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CASE STUDY

Case Study on Methotrexate Induced Oral Ulcers in Systemic Lupus Erythematosus Patient

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ABSTRACT

Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterised by the production of antibodies to components of the cell nucleus in association with a Diverse array of clinical manifestations. In this case, patient developed white patches, alopecia, rashes, photosensitivity, and visual disturbances. It was confirmed by positive results for anti nuclear antibodies (ANA) and anti ds DNA. Patient was on treatment with corticosteroids for about 6 months but were stopped because she developed puffiness of face and weight gain. During treatment with an immunosuppressive agent i.e. methotrexate, she took overdose against doctors advice, oral mucosa involved leading to formation of oral ulcers. Treatment was given for healing of ulcers and other symptoms.

KEYWORDS

Systemic Lupus Erythematous, Alopecia, Photosensitivity, Anti Nuclear Antibodies, Anti ds DNA, Ulcers

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a clinically heterogeneous disease which is autoimmune in origin, and characterized by the presence of auto antibodies directed against nuclear antigens. SLE is up to 10 times more common in women than men, and typically has a predilection for women in their childbearing years. The overall prevalence is estimated to be about 1 per 1000[1].

The exact patho-aetiology remains elusive. An extremely complicated and multifactorial interaction among various genetic and environmental factors is probably involved.

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Multiple genes contribute to disease susceptibility.

The interaction of sex, hormonal milieu and the hypothalamo–pituitary–adrenal axis modifies this susceptibility and the clinical expression of the disease.

Defective immune regulatory mechanisms, such as the clearance of apoptotic cells and immune complexes, are important contributors to the development of SLE.

The loss of immune tolerance, increased antigenic load, excess T cell help, defective B cell suppression, and the shifting of T helper 1 (Th1) to Th 2 immune responses leads to B cell hyperactivity and the production of pathogenic auto antibodies. Finally, certain environmental factors are probably required to trigger the disease (Figure 1)[2].

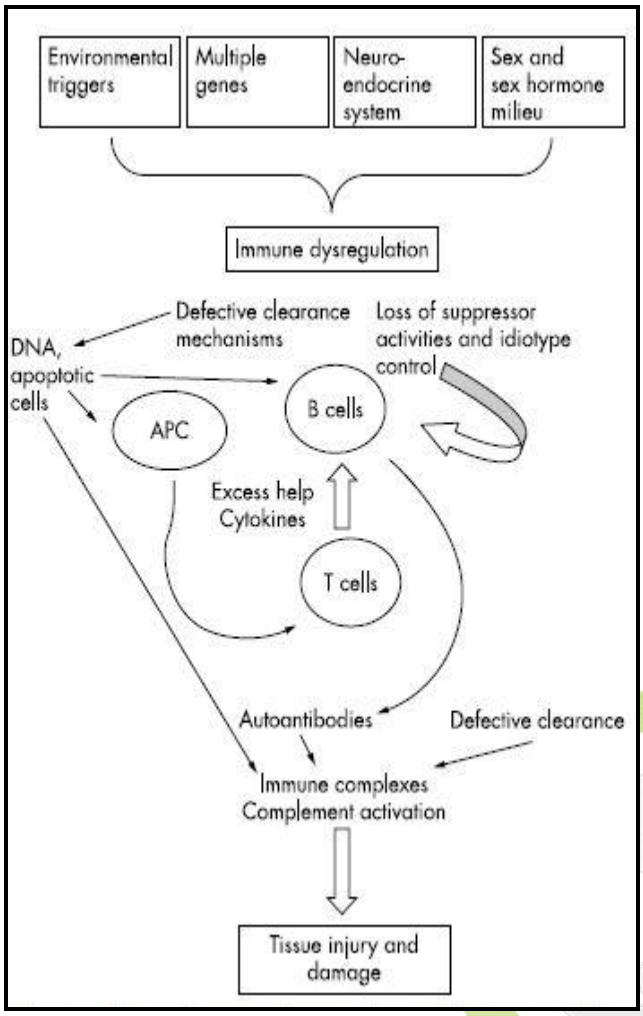

Figure 1: The pathogenesis of system lupus erythmatosus. APC antigen

Table 1: Describes the signs and symptoms of SLE. The American College of Rheumatology (ACR) recommends consideration of SLE if a patient is experiencing symptoms in two or more organ systems.

