or quinacrine, which are particularly recommended in patients with a high risk of scarring and/or the development of systemic disease. In addition, systemic corticosteroids are recommended as first-line treatment in highly active and/or severe CLE. Second- and third-line systemic treatments include methotrexate, retinoids, dapsone and mycophenolate mofetil or mycophenolate acid, respectively. Thalidomide should only be used in selected therapy-refractory CLE patients, preferably in addition to antimalarials. Several new therapeutic options, such as B-cell- or interferon alpha-targeted agents, need to be further evaluated in clinical trials to assess their efficacy and safety in the treatment of patients with CLE.

In 2011, the monoclonal antibody belimumab, a B lymphocyte stimulator-specific inhibitor, was introduced for SLE as an adjunct therapy for patients with autoantibody-positive disease who despite standard therapy show high disease activity, intolerance of other treatments, or an unacceptably high need for corticosteroids. Currently, a validated skin score is used to confirm the efficacy of belimumab on mucocutaneous manifestations.

In summary, there is a high unmet need for new therapeutic strategies, such as B-cell- or interferon-targeted agents, focusing on cutaneous manifestations in lupus erythematosus. Therefore, innovative designs of randomised controlled trials are warranted to develop new therapeutic options for patients with refractory skin manifestations in this disease.

Case 1: 40-year-old man with SLE and painful erythematous-violaceous lesions

Marzia Caproni

A 40-year-old man was diagnosed with systemic lupus erythematosus (SLE) in 2013 based on photosensitivity, Raynaud's phenomenon, positive direct Coombs test, ANA, anti-dsDNA, Sm, Ro, La, RNP antibodies and low complement, followed by malar rash and discoid lesions on the ears. He started hydroxychloroquine (HCQ) 400 mg/day, nicotinamide 500 mg/day, topical corticosteroids and calcineurin inhibitors with benefit, followed by reactivation of malar rash, worsening of immunological parameters, proteinuria and lupus nephritis two years later. Prednisone 25 mg/day and mycophenolate mofetil (MMF) 640 mg/day were added with good clinical and laboratory control. In March 2018 he was hospitalised because of suspected macrophage activation syndrome triggered by cytomegalovirus and MMF was withdrawn. As lupus reactivated, in May 2018 he restarted MMF 320 mg/day with prednisone 25 mg/day and HCQ 200 mg/day. In August 2018, rituximab was administered because of the development of sensory neuropathy with no improvement, thus he underwent intravenous immune globulin treatment with control. In 2020, he developed painful erythematous-violaceous lesions associated with small bullae and ulcers on the distal phalanges of the fingers and toes and of the tip of the nose. Skin lesions were consistent with chilblain lupus. Topical corticosteroid was added. Systemic treatments were replaced by belimumab.

Discussion Points

- Specific and non-specific skin manifestations during SLE course
- Cutaneous lupus erythematosus (CLE) guidelines
- Chilblain lupus: differential diagnosis at the time of Covid-19

Case 2: 35-year-old female with SLE and erythematous-desquamative plaques

Marzia Caproni

A 35-year-old female was diagnosed with SLE in 2013 on the basis of discoid lesions of the face and head,

photosensitivity, ANA positivity, lymphadenopathy, hypocomplementemia, leukopenia, low-grade fever and diffuse arthralgias. Comorbidities included Hashimoto's thyroiditis and fibromyalgia under L-tyroxine, baclofen and escitalopram treatment. She started HCQ 400 mg/day and prednisone 25 mg/day, tapering to 5 mg/day with initial control. After 2 years of treatment arthralgias worsened as well as skin lesions and laboratory findings. On examination, atrophic painful plaque of the scalp and erythematous-desquamative plaques on the face were revealed. Topical and IV corticosteroids were added without improvement. Patient also underwent methotrexate, cyclosporine, mycophenolate, rituximab and azathioprine treatment without improvement. We introduced mepacrine 100 mg/day with skin lesion improvement. Due to the difficulty in finding the drug, the patient stopped the treatment with reactivation of the skin manifestations and systemic involvement. We started belimumab 660 mg IV with HCQ 400 mg/day, prednisone 5 mg/day, azathioprine 50 mg/day and duloxetine 60 mg/day with control.

