Antinuclear Antibody-Negative Lupus Nephritis with Full House Nephropathy: A Case Report and Review of the Literature

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Key Words
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Abstract
Lupus nephritis (LN) is a serious and common complication of systemic lupus erythematosus (SLE) that predisposes to significant morbidity and mortality. Studies show that prompt diagnosis and treatment improves patient survival. We present a case of a 49-year-old female with an atypical presentation of LN who initially presented with new-onset hypertension, edema, arthritis, serositis and recently diagnosed leukocytoclastic vasculitis who later developed acute kidney injury, hematuria and nephrotic syndrome. Laboratory testing showed mixed cryoglobulinemia and elevated perinuclear anti-neutrophil cytoplasmic (p-ANCA) and myeloperoxidase (MPO) antibodies. SLE-related serologies were negative. Kidney biopsy showed diffuse proliferative global glomerulonephritis with a full-house nephropathy pattern on immunofluorescence suggestive of LN. Due to high clinical suspicion and renal biopsy findings, she was treated for LN with prompt renal response to immunosuppression. Cryoglobulins, p-ANCA and MPO titers normalized and the negative SLE serologies remained negative. Literature review on antinuclear antibody (ANA)-negative and seronegative LN revealed the following patient presentations: (1) renal-limited or renal and extra-renal manifestations of SLE with negative serologies and (2) renal and extra-renal manifestations of SLE with negative serologies at presentation who develop positive serologies later in follow-up. Both groups represent a unique and challenging cohort of patients who may require longer follow-up and further testing to rule out other glomerular diseases that may mimic LN on renal biopsy. The absence of SLE-related serologies should be weighed against a high pre-test probability of ANA-negative or seronegative LN. If highly suspected, the patient should be treated promptly with close monitoring.

Introduction
Renal involvement in systemic lupus erythematosus (SLE), also known as lupus nephritis (LN), is a serious relatively common complication, with up to 90% of SLE patients acquiring pathological, often irreversible, impairment in renal function [1–3]. One-hundred and 400 per 100,000 Caucasian and African-American women, respectively, develop SLE per year with the female to male ratio reported at 10–15 [1]. Between 23 and 60% of SLE patients will develop clinically-detected LN early in the course of disease. Depending on the length of follow-up...
time and patient ethnicity, this complication typically occurs within the first 3 years of SLE diagnosis [1, 4, 5]. Prompt diagnosis and treatment are critical for improvement in patient survival, as evidenced by marked improvement in 5-year survival rates from 44 to 95% over the last 50 years [6].

Patients with SLE do not always present with multi-organ clinical and laboratory findings simultaneously. A unique cohort includes patients with characteristic LN who lack clinical criteria of SLE, positive immunological serology for SLE (referred to as seronegative LN), or both. These patients may experience delay in accurate diagnosis and treatment, resulting in increased risk for progression to end-stage renal disease (ESRD). The purpose of this article is to present a case that prompted a literature review to better define these groups.

SLE, a serologically diverse, chronic autoimmune disease that can involve every organ is diagnosed after consideration of clinical, laboratory and pathological findings [7]. There are validated classification systems for lupus, including the revised American College of Rheumatology (ACR) criteria and the Systemic Lupus International Collaborating Clinics (SLICC) criteria; however, they are meant to be used for scientific purposes for clinical studies and not to diagnose SLE [8–12]. It is relevant to note, however, that the ACR guidelines included the following as qualifying immunologic criteria: antinuclear antibody (ANA), anti-deoxyribonucleic acid (anti-DNA), anti-Smith (anti-Sm) and antiphospholipid (abnormal anticardiolipin antibody, lupus anticoagulant, or a false-positive serologic test for syphilis) antibodies [11, 12]. The SLICC guidelines changed the requirement from the anti-DNA antibody to the anti-double-stranded DNA (anti-dsDNA) antibody, added positive anti-beta 2-glycoprotein I, low complement levels and a positive direct Coombs test as sufficient alternatives to the other antibodies, specified rapid plasma reagin (RPR) as the false positive test for syphilis and made immunologic criteria mandatory for diagnosis [7, 8, 13–16]. Because the SLICC, but not ACR, criteria relies on the presence of an immunologic finding for diagnosis, a seronegative LN may have qualified in clinical studies as SLE based on ACR criteria [8–12]. To add to the complexity of defining SLE in clinical practice, anti-Sjögren’s-syndrome-related antigen A (SSA) is not included as a qualifying serological test but is positive in 35–60% of SLE patients [13]. Other excluded antibodies may also be found including the anti-Sjögren’s-syndrome-related antigen B (SSB) and anti-U1 ribonucleoprotein (RNP) antibodies. Moreover, in clinical practice, the absence of antibodies does not rule out disease, as up to 5% of patients with SLE may be seronegative and diagnosis is made by the clinical and pathological presentation alone [17].