Affected organ system	Signs and Symptoms
Cutaneous	Malar rash, discoid rash, mouth/nasal sores, Raynaud phenomenon, cutaneous vasculitis, alopecia
Musculoskeletal	Arthritis, arthralgia, myositis
Renal	Hematuria, proteinuria, cellular casts, nephrotic syndrome, elevated creatinine
Cardiopulmonary	Pericarditis, pleurisy, pleural effusions, pneumonitis, pulmonary emboli, pulmonary, hypertension, myocardial infarction
Hematologic	Anaemia, thrombocytopenia, leukopenia, antiphospholipid syndrome
Neurologic	Seizure, psychosis, stroke, transverse myelitis, peripheral neuropathy
Gastrointestinal	Esophageal dysmotility, intestinal vasculitis, nausea, abdominal pain
Constitutional	fever, weight loss, lymphadenopathy

Treatment

Antimalarial Drugs–Hydroxychloroquine

Anti-malarial drugs remain the first-line treatment for patients with mild SLE along with NSAIDS. Hydroxychloroquine is effective in the treatment of mild SLE manifestations, but it is ineffective in preventing the occurrence of severe SLE manifestations.

Corticosteroids

Glucocorticoids are the mainstay of treatment in patients with SLE, especially at the beginning of a flare. They have strong anti-inflammatory effects on both acquired and innate immune pathways.

Cyclophosphamide

Cyclophosphamide defined the standard of care for lupus nephritis for many years and is usually used in conjunction with corticosteroids.

MMF

MMF is the prodrug of mycophenolic acid. The active metabolite is an inhibitor of purine synthesis and blocks the proliferation of activated T and B lymphocytes.

Azathioprine

Azathioprine, a purine analogue, has a major role in the treatment of SLE, especially as a corticosteroid-sparing agent.

Methotrexate

Methotrexate has a role in the management of resistant arthritis and skin disease in patients with SLE as a steroid-sparing agent. It does not have a role in the treatment of patients with SLE with major organ involvement[4].

Mild to Moderate Disease

Patients with mild disease restricted to skin and joints can sometimes be managed with analgesics, NSAID and hydroxychloroquine (200–400 mg daily). However, corticosteroids are also necessary (prednisolone 5–20 mg/day), often in combination with immunosuppressants such as methotrexate, azathioprine or mycophenolate mofetil (MMF).

Life-Threatening Disease

High-dose corticosteroids and immune-suppressants are required for the treatment of renal, CNS and cardiac involvement. A commonly used regimen is pulse methylprednisolone

(10 mg/kg IV), coupled with cyclophosphamide (15 mg/kg IV), repeated at 2–3-weekly intervals for six cycles.

Maintenance Therapy

Following control of the acute episode, the patient should be switched to oral immunosuppressive medication. A typical regimen is to start oral prednisolone in a dose of 40–60 mg daily on cessation of pulse therapy, gradually reducing to reach a target of 10–15 mg/day or less by 3 months. Azathioprine (2–2.5 mg/kg/day), methotrexate (10–25 mg/week) or MMF (2–3 g/day) should also be prescribed. The long-term aim is to continue the lowest dose of corticosteroids and immunosuppressant that will maintain remission[5].

CASE REPORT

A 13year old female patient was referred to our hospital complaining fever since 1yr, swelling of hands and feet, pains all over the body. Patient was taken to a private hospital 6 months back and she is on Rx calcium supplements, prednisolone 10mg OD, naproxyn, pantoprazole, hydroxychloroquine 200 HS. Treatment taken for 3-4 months, child progressively developed facial puffiness , alopecia and whitish patches all over the face, again taken to that private hospital and was asked to continue Rx and advised to R/A 1month with CBP, ESR, Sr. creatinine, AST,ALT,CPK, LDH, after that patient was referred to this hospital by district collector.

Past History

Patient had jaundice 3-4months back, took ayurvedic treatment and was relieved.

Immunisation history: did not take BCG as the scar was not seen. Immunised for polio.

Patient becomes febrile if not taking any of the prescribed medication.

The patient also complaints of difficulty in seeing, far away objects appear dark.

Presentation of Case

The patient complaints of fever since 1 yr, swelling of hands and feet, pains all over the body. Eye examination reveals retinitis pigmentosa. The child attained menarche at the age of 12 yrs, since then she did not have her next menstrual cycle. Physical examination shows facial puffiness, alopecia, under developed secondary sexual characters, weight gain, and photosensitivity.

Investigations

The level of cardiac enzyme CK MB was increased.

