Case Number 5
Systemic Lupus Erythematosus (SLE)

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Case Summary:

Demographic details:

Ms. YM, female, Attard.
Referred from: Home.

Ms. YM, a 16-year-old girl, presented to A&E with a 1 week history of progressive, bilateral, and symmetrical lower limb weakness and lethargy. She was also complaining of decreased sensation in her lower limbs and an itchy erythematous rash on the palms of her hands. A couple of weeks prior to this she had been admitted to hospital and treated for pericarditis and chest infection. Neurological examination revealed inconsistency in all muscle groups, and giveaway weakness. The patient was also noted to have abnormal behaviour. Bilateral palmar erythema and multiple splinter haemorrhages were observed. With these clinical features and the investigations carried out systemic lupus erythematosus could be diagnosed and the appropriate treatment was started. The patient will be followed up at Rheumatology, Neurology, and Ophthalmology Outpatients, with physiotherapy for rehabilitation.

Presenting complaint:

Progressive weakness in the lower limbs – 1 week
Lethargy – 1 week

History of presenting complaint:

Ms. YM presented to A&E with a one-week history of progressive weakness in her lower limbs and lethargy. She could not walk into Casualty unaided although she does not have a clear memory of these times. Four days prior to admission she also found it very difficult to get out of bed and needed to be helped to get to the bathroom. She was not able to wash herself either. Ms. YM described equal weakness in both limbs and also decreased sensation. She had no neurological symptoms in her upper limbs on admission, however developed weakness and tingling in her upper limbs 5 days after admission.

A few days after admission, she developed an itchy erythematous rash on both hands. She did not have a butterfly rash over her face and did not complain of headache. She did not experience any rigors or hot flushes. This was her first episode.

Past medical and surgical history:

Past medical history:

She was hospitalised about a month previously and treated for pericarditis and chest infection.

Past surgical history:

Nil to note.

Drug history:

Nil to note.
No known drug allergies.

Family history:

Nil to note.

Social history:

Ms. YM lives with her parents and her two sisters, in a first floor apartment. She did not finish her last year at secondary school last year because of anxiety problems and she has not been working. She enjoys horse-riding and swimming. For the past two years, she had been smoking about 5 cigarettes per day; she has not smoked since she was ill with the chest infection.

Systemic inquiry:

- General Health: Lethargic
- Cardiovascular System: No chest pain on this admission
- Respiratory System: No dyspnoea on this admission
- Gastrointestinal System: Nil to note
- Genitourinary System: Nil to note
- Central Nervous System: Possible personality change noted by relatives
- Musculoskeletal System: Lower limb weakness, arthralgia
- Endocrine System: Nil to note
- Others: Relatives also noted repetitive oro-facial movements; itchy palmar rash

Discussion of results of general and specific examination:

On examination body temperature was 37.8ºC, blood pressure was 160/104 mmHg, SpO_2 was 96%, and the respiratory rate was 17 breaths per minute.
Heart sounds were normal (S1 + S2 + 0).
Chest was clear and there was good air entry on both sides.
The abdomen was soft and non-tender.
Bilateral palmar erythema and multiple splinter haemorrhages were noted.

On neurological examination, neck flexion and extension was 5/5, there was inconsistency on examining power in all muscle groups, with giveaway weakness (4/5 in both upper and lower limbs, except left ankle dorsi-flexion 3/5 and plantar-flexion 2/5). There was normal sensation. Biceps and triceps jerks were decreased bilaterally. Glasgow Coma Scale 15. She was demonstrating abnormal behaviour (smiling inappropriately and showing “la belle indifference”, a naive and inappropriate lack of emotion and concern toward her physical symptoms).

