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Case Report

Adverse Reactions of Multi Drug Therapy of Leprosy – A Case Series

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WHO recommended multi-drug treatment (MDT) is the standard treatment for leprosy and is the cornerstone for treatment of leprosy since 1982. Rifampicin, Clofazimine and Dapsone even though relatively free of serious adverse reactions, may occasionally cause challenging adverse reactions. Among these three drugs Clofazimine has been known least to cause severe adverse reactions. In this case series we report severe anemia induced by combined effects of Dapsone and type 2 reaction, methemoglobinemia induced by Dapsone, acute renal failure caused by Rifampicin, flu like syndrome due to Rifampicin and severe drug hypersensitivity syndrome (DHS) induced by Dapsone. In all these cases patients needed hospitalization and prompt withdrawal of drugs. Alternative regimens were started and the course thereafter was uneventful in all these patients.

Key words : Methemoglobinemia, Autoimmune Hemolysis, Dapsone Syndrome, Flu like Syndrome, Dapsone, Rifampicin, Leprosy

Introduction

Multi drug therapy (MDT) introduced by World Health Organization and implemented by NLEP (National Leprosy Eradication Programme) of India is the standard treatment of leprosy. MDT is generally devoid of serious side effects. Occasionally there are reports of adverse reactions like drug induced hepatitis, drug hypersensitivity syndrome, acute renal failure and flu like syndrome caused by any one of the components of MDT (Deps et al 2007). In this case series we report major side effects encountered in leprosy patients treated with MDT. In all these patients we stopped MDT and alternative regimens were started. We report these cases as these complications may be life threatening and the physicians should be aware of these serious complications and manage these comparatively rare complications accordingly.

Case Series

Case 1

A 16 year old girl presented with hyperpigmented

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and skin colored papules and plaques over face and upper limbs of 6 months duration (Fig. 1) with associated fever. On examination she had tender subcutaneous nodules over elbows and buttocks which showed ulceration, both ulnar nerves were thickened and touch, pain and temperature sensation impaired over both feet. She was diagnosed as Hansens disease lepromatous leprosy (HD LL) with type 2 reaction (erythema necroticans), and was started on multi-bacillary (MB) MDT with oral Prednisolone and Thalidomide to take care of the Type 2 reaction. Her routine blood test including hemoglobin (Hb) - 10 gms, liver function tests (LFT), renal function tests (RFT), G6PD (glucose 6 phosphate dehydrogenase) levels were normal before starting treatment. Ear lobe slit skin smears (ELS/SSS) showed bacteriological index (BI) of 6+ and morphological index (MI) of 20%. She developed shortness of breath 10 days after starting MDT.

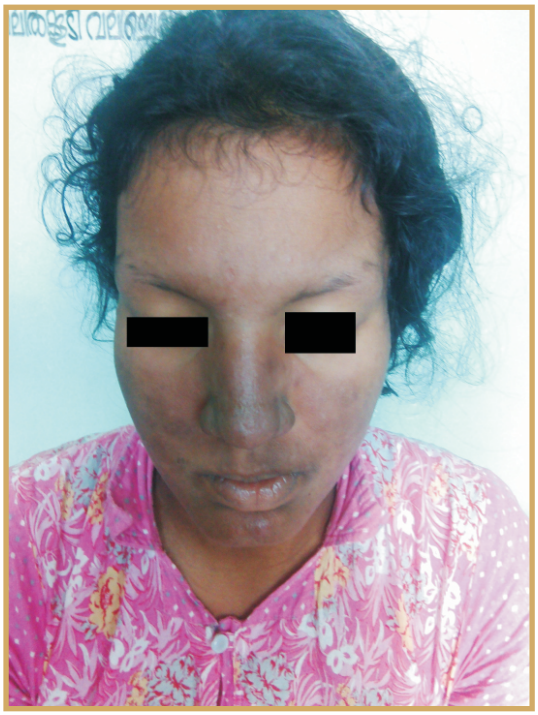

Fig. 1 : Hyperpigmented papules and plaques on face

On examination she had anemia the ulcerative lesions were healing. Her routine blood test showed Hb of 7 gm%, Dapsone was stopped and she was admitted in the hospital. Fever decreased but she developed new ENL lesions and her repeat Hb was 5.5 gm%, and total white blood cell count was 4800/cubic mm two weeks after stopping dapsone. Reticulocyte count was 2% (normal value 2-5%), Lactate dehydrogenase (LDH) levels were 358 (normal range: 230-460) and peripheral smear showed dimorphic blood picture. Direct Coombs test was positive.

Patient was given 5 packed RBC transfusions and her Hb became 10.3 gms. Steroids were tapered and Thalidomide was continued in the dose of 300 mg daily, her fever and ENL lesions subsided and hematological parameters became normal in one week.

Our final diagnosis was HD LL, type 2 reaction, anemia caused by combined effects of Dapsone and Type 2 reaction. The patient did not have features of Dapsone hypersensitivity syndrome. She was treated with alternative regimen consisting of Rifampicin 600 mg once a month, Ofloxacin 400mg and Clofazimine 300mg once a month and 50 mg daily and had uneventful course after that.

Case 2

A 19 year old boy who was the brother of first case on examination of household contacts was found to have hypopigmented macules with sensory impairment over shoulder, elbow and both feet (Fig. 2). Right common peroneal nerve and left superficial peroneal nerves were thickened and sensory impairment was present over left foot. He was a known case of congenital heart disease-atrial septal defect (ASD) and congenital hypo-

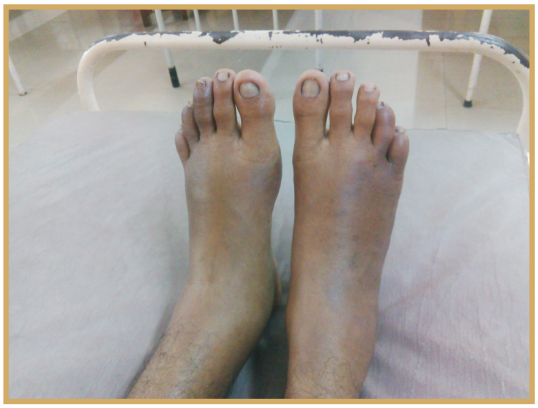

Fig. 2 : Erythematous plaque on foot

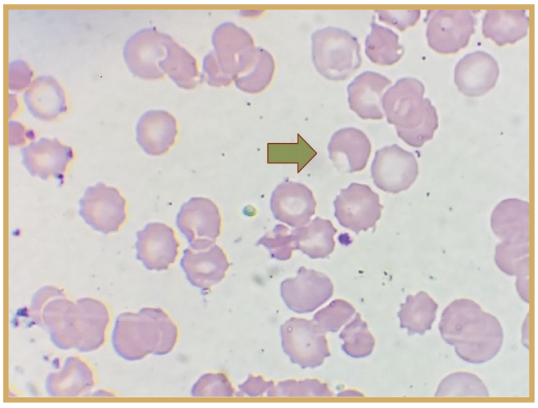

Fig. 3 : Blister cells and Bite cells

thyroidism. Slit skin smear examination showed BI 5+, MI 30%. Diagnosis of HD- Borderline lepromatous (BL) was made and investigations were done.

All the routine investigations were unremarkable, except mild elevation in total bilirubin with unconjugated hyperbilirubinemia and normal liver enzymes. Clinically patient was anicteric.

Gastroenterology consultation was done as the liver function test was deranged and they diagnosed it as a case of Gilberts syndrome. After completing 28 days of MDT patient presented to outpatient department with history of excessive tiredness, breathlessness, fever, redness over the skin lesions, high coloured urine and bluish discoloration of fingers. On examination he had anemia, pedal edema, icterus, central and peripheral cyanosis and the patient was febrile. Existing hypopigmented lesions became erythematous and tender.

Our diagnosis was HD (BL) type 1 reaction, methemoglobinemia and hemolytic anemia induced by Dapsone. Investigations showed Hb 6.7gm%, total counts (TC) 8800/cubic mm, P72, L19, M9, Platelet count – 2.2 lakh/mm^3, ESR 90mm/1hr. Urine had presence of albumin+++, Granular cast+, 24 hour urine protein was 1g. Other tests showed – Serum bilirubin 4.1/0.3 mg/dl, SGOT/SGPT-89/39U/L, ALP-89U/L, Blood urea - 44mg/dl, Serum Creatinine 1mg/dl, Serum sodium 128 meq/L, Serum potassium 4.5 meq/L, LDH-2257U/L (230-460), G6PD level – 260U/L(240-450). Methemoglobin level were 8.7% (<1%) and Reticulocyte count was 2%(0.5-2).

Peripheral smears had Bite cells and blister cells suggestive of hemolysis (Fig 3). ECHO showed large ASD with right to left shunt, mild pulmonary artery hypertension. ECG-Right bundle branch block with right ventricular hypertrophy. Chest X-Ray showed cardiomegaly.

