

## Case Report

# Diagnosis of TB Granuloma in SLE Patient by Kidney Biopsy

Chloe Declercq, Lincoln Lunga Khoza, Salah Bashir .

Department of Nephrology, Rob Ferreira Hospital, Mpumalanga, University of Witwatersrand, South Africa.

Email:salah.bashir23@yahoo.com

## Abstract

Lupus Nephritis is a common clinical manifestation affecting more than 50% of patients with Systemic Lupus Erythematosus (SLE), a chronic autoimmune disease that can affect virtually any organ. Whilst lupus nephritis is typically detected by an abnormal urinalysis with or without an elevated plasma creatinine, diagnosis is confirmed on renal biopsy. It is characterized by immunologic abnormalities including formation of immunocomplex deposits affecting the glomerular basement membrane, mesangium and/or subendothelial. It is by nature an immunocompromised state and along with its immunosuppressive treatment, lupus nephritis places a patient at high risk of opportunistic infections, including Tuberculosis (TB). A 21-year-old female presented with clinical features suggestive of lupus nephritis and a preserved renal function. The diagnosis was later confirmed on renal biopsy with an incidental finding of TB on renal histopathology. Interestingly, the patient had no constitutional symptoms or clinical history suggestive of TB. Antituberculosis treatment was initiated and mycophenolate, enalapril and prednisone was boarded after 2 weeks of TB treatment. The patient was later lost to follow up due to defaulting chronic treatment and follow up.

**Keywords:** systemic lupus erythematosus, tuberculosis, immunocompromised, granuloma

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## Introduction

The microbiology of systemic lupus erythematosus (SLE) and tuberculosis (TB) are unique. SLE is defined as an autoimmune disease that can have an affect multiple organs systems in the body. These being the central nervous system, dermatological system, cardiopulmonary system, gastrointestinal system and the renal system.

The pathogenesis of SLE involves the production of autoantibodies against self-antigens, leading to immune complex deposition and inflammation.<sup>1</sup>

Patients with SLE frequently require treatment with high doses of corticosteroids and immunosuppressive drugs, which can lead to secondary immunosuppression and increased susceptibility to infections.<sup>1,2</sup> In addition, primary defects in the innate immunity also

contribute to an increased susceptibility to infections in SLE patients whereby the patient's immune system is unable to mount a response and subsequently lead granuloma formation.<sup>1</sup>

Studies have further shown a higher incidence of TB in SLE presenting in its miliary form rather than as granuloma formation.<sup>3</sup>

On the other hand, TB is a granulomatous disease caused by *Mycobacterium tuberculosis* that can also affect multiple organs, including the lungs and kidneys.<sup>2</sup> The pathogenesis of TB involves the interaction between *M. tuberculosis* and host immune cells, leading to granuloma formation and tissue damage. The bacteria can avoid host immune responses by hiding within macrophages and other immune cells.

Granulomatous disease is a condition whereby the immune system creates granulomas, which can occur in various organ systems, including the lungs, skin, liver or kidneys. Granulomas, a cluster of various immune cells, form part of an immune response to wall off foreign substances or infections.<sup>2</sup>

A granulomatous induced inflammation causes cell injury and forms a distinct histologic pattern of tissue reaction. This inflammation is caused by a variety of conditions including infections, and autoimmune, toxic, allergic, drug, and neoplastic conditions. The tissue reaction pattern formed is distinct and assists in the pathologic and clinical differential diagnosis and thereby their management. Common patterns include a variety of granulomas, namely necrotizing, non-necrotizing, supportive, and diffuse granulomatous inflammation and foreign body giant cell reaction.<sup>2</sup>

A tuberculosis granuloma consists mainly of a collection of macrophages and highly differentiated cells including multinucleated giant cells, epithelioid cells and foamy cells. In TB, these cells are enclosed by a ring of lymphocytes. However, in SLE this mechanism is disturbed thereby preventing granuloma formation, although the pathogenesis is unclear.<sup>4</sup> There has been some reports of SLE patients having a risk of some granulomatous diseases, particularly granulomatous with polyangiitis (GPA), formerly known as Wegener's granulomatosis.<sup>4,5</sup>

