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Simultaneous Onset of *Mycobacterium kansasii* Pulmonary Infection and Systemic Lupus Erythematosus: A Case Report

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Conflict of interest: None declared

Patient: Female, 19-year-old
Final Diagnosis: Systemic lupus erythematosus
Symptoms: Cough • Fever • malaise and fatigue • polyarthralgia • skin rash
Medication: —
Clinical Procedure: —
Specialty: Rheumatology

Objective: Unknown ethiology

Background: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease resulting from dysregulation of the immune response. In genetically predisposed subjects, infections reputedly trigger an immune activation leading to autoimmunity and overt autoimmune diseases such as SLE.

Case Report: We report the case of a 19-year-old woman who presented to our hospital reporting high-grade fever, dry cough, and polyarthralgia despite a course of empiric antibiotic and steroid therapy administered by her general practitioner (GP). On physical examination, she had a malar rash, a palpable erythematous maculopapular non-itchy rash over the limbs and trunk, and mild polyarthritis. A contrast computed tomography (CT) scan of the chest showed a pulmonary right upper-lobe consolidation with air bronchogram and multiple necrotizing conglomerate mediastinal lymph nodes. Culturing of collected samples from endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) of the mediastinal lymph node revealed growth of *Mycobacterium kansasii*. Antinuclear antibodies (ANA) and lupus anticoagulant (LAC) were positive. A diagnosis of *M. kansasii* infection associated with SLE was made. She was started on anti-mycobacterial and hydroxychloroquine therapy and entered into a joint rheumatological and infectious disease follow-up. Six months later, a CT scan with positron emission tomography (PET) showed a significant reduction in size of the basal right upper-lobe consolidation and hypermetabolic activity in multiple pulmonary areas and mediastinal lymph nodes. ANA and LAC tests were repeated and remained positive. The decision was made to continue the ongoing therapy course for 1 year in total.

Conclusions: Clinical and experimental studies have suggested the association of mycobacterial infections with SLE and as a possible infectious trigger of autoimmunity. We describe a unique case of *M. kansasii* infection associated with the onset of SLE in a young woman.

Keywords: Autoimmunity • Lupus Erythematosus, Systemic • Mycobacterium Infections, Nontuberculous • Case Reports

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Background

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease resulting from chronic and recurrent activation of the immune response and characterized by the production of autoantibodies to nuclear antigens. Clinical and experimental evidence support the role of infections in the induction of SLE. Infections may participate in the break of tolerance and in triggering autoimmunity by various mechanisms [1]. Molecular mimicry, cross-reactivity, over-expression of type 1 interferon (IFN) genes, and bacterial and viral hypo-methylated DNA are suggested mechanisms of autoimmunity induction.

Nontuberculous mycobacteria (NTM) are ubiquitous environmental microorganisms usually embedded in water and soil. NTM infection is increasing worldwide and although immunosuppression significantly contributes to the risk of infection, in recent years the disease is also spreading in immunocompetent human recipients, in which about 77% is pulmonary [2].

In the last century, the possibility that mycobacterial infections could trigger autoimmune diseases was suggested. A specific relationship between mycobacteria and autoimmunity was pointed out based on the observation that the generation of autoreactive T cells was initially stimulated by exposure to the immunodominant protein antigens of mycobacteria and that patients with pulmonary tuberculosis developed sets of antinuclear antibodies characteristic of patients with SLE [3]. Furthermore, monoclonal anti-TB antibodies binding the glycolipids of part of the mycobacterial cell wall were found to react with ssDNA, dsDNA, and anti-DNA autoantibodies from SLE patients [4].

So far, 2 clinical studies have supported a possible role of mycobacterial tuberculosis (TB) in precipitating SLE in genetically predisposed patients [5,6]. In 2004 Takada and colleagues described a case of atypical mycobacterial infection from the *Mycobacterium avium* complex (MAC) which preceded the onset of SLE [7]. To our knowledge, there are no other reports of NTM possibly precipitating SLE. We herein describe the first case of NTM infection from *Mycobacterium kansasii* complicated with SLE and possibly triggering the onset of the disease.

