Valvulopathy and new onset psychosis in a patient with rheumatoid arthritis: a case to challenge the diagnosis of rhupus

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Abstract

Rheumatologic disease includes a vast array of distinct diagnostic entities. Although clinical manifestations may differ, they all share a common inflammatory reaction driven by auto-immunity. Up to 25% of patients with pathognomonic clinical features remain undiagnosed due to paucity of standardized diagnostic criteria, and therefore the use of diagnostic classifications. Patients may present with clinical features of more than one rheumatologic condition, further complicating the diagnostic process. The advent of disease modifying anti-rheumatic drugs has revolutionised care of these patients in recent years, which place the burden firmly on accurate diagnosis.

In this case report we present a young female with Rheumatoid Arthritis (RA) presenting with first onset psychosis, fever, oral mucosal ulceration and echocardiographic findings of aortic valve thickening. These lesions may be in keeping with Libman-Sacks Endocarditis (LSE) or rheumatoid valvulopathy. She was diagnosed with RA 3 years prior to presentation based on the American College of Rheumatology/ European League Against Rheumatism Collaborative Initiative (ACR/EULAR) classification criteria for RA. The patient met the diagnostic classifications of both RA and Systemic Lupus Erythematosus (SLE) and a diagnosis of rhupus was postulated, however, she tested negative for anti-double stranded deoxyribonucleic acid (anti-dsDNA) and anti-Smith (anti-Sm) antibodies.

This case illustrates the complexity of diagnosis in rheumatology. RA and SLE are well defined rheumatological conditions, but result from different immunological processes and present with different clinical presentations. Rarely, features of both diseases present in the same patient, and classification criteria are met for both conditions. Rhupus is a condition which presents as an overlap between RA and SLE, and should be recognised as a unique clinical entity with a different clinical presentation, natural history, management and prognosis. This case represents a clinical entity with overlap features of RA and SLE, but lack the auto-immune markers typical of rhupus.

Key words: Rhupus, Rheumatoid arthritis, Systemic lupus erythematosus

Introduction

Rheumatologic disease include over 200 distinct clinical syndromes primarily targeting connective tissues of multiple organ systems, and are typically associated with inflammatory symptoms impacting the quality of life and activities of daily living of those affected. Many of these diseases are multi-systemic, and affect vital organ systems that alter the prognosis and management thereof. Up to 25% of patients with pathognomonic clinical findings may remain undiagnosed as they do not meet the required criteria. Rheumatologic disease is diagnosed using classification criteria, which are generally very specific, but lack sensitivity. SLE and RA are both well-known auto-immune conditions, and present in characteristic patterns of clinical and serologic findings, easing the diagnostic process of each entity.

Rheumatoid arthritis is a condition characterized by erosive inflammation of synovial joints that may lead to progressive joint deformity, whereas SLE tends to cause non-erosive arthritis. The first-mentioned condition typically presents with a symmetric polyarthritis of smaller joints with a predilection for the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of the hands. The disease spectrum of RA may also include multiple extra-articular manifestations and implicated auto-antibodies include Anti-Citrullinated Peptide Antibodies (ACPA) and Rheumatoid Factor (RF). Diagnosis is based on the 2010 ACR/EULAR classification criteria, and includes clinical and serologic domains.

SLE is a chronic auto-immune condition that may affect any organ system of the body. A vast array of symptoms may result, but arthritis tends to be non-erosive and affect larger joints more asymmetrically. As opposed to the T-helper 1 (Th1) response of RA, inflammation in SLE is caused by a Th2 mediated reaction. The 2019 ACR/EULAR classification criteria can be utilised as diagnostic tool. Anti-dsDNA and anti-Sm antibodies are considered highly specific for SLE and, when present, are virtually diagnostic.

Different connective tissue disorders may share signs, symptoms and pathologic sequelae; overlap syndromes can be diagnosed when classification criteria for more than one disease are met. The first reference to patients diagnosed with both SLE and RA is by Toone *et al*[8] in 1963 after identifying a group of 15 patients with SLE who eventually developed erosive arthritis. Over the ensuing years many of these overlap diagnoses were made until, in 1971, Peter Schur coined the term 'rhupus', referring to patients satisfying both classification criteria.

