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Identification and Management of Steven Johnson Syndrome Induced Due to Cefixime and Ofloxacin in A Systemic Lupus Erythematosus Patient: A Case Report

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ABSTRACT

Cefixime and Ofloxacin is one of the common antibiotic combination used in India. Though antibiotic combination therapy can possess with higher complications but useful in various conditions. Cefixime and Ofloxacin induced Steven Johnson Syndrome is common in patients and can be easily identified but situations turns opposite when same complication developed in a patient with Systemic Lupus Erythematosus because, the complication in both the conditions mimic each other therefore, careful examination with supported various laboratory data and past medical/medication history helps proper identification of such conditions. Management of Steven Johnson Syndrome requires prompt withdrawal of suspected/offended drug along with supportive therapy which includes; fluid & electrolyte replacement, systemic and topical corticosteroids, topical anesthetics and antiseptic mouth washes.

Keywords: Cefixime, Ofloxacin, Steven Johnson Syndrome, Systemic Lupus Erythematosus Identification and Management.

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INTRODUCTION

Antibiotic combinations therapy is widely prescribed in India. However, combination therapy has its own advantages such as prevention of drug resistance, synergistic action in polymicrobial infections, empiric therapy and similarly it has some disadvantages like antagonism, drug-drug interactions, drug toxicity, irrational drug use and increase cost of therapy.[1, 2] Cefixime is a semisynthetic, third generation cephalosporin antibiotic, with broad spectrum of antibacterial activity. It possesses antibacterial activity by inhibition of mucopeptide synthesis in the bacterial cell wall. The most common reported adverse drug reactions include; diarrhoea, dyspepsia, nausea and vomiting. Hypersensitivity reactions like skin, rashes, erythema multiforme, urticaria, Steven Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and rarely develop prolongation of prothrombintime.[3] Ofloxacin is a synthetic, first generation fluoroquinolones antibiotic, active against broad range of bacteria & exerts its action by inhibiting DNA gyrase thereby inhibiting bacterial cell division. Adverse drug reaction includes; diarrhea, rash, pruritis, insomnia, drug fever, SJS and TEN.[4, 5] Drug-induced SJS typically begins with fever & flu like symptoms. One to three days later, signs begin to start in mucous membranes, including eyes, mouth, nose, and genitalia. A macular rash appear first on the face, neck & central trunk area then spread to the extremities and rest of the body. Lesions rapidly increase in number and size within 4 to 5 days. Large wound region leads to extreme pain, enormous loss of fluid and protein. Evaporative heat loss leads to hypothermia and may cause infection too.[6, 7] SJS was first described by Hebra in 1866 and A.M. Stevens & F.C. Johnson in 1922 as an acute severe mucocutaneous reaction affecting approximately 1 to 2/million annually.[8,9] There are more than 100 drugs assumed or identified as main cause of SJS in most of the cases.[10] Common offenders include antimicrobials, anti-epileptics and non-steroidal anti-inflammatory drugs (NSAIDs).[6] Management of SJS is prompt recognition and withdrawal of suspected/offended drug(s), corticosteroids have been used for years as mainstay therapy for SJS in most cases along with supportive care.[10] Systemic lupus erythematosus often abbreviated as SLE or lupus is a chronic multisystem autoimmune disease mainly affecting young women of child bearing age.[11] Although the specific cause of SLE is still unknown, multiple factors are associated with development of the disease, including; genetic, immune regulatory, hormonal, and environmental factors. Presence of auto-antibodies can cause tissue damage in multiple organs such as kidney, skin, central nervous system, cardiovascular system, muscles & bones, pleura, lungs and gastrointestinal tract.[7] Identification of SJS in patients with SLE is quite difficult as several

different primary cutaneous disorders have been reported to occur in association with lupus. Many of these conditions mimic SJS/TEN like. A thorough history of medical/medications, clinical presentation, recovery upon withdrawal of suspected drug and histopathological findings along with direct immune fluorescence test (DIF) are used to identify in most of the SJS cases.[12] Here we discuss a case of SJS which developed due to combination use of Cefixime & Ofloxacin in a SLE patient, its identification and appropriate management.