In summary, SLE and TB have distinct microbiological pathways. Tuberculous granuloma formation has clear histological features, whereas granuloma formation in SLE is rare due to not clearly understood pathological pathways.<sup>5</sup> But co-infection in SLE and TB does occur due the pathophysiology of SLE itself, as well as its management with the use of high dose corticosteroids and immunosuppressive therapies that lead to secondary immunosuppression and hence increased susceptibility to infections.<sup>1</sup>

### **Case presentation**

21-year-old female from Mpumalanga, South Africa

Presentation: Referred from local clinic with 2-month history of fatigue, anasarca with predominant lower limb swelling. She had no significant medical, surgical or family history. The patient denied any symptoms of fever, cough, night sweats or loss of weight. On clinical examination, patient was hemodynamically stable with blood pressure 121/78 mmHg, heart rate 90 beats per minute, saturating well on room air, with urine dipstick of 4+ blood and 3+ proteins, and negative pregnancy test.

Clinically, she had grade 3 lower limb oedema extending from both feet until her knees, without any skin lesions. She had a normal JVP, no added heart sounds or murmurs, un-displaced apex, and lung fields were clear. Abdomen was soft, non-tender, distended, had a fluid thrill but had no organomegaly.

Investigations: ECG finding showed a normal sinus rhythm and normal axis. Chest X-ray revealed bilateral small pleural effusions. Blood investigations revealed a preserved renal function with creatinine 59 mmol/L and urea 7 mmol/L. She was anaemic with haemoglobin (HB) of 9.7 g/dL and white cell count (WCC) of  $9.1 \times 10^9/L$ , CRP 1 mg/L and normal lymphocytes  $1.99 \times 10^9/L$ , total protein was 48 g/L and albumin <15 g/L. Total cholesterol 3.6 mmol/L. Urine protein-creatinine ratio (PCR) 0.365 H g/mmol creat <0.015. Autoimmune screen was done: complements were low with C3 0.33L g/L and C4 0.09L g/L, anti-nuclear antibody (Ab) positive, anti-smooth muscle Ab strongly positive, antinuclear ribonucleoprotein Ab strongly positive, anti-cardiolipin Ab IgG positive. HIV ELISA negative, and negative hepatitis studies. Ascetic tap was done with exudative sterile peritoneal fluid cultured and negative tuberculosis (TB) tests.

Renal ultrasound findings revealed normal kidney sizes with good corticomedullary differentiation. Renal biopsy was thereafter performed via ultrasound guidance and samples taken and sent for histopathology. Histopathological examination showed chronic granulomatous interstitial nephritis and features of class 3 A/C lupus nephritis and an incidental finding of TB granulomas on renal histopathology.

Management: Anti-TB treatment was initiated and started on mycophenolate mofetil (MMF) and enalapril, while continuing with prednisone following two weeks of TB treatment. Unfortunately, patient defaulted treatment and lost to follow up.

## Discussion

SLE, an autoimmune disease, causes chronic inflammation and can affect all body organs and tissues. It produces autoantibodies that target self-antigens, including nuclear components, cell surface molecules, and cytoplasmic proteins. These autoantibodies produce immune complexes that deposit in a variety of tissues and organs. They then trigger complement activation, inflammation, and tissue injury. SLE further impairs the activity and regulation of the host immune system by reducing quantity and activity of T cells, particularly CD4+ T helper cells. The resulting impaired immune function is unable to distinguish self from non-self, and therefore attacks healthy tissue.<sup>6</sup>

