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BEYOND POSITIVE ANA: UNMASKING OCCULT TUBERCULOSIS IN A YOUNG ADULT WITH SYSTEMIC LUPUS ERYTHEMATOSUS PRESENTING AS PYREXIA OF UNKNOWN ORIGIN—A DIAGNOSTIC ODYSSEY

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ABSTRACT

Background: Pyrexia of unknown origin (PUO) is one of the more difficult clinical presentations due to the overlapping features of infectious, autoimmune and malignant conditions. The diagnosis is often complicated by the presence of systemic lupus erythematosus (SLE) and tuberculosis (TB) in affected areas where TB is endemic. The distinction between disease flare and occult infection is important as immunosuppressive therapy may worsen undiagnosed tuberculosis.

Case Presentation: A 21-year-old male with persistent high-grade fever, constitutional symptoms, progressive cytopenias and recurrent hospitalizations. Initial tests included leukopenia, thrombocytopenia, positive antinuclear antibody (ANA), anti-double stranded DNA positivity, and hypocomplementemia, diagnosing systemic lupus erythematosus. Although the patient received corticosteroid treatment, fever continued and the patient later developed generalized seizures, acute pancreatitis, severe thrombocytopenia, hemophagocytic lymphohistiocytosis (HLH), fungal pneumonia, and respiratory failure which necessitated intensive care. Later extensive microbiological studies confirmed tuberculosis that required multidrug antitubercular therapy and fungal infection that required prolonged antifungal therapy. Treatment included pulse methylprednisolone, IVIG, broad-spectrum antimicrobials, antifungal therapy, antitubercular therapy, anticonvulsants and multi-disciplinary supportive care. During follow-up, the patient's laboratory parameters slowly returned to normal and the clinical situation was stable.

Conclusion: This case illustrates the as the diagnosis of SLE is made, tuberculosis should not be overlooked because of persistent fever even when the diagnosis of SLE is confirmed. A favorable outcome was the result of early multidisciplinary evaluation, frequent microbiologic evaluations, and ongoing re-evaluation of the working diagnosis.

KEYWORDS: Systemic lupus erythematosus; Pyrexia of unknown origin; Tuberculosis; Hemophagocytic lymphohistiocytosis; Fungal pneumonia; Autoimmune disease.

INTRODUCTION

Pyrexia of unknown origin continues to pose a major challenge in diagnosis as fever may persist for several days and can be due to infectious, inflammatory, autoimmune, or malignant conditions (Pannu et al., 2021). Even with the development of molecular diagnostics and imaging technologies, determining the cause often involves repeated clinical reevaluation and a multidisciplinary approach (Santana et al., 2019). Among autoimmune diseases, systemic lupus erythematosus is especially difficult because signs and symptoms—such as fever, cytopenias, rash, arthritis, serositis, and neurological—often mimic severe infections (Trapani et al., 2023).

Tuberculosis is regarded as one of the most significant opportunistic infections in patients receiving immunosuppressive therapy (Prakash et al., 2024), and is still highly prevalent in many of the developing countries. SLE patients are also prone to mycobacterial and fungal infections, as their immune system is not tightly regulated and frequently needs to be suppressed with steroids or other anti-inflammatory drugs. Therefore, fever beyond the diagnosis of SLE should not be taken as a sign of autoimmune disease activity and needs to be actively excluded (Cioboata et al., 2025; Ekeng et al., 2022).

Hemophagocytic lymphohistiocytosis (HLH) also contributes to the clinical picture and can be induced by autoimmune disorders or infection or both. Clinical manifestations of prolonged fever, pancytopenia, hyperferritinemia, hypertriglyceridemia, hepatosplenomegaly and multiorgan dysfunction are similar to that of active lupus and disseminated

infection (Kaçar & Celkan, 2022). Failure to identify these overlapping conditions could result in life-threatening issues that need intensive care support (Mukherjee & Kumar, 2025).
Report on a young adult with persistent pyrexia of unknown origin who went on to develop positive ANA and anti-double stranded DNA markers establishing the diagnosis of systemic lupus erythematosus, but whose further evaluation ultimately led to the diagnosis of hidden tuberculosis complicated by secondary HLH, fungal pneumonia, seizures, pancreatitis and a prolonged stay in intensive care unit (Soy et al., 2021; Gauiran et al., 2019). The case emphasizes the need to have a wide differential diagnosis even after a diagnosis of an autoimmune disorder has been made and the importance of repeated microbiological investigations and multidisciplinary management.