Many authors have classified rhupus as merely a subset of SLE, but significant evidence has supported the presence of this condition as a distinct entity, with a different clinical presentation, treatment and prognosis to either SLE or RA. Simon *et al*[10] defined rhupus as a symmetric and erosive polyarthropathy with accompanying signs and symptoms of SLE, and the presence of highly specific anti-dsDNA or anti-Sm antibodies.

With the scarcity of information on this condition, it is imperative that potential cases are reported and investigated to ultimately ensure further improvement in the diagnosis and management of these patients desperately in need of effective treatment. In this article we set out to report a case of a young female with RA, presenting with clinical features suggestive of rhupus.

Case report

A 24 year old Black African female presented to hospital with first-onset psychosis. She was diagnosed with RA 3 years prior to this presentation based on a positive ACPA and high RF titre (>650iU/mL). Other features included a symmetrical, erosive polyarthritis, a raised Erythrocyte Sedimentation Rate (ESR) and C-Reaction Protein (CRP), as well as a symptom duration of longer than 6 weeks. The patient is reported to have denied the diagnosis for the first 2 years and have thus been initiated on methotrexate (MTX) only 12 months prior to presentation. Further probing revealed that she had required assistance with activities of daily living and was wheelchair bound due to her hand and foot deformities.

Table 1: Vital signs upon presentation

Heart rate	102 beats per minute
Blood pressure	124/82 mmHg
Respiratory rate	18 breaths per minute
Temperature	36.2 degrees Celsius
Arterial oxygen saturation	98% on room air

Table 1 presents vital signs upon presentation. Neither her vital signs nor general physical examination were alarming, except for the visible joint deformities and an antalgic gait pattern.

Respiratory and abdominal examinations were normal. On cardiovascular examination, the Jugular Venous Pulsation (JVP) was not elevated and the apex beat was non-displaced and of normal character. The patient had no features of heart failure or pulmonary hypertension, but a high-pitched, early diastolic murmur was heard over Erb's point. She had positive Corrigan, Traube and Duroziez signs in keeping with a hyperdynamic circulation. On central nervous system examination she was orientated to time, person and place, but subjectively reported visual hallucinations. No other focal neurology was found.

Her rheumatological examination revealed no skin rashes or alopecia, but she had multiple oral ulcers on her lips and hard palate. She had multiple hand and foot deformities including bilateral hallux valgus with overriding toes and MCPJ fixed flexion deformities with IPJs in hyperextension (Figure 1). She had no wrist or ankle swelling, rheumatoid nodules or features of Raynaud's phenomenon. The patient did not report any sicca symptoms or swallowing difficulties. She subsequently underwent a thorough diagnostic workup, including a normal electrocardiogram, chest X-ray, brain Computed Tomography (CT) scan and lumbar puncture. Hand and foot X-rays revealed marked periarticular osteopenia and narrowing of joint spaces in both hands and feet, with no specific periarticular erosions. One could also appreciate bilateral hallux valgus and, due to flexed MCP, it was difficult to comment on subluxation/dislocation on the AP view (Figure 2). Dipstick examination of urine was clear and she excreted 200mg of protein per day. Haematologic investigations from the time of admission are listed in Table 2.

Figure 1: Right hand of patient with features of arthropathy (left); Valgus deformity of left hallux (right)

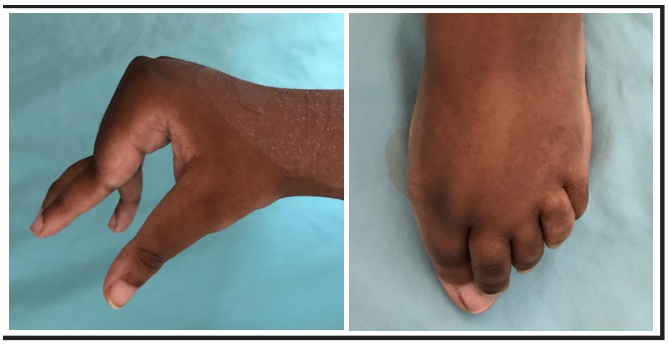


Figure 2: Radiographic evidence of hallux valgus (left); hand X-rays showing evidence of subluxation of metacarpophalangeal joints (right)

