

## THE CLINICAL IMPORTANCE OF LYMPHADENOPATHY IN SYSTEMIC LUPUS ERYTHEMATOSUS

Meltem A Melikoglu,<sup>\*\*\*</sup> Mehmet Melikoglu<sup>\*\*\*</sup>

### Abstract

Lymphadenopathy (LAP) is a frequent and usually nonspecific feature of Systemic Lupus Erythematosus (SLE). In spite of the fact that LAP usually carries no risk to the patient, SLE patients with LAP were found to have higher disease activity levels. Besides the disease itself, other causes of LAP such as infections, immunological or malignant diseases must be considered in the differential diagnosis. LAP is a prominent clinical characteristic of Kikuchi-Fujimoto's disease which is associated with fever, arthralgia, and leukopenia, features also found in SLE. As the prognosis and treatment of KFD and SLE are different, it is important to differentiate these two entities. On the other hand, the increased risk of lymphoproliferative diseases in SLE was reported in several studies. Since there is a considerable overlap between the features of SLE and lymphoma, there can be a difficulty in diagnosing lymphoma in lupus patients. An increased awareness is recommended in dealing with SLE patients with LAP and careful clinical, laboratory and pathological evaluation are often needed in order to establish an accurate diagnosis.

**Keywords:** Systemic Lupus Erythematosus; Lymphadenopathy; Kikuchi-Fujimoto's Disease; Lymphoma.

### Resumo

A linfadenopatia (LAP) é um achado comum e geralmente inespecífico do Lúpus Eritematoso Sistémico (LES).

Apesar de frequentemente não representar nenhum risco para o doente, foi constatado que os doentes com LES e LAP têm níveis de actividade da doença mais elevados. Para além da própria doença, outras causas de LAP, como infecção, doenças imunológicas ou malignas, têm que ser tidas em consideração no diagnóstico diferencial. Gânglios aumentados são típicos da doença de Kikuchi-Fujimoto que se caracteriza por febre, artralguas e leucopenia, achados também comuns no LES. Como o prognóstico e o tratamento de ambas as doenças é distinto, importa fazer um diagnóstico correcto destas entidades. Por outro lado, um risco aumentado de doenças linfoproliferativas nos doentes com LES foi documentado em vários estudos. Como existe uma grande sobreposição entre os sintomas do LES e o linfoma, o diagnóstico desta condição pode estar dificultado. Recomenda-se uma vigilância redobrada dos doentes com LES e LAP, sendo a avaliação clínica, laboratorial e imagiológica cuidadas, imprescindíveis para estabelecer um diagnóstico preciso.

**Palavras-chave:** Lúpus Eritematoso Sistémico; Linfadenopatia; Kikuchi-Fujimoto; Linfoma.

Systemic lupus erythematosus (SLE) is an immune complex disease with several clinical manifestations. Lymphadenopathy (LAP) is generally considered as a frequent and a nonspecific feature in SLE. This review is aimed to draw attention to the clinical importance of LAP in patients with SLE.

### LAP as a Manifestation of SLE

LAP has been reported in 23-34% of patients with SLE and the cumulative incidence of LAP in most series, ranges from one-third to one-half of the patients.<sup>1</sup> Nodes are usually smaller and more generalized in SLE than in rheumatoid arthritis.<sup>2</sup> In general,

\*Department of Rheumatology, Physical Medicine and Rehabilitation, School of Medicine, Akdeniz University, Antalya, Turkey

\*\*Department of Physical Medicine and Rehabilitation, School of Medicine, Ataturk University, Erzurum, Turkey

\*\*\*Department of Dermatology, School of Medicine, Ataturk University, Erzurum, Turkey

the nodes are soft, nontender and vary in size. There may be fluctuation of the LAP with SLE disease exacerbations. In spite of the fact that LAP is a nonspecific sign, usually not troublesome, and without risk for the patient, the relation between disease activity and LAP has been reported by some authors.<sup>3,4</sup> SLE patients with LAP show significantly more constitutional symptoms such as fatigue, fever and weight loss, more cutaneous and mucosal signs (malar rash, vasculitis, skin ulcers, mouth ulcers, discoid lesions, alopecia and subcutaneous lupus erythematosus), higher rate of hepatomegaly and splenomegaly, increased anti-dsDNA antibodies titers and decreased complement levels.<sup>1</sup> Also disease activity measured using the British Isles Lupus Assessment Group (BILAG) index has been found to be higher among patients with LAP, as well as the intake of steroids and antimalarials.<sup>1</sup> Some authors recommend that LAP should be included among the clinical findings indicating disease activity in SLE patients.<sup>1</sup> Generalized or peripheral LAP as the first clinical manifestation of the disease has also been reported.<sup>5-8</sup>

