Transient neuropsychiatric lupus in an elderly man

John S. Pixley, M.D.

VA Sierra Nevada Health Care System and [1]University of Nevada School of Medicine

Abstract

Systemic lupus (SLE) is an inflammatory autoimmune disease with a strong female predominance. Its most severe forms usually occur in young women. We observed an elderly (72 year old) man with a past diagnosis of "bipolar illness" treated with lithium for > than 2 decades who presented with gradual and then profound cognitive decline. This was accompanied by fever and leukopenia including lymphopenia. As part of the "work-up' for dementia/delirium an antinuclear antibody (ANA) determination was found to be positive in high titer in a homogenous pattern. Imaging studies and a lumbar puncture were negative. The following laboratory values supported acute and chronic inflammation including immune complex deposition: 1) chronic inflammatory disease pattern (i.e. anemia of inflammation, low albumin and non-descript gamma fraction banding on serum electrophoresis), 2) elevation in sedimentation rate, c reactive protein and liver enzymes and 3) low serum C3.
The patient became unresponsive and steroid therapy was initiated. Over the next 4 weeks the patient's mental status normalized and laboratory parameters improved dramatically. Within 6 months on maintenance therapy with mycophenolate mofetil and hydroxychloroquine, he remained fully oriented and ANAs were not detected. He remains fully oriented with negative ANA determinations 2 years later.
Conclusions:

1. SLE should be included in the differential diagnosis for neuropsychiatric conditions such as bipolar disorder.
2. Imaging and lumbar puncture analysis may be negative despite profound "inflammation" of the nervous system.
3. Immune activation in SLE may be episodic and transient (likely 2 episodes over a 72 year life span).

American College of Rheumatology Criteria for diagnosis of SLE

Malar Rash
Discoid Rash
Photosensitive rash
Oral Ulcers
Arthritis
Serositis (pleuritis or pericarditis)
Renal Disorder (persistent Proteinuria or cellular casts)
Neurological disorder (seizures or psychosis)*
Hematologic disorder (hemolytic anemia, leukopenia or lymphopenia on two or more occasions, thrombocytopenia)*
An abnormal antinuclear antibody titer (ANA)*
Immunologic disorder
a) Anti- ds-DNA: antibody to native DNA in abnormal titer
OR
B) Anti-Sm: presence of antibody to Sm nuclear antigen
OR
c) False positive serologic test for syphilis
d) Positive finding of antiphospholipid antibodies based on an abnormal serum level of IgG or IgM anticardiolipin antibodies or a positive test result for lupus anticoagulant
The criteria may occur sequentially over time and need not be present simultaneously!
Bold type identifies criteria observed in this patient.

Autoantibody status

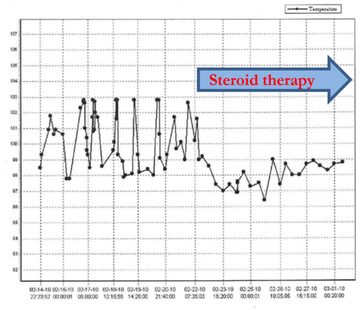
Prior to this hospitalization, there was no evidence that he suffered from a collagen vascular disease

The work-up for his deteriorating mental status to the point of unresponsiveness revealed no abnormal findings on MRI or lumbar puncture (MS panel / protein electrophoresis was not performed)
Elevation in the sedimentation rate prompted an anti-nuclear antibody determination.

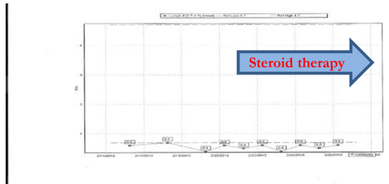
Results were as follows:
During hospitalization 1/5120 or 100 IU 1/2560 or 75 IU both homogeneous
1/640 or 50 IU homogeneous 1 month later
1/40 or 8 IU 6 months later
2 determinations 1 and 2 years after presentation were negative

Serial determinations of anti-SSA, SSB, RNP and ds-DNA have all been negative

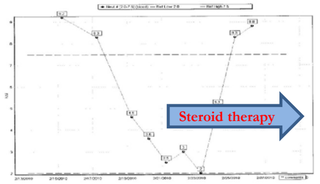
Body temperature during hospitalization



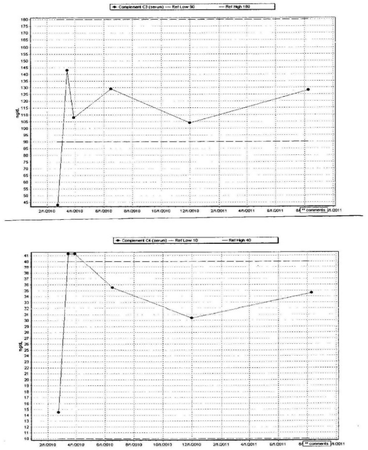
Peripheral lymphocyte count during hospitalization



Peripheral neutrophil count during hospitalization

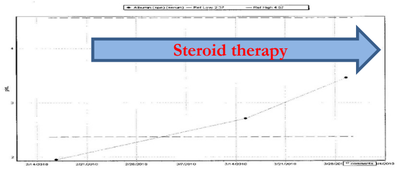


Serial serum complement determinations *



*Complement measurements are an indirect method to survey for immune complex deposition. In general complement components are synthesized in the liver, in inflammatory conditions such as this the liver increases synthesis of inflammatory proteins and decreases synthesis of albumin (i.e. the acute phase response". The serum protein electrophoresis confirmed the selective depression of serum albumin thus, the most likely reason for the depression in circulating C3 is consumption.
Note that while the C4 level was within normal limits it was markedly less than that noted after the patient recovered.

Serial serum albumin determinations



Neuropsychiatric syndromes observed in systemic lupus erythematosus (Ref 3.)

Central nervous system syndromes:
Aseptic meningitis
Cerebrovascular disease
Demyelinating syndrome
Headache (including migraine and benign intracranial hypertension)
Movement disorder (chorea)
Myelopathy
Seizure disorders
Acute confusional state
Anxiety disorder
Cognitive dysfunction
Mood disorder
Psychosis

Proposed mechanisms

Vascular abnormalities
- •Noninflammatory vasculopathy
- •Vasculitis
- •Thrombosis (Antiphospholipid syndrome*)
- •Leukoagglutination

Autoantibodies
- •Antineuronal antibodies
- •Antiribosomal P antibodies
- •Antiphospholipid antibodies

Inflammatory mediators
- •IL-2, -6, -8, and -10
- •Interferon-B
- •Tumor necrosis factor–B
- •Matrix metalloproteinase (MMP)–9
- •Complement mediated leukoagglutination**

* More likely associated with macrovascular complications (i.e. stroke)
** Possible explanation for drop in neutrophil count and low complements with diffuse CNS deterioration in our index patient

CONCLUSION

•Our understanding of central nervous system manifestations of systemic lupus remains incomplete.
•This is despite an American College of Rheumatology taskforce which developed classification criteria and case definitions for neuropsychiatric syndromes.
•As there is no diagnostic test(s), attribution of each CNS syndrome to SLE is based on clinical, laboratory and imaging criteria as occurred in this case
• 5 major publications have reported on a total of 683 of patients with SLE. While there was considerable variability in prevalence of CNS manifestations this was most attributable to "softer" manifestations such as headache and depression
•Main critique of the taskforce recommendations remains not including encephalopathy or encephalitis as a manifestation which we believe is ascribable to our index patient
•An intriguing possibility is that the previous psychotic manifestations for which patient was diagnosed with bipolar disorder were a consequence of central nervous system lupus that was not recognized.

References

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