Final diagnosis was Type 1 lepra reaction, Dapsone induced hemolytic anemia and methemoglobinemia and drug induced nephritis.

Dapsone and Rifampicin were stopped immediately and patient was started on Aspirin, Vitamin C and Vitamin E. Three packed RBC transfusions were given. Patient was started on Minocycline 100 mg, Ofloxacin 400 mg and Clofazimine 300 mg once a month and 50 mg daily. Patient is still under follow up and had an uneventful course thereafter.

Case 3

A 16 year old girl presented with a hypo-pigmented anaesthetic patch of size 3x2 cm on forehead and was started on MDT PB from outside. 3 weeks after starting MDT she developed fever and skin rash and was referred to our hospital. On examination erythematous follicular papules over neck, trunk and limbs were present (Fig 4). No nerve thickening was observed. ELS/SSS was negative. Provisional diagnosis of HD BT with Drug hypersensitivity syndrome to Dapsone was made.

Investigations revealed normal bilirubin levels, elevated SGOT/SGPT, USG abdomen showed moderate ascites, Chest X-Ray - mild pleural effusion and 24 hr urine protein was 1g.

In the presence of fever, rash and elevated liver enzymes diagnosis of dapsone syndrome was made and dapsone stopped and was started on 4 mg dexamethasone intravenously. Her hepatic and renal parameters became normal while on treatment.

While tapering her steroids she took the second dose of Rifampicin and on same day developed fever, severemyalgia, headache and erythema all over body. Routine blood examination, renal and liver function tests were within normal limits, and was managed symptomatically, 2 days later her condition improved.

Our diagnosis was flu like syndrome induced by Rifampicin, and the girl was later treated with Ofloxacin 400 mg and Clofazimine 300 mg once a month and 50 mg daily with tapering doses of steroids. On follow up progress was uneventful.

Case 4

A patient from Bihar was diagnosed as lepromatous leprosy from outside and was on treatment with MDT (MB), he developed excessive tiredness after 1 week of treatment, associated with giddiness, exertionaldyspnea, fever and nausea. His urine output was normal. On examination pallor and bilateral pedal edema was present. Multiple erythematous and skin colored discrete and confluent infiltrated papules present over face, trunk and legs. Glove and stockings type of anaesthesia was present and both ulnar nerves and right common peroneal nerves were thickened.

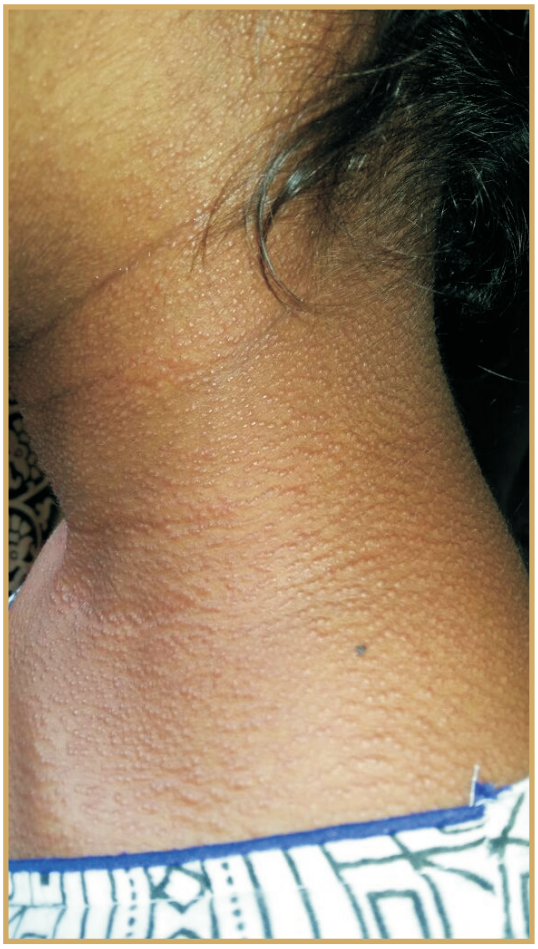

Fig. 4 : Follicular papules on neck

Investigations showed ELS/ SSS = 5+, MI = 20%, Hb 5.8gm%,TC 5600/mm^3 - P59, L22, M18, Platelet 2 lakh/mm^3, Blood urea = 170mg/dl, Serum creatinine = 13.1mg/dl, Serum Potassium = 5 meq

/L, Serum Sodium = 129meq/L,LFT- within normal limits, Serum Lactate dehydrogenase (LDH) levels were 2250U/L and Reticulocyte count 5%. Peripheral smear (PS) was suggestive of Dimorphic anemia. USG Abdomen showed increased echogenicity of both right and left kidneys.

Patient was diagnosed as HD(LL), Drug induced interstitial nephritis probably due to Rifampicin. MDT was stopped and the patient started on COM regimen (Clofazimine, Ofloxacin and Minocycline). As his urine output was normal dialysis was not done and after stopping the drug renal status improved gradually.

Discussion

In some countries like Brazil, the reported incidence of adverse reactions of MDT for leprosy varies from 38% - 44% and most occurred within 6 months of starting treatment (Goulart et al 2002, Deps et al 2007). In the first case of the series lepromatous leprosy patient developed severe anemia and was due to combined effects of type 2 reaction and Dapsone. Her G6PD level was normal, but she had 5 gm decrease in Hb level. Sen et al (1991) reported that Type 2 lepra reaction is associated with acquired hemolytic anemia and this may be due to autoantibody formation or microangiopathy. Frietasand Fleury (1996) have reported anemia, leukocytosis, reticulocytosis, and bone marrow hyperplasia in moderate to severe ENL. So anemia in this patient is due to type 2 reaction and her direct Coombs test was positive. Also patients who have mild iron, folate, or B12 deficiency will not be able to respond with the normal increase in bone marrow activity after starting dapsone, and thus can have drop in Hb.

Type 2 reaction is also associated with increased risk of thromboembolism due to diminution of fibrinolytic activity and activation of coagulation through intrinsic and extrinsic pathway by exposing collagen and secretion of thromboplastin from tissues damaged by inflammatory process (Frietasand Fleury 1996). Usually ENL is associated with leukocytosis but our patient had leukopenia.

The reported incidence of hemolytic anemia induced by Dapsone to be 24.7% and occurred within first 3 months (Deps et al 2012). This data from Brazil can not be extrapolated to Indian population and we need to document our own experiences.

Cardiovascular defect is a relative contraindication to start Dapsone (Edhegard and Hall 2013). Our second patient had ASD and developed severe methemoglobinemia and hemolysis. Hemotoxicity of Dapsone is associated with hydroxyl metabolites, which are potent oxidants. Patients with significant cardiac or pulmonary disease will not be able to tolerate low levels of methemoglobin. Met-Hb is an oxidation product of Hb in which there is an oxidized ferric iron in sixth co-ordination position instead of reduced ferrous iron in normal Hb. This oxidized ferric iron containing site is then bound to a water molecule or to a hydroxyl group. This complex is dark brown and unable to transport oxygen with a leftward shift in oxygen dissociation curve, thus leading to a decreased tissue oxygenation with subsequent hypoxic features (Price 1998). Thus the patients presents with dyspnea on exertion, palpitations and tiredness. Methemoglobin spot test will be positive and spectrophotometric quantitative analysis for met hemoglobin can also be done. The condition can be treated with Vitamin E, oral Methylene blue, Vitamin C. Indication for Methylene blue is methemoglobin levels over 30% and given either oral or intravenously. The renal insult in this patient in the form of proteinuria and cast may be due to Rifampicin or Dapsone. Incidence of Rifampicin nephrotoxicity has been reported to vary from

1.8% to 16% of all acute renal failure - ARF (Covic et al 1998). In a study conducted by (Goulart et al 2002) gastritis was the most common side effect due to Dapsone followed by hemolytic anemia, methemoglobinemia, insomnia and exfoliative dermatitis. Side effects due to Clofazimine 23% and Rifampicin 6.2% with ichthyosis being the most common side effect with Clofazimine and fever with Rifampicin (Goulart et al 2002).

Our third patient was diagnosed to have Dapsone hypersensitivity syndrome with follicular papular lesions on skin, LFT derangement, renal involvement, ascites and plural effusion. Kumari et al (2011) noted similar follicular lesions associated with DHS in their study. While she was improving on treatment with steroids she developed flu like syndrome on taking Rifampicin. The syndrome mostly occurs with the once-weekly or twice-weekly administration of Rifampicin and is rare with once-monthly treatment. However, it can occur with once monthly regimen (Covic et al 1998). The syndrome appears to be due to a hypersensitivity reaction to Rifampicin, and antibodies against it have been demonstrated. Our patient had, fever, myalgia, rash which began 4-5 hrs after administration of Rifampicin and subsided in 24 hrs.