The 2 main types of renal injury identified on renal pathology are immune complex deposition disease as characterized by the known classifications of LN and non-immune complex disease, including thrombotic microangiopathy, podocytopathy and tubulointerstitial disease. Immunofluorescence (IF) is characteristic for the presence of the 3 classes of immunoglobulins (IgG, IgM, IgA) and classic and alternative complement pathway deposits (C3, C4, C1q) [1, 7, 16, 18–20]. Because of the widespread potential derangements, a renal biopsy is critical to making the clinical diagnosis, as the pattern of LN injury identified often dictates treatment course and prognosis.

The presentation of ANA-negative LN in clinical practice may occur. A high index of suspicion should therefore be present if clinical and pathologic findings support the diagnosis. We report a case that highlights these complexities in a woman not previously diagnosed with SLE.

Case

A 49-year-old female presented with a 3-month history of poor appetite, nausea, bloating, diffuse swelling and a resolving rash. Over the same time period, she experienced a 10-pound weight gain, positional chest pressure, gross hematuria and new-onset arthritis consisting of joint pain and swelling in the ankles along with arthralgias in the metacarpophalangeal (MCP) and interphalangeal (IP) joints. She denied fevers, infections, alopecia, headache, digital ulcers and discoloration of her fingers in the cold suggestive of Raynaud’s. Her past medical history included Grave’s disease treated with radioactive iodine 3 years prior, and she was maintained on chronic levothyroxine therapy.

One month before presentation to our facility, she underwent a skin biopsy for a raised, non-pruritic, erythematous rash that, per her report, started on the lower legs and spread to the bilateral upper extremities and chest. The biopsy revealed an IgM and IgG perivascular infiltrate on IF diagnosed as leukocytoclastic vasculitis. She was treated with a topical steroid initially but did not tolerate it, so she was started on colchicine therapy and experienced a partial response. Outside laboratory results at the time of the skin biopsy included a creatinine of 1.7 mg/dl (baseline creatinine within normal limits), albumin of 3.1 g/dl, total protein of 6.3 g/dl, albumin/creati-
nine ratio of 352 mg/g and a urinalysis revealed red blood cells (>60/hpf RBCs), urine protein of 100 mg/dl and 10–20/hpf white blood cells. No evaluation was pursued at the time, and the patient presented to our facility for a second opinion.

On physical examination, she was found to be hypertensive (179/92) with a weight of 86.5 kg above her baseline of 71.5 kg. Her heart was in normal sinus rhythm. She had bilateral pulmonary rates on auscultation of the lungs, diffuse edema in the upper and lower extremities and faint residual erythematous macules on the dorsal surfaces of the chest, upper arms, hands and feet. A second rash she described as hive-like, erythematous, itchy and painful, localized around her joints (MCP and IP joints), had resolved. There was no alopecia, oral ulcers, malar rash, pericardial rub, synovitis, palpable purpura or Raynaud’s phenomenon present.

Work-up revealed a widened cardiac silhouette on chest X-ray and an EKG revealed a low voltage waveform. An echocardiogram diagnosed a moderate-to-large pericardial effusion with a left ventricular ejection fraction of 48%. The right ventricle partially collapsed in early diastole, consistent with early tamponade physiology. Based on these findings, she was directly admitted to the hospital and 590 ml of transudative pericardial fluid were drained. The initial working diagnosis was an autoimmune disorder with associated renal failure.