Differential diagnosis:

- Systemic lupus erythematosus
- Antiphospholipid antibody syndrome
- Infective endocarditis
- Pulmonary embolism
- Multiple sclerosis

- Guillain-Barré syndrome
- Conversion disorder

Diagnostic procedures:

Laboratory Exams:

Test: Complete blood count (on admission).
Justification for test: As a baseline to get an idea of haematological parameters. Patient had a variety of symptoms; she was weak, with a possibility of having anaemia. Ms. YM had a chest infection few days before so white blood cell count and differential had to be assessed.
It was repeated on several days afterwards to monitor progression.
Result:
Haemoglobin: 11.0g/dL (low)
Haematocrit: 31.6% (low)
Mean Cell Volume: 75.4fL (low)
Mean Cell Hb: 26.3pg (low)
Platelets: 58 x 109/L (low)
White blood cell count: 7.80 x 109/L (normal on admission but increased to abnormal high levels from day 5 post-admission, reaching a peak of 42.60 x 109/L on day 15 post-admission to decrease gradually afterwards).
The other parameters were within normal ranges.
Conclusion: Microcytic anaemia and thrombocytopenia. Although both occur in SLE, they could be due to several other pathologies and further investigation was necessary. The high white blood cell count indicates either an inflammatory or infective process.
Characteristic haematological disorders in SLE include haemolytic anaemia, leucopaenia, lymphopenia or thrombocytopaenia, all in the absence of a drug effect.

Test: C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (taken from day of admission to day 14 post-admission).
Justification for test: To assess if there is an inflammatory process in a multi-system disorder.
Result: On admission CRP was 49mg/L (high) and went down to 6mg/L on day 5 post-admission.
ESR on admission was 108mm/hr (high), and gradually went down to 18mm/hr on day 14 post admission.
Conclusion: High ESR and CRP confirm inflammation is present. The classical picture in SLE is a high ESR with normal CRP levels. When both ESR and CRP are high the indication is more towards infection, arthritis, or serositis.

Test: Urea (serum) and creatinine (serum) (taken regularly from the day of admission to the day of discharge).
Justification for test: As a baseline and also because urea and creatinine rise in lupus nephritis.
Result: Creatinine was always within the normal range. Urea increased from 6.60mmol/L on admission, reaching a peak of 12.40mmol/L (high) on day 8 after admission, and decreased gradually to 10.30mmol/L on the day of discharge.
Conclusion: Urea and creatinine derangements are not specific to SLE but occur in several conditions. Urea and creatinine are high only in advanced lupus nephritis so in this case, kidney involvement cannot be excluded.

Test: 3 sets of blood cultures (day 3 post-admission).
Justification for test: Suspicion of infective endocarditis after Ms. YM developed multiple splinter haemorrhages.
Result: No bacteria grown.

Conclusion: This, together with a normal echocardiogram (see below), made the diagnosis of bacterial endocarditis unlikely.

Test: Viral screen, toxoplasma and mycoplasma (done between day 2 and day 5 after admission).
Justification for test: To exclude a viral infection, toxoplasma and mycoplasma in view of lethargy and the possibility of infective endocarditis.
Result: Rubella virus IgM antibodies: negative
Syphilis serology: negative
Cytomegalovirus IgM and IgG antibodies: negative
Epstein-Barr virus IgG antibodies: positive
Epstein-Barr virus IgM antibodies: negative
Hepatitis A IgM antibody: negative
Hepatitis B surface antigen: negative
Hepatitis C antibody: negative
Herpes simplex virus IgM I/II: negative
Toxoplasma IgM antibodies: negative
Mycoplasma IgM antibody: negative
Conclusion: Ms. YM does not have a current viral, mycoplasma or toxoplasma infection. EBV results indicate that the patient does not have a recent infection, but IgG antibodies are present from an old infection.

Test: Serum antibody tests (done between day 3 and day 8 after admission)
Justification for test: Disease involving several body organs, suspecting an autoimmune rheumatic disease.
Result: Anti-Nuclear antibody (ANA): positive 1/640
Anti-ds DNA antibody: positive 82.9 U/ml (high)
ANF pattern: speckled
ANCA: negative
Anticardiolipin antibodies: positive ACA IgG >120.0 GPL U/ml (high).
ACA IgM 12.3MPL U/ml (high).
Lupus anticoagulant: positive
Conclusion: Diagnosis of Systemic Lupus Erythematosus (SLE) was made. Anti-ds DNA antibody is highly specific of SLE although it is only positive in about 60% of cases. ANA is positive in more than 95% of patients with SLE. Total antinuclear antibody (ANF) is positive in 99% of SLE patients but occurs in other diseases such as Mixed Connective Tissue Disease, Scleroderma, Sjögren's syndrome and Raynaud's disease. Anticardiolipin antibodies and lupus anticoagulant antibodies are associated with an increased thrombotic risk.

