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Delayed Diagnosis and Treatment of Systemic Lupus Erythematosus with a Psychiatric Presentation

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Glen Xiong, MD	BCBS Federal Employee Prog.	Consultant
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Patrick Romano, MD, MPH; Debra Bakerjian, PhD, APRN, RN; Noelle Boctor, MD; James Bourgeois, OD, MD for this Spotlight Case and Commentary have disclosed no relevant financial relationships

with ineligible companies related to this CME activity.

Learning Objectives

At the conclusion of this educational activity, participants should be able to:

- Describe the clinical manifestations of a primarily psychiatric presentation of systemic lupus erythematosus (SLE).
- Identify elements of the patient history that raise the probability of SLE in atypical psychotic disorder.
- Describe atypical features of primary psychotic illness that raise suspicion of SLE.
- Discuss the need for clear communication about clinical data between medical specialists.
- Appreciate that implicit bias (e.g., society stigma) about psychiatric illness may impact the degree of suspicion for psychiatric presentation of systemic illness.

The Case

An 18-year-old woman with no significant past medical history was admitted to a community hospital from a behavioral health center for evaluation and treatment of acute psychosis with paranoid delusions. The nurse practitioner managing the patient was uncertain as to whether the psychosis was due to a “primary” psychiatric condition (e.g., schizophreniform disorder, schizophrenia) or a systemic medical condition, so two consultations were obtained. On hospital day 5, a psychiatrist evaluated the patient and recommended initiation of an antipsychotic medication. On hospital day 7, the nurse practitioner learned from the patient’s father that there was a family history of systemic lupus erythematosus (SLE) and suggested that the patient be evaluated for lupus. Laboratory tests on hospital day 9 indicated borderline pancytopenia (e.g., platelet count 125,000/microliter), an elevated antinuclear antibody (ANA), and abnormally elevated anti-double-stranded DNA (deoxyribonucleic acid) (anti-ds DNA). The urinalysis, physical examination, and electrocardiogram were normal. The patient was discharged on hospital 10, but none of the treating physicians reviewed the test results until 2-3 days after discharge, and the patient was never referred for further evaluation of these findings.

The patient’s delusions and other psychotic symptoms abated over the following months, but she was admitted to a second hospital for exacerbation of psychotic symptoms six months after her first hospitalization. The medical team at this hospital quickly discovered the abnormal test results from six months earlier, documented the diagnosis of SLE, and initiated appropriate corticosteroid treatment. However, the patient died of multiple organ failure.

The Commentary

By James A. Bourgeois, OD, MD, and Glen Xiong, MD

This unfortunate case likely represented a presentation of psychotic illness as *forme fruste* or prodrome of systemic lupus erythematosus (SLE). Psychiatric prodromal states, wherein an initial “psychiatric” presentation heralds an *ultimate* course of relapsing, multisystem involvement, represent an accepted construct for multiple sclerosis and an emerging construct for SLE, based on recent research.[1,2,3] This

prodromal construct remains somewhat controversial, especially when the prodromal state primarily affects the central nervous system (CNS) and the full syndrome (as in SLE) more dramatically affects other organ systems. In SLE, the “primarily rheumatologic” full syndrome is not always clearly connected to a past psychiatric prodrome, and the psychiatric symptoms that patients experience when their multisystem illness is diagnosed can be attributed to a maladaptive emotional reaction to the diagnosis, rather than to CNS manifestations of SLE itself.

This is essentially a “lumper/splitter” argument. If one accepts that SLE is a centrally mediated, multisystem illness, it is reasonable to understand a psychiatric prodrome as heralding the initial onset of SLE with later, concurrent multisystem and CNS involvement attributable to the same underlying pathophysiology. The psychiatric prodromal concept also may lack predictive value, in that many patients (eventually) diagnosed with SLE or multiple sclerosis *may not*, in retrospect, have had a clear psychiatric prodrome. This case exemplifies the classic “zebra” in clinical diagnosis. Given the high prevalence of primary psychiatric conditions in young adults, it is difficult to estimate the posterior probability or likelihood of rare conditions that present with initial psychiatric symptoms in this population. Therefore, diagnostic and treatment approaches generally rely on expert clinical experience attuned to subtle atypical features rather than diagnostic protocols based on randomized controlled trials.

