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CASE REPORT

Kikuchi–Fujimoto disease following vaccination against human papilloma virus infection and Japanese encephalitis

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Abstract Kikuchi–Fujimoto disease (KFD) is a benign and self-limited syndrome, characterized by regional lymphadenopathy and fever. Although the pathogenesis of KFD remains unclear, infectious agents, autoimmune causes, and physicochemical factors have been suggested as triggers. However, KFD following vaccination has never been reported. We present a 14-year-old girl who suffered from fever and cervical lymph node swelling following simultaneous administration of human papilloma virus vaccine and Japanese encephalitis virus vaccine. The patient was diagnosed with KFD based on the histopathologic findings of a lymph node biopsy, and her fever and swelling resolved with oral corticosteroid therapy. Although the exact pathogenesis of the development of KFD following immunization remains unknown, this should be added to the list of potential triggers or factors associated with the development of KFD.

Keywords Kikuchi's disease · Vaccine · Histiocytic necrotizing lymphadenitis · Adverse events · Vaccination complication

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Introduction

Kikuchi–Fujimoto disease (KFD) is a benign and self-limited syndrome, first described independently by Kikuchi [6] and by Fujimoto [2] in 1972. It is characterized by regional lymphadenopathy with tenderness, usually accompanied by mild fever, fatigue, and leukopenia [7]. The diagnosis of KFD is made by lymph node biopsy; the characteristic histopathologic feature is apoptosis associated with prominent debris and phagocytic activity [1].

Although the pathogenesis of KFD remains unclear, infectious agents, autoimmune causes, and physicochemical factors have been suggested as triggers [1]. However, KFD following vaccination has never been reported. We describe herein a patient with KFD following simultaneous administration of vaccines against human papilloma virus (HPV) infection and Japanese encephalitis.

Case report

A 14-year-old Japanese girl was admitted to our hospital because of a 17-day history of bilateral enlarged and tender cervical lymph nodes and an 11-day history of high-grade fever and general fatigue. Three days before the development her illness, the patient had simultaneously received a single injection of human papilloma virus vaccine into the left deltoid muscle and a single injection of Japanese encephalitis virus vaccine into the subcutaneous space of the right deltoid muscle. The patient had previously received Japanese encephalitis virus vaccination three times without any adverse effects. The patient was allergic to squid, octopus, and kiwi fruit.

On admission, the patient was febrile with a body temperature of 38.8 °C, but otherwise appeared well. Physical

examination revealed bilateral cervical lymph node swelling with tenderness.

Laboratory studies showed a white blood cell count of 1.9×10^9/l (normal, $4.0–9.0\times10^9$/l) with 19 % neutrophils, 59 % lymphocytes, 18 % monocytes, 2 % eosinophils, and 2 % basophils, and a lactate dehydrogenase level of 337 IU/l (normal, 116–214 IU/l). Other tests for liver function, renal function, C-reactive protein level, erythrocyte sedimentation rate, red blood cell count, hemoglobin concentration, and platelet count were normal. Serology testing for hepatitis B and C, and human immunodeficiency virus was negative, while serology for Epstein–Barr virus (EBV) and human parvovirus B19 indicated past infections with these viruses. Immunoglobulin G, A, and M levels, complement C3 and C4 concentrations, and antinuclear antibody titer were normal.

An excision biopsy of the right cervical lymph node demonstrated numerous phagocytic histiocytes with abundant nuclear dust, lymphoid cells, and some immunoblasts, which were findings compatible with KFD (Fig. 1). Neutrophil infiltration or a marked increase of immunoblasts imparting a mottled appearance to the lymphoid tissue was absent.

The patient was diagnosed with KFD. Because she and her parents were very anxious about her illness, she was administered oral prednisolone (1 mg/kg/day, for 10 days), which quickly led to the resolution of her fever and lymph node swelling. The patient remained well, and laboratory examinations also reverted to normal at the 1-month follow-up visit.

Discussion

KFD has a worldwide distribution with a higher prevalence among Japanese and other Asian populations [1]. It is typically characterized by cervical lymphadenopathy with tenderness, mild fever, and fatigue, and usually a benign and self-limiting disease. Although the results of a wide range of laboratory studies are usually normal, leukopenia has been observed in 25 to 58 % of patients [1].

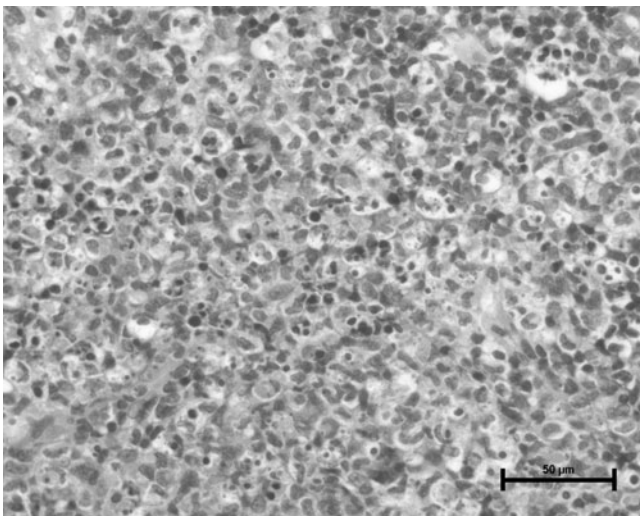

Fig. 1 Cervical lymph node biopsy showing numerous phagocytic histiocytes with abundant nuclear dust, lymphoid cells, and some immunoblasts (hematoxylin–eosin, original magnification ×400)

The diagnosis of KFD is made by lymph node biopsy. Although KFD is often reported in the literature as histiocytic necrotizing lymphadenitis, overt coagulative necrosis is not a prerequisite for this diagnosis [10]. The most striking underlying feature is apoptosis associated with prominent debris and phagocytic activity [10]. The differential diagnosis of KFD includes systemic erythematosus (SLE), infectious lymphadenitis, non-Hodgkin lymphoma, leukemia, and Kawasaki disease [1].