Laboratory evaluation revealed the following pertinent findings: anemia (hemoglobin of 11 g/dl), hypokalemia (3.0 mmol/l), hypoalbuminemia (2.9 g/dl), acute kidney injury (creatinine 1.8 mg/dl), normal sedimentation rate, hyperlipidemia (triglycerides 237 mg/dl, LDL 181 mg/dl) and an absence of monoclonal protein abnormalities. A urinalysis showed grade 3 proteinuria, 3–10/hpf RBCs, 11–20/hpf WBCs and WBC clumps. No significant casts were noted and urine culture was negative. A spot protein-to-creatinine ratio was 10.4, and a 24-hour urine collection measured 9.0 g of protein. Diagnostic evaluation so far was suggestive of both nephritic and nephrotic syndrome in the context of pericarditis, rash and arthritis.

Autoimmune serological work-up ensued and included the following: low complement levels (C3: 37 mg/dl, C4: <6 mg/dl, total: <3 U/ml) and a negative ANA (checked 3 times by enzyme-linked immunosorbent assay (ELISA)), ANA human epithelial cells (HEp-2) substrate (checked twice), anti-dsDNA antibody (checked twice by ELISA), antibodies to extractable nuclear antigens (SSA, SSB, Sm, RNP, Scl-70, Jo-1; checked once), anti-cyclic citrullinated peptide antibody (checked once) and rheumatoid factor (checked once). A normal erythrocyte sedimentation rate (checked a total of 6 times) and C-reactive protein (checked 4 times) were found. Anti-neutrophil cytoplasmic antibodies (ANCA) by indirect IF revealed a perinuclear ANCA (p-ANCA) but no cytoplasmic ANCA pattern. Titers of myeloperoxidase (MPO) antibodies were 1.8 units (positive ≥0.4). Mixed cryoglobulins (type III: IgG and IgM) were weakly positive on day 1 of presentation to the hospital and negative when rechecked on days 2, 7 and 8. Human immunodeficiency virus and hepatitis screening tests showed no previous or current infections. The finding of hypocomplementemia in the setting of positive p-ANCA and equivocal MPO antibodies was unusual, and a clinical diagnosis to tie in her overall presentation was difficult to determine. Therefore, the next step in evaluation was to obtain a kidney biopsy.

The kidney biopsy showed diffuse proliferative global glomerulonephritis (GN) histologically resembling class IV LN, with the following findings: necrosis with fibrin deposition, crescents with proliferating cells, double-contouring of the basement membrane, endocapillary proliferation and capillary loop occlusion. There was a full-house nephropathy pattern in the mesangial and peripheral capillary loops on IF (equal positivity for IgA, IgG, IgM, C1q, C3, albumin, fibrinogen, kappa and lambda) with a granular appearance. Electron microscopy (EM) showed patchy foot process effacement, basement membrane remodeling and duplication, subendothelial, intramembranous and mesangial immune-complex deposits and rare subepithelial deposits. No vasculitis or thrombi were noted.

She received intravenous methylprednisolone pulse therapy for 3 days starting on the day of her kidney biopsy. Results of the IF and EM were delayed, and in light of the severity of her findings on light microscopy, the decision was made to proceed with treatment with oral cyclophosphamide for induction therapy for presumed either LN or renal vasculitis. Once the kidney biopsy findings were finalized, further serological evaluation for LN was obtained in light of the characteristic findings of LN noted on the biopsy and these included a reactive RPR IgM (1:4) with a negative syphilis IgG and a weakly positive anti-phospholipid (cardiolipin) IgM titer (25.4 MPL with <10.0 considered negative). She was thus diagnosed with LN with an initial presentation suggestive of ANA-negative LN and was treated per the ALMS protocol [6, 21]. She was transitioned to mycophenolate mofetil 3 grams per day for 4 months. However, due to profuse diarrhea complicated by severe hypokalemia attributed to...
mycophenolate mofetil, she was transitioned to an equivocal dose of mycophenolic acid which was continued for an additional 4 months. She completed a 6-month course of a tapering dose of prednisone.