Test: Serum complement C3 and C4 (day 3 post-admission; repeated on day 6 post-admission)
Justification for test: SLE is associated with a decrease in C3 and C4 complements due to their consumption.
Result: C3 complement decreased from 1820mg/L on day 3 (high) to 1172mg/L (normal);
C4 complement decreased from 159mg/L on day 3 (normal) to 61mg/L (low).
Conclusion: The decrease in C3 and C4 compliments is consistent with SLE.

Test: Lumbar puncture (day 5)
Justification for test: CSF examination to investigate biochemistry, possibility of infection, Multiple Sclerosis (MS) or Guillain-Barré Syndrome (GBS).
Result: Normal. Nothing was cultured and biochemistry was normal.
Conclusion: CNS infection is excluded, with no evidence of MS or GBS.

Test: Arterial Blood Gases (day 8; repeated on day 9).
Justification for test: Patient had episodes of shortness of breath with pleuritic chest pain. SpO_2 on air was 93%.
Result: pO2 63.1 mmHg (low) and improved to normal range the following day.
Conclusion: Hypoxia due to temporary reduced lung efficiency.

Test: D-dimer quantitative (day 8 post-admission).
Justification for test: To assess for pulmonary embolism (PE) after the patient developed sudden onset of shortness of breath, with a recent diagnosis of pro-thrombotic antibodies.
Result: 3300
Conclusion: Although D-dimers are high, the test is not specific to PE but is also positive in other conditions such as deep vein thrombosis and disseminated intravascular coagulation. A CT pulmonary angiogram is necessary to exclude PE.

Test: Microscopy cellular casts (day 10 post-admission).
Justification for test: SLE can involve the kidneys (lupus nephritis) giving rise to cellular casts.
Result: Absent.
Conclusion: Lupus nephritis is highly unlikely.

Test: Albumin creatinine ratio (2nd morning urine) (day 16 post-admission).
Justification for test: A high ratio is an early indicator of lupus nephritis.
Result: 83.44mg/g (high)
Conclusion: A high ratio is associated with kidney involvement in SLE however it can be due to other kidney disease and hence lupus nephritis cannot be confirmed with this test alone.

Test: Serum folate, serum vitamin B12 and serum iron levels (day 2 post-admission).
Justification for test: To assess for folate, vitamin B12 and iron deficiency that may be associated with fatigue, anaemia and neurological signs of muscle weakness.
Result: Folate: 13.50nmol/L (normal)
Vitamin B12: 435.00pmol/L (normal)
Iron: 5.03umol/L (normal)
Conclusion: Excluded the possibility of folate, vitamin B12 or iron deficiency.

Instrumental investigations:

Test: Chest X-ray (CXR) (on admission) (Figures 1 and 2).
Justification for test: To assess progression from recent chest infection and pleural effusion, opacity at both bases, and local pleural thickening of lower interlobar pleura seen on CXR in the previous admission.
SLE can cause a pleural effusion.
Result: No pulmonary lesion seen. Heart not enlarged. Costo-phrenic sinuses blunted bilaterally.
Conclusion: Clearing of previous opacities at bases. No evident lung pathology from CXR.

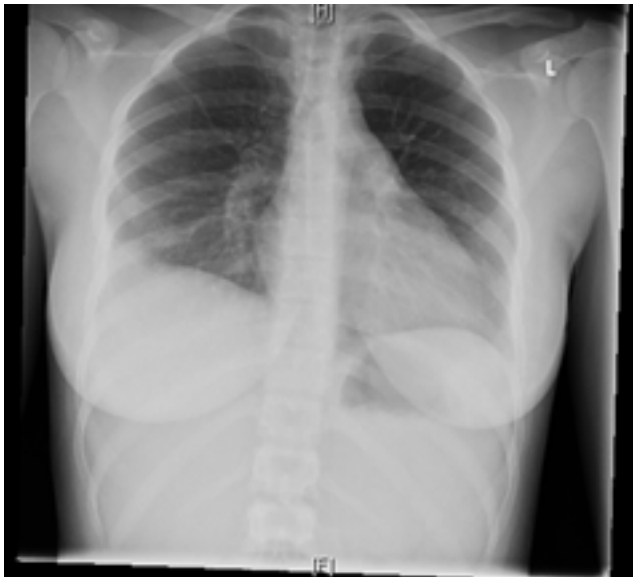

Figure 1: Chest X-ray from the previous admission, about a month before, showing right pleural effusion.

