# Key Clinical Message

When SLE-like lab results (e.g., positive anti-dsDNA, low C3) are inconsistent with physical findings, such as the absence of arthritis or nephritis, clinicians should consider diagnoses like Wilson's disease, especially in the presence of abnormal liver function and elevated INR.

**Keywords:** Wilson's Disease,Systemic Lupus Erythematosus, Hepatomegaly, Pancytopenia, Liver Injury

# 1. Introduction

Wilson's Disease (WD) is a rare autosomal-recessive disorder characterized by defective copper metabolism. Copper accumulation starts at birth, and patients usually become symptomatic in adolescence or early adulthood. Symptoms arise due to copper buildup in various organs, particularly the liver and brain 1.

Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune disease that can affect any organ. It is also known as the "Great Imitator" 2 due to its vast variability in presentations, signs, and symptoms. Despite significant research, the diagnosis and management of SLE remain complex and challenging. It can manifest in a wide array of clinical forms, ranging from mild fatigue to severe complications such as acute kidney injury, psychosis, and seizures 3.

Our patient was referred to the rheumatology clinic because of positive paraclinical tests for SLE, pancytopenia, elevated liver enzymes, and fatigue, which can all be seen in possible cases of SLE.

# This case report underscores the diagnostic complexities when distinguishing Wilson’s Disease (WD) from Systemic Lupus Erythematosus (SLE), particularly in patients presenting with hepatic and hematologic abnormalities commonly associated with both conditions.

# 2. Case History

A 19-year-old girl with no significant previous medical history except for a low mood and depression, with a suicide attempt six months prior, medication use, or illicit drug use, was referred to an internist due to a two-year history of fatigue, asthenia, easy bruising, and occasional epistaxis. These symptoms had been gradually worsening over the past six months. She had no significant family history among her first- and second-degree relatives, and her parents were not related. Routine tests revealed pancytopenia (White Blood Cell = 3.3×10^9/L, Red Blood Cell = 3.8 × 10^12/L, Hb = 10.9 g/dL, and Platelets = 59×10^9/L), normal serum creatine level of 0.9 mg/dL (normal range = 0.6-1.3), elevated liver enzymes (AST = 214 U/L [normal range: up to 38], ALT = 196 U/L [normal range: up to 31], ALP = 442 U/L [normal range: up to 480]), total bilirubin of 3 mg/dL, direct bilirubin of 1 mg/dL, and LDH of 418 U/L [normal range: up to 480], along with disturbed coagulation tests (PTT 49.4 s [normal range: 25-35], INR 1.52, PT = 22.4 s). She and her parents had no history of jaundice.

The conjugated hyperbilirubinemia increased AST and ALT, and normal ALP suggested hepatocellular damage. Considering her age, the internist ordered a viral hepatitis panel (Anti-HAV, HBc Ab, HCV Ab, HBs Ag) and markers for rheumatologic diseases and autoimmune hepatitis. The viral panel results were negative, but FANA, Anti-Ro, and Anti-CCP were positive, while AMA was negative. She had an RF (55 IU/mL [normal range: up to 20]) and ESR (20 mm/h), with CRP within the normal range (0.2 mg/dL [normal range: up to 6]). Urinalysis showed no hematuria or proteinuria. The internist referred the patient to the rheumatology clinic of Ghaem Hospital for further investigation.

Except for fatigue, her physical examination and history-taking revealed no significant findings. There was no history of arthritis, arthralgia, seizures, malar rash, skin lesions, or morning stiffness. The physical examination was normal; no findings suggested SLE or Rheumatoid Arthritis (RA). The pull test was negative, and no mouth ulcers were found.

Considering her coagulation disturbances, positive ANA profile, high liver enzyme levels, and history of easy bruising and epistaxis, the rheumatologist requested another CBC and ANA profile, serum levels of C3 and C4, ASMA, anti-LKM1, P-ANNA, liver and spleen sonography, and a liver coagulation panel (factors VIII, IX, X, and XI activity levels). The results showed a negative anti-dsDNA and Anti-Ro, low C3 serum level, normal C4 serum level, and confirmed pancytopenia (WBC = 1.7×10^9/L, RBC = 3.7 × 10^12/L, Hb = 10.5 g/dL, Platelets = 59×10^9/L) and elevated liver enzymes (AST = 218 U/L, ALT = 180 U/L, ALP = 201 U/L). While Anti-CCP, RF, ASMA, anti-LKM1, and P-ANNA were negative. Abdominal sonography showed hepatomegaly with coarse and heterogeneous echogenicity and splenomegaly with normal echogenicity. The activity levels of factors IX, X, and X1 were low, while factor VIII had a high activity level with no response to the mixing test. Serum protein electrophoresis showed low albumin and increased IgG levels (Figure 1).

**Figure 1. Serum Protein Electrophoresis shows an Increase in γ Band and a Decrease in Albumin Level**

Due to her physical examinations and lab data incompatibility, the rheumatologist admitted the patient to the rheumatology ward for further investigations.