Haematological examination reveals increased levels of neutrophils.

Immunology Report: Anti dsDNA was weakly positive (ELISA) and Anti nuclear antibodies (ANA) showed positive (ELISA).

24hrs urine analysis report shows presence of protein.

Treatment

As far as the treatment is concerned the patient received the same previous drugs Tab. hydroxychloroquine HCQ 200mg OD, HS, Tab. prednisolone 10mg OD morning, tab pantoprazole 40mg OD before breakfast. With derma opinion suncote gel over hands and face BD, sternon cream with aloe derm lotion at night, tab zincovit OD. For 8 days.

At 9th day the dose of prednisolone was decreased to 5mg OD, tab. And other drugs were added like Tab methotrexate 18mg OD once a week,(tues), Tab. folvite OD on remaining 6 days except tues, Tab. Shelcal OD. And rest of drugs were still continued for 4 days.

Patient was kept on methotrexate 20mg/OD/weekly. But she had taken methotrexate 10mg/BD for 4 days, cumulative dose 80mg against doctors advice, oral mucosa involved.

Diagnosis: Methotrexate induced ulcers – hexigel for application on ulcers.

The patient also complained of black rashes over the left arm. – Tab. Leucovarin calcium 5mg BD for 7 days, Cap. Zevit OD.

On 14th day the drugs prescribed are Tab. Augmentin 625mg BD, Syp. bevon 5ml TID, hexigel for local application orally, Tab. Paracetamol 500mg TID, chlorhexidine mouth wash, candid mouth paint for L/A 3 times, Tab. Fluconazole 100mg/OD for 7days, and rest of the drugs were stopped.

Again all the laboratory investigations were performed , in which urine examination shows presence of proteins and pus cells, decrease haemoglobin, increase ESR: 130mm/hr.

On 18th day zytee ointment oral application was added 3 times daily.

On 21st day the haematological examination shows increased platelet count: 7lakhs/cumm (N: 1.5-4lakhs/cumm) and ESR: 60mm/1st hr.

The patient was discharged on 22nd day with symptomatic relief, with discharged medications Tab. Wysolone 20mg BD, Tab. hydroxychloroquine 200mg HS, Tab. folic acid, selenium sulphide shampoo thrice a week.

DISCUSSION

SLE is a multi system disorder characterised by the presence of autoantibodies directed against nuclear antigens. In this case it was confirmed by anti nuclear antibodies (ANA) positive and anti ds DNA positive and also includes many signs such as alopecia, photosensitivity, visual disturbances, retinitis pigmentation, joint pains, black spots, white patches and oral ulcers.

Urine examination shows presence of proteins which indicates mild to moderate kidney dysfunction.

The patient was on treatment with prednisolone slowly the dose was decreased and the drug was stopped because the patient was developing facial puffiness, oedema and weight gain. Previous study also shows corticosteroids have proved to be extremely effective in the treatment of acute inflammation and chronic inflammatory diseases. However, despite their clinical success, oral corticosteroids (OCS) are used sparingly due to a broad array of serious adverse events i.e development of weight gain, facial swelling, moon face[6].

Hydroxychloroquine is effective for skin disease, joint pain and fatigue as well as it is used as supplemental therapy with glucocorticoids in severely ill patients. Methotrexate was added to treatment 20mg/ OD/ week but patient took 10mg/BD for 4 days, and developed oral ulcers. Hexigel is given for fast healing of ulcers and it kills local pathogenic irritants. Patient also presents with retinitis pigmentation it may be /may not be, due to hydroxychloroquine intake. Patient attained menarche 1 yr ago, but did not have any cycle after that, according to doctors it may be drugs induced immaturity and advised to

wait until 15yrs of age. For skin rashes suncote gel was given that acts like a sunscreen, aloe derm lotion. The patient was given symptomatic relief by the treatment.

CONCLUSION

The present case study reflects the importance of pharmacist intervention when comes to the pharmaceutical care. If proper counselling was given to the patient regarding the disease, dose and indication, the risk for developing any side effects would have been minimised. If a medication is suspected to be the cause of an oral ulceration, cooperation is essential with the prescribing doctor in order to discuss the possibility of alternative medication or dosage reduction.

Methotrexate is a non-rare prescribed medication by many medical specialists. Oral ulcers stand among its main side effects. Practitioners should be well informed about MTX prescription, in order to estimate the potential adverse effects in their patients.

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