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Meningococcemia as an initial manifestation of systemic lupus erythematosus: Report of a case and review of the literature

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CASE STUDY

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ABSTRACT

Systemic lupus erythematosus (SLE) is an inflammatory disease with a wide range of clinical manifestations and complications related to disease activity. One of them is the increase risk to infections secondary to immunological alterations due to pharmacological therapy (especially steroids). Few reports have documented the association of SLE and meningococcal infection with subsequent development of immunological activation (continuous inflammation) and intolerance of the immune system. The attempts to make an early and appropriate approach to these type of patients, generate benefits in survival rates and decrease sequelae among those who survive, especially in those in whose infection compromised central nervous system. We present the case of a patient that presented with neurological symptoms compatible with neuroeffector by *Neisseria meningitis* isolated in CSF cultures. Despite adequate antibiotic treatment the patient continued to deteriorate neurologically, and alternative diagnosis were evaluated after findings of vasculitis in brain CT scan. Immunological panel was performed with positivity of antibodies commonly present in SLE considering that infection by *Neisseria meningitis* was a trigger of immunological intolerance and development of SLE. We present the following case to understand the physiopathology and relationship between meningococcal infections, complement consumption, immunological intolerance and the development of autoimmune disease.

Key Words
Meningococcal sepsis, systemic lupus erythematosus, mortality

Implications for Practice:

1. What is known about this subject?
There are no reports of infections as the first sign of presentation of an autoimmune disease. Could be the first sign of SLE.

2. What new information is offered in this case study?
Neuroeffector by *N. meningitides* could be the first step in developing SLE.

3. What are the implications for research, policy, or practice?
All patients with infection by *N. meningitides* could have an autoimmune substrate, which could be studied, during the development of the disease.

Background

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects the connective tissue in various tissues and organs. Its aetiology is considered nowadays influence by predisposing intrinsic or extrinsic factors such as genetic susceptibility, environmental exposition, hormonal and immunoregulatory alterations.[1,2] In the last decade, there has been an increase incidence of cases and a great reduction in mortality rates.[3] Nevertheless, the risk of death

remains higher in comparison to the general population especially among young individuals and is often attributed to multiple causes specially infections.[4-6] Animal models have demonstrated the existence of CD4-T cell population depletion, complement deficiency and pharmacological immunosuppressive therapy as cofactors that can lead to a higher mortality.[7,8] The deficiency in the complement cascade favours the development and activity of systemic lupus erythematosus and increases the risk of infections by encapsulated microorganisms such as *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Neisseria gonorrhea*.[9,10]

There are few published cases describing the association between de onset of infection with isolation of *N. meningitidis* and the development of SLE, which makes its diagnosis and management more difficult when dealing with these types of patients.[11]

Case details

A 30-years-old, housewife with no past medical history was admitted to the emergency department for intermittent headache described as 8/10 using the 1-10 pain scale, associated she developed fever, myalgia, polyarthralgia, malaise and decrease strength in lower limbs. Physical examination showed vital signs within normal range, but neurological examination was positive for neck rigidity, photophobia and petechial lesions in the upper and lower limbs Table 1 without any signs of major evident bleeding considering skin findings related to disseminated bacterial infection and not controlled sepsis. A computerized brain scan was performed, and cerebral oedema was found without any signs of haemorrhage, infarcts of masses. Lumbar puncture was performed with cerebrospinal fluid (CSF) analysis positive for hypoglycorrhachia (10mg/dl), with central glucose of 110mg/dl, pleocytosis and positive stains for Gram-negative diplococci (Table 2). Laboratory test revealed increase leucocyte and neutrophil count associated with positive reactive C protein (RCP) and active inflammatory sediment in urine analysis.

Antibiotic treatment with ceftriaxone (Rocephin) was initiated with microbiological isolation in CSF cultures of *Neisseria meningitides* and we did not considered to performed meningococcal serology due to the positivity of the bacterial culture in CSF. During treatment the patient developed seizures, neurological deficit (slurred speech, loss of mobility and sphincter incontinence) with persistence of fever and deterioration in ventilator parameters requiring tracheal intubation, deep sedation and scaled antibiotic treatment. A new lumbar puncture was performed with persistent hypoglycorrhachia (Table 2) and a control brain CT scan with contrast showed areas of contrast enhancement and vasogenic oedema in left thalamic region (Figure 1A-C) considering vasculitis of the CNS *vs.* infectious vasculopathy. Even though, there was microbiological confirmation and isolation of *N. meningitides*, it was considered to rule out other diagnosis since we did not consider that finding on brain CT scan were consistent with a meningeal process. An immunological panel was taken to rule out autoimmune aetiologies that could explain the severe immunological response and the poor response to antibiotic treatment (Table 3) with positivity of biomarkers for SLE and severe activity by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) leading to the conclusion that the symptoms, signs and findings in brain CT were consistent with a cerebral vasculitis as a primary manifestation of SLE probably triggered by an infectious aetiology. Antibiotic treatment was continued, and an antimalarial agent was associated, corticosteroid therapy was deferred due the presence of concomitance meningitis. After, 4 weeks as an inpatient we were able to extubate, she gained back her strength and had total control of sphincters (possibly associated to the severe cerebral oedema). Her neurological examination later showed no sequelae and findings in CT scan persisted, except for cerebral oedema. She continued her treatment as an outpatient in a rheumatology clinic.

