

# Evaluation of a unilateral neck mass in a 16-year-old female: Kikuchi-Fujimoto disease with superimposed bacterial lymphadenitis

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## Abstract

The evaluation of pediatric neck masses offers the opportunity for consideration of a diverse range of pathologies, from infectious to neoplastic. A 16-year-old female presented with 2 weeks of worsening swelling and pain of a left-sided neck mass. Findings were consistent with Epstein–Barr virus and cytomegalovirus coinfection, but considering profound lymphadenopathy of the supraclavicular, mammillary, and axillary chains, further investigations were undertaken. Hematopathologic examination demonstrated necrotizing lymphadenitis, consistent with Kikuchi-Fujimoto disease. A diagnosis of Kikuchi-Fujimoto disease alongside chronic bacterial lymphadenitis was made on the basis of her response to clindamycin, and the chronic course of her illness and subsequent persistence of the swelling managed on an outpatient basis. The case study describes the initial diagnostic considerations and management as well as a review of the disease pathology.

## Keywords

Pediatric neck mass, Hospital medicine, Kikuchi-Fujimoto disease

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## Introduction

The differential diagnosis of pediatric neck mass is robust and can generally be differentiated into two broad categories of congenital and acquired neck masses.<sup>1</sup> Congenital neck masses may include branchial cleft cysts, thyroglossal duct cysts, cystic hygromas, laryngoceles, dermoid cysts, teratomas, hemangiomas, or ranulas.<sup>1,2</sup> Acquired masses include thyroid nodules, malignancy, goiter, reactive lymphadenopathy, Epstein–Barr virus (EBV), *Bartonella*, cytomegalovirus (CMV), human immunodeficiency virus (HIV), toxoplasmosis, lymphoma, rhabdomyosarcoma, neuroblastoma, or melanoma.<sup>1–3</sup> Among these pathologic causes of cervical lymphadenopathy, infection is the most common etiology.<sup>4</sup>

Another, more rare cause of lymphadenopathy is Kikuchi-Fujimoto disease (KFD). This is a benign lymphohistiocytic disorder characterized by cervical lymphadenopathy, fatigue, fever, hepatosplenomegaly, and weight loss.<sup>5</sup> The following case presents a diagnostic dilemma in differentiating between several etiologies in an adolescent female presenting with a left-sided neck mass.

## Case presentation

A 16-year-old Caucasian female was transferred from an outside hospital with 2 weeks of worsening swelling and pain of a left-sided neck mass. The patient experienced fatigue and intermittent low-grade fevers in the 4 months leading to her admission. The symptoms were attributed to a previous diagnosis of Lyme disease which was treated appropriately with a course of doxycycline prior to the onset of neck swelling. In the 2 weeks preceding her admission, she noticed a “lump” on the left side of her neck. The mass started as a small bump under the skin in the anterior neck and grew larger with increased tenderness. In addition, over the week prior to

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**Table 1.** Initial laboratory results.

Laboratory test	Value	Reference range
WBC count	9.44 K/ $\mu$ L	3.8–10.5 K/ $\mu$ L
RBC count	3.98 M/ $\mu$ L	3.80–5.20 M/ $\mu$ L
Hemoglobin	11.0 g/dL	11.5–15.5 g/dL
Hematocrit	33.8%	34.5%–45.0%
Platelet count	177 K/ $\mu$ L	150–400 K/ $\mu$ L
Neutrophil # (%)	1.17 K/ $\mu$ L (12.4%)	1.8–7.4 K/ $\mu$ L (43.0%–77.0%)
Lymphocyte # (%)	7.54 K/ $\mu$ L (79.9%)	1.0–3.3 K/ $\mu$ L (13.0%–44.0%)
Monocyte # (%)	0.51 K/ $\mu$ L (5.4%)	0.0–0.9 K/ $\mu$ L (2.0%–14.0%)
Eosinophil # (%)	0.03 K/ $\mu$ L (0.3%)	0.0–0.5 K/ $\mu$ L (0.0%–6.0%)
Basophil # (%)	0.16 K/ $\mu$ L (1.7%)	0.0–0.2 K/ $\mu$ L (0.0%–2.0%)
ESR	12 mm/h	0–20 mm/h
LDH	714 U/L	135–225 U/L
Uric acid	4.3 mg/dL	205–7.0 mg/dL
AST	142 u/L	4–32 u/L
ALT	121 u/L	4–33 u/L
CRP	20.4 mg/L	<5.0 mg/L
CMV IgG	8.3 U/mL	$\leq$ 0.59 U/mL
CMV IgM	229.0 AU/mL	$\leq$ 29.9 AU/mL
EBV IgM	Positive	Negative
EBV IgG	Positive	Negative
EBV early antigen	Positive	Negative
EBV nuclear antigen	Negative	Negative

ESR: erythrocyte sedimentation rate; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CRP: C-reactive protein; CMV: cytomegalovirus; EBV: Epstein–Barr virus.

admission, she became febrile, experienced trismus, limited range of motion of the neck, as well as began to experience multiple episodes of abdominal pain and vomiting.