Psychotic illness that is *ultimately* attributed to schizophrenia, other psychotic disorders, and other “primary” psychiatric illnesses with psychotic features is far more common in the young adult population than a psychotic presentation of systemic illness. The differential diagnosis for psychiatric illnesses presenting as acute psychosis in young adult patients includes schizophreniform disorder, schizophrenia, brief psychotic disorder, major depressive disorder with psychotic features, bipolar disorder (major depressive or manic episode), substance-induced psychotic disorder, autistic disorder, intellectual disability, posttraumatic stress disorder, and borderline personality disorder. However, these diagnoses are established only after health professionals use the medical history, physical examination, laboratory testing, and imaging studies (if appropriate) to effectively rule out other causes of psychotic illness.

An important concept in the diagnosis of psychotic illness is “atypical features”, referring to psychotic symptoms that are not typical for schizophrenia or other “primary psychotic” illnesses. Psychotic presentations with *atypical features*, shown in **Table 1**, lead to greater suspicion of a systemic, rather than “purely psychiatric,” illness, but this combination of findings also lacks specificity in many cases. Presentations with atypical features should lead to a more thorough diagnostic work-up, potentially including neuroimaging, electroencephalography [EEG], robust laboratory assessment, and (in selected cases) cerebrospinal fluid [CSF] studies.[4]

Table 1. Psychotic Presentations with Atypical Features[4]

• Visual, olfactory, and/or tactile rather than auditory hallucinations • Prominent cognitive impairment • Concurrent motor signs • Catatonia • Atypical age of onset • Confusion • Disorientation	• Language disturbance • Misidentification delusions (Capgras syndrome) • Constitutional symptoms (e.g., significant weight loss) • Lack of family history of psychotic disorders • Lack of personal history of schizoid personality disorder

Source: Najjar et al. 2018

Neuropsychiatric SLE (NPSLE) is reported in 25-75% of SLE patients and may include cognitive impairment, headache, anxiety, depressed mood, psychosis, seizures, sleep disturbances, and abnormal movements. [4-7] This constellation of *multiple* CNS symptoms comorbid with psychosis, especially in a young patient with new-onset psychotic illness who may have a family history of SLE or other autoimmune disease, should increase the suspicion of NPSLE as the cause of first-episode psychosis.[4-7] Mechanistically, autoimmunity may be associated with antibodies to synaptic and neuronal cell membrane proteins (e.g., anti-*N*-methyl-d-aspartate receptor antibodies).[4] This complex presentation of multiple CNS findings in addition to psychosis would not be typical of primary psychotic illness (e.g., schizophrenia, schizophreniform disorder). NPSLE can also be classified into diffuse syndromes associated with the CNS (as above) and focal syndromes associated both with the CNS (e.g., cerebrovascular disease) and the peripheral nervous system (e.g., Guillain-Barre syndrome, myasthenia gravis).[6] NPSLE risk appears to be higher in early-onset SLE than late-onset SLE.[5,8] NPSLE symptoms may evolve over time, with systemic findings such as inflammatory skin lesions and hematologic abnormalities appearing later.[3]

The diagnostic challenge remains regarding how to work up first presentation of psychotic illness to assure that systemic illnesses presenting as a psychotic episode are fully considered, as clinical intervention is different for psychotic illnesses attributable to systemic illness. A *brief* list of other illnesses that can present as isolated psychosis include substance-related conditions; syndrome of inappropriate secretion of antidiuretic hormone (SIADH) with hyponatremia; liver disease (such as hepatitis B or C with cirrhosis and hepatic encephalopathy); hyper- or hypothyroidism; folate, vitamin B12, or vitamin D deficiency; various rheumatologic diseases; Wilson's disease; human immunodeficiency virus (HIV) disease; and neurosyphilis.[9-14]

The physical examination in this setting should include a full neurological exam, assessment of height and weight, and vital signs.[9] It is common and reasonable, although relatively low yield, to obtain unenhanced computed tomography (CT) of the head, but not contrast-enhanced CT or magnetic resonance imaging (MRI) for a first presentation of psychotic illness. In *established* psychotic illness, neuroimaging is not repeated at each exacerbation, particularly if the patient experiences stereotypical recurrences.

Similarly, several laboratory studies are routinely performed in this setting, as vitamin deficiencies and other metabolic and endocrine abnormalities can present with psychotic symptoms (**Table 2**). Other

laboratory studies can be ordered secondarily, depending on the clinical context of presentation.[9,10] More invasive laboratory studies, such as lumbar puncture for cerebrospinal fluid (CSF) studies, would not be routinely accomplished initially. While SLE with a psychotic prodrome is relatively well-known, but uncommon, routine testing for SLE-specific rheumatologic markers is not routine, nor is assessment for anti-NMDA-receptor encephalitis (ANMDARE) on initial evaluation. As SLE is highly heritable, once the family history of SLE was ascertained, the nurse practitioner appropriately obtained SLE-specific laboratory studies, with positive results.[7,8]