The morphologic changes of lymph nodes have been shown as extremely variable, reflecting the variability of clinical manifestations and the disease course in individual patients with SLE. Except for lymph node necrosis, the histological findings are usually nonspecific and consist of moderate follicular hyperplasia associated with increased vascularity and scattered immunoblasts and plasma cells.<sup>9</sup> The most characteristic lymph node lesion in SLE is characterized by several degrees of coagulative necrosis with hematoxylin bodies or reactive follicular hyperplasia. The former histology is unique to SLE, but rarely seen in specimens.<sup>10</sup> Lymph node lesions of SLE patients may also be similar to those of hyaline-vascular or intermediate types of Castleman's disease or T zone dysplasia with hyperplastic follicles.<sup>10,11</sup> Lymphoplasmocytic infiltration with immunoblasts, namely, atypical lymphoplasmacytic and immunoblastic proliferation, has also been reported in SLE.<sup>10</sup> The nonspecificity and morphological variability of lymph node histology in SLE patients results in the need of increased attention to the clinical and laboratory findings as well as to the morphological features to avoid overdiagnosis and overtreatment.

## Differential Diagnosis

LAP may be a primary or secondary manifestation

of several diseases. In addition to the nonspecific causes, infections, immunological or malignant diseases and infrequent causes must be considered in the differential diagnosis of LAP. Viral infections (such as infectious mononucleosis, hepatitis, herpes and varicella-zoster virus), bacterial infections (such as streptococci, staphylococci, brucellosis, primary or secondary syphilis, tuberculosis and atypical mycobacterial infections), fungal infections (such as histoplasmosis, coccidioidomycosis and paracoccidioidomycosis), parasitic infections (such as toxoplasmosis, leishmaniasis, trypanosomiasis) and rickettsial infections may account for the observed LAP. The patient's symptoms and the clinical characteristics of LAP may be helpful in the differential diagnosis.

Kikuchi-Fujimoto's disease (KFD) may have an important place in the differential diagnosis due to the similarity between SLE and this condition. KFD or histiocytic necrotizing lymphadenitis which is often associated with fever, arthralgia, and leukopenia, features also found in SLE, is a rare and self-limiting lymphadenitis, particularly affecting young women.<sup>12</sup> KFD was first described in Japanese literature independently by Kikuchi and Fujimoto *et al* in 1972.<sup>13</sup> In spite of the higher incidence observed among oriental people, over the last decade an increasing number of cases has also been reported in Western countries.<sup>14</sup> However, these reports have been predominantly published in the pathology literature and the disease may be sometimes difficult to recognize for clinicians not familiar with this condition. The etiology of KFD remains unclear although various infections have been postulated to be the cause.<sup>13,15,16</sup> It has been hypothesized that KFD may be the result of a local hyperimmune stimulation after infection, where genetic predisposition or autoimmune origin may also play important roles.<sup>14,15</sup> The clinical characteristics are LAP, leukopenia, raised erythrocyte sedimentation rate (ESR), fever, skin eruptions, and erythematous or ulcerated oropharynx which heals spontaneously over several months.<sup>16</sup> Besides these similar findings, SLE and KFD also share clinical characteristics such as the age of onset and the female predominance.<sup>14,15</sup> The most common presentation of KFD is localized LAP, although it may also be generalized.<sup>13</sup> The affected lymph nodes are commonly localized in the posterior cervical triangle, jugular carotid chain and rarely present diffuse distribution. Although there is no definite laboratory test available for the diagnosis of

KFD, the absence of autoantibodies may be helpful to exclude other disorders. White blood cell counts in the normal range are common, but the presence of leukopenia and atypical lymphocytes can be also seen frequently. The definite diagnosis of KFD can be made only through histopathologic evaluation of the affected lymph node which reveals necrotizing lymphadenitis restricted to the cortical and paracortical areas, with partial or complete loss of follicular architecture, associated with marked karyorrhexis. Sometimes the histological characteristics of KFD are indistinguishable from those found in patients with SLE.<sup>15</sup> It has been recommended that the possibility of SLE should always be considered if a lymph node looks like KFD, so that the diagnosis of the underlying SLE will not be neglected.<sup>17</sup> In addition, KFD has been rarely reported in association with SLE, and its diagnosis can precede, follow or coincide with the diagnosis of SLE.<sup>15</sup> Whether the reported cases of KFD associated with SLE were genuine KFD or lupus lymphadenitis simulating KFD is not clear.<sup>17</sup> Moreover, such observations indicate that patient with KFD should be assessed for SLE and followed up for a possible lupus development.<sup>13,14</sup> So, an increased clinical suspicion and strict collaboration between the clinician and the pathologist may be the key for an accurate diagnosis. Despite some rare fatal cases, KFD has a benign course and usually, a special treatment for KFD is not recommended except for complicated cases or in coincidence with SLE.<sup>13</sup> As the prognosis and treatment of KFD and SLE are different, it is important to differentiate these two entities to avoid laborious investigation of infectious and lymphoproliferative diseases.<sup>12,14,15,18</sup>

