

CASE STUDIES

Burkitt's Lymphoma in a patient with systemic lupus erythematosus

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Abstract

Recent literature evidence has demonstrated a small but definite increase in the risk of malignancies in SLE patients when compared to general population. The present case study reports a rare occurrence of Burkitt's lymphoma in a 32-year-old female patient who had been diagnosed with SLE around 3 years ago. The study also discusses the possible pathophysiological links between Burkitt's lymphoma and SLE.

Keywords: Burkitt's lymphoma, Systemic lupus erythematosus, SLE

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder with complex environmental and genetic interactions. Therapeutic advances in the last 5 decades have improved the 5-year survival in more than 90% of the patients.¹ In some cases, the longer survival translates to considerable long-term morbidity, including distinct cancer-risk profiles.

Autoimmune disorders such as SLE have been associated with an increased cancer risk, particularly for certain cancer types.² However, the underlying pathophysiologic mechanisms are not fully understood. A multi-centre study involving a large cohort by Bernatsky *et al* has confirmed a slightly increased risk for hematological cancers, particularly lymphoma, in SLE patients. Most of the neoplasms reported were non-Hodgkins lymphoma (NHL), especially diffuse large B-cell lymphoma (DLBCL).³ There are only 3 case reports of Burkitt's lymphoma in SLE till date.

Case report

A 32-year-old female was diagnosed with SLE based on the presentation of disease-related symptoms namely oral ulcers, muscle pains, fever of one-month duration and malar rash. On investigations, she was detected to have myositis with raised creatine phosphokinase (CPK) levels,

leucopenia and significantly positive antinuclear antibody (ANA, 1:2560). She did not have dryness of mouth or eyes and was negative for anti-Ro and anti-La antibodies. She was initially treated with pulse methylprednisolone, and later with hydroxychloroquine 300 mg/day and prednisolone in tapering doses over one and a half years. After 3 years, the patient presented with decreased sensation of the left half of body, and difficulty in walking, and limping on left side. Further examination revealed the occurrence of objective loss of sensation for touch, temperature and pain with decreased power 4/5 in left upper and lower limbs, suggestive of hemiparesis possibly an infarct. Her clinical investigations like CBC, serum creatinine, serum calcium, phosphorus, CPK levels were normal. Magnetic resonance angiogram of brain, MRI of dorsolumbar spine, and X-ray of pelvis with both hips were normal. She was managed as neuropsychiatric SLE with escalating dose of prednisolone. Continued follow-up in outpatient department had revealed the persistence of lower limb pain and left side limping. Repetition of CPK and X-ray of both knees were normal.

Simultaneously, the patient had consulted a dentist for left jaw pain and had undergone root canal treatment for caries. However, the left jaw pain persisted and the dental CT scan showed a lesion in the left mandible. This was suggestive of osteonecrosis of jaw, as the patient was on risedronate 35 mg once a week since 1

year for the prevention of osteoporosis. After one year, she presented with vaginal bleeding and abdominal pain for past 15 days. On examination, she had pallor, left cervical lymphadenopathy, and left mandibular swelling. Investigations revealed: hemoglobin 9.6 gm%, WBC-5850 mm³, platelets: 126,000 mm³, S. creatinine:1.64 mg/dl, and LDH: 854 U/L. Ultrasound of abdomen and pelvis revealed bulky uterus and bilateral ovaries. Carcinoemberionic antigen (CEA) and CA -125 were normal. MRI of abdomen

and pelvis showed large endometrial masses with bilateral ovarian nodules, focal lesions in liver and kidneys, and marrow-replacing lesions in spine and pelvic bones. PET scan showed fluorodeoxyglucose (FDG)-avid lesions in both kidneys, liver, spleen, multiple lymph nodes, uterus, both ovaries, and brain (Fig.1). Cervical lymph node biopsy showed complete effacement of lymph node architecture with replacement by medium-sized cells with pleomorphic and vesicular nuclei, and prominent nucleoli (Fig. 2).