Case Report

A 19-year-old woman was admitted to our department on October 11, 2019 because of high-grade fever (body temperature up to 39.5°C), dry cough, and polyarthralgia. Six weeks before admission, she had experienced fever with occasional cough and general malaise. On general practitioner (GP) advice, she had undergone chest radiography, which showed a right upper-zone haziness and she was administered a 10-day course of levofloxacin (750 mg/day) with no relief of symptoms. She was then started on oral prednisone (25 mg/day gradually tapered to withdrawal) with a transient improvement in her symptoms. Two weeks later, she experienced fever again and was therefore admitted to the hospital.

On physical examination, she had a malar rash, a palpable erythematous maculopapular non-itchy rash over the limbs and trunk, and mild swelling and tenderness in her wrists, metatarsal-phalangeal joints, ankles, and right knee. Laboratory analysis on admission revealed a leukocyte count of 2.38×10^9/L (neutrophils 1.72×10^9/L; lymphocytes 0.57×10^9/L); hemoglobin 7.3 g/dL; platelet count 176×10^9/L; gamma-glutamyltransferase 69 IU/L (reference range: 5-36 IU/L); ferritin 1489 mg/dL; C-reactive protein (CRP) 231.7 mg/L; and erythrosedimentation rate (ESR) 120 mm/h. C3 and C4 complement fraction serum levels, lactate dehydrogenase (LDH), and serum β2 microglobulin were within normal limits. She was detected to be positive for both antinuclear antibodies (ANA) by immunofluorescence (IF) at 1: 320 titer with a speckled pattern and lupus anticoagulant (LAC), with a dRVV ratio of 1.79 (normal range 0.70-1.25). Antibodies to RNP, Sm, SS-A/Ro, SS-B/La, Jo-1, Scl-70, cardiolipin, and beta2GPI were all negative. Myeloperoxidase antineutrophil cytoplasmic antibody (ANCA) and proteinase 3 ANCA were both negative. Histology from a 4-mm punch biopsy of right gluteous skin lesions showed evidence of a granulocytic infiltrate with karyorrhexis in papillary derma (**Figure 1A, 1B**).

Virus profiles including HIV, hepatitis B virus, hepatitis C virus, cytomegalovirus (CMV), and Epstein-Barr virus (EBV) were negative. Multiple blood cultures were collected and all failed to grow bacteria, mycobacteria, or fungi. Urine and bone marrow cultures grew no organisms. Mantoux and QuantiFERON tuberculosis (TB) spot were negative.

A chest radiograph showed an opacity in the right upper pulmonary lobe without cavity, and bilateral sub-pleural nodular infiltrates in the upper lobes. Contrast computed tomography (CT) scans of the chest, abdomen and pelvis showed left pleural effusion, pulmonary right upper-lobe consolidation with air bronchogram and multiple necrotizing conglomerate mediastinal lymph nodes (**Figure 2A**).

Both transthoracic (TTE) and transesophageal echocardiography (TEE) showed a posterolateral and anterior pericardial effusion (0.5 cm). Fluid from a bronchoalveolar lavage (BAL) showed no evidence of acid-fast bacilli (AFB) on staining and culture. The patient underwent an endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) of the mediastinal lymph node. A molecular positivity for NTM was observed in collected samples. Further culturing revealed growth of *M. kansasii*. She was started on rifampicin (600 mg/day), isoniazid (300 mg/day), and ethambutol (1200 mg/day) and became afebrile 2 weeks later. Concomitantly, a diagnosis of