Discussion Points

- Discoid lupus erythematosus: clinical and histopathological findings
- CLE guidelines: topical treatments of discoid lupus erythematosus
- CLE guidelines: mepacrine in recalcitrant cutaneous lupus erythematosus
- Belimumab and skin lesions in SLE

Learning Objectives

- Discuss specific and non-specific skin manifestations of SLE
- Describe optimal clinical management of skin lupus in line with CLE guidelines and the role of biologic therapy
- Explain the challenges of differential diagnosis in patients with CLE

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¹Murray Urowitz, ²Eloisa Bonfá, ³Bernardo Pons-Estel. ¹University of Toronto, Canada; ²University of São Paulo Medical School, Brazil; ³Regional Center for Autoimmune and Rheumatic Diseases and the Cardiovascular Institute of Rosario, Argentina

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Case 1: 39-year-old female with a premature atherosclerotic event

Murray Urowitz

This case is of historical importance as it initiated the investigations leading to the description of the bimodal mortality program in systemic lupus erythematosus (SLE).

MB is a 39-year-old female with a history of SLE diagnosed at 19 years old. Lupus manifestations included

arthralgia/arthritis, pericarditis, significant skin involvement with photosensitivity, and malar and discoid rashes. There was no history of nephritis. Extensive skin involvement necessitated daily steroids for many years. Every attempt to taper steroids below 20 mg resulted in significant flares. She was treated with azathioprine, but despite this continued to require steroids to control symptoms over the next 19 years.

She presented to the emergency room (ER) for evaluation of retrosternal chest pain. The ER physician thought the likely etiology was pericarditis, and consideration was given to increasing the patient's steroids. However, on physical examination she was found to be hypertensive and electrocardiogram (ECG) showed evidence of an old anterolateral myocardial infarction (MI) and diffuse ST depressions. Cardiac enzymes were elevated.

Shortly after being admitted to the hospital, she developed worsening chest pain. Repeat ECG showed worsening ST depressions and acute ST elevations. She rapidly decompensated and died soon thereafter of acute MI.

Autopsy revealed cardiomegaly, and generalised atherosclerosis with severe disease of all coronary arteries, mild disease of the aorta, moderate disease of iliac arteries, severe disease of left renal artery, LAD, RCA, LCx occluded by old recanalised thrombi. There was evidence of old anterolateral infarct and new anteroapical infarct.

The pathologist concluded: 'This patient is of interest from many points of view, one of which is the development of such severe atherosclerotic disease at such an early age in a non-diabetic female.'

Discussion Point

- Premature atherosclerotic events are a major comorbidity in SLE, and early diagnosis and prevention therapy are crucial

Case 2: 20-year-old Caucasian female with hypertension

Murray Urowitz

A 20-year-old Caucasian female presented with malar rash, polyarthritis (MCPs, PIPs bilaterally), Raynaud's phenomenon, oral ulcers, and pleurisy. Serology: ANA + (1/1600 IF), anti-DNA (+), normal C3/C4, no cytopenias. There was no evidence of other organ involvement. She was treated with chloroquine 250 mg/day with good response.

Two years later she flared with polyarthritis and was treated with prednisone 40 mg/day, gradually decreased to 15 mg/day.

Her atherosclerotic risk factors included:

- BP: 130–139/80–89 mmHg
- Cholesterol: 220–240 mg/dl (managed with low-fat diet)
- Triglycerides: 250–350 mg/dl
- Ex-smoker (quit in 1982, approximately 4–5 pack-years)
- No diabetes
- No obesity (BMI=24.2)
- No family history of premature coronary artery disease

Age 24 years: Pregnancy/healthy boy with C-section due to pre-eclampsia.

Age 24–27 years: She had relapsing-remitting disease (mainly mucocutaneous and musculoskeletal): treated with prednisone 15–30 mg/day consistently, Chloroquine 250 mg/day, topical treatments. Azathioprine was added as a steroid-sparing agent but discontinued later due to a hypersensitivity reaction.

Age 27 years: She suffered an Acute MI(STEMI) with typical chest pain, ECG changes, plus elevated cardiac enzymes. Angiogram revealed completely occluded right coronary artery, moderate occlusion (approximately 50%) in circumflex and left

anterior descending arteries. She received conservative treatment: acetylsalicylic acid 650 mg/day and thiazide diuretics.

Age 28 years: This is the first time her hypertension is mentioned in rheumatology clinical notes, consistently 130–140/95–105 mmHg and attributed to glucocorticoids. Diltiazem 90 mg/day was added to her therapy.

