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Case Report

Unusual presentation and rare association of pediatric lupus

Anoop Krishna, Susy Joseph*, Rekha Krishnan, Ajith Krishnan

Department of Pediatrics, SAT Hospital, Government Medical College, Thiruvananthapuram, Kerala, India

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***Correspondence:**
Dr. Susy Joseph,
E-mail: drsusy2772@gmail.com

ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune inflammatory disorder with diverse clinical manifestations which can lead to significant morbidity and mortality. Children and adolescents represent 15% to 20% of all patients with SLE. Childhood onset SLE is a rare disease with a prevalence of 3.5 to 8.8 per one lakh children. Localized or generalized lymphadenopathy may be an uncommon presenting feature of SLE. None of the classification criteria for SLE include lymphadenopathy as a criterion including the latest 2019 American college of rheumatology (ACR) / European league against rheumatism (EULAR) criteria. Nine-year-old female child presented with history of swelling on both sides of neck associated with fever and easy fatiguability for 2 months. Clinical examination revealed significant bilateral cervical and axillary lymph nodes with hepatomegaly. Excision biopsy of lymph node was suggestive of Kikuchi Fujimoto disease (KFD). As rare association of KFD with SLE is well described in literature, despite negative clinical features and laboratory findings of SLE, including an initial negative ANA IF test, we did a repeat ANA IF, complement (C3) level and dsDNA testing, all of which turned out to be positive, confirming the diagnosis of SLE. The child was started on hydroxychloroquine and oral steroids with dramatic response. During steroid tapering she developed a flare needing the addition of azathioprine. Currently she is in remission and is under follow up. Although rare, lupus lymphadenopathy may be a presenting feature of SLE. This can even antecede the diagnosis of SLE by many years, when the presence of auto antibodies or low complement levels are not detected and are associated with higher disease activity. This emphasizes the importance of high index of suspicion of SLE in cases of lymphadenopathy, enabling early diagnosis and management which is essential for preventing morbidity and mortality.

Keywords: SLE, Children, lymphadenopathy, KFD

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multisystem inflammation and the presence of circulating autoantibodies directed against self-antigens. It occurs in both children and adults, disproportionately affecting females of reproductive age group with a ratio of 2.5:1 before puberty and 9:1 during reproductive years. Compared with adults, children and adolescents (15% to 20% of all SLE) have more severe disease and more widespread organ involvement. The most common clinical findings in SLE includes fever, fatigue, hematological abnormalities, arthralgia and arthritis.[1]

Lymphadenopathy is a benign finding in SLE commonly seen in young patients in any phase of the disease.[2] It can even antecede the diagnosis of SLE by many years, when the presence of auto antibodies or low complement levels cannot be detected. This will make early diagnosis of these cases difficult. Lupus lymphadenopathy has an estimated prevalence of 5% to 7% at the onset of disease and 15% to 30% (as high as 60%) at any stage of disease. Besides the disease itself, other causes of lymphadenopathy such as infectious and malignant diseases which are associated with SLE must also be considered in the differential diagnosis. Thus, in case of significant lymphadenopathy, lymph node biopsy is

indicated to rule out infectious or lymphoproliferative disorders associated with SLE.

As SLE is a complex highly variable disease, various sets of classification criteria have often been used by clinicians to assist diagnosis. However, while the fulfilment of classification criteria can enhance diagnostic certainty, they should never be used for diagnosis. This is because symptoms and signs of SLE may develop serially over several years which can result in inadequate or inappropriate therapeutic approaches. Also, diagnosing a disease based on classification criteria alone may lead to overtreatment. The new 2019 EULAR/ACR SLE classification criteria have a sensitivity of 96.1% and a specificity of 93.4%, thus being the most accurate set of classification criteria compared to the 1997 ACR and 2012 SLICC criteria. But lymphadenopathy is not included as a criterion even in these classification criteria. So, from the perspective of diagnosis, this implies that individual physician will perform better than a set of criteria developed by a large group of experts.

KFD or histiocytic necrotizing lymphadenitis is a condition rarely associated with SLE. It was first described in Japanese literature independently by Kikuchi and Fujimoto et al in 1972.[4] It is a rare idiopathic self-limited condition characterized by fever and cervical lymphadenopathy with spontaneous recovery in 1 to 6 months. The diagnosis of KFD can precede, postdate or coincide with the diagnosis of SLE.[5] In our case there was concomitant occurrence of both SLE and KFD. Careful attention has to be paid in differentiating between KFD and SLE because of the similar clinical presentation but different clinical course, management and prognosis. This case provides important insight into the co-existence of KFD and SLE.