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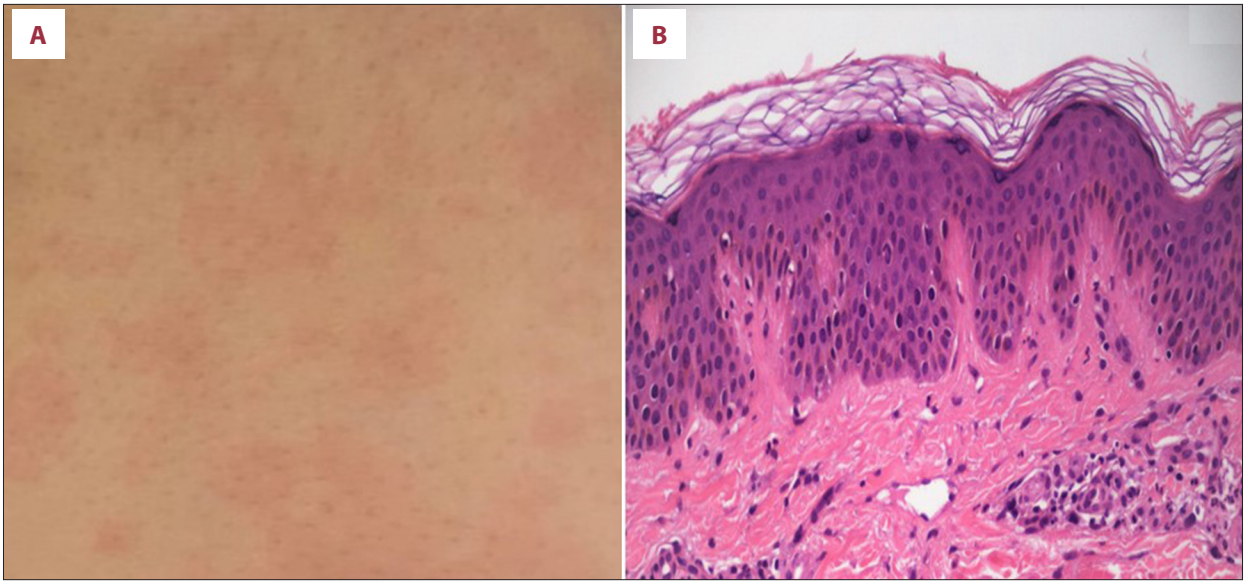

Figure 1. Erythematous maculopapular rash on the lower right limb (**A**); Granulocytic infiltrate with karyorrhexis in the papillary derma (**B**).

