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Massive Generalized Lymphadenopathy Due to Systemic Lupus Erythematosus

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Abstract

Background: Massive generalized lymphadenopathy (MGL) as an initial manifestation of systemic lupus erythematosus (SLE) is rare. **The Case:** A previously healthy 18-year-old man presented with MGL for 1 month. Subsequently, he developed fever, hypertension, fluid overload, and left abdominal pain. He had hemoglobin 89 g/L, serum creatinine 168 umol/L, serum albumin 29 g/L, prolonged activated partial thromboplastin time, heavy proteinuria, and hematuria. Fused PET/CT scanning showed hypermetabolic peripheral and internal MGL with splenic and right kidney infarctions. Autoimmune tests showed very low serum complements 3 and 4 with high titers of ANA 1/640 (N: 1/40) and anti-dsDNA 666 IU/ml (N: < 10). Serological tests for tuberculosis, syphilis, and Epstein-Barr virus were negative. Tests for hypercoagulable states were negative except for lupus anticoagulant and anti-beta2 glycoprotein I antibodies. Lymph node biopsy showed partial effacement of nodal architecture by areas of necrosis surrounded by extensive T-lymphocytic infiltration that lacked vasculitis, caseation, and granulomas. Moreover, his kidney biopsy showed class IV lupus nephritis. Initially, he was treated with intravenous Solumedrol followed by Prednisone as well as Mycophenolate mofetil for a total of 3 months. Subsequently, he received Rituximab infusion to be on a yearly basis. For his coagulopathy, he received Apixaban. He improved within 1 month. By 1 year of follow-up, he remained clinically stable and with normal laboratory as well as radiological testing. **In Conclusion:** SLE can present with MGL.

Keywords

Systemic Lupus Erythematosus, Lymphoma, Mycophenolate, Rituximab, Anti-Phospholipid Syndrome, Lymphadenopathy, PET Scan

1. Introduction

Generalized lymphadenopathy (GL) has been reported in (a) autoimmune disorders viz. Kikuchi-Fujimoto (KFD), sarcoidosis, Castleman disease, IgG4-associated disease, and systemic lupus erythematosus (SLE), (b) neoplasms viz. lymphoma, lymphoproliferative diseases, (c) infections viz. tuberculosis, Epstein Barr viral infection, and syphilis, and (d) drug side effects viz. phenytoin, allopurinol, gold, penicillin, quinidine [1]. SLE is a multisystem disease with variable phenotypic presentation. GL has been reported in 23/90 (26%) SLE patients [2]. Moreover, it was more common with disease flare (constitutional symptoms, myo-/pericarditis, myositis, cytopenia, and membranous nephritis) [3]. On the other hand, massive GL (MGL) is a portent sign of lymphoma, though rarely reported in SLE [4]. Moreover, GL has been rejected by the Systemic Lupus International Collaborating Clinics in their new classification criteria for SLE [5]. In our case report, we present a patient with MGL as the initial manifestation of active SLE, with emphasis on diagnosis, management, and prognosis.

