

Kikuchi-Fujimoto Disease and COVID-19 vaccination: Pharmacovigilance approach

Running title: Kikuchi-Fujimoto Disease and COVID-19 vaccines

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Word count: 1906

Abstract

Kikuchi-Fujimoto Disease (KFD) or histiocytic necrotizing lymphadenitis is a rare disorder characterized by subacute necrotizing regional lymphadenopathy. It is usually presented as painful cervical nodes and associated with fever, headache, night sweats, nausea, vomiting and sore throat. Etiology of KFD is still unclear, two theories have been proposed: infections and autoimmune origin. Due to recent reports of KFD related to COVID-19 vaccination, the novelty of the mechanism of these vaccines and the immunomodulated role of both matters, a literature and adverse event databases review was carried out in order to shed light on the relationship between these two matters. A search in the Spanish and the European adverse events databases (FEDRA and Eudravigilance) was performed. Search criteria were any drug and the diagnosis "*Histiocytic necrotising lymphadenitis*" according to the Medical Dictionary for Medical Activities version 25.0. All adverse events registered as June 2, 2022, were included. FEDRA encompassed two KFD reports, one related to a mRNA COVID-19 vaccine. Eudravigilance included a total of 62 KFD cases, 14 of them associated to COVID-19 vaccines and eight to other vaccines. Pharmacovigilance is of utter importance in detecting adverse events caused by new vaccines. More research is needed to establish a final connection between KFD and COVID-19 vaccines, but due to the physiopathology of the condition, how vaccines stimulate the immune system and the high number of reported KFD cases with vaccines given its rare incidence, it is plausible to think that both entities are related.

Keywords

Kikuchi-Fujimoto, vaccines, lymphadenopathy.

Impact Statement

Vaccination against COVID-19 has been done massively. Kikuchi-Fujimoto Disease has been reported an oddly high number of times, considering the low rate of this condition.

Introduction

Kikuchi-Fujimoto Disease (KFD) or histiocytic necrotizing lymphadenitis is a rare, benign self limited disorder characterized by subacute necrotizing regional lymphadenopathy. KFD was first described in 1972 by Kikuchi M and Fujimoto. First data suggested that it commonly affected young adults of Asian origin, mainly females. However, further research has shown males and females are equally affected and different cases have been reported worldwide (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 (1-3). Extranodal locations are uncommon, cutaneous involvement mostly affects the face and upper body, manifesting as rashes, nodules, erythematous papules, indurated erythematous lesions, erythema multiforme, and erythematous maculopapular lesions (4, 5). Systemic symptoms like splenomegaly and hepatomegaly occur in less than 5% of cases (1, 6). Most patients have normal laboratory findings. Analytical abnormalities seen in some of them

include elevated serum lactate dehydrogenase and aminotransferases. Leukopenia has been detected in 50% of KFD patients (6, 9).

Etiology of KFD is still unknown. Two main theories have been postulated: infections and autoimmune origin. Numerous viruses 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 and human immunodeficiency virus. Other infectious agents involved are: *Brucella* sp., *Bartonella henselae*, *Yersinia enterocolitica*, *Toxoplasma gondii*, *Entamoeba histolytica*, and *Mycobacterium* sp. (10, 11). KFD seems to be linked 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 whites (12). KFD has also been related to autoimmune diseases such as systemic lupus erythematosus (SLE), Sjögren syndrome, Graves' disease, Still's disease, etc. KFD can present concomitantly with SLE or even it has postulated to be the prequel to its development (1, 2).

KFD diagnosis is based on histopathological analysis, performing histological assessment of the affected lymph nodes. Common lymphadenopathies, infections and lymphomas can usually be mistaken, so differential diagnosis of KFD must be carried out. The most common histologic findings of KFD patients are the proliferative, necrotizing, and xanthomatous patterns. An expanded paracortex with sheets of histiocytes and plasmacytoid dendritic cells is found in the initial proliferative pattern (13, 14).

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 (11, 14). In chronic, recurrent or complicated cases, corticosteroids can play an important role. Intravenous immunoglobulins and hydroxychloroquine have been used in some cases (15, 16).

Recently, there have been reports of KFD related to COVID-19 vaccination (17-21). Due to the novelty of the mechanism of these vaccines, the quantity of covid vaccine-related KFD reports and the immunomodulated root of both matters, a literature and adverse event databases search has been conducted in order to shed light on the relationship between these two topics.