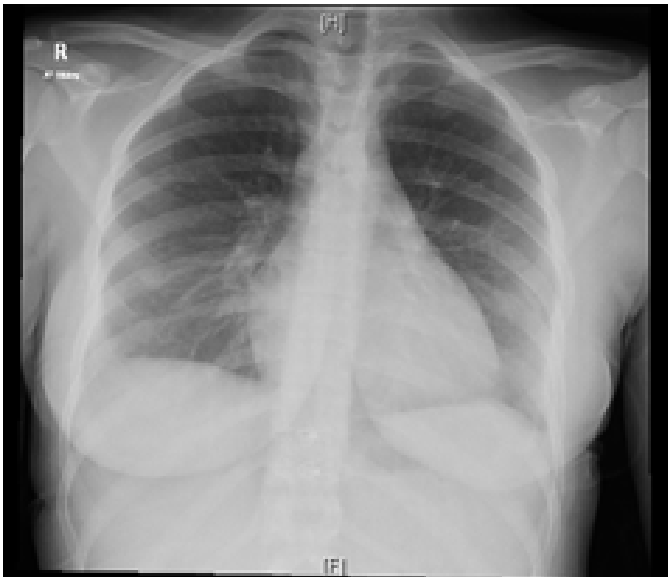

Figure 2: Chest X-ray on the day of admission, showing no pulmonary lesions and costo-phrenic sinuses blunted bilaterally.

Test: ECG (on admission).
Justification for test: Ms. YM had pericarditis a few days ago. She also had tenderness over the 6th to 8th ribs that extended posteriorly to the right scapula. SLE may cause pericarditis.
Result: Non-specific T wave inversions in anterior leads, otherwise normal sinus rhythm.
Conclusion: In acute pericarditis, ECG classically demonstrates saddle-shaped (concave) ST segment elevations throughout, however ECG may be normal.

Test: CT brain (on admission).
Justification for test: To look for brain pathology causing lower limb weakness and abnormal behaviour.
Result: Normal. No haemorrhage or fresh ischaemic changes seen.
Conclusion: No evidence of haemorrhagic or ischaemic stroke.

Test: Transthoracic echocardiogram (ECHO) on day 2 followed by a repeat ECHO and Transoesophageal echocardiogram (TOE) on day 3.
Justification for test: Ms. YM had pericarditis few days ago, and had a mild troponin rise. SLE is known to cause pericarditis. Repeat ECHO was done due to suspicion of infective endocarditis after the patient developed multiple splinter haemorrhages.
Result: No pericardial effusion. Good global left ventricular function. Aorta and left atrium had normal dimensions and the right ventricle was not dilated. Aortic valve appeared to prolapsed into the left ventricular outflow tract.
Conclusion: Possibility of pericarditis or myocarditis was excluded. Diagnosis of infective endocarditis unlikely.

Test: MR spine thoracic, lumbar/sacral (on day of admission) (Figure 3).
Justification for test: To assess for the possibility of Guillain-Barré Syndrome (GBS) or organic spinal pathology. Patient was admitted with ascending bilateral lower limb weakness and flaccid paralysis.
Result: No abnormality detected.
Conclusion: No organic spinal pathology present and GBS unlikely.

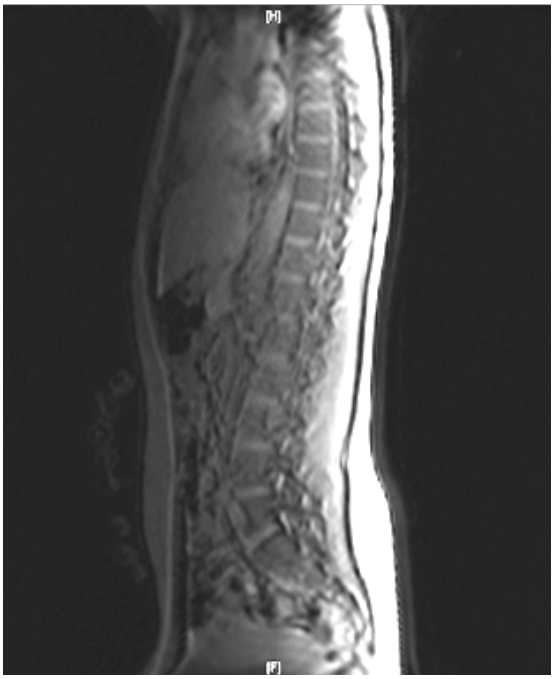

Figure 3: MR spine on the day of admission, showing no pathological finding.