At follow-up 7 months later, her blood pressure normalized while off anti-hypertensive agents. Her weight significantly improved and returned to baseline (71.5 from 86.5 kg). Her creatinine improved to 1.0 and a urine total protein to 1.8 g. The hematuria improved, and the complement levels as well as MPO titers normalized. The SLE-associated serologies that were initially negative remained negative.

Summary of Case Reports in the Literature on Seronegative LN

We performed an extensive review of the literature using the search terms: seronegative lupus, ANA-negative lupus, full house nephropathy, LN and SLE in Ovid MEDLINE. Out of 17 articles with potential cases, 8 were excluded for the following reasons: the sole laboratory testing method was no longer commonly used (such as lupus erythematosus cell preparations), serologies were positive initially on presentation, serologies became positive before treatment was initiated or this was unspecified and the types of serologies performed were not described. We found 9 articles with 55 cases of suspected ANA-negative or seronegative LN at the time of initial presentation to a physician. We divided these cases into subgroups, documenting follow-up periods with negative serologies and the duration to positive serologies: (1) LN with or without extra-renal manifestations with negative serology at both presentation and last follow-up (table 1) and (2) LN with or without extra-renal manifestations who were seronegative at presentation but who later developed positive serologies (table 2). The studies in the tables included both pediatric and adult patients with ages ranging from 5 months to 50 years [2, 22, 23]. One article was published in the 1970s, 2 in the 1980s, 1 in the 1990s and 5 after the year 2000.

A case series of an additional 14 pediatric cases (age range 1.5–13 years; mean and median follow-up: 24 and 14 months, respectively (range 6–84 months)) who tested negative for ANA and anti-dsDNA antibodies initially [25]. Two cases progressed to a diagnosis of SLE based on positive serology and/or development of extra-renal manifestations of SLE. Remaining cases were given a renal pathological diagnosis other than LN. Both case series included patients with nephrotic or nephritic features with full house nephropathy on renal biopsy on IF. In the pediatric case series, all but one received immunosuppression. Two patients had persistent proteinuria, one progressed to ESRD requiring renal transplant, and one died 7 months after initial presentation due to infectious complications [24].

Table 1 includes 10 cases from 6 articles [22, 23, 25–27]. Elapsed time at follow-up ranged from 2 months to 6 years with a mean of 23 months and a median of 19 months [2, 22–24, 26, 28, 29]. Renal pathology uniformly showed full-house nephropathy on renal biopsy on IF. Eight received documented treatment with immunosuppressant medications and 6 (60%) had documented resolution of their disease. In 4 patients, the abnormal renal clinical manifestations persisted [2, 23, 29]. One patient progressed to hemodialysis [23]. Patients with extra-renal symptoms often met ACR criteria, but no cases met SLICC criteria for SLE based on the lack of positive serology, taking note that extensive serological testing (anti-Sm, anti-phospholipid or Coomb’s testing) beyond ANA, anti-dsDNA antibodies and complement levels was not reported in most articles. Despite the lack of positive serologies, all but 2 cases received treatment soon after presenting for evaluation with good outcomes.

Table 2 describes 7 patients with ages between 8 and 28 years who developed positive serology after their initial presentation [24, 30, 31]. Time to positivity ranged from 5 months to 10 years (mean and median: both 6 years) [24, 30]. All recorded cases were found to have at least one immunoglobulin and complement protein detected on IF, with most meeting the criteria for full-house nephropathy. All patients received a form of immunosuppression. At follow-up, 3 patients had no clinical symptoms, 2 experienced improvement in their symptoms, 1 had persistent proteinuria and 1 progressed to ESRD and renal transplant.