Our fourth patient had acute renal failure induced probably by Rifampicin. He did not have any renal disease previously. Renal toxicity of Rifampicin was first reported by Poole et al (1971). Post Rifampicin ARF can occur in continuous or intermittent therapy. Acute interstitial nephritis (AIN), rapidly progressive glomerulonephritis, acute tubular necrosis and nephrotic syndrome can occur. Post rifampicin ARF is usually associated with autoimmunehemolysis, anemia (96%), thrombocytopenia (50%), hepatic injury (25%), disseminated intravascular coagulation – DIC (Covic et al 1998). Our patient had anemia and hemolysis. Renal function recovery is 96% in 90 days. Severity of immune process and duration of oliguric phase are the prognostic markers. Our patient recovered in 7 days without dialysis.

Conclusion

Although MDT is safe in hands of physicians, we should be aware of the possible adverse reactions associated and patients should be monitored for development of any complications. Dapsone and Rifampicin can cause serious adverse effects and the monitoring guidelines should be strictly followed. It is always better to do G6PD levels before starting Dapsone, and to keep the patients with low levels at close monitoring. The patients should be educated regarding the possible side effects and symptomatology and report accordingly. The treating physicians should be trained regarding the management of complications and use of alternative regimens.

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A CLINICAL STUDY OF ACNE VULGARIS

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ABSTRACT

BACKGROUND

Acne vulgaris is a highly prevalent chronic inflammatory disease of pilosebaceous unit affecting teenagers and young adults. Prognosis of acne is generally good, especially in mild acne. But, this disease reduces the self-esteem, their sense of identity and can severely compromise quality of life. All clinicians caring for children and adolescents should be familiar with this problem. Early diagnosis, proper treatment and timely counselling reduce the overall impact of disease to individuals.

MATERIALS AND METHODS

This is a prospective study conducted in the Department of Dermatology at Government Medical College, Kottayam, Kerala, in 200 patients who presented to the outpatient clinic with a clinical diagnosis of acne vulgaris who have not yet received any medical treatment for the disease and consented to participate in the study.

RESULTS

Male-to-female ratio of 1.43:1. 61.5% patients were in the 2nd decade. 4% were more than 30 years old. Duration of the disease at the time of presentation ranged from 3 weeks to 30 years. 42.5% complained of mild itching and 18.5% had burning sensation. 48.5% attribute exacerbation of disease after food intake. 72.5% acne patients had seborrhoea. Hirsutism and Acanthosis nigricans were present in 7.31% and 4.87% female patients, respectively. 50% with hirsutism and 25% with Acanthosis nigricans had polycystic ovarian disease and severe grades of acne. 25.6% females complained of premenstrual exacerbation of the disease. 26% of the patients showed exacerbation in summer. Smokers had severe grades of acne vulgaris compared to nonsmokers. Comedones were present in all and they were the predominant lesions in majority. Inflammatory papules were the 2nd most common lesions. Severe grades of acne were more common in patients with age ≥20 years. Severity of the disease increases with long duration of the disease. Relatively high incidence of post-acne scarring and post-inflammatory hyperpigmentation was observed.

CONCLUSION

Severe acne should be examined and investigated for underlying systemic diseases. Milk and dairy products have not much role for the exacerbation of acne in our area. 31% patients noticed exacerbation of their lesions after intake of eggs, 40(20%) after intake of oily food, 9(4.5%) after intake of milk and milk products, 9 after eating meat and 5 following intake of fish. Other exacerbating factors noted were summer month (26%), emotional stress (15.5%), sun exposure (23%), use of scalp oil (12%) and prolonged sweating (3%).

KEYWORDS

Acne Vulgaris, Propionibacterium Acne, Comedones Acne Scars.

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BACKGROUND

Acne vulgaris is a chronic, self-limiting and inflammatory disease of the pilosebaceous units occurring in the adolescent age group.[1] 90% of patients are between puberty and 30 years.[2] 54% of males and 40% of the females are above 20 years of age.[3]

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It is a polymorphic disease characterised by seborrhoea, open and closed comedones, erythematous papules and pustules.[1] The primary sites of involvement are face, chest, back and shoulders.[1] Pigmentation following the involution of the lesions may persist for several months. Permanent scars maybe left following the inflammatory lesions.[4]

Acne is a multifactorial disease. Predisposing factors are genetic, endocrine, diet, cosmetics, drugs, sunlight, seasonal variation, etc. Pathogenesis and aetiology are follicular epidermal hyperproliferation, excess sebum production, colonisation and activity of propionibacterium acnes and inflammation.[5] During the period of activity, the course is variable with spontaneous flare-ups and remissions.[6] This study was carried out to find out clinical

profile of acne vulgaris, the various environmental factors that can precipitate or aggravate acne vulgaris and to find out the complications and the sequelae of the disease.

MATERIALS AND METHODS

This prospective study was conducted in the Department of Dermatology at Government Medical College, Kottayam, Kerala. The study population included was 200 patients who presented to the dermatology outpatient clinic with a clinical diagnosis of acne vulgaris who have not yet received any medical treatment for the disease and consented to participate in the study.

A detailed history was taken regarding duration of acne, age of onset, relation of disease severity to stress, cosmetics, sun exposure, sweating, smoking, menstrual cycle, drug intake and use of indigenous medicines. Particular mention was given to the history of specific food items, which the patients noticed to have precipitated or exacerbated their disease.

History of concurrent or past diseases like seborrhoea and family history of acne with particular reference to scarring tendency was also taken. The acne prone areas were examined in detail regarding the sites of involvement, number and character of the lesions, the type of post acne scars and hyperpigmentation. Associations like hirsutism and Acanthosis nigricans were also noted.

The diagnosis of acne vulgaris was made by the presence of comedones/papules with/without pustules/nodules/cysts and abscesses at the acne prone sites. The acne was graded using a simple grading system described by Tutakne et al.[7]

Grade 1- Comedones and occasional papules.
Grade 2- Papules, comedones, few pustules.
Grade 3- Predominant pustules nodules and abscesses.
Grade 4- Many cysts, abscesses, widespread scarring.

Routine investigations and other relevant investigations as indicated according to individual patients were done. Institute ethical committee clearance was obtained. Data collected from the patients were tabulated in a Microsoft excel worksheet and analysed.

RESULTS

Male-to-female ratio of 1.43:1. Age of the patients ranged from 12 years to 47 years. 123 (61.5%) patients were in the 2nd decade. The youngest patient was 12-year-old male and the eldest was a 47-year-old male.4% were more than 30 years old.

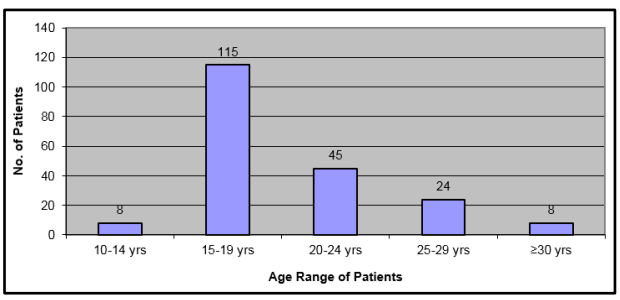

Figure 1. Age Range of Patients

148 patients were students, of which, 98 were males and 50were females. Duration of the disease at the time of presentation ranged from 3 weeks to 30 years. 63.5% attended within 4 years of onset of the disease. 19.5% seeked medical care within 1 year and 17.5% within 2 years of onset of the disease. 22 patients were having acne for more than 10 years at the time of presentation, and of these, 2 were having the disease for more than 30 years.

189 patients had onset of disease before 20 years of age, out of which, 95 had disease onset between15 and 19 years and the remaining developed disease between 10 and 14 years. Only 11 (5.5%) had started developing lesions after20 years. Nobody had history of disease onset after 25 years.

37.5% patients were asymptomatic. 42.5% complained of mild itching and 18.5% had burning sensation. Painful and tender lesions were present in15.5% patients.88 patients gave the history of frequent picking or squeezing of the lesions.

51.5% could not attribute their exacerbation to the intake of any particular food items. Among the remaining, 31% patients noticed exacerbation of their lesions after intake of eggs, 40(20%) after intake of oily food, 9(4.5%) after intake of milk and milk products, 9 after eating meat and 5 following intake of fish.

Other exacerbating factors noted were summer month (26%), emotional stress (15.5%), sun exposure (23%), use of scalp oil (12%) and prolonged sweating (3%). None of the patients had exacerbation of acne in winter season, cosmetic usage and were not on any drugs for chronic diseases. 9 male patients gave history of exacerbation during smoking, and among them, 3 had severe grades of acne.

72.5% acne patients had seborrhoea. Markers of androgenicity like hirsutism and Acanthosis nigricans were present in 7.31% and 4.87% female patients, respectively. None of them had diabetes mellitus. 50% with hirsutism and 25% Acanthosis nigricans had polycystic ovarian disease and severe grades of acne.16 of the total 82 females in our study had irregular cycles and 21(25.6%) complained of premenstrual exacerbation of the disease.

Skin types were type V in 54.5%, type IV in 30.5% and type III in 15%.