Case Presentation

A 21-year-old previously healthy male, presented with persistent high-grade intermittent fever, generalized weakness, loss of appetite, progressive weight loss, myalgia and fatigue. His symptoms continued in the subsequent weeks and he had been admitted on several occasionsto local health care establishments for evaluation of pyrexia of unknown origin (PUO). Laboratory examinations revealed a progressive decrease in leukocytes and thrombocytes and mild normocytic anemia, with no obvious infectious cause. Liver function tests were elevated for transaminase levels and renal function was preserved. An extensive diagnostic work-up was undertaken because of the persistent fevers with cytopenias, focusing on infectious, autoimmune, hematological, and malignant causes.
The immunological evaluation was further done which showed positive antinuclear antibody (ANA) with positive anti-double stranded DNA antibody and low level of complement, confirming the diagnosis (Systemic Lupus Erythematosus or SLE) according to the clinical and immunological criteria. Concurrently, the patient's condition progressed to oral ulcers, alopecia, chronic fever and progressive pancytopenia with constitutional features of active systemic autoimmune disease. High dose corticosteroid therapy was started after consultation with a rheumatologist. However, this patient's fever persisted, and the patient was suspected to have either resistant lupus or an underlying subclinical infection.
The patient became acutely ill during his hospitalisation. He had a generalized tonic-clonic seizure, with loss of consciousness, generalized tonic posturing, frothing at the mouth and eyes rolling upwards for about 2 minutes. He was then noticed to be short of breath and subsequently intubated and admitted to the intensive care unit after the seizure. In critical care management, he witnessed an episode of ventricular tachycardia and cardiac arrest at the referring hospital, which was successfully resuscitated before his arrival at Rela hospital where advanced multidisciplinary management was carried out.
The laboratory evaluation was thorough, and the results included significant hyperferritinemia, very high triglycerides, elevated lactate dehydrogenase (LDH), and continued cytopenias, leading to a high clinical index of suspicion for secondary hemophagocytic lymphohistiocytosis (HLH) in the setting of active systemic lupus erythematosus (SLE). The serial complete haematological tests showed marked leukopenia, lymphopenia, thrombocytopenia and anaemia; biochemical investigations showed elevated hepatic transaminases, hypoalbuminemia and ongoing inflammatory activity. A bone marrow examination did not show abnormalities of the haematological system but confirmed an inflammatory process, which is compatible with immune-mediated marrow suppression.
In the presence of persistent fever in spite of immunosuppressive therapy, microbiological investigations were repeated multiple times during intensive care admission. Fungal growth seen in respiratory cultures was consistent with pulmonary aspergillosis, requiring long-term antifungal treatment. Ralstonia mannitolilytica was later isolated on blood culture but no further cultures were grown. Although broad-spectrum antimicrobial therapy was instituted, fever persisted and further investigations for occult infections were carried out. Because of the patient's prolonged febrile illness, immunocompromised status and clinical deterioration, tuberculosis was actively pursued and ultimately confirmed. Besides the continued treatment of SLE and HLH, multi-drug anti-tubercular therapy was started.
The patient also had the development of acute pancreatitis during the course of his illness, which was deemed secondary to active lupus as other common causes were excluded. Imaging findings showed inflammation of the pancreas with no biliary obstruction noted and serial biochemical studies showed an increase in pancreatic enzymes and inflammatory markers. Theclinical course was found to be gradual, with conservative management, nutritional support and treatment of underlying auto-immune disease.
Treatment involved coordinated multidisciplinary management with the input of the rheumatologists, infectious disease specialists, intensivists, neurologists, hematologists, pulmonologists, and gastroenterologists. Methylprednisolone was given in pulses intravenously followed by oral glucocorticoids, intravenous immunoglobulin (IVIG), hydroxychloroquine, broad-spectrum antibiotics, antifungals, antitubercular drugs, anticonvulsants as needed, platelet transfusion and intensive care with comprehensive supportive measures. Slowly improving leukocyte counts and inflammatory markers were observed in the laboratory over time, with progressive improvement of thrombocytopenia over time. Severe multisystem involvement did not impair renal function during the illness.
After a prolonged hospital stay and intensive multiple-care, the patient showed progressive clinical recovery, with resolution of fever, stabilization of hematological parameters, improvement of respiratory status, recovery from fungal pneumonia, control of seizure activity, and was successfully transferred to outpatient care. At the time of discharge, he continued to receive systemic lupus erythematosus (SLE) maintenance therapy along with antitubercular therapy and close follow-up with the rheumatology, infectious diseases, hematology, and neurology services.