As stated earlier, SLE patients are at a higher risk of TB due to their immunocompromised state due to SLE itself, as well as its treatment with immunosuppressive drugs.<sup>1</sup> Granuloma formation, TB's trademark immune response, a structured collection of macrophages, epithelioid cells, multinucleated giant cells, lymphocytes, fibroblasts, in an extracellular matrix. Granuloma formation is the immune system's protective mechanism to conceal TB and prevent its spread to other tissues.<sup>7</sup> The relationship between SLE and TB is interesting and complicated. On one hand, SLE influences the immune system by impairing the balance between

Th1/Th2/Th17 cytokines, reducing macrophage function, affecting nitric oxide synthase (NOS) expression and nitric oxide (NO) production, enhancing apoptosis of TB infected cells, increasing predisposition to necrosis in granulomas, and accelerating fibrosis in lung tissue.<sup>7</sup> Studies have further shown a higher incidence of TB in SLE presenting in its miliary form rather than as granuloma formation.<sup>3</sup>

On the other hand, TB can influence SLE's role in immune activity. It does this by triggering autoimmunity through molecular mimicry or bystander activation, accelerating autoantibody production, inducing SLE flares or exacerbations, and interacting with SLE treatment therapies used.<sup>8</sup>

Several studies have been performed and reported a relationship between SLE, TB and granuloma formation. A study by Chen et al. described the histopathology of lung granulomas in SLE patients with TB, SLE patients without TB, and non-SLE patients with TB. The study showed increased caseous necrosis, reduced fibrosis and reduced calcification in granulomas found in SLE patients with TB as compared to the non-SLE patients with TB. It also revealed reduced NOS2 expression, increased TGF- $\beta$  expression in the granulomas of SLE patients with TB than in non-SLE patients with TB. This suggests SLE's response to TB being that of tissue damage and inflammation promotion rather than granuloma formation in an attempt to conceal TB and prevent its spread. No remarkable difference in granuloma size or quantity was observed between SLE patients with TB and non-SLE patients with TB. The study did not investigate the relationship between SLE treatment and granuloma formation. This was due to the

SLE with TB patient population pool not receiving immunosuppressive therapies at time of diagnosis.<sup>9</sup>

A study done by Liu et al. investigated cytokine and chemokine expression found in pulmonary granulomas within SLE patients with TB, non-SLE patients with TB, and healthy controls. The study revealed increased expression of IL-6, IL-10, IL-17A, IL-23, CCL2, CCL5, and CXCL10 in granulomas of SLE patients with TB as compared with SLE patients without TB and the healthy controls. It further displayed reduced expression of IF- $\gamma$ , TNF- $\alpha$ , IL-12p40, and IL12p70 in granulomas of SLE patients with TB as compared with the other two study populations. These results promote the understanding of SLE limiting TB clearance and causing inflammation and tissue damage through alteration of the cytokine profile in granulomas from Th1-dominated to Th2/Th17-dominated response. No remarkable difference in granuloma size or quantity was also observed in this study between SLE patients with TB and non-SLE patients with TB. The study also did not investigate the relationship between SLE treatment and granuloma formation. This was due to majority of the SLE with TB patient population pool only receiving low dose corticosteroids.<sup>10</sup>

In summary, the studies reveal how SLE alters TB granuloma composition rather than its quantity through SLE's effect on cytokine expression, histological features, and macrophage activity within granulomas. This alteration produces inflammation, fibrosis, limited bacterial elimination, increased necrosis, and reduced lung function as seen in pulmonary granulomas. The role of SLE treatment and its effect on TB granulomas is unclear due to both studies having SLE

patients with TB either on low dose corticosteroids or on no immunosuppressive therapy at all. Therefore, more research is indicated to further explore the relationship and pathophysiology between SLE, TB and granuloma formation.<sup>10</sup>

### Conclusion

SLE is an immunocompromised condition due to the nature of the disease itself as well as the immunosuppressive therapies

used in its treatment. Thereby placing these patients at higher risk of TB co-infection. However, due to SLE's pathophysiology, granuloma formation is rare and patients more often present with miliary TB. What makes this case study interesting is that this SLE patient had no constitutional symptoms of TB, and diagnosis was only made on renal biopsy which revealed TB granulomas.

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