Materials and methods

A search in the Spanish adverse events database (FEDRA) and the European adverse events database (Eudravigilance) was carried out. Search criteria were any drug and the diagnosis "*Histiocytic necrotising lymphadenitis*" according to the Medical Dictionary for Medical Activities version 25.0 (MedDRA). All adverse events registered as June 2nd 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.

Results

FEDRA encompassed two KFD adverse reports, one related to methotrexate and the other to elasomeran (Spikevax®). On the other hand, Eudravigilance included a total of 62 KFD cases, of which 14 were associated to COVID-19 vaccines (table I) and 8 to other vaccines (table II).

Regarding COVID-19 vaccines associated reports, 11 cases occurred after Cominarty® vaccination, two after Vaxzevria® and 1 following Spikevax®. Median age was 27 (interquartile range 10-52). Most notifications were from pharmaceutical industry (85.7%), except cases 1 and 5. Three adverse reports were obtained through scientific literature (cases 3, 6 and 8) and the rest were spontaneous notifications. Out of the 14 cases, ten were considered serious and 9 required hospitalization.

In relation to other vaccines, five cases of KFD related to papilloma virus vaccine were found (one of them had also the Japanese encephalitis vaccine as suspected drug). More over 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 bacille Calmette-Guerin. Median age was 25 (interquartile range: 12-45). Six of these cases had another type of lymphadenopathy as well. Eight of them were serious and seven required hospitalization.

Discussion

KFD is a rare condition whose real incidence is unclear, though it is estimated to be between 0.5% and 5% of all histological analyzed lymphadenopathies (1). Its symptoms are often mistaken with other lymphadenopathies and due to its self-limitation, is underdiagnosed. Other kind of reported lymphadenopathy is Hypermetabolic Vaccine Related Lymphadenopathy, characterized by frequent and painless lymphadenopathy, which appears usually the day after vaccination, with few symptoms and resolves within a few days (22). The onset of lymphadenopathies caused by COVID-19 vaccines is well established. Only in the Spanish national adverse events database, 3,927 events categorized under the MedDRA term "*Lymphatic system disorders*" have been reported for Vaxzevria®, Spikevax® or Comirnaty® (consulted on June 9, 2022). This means that many of these cases could have been KFD and were not properly diagnosed.

Typically, symptoms are mild, although children suffer more often severe fevers and have a higher risk of lymph node necrosis (9). In some cases, KFD symptoms may be confused with lymphomas, so a proper diagnosis is mandatory in order to avoid invasive tests and not startle patients.

It has been postulated that KFD represents a disproportionate T-cell-mediated immune response to a variety of antigens in genetically susceptible patients (3). mRNA vaccines induce a rapid and localized infiltration of neutrophils, monocytes, and dendritic cells into the draining lymph node after vaccination. mRNA-type COVID-19 vaccines rapidly induce CD8+ T-cell production, favoring their efficacy (23). Of the total of 14 cases reported with COVID-19 vaccines, 12 are related to mRNA vaccines, one to Spikevax® and 11 to Comirnaty®, this disproportion might be due to the greater number of vaccines administered with tozinameran.

According to the data in Table 1, case 2 corresponds to a male of Asian origin, which fits with the data observed in the literature (1, 3, 18). In seven cases some type of lymphadenopathy was also reported. The literature reviewed shows that KFD frequently presents concomitantly with this type of adverse event (1, 2, 4, 8). Case 7 is a 24-year-old male who is diagnosed with SLE, at the same time as KFD is reported. Case 14 corresponds to a 12-year-old girl, in whom Kawasaki disease was also suspected due to compatible clinical manifestations (pyrexia, hemophthalmia, lip reddening, swollen right cervical nodes). According to other reported cases, KFD can appear concomitantly with rheumatic diseases (1, 2). Of the data obtained with other vaccines, we highlight case 3, corresponding to a 13-year-old girl from Japan, in whom splenomegaly and elevated transaminases were observed, described in the literature as infrequent complications associated with KFD. Patients of young age and female gender were observed, mainly in non-COVID vaccines, which fits with the initially described incidence of this pathology.

Cases of KFD associated with COVID-19 infection have also been reported (24, 25). Taking into account the possible viral origin, it seems logical to think that COVID-19 may also somehow induce the onset of KFD, as do the numerous viruses already described as possible causative agents.

Several cases in the literature of KFD associated with other vaccines can be found, especially human papillomavirus vaccine (26). Although the causal relationship between vaccination and KFD is not proven, the T-lymphocyte-mediated immune response at the lymph node level could contribute to the development of KFD. Overall, the fact that 35% of the cases in Eudravigilance are associated with some type of vaccine, reinforces the published evidence regarding the development of KFD after vaccination, even though more research is required.

