Kikuchi-Fujimoto-like lymphadenopathy following COVID-19 vaccine: diagnosis and management

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SUMMARY

A woman in her mid 40s presented for breast imaging after 1 week of painful and enlarged right axillary lymphadenopathy. She denied history of fever, weight loss, night sweats fatigue, cat scratch or other trauma. She received the second dose of Pfizer COVID-19 vaccine 3 months previously on the contralateral arm. A mammogram demonstrated a single, asymmetric, large and dense right axillary lymph node. Ultrasound confirmed a 2.5 cm lymph node with cortical thickening of 0.6 cm. Ultrasound-guided core biopsy showed necrotising lymphadenitis with associated aggregates of histiocytes and plasmacytoid dendritic cells. Potential causes of necrotising adenitis including *Bartonella*, tuberculosis, Epstein-Barr Virus, herpes simplex virus, systemic lupus erythematosus and lymphoma were excluded. In the absence of any identifiable infectious or autoimmune causes, and given the temporal relatedness with vaccine administration, it was determined that the Kikuchi-Fujimoto-like necrotising lymphadenitis was likely secondary to the COVID-19 vaccine. To date, there has been no casual association made between the COVID-19 vaccine and KFD necrotising lymphadenitis.

BACKGROUND

The evaluation of unilateral axillary adenopathy is a common clinical scenario with a wide differential diagnosis including benign and malignant etiologies. Benign causes are usually preceded by a recent upper respiratory tract or upper extremity infection, or trauma to the ipsilateral extremity including recent ipsilateral vaccination. Benign reactive lymph node hyperplasia has become an especially frequent cause of transient adenopathy in the era of COVID-19 vaccines, requiring specific attention to vaccination dates and laterality for interpretation and management, which is most often clinical observation. When a common, benign, cause is excluded or the vaccination laterality and history are not conclusive, malignancy must be considered. Breast cancer is the most common malignant cause of axillary adenopathy in women, requiring clinical and imaging evaluations such as mammography and ultrasound.

We report a case of Kikuchi-Fujimoto disease (KFD)-like histiocytic necrotising lymphadenitis associated with COVID-19 vaccine administration. KFD is an uncommon benign and self-limited disease which most commonly presents with systemic B-type symptoms including fever, malaise and night sweats. KFD usually involves cervical lymph nodes with rarer cases involving axillary and supraclavicular nodes.[1–5] The causes of KFD are unknown, and usually attributed to multiple viral infections,[6–10] including most recently COVID-19 infection.[11] A subset of postvaccination reactive adenopathy including COVID-19 vaccine adenopathy may be attributed to KFD-like adenopathy, a finding which is particularly relevant at this time. While most postvaccine reactive adenopathy tends to resolve within 3 months, adenopathy which presents or persists after this period may require a percutaneous biopsy to rule out malignancy. The diagnosis should be considered in patients with postvaccine, lingering adenopathy, with or without systemic symptoms, in whom biopsy yields histiocytic necrotising adenitis for which other known causes are excluded. As of now, there has not been an established causation between the COVID-19 vaccine and KFD.

CASE PRESENTATION

An otherwise asymptomatic woman with no personal or family history of breast cancer presented with a painful, palpable right axillary lymph node. She denied fever, night sweats or malaise. On clinical examination, in addition to the palpable right axillary lymph node, a slightly prominent left inguinal lymph node was palpated. Her general examination was normal. Mammographic and sonographic evaluations were stable and negative, without any signs to suggest a breast primary malignancy. She denied any recent viral or upper respiratory infection or trauma to her right arm. She had no history or signs of cat scratch disease, herpes simplex virus (HSV), cytomegalovirus (CMV), mononucleosis, tuberculosis (TB), systemic lupus erythematosus (SLE) or lymphoma. She received the second dose of Pfizer COVID-19 vaccine 3 months prior on the left arm, immediately after which she only experienced mild and transitory general malaise without axillary symptoms.

INVESTIGATIONS

At the time of referral to the breast imaging service, a bilateral mammogram demonstrated a new, large, and dense right axillary mass with irregular margins on the mediolateral oblique view without other mammographic abnormalities (figure 1). On ultrasound, the lymph node measured 2.5 cm, with a markedly hypoechoic cortex which measured 0.6 cm and mild hilar displacement (figure 2).

Due to the irregular margins, the lack of systemic symptoms or a history of known causes of unilateral axillary adenopathy, an ultrasound-guided core biopsy was performed using a 14-gauge needle and automated gun (figure 3).