Discussion

LN is a serious and frequent complication of SLE that can cause significant morbidity and mortality if left untreated [1]. Seronegative and ANA-negative LN cases
<table>
<thead>
<tr>
<th>Author</th>
<th>Cases (total in article)</th>
<th>Age, years</th>
<th>Initial negative lab tests</th>
<th>Initial clinical or pathology findings</th>
<th>Late clinical or pathology findings</th>
<th>Immunosuppressive treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adu et al. [22], 1983</td>
<td>2 (17)</td>
<td>23</td>
<td>ANA, ADNA, C3, C4, C4 IgG</td>
<td>Nephrotic syndrome, membranous and mesangial GN, immune deposits at multiple sites</td>
<td>ANA, ENA, C3, C4, C4 IgG, IgG, IgA, C3, C4</td>
<td>Pred 60 mg/m²/day for 3 doses → CYC 1 mg/kg/day, AZA 1 mg/kg/day</td>
<td>No extra-renal manifestations negative after 2–6 years</td>
</tr>
<tr>
<td>Enriquez et al. [26], 1988–1989</td>
<td>3 (3)</td>
<td>22 months</td>
<td>ANA, ENA, C3, C4, C4 IgG</td>
<td>Anasarca, nephrotic syndrome thought to be idiopathic minimal change disease</td>
<td>ANA, ENA, C3, C4, C4 IgG, C3 C4</td>
<td>Pred 60 mg/m²/day → AZA 60 mg/m²/day, CYC 1 mg/kg/day</td>
<td>Nephrotic syndrome resolved 19 months out</td>
</tr>
<tr>
<td>Cobeñas et al. [2], 2003</td>
<td>1 (1)</td>
<td>5 months</td>
<td>ANA, DNA, ANCA, anti-phospholipid antibodies, anti-Sm, anti-RNP, anti-SSA, anti-SSB, anti-histone antibodies, Coomb's test</td>
<td>Malaise, pallor, purpuric rash, ITP, Coombs negative anemia</td>
<td>ANA, DNA, ENA, C3, C4 IgG, C3 C4</td>
<td>Pred → MPP, IVIG → Pred → Pred, CYC → AZA</td>
<td>Proteinuria resolved for 1 year at last follow-up</td>
</tr>
<tr>
<td>Kim et al. [20, 29], 2009</td>
<td>1 (1)</td>
<td>16 months</td>
<td>ANA, anti-dsDNA, ENA, anti-phospholipid antibodies, anti-cardiolipin Ab, lupus anticoagulant, anti-RNP, anti-Sm, anti-Ro, anti-LA, RF</td>
<td>Arthritis, rash, photosensitivity, synovitis, lymphopenia, mild pericardial effusion, leukocytoclastic vasculitis without immune deposits on skin biopsy</td>
<td>ANA, DNA, C3, C4 IgG, IgM, IgA, C3, kappa, lambda</td>
<td>Pred 1 mg/kg/day × 1 month tapered over 7 months → Pred, CYC → MMF</td>
<td>Symptoms resolved, serologies remain negative at 2 years</td>
</tr>
<tr>
<td>Huerta et al. [23], 2012</td>
<td>2 (4)</td>
<td>50</td>
<td>ANA, anti-DNA, C3, C4 IgG, IgM, IgA, C1q, C3, kappa, lambda</td>
<td>Edema, nephrotic syndrome, hematuria, hypertension, renal insufficiency</td>
<td>ESR, proteinuria</td>
<td>Pred, CYC (did not tolerate CYC) → MMF</td>
<td>HD-dependent 5 months after treatment, serologies negative after 8 months</td>
</tr>
<tr>
<td>Elcioglu et al. [19, 28], 2014</td>
<td>1 (1)</td>
<td>48</td>
<td>ANA, anti-dsDNA, RF, anti-CCP, ANCAs, anti-RNPs, anti-SSA, anti-SSB, anti-Sm, anti-cardiolipin antibodies</td>
<td>Arthritis, fatigue, weight loss, scalp lesions, growth retardation, posterior subcapsular cataracts</td>
<td>ANA, anti-dsDNA, RF, anti-CCP, ANCAs, anti-RNPs, anti-SSA, anti-SSB, anti-Sm, anti-cardiolipin antibodies</td>
<td>Pred, salazopyrin, MPP (for presumed seronegative rheumatoid arthritis) → HCQ 400 mg/day × 3 days, Pred, CYC 1 mg/kg/day × 1 day → MPP 48 mg/day × 68 days</td>
<td>Remission after 3 months, symptoms resolved and uric acid normalized at 3 months</td>
</tr>
</tbody>
</table>

*Age in years unless otherwise specified.