Clinical Timeline

Time Period	Clinical Events

December 2025	A 21-year-old man with no history of disease developed intermittent fever, generalized weakness, anorexia and fatigue. Laboratory tests initially confirmed vitamin D deficiency, and renal and hepatic function were normal. Symptomatic treatment was started.
January 2026	Failure to respond to antibiotics treatment. Progressive leukopenia and thrombocytopenia were observed. Persistent pyrexia of unknown origin (PUO) fueled the extensive evaluation of the patient for infectious, haematological and autoimmune disorders.
February 2026	Autoimmune testing was positive for ANA, anti-dsDNA antibodies and low complement, confirming Systemic Lupus Erythematosus (SLE). Treatment was begun with high dose corticosteroid treatment supervised by rheumatologists.
March 2026	Immunosuppressive treatment failed to inhibit the fever. Cytopenias became worse, and hematological evaluation was repeated. Bone marrow examination was negative for hematological malignancy.
April 2026	The patient progressed to develop acute pancreatitis, progressive pancytopenia, features of systemic inflammatory disease with markedly raised ferritin levels, which suggested secondary hemophagocytic lymphohistiocytosis (HLH).
May 2026	Clinical deterioration was noted as generalized tonic-clonic seizure, respiratory failure and admission to intensive care unit, with one cardiac arrest and successful resuscitation before admission to Rela Hospital. Long-standing microbiological analysis revealed fungal infection of the lungs and latent TB.
Late May–June 2026	Pulse methylprednisolone, IVIG, antifungal, antitubercular and anticonvulsant therapy and intensive care were administered to the patient. The hematological parameters gradually improved with improvement of fever and clinical stabilization in serial investigations.

Investigations

Initial laboratory studies revealed progressive leukopenia, thrombocytopenia, and mild normocytic anemia, which implied a bone marrow suppression or systemic inflammatory disorder. Liver function tests showed that the levels of serum transaminases, were elevated whilst the levels of serum creatinine and electrolytes, were within normal limits during the majority of the illness. A repeat CBC revealed progressive pancytopenia that required additional work-up.

Immunological criteria for SLE were met with positive antinuclear antibody (ANA), positive anti-double stranded DNA antibody (Anti-dsDNA), and hypocomplementemia (low C3 levels) on autoimmune studies. These results were consistent with patient's persistent fever, constitutional symptoms, cytopenias, and multisystem involvement.

Bone marrow biopsies revealed hypocellular marrow, though no leukemia, lymphoma or other hematological malignancies were seen, favoring an inflammatory or autoimmune cause of pancytopenia.

All inflammatory markers were abnormal, with a markedly elevated ferritin level (approximately 4940 ng/mL), hypertriglyceridemia, elevated lactate dehydrogenase, persistent cytopenias, in keeping with the clinical criteria for secondary hemophagocytic lymphohistiocytosis (HLH).

Radiological examination revealed acute pancreatitis, but no evidence of biliary obstruction. MRI brain after seizure attacks did not show any acute ischemic or hemorrhagic pathology. The chest imaging revealed pulmonary infiltrates in keeping with infectious pneumonitis.

The fever continued to be seen despite corticosteroid treatment and repeated microbiological investigation was carried out. Fungal organisms agreeing with a diagnosis of pulmonary aspergillosis were recovered from respiratory cultures and a single blood culture yielded Ralstonia mannitolilytica. The clinical suspicion was raised and eventually TB was diagnosed, after which the patient was put onto multiple drugs for TB.

