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CASE REPORT

Baffling Case of a Patient With History of Lupus in a COVID-19 Pandemic

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Abstract

Systemic lupus erythematosus (SLE) is an autoimmune disease with a myriad of clinical presentations and periodic flares. We present a case of a young lady with a history of SLE who presented with constitutional symptoms 1 week after starting Isoniazid and Rifampin for treatment of latent TB. Her presentation shared similarities with several diseases including TB lymphadenitis, SLE flare, Kikuchi-Fujimoto Disease (KFD) and hemophagocytic lymphohistiocytosis (HLH) posing a diagnostic dilemma. Additionally, she presented not long after the onset of the global COVID-19 pandemic, further expanding the differential diagnosis. She was ultimately diagnosed with a severe SLE flare caused by rifampin induced suppression of the CYP3A4 system, thereby reducing the therapeutic efficacy of steroids. This case highlights the deadly potential of drug−drug interactions, especially in patients with autoimmune conditions.

Keywords: Systemic lupus erythematosus, Kikuchi-Fujimoto disease, Lymphadenopathy, Hemophagocytic lymphohistiocytosis, Latent tuberculosis

1. Background

Acute flares of systemic lupus erythematosus (SLE) can be induced by infections, pregnancy, stress, immunosuppression or medications. The hyperinflammatory state of a flare can be difficult to differentiate clinically from COVID-19 pneumonia and hemophagocytic lymphohistiocytosis (HLH). A high index of suspicion is necessary as both SLE flares and HLH can be life threatening even with appropriate treatment. Here, we report a case of a 31-year-old woman who developed constitutional symptoms shortly after starting treatment for latent TB and was ultimately diagnosed with a severe SLE flare caused by interactions between steroids and Rifampin. She improved significantly after stopping rifampin without a need for escalation in the dose of home steroids. This case emphasizes the importance of reviewing potential medication interactions before starting a new medication.

2. Case

A 31-year-old woman presented to the Emergency Department (ED) with generalized fatigue and lethargy. Medical history was significant for type II diabetes mellitus, sickle cell trait and SLE complicated by lupus nephritis class III. SLE was diagnosed one-year prior following presentation with discoid cutaneous lesions and high ANA titers with initiation of hydroxychloroquine. Her lupus course was marked by flare manifesting as pericardial and pleural effusion treated with pulsed IV Methylprednisolone 100 mg daily for 3 days and transitioned to prednisone 20 mg. Before prednisone could be tapered, lupus nephritis developed with plans to start cyclophosphamide during which latent TB was diagnosed and she was started on isoniazid (INH) and rifampin (RFP). Labs on presentation showed leukopenia, thrombocytopenia, mild transaminitis and elevated inflammatory markers with mild atelectasis in bilateral lower

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lobes on a chest x-ray. Her symptoms were thought to be due to COVID-19 infection and she was sent home to self-quarantine while awaiting SARS-CoV-2 PCR test result. She returned two days later with abdominal pain, nausea, vomiting, diarrhea, and fevers. Vital signs revealed a temperature of 101°F, BP 110/82, HR 122, RR 24 and SpO2 100% on room air. Labs on the day of admission showed persistent leukopenia, thrombocytopenia, rising inflammatory markers and worsening transaminitis. Details of lab results from her initial ED visit and on the day of admission are shown in Table 1. In addition, CT chest, abdomen and pelvis was notable for bulky adenopathy in bilateral axilla, iliac, and inguinal regions.

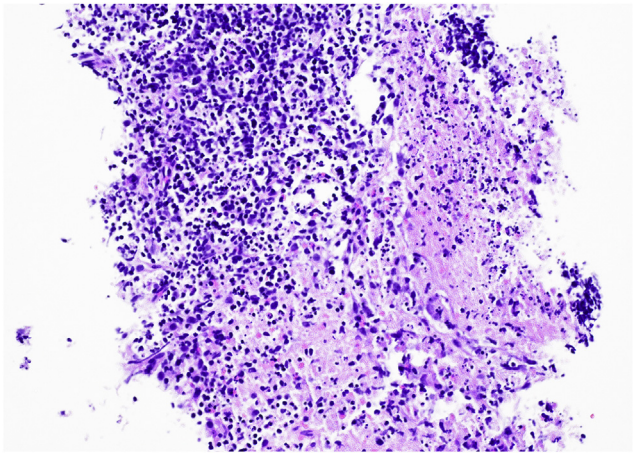

Fig. 1. Lymph node biopsy showing necrosis and patchy areas of cellular apoptosis with abundant karyorrhectic debris.