2. The Case

An 18-year-old man presented with MGL for 1 month. Subsequently, he had low-grade fever, malaise, anorexia, shortness of breath, generalized body swelling, and sharp pain in the left upper abdomen. The patient did not have a previous history of medical or surgical disease and denied recent or chronic intake of drugs. On his initial physical examination, he was in distress due to shortness of breath and abdominal pain. Blood pressure was 170/105 mm Hg, temperature was 37.8˚C, and he weighed 95 kg. He had massive enlargement of cervical (**Figure 1**), axillary, and inguinal lymph nodes with raised jugular venous pressure and bilateral lower limb oedema. Systemic examination showed bilateral basal lung rales. His initial laboratory investigations are summarized in **Table 1**. He had normal peripheral leucocyte and platelet counts, yet hemoglobin was 89 g/L with normal transferrin saturation% and vitamin B12 levels. Serum urea and creatinine were elevated at 10 mmol/L and 168 umol/L, respectively. Serum sugar, electrolytes, and liver functions were normal except for albumin at 29 g/L. CRP was 38 mg/L (Normal < 8). Prothrombin time was normal, yet activated partial thromboplastin time was double the upper limit of normal. Urine routine and microscopy revealed heavy proteinuria and hematuria. Twenty-four-hour urine collection revealed creatinine clearance at 0.6 ml/second and proteinuria at 4 g/day. Chest x-ray and high-resolution chest scan showed pulmonary venous congestion and bilateral pleural effusions with hilar lymphadenopathy without nodules or apical scars. ECG was normal. Abdominal and pelvic ultrasound showed moderate hepatosplenomegaly with a wedge-shaped defect in the spleen and moderate ascites. Subsequently, computerized tomography (CT) scan of the abdomen and pelvis, with contrast, confirmed the splenic infarct and also a right renal one (**Figure 2**). PET/CT F18 FDG whole body scan showed multiple hypermetabolic cervical, inguinal, thoracic, and abdominal lymphadenopathy as well as the splenic infarction (**Figure 3**).

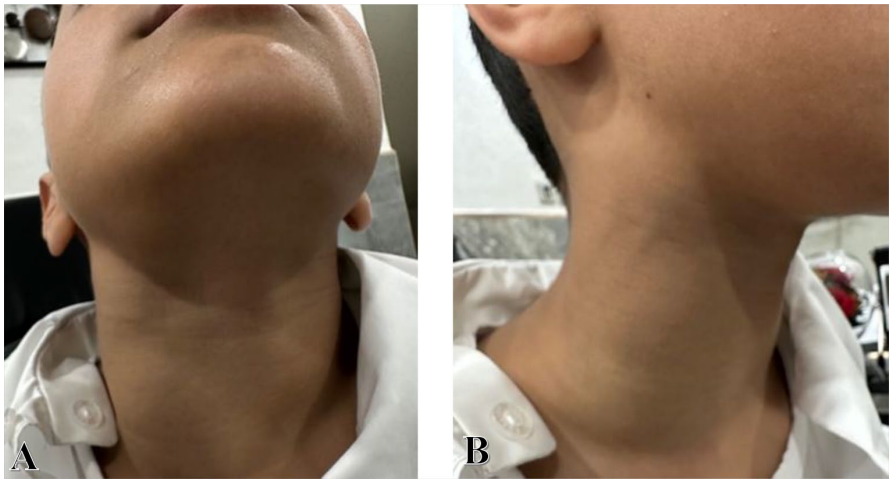

Figure 1. Massive bilateral (A) & (B) cervical lymphadenopathy.

Table 1. Flow chart of demographical data and biochemical changes of a treated patient with lupus massive lymphadenopathy.

		Time (months)		
		0	1	12
Age, gender & race:	18 years, male, White			
Clinical data:				
	Manifestations	1 month of fever, fluid overload, splenic infarction and massive generalized lymphadenopathy		
	Blood pressure: (120-80 mm Hg)	170/105	120/80	120/80
	Body weight: (Kg)	95	88	85
Laboratory tests:				
	Hemoglobin: (130-160 g/L)	89	116	124
	Serum:			
	urea (4-6 mmol/L)	29	33	41
	creatinine (60-120 umol/L)	168	110	95
	albumin (35-50 g/L)	21	22	43
	Hematuria: (-)	Excess/HPF	10 per HPF	(-)/HPF
	24-hour urinary protein: (< 150 mg)	4000	1200	510
Autoimmune tests:		High ANA, antidsDNA, Low C3&4	Normal	Normal
Infections (TB, EBV, $, HIV):		Negative	Negative	Negative
Lymph node and kidney biopsy:		Necrotizing lymphadenopathy & class 4 lupus nephritis		
Radiological tests:				
	HRCT chest:	Hilar lymphadenopathy		Resolved
	Abdominal and pelvic CT:	Diffuse lymphadenpathy & splenic infarction		Resolved
	PET scan:	Hypermetabolic diffuse lymphadenopathy and splenic infarction		Resolved
Management:				
	Corticosteroids	3 months		
	Mycophenolate mofetil	3 months		
	Rituximab			