Types of Acne Lesions	Number of Patients	%
Closed comedones	200	100
Open comedones	127	63.5
Papules	130	65
Pustules	88	44
Nodules	22	11
Cysts	2	1
Abscesses	7	3.5

Table 1. Showing the Type of Lesions Present

Face was involved in all and facial involvement alone was seen in 38% patients. Extension of the lesions to the neck was present in 52.5% patients. Involvement of the upper trunk in 52.5% and upper arm in 24% patients. On

face, cheeks were involved in all, forehead in 82%, nose in 69.5% and jaw area in 57% patients.

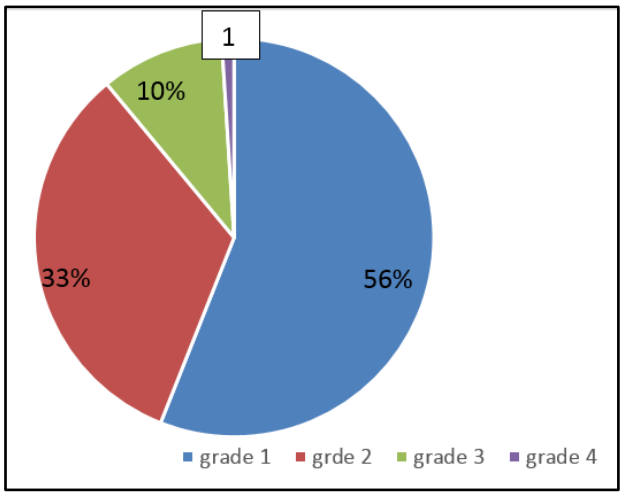

Figure 2. Grades of Acne

The severe grades of acne showed a peak age of onset between 10 and 19 years. It was observed that the severity of the disease increases with increase in the duration of the disease. Out of the total 57 patients presented with duration more than 5 years, grade 3 and 4 acne constituted 26.31% (15) patients, whereas in the other group of patients (total 143) with ≤5 years disease duration. The severe grades of acne constituted only 4.89% (7) patients.

Scars- Scarring was present in 59.5%. Cheeks were the most common site involved in all.

Icepick scars	31%
Box scars	16.5%
Rolling scars	4%

Table 2. Types of Scars

Post-acne hyperpigmentation was observed in 107 (53.5%) patients.

DISCUSSION

Peak incidence was noted in the 2nd decade. 78% of the patients were students. The mean age of patients in a south Indian study was 19.78 years (SD ± 4.94).[8]

94.5% patients had onset of disease before 20 years of age, only 5.5% had started developing lesions after the age of 20. Androgen hormone, which is implicated as the initial trigger for acne is secreted more during pubertal age group in both males and females.[2]

37.5% of the patients were asymptomatic. Itching was the predominant symptom (42.5%). Acne is usually asymptomatic. Itching is a rare symptom of acne and maybe possibly relate to the release of histamine-like compounds from propionibacterium acnes. Inflammatory lesions maybe tender and painful. Reactive oxygen species produced by the neutrophils may have a role in mediating the inflammation in these lesions.

Historically, much debate has surrounded the subject of diet in the management of acne. Recently, there has been a reappraisal of the diet and acne because of a greater understanding of how diet may affect endocrine factors involved in acne.[9] High-glycaemic diets maybe a significant contributor to the high prevalence of acne seen in Western countries.[9] High-glycaemic diet stimulate the secretion of insulin, which triggers the release of IGF-1.[10] IGF-1 has direct effect on pilosebaceous unit and has been shown to stimulate hyperkeratosis and epidermal hyperplasia. High glycaemic diet also decreases sex hormone binding globulin concentration thereby increases free androgens.[11] These facilitate acne formation.

Another well-studied diet is milk and dairy products, which carry hormones and bioactive molecules, some of these products survive digestion, that have the potential to aggravate acne.[9] 51.5% could not attribute their exacerbation to the intake of any particular food items. But, 31% noticed exacerbation of the lesions after intake of eggs, 20% after intake of oily foods and 4.5% after intake of milk and milk products.

Although, many drugs including halogenated compounds, progestogens, oral contraceptive pill (sometimes it helps acne), corticosteroids, isoniazid and lithium are known to cause acneiform eruptions.[12] None of the patients in our series attributed their disease onset or exacerbation with intake of drugs.

The improvement of acne in summer and exacerbation in winter is a conventional dermatological concept.[13] Studies done in the past have shown varied results regarding seasonal variation in acne vulgaris. An Indian study showed that majority of patients with acne vulgaris worsened during summer.[13] In our study, also 26% of the patients showed exacerbation in summer.

Stress is frequently implicated in the aggravation of acne, while acne itself induces stress.[14] In our study, 15.5% patients had exacerbations during periods of emotional stress. Cutaneous neurogenic factors may contribute the exacerbation of disease.

According to Cunliffe et al, a positive family history of acne is obtained in 40% of patients.[2] 56% of our patients had first-degree relatives with present or past history of acne, and of these, 40% were having scarring.

It is well known that seborrhoea plays a central role in the pathogenesis of seborrhoeic dermatitis and acne vulgaris, because both are androgen-mediated diseases.[16] In a Spanish study involving 2159 patients with seborrhoeic dermatitis, it was found that 35% of the subjects had acne vulgaris. 72.5% patients had seborrhoea in our study.

Premenstrual flare of acne reportedly occurs in 70% of female acne patients.[2] The pilosebaceous duct becomes smaller between days 15 and 20 of the menstrual cycle and the blockage leads to premenstrual acne. Progesterone and oestrogen have pro- and anti-inflammatory effects and alteration or modulation of these hormones maybe another explanation.[2,15] Premenstrual flare was noticed in 25.6% of patients.

The incidence of hirsutism and irregular periods observed in earlier studies varied between 0% to 21%.[16] The corresponding figures in our study were 7.31% and 19.5%. Cibula et al reported that there is no correlation between acne severity and clinical markers of androgenicity in women.[16] But, Reingold and Rosenfield have found an association between acne, hirsutism and menstrual disturbance.[17] We observed that 50% hirsute and 25% of Acanthosis nigricans patients had severe grades of acne.

The relationship between smoking and acne vulgaris is controversial. We observed smokers had severe grades of acne vulgaris compared to nonsmokers. Since, the number of smokers is small, no valid conclusion can be derived from this. Impaired vasoreactivity, relative ascorbic acid deficiency, impaired collagen synthesis and wound healing in smokers may play some part in the underlying pathogenesis for the association between smoking and acne.[18]

Acne vulgaris is a polymorphic disease.[1] The primary and the pathognomonic lesion of acne vulgaris is comedones.[19] Closed comedones were present in all patients in this series and they were the predominant lesions in 58.5%. Acne vulgaris occurs in sites, which are rich in pilosebaceous units. We noticed facial particularly cheek involvement in all patients, upper trunk and neck was involved in 52.5% and arms were involved in 24%. These observations are in accordance with other studies.[1,2]

Although, it is a hospital-based study, patients with grade 1 (predominantly comedonal) acne vulgaris outnumbered than more severe inflammatory forms of the disease.

Severe grades of acne were more common in≥20 years. This is in accordance with studies conducted by Coller et al, which showed that severe acne occurred commonly in patients of older age group.[20] According to Goulden V et al, males tend to show severe forms of the disease.[5] But, we observed severe grades of acne more prevalent in females (8%) compared to males (3%).

It was observed that the severity of the disease increases with increase in the duration of the disease. Out of the total 57 patients presented with duration more than 5 years, 26.31% patients had grade 3 and 4 acne, whereas 143 patients with ≤5 years duration, the severe grades of acne constituted only 4.89%. In a south Indian study conducted by Adithyan et al, it was found that patients with longer duration of the disease had more severe acne vulgaris.[8]

Post-acne scarring was noticed in 59.5% of our acne patients. The icepick scars were the most common type (52.1%). Post-acne hyperpigmentation was observed in 53.5% of the patients in our study. The findings in our study were in accordance with those of Kane et al.[19]

The relatively high incidence of post-acne scarring and pigmentation maybe a phenomenon in the South Indian race with skin type IV and V.[1,19]

CONCLUSION

57.5% patients were in the age group 15-19 years and the majority was students. 63.5% of the patients presented within 4 years of the onset of the disease. A definite association between dietary factors and acne exacerbation could not be found in 51.5% of the patients. Seasonal variation was observed in only 28% of the patients, most of them showing exacerbation during summer months. Most common associated disease was seborrhoea of the scalp. Face was involved in all cases and face involvement alone was seen in 76 patients.

Closed comedones and inflammatory papules were the predominant lesions. Severe grades of acne were more prevalent in females above 20 years. Hirsutes and females with Acanthosis nigricans had severe grades of acne. 94.5% of the patients had their disease onset before 20 years of age and none had their onset of disease after the age of 25. Severity of acne is directly proportional to the duration of the disease.