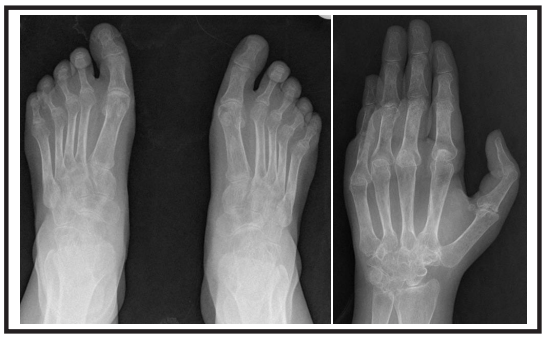
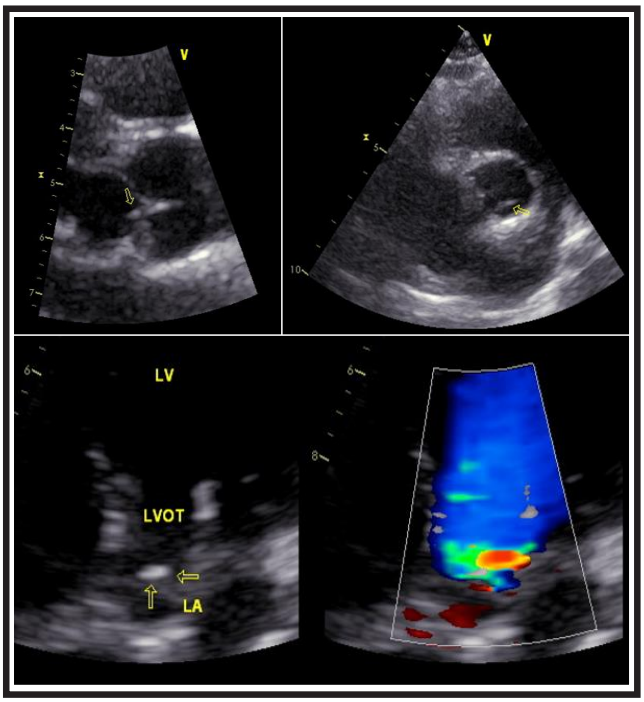


Table 2: Patient blood results

Test	Result	Reference range
Sodium [mmol/L]	132	136 – 145
Potassium [mmol/L]	4.1	3.5 – 5.1
Urea [mmol/L]	2.8	2.1 – 7.1
Creatinine [umol/L]	48	49 – 90
White cell count [x10^9/L]	11.58	3.90 – 12.60
Haemoglobin [g/dL]	10.5	11.6 – 16.4
Mean corpuscular volume [fL]	68.2	78.9 – 98.5
Mean cell haemoglobin concentration [g/dL]	28.4	32.7 – 34.9
Platelets [x10^9/L]	465	186 – 454
Total protein [g/L]	82	60 – 78
Albumin [g/L]	35	35 – 52
Total bilirubin [umol/L]	3	5 – 21
Conjugated bilirubin [umol/L]	1	0 – 3
Alanine aminotransferase [U/L]	26	7 – 35
Aspartate aminotransferase [U/L]	15	13 – 35
Alkaline phosphatase [U/L]	93	42 – 98
Gamma-glutamyl transferase [U/L]	37	<40
C-reactive protein [mg/L]	48	<10
Erythrocyte sedimentation rate [mm/Hr]	44	0 – 10
Thyroid stimulating hormone [miU/L]	1.15	0.35 – 5.50
Thyroxine [pmol/L]	16.0	11.5 – 22.7
Blood culture – aerobic, anaerobic [result]	No growth	
HIV ELISA [result]	Negative	
Treponema pallidum haemagglutinin assay [result]	Negative	
Rheumatoid factor [iU/ml]	>650	<20
Uric acid [mmol/L]		0.16 – 0.36
Anti-citrullinated peptide antibody [result; titre]	Strong positive; 182	
Anti-nuclear antibody – HEP2 cells [result; titre]	Positive; 320	
Anti-nuclear antibodies pattern	Homogenous	

On echocardiography the patient was found to have thickened aortic valve leaflets with flutter seen in diastole and moderate aortic regurgitation (Figure 3). These lesions may be related to either RA associated valvulopathy or LSE (associated with SLE). The heart appeared structurally normal, with no other leaflet abnormalities.