CASE REPORT

A 9-year-old female child who was 1st born of non-consanguineous marriage with no significant past illness presented with history of swelling on both sides of neck associated with fever and fatigability for 2 months. Swelling was painless with no history of dysphagia and dyspnea. There was no history of recent weight loss, bone pain, skin rashes, skin or mucous membrane bleeds, joint pains or swelling, edema, hematuria, or frothy urine. There was no history of contact with tuberculosis or domestic animals.

She had no pallor, her pulse rate was 90/minute, respiratory rate 25/minute, BP 110/68 mm of Hg. Her weight was 30 kg (Between 0 and +1 SD), Height was 138 cm (+1 SD), Bilateral multiple anterior and posterior cervical lymph nodes (ranging 1×1.5 cm to 2×2 cm) and bilateral axillary lymph nodes (ranging 1.5×2 cm to 2.5×3 cm) were enlarged. The nodes were mobile, non-tender, discrete and non-adherent. There were no rashes, oral ulcers, petechial spots, or eschar. Her musculoskeletal examination was also normal. There was hepatomegaly (liver span: 13 cm), spleen was not palpable. Respiratory system examination revealed good air entry with bilateral basal fine crepitations. Other systems were within normal limits.

Her blood reports are depicted in Table 1.

Table 1: Blood investigations.

Tests	Results
Hemoglobin	12.4 g/dl
Total count	12,000 cells/mm^3
Differential count	P68L26E6
Peripheral smear	No atypical cells
ESR	105 mm/hour
CRP	Negative
CPK	Negative
ANA	Negative
Renal function test	Normal
Liver function test	Normal
Urine routine	Normal
HIV	Negative
HBV	Negative
CMV-PCR	Negative
EBV-PCR	Negative
Toxoplasma IgM	Negative
Brucella IgM	Negative
Paul Bunnel test	Negative
Scrub PCR	Negative
Blood culture and sensitivity	Sterile

Other investigations were: Mantoux test and sputum CBNAAT were negative. Chest X ray revealed bilateral perihilar opacities (Figure 1). Ultrasound neck showed extensive bilateral cervical lymph nodes with largest one measuring 3×3.5 cm. There is no evidence of necrosis and fatty hilum of lymph nodes were preserved. FNAC lymph node were unremarkable except for reactive changes. CT chest findings were suggestive of bronchopneumonia with bilateral minimal pleural effusion as well as there was no hilar lymphadenopathy noted.

Child was initially started on multiple antibiotics for bronchopneumonia but her fever, lymphadenopathy and constitutional symptoms persisted. So suspecting malignancy, bone marrow study was done which was normal. Excision biopsy of the biggest axillary node was done to rule out lymphoma. The report of excision biopsy of lymph node was suggestive of KFD/ histiocytic necrotizing lymphadenitis (Figure 2). Irregular paracortical areas of coagulative necrosis with abundant karyorrhectic debris surrounded by clusters of histiocytes, plasmacytoid monocytes, lymphocytes with characteristic absence of neutrophils.

Since there is an association between KFD an SLE (1.3% to 7% in general population) and the histological features

suggestive of KFD in lymph node biopsy, we did a repeat testing for ANA-IF which came as positive with a titre of >1 in 100. Further evaluation showed low C3 and very high titers of dsDNA. Thus, she was classified as SLE with a score of 16 according to 2019 ACR/EULAR criteria (fever-2, serositis-5, ANA positivity, dsDNA positivity-6 and low C3-3). Her DCT and APLA profile were negative. She was started on steroids and hydroxychloroquine. There was a dramatic improvement in her symptoms with regression of lymphadenopathy. Over the course, she developed photosensitive rash and joint symptoms when her steroids were tapered. Azathioprine was added and she went into remission and is currently under our follow up.

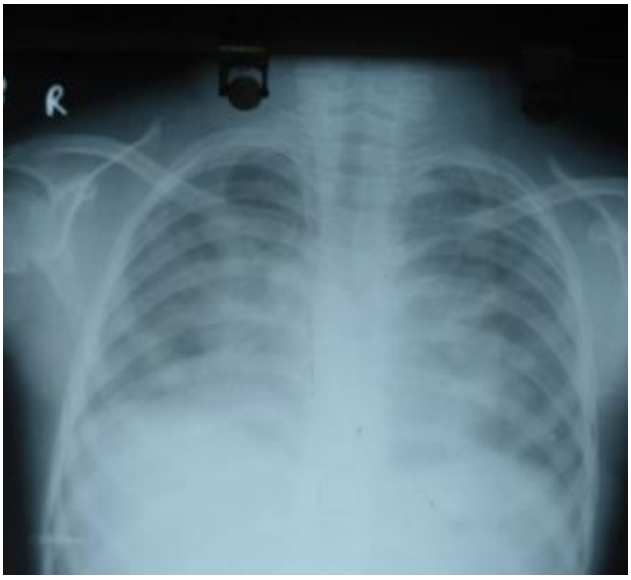

Figure 1: Chest x- ray of bilateral perihilar opacities.