Differential Diagnosis

On initial presentation, the patient had prolonged fever and pancytopenia and the differential diagnosis was wide. Further work up was warranted due to progressive constitutional symptoms and prolonged pyrexia, where infectious etiologies such as bacterial sepsis, infective endocarditis, tuberculosis, viral infections and invasive fungal disease were taken into consideration. During the hospital stay, serial blood cultures, imaging tests and microbiological tests were carried out.

Another large group of diagnoses that needed to be considered were autoimmune conditions. The diagnosis of systemic lupus erythematosus was strongly supported by positive ANA, anti-double stranded DNA antibodies, low levels of complement, chronic cytopenias and multiple organ involvement. However, fever which persisted despite immunosuppressive treatment indicated that active infection was present with auto-immune disease and not just isolated lupus flare.

Exclusion of hematological malignancies (HMs) occurred via bone marrow examination, peripheral blood examination, and serial hematological assessments.

Persistent fever, cytopenias, hyperferritinemia, hypertriglyceridemia, elevated LDH and multiorgan dysfunction were significant features, making secondary HLH a strong possibility in the differential diagnosis. The final diagnosis was active SLE with secondary HLH and occult tuberculosis and pulmonary aspergillosis.

Treatment

Multidisciplinary cooperation was needed including involvement of rheumatologists, infectious disease doctors, intensivists, neurologists, hematologists, pulmonologists and gastroenterologists.

After the diagnosis of systemic lupus erythematosus was confirmed, pulse intravenous methylprednisolone was given followed by maintenance oral corticosteroid and hydroxychloroquine to limit the autoimmune process. Severe immune mediated cytopenias and suspected HLH were treated with intravenous immunoglobulin (IVIG) therapy.
Empirical broad spectrum antimicrobial therapy was started during evaluation of persistent fever. Voriconazole and then isavuconazole was used for antifungal treatment after diagnosis of pulmonary aspergillosis. Standard multidrug antitubercular therapy was started upon tuberculosis diagnosis and supervised by a specialist.
Levetiracetam (Keppra) was given for generalized tonic-clonic seizure. Intravenous fluid, nutritional support, analgesics and management of the underlying autoimmune disorder were all employed in the treatment of acute pancreatitis. In addition, the patient was given platelet transfusion, blood product support as needed, gastric protection, electrolyte replacement and intensive care support, especially mechanical ventilatory support during respiratory failure.

Outcome and Follow-up
Combined immunosuppressive therapy and treatment of concurrent infections led to gradual improvement of the patient. Fever gradually resolved, inflammatory markers were reduced, and serial complete blood counts revealed resolution of a leukocytosis and the normalization of thrombocytopenia. Secondary HLH was resolved with the decrease in ferritin levels. Follow-up showed improvement of liver function tests. Antiepileptic therapy was started and no further seizures were recorded. After long-term antifungal treatment there was improvement in the respiratory symptoms, and the treatment of tuberculosis was continued as per national guidelines. Patient was clinically stable at discharge and continued on maintenance corticosteroid, hydroxychloroquine, antitubercular medication, antifungal medication and
supportive care with regular follow-up visits with rheumatology, infectious disease, hematology and neurology services.