CASE REPORT

A 35 years old female patient was admitted in general medicine department with chief complaints of rashes over face, neck & extremities with oral ulcers since 3-4 days which developed after taking medications prescribed by local doctor.

On examination (O/E)

Patient was conscious & coherent

Rashes were positive over face, neck and extremities with oral ulcers

Febrile

Pulse rate (P.R) was elevated to 130 beats /min

Blood pressure (B.P) was 110/70 mmHg

Cardiovascular sound and per-abdomen were found to be normal at diagnosis (NAD)

Crepitations and wheezing were positive in respiratory sound

Past medical/ medication history

Fever, backache and body pains since 6 months, for which she used to take anti-pyritic OTC medication. Using these medication fever and pain used to subside but reappear within a week after discontinuing of the drug.

Seven days prior to our hospital visit she visited local ortho and maternity hospital and was diagnosed as lower back pain (LBA) and prescribed with the following medications for three days

1. Tab Paracetamol 650mg b.i.d
2. Tab Cefixime 200mg + Ofloxacin 200mg b.i.d
3. Tab Pantoprazole 40mg OD

She was asked to review after 3 days and upon review visit she was re-prescribed with following medications for 5 more days:

1. Tab Cefixime 200mg + Ofloxacin 200mg b.i.d
2. Tab Paracetamol 650mg b.i.d

3. Tab Multivitamin OD
4. Tab Rabeprazole Sodium 20mg OD

She used to develop rashes, itching whenever she takes medication particularly tab Cefixime + Ofloxacin. Suspecting drug reaction she had stopped the drug yesterday

Provisionally she was diagnosed as 'fever for evaluation, ?SJS may be due to Cefixime & Ofloxacin & ?SLE'

Her lab report shows

Complete blood picture (CBP): White blood cells (WBC): 3.1 $10^3/mm^3$ (3.5-10.0), red blood cells (RBC): 4.43 $10^6/mm^3$ (3.80-5.80), haemoglobin (HGB): 9.8 g/dl (11.0-16.5), hematocrit (HCT): 35.7 % (35.0-50.0), platelet count (PLT): 202 $10^3/mm^3$(150-390), mean corpuscular volume (MCV): 81 um^3 (80-97), mean corpuscular haemoglobin (MCH): 22.1 L pg (26.5-33.5), mean corpuscular haemoglobin count (MCHC): 27.5 L g/dl (31.5-35.0), red cell distribution (RDW): 15.5 H% (10.0-15.0), mean plate volume (MPV): 8.9 um^3 (6.5-11.0), platelet distribution width (PDW): 9.0 L% (10.0-18.0)

Erythrocyte sedimentation rate (ESR): 1^{st} hour 50mm/hr (0-8) and 2^{nd} hour 90mm/hr (0-15)

Liver function test (LFT): Total serum bilirubin (TSB): 05 mg% (0.3-1.0 mg %), serum glutamic pyruvic transaminase (SGPT): 60 IU/L (0-45 IU/L), alkaline phosphatase 73 IU/L (44 to 147 IU/L)

Random blood sugar: 101 mg/dl (80-160 mg/dl), blood urea: 21 mg/dl (10-45 mg/dl), serum creatinine: 0.8 mg/dl (0.5-1.5mg/dl)

Anti nuclear antibodies (ANA) Result: Positive for ANA suggestive of ss DNA & ds DNA

Serum Electrolytes: Sodium: 148 mEq/L (135-150)**,** potassium: 2.3 mEq/L (3.5-5.5), chloride: 97 mEq/L (95-105)

Anti Double Stranded DNA Antibodies (Anti ds DNA) Result: Positive ++

Anti smD1 Immunoblot Assay Result: Sm (Smith) strong positive ++++

Complete urine examination (CUE):

