High C-reactive protein in afebrile systemic lupus erythematosus patients without palpable synovitis: pericardial involvement should be considered

Sirs,

Systemic lupus erythematosus (SLE) is a heterogeneous multisystem autoimmune disease. It is widely believed that C-reactive protein (CRP) remains normal or only modestly elevated in uninfected SLE patients despite intense disease activity (1-2). However, it is often difficult to differentiate between a disease flare and infection when SLE patients have high CRP, especially when it presents with concomitant fever. Cardiac involvement in SLE is not uncommon, and most commonly manifests as pericardial effusion and/or pericarditis, which may progress into more life-threatening large effusions and tamponade (3-4).

We describe three afebrile female SLE patients without palpable synovitis who developed pericardial effusion and/or pericarditis and elevated CRP. They consecutively presented between April and June 2020 at the University Hospital of Kerry, Ireland (Table I). All patients fulfilled the new European League against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria for SLE (5). CRP levels were measured by immunoturbidimetric assay on a Beckman Coulter AU analyser (Beckman Coulter, CA, USA).

The first patient was a 67-year-old female on maintenance hydroxychloroquine 400 mg daily and mycophenolate mofetil 500 mg twice daily, who presented to the emergency department (ED) with a 3-week history of non-specific symptoms, mainly fatigue. She denied any shortness of breath or chest pain. She was afebrile with normal vital signs and, apart from looking pale, physical examination was unremarkable, including normal heart sounds without murmur and no palpable synovitis. Blood analysis demonstrated CRP of 255mg/L, haemoglobin (Hb) of 7.8g/dL, platelet count of $631x10^9$/L, lymphocytes of $0.39x10^9$/L, mildly elevated transaminases (AST 64 U/L; ALT 63U/L) and normal renal function. Urine dipstick was negative for protein or blood.

Initial cardiac screening (including ECG and serial troponins) was unremarkable. Septic screen was negative, including negative nasopharyngeal SARS-CoV-2 RT-PCR swab. Chest radiograph evidenced newly developed cardiomegaly without pleural effusion or infiltrate that prompted an urgent transthoracic echocardiogram (TTE). This revealed large posterolateral pericardial effusion, mildly impaired left ventricular function without tamponade or constrictive features. Computed tomography pulmonary angiogram (CTPA) revealed small left sided pleural effusion, but no evidence of pulmonary embolus (PE). She remained haemodynamically stable and was transferred to the coronary care unit for close observation. Her symptoms and CRP levels responded promptly with high-dose oral prednisolone taper and low dose colchicine, while her Hb slowly improved and serial echocardiogram demonstrated full resolution of pericardial fluid and ventricular function.

The second patient was a 47-year-old female presenting with substernal pleuritic chest pain associated with positional variation and dyspnoea. She had non-specific arthralgia and no evidence of clinical synovitis. She had been previously diagnosed with SLE fulfilling the diagnostic criteria at a different rheumatology centre; however, her hydroxychloroquine was eventually stopped after she remained in remission for several years. There was no history of thromboembolic events or rheumatic fever. Blood analysis demonstrated mild but persistently elevated CRP (between 9–21mg/L within 12 months), low platelet of $101x10^9$/L with normal liver and renal profiles. Initial cardiac screening and septic screen were negative. TTE demonstrated a small pericardial effusion and moderate aortic regurgitation. She was given a rapid tapering dose of oral steroid therapy, recommenced taking hydroxychloroquine and started on azathioprine with resolution of all symptoms, blood indices and pericardial effusion (on repeated TTE).

The third patient was a 64-year-old female previously diagnosed with seronegative inflammatory arthritis after initially presenting with symmetrical polyarthritis; however, failed multiple disease-modifying anti-rheumatic drugs (DMARDs) including conventional DMARDs, several anti-tumour necrosis factors (anti-TNFs) and a janus kinase (JAK) inhibitor. She then developed recurrent dyspnoea associated with pleuritic-type chest pain and presented on several different occasions to the ED with normal initial cardiac screening and CTPA. TTE demonstrated small but stable pericardial effusion (compared to previous TTE).

These findings combined with 1) persistent but mildly elevated CRP (between 6–42 mg/L) within a period of 18 months; 2) development of significant lower limb rashes; 3) ultrasound demonstrating synovial thickening of multiple joints but without evidence of acute synovitis; this prompted a reassessment of her diagnosis. Antibodies were positive for ANA, anti-dsDNA, and crithidia anti-dsDNA with negative anti-histone antibody. She was started on an oral steroid taper but was never really able to be weaned off steroids completely or reduced to lower acceptable doses; she was subsequently put on rituximab with a resolution of symptoms, CRP and TTE finding.

Despite no current established predictive factors to assess patients who are at greatest risk to develop pericarditis in SLE patients, our small case series highlights: 1) presence of markedly elevated CRP (>50mg/L) especially without development of fever or palpable synovitis in SLE patients should warrant prompt

Table I. Summary of SLE patients with elevated CRP and pericardial involvement.

	Patient 1	Patient 2	Patient 3
ANA	+	+	+
Anti-dsDNA	+	+	+
Antiphospholipid antibodies	-	+	-
Low C3/C4	Both	Both	-
Leukopenia	+	+	-
Lymphopenia	+	+	+
Thrombocytopenia	-	+	-
Oral ulcers	-	+	-
Renal disease	-	-	-
ECHO findings			
Pericardial involvement	Large posterolateral effusion	Small effusion	Small posterior effusion
Valvular status	Thickened AV	Thickened AV/MV Moderate AR/MR	Normal
Concomitant pleural effusion	Small left effusion	-	-

cardiac investigation (including urgent echocardiogram) to avoid delay in the diagnosis of a possible life-threatening pericardial disease and subsequent life-saving intervention; and 2) persistently mild/modest elevation of CRP may reflect chronic serositis in SLE patients.

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Competing interests: none declared.

Clin Exp Rheumatol 2021; 39 (Suppl. 128): S23-S24.

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