Concurrence of Active Systemic Lupus Erythematosus and Pulmonary Tuberculosis: A Case Report Highlighting Challenges in a Lower-middle-income Country

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Abstract

The complex and multisystemic characteristics of systemic lupus erythematosus (SLE) pose considerable challenges in its accurate diagnosis, leading to suboptimal outcomes and elevated mortality rates. This case report underscores the need for improved diagnostic approaches and targeted interventions, emphasizing the impact of misdiagnosis on SLE patients in resource-constrained settings. It describes a 19-year-old male patient who suffered from endobronchial TB and sepsis, exacerbating an acute lupus flare.

Keywords: Systemic Lupus Erythematosus, Infection, Pulmonary Tuberculosis, Lower Middle-Income Country.

Background

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease associated with exacerbations called SLE flares. Autoimmunity often impacts cardiopulmonary, mucocutaneous, musculoskeletal, renal, and central nervous systems.[1]

The global burden of the disease has been poorly understood, estimating prevalence ranging from 13.0 to 7713.5 per 100,000 individuals.[2] However, the effect of androgens and estrogen makes it more prevalent in women of all ages.[3] Presentation of SLE during the childbearing period is the most common, with 31 as the mean age identified from a study of 198 patients from Aga Khan University Hospital, Pakistan.[4] Although no definitive cure for SLE exists, treatment and lifestyle modifications can drastically improve the quality of life.[5]

Often in lower-middle-income countries, autoimmune diseases like SLE can be misdiagnosed as other mimicking illnesses, contributing to poor outcomes and higher mortality. A shortage of trained healthcare workers and specialists can result in the inability of doctors to make accurate clinical decisions.[6] Autoimmune diseases and infections can sometimes present with vague symptoms such as body aches, fatigue and fever, making it difficult to grasp, leading to diagnostic delays in patient care.

Mycobacterium tuberculosis is the pathogen behind tuberculosis (TB) and remains a leading cause of death in the developing world. It most commonly presents as pulmonary TB, while it can also infect other organs manifesting as extrapulmonary TB, furthering complications. Almost 5% of the 10.4 million cases of TB were resistant to at least

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two of the first-line drugs used to treat the disease due to mutations in its single, circular chromosome.[7]

The pathogenicity of this agent is its ability to evade host immune responses by sequestering in granulomas. Both adaptive and innate immunity act to keep the mycobacterium in its latent yet active stage, which is the fate of 90% of the asymptomatic infected individuals. However, when host immunity is compromised, the facultative intracellular organism can break through from the infected macrophages and disseminate to other sites and tissues.[8]

Patients with SLE are at risk of reactivating TB due to immune abnormalities and immunosuppressive therapy. Evidence suggests that mycobacterial infection plays a role in developing and worsening SLE symptoms. The presence of Anti-Nuclear Antibody (ANA) and RF (Rheumatoid Factor) in the serum of patients with active TB is likely an example of molecular mimicry between mycobacterial and host self-antigens.[9,10]

In 2016, an international consensus defined sepsis as life-threatening organ dysfunction resulting from a dysregulated host response. Clinically, organ dysfunction is recognized by an increase in Sequential [Sepsis-related] Organ Failure Assessment (SOFA) scores by 2 points or more.[11] It is a complication that can arise from any infection and can quickly exacerbate if not treated promptly. Symptoms of sepsis are non-specific, with a clinical presentation that relies on the foci of the infection.[12] The pathophysiology of sepsis is not yet fully understood. Still, it involves the excessive release of cytokines like tumor necrosis factor-α and interleukin-1, eventually leading to a "cytokine storm," causing widespread inflammation.[13]

Infections significantly contribute to the morbidity, hospitalization, and mortality of those with SLE due to abnormalities in immune regulation. Treatment for SLE, which includes glucocorticoids, immunosuppressive agents, and biologics, may increase susceptibility to opportunistic infections.[14]

Bacterial pathogens cause 80% of infections observed in individuals with SLE, primarily affecting the respiratory tract, skin, and urinary tract.[14] The Hopkins lupus cohort study found that disease activity measured by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) is a predictive factor for infection-related hospitalizations among patients with bacteremia compared to those without it.[15]

In regions with a high prevalence of tuberculosis, around 5-7% of individuals diagnosed with systemic lupus erythematosus (SLE) exhibit active TB infection, while approximately 18-25% have latent TB.[16] The manifestation of TB in SLE is often observed beyond the pulmonary sites and may result in a much more severe pulmonary and disseminated involvement.

