- Managing the risks and benefits of corticosteroids during pregnancy

Case 3: Anticoagulants during pregnancy

Angela Tincani

A 27-year-old female (Elena) came to our pregnancy clinic in 2005 because she wanted to plan a pregnancy. Her SLE was in complete longstanding remission, she had normal blood pressure, normal body weight (50 kg, BMI=20) and she had quit smoking one year earlier.

Previous history: Her SLE was diagnosed in 1996 (age 18 years) in another institution based on glomerulonephritis, polyarthritis, skin rash, anti-nuclear antibodies and anti-dsDNA at high titer. She had been treated with high dose oral steroids, cyclophosphamide, methotrexate, azathioprine, and hydroxychloroquine. She had been diagnosed with deep venous thrombosis in the right lower limb in 2000 (age 22 years) when she was found to be triple antiphospholipid antibody positive and started in warfarin.

Maintenance treatment: Prednisone 5 mg every other day; hydroxychloroquine 200 mg/day and warfarin INR target 2–3. In 2004 she underwent a voluntary abortion at 8 weeks for fetal exposure to oral anticoagulation. She was told that the fetus might suffer from malformations.

We advised the patient to maintain warfarin and stop it as soon as the pregnancy test was positive (perform an early test, at the very first day of menstrual delay) when low molecular weight heparin should be started. The treatment during pregnancy included enoxaparin (4000 UI twice a day), low-dose aspirin, prednisone 5 mg every other day, hydroxychloroquine and folic acid.

Elena delivered a healthy baby girl at 38 weeks of gestation. Heparin was restarted 12 hours after delivery and the treatment was switched back to warfarin one week later. The possibility of breast feeding was discussed.

Three months later she asked for contraception: According to the risk profile and the patients desire progesterone-releasing intrauterine device was chosen.

Discussion points

- How to administer anticoagulant treatment during pregnancy and puerperium
- Risks and benefits of breast feeding
- Problems related to contraception in SLE patients

Case 4: Unplanned pregnancy

Ricard Cervera

A 28-year-old African woman with a 15-year history of SLE was admitted at the Hospital Clinic of Barcelona at Week 38 of pregnancy because of high blood pressure.

She had been diagnosed of lupus nephritis at the age of 14 years and suffered several flares since. When she get married at the age of 26 year, she wanted to become pregnant and was referred to a preconception counselling clinic in order to be advised regarding pregnancy in SLE. The attending physician provided information regarding the need to wait until lupus nephritis was under control and no potential teratogenic drugs were used. However, a positive test for pregnancy was detected just 2 weeks later.

Discussion points

- How to deal with an unplanned pregnancy
- Managing high blood pressure during pregnancy

Learning objectives

- Discuss principles and strategies for preconception counselling in patients with systemic lupus erythematous
- Recognise clinical and laboratory features which help assess pregnancy complications in SLE patients
- Describe strategies for the management of pregnancy complications in SLE patients

04 CHALLENGES IN LUPUS NEPHRITIS

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Case 1: 27-year-old female with a 5-year history of SLE

Richard Furie

A 27-year-old female with a 5-year history of systemic lupus erythematosus (SLE) was admitted to the hospital because of confusion and fever. Past manifestations of SLE included polyarthritis, rash, recurrent episodes of pericarditis, and anaemia (but no nephritis). A flare 2 months prior to admission, consisting of pericarditis, fever, hypocomplementaemia, and a 2-fold rise in anti-DNA antibodies, was successfully treated with prednisone 40 mg/day; prednisone was subsequently tapered. At the time of admission, medicines included hydroxychloroquine 400 mg/day, prednisone 15 mg/day, calcium, and a vitamin.

The patient was given broad-spectrum antibiotics for the treatment of sepsis and/or bacterial meningitis. Methylprednisolone 60 mg/day was also administered. However, the patient's mental status worsened, and she became comatose. All cultures were sterile. Her creatinine, which was 0.6 mg/dL at baseline, rose 3-fold.

The impression was that of a flare of SLE complicated by anaemia, thrombocytopaenia, nephritis and CNS disease. 'Pulse' steroids were administered for 3 days without subsequent improvement. Intravenous gamma-globulin failed to improve the thrombocytopenia, and her creatinine continued to rise.

Discussion points

- Diagnosis and treatment of thrombotic microangiopathy (TMA)
- Proposed modifications to the classification of lupus nephritis

Learning objectives

- Describe the clinical presentation of TMA
- Discuss treatment options of TMA
- Review proposed modifications to the classification of lupus nephritis

Case 2: 16-year-old male with active SLE, trace protein and hematuria

Dimitrios Boumpas

A 16-year-old male (60 kg) presents with active SLE (SLEDAI 10). He has active serology with low C3 and C4, anti-DNA is positive at low titer. Normal Cr, albumin and HCT. Urinalysis shows trace protein (300 mg/dL) with 510 RBCs in the urine. He was treated with hydroxychloroquine and prednisone 20 mg/day and was referred to you 4 weeks later. His SLEDAI is now 4 (rash, serology) and urinalysis shows trace protein and hematuria.