Blood cultures and procalcitonin tests were negative. Serological viral tests viz. QuantiFERON-TB Gold, antibodies (IgA, M, G) to viral capsid antigen of Epstein Barr Virus, Treponema pallidum particle agglutination, and HIV were also negative. Autoimmune tests showed very low serum complements 3 and 4, with high ANA and anti-dsDNA titers at 1/640 (N: 1/40) and 666 IU/ml (N: < 10). Tests for hypercoagulable states were negative except for lupus anticoagulant and anti-beta2 glycoprotein I antibodies. Lymph node biopsy showed partial effacement of

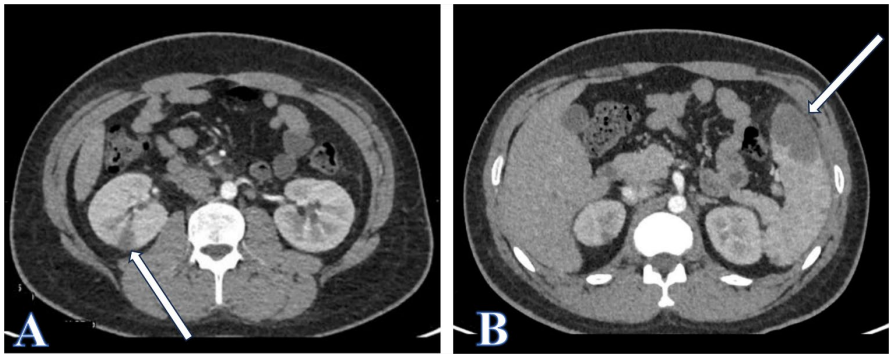

Figure 2. Axial view of CT scan of the abdomen showing infarctions (arrows) in: (A) right kidney and (B) in the spleen.

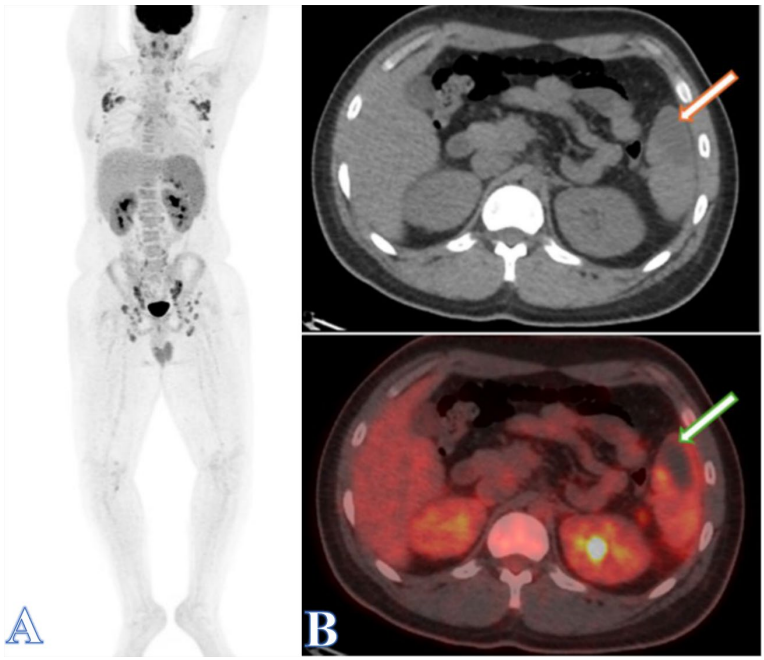

Figure 3. Showing: (A) Maximum intensity projection (MIP) images of a PET scan revealing increased FDG uptake in all lymph nodes and spleen as well as (B) axial CT and Fused PET/CT images showing a photopenic–hypodense area in the spleen (arrows) representing infarction.