There is no specific treatment for KFD, and only symptomatic treatment should be used to relieve distressing local and systemic complaints [1]. However, some patients with severe or persisting symptoms have been treated with corticosteroids [1].

Although the cause of KFD remains unknown, the clinical presentation, course, and histologic changes suggest a T cell-mediated hyperimmune reaction induced by diverse antigens such as infectious agents or physicochemical factors [1]. As infectious agents, viruses (EBV, human parvovirus B19, human herpes virus type 6, and cytomegalovirus), bacteria (*Yersinia enterocolitica*, *Brucella* sp., *Bartonella henselae*), and protozoa (*Toxoplasma gondii*) have been postulated to trigger KFD [1]. Several physicochemical factors have been pointed out as triggers of KFD, which included pacemaker implantation and ruptured silicone breast implant [1].

Furthermore, an association between KFD and autoimmune disorders has been shown, including SLE, mixed connective tissue disease, antiphospholipid antibody syndrome, and scleroderma [1, 7]. Imamura et al. reported that electron microscopy has often revealed tubuloreticular structures in histiocytoid cells of lymph node lesions of patients with KFD, and they hypothesized that KFD might reflect a self-limited SLE-like autoimmune condition induced by virus-induced transformed lymphocytes [5]. One study suggested that KFD might represent an exuberant T cell-mediated immune response in people genetically susceptible to a variety of nonspecific stimuli because some HLA class II genes were more frequent in patients with KFD [9].

While KFD following vaccination has never been reported, viral vaccines might induce KFD because they have some viral or other antigens, which could lead to aberrant immune response in vaccine recipients. Our patient developed KFD following simultaneous administration of HPV and Japanese encephalitis virus vaccines. Because the patient had previously received Japanese encephalitis virus vaccine three times without any adverse effects, HPV vaccine was the more likely

cause of KFD in our patient. Studdiford et al. reported a patient with lymph node swelling after HPV vaccination [8]. Since that patient had not undergone lymph node biopsy, the exact diagnosis and the pathogenesis of the swollen lymph nodes of their patient were unclear.

Lymphadenitis occurring after administration of a vaccine is called postvaccinal lymphadenitis [4]. It is a reactive response to the vaccination and can be caused by vaccines against small pox [8], influenza [3], varicella zoster, BCG, and pneumococcal [4]. The most characteristic histopathologic finding of postvaccinal lymphadenitis is a marked increase in immunoblasts, which intermingle with well-differentiated lymphocytes and impart a mottled appearance to the lymphoid tissue [4]. The lymph node biopsy of our patient revealed numerous phagocytic histiocytes with abundant nuclear dust and without marked immunoblast proliferation, which was compatible with KFD but not with postvaccinal lymphadenitis.

In summary, we have described a patient with KFD following vaccination against HPV infection and Japanese encephalitis. Although the precise pathogenesis of the development of KFD following vaccination remains unknown, vaccination should be added to the list of potential triggers or factors associated with the development of KFD.

Conflict of interest We declare that we have no conflict interest.

References

1. Bosh X, Guilabert A, Miquel R, Campo E (2004) Enigmatic Kikuchi–Fujimoto disease: a comprehensive review. Am J Clin Pathol 122:141–152
2. Fujimoto Y, Kozima Y, Yamaguchi K (1972) Cervical subacute necrotizing lymphadenitis: a new clinicopathological entity. Naika 20:920–927, in Japanese
3. Gundogdu Z, Seyhogullari M (2010) Lymphadenitis as a rare side effect of H1N1 vaccine in a child. Case Report Med 2010:459543
4. Hartsock RJ (1968) Postvaccinial lymphadenitis. Hyperplasia of lymphoid tissue that simulates malignant lymphoma. Cancer 21:632–649
5. Imamura M, Ueno H, Matsuura A, Kamiya H, Suzuki T, Kikuchi K, Onoe T (1982) An ultrastructural study of subacute necrotizing lymphadenitis. Am J Pathol 107:292–299
6. Kikuchi M (1972) Lymphadenitis showing focal reticulum cell hyperplasia with nuclear debris and phagocytes: a clinicopathological study. Nippon Ketsueki Gakkai Zasshi 35:379–380, in Japanese
7. Kucukardali Y, Solmazgul E, Kunter E, Oncul O, Yildirim S, Kaplan M (2007) Kikuchi–Fujimoto disease: analysis of 244 cases. Clin Rheumatol 26:50–54
8. Studdiford J, Lamb K, Horvath K, Altshuler M, Stonehouse A (2008) Development of unilateral cervical and supraclavicular lymphadenopathy after human papilloma virus vaccination. Pharmacotherapy 28:1194–1197
9. Tanaka T, Ohmori M, Yasunaga S, Ohshima K, Kikuchi M, Sasazaki T (1999) DNA typing of HLA class II genes (HLA-DR, -DQ and –DP) in Japanese patients with histiocytic necrotizing lymphadenitis (Kikuchi's disease). Tissue Antigens 54:246–253
10. Tsang WY, Chan JK, Ng CS (1994) Kikuchi's lymphadenitis. A morphologic analysis of 75 cases with special reference to unusual features. Am J Surg Pathol 18:219–231