Fig. 1: PET-CT image showing FDG uptake at multiple sites

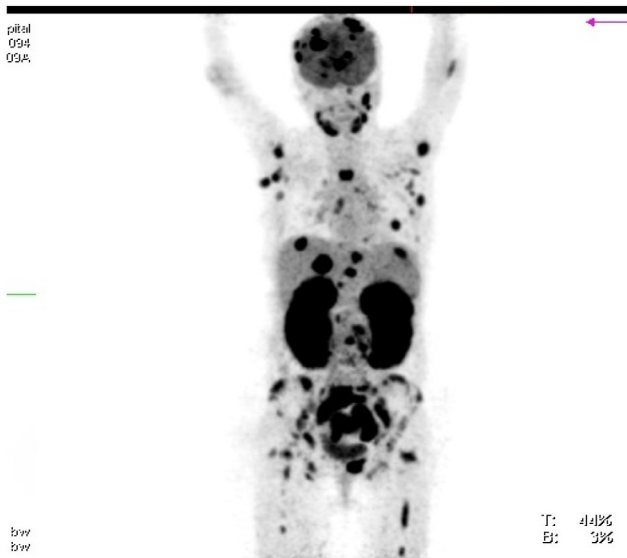


Fig. 2: Histopathology slide of cervical lymph node with hematoxylin and eosin stain

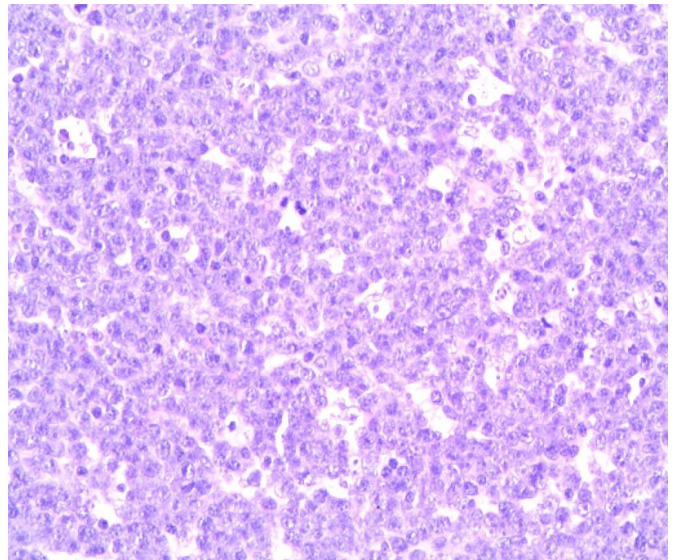


Fig. 3: CD20 staining showing all cells positive for same

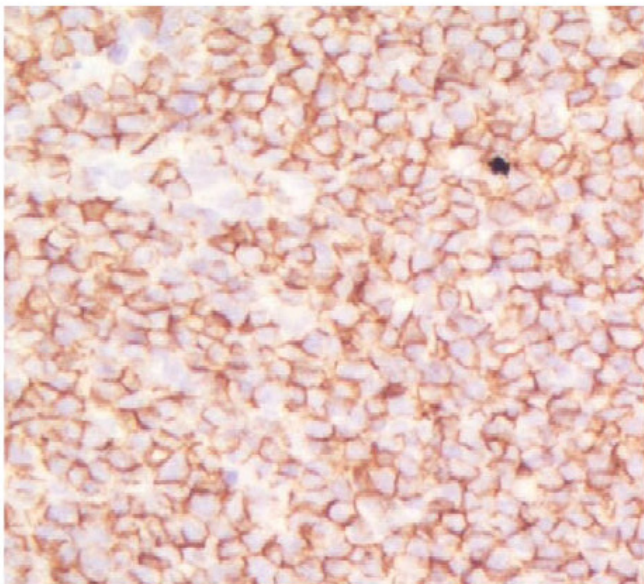
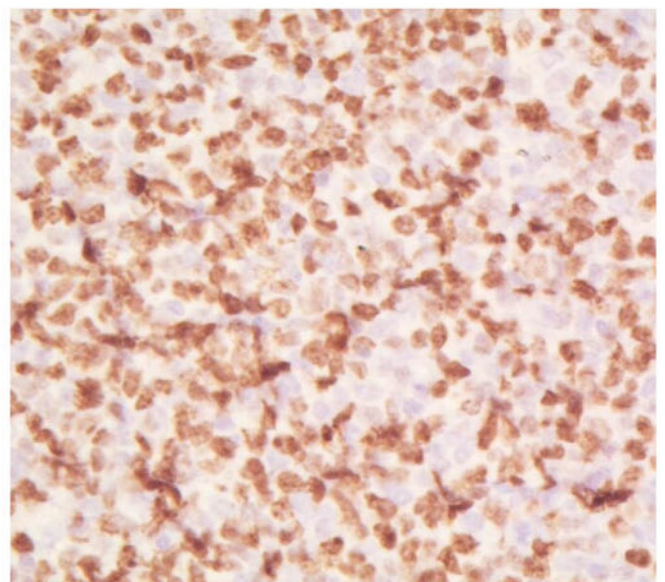