Discussion

Systemic lupus erythematosus (SLE) is an autoimmune disease,[12] with high incidence among young women of childbearing age,[13] it is characterized by a heterogeneous clinical manifestations and multiple organ involvement (dermatological, renal, neurological, haematological or rheumatologic). The onset of the disease can be insidious, making early diagnosis difficult[14,15] and mortality related to complication by SLE can be as high as 30 per cent per cent per cent many of them related to infections according to recent multicentre registries.[16,17] When SLE concomitantly appears associated to bacterial infections, clinician must have experience in order to differentiate between autoimmune disease activity *vs.* new activation of the autoimmune disease secondary to infection *vs.* infection itself.[18,19]

Factors that predispose to infections in patients with SLE have been well established and include the use of immunosuppressant, intrinsic dysregulation of the immune system, genetic factors and defects in humoral and cellular immunity,[20,21] so common pathogens as opportunistic infections must always be ruled out.[22] Several publications have demonstrated de relationship between SLE and infection by *N. meningitides* (Table 4), however, none of

these have demonstrated infection of the SNC as a marker of disease onset which could suggest somehow that bacterial infections by this type of Gram negative bacteria would be an initial trigger for the development of SLE in a previously healthy individual.

N. Mmeningitides is a Gram-negative, encapsulated, colonizing nasopharyngeal mucosa colonizer. Most invasive infections worldwide are caused by six groups A, B, C, W, X and Y[23] and hereditary complement deficiencies somehow increase susceptibility to meningococcal infections. However, it is still not clear if patients with acquired deficiencies (autoimmune diseases, dysfunction of reticuloendothelial system, functional asplenia, nephropathies or liver disease) are at higher risk of developing autoimmunity triggered by contact with this type of bacteria.[24-26] Among the complement deficiencies the most reported are those that are acquired and most of the time result in multiple defects in the complement cascade. However, scientific reports validate the fact that acquired defects in the complement system result in a higher risk for meningococcal infections as seen in patient with SLE disease.

Meningococcal infections have been reported to have a high correlation with deficiencies of C3, properdin/factor P and late components of the complement system.[27] Manifestations range from fever and bacteraemia to shock and death. The complement profile in patients with SLE resembles the profile found in patients with hereditary complement deficiencies, which have also a higher association with meningococcal infections. Immunoglobulin deficiency, defects in chemotaxis and phagocytic activity also play a role in increased susceptibility to infections. Although, complement deficiency in lupus is one of the most frequent abnormalities the reported cases are not numerous.[23,27]

Zenone et al.[23] and Dobos et al.[28] reported patients with SLE (without pharmacological therapy) had confirmed infection by *N. Meningitides* in their cohorts, suggesting that SLE patients are in an immunosuppression state even without the use of these group of drugs and complement deficiencies persist over time leading to an increase risk of infections by *N. meningitides* but also by other encapsulated microorganisms.[28,29]

The importance of this case relies in the clinical presentation, despite an adequate management for meningitis and pathogen isolation. This patient continued with neurological deterioration and CT brain findings were consistent with alteration seen commonly in vasculitis secondary to autoimmune disease. We considered that patients with complement deficiencies, active infections by Gram negative bacteria in the group of Neisseria and who do not response to antimicrobial therapy should be studied with an autoimmune panel.[30-32]

Conclusion

Infections in patients with SLE are related to a higher mortality (up to 30 per cent per cent per cent); it is necessary to have a high clinical suspicious in order to rule out hidden autoimmune pathologies in young patients with no clear risk factors and severe infections. This reports intents to present those patients whose humoral and cellular alterations in immunity can lead to severe, unusual and life-threatening conditions. Establishing and early and effective diagnosis leads to initiation of effective therapy for autoimmune diseases and subjacent infection leading to better survival rates among these group of patients.