Objective

Here we present a case report of a 19-year-old Asian male diagnosed three months earlier with inflammatory polyarthritis, presenting to the Emergency Department with what seems like an SLE flare but later diagnosed with Endobronchial tuberculosis and gram-negative sepsis superimposed on his acute lupus flare during the clinical course.

Case Presentation

A 19-year-old male of Pakistani origin presented to the Emergency department with complaints of recurrent fevers, documenting 102F as the maximum temperature recorded. He complained of inflammatory pain in his small and large joints, and he also seemed distressed due to continuous coughing.

His medical history revealed he was diagnosed with inflammatory polyarthritis three months ago. He was treated with Hydroxychloroquine (200 mg PO bid), after which his symptoms improved, except a recent recurrence in fever.

Further history revealed that he was a shopkeeper and a smoker. For a few months, he was experiencing dry mouth, and in the last six months, he documented losing five kilograms of weight. He had a history of oral ulcers and rashes on his abdomen, trunk, and face. No risk factors for HIV or Hepatitis B were present.

Upon physical examination, he appeared pale, distressed, and lean. Oral ulcers were positively revealed, while edema, lymphadenopathy, and rashes were not visible. His vitals recorded at the time were: Heart rate: 112/min, Blood pressure: 106/56mmHg, Temperature: 38ºC and Respiratory rate: 22/min.

Systemic examination revealed decreased breath sounds bilaterally with left-sided crackles on the chest. S3 ventricular gallop or pericardial friction rub were not audible. The abdomen was distended with positive shifting dullness. However, there was no visceromegaly. The central nervous system exam was unremarkable.

Investigations

Chronic history of recurrent fever with polyarthritis mandated workup for causes of chronic inflammatory disease. Hence, the initial blood workup consisted of a complete blood count (CBC), liver function tests (LFT), serum creatinine, serum albumin, and testing inflammatory markers: C-Reactive protein (CRP) and Erythrocyte sedimentation rate (ESR).

The blood tests revealed Haemoglobin: 7.4 g/dl below the normal range (10.9 g/dl - 15.2 g/dl) and MCV: 84fl. White blood cells were also lower: 3.2 x10x9/L than the normal range (3.4-9.6), with the following composition (N: 46%, L:34%, M: 13%). Platelet count: 237 x109/L and CRP: 3.24mg/dl was within normal limits, while ESR was elevated at 105 mm/hr. Albumin was measured to be slightly lower at 3.2g/L, while creatinine was found normal at 1.2 mg/dl.

The Liver function tests, which included ALT:134 IU/L, AST: 78 IU/L, T.bil:1.7 mg/dl (Direct: 1.4mg/dl, Indirect: 0.3mg dl), and GGT: 342 IU/L were all raised from the normal limits, suggestive of a mixed hepatocellular and cholestatic pattern. A baseline chest x-ray and a chest CT

scan were ordered as shown in Figure 1 and 2 respectively, highlighting abnormalities.

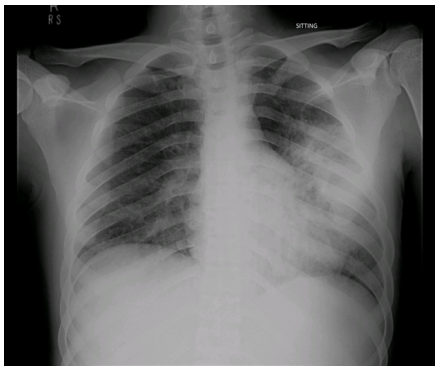

Figure 1: Baseline Chest X-ray Showing an Opacity can be Seen in Left Upper Mid Zone Associated with Air Bronchogram.