The patient sought treatment from several providers prior to presentation with an ultimate diagnosis of sialadenitis for which azithromycin was prescribed. After 2 days of azithromycin, there was no improvement in the size of the mass nor her pain. Initial laboratory investigations at an outside hospital revealed lymphocytosis and elevated liver enzymes. Computed tomography (CT) of the face/neck with intravenous (IV) contrast demonstrated a 4.8 cm by 3.9 cm by 2.5 cm mass interpreted as a branchial cleft cyst anterior to the left sternocleidomastoid. At this time, the patient was transferred to the Cohen Children’s Medical Center of New York for further evaluation and management.

On admission, her vital signs were within normal limits and there were no signs of respiratory distress. The left-sided neck mass was described as a 4-cm non-fluctuant, matted mass, located just lateral to the laryngeal prominence extending posteriorly to the subauricular region with associated tenderness but without overlying skin changes. Bilateral tonsillar enlargement (left greater than right), erythema, and exudate were also noted. Her initial laboratory findings are summarized in Table 1. Her laboratory testing indicated acute CMV and EBV coinfection. *Bartonella* serology was negative. Her manual smear demonstrated increased reactive lymphocytes and large granular forms. During the patient’s hospital course, additional imaging included ultrasound of the head/neck which demonstrated a possible necrotic left-sided lymph node with multiple enlarged lymph nodes bilaterally. Upon further evaluation, repeat CT neck/soft

tissue demonstrated a 4.2 cm by 4.1 cm by 3.5 cm necrotic lymph node, bilateral cervical chain lymphadenopathy, partially visualized mediastinal, supraclavicular, and axillary lymphadenopathy, as well as a right upper lung opacification. Further imaging to investigate the extent of lymphadenopathy included CT chest, abdomen, and pelvis with contrast, revealing enlarged thoracic and abdominal pelvic nodes, hepatosplenomegaly, moderate bilateral pleural effusions, small pericardial effusion, and abdominopelvic ascites (Figure 1). To further elucidate the origin of this systemic involvement, the Infectious Disease, Hematology/Oncology, and Otolaryngology subspecialty teams unanimously recommended a tissue biopsy of the large left-sided cervical lymph node demonstrated on CT. Pediatric General Surgery completed guided biopsy of the cervical lymph node which was successfully obtained without any complications. Pending biopsy results, the patient completed a course of clindamycin as an inpatient and was discharged home in stable clinical condition.

Gram stain and culture of the specimen did not reveal any organisms or growth. Similarly, no organisms were visualized under acid fast smear. Flow cytometry was not performed due to insufficient number of viable cells. However, hematopathologic evaluation of the specimen described necrotizing lymphadenitis.

## Discussion

Given the presence of necrotizing lymphadenopathy in the setting of EBV infection, this case is most consistent with the



**Figure 1.** Axial CT with contrast. (a) Left-sided neck mass. (b) 1.8-cm-long axis lymph node anterior to the right psoas muscle. (c) 1.9-cm-long axis lymph node in the anterior aspect of the superior mesenteric vessels.

diagnosis of KFD. However, her hospital course allowed for the consideration of several unique diagnostic and therapeutic possibilities.

Early in the course of patient's admission, infection remained the leading differential diagnosis. The neck mass was initially managed as an infected branchial cleft cyst, however upon further radiologic investigation and interpretation, there was a concern for tonsillar abscess with reactive lymphadenopathy. In this case, CT scan and ultrasound both proved extremely valuable both in diagnosis and determination of the necessity of intervention. Initially, the patient showed modest improvement during treatment of the suspected tonsillar abscess with clindamycin.

In this case, clindamycin was continued on the basis of clinical improvement and presumed superinfection with *Staphylococcus aureus*. Given high rates of community colonization with Methicillin-resistant *Staphylococcus aureus* (MRSA) and that she had recently undergone an invasive procedure, the team elected to continue with antimicrobial coverage for MRSA despite the lack of definitive species and sensitivities from her wound culture.

Beyond this acute infection, her laboratory results yielded other interesting findings. Infectious mononucleosis is a common infection in childhood and adolescence caused by multiple organisms, commonly due to EBV or CMV, although more frequently by the former. Symptoms may include fever, tonsillar pharyngitis with exudate, and lymphadenopathy. Elevated liver transaminases are also commonly seen.<sup>5</sup> Due to this patient's insidious presentation consisting of these symptoms in the setting of 4 months of fatigue, infectious mononucleosis remained on the list of differential diagnoses, especially during initial presentation.