# 3. Methods

She received Prednisolone 1 mg/kg/day and IVIG for six days.However, her pancytopenia and high liver enzyme levels did not improve. To rule out cirrhosis, an abdominal CT scan with and without injection and Color-Doppler ultrasound of the portal vein was performed. An endoscopy was also performed to check for esophageal varices; no varices were found. The Color-Doppler ultrasound showed no thrombosis, normal blood flow, and portal vein diameter. The abdominal CT scan showed hepatomegaly with heterogeneous parenchymal density, an enlarged spleen with normal density, and several lymphadenopathies in para-aortic and retrocaval regions, suggesting lymphoma (Figure 2).

**Figure 2. Axial Non-contrast CT scan with Mildly Heterogenous Liver, which appears Normal on the Post-contrast Image with Enlargement of the Spleen**

However, the patient had no history of B symptoms (unintended weight loss, low appetite, or night sweats), and Peripheral Blood Smear (PBS) showed no abnormal white blood cells. Bone marrow aspiration showed normal bone marrow activity, suggesting peripheral pancytopenia.

On the seventh day of her admission, she became gradually agitated and aggressive, had a generalized tonic-clonic seizure, experienced a decrease in consciousness level, and went into a coma (GCS = 3), leading to immediate ICU admission. The vital signs were normal. Her pulse rate was 80/min. Her respiratory rate was 22/min. Her blood pressure was 126/71 mmHg, and her body temperature was 98º F. Her oxygen saturation was 98% on room air. Lab data showed within normal range serum electrolytes (Na = 138 [normal range: 135-145 mEq/L] K = 3.7 [normal range: 3.5-5.3 mEq/L]) and a mild respiratory alkalosis (pH = 7.49, pCO2 = 29 mmHg and HCO3 = 23.3). A brain CT scan showed effacement and slit in both lateral ventricles with brain edema and no mass lesion, prompting an MRI due to her acute condition.

A neurology consult requested a brain MRI with and without injection and MRV, revealing hypersignal intensity in both globus pallidi on T1-weighted images without enhancement and restriction, compatible with toxic or metabolic encephalopathy (Figure 3). Noabnormality was seen after the GD injection. MRV showed no thrombosis and was reported as normal.

**Figure 3. Symmetrical High T1 Signal is seen within the Bilateral Globus Pallidi with a Normal Appearance on T2W Images.**

Ophthalmologic examination was negative for Kayser-Fleischer rings or Sunflower cataracts.

After correcting the INR with vitamin K and receiving multiple FFP and platelet transfusions, a lumbar puncture to rule out septic meningoencephalitis, including TB and HSV PCR, was performed and came back negative. Given the paraclinical results indicating hepatic encephalopathy, she was listed for a liver transplant and was treated with mannitol and lactulose in the ICU. She fully recovered and became conscious and oriented after 24 hours. A liver biopsy revealed nodular liver and fibrosis with portal and lobular inflammation, suggesting metabolic disorders such as Wilson's Disease or autoimmune hepatitis (Figure 4).

**Figure 4. The patient’s Liver Biopsy showed Nodular Liver and Fibrosis with Portal and Lobular Inflammation**

Further copper concentration measurement in the liver biopsy showed a high level of copper (260 µg/g dry weight [normal range: up to 50 µg/g]). Serum ceruloplasmin was low (157 µg/dL [normal range: 204-407]), and 24-hour urine copper excretion was high (168 µg/24h [normal range: 15-70 µg/24h]), confirming Wilson's Disease.

# 4. Conclusion and Results

Following the confirmation of Wilson’s Disease, treatment was initiated with zinc sulfate (25 mg three times daily) and Trientine (1250 mg/day) to reduce copper accumulation and promote its excretion. The patient's pancytopenia and coagulation abnormalities showed progressive improvement, indicating a favorable response to treatment (WBC = 6.28×10^9/L, RBC = 3.47×10^12/L, Platelets = 70×10^9/L, PT = 34s, PTT = 35, INR = 1.11) and her liver enzymes began to normalize (AST = 33 U/L, ALT = 110 U/L, ALP = 498 U/L). She was discharged five days later with a good general well-being. During her regular examinations, she showed significant improvement.

# 5. Discussion

This case report describes a 19-year-old female initially suspected to have Systemic Lupus Erythematosus (SLE) due to her symptoms of fatigue, pancytopenia, elevated liver enzymes, and positive autoimmune markers. However, further investigations revealed Wilson's Disease (WD) as the correct diagnosis, highlighted by abnormal liver biopsy findings, high hepatic copper content, low serum ceruloplasmin, and elevated 24-hour urine copper excretion.

Wilson's Disease primarily targets the liver and brain, similar to SLE, which can present with neurological and hepatic manifestations 1,3.

While the involvement of SLE in the onset of asymptomatic liver disease remains a topic of debate, many experts acknowledge that SLE frequently results in subclinical liver dysfunction, referred to as lupus hepatitis. This condition is a nonspecific reactive liver disease, primarily driven by complement deposition and vasculitis-induced damage to the liver. Research indicates that hepatomegaly is present in about 20-40% of SLE patients and is often associated with autoimmune hepatitis, lupus hepatitis, or drug-induced liver injury. However, hepatomegaly is relatively uncommon in SLE and typically signals the coexistence of autoimmune or drug-induced hepatitis 4.