Discussion points

- Identify patients at higher risk to develop nephritis and look for renal disease -especially when active- by urinalysis
- Do not underestimate hematuria-especially if active serology and extrarenal lupus. Best to do a biopsy irrespective of the presence or not of proteinuria
- Have a low threshold for renal biopsy. If you think about it, just do it (unless contraindicated)
- Look for crescents/fibrinoid necrosis and tubular atrophy and interstitial fibrosis in the biopsy report
- Stratify according to severity (histologic and clinical factors) and treat accordingly. For most patients mycophenolate mofetil (MMF) is the drug for initial choice based upon its lack of gonadal toxicity
- In patients with chronic disease and scaring in the kidney, or those with nephrotic range proteinuria, may need to wait longer for proteinuria to subside
- Proteinuria is a good prognostic factor (if below 0.7 mg/dl) irrespective of hematuria
- Hematuria/active urine sediment are reliable indicators for activity and flare but not for prognosis

Case 3: 25-year-old woman with arthritis, photosensitive rashes, leukopenia and thrombocytopenia and positive lupus serologies

A 25-year-old woman presents with arthritis, photosensitive rashes, leukopenia and thrombocytopenia and positive lupus serologies. Her proteinuria is 1.3 gm/day and she has hematuria, normal serum creatinine and albumin 3.2g/day. Renal biopsy showed focal proliferative lupus nephritis (Class IIIa with AI 7 and CI 0). She was treated with MMF and then with azathioprine because of contemplation of pregnancy reaching remission. Two years later she has nephrotic range proteinuria, increased creatinine to 1.4 mg/dl, and a biopsy consistent with pure membranous lupus nephropathy. No chronicity.

Discussion points

- Membranous nephropathy has a more benign course. Histologic transition may be observed
- Patients with nephrotic range proteinuria and impaired renal function are at greater risk for end stage renal disease and require more aggressive therapy
- Anticoagulant treatment in cases of nephrotic syndrome with serum albumin <20 g/L, presence of antiphospholipid antibodies or other pro-thrombotic conditions

Learning objectives

- Recognise, document and treat renal disease in SLE
- Explain how membranous disease differs from proliferative disease?
- Describe the targets of therapy
- Describe treatment of refractory disease

State-of-the-art Lecture: Measuring Outcomes

01 T2T, LLDAS AND REMISSION: OPERATIONAL DEFINITIONS MEET REALITY?

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In the wake of the effect of the treat-to-target (T2T) approach in rheumatoid arthritis and other rheumatic conditions, remission and low disease activity (LDA) have recently been the objective of a number of studies in systemic lupus erythematosus (SLE), where the validity of some definitions for their effect on organ damage were tested.

Remission An agreement on the principles that should guide the development of the definition of remission was published in 2017,[1] and some new definitions of remission have been proposed.[1-3]

All definitions distinguish two subtypes of remission, namely complete (no serological and clinical activity) and clinical (serologically active clinical quiescent disease). They differ in terms of allowed therapies and disease activity indices used. To be defined as a therapeutic goal, a potential target should be achievable by a significant proportion of patients. Prolonged remission was rarely reported in the past, but in the last few years it has been shown that durable remission might be not anymore rare in SLE.[3-6] Discrepancy can be due to the application of definitions of remission different from those used in the past, together with improved knowledge and management of the disease.

All the aforementioned definitions of remission succeeded in identifying patients with a better disease outcome.

DORIS and Zen definitions are close on several aspects,[1 3] with the substantial difference of excluding the physician global assessment (PGA) by Zen *et al*. PGA has the known limitation of having relevant inter-observer variability[7] and, moreover, a significant difference between pre-laboratory and post-laboratory PGA was highlighted.[8]

Interestingly, comparable results in terms of prevalence of remission and of protective effect on damage progression were obtained using either Zen's[3 4] or DORIS' definition,[2 4] suggesting that exclusion of PGA might not alter the ability to identify patients with better prognosis and that achievement of clinical SLE disease activity index (SLEDAI)-2K equal to zero is probably the main driver of the protective effect of remission.

Low disease activity

The concept of LDA has recently been proposed in SLE and preliminary data suggest that patients achieving LDA have better outcomes.[2 9-11]

Three definitions of LDA have recently been set up: Those by Franklyn *et al*.[9] (10) and Ugarte *et al*.[2] are similar, although the latter does not consider PGA. These definitions were tested in different cohorts with promising results, with patients in LDA having lower damage progression than those without LDA.

The definition by Polachek *et al*. is quite different, with the cut off for definition being a clinical SLEDAI-2K ≤2, and antimalarials the only medications allowed.[10] This definition was associated with improved outcomes in the original cohort, but it has not been validated in other cohorts.

Notably, measurement of disease activity should be continuous for defining LDA and not categorical (item present/absent) as SLEDAI is, being thus inadequate to capture low-intermediate activity in each single organ domain. In fact, LDA should not only correspond to milder lupus manifestations, but it should identify patients with low activity irrespective of the type of manifestations (e.g. low persistent proteinuria, low-active arthritis). Thus, SLEDAI is not adequate to define LDA and to separate remission from LDA on a continuum. In this regard, PGA, which is indeed a continuous index, could be helpful in complementing SLEDAI; however, PGA does not include objective measure of disease activity and, as mentioned above, it has a number of substantial limitations.

A new disease activity index named SLE-DAS ('http://sle-das.eu/') has recently been proposed and validated,[12] which is a continuous disease activity index with a higher sensitivity to