On the other hand malignant conditions such as Hodgkin's or non-Hodgkin's lymphomas, acute or chronic lymphocytic leukemia, hairy cell leukemia, malignant histiocytosis and metastasis from numerous primary sites may also cause lymph node enlargement. The increased risk of malignancies in autoimmune conditions such as SLE has been reported in several studies since 1970s and the most dramatic increased risk has been shown for haematological malignancies.<sup>19,20</sup> Although there has been an accumulation of well-documented data about the increased risk of non-Hodgkin's lymphoma (NHL) in SLE patients, the results of recent studies have indicated that the risk is increased not only for NHL, but also for other malignancies arising from B-lymphocytes, including

Hodgkin's lymphoma (HL).<sup>10,21,24</sup> In a study evaluating 9,547 SLE patients from 23 centers for a total of 76,948 patient-years, standardized incidence rate for all hematologic malignancies was 2.75 and 3.64 for NHL.<sup>25</sup>

The data about the etiology and the pathogenesis of lymphoma development in SLE is still limited. Similarities between immunological disturbances that characterize both rheumatic conditions and lymphomas can suggest a linkage connecting these conditions.<sup>26</sup> In addition, side effects of immunosuppression or viral infection caused by Epstein Barr, herpes simplex, herpes zoster and polyoma viruses, which are potentially oncogenic, may be another possibility.<sup>20-22</sup> Despite the increasing number of studies investigating the relationship between rheumatic diseases and lymphoproliferative disorders, whether these malignancies are due to immunologic derangements, genetic factors, viruses, or medication remains unknown.<sup>23</sup> Although the presence of certain clinical SLE phenotypes including haematological manifestations (autoimmune haemolytic anaemia and leucopenia), *sicca* symptoms, salivary gland swellings and pulmonary infiltrates has been reported to be associated with increased risk of lymphoma, no relation between malignancies and treatment with the traditional antirheumatic cytotoxic drugs, such as azathioprine and cyclophosphamide, could be depicted.<sup>20,21</sup> In another study, it was found that the average age at diagnosis of SLE was relatively low, end-stage organ damage was severe and the disease duration was fairly long in those patients with NHL, which may reflect moderately high SLE activity over the years preceding the diagnosis of NHL.<sup>23</sup> Malignant lymphomas were found at nodal sites in most patients with systemic rheumatic diseases and LAP was shown as one of the more frequent clinical signs of lymphoma in SLE patients.<sup>21,27</sup> Fever, weight loss, LAP, splenomegaly and hepatomegaly are common both in lymphoma and SLE. The considerable overlap between features of both diseases, can make lymphoma diagnosis difficult in the presence of SLE.<sup>28</sup> Persistent LAP in a patient with SLE not responding to treatment may be indicative of lymphoma.<sup>28</sup> It is also recommended to search for NHL in cases with prominent LAP and massive splenomegaly.<sup>9</sup> Patient's age, physical findings, and serologic studies can be helpful<sup>10</sup>, but lymph node biopsy may be needed in such patients.<sup>29</sup>

The indications for lymph node biopsy are im-

precise, although this may be an important diagnostic tool. Biopsy may be suggested if the patient's history and physical findings are suspicious. It is recommended that in the case of LAP onset in a patient with a previously established diagnosis of SLE, fine needle biopsy may be sufficient as diagnostic, but in uncertain clinical situations differential diagnosis requires the evaluation of lymph node biopsy by an experienced pathologist.<sup>14</sup> Since lymphoma cannot be excluded by clinical diagnosis, the frequency of lymph node biopsy in SLE patients exhibiting LAP seems to be increasing.<sup>10</sup>

Because there is considerable overlap between the features of SLE and lymphoma, the importance of a careful clinical and laboratory evaluation is necessary for correct diagnosis and clinicians caring for SLE patients should keep the lymphoma risk in mind and regularly check for LAP.<sup>20,21</sup>

### Approach to the patient

It is known that most of the information necessary for the approach to a patient with LAP comes from the medical history and a physical examination. Patient's age, gender, use of drugs may be important points. LAP in a child or young adult is usually related to benign conditions such as infections, but after the age of 50, the incidence of malignant disorders increases.<sup>30</sup> Symptoms of infection such as cough, fever and night sweats, or symptoms suggesting malignancy such as fatigue and weight loss may contribute to the approach. The characteristics of the lymph node on physical examination, the extent, the size, the anatomical localization and tenderness can provide useful clues. In patients with SLE, atypical LAP locations and unusually large lymph nodes should raise clinical suspicion of another underlying disease.