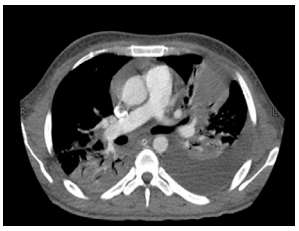

Figure 2: Chest CT. Under Lung Window Settings, Consolidation within Bilateral Lower Lobes and Left Lingular Segment with Patchy Infiltrates in Right Upper, Right Lower, and Left Lower Lobe can be Seen.

Due to inflammatory polyarthritis and the presenting clinical scenario, connective tissue disease was suspected. An immunology workup showed a triple positive ANA level, Anti Double-stranded DNA levels at 48.8 IU/ml, normal complement levels (C3: 0.39g/L, C4: 0.17 g/L), 3+ Coombs test, and elevated Lactate Dehydrogenase (LDH) levels (869 IU/L).

Differential Diagnosis

Bicytopenia and increased inflammatory markers raised suspicion relating to multiple inflammatory conditions like SLE, Rheumatoid Arthritis, Sjogren's syndrome, Overlap syndrome, and autoimmune hemolytic anemia. The patient presented with systemic symptoms like chronic recurrent fever and cough, rashes, sicca symptoms, oral ulcers, and weight loss. His medical history of inflammatory polyarthritis was also essential to consider.

Based on the initial workup, past medical history, and presenting complaint, he was suspected of experiencing an acute lupus flare and was immediately started on high-dose steroids. However, his condition deteriorated with the onset of a productive cough, fever, and shortness of breath, necessitating elective intubation for hypoxemic respiratory failure. Subsequently, bronchoscopy in the Intensive Care Unit (ICU) demonstrated an endobronchial lesion, and Acid Fast Bacilli sputum smear, culture, and GeneXpert from Bronchoalveolar Lavage (BAL) were consistent with mycobacterium tuberculosis infection. BAL cultures for Raoultella Terrigens also came out positive in the patient. It was a rare presentation of endobronchial TB in male lupus.

The patient also suffered from anti-phospholipid antibody syndrome as his lupus anticoagulant was detectable, which exacerbated his condition leading to a deep vein thrombosis while in ICU. Anticoagulation therapy was initiated with enoxaparin followed by warfarin, further complicating the case as the patient then suffered a Gastrointestinal bleed. An Inferior Vena Cava filter was inserted to prevent further thromboembolism.

The patient was commenced on anti-tuberculous therapy and IV Fosfomycin for Raoultella terrigens pneumonia. Hydrocortisone 50mg IV every six hours was administered as a stress dose for sepsis. For SLE, hydroxychloroquine (HCQ) 200mg BD was continued. The patient remained in ICU for three weeks and then extubated on BiPaP. He recovered expeditiously and was discharged after six weeks of prolonged hospitalization. His TB treatment was completed over the next six months, and he remained well. His SLE remained in remission on HCQ and anticoagulation.

Discussion

The clinical and biochemical presentation of bacterial infections such as pneumonitis, arthritis, and meningitis often overlap with active lupus. They can be misinterpreted as SLE flares leading to delayed or missed diagnosis. Therefore, approximately 25% of individuals with SLE who contract infections ultimately succumb to them.[17]

The heterogeneous, multisystemic nature of SLE can make diagnosing it challenging. Immunologically, it is considered a type III and type II hypersensitivity reaction resulting from losing immune tolerance. The defects in adaptive and innate immunity, consequently over-activating T and B cells and autoantibody generation against nuclear antigens, are the hallmarks of SLE.[1] As a result, a classification criterion seeks to assist physicians in recognizing SLE through biomarkers and clinical signs.[18]

Our patient suffered from Raoultella Terrigens and tuberculosis infections, initially misdiagnosed as SLE flares due to their similar acute febrile phase. Antibiotic therapy with reduced immunosuppressive treatment is necessary for SLE patients with an infection, whereas a flare requires increased doses of immunosuppressants; thus, distinguishing between the two becomes even more critical. Certain biomarkers specific to each condition must be measured accurately to identify and effectively manage an infection before it triggers an SLE flare-up.