CIC = Circulating immune complexes measured by C1q solid-phase binding assay, PRED = prednisone, CYC = cyclophosphamide, AZA = azathioprine, VDRL = venereal disease research laboratory test, ITP = idiopathic thrombocytopenic purpura, MPP = methylprednisolone pulse therapy, IVIG = intravenous immunoglobulin, HD = hemodialysis, MMF = mycophenolate mofetil, HCQ = hydroxychloroquine.
<table>
<thead>
<tr>
<th>Author</th>
<th>Cases</th>
<th>Age, years</th>
<th>Initial clinical or lab findings</th>
<th>Initial negative lab tests</th>
<th>IF</th>
<th>Late clinical findings</th>
<th>Late (+) serology</th>
<th>Time to (+)</th>
<th>Immunosuppressive treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cairns et al. [30], 1979</td>
<td>3 (11)</td>
<td>19</td>
<td>Nephrotic syndrome, acute renal failure</td>
<td>ANF, LE prep</td>
<td>IgA, IgM, C3 then IgG, C1q, C3, C4</td>
<td>Proteinuria</td>
<td>ANF, CH50, C3, anti-DNA (borderline)</td>
<td>6 years</td>
<td>Steroids, AZA</td>
<td>No clinical symptoms, positive serology</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td></td>
<td>Nephrotic syndrome</td>
<td>ANF</td>
<td>Third biopsy: IgM, C4, IgA, IgG, C3, C1q</td>
<td>Proteinuria</td>
<td>ANF, anti-DNA, low CH50</td>
<td>5 months</td>
<td>Steroids</td>
<td>Proteinuria persisted</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td></td>
<td>Idiopathic glomerular disease</td>
<td>ANF, anti-DNA, complement</td>
<td>IgM, C3</td>
<td>Unknown</td>
<td>ANF, low CH50, anti-DNA</td>
<td>5–6 years</td>
<td>Steroids</td>
<td>No clinical symptoms</td>
</tr>
<tr>
<td>Gianviti et al. [24], 1999</td>
<td>3 (17)</td>
<td>9</td>
<td>Proteinuria, hematuria, acute renal failure</td>
<td>ANA, anti-dsDNA, complement, anti-U1 RNP, anti-cardiolipin, anti-U1 RNP, anti-Sm, anti-SSB, anti-SSA, anti-Scl-70, PCNA, anti-Jo-1</td>
<td>IgG, IgA, +/- IgM, C1q, C3</td>
<td>Renal failure → fever, arthralgias, asthenia, hemolytic anemia, thrombocytopenia</td>
<td>ANA, dsDNA</td>
<td>5 years</td>
<td>MPP 15 mg/kg/day × 3 days → PRED 2 mg/kg/day × 1 month tapered to 0.5 mg/kg qd × 4 months, CYC 2 mg/kg/day × 9 weeks → PRED 1 mg/kg/day</td>
<td>Renal transplant 7 years after diagnosis with positive serology at 9 years post-diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Autoimmune thrombocytopenia, hemolytic anemia → nephrotic syndrome, direct Coombs (+)</td>
<td>Coomb’s positive, ANA, anti-dsDNA, complement, anti-cardiolipin, anti-U1 RNP, anti-Sm, anti-SSB, anti-SSA, anti-Scl-70, PCNA, anti-Jo-1</td>
<td>IgG, IgA, +/- IgM, C1q, C3</td>
<td>None</td>
<td>ANA, dsDNA</td>
<td>4–8 years</td>
<td>MPP 15–20 mg/kg/day × 3 days → PRED 1 mg/kg/day × 2 months then 0.3–0.5 mg/kg qod, chlorambucil 0.2 mg/kg/day × 6 months</td>
<td>Nephrotic syndrome resolved with positive serology at 7 years</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td></td>
<td>Proteinuria, hematuria</td>
<td>ANA, anti-dsDNA, complement, anti-cardiolipin, anti-U1 RNP, anti-Sm, anti-SSB, anti-SSA, anti-Scl-70, PCNA, anti-Jo-1</td>
<td>IgG, IgA, +/- IgM, C1q, C3</td>
<td>None</td>
<td>ANA, dsDNA, U1-RNP (1400)</td>
<td>10 years</td>
<td>CYC 2 mg/kg/day × 2 months, PRED 0.4 mg/kg/day × 1 month then 0.5 mg/kg qd × 3 months → PRED 1 mg/kg/day × 1 month then 0.5 mg/kg qd, AZA 2 mg/kg/day</td>
<td>No clinical symptoms, serologies remained positive at 10 years</td>
</tr>
<tr>
<td>Ozdemir et al. [31], 2005</td>
<td>1 (1)</td>
<td>28</td>
<td>Oliguria, edema, hypertension, pulmonary congestion, ascites, anemia, renal insufficiency, nephrotic syndrome</td>
<td>ANA, anti-dsDNA, C3, C4, p-ANCA, c-ANCA, immunoglobulin</td>
<td>IgA, IgM, IgG, C1q, C3, fibrin</td>
<td>Fever, pulmonary infiltrates, renal failure</td>
<td>ANA Not specified</td>
<td></td>
<td>PRED → MPP, CYC</td>
<td>Proteinuria and renal function improved, serology became positive, follow-up period not specified</td>
</tr>
</tbody>
</table>