Age 29 years: She experienced unstable angina, was admitted to Hospital and had a triple bypass. The operation was uneventful. Propranolol 20 mg bid was added. There had been no active disease (clinically and serologically for the last 6 months before the surgery).

The patient remained well after the bypass surgery. BP was controlled. Gemfibrozil 600 mg/day was added for cholesterol/triglycerides.

Age 30 years: Her second pregnancy with birth of a healthy girl by C-section. She remained clinically/serologically quiescent afterwards and tapered prednisone successfully, discontinuing at age 30 years. Maintenance therapy was chloroquine 250 mg/day. There were no other complications. She died at the age of 50 (cause unknown).

Discussion Point

- This patient was not clinically hypertensive according to older guidelines. However, she was hypertensive according to the new AHA guidelines of <130/<80 which should become our new standard for diagnosing and treating hypertension in SLE

Case 3: Managing cardiovascular risk in a 50-year-old woman diagnosed with SLE 10 years ago

Eloisa Bonfá

A 50-year-old woman diagnosed with SLE 10 years ago, presented with malar rash, polyarthritis, thrombocytopenia, proteinuria, hypertension, normal creatinine, positive anti-dsDNA and low complement. She had been a smoker for 15 years. She was treated with mycophenolate mofetil (MMF) prednisone, hydroxychloroquine (HCQ), anti-hypertensive with complete renal response in 6 months and sustained remission since then. Carotid ultrasound revealed presence of plaques. She had a history of diabetes controlled with metformin and her father had a history of MI.

She currently has no complaints or features of lupus. Her BP is 120/80 on MMF (1.0 g/day), HCQ and ACE inhibitor. Her labs are presently normal, except for TC 265 mg/dL; LDL 183 mg/dL; HDL 52 mg/dL; TG150 mg/dL.

Discussion Point

- What do you consider the most appropriate management for cardiovascular risk for this patient?

 1. High-risk patient (target LDL <100 mg/dL): Start on high dose statin and other measures (lifestyle intervention, smoking cessation, diet orientation, blood pressure control and check contraceptive drugs/hormonal replacement therapy) and reduce dose according to LDL levels.
 2. High-risk patient (target LDL <70 mg/dL): Start on high dose statin, low dose aspirin (ASA) and other measures and reduce dose according to LDL levels.
 3. High-risk patient (target LDL <70 mg/dL): Start on high dose statin and other measures and reduce dose according to LDL levels.
 4. High-risk patient (target LDL <70 mg/dL): Start on high dose statin and other measures and sustain dose independent of LDL levels.
 5. High-risk patient (target LDL <100 mg/dL). Start on low dose statin and other measures. Adjust statin as necessary.

Case 4: Managing cardiovascular risk in a 35-year-old woman diagnosed with SLE 3 years ago

Eloisa Bonfá

A 35-year-old woman diagnosed with SLE 3 years ago, presented with malar rash, polyarthritis, thrombocytopenia, proteinuria, hypertension, normal creatinine, positive anti-dsDNA and low complement. She is a non-smoker. She was treated with MMF, prednisone, HCQ, anti-hypertensive with complete renal response within 6 months and sustained remission since then.

She currently has no complaints or features of lupus. Her BMI=24Kg/m², BP 120/80 on MMF (1.0 g/day) and an ACE inhibitor. She self-discontinued HCQ 1 year ago. Presently her labs are normal, except for TC 168 mg/dL; LDL 120 mg/dL; HDL 30 mg/dL, TG 90 mg/dL.

Discussion Point

- What do you consider the most appropriate management for cardiovascular risk for this patient?
- 1. Low-risk patient (target LDL <100 mg/dL): Start on low dose statin and other measures (lifestyle intervention, smoking cessation, diet orientation, blood pressure control and check contraceptive drugs/hormonal replacement therapy).
- 2. Low-risk patient (target LDL <100 mg/dL): Start on low dose statin, HCQ and other measures.
- 3. Low-risk patient (target LDL <100 mg/dL): Start on HCQ 3 months and other measures if no improvement, add low-dose statin.
- 4. Low-risk patient (target LDL <100 mg/dL): Start on HCQ 3 months and other measures. Check for hypothyroidism. If no improvement, add low dose statin.
- 5. Low risk patient (target LDL <100 mg/dL): No need for specific therapy for dyslipidemia. Lifestyle intervention, smoking cessation, diet orientation, blood pressure control and check contraceptive drugs and hormonal replacement therapy. If no improvement, add low dose statin.