A wide range of biomarkers are validated to have predictive significance in distinguishing infections from lupus flares in a febrile patient. They include C-reactive protein (CRP), procalcitonin (PCT), Mannose-binding lectin (MBL) and Neutrophil-to-Lymphocyte Ratio (NLR).[19] However, the foremost challenge physicians face is the affordability of these biomarkers in low- and middle-income countries (LMIC), such as Pakistan. The usual culture of out-of-

pocket payments at the time of healthcare delivery can deem financially catastrophic to most patients; hence, a modified diagnostic approach is required.

Procalcitonin (PCT), a glycoprotein precursor of calcitonin, is elevated in the serum during bacterial infection but not in non-infectious or lupus flare states. Its production increases in response to bacterial endotoxins and proinflammatory mediators, such as IL-1B, hours before a bacterial infection's onset but decreases once the infection subsides.[20]

A study by Chen *et al.*[21] concluded that serum PCT and CRP levels were considerably elevated in SLE with bacterial infections compared to flares, with PCT being more specific in distinguishing the two. In this young man, the Procalcitonin level was 21.34 ng/ml (Procalcitonin levels > 2.0 ng/mL represent an increased risk of severe sepsis and septic shock). Therefore, this information should facilitate the identification of a bacterial infection as the likely diagnosis rather than a flare. On the other hand, CRP levels were recorded as high as 3.24mg/dl (Normal range 0-0.5ng/mL)[22], further confirming an infectious state.

Various studies have shown the potential of neutrophil-to-lymphocyte ratio (NLR) as a biomarker to distinguish between infection and flare. Its high sensitivity and cost-effectiveness make it an encouraging marker. Infected individuals with lower lupus disease activity exhibited increased NLR levels compared to non-infected lupus patients, irrespective of their SLEDAI score.[20]

Incorporating routine laboratory testing of PCT, CRP, and NLR may prove beneficial in diagnosing bacterial infections among patients. Nevertheless, the cost implications associated with conducting a PCT test makes it less popular particularly in resource-scarce countries like Pakistan where its utility is variable depending on different settings.

Individuals diagnosed with SLE demonstrate heightened susceptibility to TB secondary to their inherent immunocompromised condition and utilization of corticosteroid therapy.[23] SLE-TB (TB) incidence is reported to be as high as 1.16 per 100 person-years, especially in high-burden TB countries such as Pakistan in the meta-analysis by Wu *et al.*[24]. TB in such high-risk patients should be detected via PCR as it remains the most effective form of diagnosis of tuberculosis, evidencing high specificity (100%), sensitivity (97.2%), and positive predictive values (100%).

Infection prevention becomes imperative in SLE patients to reduce morbidity and mortality of immunocompromised patients. Influenza and pneumococcal vaccines should be administered promptly. However, live-attenuated vaccines should be avoided in individuals undergoing immunosuppressive therapy as it may result in adverse reactions. If preventative measures are not achieved, early identification of infection by investigating diagnostic biomarkers and avoiding misdiagnosis as a flare is a determinant factor in reducing the severity of the disease and better survival. Once an infection is diagnosed, antimicrobial therapy should be initiated and adjusted promptly by assessing the risks specific to the patient's condition.

Availability of Data

Data sharing does not apply to this article as no datasets were generated.

Conflicts of Interest

The authors declare there are no conflicts of interest.

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Author's Contributions

We affirm that all individuals listed as authors agree that they have met the criteria for authorship and agree to the study's conclusions. NN managed the patient as a primary care physician and critically reviewed all the information in the manuscript before submission. SW and AJ wrote the initial case report draft and performed a literature search. OM reviewed the manuscript for content and clarity and made necessary revisions before submission.

Ethical Approval

All authors have agreed to authorship, read and approved the manuscript, for publication.

Consent

Informed consent to publish was obtained from the patient by the principal investigator.

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