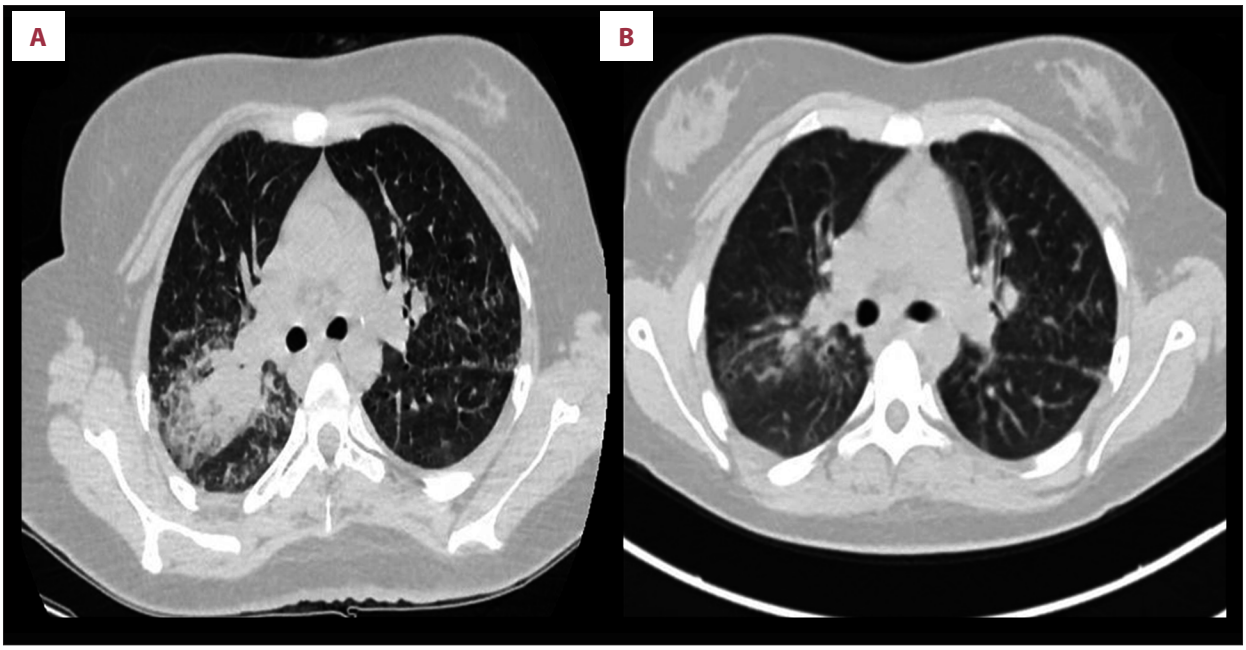

Figure 2. Contrast computed tomography (CT) comparison images of the pulmonary right upper-lobe consolidation with air bronchogram upper-lung infiltrates at the time of hospital admission (**A**) and after 6 months of treatment (**B**).

SLE was made based on the 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria. Hydroxychloroquine (400 mg/day) was started. The patient was referred for a quarterly rheumatological and infectious disease follow-up. She has experienced disappearance of skin rash, cough, and arthralgia. Laboratory findings have also improved and no treatment-related adverse events have been recorded up to now. A 6-month follow-up CT scan with positron emission tomography (PET) has revealed a significant reduction in size of the basal right upper-lobe consolidation, along with mild hypermetabolic activity in multiple pulmonary areas, mainly in the right upper lobe and mediastinal lymph nodes (**Figures 2B, 3**). BAL fluid was negative for AFB and no further cultures have been taken so far. Immunological tests were repeated and confirmed both ANA (titer of ≥1: 320, speckled pattern) and LAC positivity. The decision was made to maintain the ongoing therapy for 1 year in total, considering the patient's appreciable clinical improvement.

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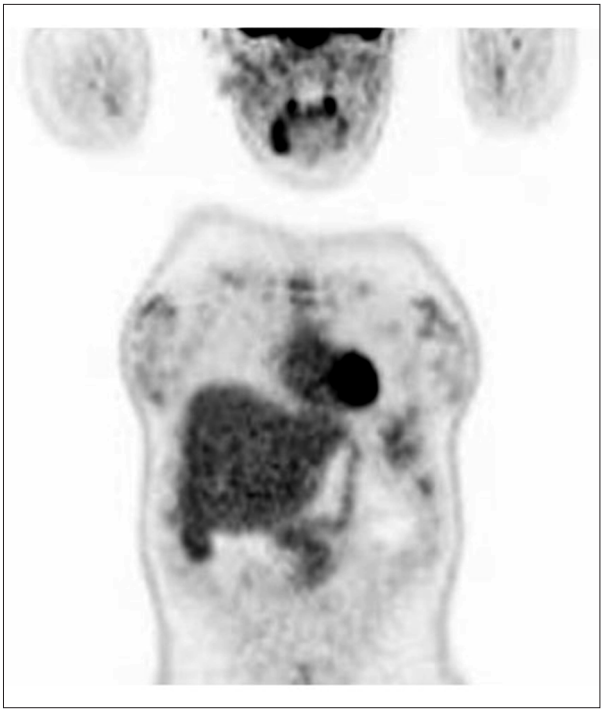

Figure 3. ^{18}Fluorodeoxyglucose PET/CT scan at 6 months follow-up, showing increased, not heterogeneous, radiotracer uptake within the right upper pulmonary lobe and multiple bilateral paratracheal, subcarinal, and hilar lymph nodes.

Discussion

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by production of autoantibodies and multi-organ damage. Activation of both the innate and the adaptive immune systems occurs in SLE, leading to the breach of self-tolerance and the emergence of autoreactive T cells. Chronic infections can activate autoreactive B cells and can induce their differentiation into memory cells, thus initiating autoimmunity in genetically predisposed subjects [1].