nodal architecture by areas of necrosis surrounded by extensive lymphocytic infiltration with few neutrophils, yet without eosinophils, plasma cells, and histiocytes (**Figure 4(A)**, **Figure 4(B)**). There was no evidence of vasculitis, caseation, or granuloma formation. On immunostains, those lymphocytes were positive for CD3 (T-cell marker) and restricted for CD20 (B-cell marker) (**Figure 5(A)**, **Figure 5(B)**). Moreover, it showed normal restriction of large B-lymphocytes (Bc12 positive) only to germinal centers, not diffuse as in lymphoma, as well as its normal limited area of proliferation (Ki67) (**Figure 6(A)**, **Figure 6(B)**). Hence, lymphoma was excluded. In addition, immunostains for histiocytes (CD68) were negative; hence KFD was excluded. Moreover, his kidney biopsy revealed global

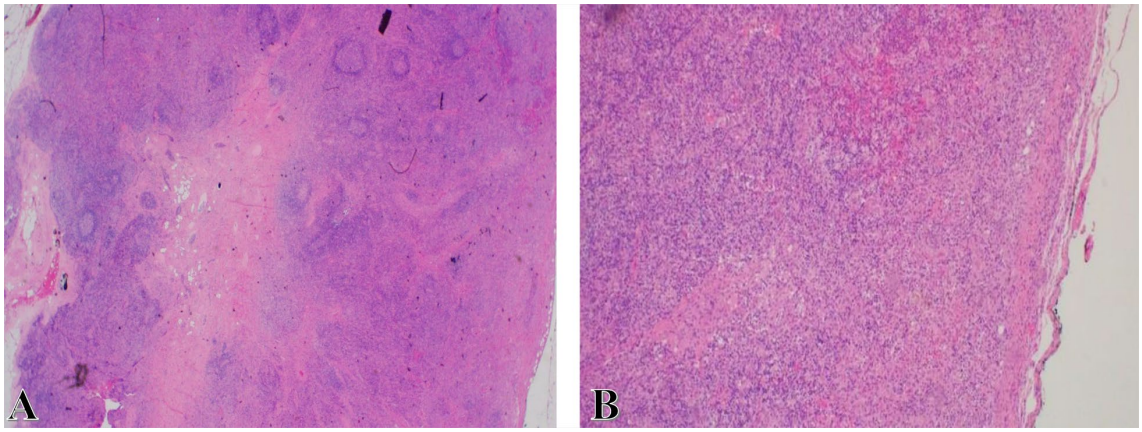

Figure 4. Photomicrograph of lymph node biopsy showing partial effacement of the nodal architecture (A), (H&E ×200) by areas of necrosis surrounded by extensive Lymphocytic infiltration with few neutrophils without vasculitis, caseation, or granuloma formation (B) (H&E 400).

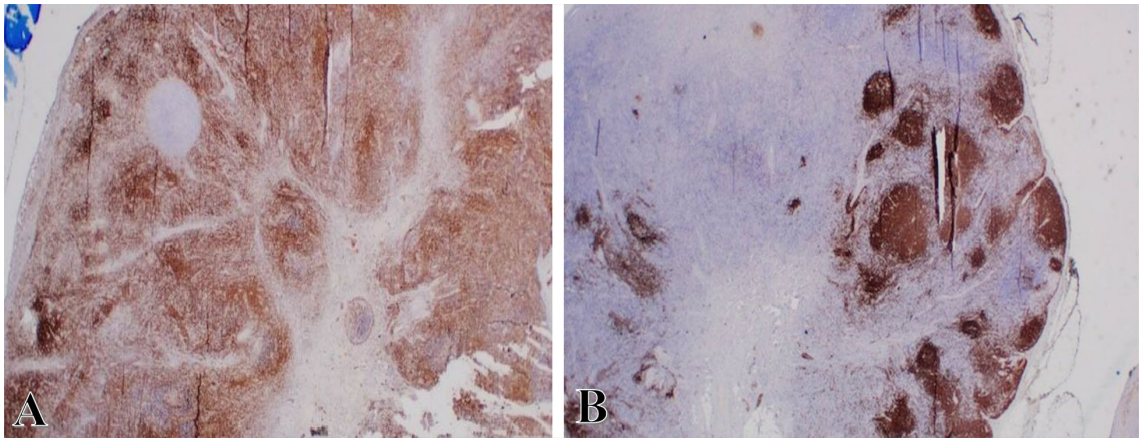

Figure 5. Photomicrograph of an immunostain of infiltrated germinal centers in a lymph node. biopsy by T-lymphocytes (CD3-positive) in (A) and negative for B-lymphocytes (CD20) in (B).