Generalized LAP, defined as involvement of three or more noncontiguous lymph node areas, has been reported to be frequently associated with non-malignant disorders such as infections, SLE or other inflammatory diseases.<sup>30</sup> So the appearance of a generalized LAP may orient the physician more directly toward serological and hematologic testing. However, localized LAP first requires a careful clinical examination of all the zones that are anatomically afferent to the enlarged lymph nodes.<sup>31</sup> The anatomical region of the LAP is also important in the evaluation of patients. The most frequent site of regional LAP is the neck and its most

common causes are upper respiratory infections. The enlargement of supraclavicular and scalen nodes should be considered as abnormal.<sup>30</sup> Except for infancy, and in the inguinal area at any age, the presence of one or more lymph nodes larger than 1 cm in diameter needs further investigation if a definite cause cannot be identified.<sup>31</sup> In addition, the tenderness is usually secondary to inflammatory process and nodes involved by lymphoma tend to be nontender, large, mobile and rubbery.<sup>30</sup>

### Conclusion

SLE is a condition with very heterogeneous manifestations one of which is lymph node enlargement. Although LAP is commonly considered a frequent and nonspecific feature of SLE, it requires careful assessment since disease activity was found to be higher among these patients. This may also be the first clinical manifestation of SLE. The differential diagnosis of LAP is crucial because lymph node enlargement may be a sign of other benign or malignant disorders. Patient's medical history, physical examination, selected laboratory tests and lymph node biopsy may be helpful in the approach to the patient. The lymph node characteristics, the extent, the size, the anatomical localization and tenderness can provide useful clues. An increased clinical awareness can be the key for the accurate diagnosis in dealing with SLE patients with LAP.

### Correspondence to

Meltem Alkan Melikoglu  
Physical Medicine and Rehabilitation  
School of Medicine, Ataturk University, Erzurum  
Turkey  
E-mail: mamelikoglu@gmail.com

### References

1. Shapira Y, Weinberger A, Wysenbeek AJ. Lymphadenopathy in systemic lupus erythematosus. Prevalence and relation to disease manifestations. *Clin Rheumatol* 1996;15:335-338
2. Calgüneri M, Ozturk MA, Ozbalkan Z et al. Frequency of lymphadenopathy in rheumatoid arthritis and systemic lupus erythematosus. *J Int Med Res* 2003;31:345-349
3. Schur, EH. Clinical features of SLE. In: *Textbook of Rheumatology*. Eds.: Kelly, W.N., Harris, E.D., Jr, Ruddy, S., Sledge, C.B. Philadelphia, WB Saunders, 1989, 1111
4. Rothfield, N.E Systemic lupus erythematosus: clinical aspects and treatment. In: *Arthritis and Allied Condi-*