References

1. Tsokos GC. Systemic lupus erythematosus. N Engl J Med. 2011;365:2110–21.
2. D'Cruz DP, Khamashta MA, Hughes GR. Systemic lupus erythematosus. Lancet. 2007;369:587–96.
3. Lisnevskaia L, Murphy G, Isenberg D. Systemic lupus erythematosus Lancet. 2014;384:1878–1888.
4. Urowitz MB, Gladman DD, Tom BD, et al. Changing patterns in mortality and disease outcomes for patients with systemic lupus erythematosus. J Rheumatol. 2008;35:2152–58.
5. Cervera R, Khamashta MA, Hughes GR. The euro-lupus project: epidemiology of systemic lupus erythematosus in Europe. Lupus. 2009;18:869–74.
6. Carrizosa JA, Aponte J, Cartagena D. Factors associated with mortality in patients with autoimmune diseases admitted to the intensive care unit in Bogota, Colombia. Front. Immunol. 2017;8:337.
7. Navarra SV, Leynes MS. Infections in systemic lupus erythematosus. Lupus. 2010;19(12):1419–24.
8. Cook HT, Botto M. Mechanisms of disease: the complement system and the pathogenesis of systemic lupus erythematosus. Nat Rev Pract Rheumatology. 2006;2(6):330–7.
9. Ho A, Barr SG, Magder LS. A decrease in complement is associated with increased renal and hematologic activity in patients with systemic lupus erythematosus. Arthritis Rheum. 2001;44:2350–2357.
10. Danza A, Ruiz-Irastorza G. Infection risk in systemic lupus erythematosus patients: susceptibility factors and preventive strategies. Lupus. 2013;22:1286–1294.

11. Feliciano R, Swedler W, Varga J. Infection with uncommon subgroup Y Neisseria eningitides in patients with systemic lupus erythematosus. Clin Exp Rheumatol. 1999;17:737–40.
12. Fessler BJ. Infectious diseases in systemic lupus erythematosus: Risk factors, management and prophylaxis. Best Pract Res Clin Rheumatol. 2002;16:281–291.
13. Firestein G, Budd R, Gabriell SE, et al. Kelly´s Textbook of Rheumatology 9th edn. Saunders; 2013.
14. Crow M. Systemic lupus erythematosus. In L Goldman, A Shafer, eds., Goldman-Cecil Medicine, 24th edn. 2016;2:1769–1777.
15. Thong B, Olsen N. Systemic lupus erythematosus diagnosis and management. Rheumatology. 2016;26:i3–13.
16. Thomas G, Mancini J, Jourde-Chiche N, et al. Mortality associated with systemic lupus erythematosus in France assessed by multiple-cause-of-death analysis. Arthritis Rheumatol. 2014;66:2503–2511.
17. Aponte J, Carrizosa J, Sanchez A, et al. Procalcitonin and eosinopenia as potential biomarkers of infection in critically ill patients with systemic lupus erythematosus. Lupus Sci Med. 2017.
18. Rúa-Figueroa I, López-Longo J. Incidence, associated factors and clinical impact of severe infections in a large, multicentric cohort of patients with systemic lupus erythematosus, Semin Arthritis Rheum. 2017;47:38–45.
19. Petri M. Infection in systemic lupus erythematosus. Rheum Dis Clinic NA. 1998;2:423–456.
20. Rúa-Figueroa I, Nóvoa J, García-Laorden MI, et al. Clinical and immunogenetic factors associated with pneumonia in patients with systemic lupus erythematosus: a case–control study. J Rheumatol. 2017;41:1801–1817.
21. Tsokos GC, Ballow JE. Cellular immune responses in systemic lupus erythematosus. Prog Allerg. 1984;35:93–t61.
22. Zandman-Goddard G, Shoenfeld Y. SLE and Infections. Clin Rev Allergy Immunol. 2003;25(1):29–39.
23. Zenone T, Sartre J, Gibert C, et al. Infection with Neisseria eningitides serogroup Y revealing systemic lupus erythematosus. Lupus. 2010;19:1676–1678.
24. Lewis L, Ram S. Meningococcal disease and the complement system. Virulence. 2014;5(1):98–126.
25. Iliopoulos AG, Tsokos GC. Immunopathogenesis and spectrum of infections in systemic lupus erythematosus. Semin Arthritis Rheum. 1996;25:318–36.
26. Ellison R, Kohler PF, Curd JG, et al. Prevalence of congenital or acquired complement deficiency in patients with sporadic meningococcal disease. N Eng J Med. 1983;308(16):913–6.
27. Ross SC, Densen P. Complement deficiency states and infection: Epidemiology, pathogenesis and consequences of neisserial and other infections in an immune deficiency. Medicine (Baltimore). 1984;63:243–273.
28. Dobos GJ, Meske S, Keller E, et al. Successful therapy of meningococcal sepsis in acute disseminated lupus erythematosus with plasmapheresis, immunosuppression, and antibiotics. J Mol Med. 1990;68:976–980.
29. Garty BZ, Nitzan M, Danon YL. Systemic meningococcal infections in patients with acquired complement deficiency. Pediatr Ailergy Immunol. 1993;4(1):6–9.
30. Mitchell SR, Nguyen PQ, Katz P. Increased Risk of neisserial infections in systemic lupus erythematosus. Seminars in Arthritis and Rheumatism. 1990;20(3);174–184.
31. Betrosian A, Balla M, Papanikolaou M, et al. Meningococcal purpura fulminans in a patient with systemic lupus erythematosus: a mimic for catastrophic antiphospholipid antibody syndrome? Am J Med Sci. 2004;327(6):373–375.
32. Royo – Villanova C, Cepeda J, Navarro V. Neumonía por neisseria eningitides en mujer de 47 años con lupus eritematoso sistémico. Enferm Infecc Microbiol Clin. 2001;19(4):188–9.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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PATIENT CONSENT