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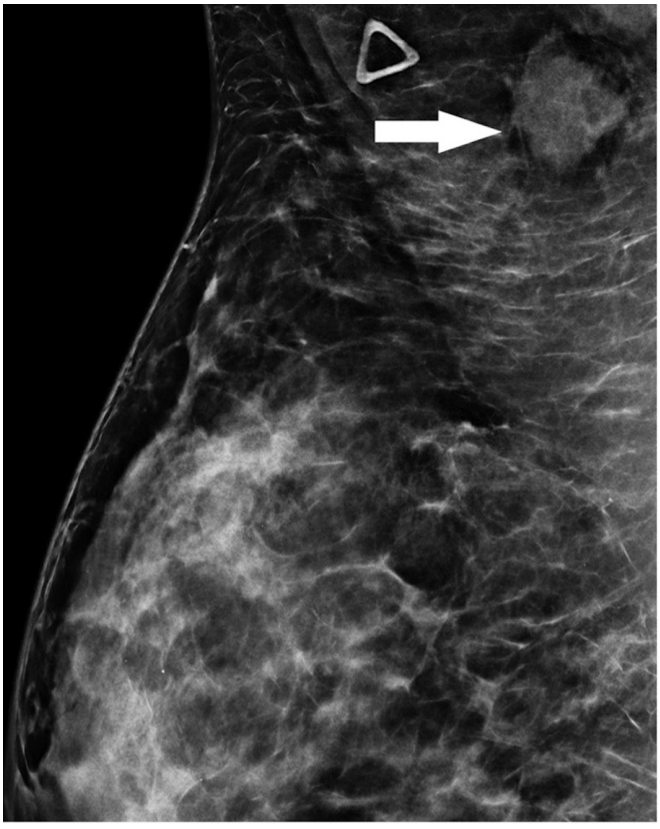

Figure 1 Cropped right mediolateral oblique synthetic two-dimensional view showing an enlarged, dense right axillary mass with irregular margins (arrow) corresponding to the palpable abnormality as denoted by a triangular marker.

Histopathological tissue sections showed necrotising lymphadenitis with associated aggregates of histiocytes and plasmacytoid dendritic cells, suggesting an infectious or inflammatory/autoimmune aetiology (figure 4). Within the necrotic foci, cellular debris and apoptotic cells were seen, but neutrophils were only very rarely identified. Necrotic foci were surrounded by aggregates of histiocytes, including ceroid macrophages. By

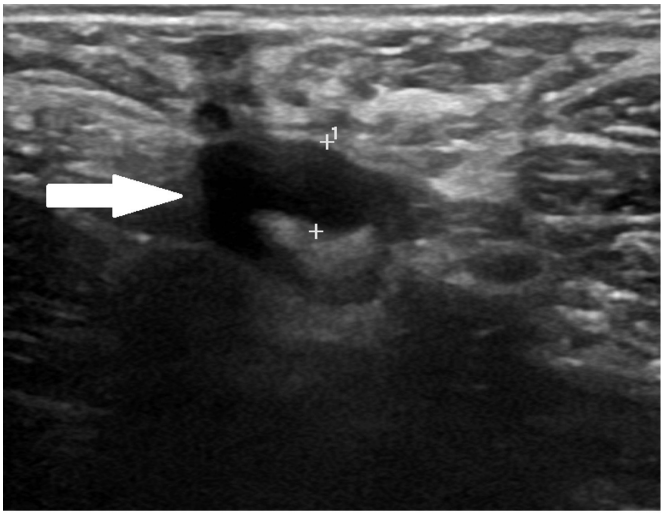

Figure 2 Right axillary ultrasound showed an enlarged axillary lymph node with a 0.6 cm hypoechoic cortex with mild hilar displacement (arrow) corresponding to the palpable and mammographic mass.

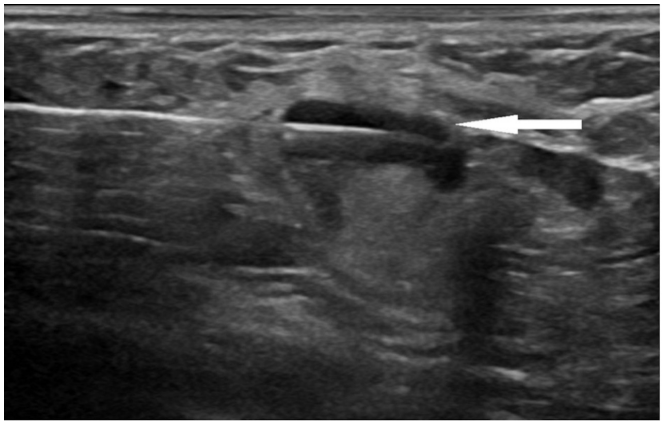

Figure 3 Ultrasound-guided core biopsy (arrow) with a 14-gauge needle and automated gun.

immunohistochemistry, CD20-positive B cells were present in aggregates and in a scattered paracortical distribution. B cells were small in size without cytological atypia. CD3-positive T cells were relatively more abundant and present within the nodal paracortex surrounding B-cell aggregates. CD123 confirmed the presence of aggregates of plasmacytoid dendritic cells surrounding necrotic foci. CD68 highlights frequent histiocytes which were present in aggregates surrounding necrotic foci and also in a diffuse paracortical distribution.