Several cases of CMV and EBV coinfection in adults have been reported.<sup>6,7</sup> EBV and acute CMV infection can both present with fever, cervical lymphadenopathy, pharyngitis, and fatigue.<sup>7</sup> In children affected by EBV/CMV coinfection, rate of multipathogen involvement is estimated at 63.6%.<sup>8</sup> Of note, EBV Viral Capsid Antigen (VCA) IgM and CMV IgM dual positivity may be regarded as a false-positive finding in pediatric populations, particularly in younger children with elevated liver enzymes.<sup>9</sup> This patient's laboratory results suggested both acute EBV and CMV infection, both of which likely contributed to her presentation.

In addition, given the patient's profound widespread lymphadenopathy and prolonged fever in the setting of fatigue, a common constitutional symptom, an oncological work-up was undertaken. Although the initial battery of laboratory tests did not suggest a neoplastic process, the concern remained for the possibilities of KFD or hemophagocytic lymphohistiocytosis (HLH). Acquired HLH is often associated with a viral infection and fever.<sup>10,11</sup> However, given the patient's stable clinical status and the absence of elevated ferritin level or splenomegaly, HLH was ultimately not pursued as one of the primary diagnostic considerations.<sup>11</sup> If there had been a higher suspicion for HLH, an evaluation of repeat cell counts with differential, triglyceride level, fibrinogen level, natural killer functional assay, and soluble IL-2R $\alpha$  level would have been valuable in a more thorough evaluation of the possibility of HLH in this patient.<sup>11</sup>

This patient's presentation, despite her age and ethnicity, is consistent with the majority of cases of KFD. Histiocytic necrotizing lymphadenitis was first described by Kikuchi and separately by Fujimoto, Kojima, and Yamaguchi in 1972.<sup>12</sup> This self-limiting condition is characterized by elevated acute phase reactants and leukopenia or lymphopenia.<sup>5</sup> Cutaneous manifestations are reported in 16%–40% of patients, typically revealing histiocytic aggregates, atypical lymphoid cells, karyorrhectic debris, and patchy necrosis.<sup>12</sup> KFD typically resolves in 1–4 months without specific treatment.<sup>5,13</sup> However, in severe cases, successful treatment has been reported with corticosteroids and intravenous immunoglobulin.<sup>13</sup> Recent studies contest the association of KFD and EBV positivity, with certain centers demonstrating EBV reactivity in only 26.7% of pediatric cases.<sup>14</sup>

The etiology of KFD remains incompletely understood with continued research evaluating the contributions of viral and autoimmune processes.<sup>5</sup> It typically is more common in Asian populations with a female predominance with most presentations in adulthood prior to the fourth decade of life, more rarely in pediatric or elderly populations.<sup>5</sup> Several viral infections have been associated with the development of KFD including EBV, human herpesvirus 6, human herpesvirus 8, parvovirus B-19, herpes simplex virus, cytomegalovirus, and

varicella zoster, though no studies have demonstrated causality.<sup>5</sup> Among pediatric cases, EBV is commonly reported.<sup>5</sup>

Furthermore, an immunologic component has been postulated as an etiopathogenic mechanism. Lymphoid follicles or follicular hyperplasia alongside CD68 and myeloperoxidase-positive histiocytes, CD68- and CD123-positive plasmacytoid dendritic cells, variable CD8-positive lymphocytes, and immature immune cells upon immunohistochemical evaluation have all been demonstrated in KFD.<sup>5</sup>

KFD has demonstrated an association with systemic lupus erythematosus (SLE), with reports of preceding, concomitant, and subsequent diagnosis with KFD.<sup>5</sup> For this reason, the patient requires close follow-up not only for her lymphadenopathy but also to consider the development of SLE as she ages.

Ultimately, our patient was determined to carry the diagnoses of KFD with superimposed chronic bacterial lymphadenitis. This may account for her response to clindamycin and the chronic course of her illness. After discharge from the hospital, she initially improved, but has subsequently had several outpatient visits related to persistence of the swelling of her left-sided cervical lymph nodes. It is possible that this represents a recurrence of KFD, but this would be unusual, as the recurrence rate is less than 5%. It is more likely that this again is a bacterial superinfection, and this has been managed as an outpatient with courses of clindamycin with subsequent improvement in her symptoms.

## Patient perspective

This case demonstrated the profound effects of a complex, inpatient work-up on a teenage patient and her family. In the face of uncertainty, the patient and family expressed moments of doubt and anxiety regarding the prognosis. It was essential for the clinical team to practice clear, empathic communication with shared decision-making while navigating toward the proper diagnosis and treatment plan.

## Conclusion

Although a rare diagnosis in children, particularly those of Caucasian ancestry, KFD represents a unique pathology underlying pediatric cervical lymphadenopathy. This case presents further evidence to the association with EBV and may present a new consideration of bacterial superinfection upon underlying necrotizing lymphadenitis. This case provided a valuable learning opportunity to review a comprehensive evaluation of multiple etiologies for neck pathology in the pediatric population.

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