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Letter to the Editor

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Kikuchi-Fujimoto Disease: a rare type of lymphadenopathy and its plausible relationship with human papillomavirus vaccines

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Sir,

Kikuchi-Fujimoto Disease (KFD) or histiocytic necrotizing lymphadenitys is a rare, benign self-limited disorder characterized by subacute necrotizing regional lymphadenopathy. It was thought that it commonly affected young Asian adults, mainly females. However, further research has shown that males and females are equally affected, and different cases have been reported all over the world [1,2].

KFD is usually presented as painful cervical nodes and is frequently associated with fever, headache, night sweats, nausea, vomiting and sore throat. Cervical lymphadenopathy is evidenced in 60-90% of cases, with concomitant involvement of axillary and/or supraclavicular lymph nodes [1,2]. Extranodal locations are uncommon [3]. Systemic symptoms like splenomegaly and hepatomegaly occur in less than 5% of cases [1]. Most patients have normal laboratory findings. Analytical abnormalities in some patients include elevated serum lactate dehydrogenase and aminotransferases. Leukopenia has been detected in 50% of KFD patients [4,5].

Etiology of KFD is still unknown. Two main theories have been postulated: infections and autoimmune origin. Numerous viruses and other infectious agents have been proposed as etiologic agents of KFD: Epstein-Barr virus; herpes simplex virus; varicella zoster virus; human herpesviruses 6, 7, and 8; parvovirus B19; paramyxovirus; parainfluenza virus; rubella; cytomegalovirus; hepatitis B virus; human immunodeficiency virus; *Brucella* spp., *Bartonella henselae, Yersinia enterocolitica, Toxoplasma gondii, Entamoeba histolytica,* and *Mycobacterium* spp. [6]. KFD seems to be related to an overactive T-cell-mediated immune response [2, 3]. Patients diagnosed with KFD frequently have human leukocyte antigen (HLA) class II alleles, specifically HLA-DPA1 and HLA-DPB1, which are more prevalent among Asians and rare or absent in Caucasians [7].

KFD diagnosis is based on histopathological analysis. The disease may resolve spontaneously without treatment. NSAIDs or paracetamol are first line of treatment for symptomatic control. Despite the overall prognosis is satisfactory, symptoms can last up to weeks or months [8,9]. In chronic, recurrent or complicated cases; corticosteroids, intravenous immunoglobulins and hydroxychloroquine can represent an alternative [10].

The human papillomavirus (HPV) is a known etiological agent of cervical cancer and other types of cancer, reason why vaccination campaign is established for certain population groups. There are three different marketed vaccines that differ in the number of serotypes they contain; the bivalent vaccine (HPV2), which protects against HPV types 16 and 18; the tetravalent vaccine (HPV4), which protects against types 16, 18, 6, and 11; the 9-valent vaccine (HPV9), which protects against types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

It is already widely proven that vaccines are effective, cost-effective and safe [11]. However, there have been reports of subacute course or complicated lymphadenopaties associated with HPV vaccination [12,13]. KFD associated to HPV vaccination has only been reported in the literature once [14].

Recently, there have been reports of KFD related to vaccination, mainly to COVID-19 vaccines [15]. Due to this growing increase, the immunomodulatory mechanism of vaccination and the underdiagnosis of KFD, a literature and adverse events databases search has been conducted to assess the possible relation between HPV vaccines and KFD.

A search in the Spanish adverse events database (FEDRA) and the European adverse events database (Eudravigilance) was carried out. To be aware of KFD cases, search criteria were "*HPV Vaccines; Gardasil® and Cervarix®*" **and** the diagnosis *"Histiocytic necrotising lymphadenitis"*, as well as a search of *"Histiocytic necrotising lymphadenitis"* for any drug. To know the cases with any other lymphadenopathy a new search with

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Table 1 HPV vaccines associated KFD cases in Eudravigilance

Case	Sex	Country	Vaccine	Other immune disorders*	Outcome**	Seriousness
1	F	Germany	Gardasil (16,18)®	Lymphadenopathy	Recovered	No
2	F	Japan	Cervarix®	Lymphadenopathy	Not recovered	Hospitalization
3	F	Japan	Cervarix®	Lymphadenopathy Splenomegaly Elevated aminotrasnferases	Recovered	Hospitalization
4	F	Japan	Cervarix® Encevac®	Painful lymphadenopathy	Recovered	Hospitalization
5	F	Portugal	Gardasil (6,11,16,18)®	Lymphadenopathy	Recovering	Hospitalization

*** Other reported AE apart from KFD. **At time of notification**

the criteria "*lymphadenopathy and linphadenitis*" for the same vaccines was conducted. According tothe Medical Dictionary for Medical Activities version 25.0 (MedDRA). All adverse events registered as September 18th 2022 were included.