Table 2. Laboratory Studies for First Episode Psychotic Illness[9-14]

• Urine drug screen • Basic metabolic panel • Liver associated enzymes • Thyroid stimulating hormone • Vitamin B12 • Vitamin D • Folate • Antinuclear antibody (ANA) screen	• Ceruloplasmin • Erythrocyte sedimentation rate (ESR) • Human immunodeficiency virus • Antitreponemal IgG • Cerebrospinal Fluid analysis (ESR, cell count, and, when indicated, antineoplastic antibodies, limbic encephalitis antibody panels)

Source**:** Chapman et al., 2011; Dorney and Murphy, 2021; Esque et al., 2022; Kayster et al., 2010; Pollack et al., 2019; Skikic and Arriola, 2020.

The combination of a psychotic presentation with positive SLE-specific laboratory results is enough to conclude that this patient probably had SLE-related psychotic disorder, but the patient should then have promptly had CSF studies, MRI, and an urgent rheumatology consult for a trial of immunomodulation.[1] In such a case, immunomodulation (often with corticosteroids) may improve psychotic symptoms. Ironically, corticosteroids *themselves* (especially high dose prednisone) may improve the systemic manifestations but worsen the CNS disease, rendering the patient “systemically improved but psychiatrically worse”, at least temporarily.[15] Other immunomodulators may also be used in NPSLE just as in systemic SLE. High quality evidence for the optimal treatment approach is lacking.[16] Smoking may be associated with increased SLE disease activity, so smoking cessation is strongly encouraged.[3,7]

An empiric trial of antipsychotic pharmacotherapy would be typical in a case of this type, even with concurrent immunomodulation, though there would be uncertainty about whether any subsequent clinical improvement was attributable to the antipsychotic, immunomodulator, or both. If a patient with SLE-related psychotic illness has a robust treatment response, they may not need the several months of antipsychotic prophylaxis that would be routine in purely psychotic illness (e.g., schizophreniform disorder, schizophrenia). Antipsychotic treatment resistance is a common feature and should lead clinicians to look for additional CNS or systemic causes of new-onset psychosis. However, this patient did not demonstrate antipsychotic treatment resistance, providing another missed opportunity for timely diagnosis. More specifically, the CNS SLE abated with antipsychotic treatment, even without immunomodulation. There was apparently no other manifestation of CNS SLE such as CNS inflammation or systemic symptoms such as

headache, cognitive impairment, seizures, and stroke.

In the second clinical encounter, it appeared that a psychotic exacerbation occurred, but again systemic symptoms were not readily apparent. Despite the possibility of targeted treatment, the patient died suddenly of organ failure.

Approaches to Improving Patient Safety

The tragedy in this case is that there was clinical suspicion of SLE based on the family history, and at least initially appropriate screening laboratory studies were done and reported as positive. This profile would have obligated an urgent rheumatology referral and inpatient admission for CSF studies, MRI, and trial of immunomodulation. Close collaboration with consultation-liaison psychiatry would have been needed to manage antipsychotic medication, monitor for and manage delirium, and adjust psychotropic medications depending on the patient's response. It may well have been that this patient could have had a favorable result with this management plan. It is unclear why obviously abnormal laboratory studies were not acted upon to effectuate the needed rheumatology consult and urgent SLE work up.

Failure to follow-up on abnormal laboratory results is not an uncommon system or process error and can lead to dire consequences for patients. Automatic checks may be implemented in electronic health record (EHR) systems to ensure that laboratory results are reviewed (and marked as reviewed). If a critical laboratory result has not been reviewed within a certain time period, automatic prompts may be sent to the ordering physician as well as the primary physician of record.

In this case, the lack of apparent systemic symptoms and predominant presentation of psychosis reduced the likelihood of the patient seeking primary medical care. Finally, psychotic and cognitive symptoms may have also impaired the patient's ability to appropriately perceive subtle systemic symptoms. In this context, the lack of a primary care physician to coordinate post-discharge care may have contributed to the failure to follow up on abnormal laboratory tests.

Take-Home Points

- Systemic lupus erythematosus (SLE) involving the central nervous system can have a primarily psychotic presentation at illness onset.
- Psychotic presentation may be a prodrome for later presentation of full spectrum SLE.
- Psychotic presentations in patients with strong family history or personal history of SLE mandate appropriate laboratory screening and other interventions to rule in or rule out the diagnosis of SLE.
- Psychotic symptoms, even if attributable to SLE, can still respond to antipsychotic treatment but such patients still need full systemic disease workup and monitoring.
- Health systems should develop processes to facilitate timely follow-up on ordered tests with pending results, even after discharge.

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