Since the late 1980s, the literature has suggested an association of mycobacterial infections with SLE and as a possible infectious trigger of autoimmunity. Mycobacterial infections cause an immune activation in which the innate immune system seems to play a key role in driving the autoimmune process. In 1988 Young and colleagues demonstrated that the immunodominant protein antigens of mycobacteria are stress or heat shock proteins (HSPs) [8]. When a process of infection occurs, both the microorganism and the invaded host cells respond by producing high levels of stress proteins. Based upon the observation that HSPs of *M. tuberculosis* are closely homologous to stress proteins in mammals, the mechanism of a molecular mimicry was advocated to support the hypothesis of mycobacterial infection acting as a trigger of autoimmune response and, eventually, overt autoimmune disease expression. Interestingly, some HSPs can also bind to a variety of other proteins and nucleic acids, resulting in the formation of immunogenic particles that are targets of marker sets of SLE autoantibodies. In recent decades, the identification of pattern recognition receptors on dendritic cells (DCs), which under homeostatic conditions actively contribute to maintaining self-tolerance, has provided further insight into the molecular pathways of activation of the innate immune system and its ability to drive autoimmune pathology. DCs are triggered upon encounter of factors termed danger-associated molecular patterns (DAMPs), which contain both microbial and endogenous molecules, and are able, in turn, to activate naïve T cells. Toll-like receptors (TLRs), which are members of this immune receptor family, and antimicrobial peptides, which are components of neutrophil granules and act as potent chemoattractants for mononuclear cells, dendritic cells, and CD45RA+ and CD8+ T-lymphocytes, have also been implicated in the process of infections, possibly triggering autoimmune diseases such as SLE [9-11].

The hypothesis of *M. tuberculosis* acting as a trigger of SLE has been supported by a nationwide population-based dataset of TB patients in Taiwan, where TB was reported as the greatest potential risk factor for precipitating SLE [5]. A previous clinical study in the endemic area of India had drawn similar conclusions [6]. Also, a transient triggering of autoimmunity in an otherwise immunocompetent individual which restored soon after a proper therapeutic regimen was started for a dual TB and fungi infection has been reported [12]. While in the last decades an increasing incidence of NTM infections that outnumber *M. tuberculosis* disease in tuberculosis-nonendemic countries has been recorded, clinical studies supporting a possible role of NTM in triggering autoimmunity are scarce [2]. In 2004 Takada and colleagues reported a case of pulmonary MAC infection which preceded by at least 3 months the onset of a severe SLE with renal involvement and required a combined course of intermittent intravenous cyclophosphamide pulse therapy, methylprednisolone, and mizoribine [7]. To the best of our knowledge, we describe here the first case of *M. kansasii* infection associated with the onset of SLE. Indeed, the scientific literature has so far reported the occurrence of *M. kansasii* infection in patients with a clinical history of SLE receiving immunosuppressive therapy [13-19]. *M. kansasii* is a slow-growing NTM, ubiquitous in the environment and widespread in water and soil.

The incidence of *M. kansasii* infections has increased worldwide, also spreading in healthy adults, in whom pulmonary disease and lymphadenitis are most common.

Unlike the case reported by Takada et al, in our case *M. kansasii* pulmonary infection was diagnosed simultaneously with

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SLE, which was prominently cutaneous and articular and seems to be under control by hydroxychloroquine treatment regimen to date. Nevertheless, we cannot rule out the possibility that in our young female patient pulmonary infection has preceded by at least 1 month the onset of SLE. Unfortunately, we have no data to support this hypothesis, as neither a pulmonary CT scan nor cultures were performed before her admission to the hospital.

The diagnosis of *M. kansasii* infection was challenging, as it is difficult to grow in culture and, as in the case of our patient, molecular techniques were required to strengthen its identification.

Conclusions

We present a unique case of *Mycobacterium kansasii* infection associated with the new diagnosis of SLE in a young woman. We emphasize, due to the increasing incidence of *M. kansasii* infection in tuberculosis-nonendemic countries, the need to pursue a comprehensive diagnostic process, which may also require the use of invasive diagnostic procedures and molecular techniques, in the presence of persisting, although non-specific, clinical symptoms in otherwise immunocompetent patients.

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