In this case, specific clinical and laboratory findings did not match with SLE or autoimmune hepatitis. Although Prothrombin Time (PTT) can be abnormal in SLE, the presence of high INR, along with a coarsely enlarged liver 5,6, led the rheumatologist to lean more toward a liver injury rather than SLE: the negative AMA, ASMA, and P-ANNA. Anti-LKM1, coupled with no response to corticosteroids, significantly lowered the probability of autoimmune hepatitis 7.

This case presented several diagnostic pitfalls. Positive ANA and RF can also be seen in WD, but anti-Ro antibodies and low C3 levels are not typically reported in WD 8 and mislead the diagnosis. The absence of Kayser-Fleischer rings in the eyes, a hallmark of WD 1, was another diagnostic challenge. Additionally, symptoms like pancytopenia, fatigue, and a history of depression are common in both WD and SLE, complicating the diagnosis further 1,9. Moreover, the patient's age (19 years) posed a diagnostic pitfall since the onset of both diseases typically occurs in early adulthood . Anti-Ro (SSA) antibody is associated chiefly with Sjögren's syndrome. It can also be found in SLE and other rheumatic diseases but can be positive, especially in low titers in approximately 15% of healthy individuals. False positives are less common but still can occur 10.

Low complement levels, particularly C3, in SLE, are primarily due to immune complex formation that activates and consumes complement proteins, and they are mainly suggestive of high disease activity 11. However, complement levels can also be reduced due to liver dysfunction, as the liver synthesizes these proteins, a key pathology in Wilson’s Disease (WD) 12. In the absence of SLE symptoms and signs of high activity, such as lupus nephritis or arthritis, other mechanisms, including liver dysfunction, should be considered. It is crucial not to attribute low complement levels solely to autoimmune processes in the absence of signs and symptoms of SLE.

Several case reports have documented the overlap of SLE and WD, complicating the diagnosis and treatment strategies. For instance, Hadef et al. reported a case of a 12-year-old boy with concurrent WD and SLE, where both conditions were diagnosed simultaneously. The patient initially presented with hemolytic anemia and impaired liver function, leading to the suspicion of WD. Further investigations confirmed both WD and SLE, and the patient responded to treatment with corticosteroids and chelation therapy 13​​.

Zhang et al. described a 35-year-old woman with SLE who was later found to have WD during her routine follow-up due to unexplained liver fibrosis. Genetic testing confirmed WD, and the patient was treated with zinc sulfate and medications for SLE. This case underscores the importance of considering WD in patients with unexplained hepatic involvement in SLE 14​​.

Yang et al. presented a case of a 9-year-old girl diagnosed with both SLE and WD. Despite effective control of her SLE symptoms, her liver function did not improve, leading to the suspicion of WD. Genetic testing confirmed the diagnosis, and the patient underwent liver transplantation. Unfortunately, she passed away shortly after the surgery, highlighting the severe implications of delayed diagnosis and treatment 15.​

However, the patient did not respond to SLE treatment in this case. In contrast, WD treatment with Zinc Sulfate and Trientine significantly improved pancytopenia, elevated liver enzymes, and impaired INR. This response indicates that the case was not an overlap of SLE and WD but rather a misdiagnosis of SLE in the presence of WD.

This case highlights one key point: positive ANA profile results alone are insufficient to diagnose SLE. Physicians must consider other laboratory data, such as impaired INR and hepatomegaly, which are uncommon in SLE.

The absence of typical physical examination findings should be strongly considered, as emphasized in the 2019 EULAR/ACR criteria 16. Physicians should avoid unnecessary lab tests that can mislead the diagnostic approach and increase the burden on the healthcare system 17. The case emphasizes the importance of comprehensive clinical evaluation and the interpretation of laboratory tests in the context of the patient’s overall condition 18. Highlighting the famous quote in medicine: Treat the patient, not the disease 19.

## 5.1. Conclusion

This case report underscores the diagnostic challenges in distinguishing between SLE and WD. It emphasizes the importance of thorough investigation and consideration of WD in patients with hepatic and hematologic abnormalities unresponsive to conventional treatments for autoimmune diseases. Early diagnosis and appropriate treatment of WD are essential to improve patient outcomes and prevent irreversible organ damage.

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# Authors’ Contributions

Mandana Khodashahi: Conceptualized the article, supervised the manuscript writing, and edited and revised the manuscript.

Najmeh Mohajeri: Assisted with data extraction and patient follow-up.

Moeid Reza Alipour and Reza Khademi: Contributed to data extraction and patient follow-up.

Nama Mohamadian Roshan: Provided expertise in pathology biopsy and assisted with diagnosis confirmation.

Behzad Aminzadeh: Reviewed the CT scan and MRI, aiding in the diagnosis confirmation.

Muhammed Joghatayi: Drafted the primary manuscript, revised it, and assisted with data extraction and administration.

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