Histological evidence of malignancy was not identified. Concurrent flow cytometry was negative for detection of abnormal B-cell or T-cell populations. Special stains for micro-organisms including Grocott methenamine silver (GMS) stain

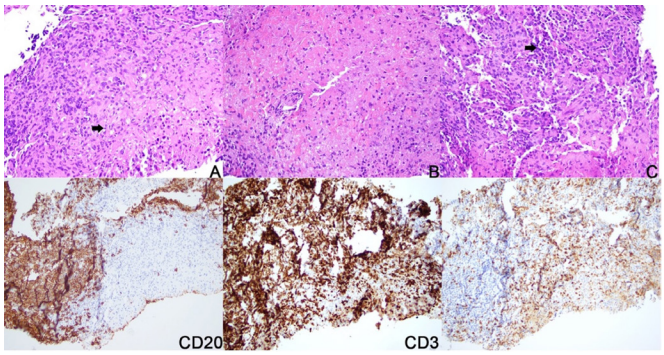

Figure 4 Histopathological features of lymph node biopsy. Core needle biopsies of lymph node showed multifocal necrotising lymphadenopathy characterised by foci of necrosis surrounded by reactive appearing small lymphoid cells, histiocytes and plasma cells. The interface of the viable reactive lymphoid cells (left of arrow) and the necrotic foci (right of arrow) is shown (A, H&E stain, ×40 magnification). Foci of necrosis showed apoptotic cellular debris and haemorrhage (B, H&E stain, ×40 magnification). The lymphoid cells at the interface and surrounding foci of necrosis are small and mature without overt cytological atypia (C, arrow; H&E stain, ×40 magnification). Immunohistochemistry testing confirmed the presence of small B cells expressing CD20 and small T cells expressing CD3, the former present in perinecrotic foci in the latter also present within necrotic foci. CD68 highlights reactive histiocytes present within necrotic foci (CD20, CD3 and CD68 immunohistochemistry stained slides, ×20 magnification). Not shown are negative for organisms stains including GMS fungal stain, acid–fast bacillus stain, Warthin-Starry silver stain, cytomegalovirus and herpes simplex virus immunohistochemistry stains.

for fungal organisms, acid–fast bacillus stain for acid–fast bacilli, and Warthin-Stary stain for *Bartonella* species were negative. Immunohistochemistry for CMV and HSV were negative.

Immunoglobin M for Epstein-Barr virus, PCR for HSV and an autoimmune panel including antinuclear antibodies direct, were negative. A complete blood count demonstrated a haemoglobin of 13.7 g/dL and haematocrit of 41.6%. Differential and platelets, sedimentation rate and C reactive protein were within normal limits, excluding haemolytic anaemia. Rheumatoid arthritis factor and antinuclear antibodies to exclude SLE were also negative. The exclusion of these known causes of necrotising adenitis combined with the histopathological findings supported KFD-type lymphadenopathy. Given the lack of any viral or systemic symptoms or recent epidemiological contact history, an active COVID-19 infection was not considered. The history of recent vaccination supported the association of KFD-like lymphadenopathy related to COVID-19 vaccine, but it is important to note that there has not been a proven causation between the vaccine and KFD.

DIFFERENTIAL DIAGNOSIS

Malignant differential considerations for unilateral axillary adenopathy include breast cancer, which can be the presenting symptom in 4%–12%[12] of breast cancer diagnoses, lymphoma, leukaemia, melanoma, and thyroid, lung and ovarian cancers.[13] Benign causes of axillary adenopathy include regional infectious processes such as paronychia, *Bartonella henslae* infection or cat scratch fever,[14] and sporotrichosis caused by *Sporothrix schenckii*[15]; these typically appear ipsilateral to the site of infection.

A more benign aetiology of swollen axillary lymph nodes is postvaccine ipsilateral reactive lymphadenitis, including most recently, the COVID-19 vaccine.[16 17] A specific causational relationship between the COVID-19 vaccine and KFD has not yet been made. When a patient lacks a pertinent history or findings suggestive of malignant or infectious causes of adenopathy and there is a remote or contralateral history of vaccination, histological investigation is warranted.