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Original Article

Chromoblastomycosis in Kerala, India

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ABSTRACT

Background: We are reporting 35 new cases of Chromoblastomycosis from Central Kerala. A majority of the cases from India are reported from the Sub Himalayan belt and South India. The disease scenario in India and abroad is briefly reviewed. **Aims:** To study chromoblastomycosis in Central Kerala including the demographic and clinico-investigative profile. **Methods:** This report is a retrospective record analysis of 35 cases of chromoblastomycosis who presented to the Dermatology Outpatient department of our tertiary center from January 2003 to July 2010 after obtaining Institutional Review Board approval. **Results:** The disease was found to be more common among male agriculturists. The majority of cases were from the central districts of Kerala in and around the Western Ghats. The lower extremity (60%) was more affected with 40% of the subjects remembering a prior history of trauma. Sclerotic bodies were demonstrable in scrapings from black dots in 42.8%. The characteristic mixed mycotic granuloma was demonstrable in 77.1% of cases. The most common species isolated was *Fonsecaea pedrosoi.* **Conclusions:** Chromoblastomycosis is very common in Central Kerala. The disease mainly affects male agriculturists especially those employed in rubber plantations. The most common organism is *F. pedrosoi.*

Key words: Chromoblastomycosis, *Fonsecaea pedrosoi,* mixed mycotic granuloma, sclerotic body

INTRODUCTION

Chromoblastomycosis is a chronic fungal infection caused by different species of dematiaceous fungi such as *Fonsecaea pedrosoi, Phialophora verrucosa, Fonsecaea compacta, Cladophialophora carrionii* and other species. The disease is characterized by the presence of thick walled, brownish, septate sclerotic bodies in the tissues. A majority of cases have been reported from the tropics and subtropics. We herein report 35 cases of chromoblastomycosis from a tertiary care institution in Central Kerala, India.

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METHODS

This report is a retrospective record analysis of 35 cases of chromoblastomycosis who presented to the Dermatology Outpatient department of our tertiary center from January 2003 to July 2010 after obtaining Institutional Review Board approval. A detailed history including demographic data, occupation, and history of trauma were recorded. Cutaneous and systemic examinations were performed and the findings were noted. Microscopic examination of scrapings from the surface black dots was performed using 10% potassium hydroxide. A skin biopsy was taken from the lesions and subjected to histopathologic examination with routine Hematoxylin and Eosin stain. No special stains were used. A separate skin tissue sample was sent for

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fungal culture using Sabouraud's dextrose agar and also AFB culture. Other co-morbidities like diabetes mellitus were noted. Our experience with treating 10 of the cases with Saturated Potassium iodide solution is included.

RESULTS

The youngest patient was 25 years of age and the oldest was 69. There were 30 males and 5 females. Twenty-one were employed in various agricultural tasks including rubber tapping. The cases were from central Kerala, majority from our district (28) and the rest from adjoining districts (7). Twenty cases were from the Western Ghats and its premises [Table 1]. The rest were from the immediate adjoining zones and midlands. Twenty-one cases had lower limb lesions, 11 had upper limb lesions, and the remaining 3 had truncal lesions. Fourteen of them recalled a history of trauma including penetrating injury (4), abrasion (4), laceration (4), and burns (4). Twenty-four were asymptomatic while the remaining 11 experienced symptoms including itching, pain, or both. All the patients presented with plaques of varying morphology with sizes ranging from 12 × 8 cm to 3 × 2 cm [Table 2]. Extracutaneous involvement was not seen in any of the cases. Scrapings from black dots gave positive results for sclerotic bodies in 15 of the cases. All of the cases were histopathologically proven with the characteristic brownish thick-walled sclerotic bodies being demonstrable in all the cases either within or outside the giant cells [Table 3].

Isolation of the organism in culture was possible in 31 cases. The most common species identified was *F. pedrosoi* (24). The other species identified included *F. dermatitidis* (3), *F. compactum* (2), *P. verrucosa* (1) and *Cladosporium* species (1). As proper follow up data is missing for some of the old cases, we couldn't include the data regarding treatment of all the cases [Table 4]. But we found excellent response to saturated Potassium iodide solution in 10 of the cases [Table 5]. The other drugs given included Terbinafine and Itraconazole [Figures 1-13].

DISCUSSION

Chromoblastomycosis was originally reported from Brazil. It was first reported from India in 1957 by Thomas *et al*.[1] Other than India and Brazil, Chromoblastomycosis has been reported from Madagascar, Sri Lanka, West Central Africa, Japan, Mexico, Cuba, Dominican Republic, Nepal, Australia, and Venezuela.[2-14] According to one report,

Table 1: Geographic distribution of cases

Type of landscape	No. of cases
Western Ghats high ranges	4
Foothills of Western Ghats	16
Midland	15

Table 2: Morphology of lesions

Morphology	No. of cases	Additional features
Verrucous plaques	31	Surface black dots (19) Atrophy (5) Hypertrophy (3)
Hyperkeratotic plaques with scaling	3	
Nodular cauliflower-like growth	1	

Table 3: Histopathological features of chromoblastomycosis

Histologic features	No. of cases	Additional features
Mixed mycotic granuloma with sclerotic bodies within or outside giant cells	27	Pseudoepitheliomatous hyperplasia (24) Acanthosis (18) Hyperkeratosis (15)
Granuloma composed of epitheloid cells, lymphocytes and plasma cells with sclerotic bodies	5	Papillomatosis (4) Epidermal microabscesses (3)
Collections of epitheloid cells and lymphocytes in dermis with giant cell formation and sclerotic bodies	3	Dermal microabscesses (3) Foci of collagenisation (1)

Table 4: Our treatment modalities

Drug	Dosage
Saturated potassium iodide solution (1000 gm in 1000 ml of distilled water)	Started as monotherapy at a rate of one drop thrice daily. The rate is increased by one drop per dose every day until a maximum of 40 drops thrice daily. Maintained at that level until complete resolution. The dose is then tapered at a rate of 1 drop/dose/day
Terbinafine	250 mg twice daily until complete resolution
Itraconazole	200 mg once daily

Madagascar represents the most important focus of this fungal disease.[7] Brazil is another country reporting large number of cases.[2-6] In most of these reports, chromoblastomycosis is seen to be a disease of rural male agriculturists and the commonest etiological agent is *F. pedrosoi*.

In India, Thomas *et al* first reported two cases of chromoblastomycosis from Assam.[1] Since then, there has been several case reports from the Sub-Himalayan belt, Western and Eastern coasts. Rajendran *et al* in 1997 reviewed 30 cases till then from all over India and reported 4 new cases including 2 cases from Jammu and Kashmir and Bihar.[15] Sharma *et al* in 1999 also reviewed the Indian scenario and reported four more cases.[16] Kumar *et al* reported two cases in 2000 and Sharma A reported four cases from Assam in 2010.[17,18] All these areas have warm and humid climatic conditions and it is seen that the Central and North Western arid zones of the country are free of the disease.[16] Among the previously reported cases, 18 were from South India [Andhra Pradesh (5), Karnataka (5), Tamil Nadu (4), Kerala (3), Pondicherry (1)] [Table 6].[15]

Table 5: Our experience with potassium iodide therapy for chromoblastomycosis

Time for resolution with potassium iodide	No. of patients
1 to 3 months	3 patients
4 to 6 months	6 patients
7 to 9 months	1 patient

We herein report 35 cases of chromoblastomycosis from central Kerala. Our cases were from the foothills of Western Ghats and adjoining midland areas. The foothill areas of Western Ghats and the adjoining areas