2.1. Investigation and treatment

The initial plan of treatment included broad spectrum antibiotics due to concern for an infection, discontinuation of rifampin and INH due to elevated transaminases and continuation of her home dose of prednisone and HCQ.

Given the presence of lymphadenopathy, abnormal laboratory results and her clinical presentation, extensive workup was performed for a broad differential diagnoses including infections, TB lymphadenitis, SLE flare and hemophagocytic lymphohistiocytosis (HLH). Blood cultures were negative for bacterial, fungal, and TB infections. ANA titers were elevated at 1:1280 with decreased C3 37 mg/dL (76–100 mg/dL), pointing to an autoimmune case. Tests for HLH revealed mildly elevated sIL-2R at 2137 pg/mL (532–1891 pg/mL) and low NK cell activity at 48 cells/uL (70–760 cells/uL). A lymph node biopsy was done which revealed necrotizing lymphadenitis without evidence of lymphoproliferative disorders or infections (Fig. 1). These findings were concerning for Kikuchi-Fujimoto disease (KFD) or lupus lymphadenitis. A bone marrow biopsy showed normocellular marrow without evidence of hemophagocytosis, favoring reactive changes from infection or autoimmune disease. With these findings, HLH and infection were thought less likely but rather lymphadenitis from a lupus flare or KFD. The patient's symptoms improved on her home dose of prednisone and HCQ after discontinuation of RFP and INH, suggesting that the most likely cause of her presentation was an SLE flare due to drug–drug interactions.

2.2. Outcome and follow up

She was discharged in stable condition on her home medications except for INH and RFP. On rheumatology follow-up, she was started on immunosuppressive medicines. This allowed subsequent resumption of a course of isoniazid and

Table 1. Comparison of labs between ED visit and Hospital admission.

Labs	2 days prior to admission	Day of admission	Reference
WBC	1.79	2.98	4–11 × 10^3/μ L
Manual Bands	5	46	3–17%
Hemoglobin	11.3	15.1	12.5–15 g/dL
Platelet	112	102	140–400 × 10^3/μ L
Creatinine	0.81 mg/dL	2.97 mg/dL	0.5–1.00 mg/dL
CRP	6.78 mg/dL	8.31 mg/dL	<0.05 mg/dL
LDH	452 IU/L	1984 IU/L	81–216 IU/L
Ferritin	3783 ng/mL	38467 ng/mL	15–150 ng/mL
Fibrinogen	–	387 ng/mL	164–533 ng/mL
D-Dimer	–	>20	<0.05 ug/ml
Procalcitonin	5.28	<0.09	≤0.10 ng/mL
Triglyceride	100.9	357	≤200 mg/dL
AST	86	476	4–31 IU/L
ALT	46	197	4–31 IU/L
SARS-CoV-2	Negative	Negative	Negative

rifampin and successful completion of treatment of latent TB.

3. Discussion

Systemic lupus erythematosus (SLE) is an autoimmune disease that causes multiorgan damage due to auto-antibody formation against the self-antigen. The clinical features of SLE flares are manifold and frequently overlap with many disorders. In the midst of a global pandemic, it is reasonable to consider SARS-CoV-2 infection as one of the differentials in patients presenting with fevers and elevated inflammatory markers. The presence of nausea, vomiting, diarrhea, lethargy and fevers further increased suspicion of SARS-CoV-2 infection. However, this was deemed unlikely after two negative PCR tests.

Patients with SLE on immunosuppressants are more susceptible to infections, which should always be considered in febrile patients with increased inflammatory markers. Because of the significant lymphadenopathy on presentation, infectious causes such as toxoplasmosis lymphadenitis, infectious mononucleosis, and herpes simplex lymphadenitis were considered. Other non-infectious differentials included nodal colonization by acute myeloid leukemia, metastatic adenocarcinoma and Hodgkin's lymphoma. However, aforementioned infections were ruled out with negative PCR, antibodies and cultures of blood and lymph node. There was also no evidence of malignancy on lymph node and bone marrow biopsy.