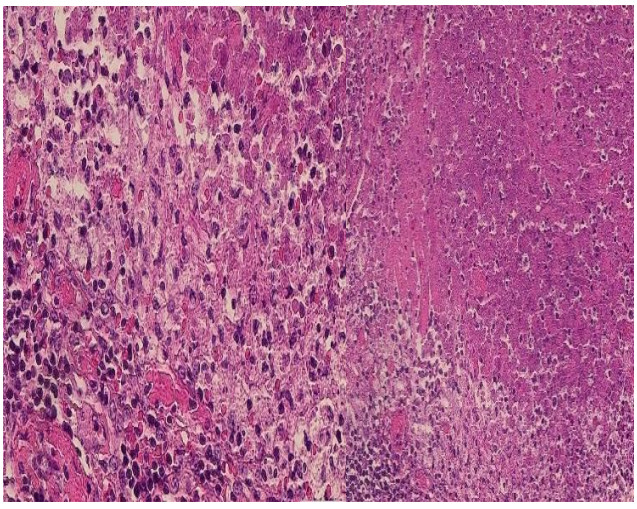

Figure 2: Histology from biopsy showing irregular para-cortical areas of coagulative necrosis with abundant karyorrhectic debris surrounded by clusters of histiocytes, plasmacytoid monocytes and lymphocytes with characteristic absence of neutrophils.

DISCUSSION

The clinical presentation and evolution of SLE shows a wide variation. Some degree of lymphadenopathy is frequently a characteristic of established SLE, but it is rarely the primary presenting feature.[6] In our case lymphadenopathy was the primary presenting feature and it was associated with constitutional symptoms. Lupus lymphadenopathy can be classified as localized (2 lymph node groups) or generalized (three or more lymph node groups). It mainly involves cervical and axillary nodes. Lymph node biopsy in lupus commonly shows reactive follicular hyperplasia with or without atypical cells and is considered as a nonspecific finding.[7] Coagulative necrosis with hematoxylin bodies typical of SLE is rarely seen.[7] A classification of the patterns of lymph node lesions in SLE, similar to the classes of lupus nephritis has been suggested; however, these types do not seem to be specific enough to establish the diagnosis of SLE.

In KFD, clinical, histopathological, and immune histochemical features appear to point to a viral etiology, a hypothesis that still has not been proven. Electron microscopy showed tubular reticular structures in the cytoplasm of stimulated lymphocytes and histiocytes in patients with KFD. Since these structures are also seen in the endothelial cells and lymphocytes of patients with SLE and other autoimmune diseases, it was hypothesized that KFD may reflect a self-limited autoimmune condition induced by virus infected transformed lymphocytes. The diagnosis of KFD merits active consideration in any nodal biopsy showing fragmentation, necrosis and karyorrhexis especially in young individuals presenting with fever and lymphadenopathy.[8]

The differentiation of KFD from SLE can sometimes be problematic because both can show similar clinical and histological features. Also, KFD has been reported in association with SLE.[9] The lack of predictive markers of KFD evolving into SLE means that all patients diagnosed with KFD should receive periodic clinical and serological follow up for several years to detect possible evolution of SLE.[4,10-12]

CONCLUSION

Although uncommon, lymphadenopathy may be a presenting feature of SLE and may precede other symptoms of SLE by many years. So, SLE should be considered as a diagnostic possibility in children presenting with local/diffuse lymphadenopathy and constitutional symptoms. Lupus lymphadenopathy is found to have higher disease activity levels and hence has to be diagnosed and managed without delay to decrease morbidity and mortality. The association of KFD and SLE is well documented and KFD may be one of the manifestations of SLE. This case report emphasizes the association between KFD and SLE and children with KFD will require a systematic survey and regular follow

up to rule out progression to SLE. An increased awareness among clinicians is recommended in pediatric patients presenting with lymphadenopathy, so that a careful clinical, laboratory and pathological evaluations are often needed to establish an accurate diagnosis and timely management.

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