Fig. 4: Slide picture showing MIB-1 proliferation index



Immunohistochemistry showed expression of CD20 and PAX 5 strongly and diffusely (Fig. 3), BCL2 focally positive, and MIB-1 proliferation index 98% (Fig. 4).

Based on the investigations, a diagnosis of high-grade diffuse large B-cell non-Hodgkin's lymphoma (DLBCL) was made. In view of high proliferation index (98%), the biopsy was tested for chromosome 8:14 (MYC-IGH) translocation, a characteristic feature of Burkitt's lymphoma. Cerebrospinal fluid (CSF) analysis for malignant cells was positive (Fig. 5). Since the patient condition was deteriorating, she was started on rituximab, cyclophosphamide, hydroxydanurubicin, vincristine and prednisolone (R-CHOP) chemotherapy for DLBCL. After C-MYC/IgH report positivity confirming Burkitt's

lymphoma, chemotherapy schedule was changed to dose-adjusted E-POCH (etoposide, prednisolone, vincristine, cyclophosphamide, hydroxydaunorubicin) alternating with high-dose methotrexate and cytarabine for another 7 cycles. Good treatment response was confirmed after 3 cycles based on PET scan. She had completed eight cycles of chemotherapy and responded well to the treatment (Fig. 6).

Discussion

Although the therapeutic advances have contributed to improved survival rate of SLE, the disease-related morbidity is considerably high. Cancer risk has been identified as one of the important causes of disease-related morbidity. Several studies have evaluated the association between

Fig. 5: CSF showing malignant cells

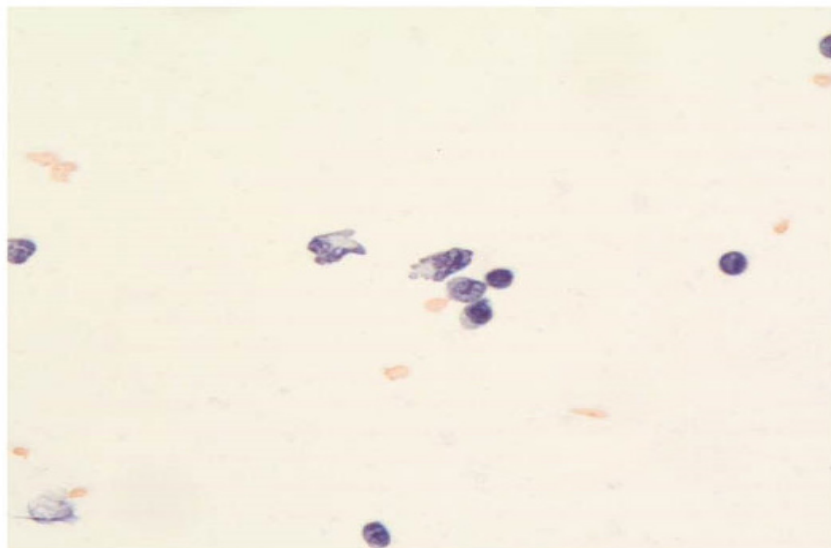


Fig. 6: Pet CT images after 8 cycles of chemotherapy showing complete resolutions of lymphoma



autoimmunity and cancer.² The factors that are speculated to influence the association include medications of SLE and interaction between treatment and viral exposure. Clinical characteristics like co-existing Sjogren's syndrome or other overlap syndromes may increase the cancer risk.⁴ Fairly wide confidence interval (CI) noted in various estimates corroborate the increased risk of cancer in SLE. According to these estimates, the standardized incidence ratio (SIR) for overall cancer ranged from 1.1 (95% CI 0.7-1.6) (5) to 2.6 (95% CI 1.5-4.4).⁶

