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Abstract

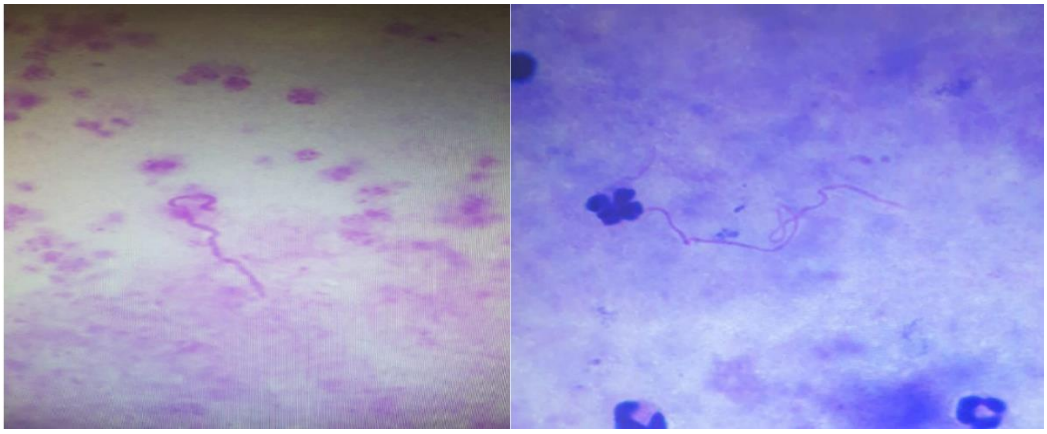
Fifty two year old women with long-term history of Systemic Lupus Erytematosus (SLE) presented with relapsing fever (RF) (39˚) of 2 weeks onset. Her permanent therapy was prednisone. Possible reasons discussed, tested and hidden icons unraveled.

Keywords: Relapsing fever; Borreliosis; Systemic autoimmune disease; Macrophage activating syndrome

Clinical Image

Fifty two year old women with long-term history of systemic lupus erytematosus presented with relapsing fever (39˚) of 2 weeks onset. Her permanent therapy was prednisone. Two months before she was hospitalized because exacerbation of arthralgia and treated with intravenous corticosteroids. Then on admission single febrile spike 39˚ occurred. She denied trips or aboard travels. On last admission, her mental and physical examination was unremarkable apart from fever, chills and tachycardia.

Figure 1: *Large spirochets (6-8 sizes of neutrophils) on smear of thickened blood drop, taken during fever relapse (X100, Giemsa stain).*



Febrile period of several days followed unfebrile state. Normocytic Coombs negative anemia 6.5g/l, leucopenia 2000/mcl, high inflammatory markers, high anti-DNA (300) and ferritin (1500), low range proteinuria (<1g/l) were observed. Platelet count and C3-4 were normal. Liver enzymes of hepatocellular and cholestatic groups were elevated. Multiple bacterial cultures, wide range of virology, lumbar puncture results and echocardiography (TTE/TEE) did not revealed any pathogen. Total body CT, bone scannogram, FDG-PET, gastro-entero-colonoscopy with biopsy were negative for lymphadenopathy, vasculitis, malignancy, infection, celiac or Whipple disease. Bone marrow revealed neither macrophage-activating syndrome (MAS) no hematological malignancy, vasculitis, granulomatosis or infection. Trial of high dose dexamethasone IV failed to reduce fever, raising question about active SLE. Amikacin was not effective. Adult Still disease exhibits rash, arthritis and leucocytosis, which absent. During fever attack peripheral blood for thickened drop, checked with Giemsa stain microscopy,

showed large spirochets (long 100 and 77nm, wide 3 and 0.75nm) (Figure 1). Blood samples sent for PCR verification and serology were negative [1]. Doxicyclin therapy 9 days failed and ended due to vomiting. Hepato-cellular impairment disappeared. Ceftriaxone 2g/day IV initiated. At day 9 of ceftriaxone therapy acute cholestasis developed: increased alkal phosphatase, GGT, fever 39.3. Cefriaxone canceled, but liver enzymes continued to increase along to relapsing fever. Liver biopsy followed and resumed as mild non-specific periportal plasma cell inflammation. Control thickened drop microscopy during fever flare was negative for borrelia. After three events fever disappeared. Inflammatory markers, liver enzymes and ferritin stayed increased. Seven days after ceftriaxone discontinuation, non-bloody diarrhea and abdominal pain developed. Feces for Clostridium and viral-bacterial pathogens were negative. On day 6 of diarrhea hemorrhage discharges appeared. Abdominal CT and sigmoidoscopy interpretated as pancolitis with mucose petechia and ascitis. Abdominocentesis showed sterile clear yellow fluid with low serum albumin ascitis gradient (serositis) and low cytosis predominantly mononuclear (WBC 160, 90% mononuclears). Repeated stool tests were positive for Clostridium. Flagyl therapy along with IV methylprednisolone followed and abdomial pain and diarrhea stopped, ascitis reduced. Inflammatory markers, liver enzymes and ferritin progressively expanded. One-day dose reduction of methylprednisolone IV 50% followed by fever relapse. Suggestion about sytemic adult Still-like disease with fever, hyperferritinemia, liver function abnormalities, serositis came for consideration. Differential diagnosis with similar manifestations was MAS secondary to SLE. Serum IL-2R taken as a sensitive marker of MAS proved to be above reported cutoff (3200 vs 2500 U/ml). This raised possibility of the bone marrow negative MAS, complicating autoimmune disease. Due to leucopenia and abnormal liver function, immune supression was limited to ciclosporin 50mg/day. Intravenous immunoglobulins (IVIG) were initiated (90g IV for 4 days).

Borreliosis due to Lyme disease (B. burgdoferi) (21 species) has had no reports in Israel. Meanwhile, 29 other species of borrelia present with tick vectors (TBRF- tick born relapsing fever). Borrelia persica and borrelia hispanica are dominant pathogens [2,3]. That have size of 20-30nm X 0.3nm (2-3 sizes of neutrophils). Their harbor are ticks of caves and slots. Our pathogen is large spirochet, described at yosters and digestive tract of cockroaces [4]. Borreliosis requests 2 weeks of oral or intravenous therapy. Resistant pathogens respond to combined therapy with doxicyclin, ceftriaxone and daptomycine [5]. Ceftriaxone creates sludges with calcium of biliar tracts and causes cholelithiasis [6].

We observed hard way to diagnose and treat relapsing fever. One problem was possible side effects of drugs: cholestatic enzymes elevation, clostridium complication of antibiotics. The second was relative slow response of the pathogen to antibiotics. Third was PCR and serology negativity in case of obvious demonstration of spiral agents on thickened drop stainning. That may be due to corticosteroid therapy. Forth was continuation fever, cholestasis and pancolitis development, which was not explained by Clostridium coming later. IV corticosteroid therapy along with IVIG - ciclosporin may be relevant participants in therapy of underlined autoimmune syndrome. Borreliosis might be a trigger. Pancolitis might be a part of target organ involvement. SLE as presentation of adult Still's disease has recently been reported [8]. Both SLE and MAS also develop hyperferritinemia similar adult Still disease. Further follow up was afebril, liver enzymes reduced 40% after 8 days, albumin increased (2.5 to 3.15g/L), CRP reduced to normal, ferritin and ESR stayed elevated. In conclusion, you see relapsing fever with hyperferritinemia – seek hidden icons: borreliosis, adult still's disease, MAS due to autoimmune disease.

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