DISCUSSION
This is a case of pyrexia of unknown origin in a young adult with mixed autoimmune and infectious conditions that is of exceptional diagnostic difficulty. Persistent fever despite immunosuppressive treatment suggested that the clinical deterioration was not solely due to autoimmune disease as the diagnosis of systemic lupus erythematosus was confirmed by the presence of positive ANA and anti-double stranded DNA antibodies. This highlights the key clinical principle that the diagnosis of an autoimmune disease should not stop the hunt for a concurrent infection, especially in TB endemic areas.
Both immune dysregulation and corticosteroid therapy contribute to impaired cell-mediated immunity and make tuberculosis an important opportunistic infection in SLE. Tuberculosis and active lupus share common constitutional symptoms, cytopenias, increased inflammatory markers and multiorgan involvement, which often delay diagnosis. In the current case, the diagnosis of occult tuberculosis was only made as a result of multiple microbiological examinations after a thorough initial evaluation. This delay emphasizes that when fever persists despite what appears to be appropriate treatment, there is a need for continuous reassessment.
The presence of secondary HLH made diagnosis difficult. This is a hyperinflammatory syndrome involving uncontrolled activation of macrophages and lymphocytes leading to cytokine storm and multiorgan dysfunction, which is known as hyperlamminopathy (HLH). Signs and symptoms of fever, pancytopenia, hyperferritinemia, hypertriglyceridemia, elevated LDH, hepatic dysfunction, and neurological abnormalities are similar to those seen in active lupus and severe infections. This patient's recognition of a HLH was critical as the mortality rate is high if the treatment is delayed. Hematological recovery and stabilization were probably hastened by early use of pulse corticosteroid and IVIG therapy.
Another serious life-threatening complication was pulmonary aspergillosis. Fungal infections that occur when there is an opportunity are now being seen in patients with SLE who are taking high doses of corticosteroids or intensive immunosuppression. However, in an immunocompromised host, a combination of invasive fungal infection and tuberculosis is a powerful agent which contributes to a high morbidity with a carefully balanced immunosuppressive and antimicrobial treatment. This successful management required a close interaction between the different specialties including rheumatology, infectious diseases, haematology, neurology, pulmonology and intensive care.
This case also highlights the message of serial investigations and not a single diagnostic test. Important parameters in elucidating overlapping disease processes were dynamic changes in complete blood counts, ferritin, complement levels, liver function tests, microbiological cultures and response to treatment. The bone marrow biopsy did not reveal the presence of any haematological malignancy, and therefore further investigation was directed at autoimmune and infectious causes. As a result of continuous re-evaluation, diagnosis was not closed too early and the patient eventually recovered from SLE, secondary HLH, tuberculosis and pulmonary aspergillosis.
Finally, it is important to keep a wide differential diagnosis in mind when patients present with persistent pyrexia of unknown origin and have positive autoimmune serology. Even after the diagnosis of systemic lupus erythematosus, occult tuberculosis should be considered as an important differential diagnosis in tuberculosis-endemic areas. The treatment of these complex multisystem presentations requires careful interpretation of the changing laboratory picture, repeated bacteriological work-up and early multidisciplinary management.

CONCLUSION
The difficulties associated with the diagnosis of pyrexia of unknown origin (PUO) in a young adult patient with concurrent autoimmune and infectious disease. ANA positivity, anti dsdna antibodies, and hypocomplementemia confirmed the diagnosis of Systemic Lupus Erythematosus (SLE) although the fever was not improving with immunosuppressive therapy, further investigation was warranted, and ultimately led to the discovery of occult TB, secondary hemophagocytic lymphohistiocytosis (HLH) and pulmonary aspergillosis. The combination of these factors resulted in a considerable

diagnostic burden as the clinical features of these conditions were very similar, with the risk of delay in diagnosis and poor decisions regarding treatment.

A multidiciplinary approach with the participation of the teams of the Rheumatology, Hematology, Infectious diseases, Neurology, Pulmonology, Gastroenterology and Intensive care teams was employed for successful management. The gradual clinical improvement and stabilization that were observed were due to early recognition of disease progression, repeated microbiological studies, serial laboratory monitoring and early introduction of steroids, intravenous immunoglobulin, antitubercular drugs, antifungal agents, anticonvulsants, and intensive care.

This case illustrates the importance of continuing to look for co-existing infections even when considering the diagnosis of an autoimmune disease, especially in TB endemic areas. Any recurrent or persistent fever in a patient with SLE should prompt a re-evaluation in search of an undiagnosed infection and hyperinflammatory syndromes like HLH. The timely diagnosis of the overlapping disease processes and the coordinated management of the disease by several specialties are the most important to minimize the morbidity and optimize clinical prognosis. This diagnostic journey highlights the need to have a wide differential diagnosis and a step-wise approach with evidence-based thinking in evaluating a patient with chronic fever and multisystem involvement.

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