Test: MR head (done on day 3; repeated on day 6 and day 20) (Figure 4).
Justification for test: To assess for any pathology causing muscle weakness or accounting for the behavioural changes.
Result: In the first MR head, multiple oval lesions of high signal intensity were noted in both periventricular regions and posterior fossa on both sides.
The repeat MR on day 6 showed a mild increase in the number of lesions in the cerebellum and right posterior cerebral cortex and subcortical white matter.
The repeat MR on day 20 showed an improvement in the lesions, but there were new areas of cortical high signal intensity in the right parietal and right frontal lobes, best seen on FLAIR sequence.
Conclusion: The first MR head results suggested a demyelinating disease.
Several micro-infarcts in the MR head suggest the possibility of emboli.

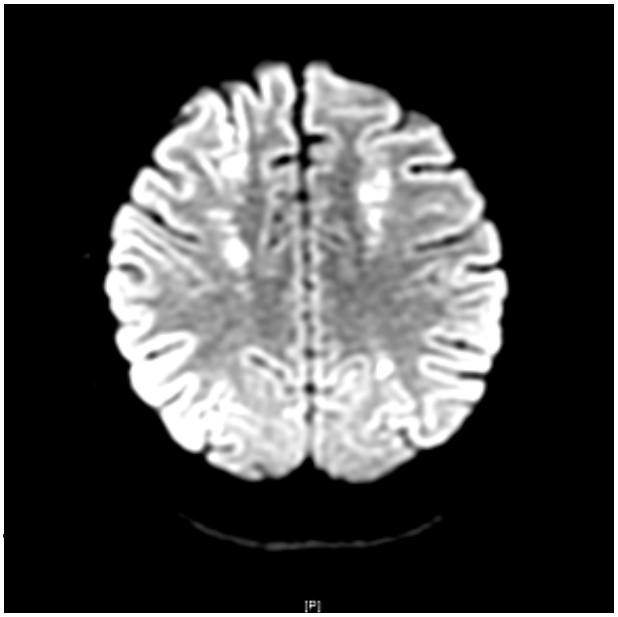

Figure 4: MR head on day 20 post-admission, showing multiple areas of cortical enhancement in both cerebral hemispheres. New changes of cortical high signal intensity in the right frontal and right parietal lobes.

Test: Electromyography (EMG) (day 3).
Justification for test: Weakness in several muscle groups in both upper and lower limbs.
Result: Asymmetrical sensory responses.
Conclusion: No specific conclusion.

Test: Electroencephalography (EEG) (day 4; repeated on day 13).
Justification for test: Behavioural changes (such as smiling inappropriately).
Result: Bihemispheric slowing.
Conclusion: Presence of encephalopathy.

Test: CT pulmonary angiogram (day 8).
Justification for test: To exclude pulmonary embolism after the patient experienced sudden onset shortness of breath, in view of having antibodies predisposing her to thrombotic events. SLE increases the risk of both arterial and venous thrombosis.
Result: Bilateral ground glass appearance.
Conclusion: Pulmonary embolus excluded. Changes likely to be due to congestion. However they could also be due to other pathology.

Test: Lung function tests (day 16).
Justification for test: SLE may affect the lungs rarely, giving rise to a restrictive lung defect. Patient had shortness of breath.
Result: Restrictive pattern found but quality was poor.
Conclusion: Possible lung involvement.

Test: Bone Mineral Density scan.
Justification for test: SLE carries an increased risk for osteoporosis.
Result: No T-score or Z-score values were recorded.
Conclusion: No osteoporosis as yet.