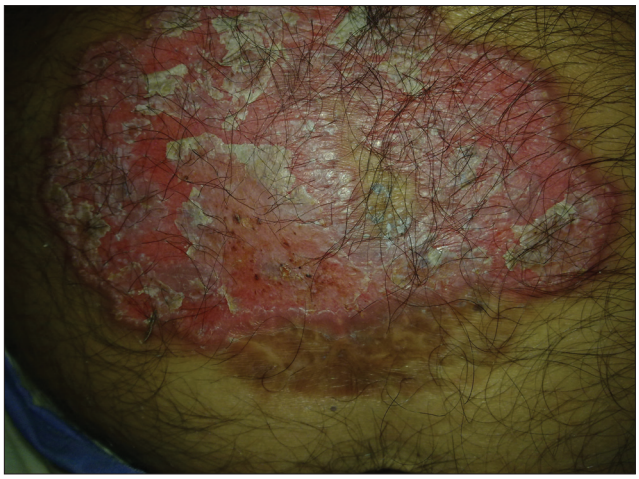

Figure 1: A scaly plaque with surface black dots

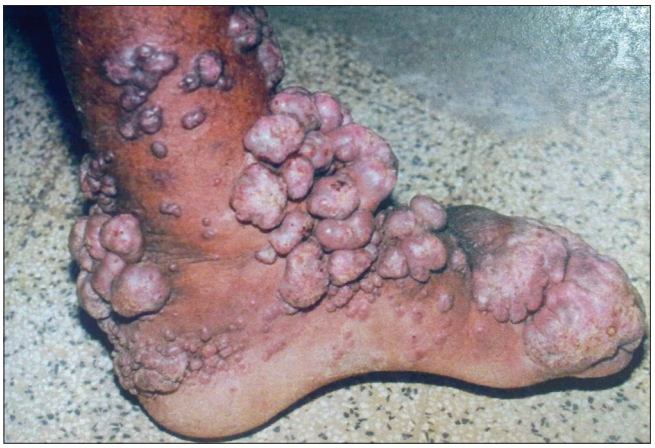

Figure 2: A case of chromoblastomycosis with nodular, cauliflower-like lesions

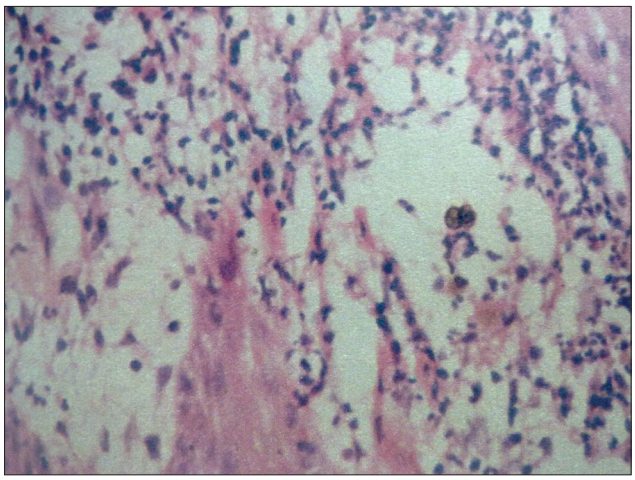

Figure 3: Mixed mycotic granuloma with sclerotic body (H and E, ×40)

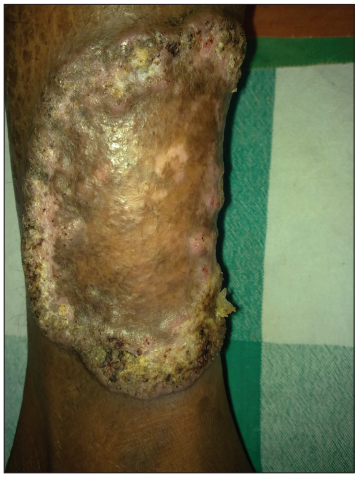

Figure 4: A verrucous crusted plaque with central atrophy

Figure 5: Black colored colonies when grown on agar media

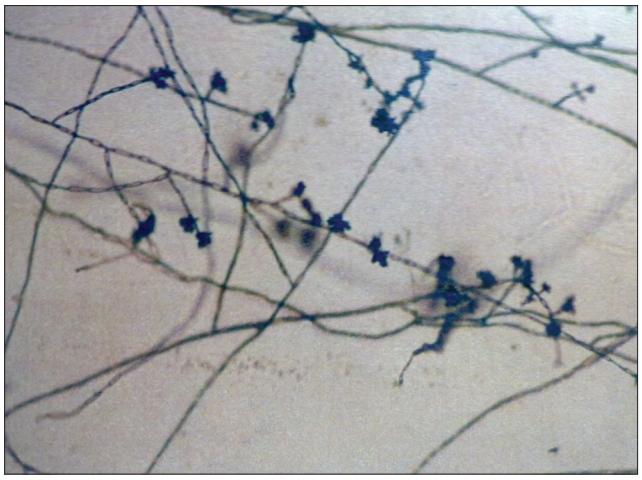

Figure 6: *Fonsecaea pedrosoi*

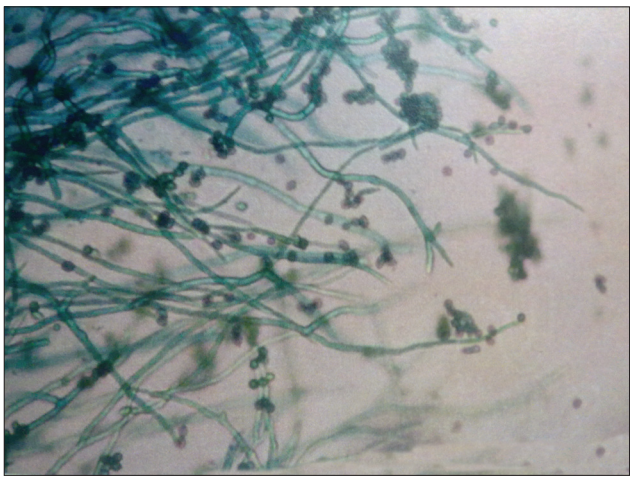

Figure 7: *Fonsecaea compactum*

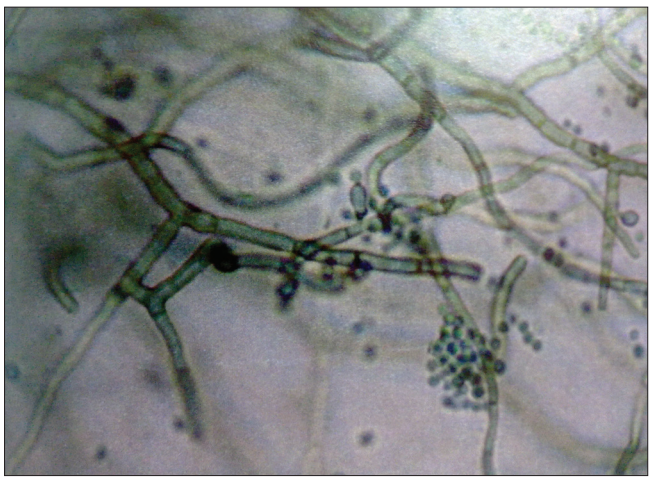

Figure 8: *Phialophora verrucosa*

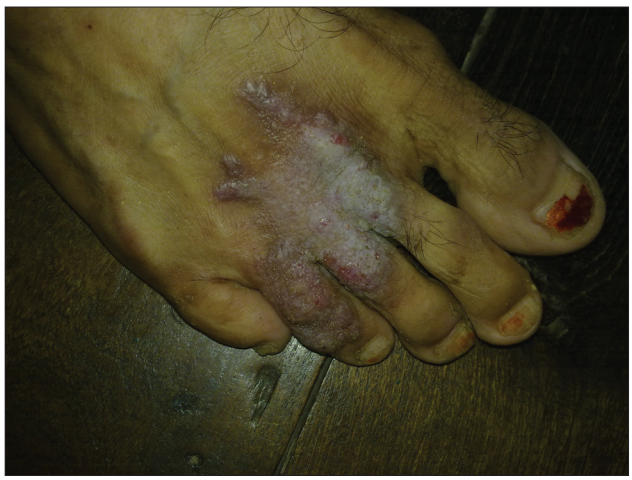

Figure 9: Scaly plaque on the right foot

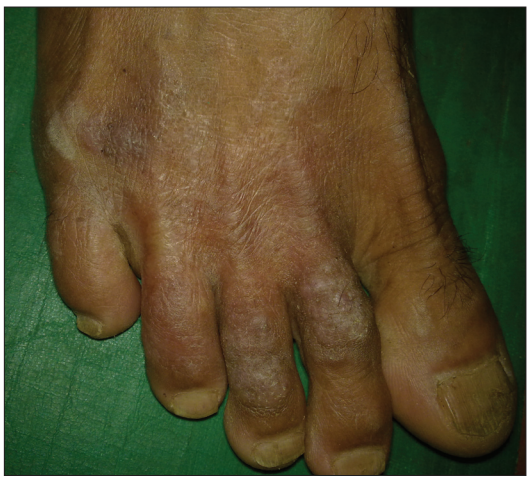

Figure 10: The same patient after 4 months of treatment with potassium iodide

are well known for their rubber plantations where there is plenty of decaying vegetative matter. Such an environment could be favorable for the growth of the fungus. The etiological agents of chromoblastomycosis have been discovered from soil, wood, vegetable debris, and similar substances.[19] Most of our patients