In the cases studied and registered in the pharmacovigilance databases, latencies ranging from one day to three months are observed, a highly variable value that is largely conditioned by the difficulty of establishing a date of onset of the adverse event, given the evolution of the same. In 50% of the cases this data is unknown. In any case, the latencies observed are compatible with the hypothetical causal relationship between the vaccine and the adverse event.

Despite having a self-limiting and benign course, most patients registered in Eudravigilance were considered severe and required hospitalization. Early diagnosis would have avoided unnecessary diagnostic tests and prolonged hospitalization, reducing both direct and indirect health care costs. Knowledge of this entity is important to optimize health care in patients presenting with lymphadenopathy of subacute course or with some complication.

Conclusion

KFD is an entity of probably multifactorial origin, difficult to diagnose and whose notoriety has been growing in recent times, especially thanks to the cases reported with COVID-19 vaccines. Although the relationship between KFD and vaccination is not clearly established, taking into account the few data available, we consider that the increase in cases in the latest reported data reinforces the hypothetical causality. Research is needed to better understand the origin of the disease.

The short time elapsed between the start of worldwide vaccination campaigns against COVID-19 and the number of reported cases highlights the importance of pharmacovigilance. It is essential to raise awareness among all healthcare professionals of the importance of reporting

any suspected adverse events in order to have solid safety data and therefore being able to take appropriate action, if necessary.

Acknowledgements

Data to carry out this paper comes from FEDRA and Eudravigilance databases, which are managed by the Spanish Agency of Medicines and Medical Devices (AEMPS) and do not represent the AEMPS regarding this issue.

Conflict of interest statement

The authors declare no conflicts of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

Adrián Rodríguez-Ferreras collected and interpreted the data, conceived and designed the study and wrote the paper. Iván Maray contributed to review and write the paper. All other authors contributed to interpret the data. Jesús Ruiz-Salazar supervised the study and approved the final version of the manuscript.

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Table I. COVID-19 vaccines associated KFD cases in Eudravigilance

Case	Sex	Age	Vaccine	Latency*	Other immune disorders**	Outcome***	Seriousness
1	M	47	Spikevax®	74 days	-	Recovering	Yes
2	M	41	Vaxzevria®	-	Cervical node	-	-
3	M	18	Comirnaty®	-	Cervical swelling	Recovered	Hospitalization
4	M	52	Comirnaty®	-	-	Recovering	-
5	F	31	Comirnaty®	3 months	-	Recovered	Hospitalization
6	F	34	Comirnaty®	2 months	Axillar lymphadenopathy	Not recovered	-
7	F	24	Comirnaty®	-	LES	Recovered	Hospitalization
8	M	13	Comirnaty®	11 days	-	Not recovered	Hospitalization
9	F	38	Comirnaty®	-	Lymphadenopathy	Recovering	Hospitalization
10	F	48	Vaxzevria®	20 days	-	Recovered	Hospitalization
11	M	12	Comirnaty®	-	Painful cervical lymphadenopathy	-	-
12	F	13	Comirnaty®	-	-	Recovered	Hospitalization
13	F	10	Comirnaty®	1 day	Lymphadenopathy	Recovered	Hospitalization
14	F	12	Comirnaty®	1 day	Kawasaki disease	Recovered	Hospitalization

*SLE (systemic lupus erythematosus). *Time between vaccination date and symptoms onset. ** Other reported AE apart from KFD.*

****at time of notification*

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Table II. Non COVID-19 vaccines associated KFD cases in Eudravigilance

Case	Sex	Age	Country	Vaccine	Other immune disorders*	Outcome**	Seriousness
1	F	-	Germany	Gardasil (16,18) [®]	Lymphadenopathy	Recovered	No
2	F	12	Japan	Cervarix [®]	Lymphadenopathy	Not recovered	Hospitalization
3	F	13	Japan	Cervarix [®]	Lymphadenopathy Splénomegaly Elevated aminotransferases	Recovered	Hospitalization
4	F	14	Japan	Cervarix [®] Encevac [®]	Painful lymphadenopathy	Recovered	Hospitalization
5	F	45	USA	Influenza	Painful axillary lymphadenopathy	Recovering	Hospitalization
6	F	-	Saudi Arabia	BCG	-	Recovering	Hospitalization
7	M	45	France	Repevax [®]	-	Recovered	Hospitalization
8	F	25	France	Repevax [®]	-	Recovered with sequelae	Yes
9	F	26	Portugal	Gardasil (6,11,16,18) [®]	Lymphadenopathy	Recovering	Hospitalization

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

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