Therapy:

Drugs:

Drug Name	Dosage	Frequency	Type	Reason
Omeprazole	20mg	Bd	Proton pump inhibitor	Heartburn
OStrong	1 tab	Daily	Calcium and Vitamin D supplements	Osteoporosis prevention
Warfarin	4mg	Daily; for 3 days	Anticoagulant	Prevention of further thrombosis in cerebral vessels
Prednisolone	25mg	Daily; for 21 days	Corticosteroid	Immunosuppression (high dose used during an acute phase)
Prednisolone	20mg	Daily; for 14 days after the 21 days of 25mg	Corticosteroid	Immunosuppression
Prednisolone	15mg	Daily; for 7 days after the 14 days of 20 mg	Corticosteroid	Immunosuppression
Hydroxychloroquine sulfate	200mg	Bd	Antimalarial	For joint and skin symptoms of SLE

Diagnosis:

Ms. YM's previous admission with pericarditis and chest infection, her splinter haemorrhages, and the

presence of multiple lesions of high signal intensity on MR Head might point towards the diagnosis of infective endocarditis with embolic phenomena. However, she was not septic clinically, and apart from involvement of the heart, lung, and nervous system, there was also involvement of the musculoskeletal system (arthralgia) and skin (palmar erythema). This indicates the presence of a systemic disease, such as systemic lupus erythematous. Ms. YM is also of the appropriate age and gender for the onset of this disease[1, 2, 3]. Thus the antinuclear antibodies were tested and found to be strongly positive.

When a patient fits 4 or more of the below 11 criteria (serially or simultaneously), systemic lupus erythematosus can be diagnosed: [4, 5]

- Malar rash: fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds.
- Discoid rash: erythematous raised patches with adherent keratotic scales and follicular plugging, with or without atrophic scarring.
- Photosensitivity: unusual reaction to light on exposed skin.
- Oral ulcers: oral or nasopharyngeal ulceration, usually painless.
- Non-erosive arthritis: involving 2 or more joints with tenderness, swelling, or effusion
- Serositis: pleuritis or pericarditis.
- Renal disorder: persistent proteinuria or cellular casts.
- CNS disorder: seizures or psychosis.
- Haematological disorder – haemolytic anaemia or leucopenia or lymphopenia or thrombocytopenia.
- Immunological disorder – anti-dsDNA, anti-Sm, or antiphospholipid antibody.
- Positive antinuclear antibody (ANA).

Apart from the positive antinuclear antibody, Ms. YM also had a haematological disorder (thrombocytopenia and microcytic anaemia), positive ds-DNA, a history of pericarditis and a positive lupus inhibitor screen and abnormal serum levels of IgG and IgM anticardiolipin antibodies, indicating the presence of antiphospholipid antibodies. The diagnosis of infective endocarditis was also made more unlikely by the absence of bacterial growth from blood cultures and by the result of the echocardiogram. Thus the diagnosis of systemic lupus erythematosus could be made. The micro-infarcts seen on the MR head are most probably due to thromboembolic events as a result of antiphospholipid antibody syndrome, that is secondary to SLE.

Final Treatment and Follow ups:

After discharge she will be followed at Neurology Outpatients and Rheumatology Outpatients in 6 weeks. She also has a follow-up appointment at Ophthalmology Outpatients in 6 months' time, because of possible ocular toxicity associated with hydroxychloroquine therapy.

Ms. YM will continue physiotherapy as an outpatient.

In view of her warfarin therapy she needs to be followed at ACC and Phlebotomy for regular monitoring of INR.

Fact Box 5:

Title: Systemic Lupus Erythematosus (SLE)

Overview:

SLE is an inflammatory, autoimmune rheumatic disease that affects several systems in the body, with clinical features ranging from arthralgia and rashes to serious cerebral and renal effects.

Risk Factors: The exact cause of SLE is not known, but predisposing factors include:

- Heredity: higher concordance rate in monozygotic twins.
- Genetics: around 20 genes have been linked to SLE, such as homozygous deficiencies of complement genes C1q, C2, or C4.
- Sex hormone status: premenopausal females are most commonly affected.
- Drugs: a mild form of SLE can be induced by hydralazine, isoniazid, procainamide, and penicillamine.
- UV light: this can trigger flare-ups, especially in the skin.
- Exposure to Epstein-Barr virus (EBV): EBV can possibly be a trigger for SLE.

Signs and Symptoms:

Clinical features vary between different patients, but the most common are fatigue, arthralgia, and skin problems. Figure 5 below shows the various systemic clinical features.