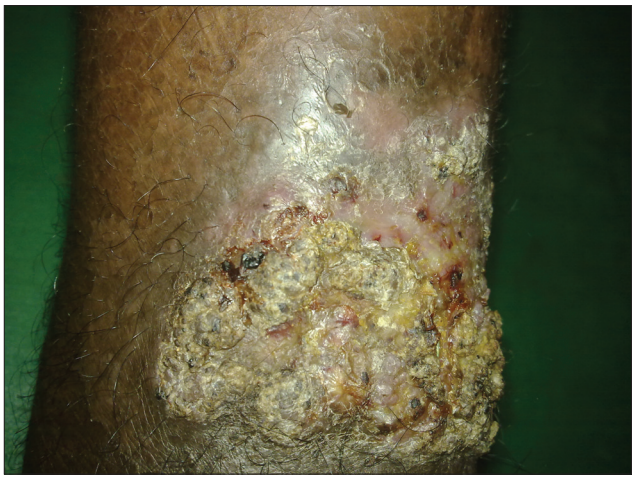

Figure 11: Scaly verrucous plaque on the right leg

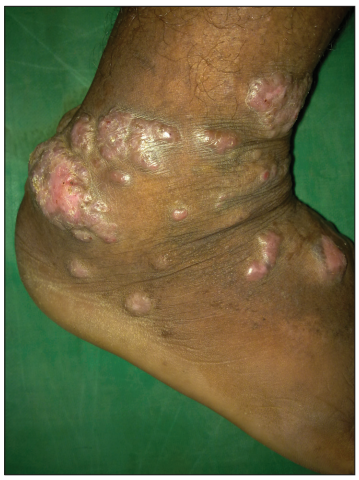

Figure 12: Multiple plaques on the leg

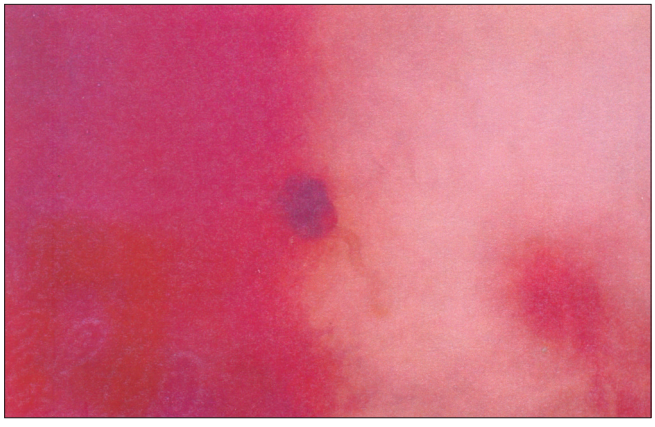

Figure 13: Sclerotic bodies arranged in a group

were employed in various agricultural tasks including rubber tapping. Rural males from an agricultural background were commonly affected which is the common pattern of the disease worldwide.[3,8,9,12]

Table 6: A few case series from india and abroad

1957-1997	India	Rajendran *et al*.[15] Sharma *et al*.[16]	30
1973	Kenya	Cameron *et al*.[10]	33
1995	Gabon, West Central Africa	Kombila *et al*.[9]	64
1996	Madagascar	Esterre *et al*.[7]	1343
1996	Australia	Santos *et al*.[13]	6
1997	India	Rajendran *et al*.[15]	4
1997	Sri Lanka	Attappattu *et al*.[8]	71
1998	Brazil	Silva *et al*.[2]	325
1999	India	Sharma *et al*.[16]	4
2000	India	Kumar *et al*.[17]	2
2001	Brazil	Minotto *et al*.[3]	100
2006	Venezuela	Pérez-Blanco *et al*.[14]	22
2007	Nepal	Pradhan *et al*.[12]	13
2010	Brazil	Correia *et al*.[5]	27
2010	India	Sharma *et al*.[18]	4
2011	Brazil	Mouchalouat *et al*.[6]	18

The relationship with trauma correlates well with the predominant involvement of extremities among agriculturists. The most common species of fungus isolated was *F. pedrosoi*. *F. pedrosoi* is the most common organism causing Chromoblastomycosis worldwide and is also the most common isolate in humid tropical climates.[2-6,9]

We could obtain positive results with fungal scraping study using 10% potassium hydroxide in 42.8% of the cases. Fungal scraping study is a simple and non invasive test for the diagnosis of this subcutaneous mycosis.[20,21]

Potassium iodide is considered to be an effective drug for chromoblastomycosis.[22] The therapeutic response to Itraconazole and Terbinafine are thought to be better if the causative agent is *C. carrionii*.[23] Our most common isolate was *F. pedrosoi*. We tried potassium iodide in some of our patients and found it to be cost effective, especially in a setting like ours.

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Original Article

Low dose intravenous immunoglobulins and steroids in toxic epidermal necrolysis: A prospective comparative open-labelled study of 36 cases

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ABSTRACT

Background: Toxic epidermal necrolysis (TEN) is a severe adverse drug reaction associated with high mortality. Though different modalities of treatment are advocated, there is no consensus regarding specific therapy. Corticosteroids have shown conflicting results and for high dose intravenous immunoglobulins (IVIG), cost is a limiting factor. **Aim:** To find out the effectiveness of combination therapy with low-dose IVIG and steroids versus steroids alone in our TEN patients. **Methods:** After obtaining Ethical Committee approval, 36 consecutive TEN patients (2008-2012) were alternately allocated to 2 groups – Group A was given combination of low-dose IVIG (0.2-0.5 g/kg) and rapidly tapering course of steroids (intravenous dexamethasone 0.1- 0.3 mg/kg/day tapered in 1-2 weeks) while Group B was given same dose of steroids alone. Outcome parameters assessed were time taken for arrest of disease progression, time taken for re-epithelization, duration of hospital stay and mortality rates. **Results:** Both groups had 18 patients. Baseline characteristics like age, sex ratio, SCORTEN, body surface area involvement and treatment interval were comparable. Time for arrest of disease progression and for re-epithelization was significantly lowered in Group A (P = 0.0001, P = 0.0009 respectively). Though duration of hospital stay and deaths were less in Group A, difference was not statistically significant. SCORTEN based standardized mortality ratio (SMR) analysis revealed that combination therapy reduced the probability of dying by 82% (SMR = 0.18 ± 0.36) and steroids by 37% (SMR = 0.63 ± 0.71). Difference in SMR was statistically significant (P = 0.00001). No significant side effects due to either modality were found in any of the patients. **Conclusion:** Combination therapy with low-dose IVIG and steroids is more effective in terms of reduced mortality and faster disease resolution when compared to steroids alone in TEN.

Key words: Combination therapy, low dose intravenous immunoglobulins, toxic epidermal necrolysis

INTRODUCTION

Toxic epidermal necrolysis (TEN) is a life threatening severe cutaneous adverse drug reaction. It is caused by widespread keratinocyte apoptosis mediated by the Fas- Fas ligand and the perforin – granzyme pathway.[1] Beyond immediate cessation of the offending drug and adequate supportive care preferably in a burns unit, a lack of clarity prevails regarding specific management. The available studies reveal a dichotomy of opinion regarding the effectiveness of both corticosteroids and intravenous immunoglobulin (IVIG) in the treatment of TEN.[2] Furthermore, the increased cost of high dose IVIG, the more recently favored biologic, preclude their use in most of our patients.

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This situation prompted us to try a combination therapy with IVIG and steroids as they target the disease at different levels of pathogenesis. The exact dose of IVIG effective in TEN differs in various studies with most of them employing a total cumulative dose between 1.5 g/kg and 3.5 g/kg.[3] A few studies have reported improvement even with a low-dose of 0.1 - 0.5 g/kg.[4,5] As the inhibition of Fas-Fas ligand interaction by IVIG is not an 'all or none' phenomenon, and the lower cumulative dosing considerably increased the affordability of IVIG in our patients, we considered it worthwhile to probe its effect.

To the best of our knowledge, the combination of low-dose IVIG and steroids is a novel therapeutic option in TEN, not reported in any trials previously. We hypothesize that while the lower dose of IVIG improves the safety and affordability, the addition of steroids might increase the effectiveness by a possible synergistic effect.

METHODS

A prospective open labeled study was conducted in the Dermatology ward of our center, which is an 837-bedded tertiary care teaching hospital. Ethical clearance for this study was obtained from the Institutional Review Board. Informed consent was taken from all the patients/guardians after detailed explanation of study procedures. The study subjects were all consecutive patients diagnosed and admitted as TEN in the 4 year time interval between February 2008 and January 2012. The diagnosis was based on the history of drug ingestion (WHO causality definition – certain/probable),[6] clinical findings with body surface area (BSA) involvement of > 30% as per Bastuji- Garin classification[7] and exclusion of similar disorders, especially autoimmune bullous disorders. Tzanck smear examination was done in all patients. Skin biopsy was performed only in doubtful cases to avoid further trauma. Complete blood investigations, urine microscopy and cultures, chest X-rays, Venereal Disease Research Laboratory test, ELISA for HIV, antinuclear antibody, blood cultures and pus cultures were also done.

Out of the total 38 patients who were admitted with TEN during the study period, two patients with contraindications to steroid/IVIG treatment were excluded from the study. The remaining 36 patients were alternately allocated to two groups of 18 each. The patients in the combination therapy group (Group A) were treated with IVIG in a cumulative dose of 0.2 - 0.5 g/kg (Trade name - GAMMA I.V., manufactured by Bharat Serums and Vaccines Limited) divided over 3 days along with systemic steroids. The preferred systemic steroid preparation used was intravenous dexamethasone in a dose of 0.1-0.3 mg/kg/day and rapidly tapered within 1-2 weeks according to response. Group B patients were treated with the same dose of steroids alone. Patients in both groups were given intensive supportive treatment along with prompt and meticulous ophthalmic care and care of oral and genital mucosa. Since there is no test to identify the offending drug beyond doubt, all ongoing medications were stopped/substituted. Immediate complications and side effects of the treatment modalities, if any, were noted in all patients. After discharge, all patients were scheduled for follow-up visits until 6 months and long-time complications, if any were recorded.