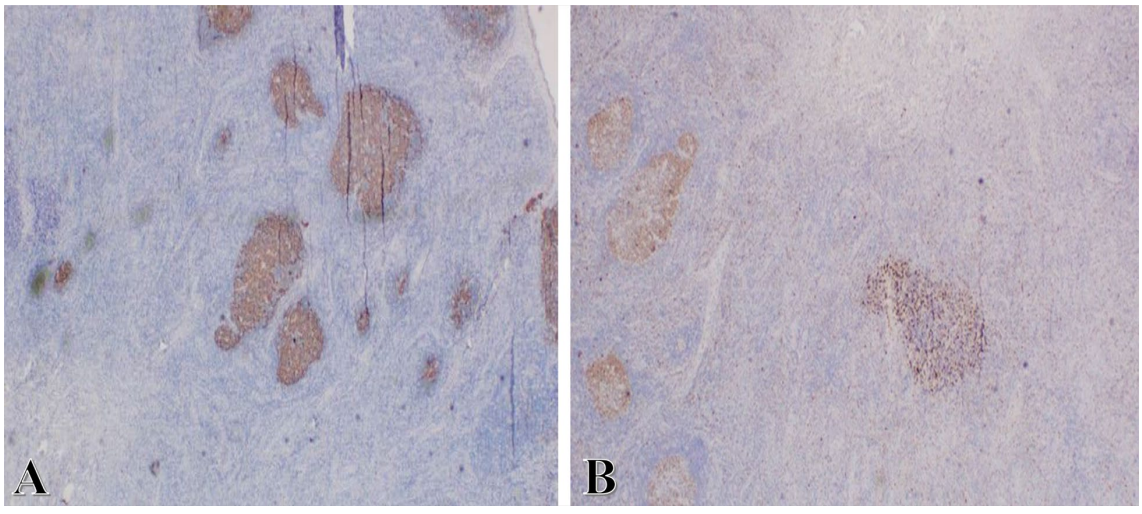

Figure 6. Photomicrograph of immunostains of a lymph node biopsy showing: (A) normal Restriction of large B-lymphocytes (Bc12 positive) to germinal centers, not diffuse. as in lymphoma and (B) normal, limited area of proliferation in it (Ki67).

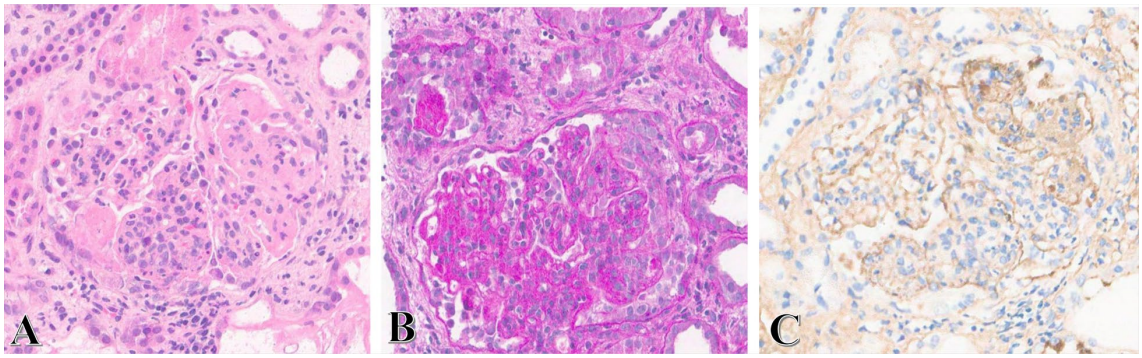

Figure 7. Photomicrograph of a kidney biopsy showing a glomerulus with diffuse cellular Proliferation with necrosis in (A) and extensive wire-loop formations and crescent in (B) with diffuse IgG deposition (C).