- tions. Ed.: McCarty, D.J., Philadelphia, Lea & Febiger. 1989, 1038
5. Hrycek A, Olszanecka-Glinianowicz M, Wanat-Wi\_niewska M. Case report of patient with systemic lupus erythematosus proceed with lymphadenopathy. *Pol Arch Med Wewn* 2006;116:771-776
  6. Kitsanou M, Andreopoulou E, Bai MK et al. Extensive lymphadenopathy as the first clinical manifestation in systemic lupus erythematosus. *Lupus* 2000;9:140-143
  7. Biner B, Acuna\_B, Karasaliho\_lu S et al. Systemic lupus erythematosus presenting with generalized lymphadenopathy: a case report. *Turk J Pediatr* 2001;43:94-96
  8. Bukiej A, Undas A, Pituch-Noworolska A et al. Association of peripheral lymphadenopathy with anti-Ro and anti-La antibodies in a family with systemic lupus erythematosus. *Scand J Rheumatol* 2003;32:52-54
  9. Papadaki HA, Xylouri I, Katrinakis G et al. Non-Hodgkin's lymphoma in patients with systemic lupus erythematosus. *Leuk Lymphoma* 2003;44:275-279
  10. Kojima M, Motoori T, Asano S et al. Histological diversity of reactive and atypical proliferative lymph node lesions in systemic lupus erythematosus patients. *Pathol Res Pract* 2007;203:423-431
  11. Kojima M, Nakamura S, Oyama T et al. Autoimmune disease-associated lymphadenopathy with histological appearance of T-zone dysplasia with hyperplastic follicles. A clinicopathological analysis of nine cases. *Pathol Res Pract* 2001;197:237-244
  12. Okuzawa C, Kuroiwa T, Kaneko Y et al. Kikuchi's disease accompanied by lupus-like butterfly rash. *J Rheumatol* 2003;30:857-859
  13. Lin HC, Su CY, Huang CC et al. Kikuchi's disease: a review and analysis of 61 cases. *Otolaryngol Head Neck Surg* 2003;128:650-653
  14. Komócsi A, Tóvari E, Pajor L et al. Histiocytic necrotizing lymphadenitis preceding systemic lupus erythematosus. *J Eur Acad Dermatol Venereol* 2001;15:476-480
  15. Santana A, Lessa B, Galvão L et al. Kikuchi-Fujimoto's disease associated with systemic lupus erythematosus: case report and review of the literature. *Clin Rheumatol* 2005;24:60-63
  16. Rao GS, Vohra D, Kuruvilla M. Is Kikuchi-Fujimoto disease a manifestation of systemic lupus erythematosus? *Int J Dermatol* 2006;45:454-456
  17. Hu S, Kuo TT, Hong HS. Lupus lymphadenitis simulating Kikuchi's lymphadenitis in patients with systemic lupus erythematosus: a clinicopathological analysis of six cases and review of the literature. *Pathol Int* 2003;53:221-226
  18. Mootsikapun P, Sirijerachai J, Nanagara R. Kikuchi-Fujimoto's disease, histiocytic necrotizing lymphadenitis, mimicking systemic lupus erythematosus. *J Med Assoc Thai* 2002;85:1037-1041
  19. Bernatsky S, Ramsey-Goldman R, Isenberg D et al. Hodgkin's lymphoma in systemic lupus erythematosus. *Rheumatology (Oxford)* 2007;46:830-832
  20. Sultan SM, Ioannou Y, Isenberg DA. Is there an association of malignancy with systemic lupus erythematosus? An analysis of 276 patients under long-term review. *Rheumatology (Oxford)* 2000;39:1147-1152
  21. Löfström B, Backlin C, Sundström C et al. A closer look at non-Hodgkin's lymphoma cases in a national Swedish systemic lupus erythematosus cohort: a nested case-control study. *Ann Rheum Dis* 2007;66:1627-1632
  22. Cibere J, Sibley J, Haga M. Systemic lupus erythematosus and the risk of malignancy. *Lupus* 2001;10:394-400
  23. King JK, Costenbader KH. Characteristics of patients with systemic lupus erythematosus (SLE) and non-Hodgkin's lymphoma (NHL). *Clin Rheumatol* 2007;26:1491-1494
  24. Hansen A, Lipsky PE, Dörner T. B-cell lymphoproliferation in chronic inflammatory rheumatic diseases. *Nat Clin Pract Rheumatol* 2007;3:561-569
  25. Bernatsky S, Boivin JF, Joseph L et al. An international cohort study of cancer in systemic lupus erythematosus. *Arthritis Rheum* 2005;52:1481-1490
  26. Backlin C, Sundström C, Ekbohm A et al. A closer look at non-Hodgkin's lymphoma cases in a national Swedish systemic lupus erythematosus cohort: a nested case-control study. *Ann Rheum Dis* 2007;66:1627-1632
  27. Kojima M, Itoh H, Shimizu K et al. Malignant lymphoma in patients with systemic rheumatic disease (rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and dermatomyositis): a clinicopathologic study of 24 Japanese cases. *Int J Surg Pathol* 2006;4:43-48
  28. Bhalla R, Ajmani HS, Kim WW et al. Systemic lupus erythematosus and Hodgkin's lymphoma. *J Rheumatol* 1993;20:1316-1320
  29. Kojima M, Motoori T, Itoh H et al. Distribution of Epstein-Barr virus in systemic rheumatic disease (rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis) with associated lymphadenopathy: a study of 49 cases. *Int J Surg Pathol* 2005;13:273-278
  30. Henry PH, Longo DL. Enlargement of lymph nodes and spleen. In: Fauci AS, Braunwald E, Isselbacher KJ, Wilson JD, Martin JB, Kasper DL et al, eds. *Harrison's Principles of Internal Medicine*. 14th ed. New York: McGraw-Hill; 1998; 345-351
  31. Ghirardelli ML, Jemos V, Gobbi PG. Diagnostic approach to lymph node enlargement. *Haematologica* 1999;84:242-247