Macroscopic Examination: Color: pale yellow (pale yellow)**,** appearance: clear (clear)**,** specific gravity: 1.015 (1.016-1.022), reaction/PH: neutral 7.0 (4.6-8)**,** proteins: nil (nil-trace)**,** sugar (glucose): nil (nil)**,** urobilinogen: normal (0.2-1 mg/dl)**,** bilirubin: negative (0-0.02 mg/dl), ketones: negative (negative), nitrites: negative (negative)

Microscopic examination: Pus cells: 1-2/HPF (0-5/HPF)**,** R.B.C: nil (0-2/HPF)**,** epithelial cells: 1-2/HPF (0-8/HPF)**,** casts: nil (nil)**,** crystals: nil (nil)

Based on medical history, clinical examination and laboratory findings; patient was finally diagnosed as a case of **"SJS due to Cefixime & Ofloxacin with SLE"**

Drugs on admission:

1. IV DNS 1 unit (Dextrose normal saline 500ml)
2. Tab PCM 500mg t.i.d (Paracetamol/Acetaminophen)
3. Inj Taxim 1gm IV b.i.d (Cefotaximsodium)
4. Tab Pantop 40mg b.i.d (Pantoprazole sodium)

On day 2(October 29, 2014**)** Patient condition was same & same medication was continued.

On Day 3(October 30, 2014**)** Patient was referred to dermatologist. Dermatologist examination shows puffiness of face with periorbital edema positive, more in lower eye lids, diffuse erythma, hyper pigmented lesions, and rashes associated with crusting over face, lips and ear lobes. Trunk and extremities were less affected, scalp diffuse alopecia positive, nails normal and was confirmed as a case of Cefixime and Ofloxicin induced SJS with ?SLE

In addition to existing medications dermatologist prescribed:

1. Inj Decadron 2CC IV b.i.d (Dexamethasone sodium phosphate 4mg/CC)
2. Syrup Potchlor 2tsp in a glass of water t.i.d (Potassium chloride IP 1.5 gm/15ml
3. Chlorhexidine mouth wash t.i.d (Chlorhexidine gluconate 0.2% w/v)
4. TESS gel for local application b.i.d (Triamcinolone acetonide IP 0.1 % w/w)

On day 4(October 31, 2014) Patient was conscious & coherent, afebrile, per-abdomen was NAD, PR 80 beats/min, B.P 110/90 mmHg. Mucopain gel (Benzocaine IP 20% w/w) for local application was added to existing medications.

Same medication was continued for day 5(November 1, 2014) and day 6(November 2, 2014)

On day 7(November 3, 2014) Patient was conscious & coherent, afebrile, per-abdomen was NAD, PR 82 beats/min, B.P 110/90 mmHg

1. Tab HCQ 200mg b.i.d (Hydrochloroquine sulphate) and
2. Lycor 1% gel for local application (Hydrocortisone 1% w/w) were added to existing prescription

On day 8(November 4, 2014) Patient was conscious & coherent, PR 80 beats/min, B.P 110/90 mmHg, cardiovascular sound and per-abdomen were NAD, rashes and lesions decreased same medication was continued this day and also for next four days

On day 13 (November 9, 2014) Patient was stable, general condition was fair, rashes were decreased

She was freshly prescribed with

1. Inj Taxim 1gm IV b.i.d
2. Inj Decadron 2CC IV b.i.d
3. Tab HCQ 200mg b.i.d
4. Lycor 1% gel for local application
5. Tab PCM 500mg t.i.d
6. Tab Pantop 40mg b.i.d
7. Mucopain gel for local application

Same medication was continued for day 14(November 10, 2014) and day 15(November 11, 2014)

On day 16(November 12, 2014) Patient was stable, general condition was fair Inj Taxim was stopped and rest all medication were continued.

On day 17(November 13, 2014) Patient was stable, general condition was fair; rashes and lesions were completely resolved and patient was fit to discharge from the hospital and was discharged with following prescription:

1. Tab Pantocid 40 mg OD (Pantoprazole sodium)
2. Tab Omnacortil 20mg OD (Prednisolone)
3. Tab Livogen OD (Ferrous fumarate IP 152mg equivalent to 50mg elemental iron and Folic acid IP 1500mcg)
4. Tab A to Z OD (Antioxidants, multivitamin & mineral) and was directed to visit the OPD of dermatology after two weeks for follow-up.