and diffuse endocapillary hypercellularity associated with karyorrhexis, wire loop formation, and cellular crescents (**Figure 7(A)**, **Figure 7(B)**). Immunoperoxidase stains were positive for mesangial and capillary all immunoglobulins, C3, and C1q (**Figure 6(C)**). Hence, diagnosis of systemic lupus erythematosus was confirmed and lymphoma as well as infections were excluded. The patient was treated with Solumedrol 1 g intravenously for 3 days followed by Prednisone 1 mg/kg. Moreover, he received (a) Mycophenolate mofetil 1 g twice daily, and (b) an initial bolus dose (5000 units) of intravenous unfractionated heparin followed by a maintenance dose of 1000 units/hour for 48 hours, which was changed to Apixaban 5 mg twice daily. Omeprazole 20 mg daily was added to protect his stomach from stress and corticosteroid-induced ulcerations as well as Furosemide for his fluid overload and hypertension. By 1 month, his (a) systemic manifestations, fluid overload, and lymphadenopathy had disappeared, (b) serum creatinine and albumin had returned to normal, and (c) repeat PET scan showed resolution of his systemic lymphadenopathy. Hence, his Prednisone dose was gradually reduced until reaching 5 mg by the end of 3 months. Subsequently, intravenous infusion of 1 g of Rituximab followed by another 1 g 2 weeks later was given, followed by tapering of Mycophenolate and Prednisone until discontinuation 1 month later. On such management, he remained stable, clinically and by laboratory testing, up to 1 year of follow-up.

3. Discussion

Diagnosis of MGL can be established by PET scan that discloses hypermetabolic inflammatory and malignant disorders [6]. Its differential diagnosis is complex and challenging, as in our patient. By history, specific drug-exposure was excluded. Despite his non-localizing initial manifestations of systemic illness, viz. fever, weight loss, anorexia, and malaise, he had evidence of fluid overload induced by acute kidney injury that was associated with glomerular disease (proteinuria and hematuria) [7]. The latter stemmed autoimmune workup that disclosed SLE activity (low serum complements and high ANA and anti-dsDNA titers) [8]. Moreover, high aPTT and splenic infarction stemmed from coagulopathy workup that disclosed antiphospholipid syndrome secondary to his SLE [9].

Furthermore, diagnosis of class 4 lupus nephritis confirmed the diagnosis of active SLE [10]. Lymph node biopsy and testing with immunostains were essential to (a) exclude an associated lymphoma and (b) confirm lupus adenitis [11]. The latter displayed (a) partial effacement by T-cell infiltration (positive CD3), contrary to lymphomatous involvement with diffuse nodal involvement with B-cells (positive CD20), and (b) normal restriction of large B-lymphocytes (Bcl2 positive) to germinal centers, not diffuse as in lymphoma, and with normal proliferation in it (Ki67). Moreover, leukemia was excluded by absence of pseudonodules of atypical cells/blasts. The spectrum of MG other than lymphoproliferative diseases, relevant to our case, is summarized in **Table 2**. The autoimmune diseases include KFD, sarcoidosis, multicentric Castleman disease, and IgG4-associated disease.

Table 2. Differential diagnosis of generalized lymphadenopathy.

