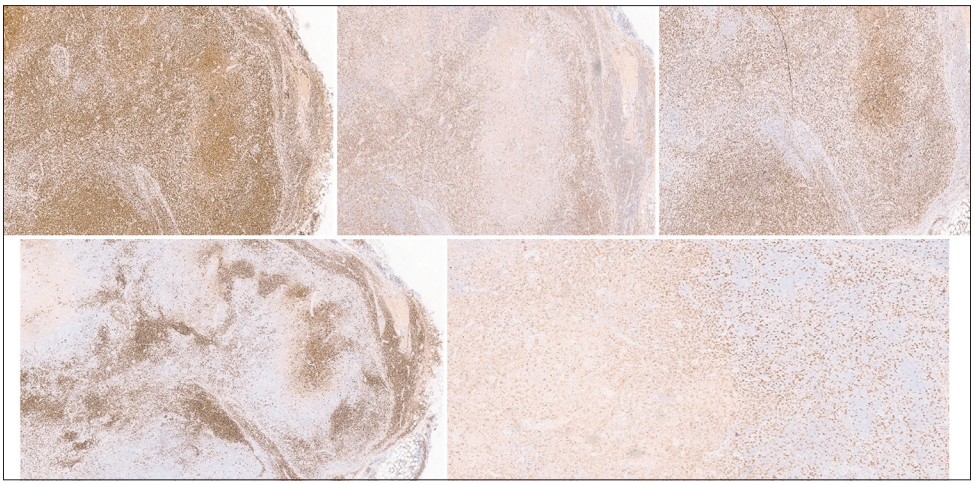

**Figure 2:** Immunohistochemistry of lymph node biopsy showing 1. Paracortical T zone highlighted by CD3+ T cells. 2. CD4 cells. 3. CD 8 cells. 4. Residual follicles and subcapsular B cells positive for CD20. 5. Reactive histiocytes highlighted by CD68

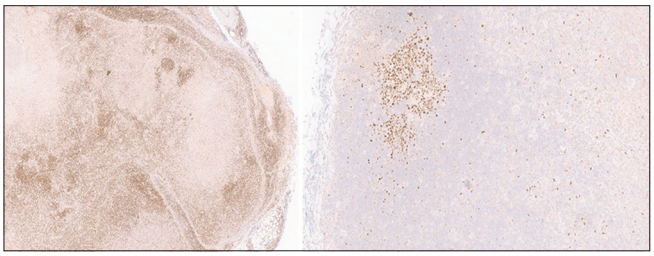

**Figure 3:** Immunohistochemistry of lymph node biopsy showing 1. BCL 2 positive in the T zone. 2. BCL6 positive in the residual follicles

Anaemia, leukopenia, thrombocytopenia may be seen in KFD, though its more common in patients with extra cervical lymph node involvement. Hepatomegaly and splenomegaly are also more common in patients with extra cervical lymph node involvement.[11] Our patient had cervical and supraclavicular lymph node involvement, leukopenia and hepatosplenomegaly. There is no diagnostic test for KFD. Histopathological features include lymphoid hyperplasia with proliferation of CD 68+ histiocytes. There is absence of neutrophils and eosinophils. There is necrosis due to histiocytic karyorrhexis. Features like absence of vessel wall vasculitis, haematoxylin bodies help to differentiate from autoimmune causes. Negative bacterial, tubercular cultures and molecular studies like Cartridge based nucleic acid amplification tests (CBNAAT) help to differentiate from infectious causes. Immunohistochemistry and flow cytometry plays an important role in distinguishing KFD from malignancy especially lymphoma.[12] In our case of cervical and supraclavicular lymphadenopathy, there were no clinical features suggestive of any autoimmune disease, the histopathology was suggestive of necrotising histiocytic lymphoid hyperplasia and the absence of neutrophils, eosinophils, vessel wall vasculitis, haematoxylin bodies, Reed Sternberg cells, plasma cells and negative aerobic, MTB cultures, anti-nuclear antibodies clinched the diagnosis of KFD.

The disease is usually self-limited and treatment is usually conservative with antipyretics and NSAIDs.[13] Steroids and intravenous immunoglobulin (IVIg) have been used in refractory cases.[14] The disease can recur in a few cases and a few patients can develop systemic autoimmune diseases over a course of time. Cases of early and late recurrences have been reported.[15,16] The presence of extra nodal symptoms, lymphopenia and positive antinuclear antibody have been associated with recurrence.[17]

## CONCLUSION

HPV vaccine can induce KFD. High index of suspicion, necrotising histiocytic lymphoid hyperplasia on histopathology, excluding infective, autoimmune and malignant causes can help to clinch the diagnosis. It is usually self-limited and resolves over a few weeks.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

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