ANF = Anti-nuclear factor; AZA = azathioprine; PCNA = proliferating cell nuclear antigen; MPP = methylprednisolone pulse therapy; c-ANCA = cytoplasmic ANCA; PRED = prednisone; CYC = cyclophosphamide.
pose a significant challenge to prompt diagnosis and treatment [6]. Our literature review revealed that LN can present without positive SLE serologies and may or may not convert to positive ones in the immediate follow-up period. One must not rely on serologies or ACR or SLICC classification criteria to establish the diagnosis of LN. Recognizing the variable presentation of LN is important in order to ensure prompt treatment, noting that serological manifestations of SLE in some patients may develop years after onset of LN.

Our patient presented with simultaneous renal and extrarenal manifestations of SLE. Her initial evaluation was negative for commonly present serologies of SLE such as ANA (by both ELISA and IF HEP-2 substrate), anti-dsDNA and anti-Sm. It was not until the kidney biopsy confirmed the suspicion of LN that further serologic testing for SLE to include an antiphospholipid antibody was obtained. Therefore, after extensive serological evaluation, she met SLICC and ACR classification criteria for SLE. The equivocal vasculitis serologies and positive mixed cryoglobulinemia, which can be present in SLE patients, were red herrings and challenged the unifying diagnosis of SLE at the time of clinical presentation [32]. While the serological testing was suggestive of the possibility of ANCA- or cryoglobulin-associated vasculitis, characteristics findings for these diseases was lacking on renal biopsy. Specifically there was no evidence of intraluminal thrombi on light microscopy or ‘fingerprint’ pattern of cryoprecipitates in the subendothelial deposits on EM, and the full-house nephropathy finding was inconsistent with ANCA associated renal vasculitis. For these reasons, the kidney biopsy was paramount to rule out other possible disease processes to facilitate prompt initiation of correct treatment for LN.

LN is heavily dependent on the development of systemic autoimmunity. The degree of immunological dysregulation is determined by a multitude of genetic variants and environmental triggers such that each patient with LN may have their unique genetic predisposition that determines disease onset and clinical manifestation [33]. This may explain the heterogeneous manifestations of LN as highlighted by the results of the literature review reported here.