The study was conducted in accordance with the ethical standards established in the Declaration of Helsinki. Since FEDRA and Eudravigilance are anonymized, no informed consent was required.

FEDRA encompassed only three KFD adverse reports, one related to methotrexate, other to elasomeran (Spikevax®) and the other to tozinameran (Comirnaty®). No case of KFD associated to HPV vaccines was found. On the other hand, Eudravigilance included a total of 62 KFD cases, of which 5 were associated to HPV vaccines (table I) and 19 to other vaccines.

Regarding HPV vaccines associated reports, 3 cases occurred after Cervarix® vaccination [one case also had the Japanese encephalitis vaccine as suspected drug, Encevac®, and two after Gardasil®. Median age was 13 (range 12-26). Out of the 5 cases, four required hospitalization and in all five cases other lymphadenopathy was also notified.

In case 2, screening for influenza A and B viruses was negative. In case 3, the following serologies were negative: adenovirus, CMV, enterovirus, VEB, VHA, VHB, toxoplasma and mycoplasma. In both cases 2 and 3, Quantiferon test was also negative. In case 4, serologies for VEB, VIH, VHB, VHC and parvovirus B19 were negative.

Concerning "*lymphadenopathy and linphadenitis*", 7 cases for Cervarix® and 16 for Gardasil® were found in FEDRA. Whereas 108 and 547 cases were found for Cervarix® and Gardasil®, respectively, in Eudravigilance.

In relation to other vaccines, 15 cases of KFD related to COVID-19 vaccines were found. Moreover two reports of KFD disease connected to tetanus, diphtheria, pertussis, and polio disease vaccine, one case of KFD related the flu vaccine was reported, and other one with bacilli Calmette-Guerin. Median age was 30 (range 10-52). Six of these cases had another type of lymphadenopathy as well. Eight of them were serious and seven required hospitalization.

KFD is a rare entity, which real incidence is unknown. Due to its self-limited course and its common symptoms, it is often mistaken with other lymphadenopathies, and is probably underdiagnosed [6].

The current incidence of lymphadenopathy with HPV vaccines is not clearly established. Data Sheets of bi and tetra-valent vaccines describe the frequency of lymphadenopathy as "not known", whilst in the 9-valent vaccine it is described as "rare". Underreporting and the fact that the data reported in pharmacovigilance databases may be incomplete, are a clear limitation to assess a relationship.

In the Spanish national adverse events database, 25 events categorized under the MedDRA term *"Lymphatic system disorders"* have been reported for bi, tetra and 9-valent vaccines. This means that some of these cases could have been KFD and might have not been properly diagnosed.

According to table 1, 3 of 5 cases correspond to female of Asian origin, which fits the data available. The literature review shows that KFD frequently presents concomitantly with other lymphadenopathies [1], and in the five cases described, any lymphadenopathy was also reported apart from KFD. The T-lymphocyte-mediated immune response at the lymph node level post-vaccination could also contribute to the development of KFD [1]. In three of five cases, negative microbiological test were available. Taking into account the infectious origin of KFD and the immunomodulated mechanisms, plausible causal relationship may be reinforced, although more research is required.

Symptoms of KFD may be confused with lymphomas, making proper diagnosis mandatory to avoid unnecessary clinical tests. Four cases required hospitalization. Knowledge of KFD could have avoided prolonged hospitalization as well as reduced health care costs.

KFD is an entity of probably multifactorial origin and re-

search is needed to understand the origin of the disease. Reporting of suspected adverse events is essential to assess the real incidence and to optimize patient management presenting with lymphadenopathy of subacute course or with some complication.

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CONFLICT OF INTEREST

Authors declare no have conflict of interest.

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