		Diagnosis	LN biopsy
disorder	Autoimmune disorders		
	Kikuchi histiocytic necrotizing lymphadenitis	Clinical & LN biopsy	Histiocytic necrotizing granulomata & (+) CD68
	Systemic lupus erythematosus	Clinical, laboratory & serology, kidney & LN biopsy	Partial effacement of nodal architecture areas of necrosis surrounded by T-lymphocytes
	Sarcoidosis	Clinical & LN biopsy	Non-caseating granulomata with
	Castleman disease	LN biopsy, low CD4 and (+) human herpes virus-8	Angiofollicular hyperplasia
	IgG4 disease	Clinical, serology and biopsy	increase IgG4 (+) plasma cells & IgG4:IgG plasma cells (> 40%)
	Infections		
	Tuberculosis	Quantiferon test & Caseating granuloma in LN biopsy	Caseating granulomata
	Syphilis	Treponema Pallidum immobilization test	Reactive
	Viruses: HIV, EBV, CMV, Herpes-6	Serology	Reactive
	Malignancy		
	Lymphoma	LN biopsy	Diffuse nodal effacement, invasion of capsule, with immunoblasts and large B-anablastic cells (Reed-Sternberg) & (+) CD30
	Leukemia	Blast cells in blood & BM biopsy	Loss of distinct follicles with proliferation pseudonodules of atypical lymphocytes in CLL or blasts in AML
	Drugs		
	phenytoin, allopurinol, gold, penicillin, quinidine	History	Reactive

Abbreviations: Reactive: follicular hyperplasia (mixture of small & large lymphocytes, centrocytes and plasma cells with neutrophils if acute lymphadenitis).

KFD is a rare self-limited disease with fever, upper respiratory tract infection, leucopenia, and cervical adenopathy, yet 20% may manifest as MGL [12]. It is an immune-mediated response due to infection and has been reported to coincide with, precede, or follow the diagnosis of SLE [13]. Histopathologically, its lymphadenopathy is histiocytic necrotizing granulomata with (+) CD68, which was lacking in our patient. Sarcoidosis is another multi-system autoimmune granulomatous disorder that has a similar presentation to our patient. Its classic presentation is bilateral hilar adenopathy with progressive lung fibrosis. It can be associated with erythema nodosum, sarcoid arthropathy, eye disease (iridocyclitis, iritis, and chorioretinitis), and rarely with splenic infarcts, cardiac involvement, and peripheral adenopathy [14]. Histopathologically, its lymphadenopathy is characterized by non-caseating/non-necrotic granulomas, which was lacking in our patient. Moreover, his lymph node biopsy excluded (a) multicentric Castleman disease, which is characterized by hyperplastic germinal centers, sheets of plasmacytosis, and hypervascularity with hyalinosis (angiofollicular hyperplasia) and prominent mantle zones "onion-skin appearance" [15], and (b) IgG4 AD, which is characterized by extrafollicular infiltration by plasma cells, mostly of IgG4 subclass (>100/HPF), with increased ratio of IgG4:IgG positive plasma cells (>40%) [16]. Infectious etiology of MGL, viz. syphilis, tuberculosis, human herpes virus-6, Epstein–Barr virus, cytomegalovirus, and human immunodeficiency virus, were excluded by serological tests. In those diseases, lymph node biopsy exhibits reactive lymphadenopathy (mixture of small & large lymphocytes, centrocytes, and plasma cells with neutrophils if acute lymphadenitis) except for caseating granulomata in tuberculosis [17] [18]. Both were lacking in our patient. Our patient with such an aggressive lupus flare responded well to our reported protocol of a short course (3 months) of 2 anti-proliferative agents (tapering dose corticosteroids and MMF) followed by yearly Rituximab alone, which confirms its efficacy and safety in the treatment of severe SLE and nephritis [19]. Such MGL cleared after remission of SLE activity with our therapy, indicating its benign prognosis. Moreover, the choice of Apixaban in our patient with severe coagulopathy induced by SLE-associated antiphospholipid syndrome was for its (a) ease of long-term use (without need for frequent monitoring and limited drug-interactions) over warfarin in such non-valvular coagulopathy/embolization, and (b) its safety in patients with renal impairment compared to other direct oral anticoagulants [20].

4. Conclusion

MGL, though rare, may present as the initial manifestation of active SLE. Fortunately, it is amenable to our protocol of therapy.

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Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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