Picture: Showing rashes and lesions over face, lips and extremities

RESULTS AND DISCUSSIONS

SJS has been well known in patients with multisystem disorders, particularly those of autoimmune etiology. Numerous case reports have been described the occurrence of drug induced SJS in patients with lupus.[13] Drug-induced SJS/TEN and SJS/TEN-like lupus can present with similar clinical and histological findings; same as in this case, coexistence of both (SJS & SLE) possibilities made difficult task to make a specific diagnosis. However reported literatures have revealed that when SJS/TEN-like lupus is suspected in patients with lupus, distinction can be made based on some typical clinico-pathologic correlation such as;

- The skin lesions develop more slowly over weeks to months in TEN-like lupus, rather than in hours to days like SJS/TEN, with an initial photo-distribution, where as in drug induced SJS a macular rashes appears first on face, neck, central trunk area, and spread to extremities and then to rest of the body.[14]
- Absence of genital/perianal erosions compared with drug induced.[15]
- Completely absent or only mild focal erosive mucosal involvement may favors lupus over SJS/TEN.[16]
- Mucosal involvement is an invariable feature of Stevens-Johnson syndrome.
- Recent history of drug (suspected) intake.[17]

In this case, skin rashes first appeared on face and later spread to extremities with prominent mucosal involvement, distribution of detachment was not limited to photo distribution, recent medication history of drug exposure & there were complaints of skin rashes upon intake of the suspected drug. On the other hand; specific laboratory findings also shown that the patient is positive for SLE. Considering all parameters such as typical clinical features, past medical/medication history, laboratory findings, and dermatologist findings were combined together to finally diagnose as a case of SLE and Cefixime & Ofloxacin induced SJS. Management of drug induced SJS include; early identification and withdrawal of the offending drug. Rapid initiations of supportive care by fluid and electrolyte replacement, for painful lesions topical anesthetics like Benzocaine and Lignocaine hydrochloride were applied.[10] Topical corticosteroids like Hydrocortisone, Clobetasol propionate, Betamethasone, Triamcinolone acetonide can be used for reducing swelling, itching and redness of skin. Whereas systemic glucocorticoids like Dexamethasone, Prednisolone and Methyl prednisolone were used to counteract the effect of inflammatory mediators released from mast cell. Although clinical evidence for the use of systemic immunosuppressive therapy is lacking, but in common practice

this is often prescribed.[9, 18, 19] In our case, drug was withdrawn and systemic glucocorticosteroids (Dexamethasone sodium phosphate), intravenous fluid (Dextrose normal saline) topical anesthetics (Benzocaine) topical corticosteroids (Triamcinolone acetonide & Hydrocotisone) were used along with the antiseptic mouth wash (Chlorhexidine gluconate) for oral ulcers which resulted in complete remission of rashes within 17 days. Whereas in case of SLE treatment and management; SLE cannot be cured, but it can be control the development of acute severe flare up and suppress symptoms to an acceptable level and to prevent further organ damage. Glucocorticoids are widely used as a first-line treatment for autoimmune diseases along with hydroxychloroquine and Analgesics.[14, 16, 20] Same as in this case, glucocorticoids and hydroxychloroquine were used. It has been noticed that there were similarities in the treatment of SLE and SJS which include use of Glucocorticoids, for skin care & management topical anaesthetics & corticosteroid, and supportive care by fluid and electrolyte replacement.

CONCLUSION

This case highlights the challenge of identifying SJS in patients with SLE though cutaneous complications occur in association with SLE are different than SJS but many of which can mimic SJS/TEN like, however detailed clinical examination, clinical findings and past medical/medication history, patients respond upon drug (offending) withdrawal are some important factors which gives clear picture to make a final diagnosis. Patients experiencing any untoward reaction with drug use should stop from taking medication any further and report immediately to healthcare professionals to prevent further complications.

INFORMED CONSENT FORM

Written informed consent was obtained from the patient for publication of this case report and any accompanying images

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