The authors, Aponte JE, Estupiñán MF, Díaz M, Hurtado D, Sanchez A, Ospina MT, Forero Y, Zambrano P, Zapata M, declare that:

1. They have obtained written, informed consent for the publication of the details relating to the patient(s) in this report.
2. All possible steps have been taken to safeguard the identity of the patient(s).
3. This submission is compliant with the requirements of local research ethics committees.

Table 1: Laboratory results

Blood count		**Renal function**	
Leukocytes	31.14×10*3/ul	**BUN**	66.7mg/dl
Lymphocytes	2.22×10*3/ul	**Creatinine**	1.54mg/dl
Neutrophils	27.81×10*3/ul	**Hepatic function**	
Monocytes	12×10*3/ul	**AST**	67UI/L
Haemoglobin	14.1g/dl,	**ALT**	34UI/L
Haematocrit	42.10%	**Reactive C protein:** 330mg/dl	
Platelets	132×10*3/ul	**HIV: Negative**	

Table 2: CSF analysis

Criteria	**Lumbar puncture no. 1**	**Lumbar puncture no. 2**
Aspect	Unclear	Clear
Glucose	1mg/d	38mg/dl
Proteins	89mg/dl	37mg/dl
Leucocytes/mm^3	9600 (Neutrophils 90%- Lymphocytes 10%	0
Red blood cells/mm^3	320	0
Serology VDRL	Non-reactive	Non-reactive
Fungus stain	Negative	Negative
Micobacterial stain	Negative	Negative
Gram stain	Diplococcus Gram negatives ++	Negative

Table 3: Immunological profile

C3	32.70mg/dl
C4	4.80mg/dl
Antinuclear antibodies (ANAS)	1/640 -
Antinuclear antibodies (ANAS)	1/640 - Centromeric pattern
Anti RO antibody	Positive

Table 4: Reported cases of *N. meningitidis* infection in SLE patients

Author	Age	Diagnosis SLE	Treatment	Features	Serum complement
Zenone et al. (23)	19 y/o.	Non-previous diagnosis	No treatment	Blood stream infection	C3=0.4g/L (0.75–1.4)
					C4=0.07g/L (0.1–0.34)
Feliciano et al. (11)	18 y/o.	5 y/o.	Prednisone 25mg. qd.	Tenosynovitis	C4=66U/mL (130-410U/ml)
	14 y/o.	14 y/o.	Prednisone 15mg. qd.	Meningitis	C3=52mg/dL.
			Hydroxychloroquine 400mg. qd.		C4=19mg/dL.
	24 y/o.	8 y/o.	Prednisone 15mg. qd.	Fulminant Meningococcaemia	C3=45 mg/dL.
			Hydroxychloroquine 400mg. qd.		C4=<10mg/dL.
			Azathioprine 50mg. qd.		
Dobos et al. (28)	17 y/o.	5 y/o.	No therapy in 3 years	Meningococcaemia	C3=0.74g/l (0.75–1.4)
					C4=0.21g/l (0.1–0.34)
Mitchel et al. (30)	19 y/o.	2 y/o.	Metilprednisone 4mg. qd.	Blood stream infection	C3=76mg/dL
					C4=9mg/dL
	24 y/o.	5 y/o.	Hydroxychloroquine plus salicylates	Septicaemia	C4 12 [nl>15mg/dL]
					C3 78 [nl>90mg/dL]
	18 y/o.	5 y/o.	Hydroxychloroquine plus prednisone	Meningitis	C3: 59mg/dL
					C4: 9mg/dl.
	17 y/o.	2 y/o.	Prednisone	Septicaemia	C3 55mg/dL
					C4 6mg/dL.
Betrosian et al. (31)	23 y/o.	2 years old	Prednisone 5mg. qd.	Purpura Fulminans	No reported
Royo– Villanova et al. (32)	47 y/o.	2 y/o.	Prednisona 5mg. qd.	Pneumonia	C3 69mg/dL
					C4 5.4mg/dL

Figure 1: Computed axial computed tomography scan of the skull. Hypertense lesion in left thalamic region (vasculitis) 1A. (Axial section) 1B. (Coronal section) 1C. (Sagittal section)