Figure 3: Aortic valve thickening valvular vegetation on aortic valve projecting into the ventricle (top-left); vegetation in left ventricular outflow tract (top-right, bottom-left); aortic regurgitation (bottom-right



She had multiple episodes of low-grade fever during her 21-day hospital stay, but infective endocarditis was ruled out by means of serial blood cultures and inflammatory markers. By day 4 of the patient's admission, her psychotic symptoms had abated. No malingering or psychosomatic disorder was suspected.

A preliminary diagnosis of an overlap syndrome (rhupus) was made based on meeting the classification criteria of both RA and SLE according to the ACR/EULAR classification. Features of SLE included intermittent fever, psychosis, oral ulceration, active arthritis and possible LSE on echocardiogram. Further workup included normal complement C3/C4 levels, and negative results for anti-dsDNA, Extractable Nuclear Antibodies (ENA), anti-Sm antibody, Anti-Smooth Muscle Antibody (ASMA), anti-ribonucleoprotein antibody, anti–Sjögren's-syndrome-related antigen A (Ro) and B (La) autoantibodies, Anti-Jo-1 antibody and anti-Scleroderma-70 antibody.

The patient remained haemodynamically stable throughout her admission of 21 days, during which MTX was changed to hydroxychloroquine. She was eventually discharged with future follow-up at a specialized rheumatology outpatient's clinic, where she receives ongoing management for rhupus.

Discussion

This case illustrates the complexity of diagnosis in rheumatology. The clinical picture in this case is strongly suggestive of an overlap between RA and SLE as the patient met the classification criteria of both. Certain diagnostic features were difficult to ascribe to either RA or SLE, as evidenced by the following:

(i) Aortic valve thickening may be related to RA valvulopathy or LSE as a consequence of SLE.
(ii) Psychosis may rarely result from MTX therapy.
(iii) Arthritis is common in RA and SLE, although RA tends to cause a more erosive and debilitating arthritis.

The negative anti-dsDNA, and ENA and anti-Sm antibodies make the diagnosis of SLE less likely and a positive ANA may be present in severe RA. Psychosis, intermittent fever and oral ulceration were out of keeping with a diagnosis of RA.

An important lesson to learn from this case would be the correct implementation of the classification criteria for rheumatological conditions. Even though this patient had psychosis, oral ulcers and fever, the diagnosis of SLE cannot be made due to the lack of serological features. The valvulopathy and the arthritis are features of both RA and SLE and the decision needs to be made whether these features weigh more heavily on the side of SLE or RA. RA is much more likely due to the significantly raised RF and positive ACPA as well as the X-ray evidence of erosive arthritis. The psychosis cannot be explained well and should be monitored, but may be psychological or related to therapy (corticosteroids, MTX and non-steroidal anti-inflammatory drugs). The proteinuria should also be monitored. It is not significant enough to diagnose lupus nephritis. A score of 7 is achieved in SLE classification criteria when arthritis is excluded.

The case demonstrates the shortcomings of the classification criteria and how it may be confounded by clinical features of more than one distinct clinical entity. It also demonstrates that criteria can only be used with confidence if no other possible explanations for these criteria are present. Common sense and experience remain critical in diagnosing medical conditions, especially those that do not have a gold standard diagnostic test. Strict classification criteria of rhupus has not yet been agreed upon by consensus decision, and the definition proposed by Simon *et al*[14] requires the presence of specific autoantibodies that are absent in this case. These findings may implicate that a broader definition and more inclusive criteria be developed for rhupus. Ultimately, it is important to be aware of rhupus and the possibility of overlapping auto-immune conditions.

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