Differential diagnoses associated with histiocytic necrotising lymphadenopathy include lymphoma,[18] TB,[8] acute infectious mononucleosis,[7] Herpesviridae infection,[6 9] *B. henslae* infection[19] and SLE[20] with or without autoimmune haemolytic anaemia,[21] as well as other autoimmune disorder-associated lymphadenitis, drug effect and KFD.[2]

TREATMENT

KFD is a benign, self-limited disease.[1–5] Recovery times range from days to a few weeks. Supportive treatment of symptoms includes non-steroidal anti-inflammatory drugs, short-term corticosteroids, with a few recent reports of hydroxychloroquine for management of complicated cases.[18 22]

OUTCOME AND FOLLOW-UP

Given the lack of systemic symptoms, the patient was reassured that the palpable lymph node would resolve spontaneously. Within a few weeks, it was no longer tender and had decreased in size on clinical inspection. The patient did not develop any further signs or symptoms of other systemic causes of KFD.

DISCUSSION

KFD is an uncommon, benign and self-limited entity consisting of subacute histiocytic necrotising lymphadenopathy which most commonly involves cervical lymph nodes.[23] It may rarely be accompanied by hepatomegaly and splenomegaly,[2 3] and by non-specific systemic symptoms such as fever, weight loss, nausea, vomiting, weakness, headache, arthralgia, night sweats, upper respiratory symptoms and sore throat. It most commonly affects women, younger than 40 years, initially thought to be more common in Asia.[4] The exact cause is unknown and controversial but has been associated with infectious agents such as Epstein-Barr virus,[6] HSV[7 9] and CMV,[9 10] as well as vaccinations for influenza and human papillomavirus.[5]

Given the more common presentation of cervical adenopathy, KFD has rarely been associated with breast imaging with only a single reported case of mammographically detected KFD in a young, otherwise asymptomatic Asian woman with a non-tender palpable right axillary mass. Mammographic features consisted of asymmetrically enlarged, oval, circumscribed, dense, non-calcified axillary masses.[24] Mammographic and sonographic features are non-specific and include those of abnormal lymph nodes involved by lymphoma which are enlarged, round and dense on mammography with hypoechoic, thickened cortices and hilar displacement on ultrasound.[25]

Recently, a case was reported after COVID-19 infection.[11] Three recent cases have been reported of KFD following COVID-19 vaccination with cervical and axillary adenopathy presenting between 10 days and 35 days after vaccination.[26 27] To our knowledge, this patient presented with the longest interval between vaccination and clinical presentation and is especially unusual, given the contralateral axillary location.

The incidence of post COVID-19 vaccine ipsilateral adenopathy, initially reported as 0.3% for the Pfizer BioNTech vaccine[16] and 11.6% in the Moderna COVID-19 trial,[17] led to recommendations from the breast imaging societies for postponement of routine screening for 4–6 weeks after vaccination to avoid the misinterpretation of ipsilateral adenopathy, and follow-up imaging after 3 months to confirm resolution when identified. The incidence was later found to be as high as 2.4%–35% in women undergoing screening mammography and or ultrasound.[28–30] Because of this and the long-lasting consequences of the current pandemic including recommendations for additional booster vaccinations, new recommendations have been made to pursue screening and breast imaging, regardless of vaccination status. In addition, ipsilateral adenopathy thought to be due to recent vaccinations may be considered benign, obviating the need for short-interval follow-up.

This case is atypical and would not be covered by these guidelines, due to the contralateral nature of the vaccination, and therefore warranted biopsy for histological diagnosis. The diagnosis of histiocytic necrotising adenitis after COVID-19 vaccine can be attributed to KFD in the absence of other malignant and

Learning points

- In the absence of a known benign or malignant cause of unilateral axillary adenopathy, an image-guided biopsy is warranted for a definitive histological diagnosis.
- Necrotising adenitis has a wide differential diagnosis which includes lymphoma, herpes simplex virus, Epstein-Barr virus, cytomegalovirus, systemic lupus erythematosus and Kikuchi-Fujimoto disease (KFD).
- KFD, as a diagnosis of exclusion in necrotising adenitis, may be secondary to COVID-19 vaccine or infection for up to 3 months after vaccination; this is still a new phenomenon and the COVID-19 vaccine has not been proven to cause KFD.

infectious causes. It is important to note that, to date, there has been no proven relationship between KFD and the COVID-19 vaccine, and a single case report does not constitute evidence of an association.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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