Tuberculous lymphadenitis was another consideration due to recent latent TB diagnosis and extensive lymphadenopathy on imaging but lymph node biopsy and culture were negative for TB.

Further complicating matters was the presence of bicytopenia, an increase in ferritin from 3783 ng/mL to 38467 ng/mL over the span of 2 days, and worsening transaminitis in the presence of lymphadenopathy. This raised concern for hemophagocytic lymphohistiocytosis (HLH), which is a life-threatening disorder involving excessive activation of macrophages and T cells, leading to production of pro-inflammatory cytokines and a hyper-inflammatory state. HLH can be classified as either primary HLH, which occurs due to a genetic defect, or secondary HLH, which is triggered by infection, malignancy, immunosuppression, or autoimmune diseases like SLE.[1] The diagnostic criteria for HLH is taken from the HLH-2004 trial, and 5 out of the following 8 criteria must be met: fever >38.5 F for >7 days, splenomegaly, bicytopenia, hypertriglyceridemia or hypofibrinogenemia, ferritin >500 ng/mL, elevated sIL-2R > 2400 U/mL, low NK cell activity, and presence of hemophagocytic cells in spleen, lymph nodes or bone marrow.[2] Our patient did meet 5 of the 8 criteria (fever, bicytopenia, hypertriglyceridemia, elevated ferritin, and low NK cell activity). However, BM and LN biopsy were negative for hemophagocytosis. While it is important to note that hemophagocytosis is only present in about 70% of HLH cases,[3] the timeline of symptom onset shortly after the initiation of new medications, and improvement after discontinuing these medications while on her home dose of prednisone, all made SLE flare a more likely diagnosis than HLH.

The results of the lymph node biopsy added yet another differential. The biopsy showed necrotizing lymphadenitis which can be seen either in Kikuchi-Fujimoto disease (KFD) or an SLE flare. KFD is a lymphohistiocytic disorder first reported in 1972 where patient presents with fevers, lymphadenopathy and necrotic foci on LN biopsy. It was initially proposed to be associated with a viral or post viral etiology but this remains yet to be proven.[4] It often presents with lymphadenopathy, particularly of the cervical lymph nodes and is accompanied by non-specific laboratory abnormalities such as elevated ESR/CRP, leukopenia, anemia, elevated ferritin or LDH.[5] Diagnosis is established with a lymph node biopsy showing necrosis. While KFD typically has a benign self-limiting course, there have been 3 reported deaths from KFD.[6] There are no specific treatments available outside of supportive care but steroids have been used with successful recovery.[7–9] The association between SLE and KFD was examined by Yasar et al. with 32 patients in which they noted 19% of patients with KFD later developed SLE, and 12% of KFD patients had a previous diagnosis of SLE.[10]

SLE flares can be induced by infection, trauma, stress, or initiation of new medications. After a recent diagnosis with latent TB, the patient received appropriate treatment with isoniazid and rifampin. However, as described above, she became severely ill shortly, requiring progressive care admission with an elusive diagnosis. Extensive workup was mostly unrevealing except for the fact that she may have had KFD, which is typically self-limiting. However, her presentation was most likely caused by an SLE flare. The interaction between TB and SLE is complex; patients with SLE are at increased risk of TB from steroid induced immunosuppression and impaired immunity from the SLE itself. Conversely, active TB infection can also induce or exacerbate a lupus flare, but this has not been reported in latent TB infections.[11] It is well established that rifampin induces the CYP3A4 system, which

can increase the hepatic clearance of steroids by 45% ($p < 0.01$) and also decrease steroid availability to tissues by 66%, altogether reducing the therapeutic effect of steroid.[12,13] Symptom onset shortly after initiation of rifampin, rapid improvement after its discontinuation and the fact that she did not require an escalation in her home dose of prednisone and HCQ are highly suggestive that a drug–drug interaction was the trigger. Careful review of medication interactions is required prior to starting new medications to prevent similar flares.

3.1. Take home points

- Potential medication interactions should always be reviewed before starting a new medication.
- Rifampin decreases the therapeutic efficacy of steroids which may induce SLE flares in patients on treatment for TB if the steroid dose is not adjusted.
- The diagnostic criteria of HLH should be reviewed when treating patients with SLE flares as the presentation can be similar and it is potentially fatal.

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