Learning Objectives

- Describe the present burden of atherosclerotic vascular disease in SLE
- Explain the occurrence of subclinical and preclinical disease
- Discuss approaches for better control of risk factors for the future including hypertension and hyperlipidemia
- Describe possible beneficial effects of antimalarials

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FERTILITY AND PREGNANCY ISSUES IN PATIENTS WITH LUPUS NEPHRITIS

¹Liz Lightstone, ²Angela Tincani, ³Sandra Navarra. ¹Imperial College London, UK; ²University of Brescia, Italy; ³University of Santo Tomas, Manila, Philippines

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Case 1: Pre-pregnancy counselling for women with lupus nephritis

Liz Lightstone

An African Caribbean woman was diagnosed with systemic lupus erythematosus (SLE) in 2009 aged 21 years. At that time, she had severe Class IV lupus nephritis (LN) with crescents and acute kidney injury and was treated with steroids and cyclophosphamide. She achieved good clinical remission and was maintained for several years on low-dose prednisone, mycophenolate mofetil (MMF), hydroxychloroquine

(HCQ) and irbesartan. Antiphospholipid and lupus anticoagulant were negative, she was anti Ro positive with no extra renal manifestations.

She attended for pre-pregnancy counselling in July 2017 aged 29 years. She was off steroids but still taking MMF and irbesartan. Her creatinine was 97 umol/l with eGFR 70.8 mls/min (59 mls/min not corrected for race) and she had no proteinuria. Her labs at that time were ANA 1:320; dsDNA titer 10 units/ml; C3 normal; and C4 low 0.13 g/l. The counselling addressed fertility (in light of previous cyclophosphamide), contraception, as well as medicines management; in particular, what to stop (i.e. MMF and irbesartan), what to continue (i.e. HCQ) and what treatments might be added (i.e. azathioprine, aspirin, folic acid). The evidence base for advice regarding timing, risks to her and to the baby came from the PROM-ISSE study, meta-analyses and the Italian series (Moroni *et al*). Her key risk factors for adverse pregnancy outcomes were being non-white, on an antihypertensive, and having anti Ro antibodies but she was in a good remission from her lupus. I advised her to continue to use contraception whilst weaning off her MMF and to consider trying to conceive, if all remained well, when off her MMF for at least 3 months.

She presented pregnant in December 2017 but had not stopped either her MMF or irbesartan, despite the advice to do so back in July that year. We discussed the risks to the baby of first trimester exposure and she declined termination. Coincident with the pregnancy, she was serologically more active, and became symptomatic with joint pains, rising creatinine and hypertension and developed significant proteinuria. During the workshop we will discuss the pros and cons of renal biopsy in pregnancy and how we managed a really major flare. Also, the difficulty of diagnosing pre-eclampsia in a patient with active LN. The pregnancy was ultimately successful. She was treated with rituximab and MMF post-partum and again advised regarding contraception. The story continues in 2020!

Case 2: Lupus nephritis in pregnancy

Angela Tincani

Maria is a 39-year-old woman who consulted at 21 weeks of gestation for the sudden occurrence of proteinuria (3.8 g) during a previously uncomplicated pregnancy with normal fetal growth.

She had a history of undifferentiated connective tissue disease, diagnosed in 1997, because of thrombocytopenia (48,000 platelets per microliter) and Raynaud's; positive ANA, anti U1RNP. She was successfully treated with corticosteroids, which were stopped in 2000. She has had Hashimoto thyroiditis, treated with levothyroxine since 2000.

In 2014 she had vaginal delivery of a female baby at 40 weeks of an uncomplicated pregnancy without any treatment. In 2016 and 2017 she had three early miscarriages at 8, 7 and 9 weeks.

During our first evaluation (29th March 2019), she presented acrocyanosis and modest feet oedema. Proteinuria was 4 g with normal renal function; positive ANA and anti Sm/RNP; low titer anti ds DNA; positive anti-cardiolipin and anti β2 glycoprotein1 IgG.

In the last week she was treated with prednisone 50 mg/day plus low dose aspirin (LDA) and low molecular weight heparin (LMWH).

Azathioprine (AZA) was added, but because of increasing proteinuria (9.8 g) one week later she was admitted to the Obstetric Department. She was given three small pulses of