In the cohort of patients with clinical and pathological evidence of LN with absent serologies at presentation and at last follow-up (table 1), 40% were in the pediatric population (age range 22 months–4 years). One might postulate that, for that cohort, longer follow-up is needed to monitor for development of positive serologies later in life. Alternatively, it is possible that the pathomechanism of autoimmunity in SLE is different in the pediatric population. In adults with seronegative LN and absent extrarenal manifestations, some have advocated that other disease processes that present as full-house nephropathy on renal biopsy should be considered. These include IgA nephropathy, post-infectious GN, idiopathic membranous, C1q nephropathy and membranoproliferative GN [25, 34, 35]. For these patients, further diagnostic testing may be needed to assist in clinical diagnosis. Ultimately, treatment response may be the only indicator that a diagnosis other than LN may be at play.

Only 3 patients were identified in the literature with renal and extra-renal manifestations and absent serologies for SLE [2, 28, 29]. One was a pediatric patient and the other 2 were adults. One patient had follow-up at 2 months, one at 2 years and follow-up was not reported for the third. This presentation appears rare and longer follow-up while on decreased or absent immunosuppression may be needed to evaluate for development of positive serologies. Development of positive serologies may be delayed by up to 10 years (table 2). When the severity of autoimmunity leads to systemic involvement, it is likely inevitable that positive serologies will become apparent once the disease activity is no longer suppressed. Because SLE involves chronic auto-reactivity of T and B cells, the loss of self-tolerance is always present and therefore detectable positive serologies may only be present in some patients when there is uncontrolled disease activity.

Auto-antibodies have been heavily utilized for screening for and diagnosis of SLE [17]. However, individuals without SLE can test positive for ANAs: 32% at a 1:40 titer and 5% at a 1:160 titer [1, 9]. In the absence of clinical or pathological evidence of the disease, however, SLE diagnosis cannot be made. Auto-antibodies may indeed be present and contribute to the formation of immune complexes, but they may not be detected with current standard tests [17, 20]. Partly because of this, complement levels were incorporated in the SLICC guidelines as evidence of downstream deleterious effects of immunoglobulin activation of the complement pathway [8, 36]. One report implied that in severe nephrotic syndrome, antibodies may be absent due to urinary losses [37].

With the advent of new therapeutic approaches for the management of SLE, 5-year survival rates have improved from 44% in the 1950s to at least 95% in the 2000s [6, 38]. Of those diagnosed with class IV LN, 17% were alive at the 5-year mark in the 1950s compared to 90–95% in the 2000s. The incidence of LN and subsequent ESRD, how-

ANNA-Negative LN

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ever, has not changed significantly, and current established treatment approaches have not shown significant change in the degree of renal remission. Management of patients with LN and absent SLE diagnosis is therefore extremely challenging, considering that LN treatment trials only enrolled patients with clinical diagnosis of SLE based on ACR criteria. For this reason, prompt recognition of LN and maintaining a high level of suspicion for LN in patients who lack positive serologies of SLE is of paramount importance in order to ensure early treatment and adequate monitoring and follow-up.

It should be noted that this review was limited by the variable serology performed and reported in the literature, thereby resulting in a lack of knowledge of or lack of confirmation of SLE with additional serological tests. Because of the large number of available tests and lack of standardization for testing beyond the routine antibody screens, we predict some variability in serological reporting to continue.

References


Conclusion

Our case report highlighted the clinical conundrum of a patient presenting with arthritis, serositis and renal failure with many negative serologies classically associated with SLE and LN. The kidney biopsy showed diffuse proliferative GN and a full house nephropathy pattern consistent with LN. Prompt treatment led to early remission. The literature review highlighted the variable presentation of LN and emphasized 2 cohorts of patients, one with LN with or without extra-renal manifestations of SLE and negative serologies and the other with renal and extra-renal manifestations who developed positive serologies later in follow-up. If there is a suspicion for LN, a lack of SLE antibodies on standard testing should be weighed against the pre-test probability of seronegative or ANA-negative LN. If highly suspected, the patient should be treated promptly and appropriately with close monitoring.