In a large multicenter study involving 9547 patients from 23 centres, SLE patients showed 4-fold increased risk for non-Hodgkins lymphoma (NHL).⁷ In addition, increased incidences of leukemia, cancers of vulva, lung, thyroid, and liver were noted. Hence, the overall cancer risk in SLE is slightly increased compared to general population. There are various possible explanations on the association between lymphoma and SLE. The juxtaposition of an oncogene adjacent to a gene important for immune cell function may facilitate the development of lymphoma.⁸ Enhanced lymphocyte proliferation associated with autoimmunity might be responsible for some of the elevated lymphoma risk noted in autoimmune diseases like SLE.

Diffuse large B cell lymphoma (DLBCL) is the most common NHL.^{3,9} The development of this NHL subtype from activated lymphocyte suggests that chronic inflammation might increase the risk of lymphoma in autoimmune diseases like SLE.¹⁰ A proliferation-inducing ligand (APRIL) is one of the highly expressed cytokines in DLBCL lymphoma. Increased levels of APRIL has been suggested as a risk factor for onset of SLE. The increased expression of APRIL in DLBCL lymphoma in some patients may indicate that APRIL may be mediating lymphoma development in SLE.¹¹ Furthermore, DLBCL lesions found in SLE patients seem to strongly express APRIL (a proliferation inducing ligand), which is essential for B-cell survival and development.¹¹ The mechanisms by which APRIL facilitate the development of lymphoma has not been elucidated. However, it seems to play a role in allowing NHL B-cells to overcome apoptosis.¹²

Burkitt's lymphoma is more common in males than females. The three clinical variants of Burkitt's are endemic, sporadic and immunodeficiency-associated, especially in HIV patients. Burkitt's lymphoma in SLE is a rare occurrence and so far, only 3 cases have been reported.^{13, 14, 15} The Epstein Barr virus (EBV) is implicated to have a role in the pathophysiology of SLE and increasing the risk of malignancy.¹⁶ EBV-seropositivity is only slightly increased in patients with SLE

compared to general population. Increased viral load, EBV mRNA expression, and EBV-directed antibodies were noted in patients with SLE compared to healthy controls.¹⁷ Certain studies have evaluated the potential role of medications in mediating lymphoma risk in SLE. A case-cohort analysis of a multicenter international SLE cohort suggested an increased risk of lymphoma in subjects exposed to cyclophosphamide as well as to cumulative glucocorticosteroids compared to SLE controls without cancer.

A link between primary Sjogren's syndrome and lymphoma has been reported by many studies and it has been suggested that lupus-induced secondary Sjogren's syndrome could account for elevated risk of hematologic malignancies. This has been demonstrated in a study done by Bernatsky *et.al*.¹⁸ However, the present patient did not have clinical features like dryness of mouth or eyes and her anti-Ro and anti-La antibodies were negative.

Conclusion

Burkitt's lymphoma is a rare occurrence in SLE patients. Although increased occurrence of NHL in SLE has been reported, it is a rare event with incidence rate of only one in 2000 person-years of follow-up. Inadequate viral clearance and drugs like cyclophosphamide have been implicated as a risk factor for hematological cancer in SLE. A careful screening is thus important in SLE population, as flare of the disease and malignancy may mimic each other. Fever onset, myalgia, cytopenia, and constitutional symptoms are always attributed to disease flare and these symptoms may cause misdiagnosis of cancer. Hence there should be high suspicion of cancer when symptoms are unexplained and do not respond to treatment. In addition, the patient should be educated regarding the adoption of cancer preventive measures like smoking cessation.

Competing interests

The authors declare that they have no competing interests.

Citation

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