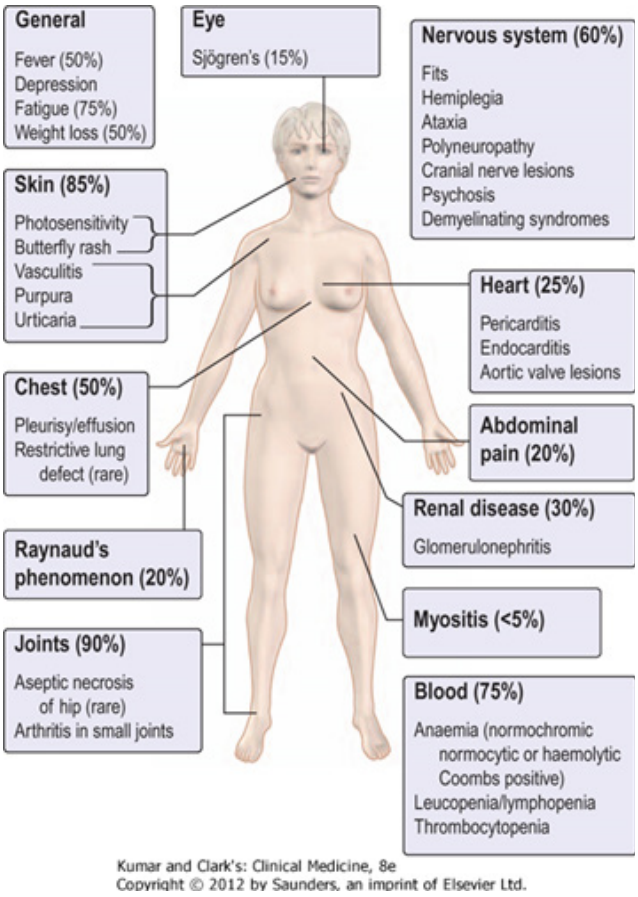

Figure 5: Clinical Features of SLE

Investigations

- Blood:
  -Complete blood count: anaemia of chronic disease/autoimmune haemolytic anaemia, leucopenia, lymphopenia, thrombocytopenia.
  -Erythrocyte sedimentation rate (ESR): raised.
  -Urea and creatinine: raised when there is renal involvement.
  -Autoantibodies: anti-nuclear antibody (ANA), anti-dsDNA, anti-Ro, anti-Sm and anti-La most significant; antiphospholipid antibodies present in 25-40% of cases.
  -Serum complement: C3 and C4 reduced during active disease.
- Histology: immunofluorescent abnormalities with deposition of IgG and complement on kidney and skin biopsies.
- Imaging: CT scans may show infarcts or haemorrhages and cerebral atrophy; MRI can detect white matter lesions.

Treatment:

- General management measures: discussion with the patient regarding the effect of the disease on lifestyle, advice such as avoidance of excessive sun exposure and cardiovascular risk factors.
- Symptomatic treatment with NSAIDs for arthralgia, fever, etc.
- Topical corticosteroids for cutaneous lupus; also use of sun protection cream and avoidance of excessive sun exposure.
- Antimalarials, such as hydroxychloroquine, for skin disease, fatigue, and arthralgias not responsive to NSAIDs. However care must be taken because of the risk of retinal toxicity with such drugs.
- Severe, acute flares of haemolytic anaemia, thrombocytopenia, nephritis, arthritis, pleuritis, pericarditis, and cerebral disease require high-dose corticosteroids.
- Renal and cerebral disease would also require immunosuppressive drugs, such as cyclophosphamide, mycophenolate mofetil, azathioprine, and rituximab.

Prognosis and Complications:

SLE is a chronic condition, with a relapsing and remitting course. 10-year survival rate is around 90%, but it may be decreased if major organs are involved. Early on, death may be due to renal or cerebral disease or infections, while later cardiovascular disease would be more common. Patients with SLE have increased risk of developing certain cancers, especially lymphoma, as well as of cardiovascular disease and osteoporosis. Although fertility is usually normal, pregnancy in SLE patients carries risk for complications, such as thrombosis, pre-eclampsia, infection, and patients may have recurrent miscarriages, especially if positive for antiphospholipid antibodies. If an SLE patient becomes pregnant, she would require a review of her medications. Exacerbations may be more frequent post-partum.

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