SCORTEN

SCORTEN, a severity-of- illness score for TEN patients described by Bastuji- Garin *et al*.[7] was calculated for each patient at the time of admission. Each point is allotted for one of the following parameters – age > 40, malignancy, heart rate > 120/min, initial % of epidermal detachment > 10 %, Blood urea > 28 mg/dl, RBS > 252mg/dl and serum bicarbonate < 20 mEq/L. The score ranges from a minimum of 0 to a maximum of 7 and is thought to accurately predict risk of death in TEN patients. A score of 0-1 is associated with a 3.2% risk of mortality whereas if the score is ≥ 5, the risk of death is 90%.[8]

Statistical analysis

Data was entered in Microsoft Excel and analyzed by the software SPSS, version 16.0. The measures of outcome determined were - the time taken for arrest of disease progression (no new lesions, Nikolsky turned negative, exudation reduced), time taken for re-epithelization, duration of hospital stay and the mortality rates. The analysis of mortality rates was done on the basis of SCORTEN; the actual death rates were compared to SCORTEN predicted mortality rates by standardized mortality ratio (SMR) analysis (SMR = total observed deaths/total expected deaths). The statistical comparisons of the qualitative data were done using Chi- square test and quantitative data using Student's *t* - test. Statistical significance

was defined as $P < 0.05$. Multivariate analysis using multiple linear regression was also performed wherever appropriate.

RESULTS

The average age was 37 years (6–68years) of which 6 were children. Females dominated (20/36). The most common drugs implicated were aromatic anticonvulsants (24/36, 66.67%) with carbamazepine responsible in 12 cases, phenytoin in 9, both together in 2 and phenobarbitone in 1 case. The most common indication for starting these drugs was seizure disorder followed by head injury. One patient had malignancy with brain metastasis and another had an astrocytoma. There were 2 patients with HIV in this cohort, both with CD4 counts < 200, who were started on anti retroviral treatment containing nevirapine within the last 2 months.

The mean incubation period was 16.02 ± 6.80 days. The mean percentage of BSA involved (detached/detachable) was 51.16%. There were a total of four deaths (11.11%); 1 in Group A and 3 in Group B. The death in Group A occurred in a 68 year old patient with multiple co-morbidities, on the 4th day of admission. The cause of death was attributed to sepsis, not responding to antibiotic treatment. Of the three deaths in Group B, 2 occurred as a result of pneumonitis with acute respiratory failure and the 3rd patient suffered from multi-organ failure. The three deaths occurred on the 8th, 7th and 9th day of admission respectively. All the deaths occurred despite intensive critical care treatment supervised by a panel of specialists.

During the clinical course of the disease, commonest complications encountered were bacterial infections; which were noted in 15 patients (skin – 6, urinary tract -3, respiratory tract -6, positive blood cultures - 5) all of whom responded to broad spectrum systemic antibiotics except one who succumbed to septicemia. Furthermore, there was one patient who developed thrombocytopenia and another who developed agranulocytosis. The long term complications noted were – pigmentary alteration in seven patients, vulvar synechiae in one, ocular symblepharon in one and corneal epithelial defects in two patients. No major immediate or long term treatment related side effects were noted in any of the patients.

Of the six pediatric patients in this cohort, all were females except one. The causative drug was aromatic anticonvulsants in five of them (started for seizure disorder in four and following head injury in one). Mean incubation period was 15 days, mean BSA involvement was 43.83%, and median SCORTEN was two. Three of them were treated with combination therapy and the others with steroids alone. No deaths occurred. Average time taken for arrest of progression was 5.33 days, for re-epithelization was 9.67 days and mean duration of hospital stay was 15.5 days. No long term complications were seen except for pigmentation.

On comparing the baseline characteristics of group A and group B, i.e., age, sex, SCORTEN, BSA involvement and interval between onset of disease and initiation of treatment [Table 1], all were found to be comparable ($P > 0.05$) in both the groups.

On comparing the outcome parameters of Groups A and B [Table 2], a statistically significant difference was noted between the two groups in the time taken for arrest of disease progression, and time taken for epithelization [Figures 1 and 2]. This means that the addition of low-dose IVIG to steroids resulted in an earlier clinical improvement. The duration of hospital stay and mortality rate even though less in the combination group, the difference was not statistically significant. Multivariate analysis with all explanatory variables were done by multiple linear regression model using dependent variables as time taken for arrest of progression of disease and time for epithelization. Only the treatment given was found to be a significant explanatory variable in the regression model in both.

Table 1: Comparison of baseline characteristics of Groups A and B

Baseline parameters	Group A	Group B	*P* value
Mean Age ± SD (in years)	35.44 ± 17.74	38.56 ± 17.56	0.60
Male:Female ratio	4:5	4:5	
Median SCORTEN (interquartile range)	3 (2-3)	2.5 (2-3)	0.44
Mean BSA ± SD (in %)	52.83 ± 11.61	49.50 ± 14.05	0.30
Mean treatment interval ± SD (in days)	4.89 ± 2.32	5.39 ± 4.35	0.67

SD: Standard Deviation. SCORTEN: Severity-of-illness score in toxic epidermal necrolysis. BSA: Body surface area. Treatment interval - Interval from onset of disease to initiation of treatment

Table 2: Comparison of outcome parameters of Groups A and B

Outcome parameters	Group A	Group B	*P* value
Mean duration of arrest of progression ± SD (in days)	3.94 ± 1.94	5.93 ± 1.44	0.0001
Mean time taken for epithelisation ± SD (in days)	8 ± 2.24	10.93 ± 2.25	0.0009
Mean duration of hospital stay ± SD (in days)	13.33 ± 5.40	15.33 ± 6.22	0.31
Deaths (in %)	5.6	16.7	0.30
SMR	0.18 ± 0.36	0.63 ± 0.71	0.00001

SD: Standard deviation. SMR: Standardized mortality ratio

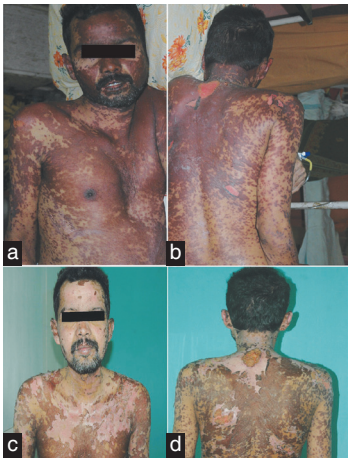

Figure 1: A patient with phenytoin induced toxic epidermal necrolysis treated with combination therapy (a, b) on the 2nd day of admission. (c, d) The same patient on day 9

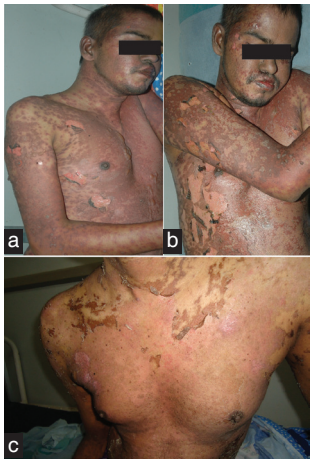

Figure 2: A patient with carbamazepine induced toxic epidermal necrolysis treated with intravenous dexamethasone alone (a) on the 1st day of admission. (b) on the 2nd day. (c) The same patient on day 12

On comparing the actual mortality rates to SCORTEN predicted mortality rate [Table 3], it was found that combination therapy highly reduced the chances of death. While the SCORTEN predicted mortality in Group A patients was 5.49 deaths, in fact only 1 death occurred. SMR analysis revealed that there is an 82 % less probability of dying when treated with combination therapy. In the steroid group, SCORTEN predicted mortality was 4.76 deaths while actually there were only three deaths. SMR analysis revealed that steroids lower the probability of dying by 37%. Thus, though not as effective as the combination therapy, steroids alone also tended to reduce the mortality rates of our TEN patients. However, the difference in SMR between the groups was found to be statistically significant ($P = 0.00001$) indicating a superiority for combination therapy in terms of mortality also.

DISCUSSION

Although TEN has been a well-recognized clinical entity since it was described by Lyell in 1956, there is no formally established systematic protocol for its treatment.[2] Corticosteroids have been routinely used in our center for the management of TEN since the past decade and we have found it useful in achieving early control of the disease despite many studies claiming otherwise. The general negative opinion about corticosteroids is probably because they are often given too late, in too low a dose and for too long.[9] Many studies from India have claimed beneficial effects with systemic corticosteroids[10,11] and according to the therapeutic guidelines published by the Indian Association of Dermatologists, Venereologists and Leprologists, corticosteroids have a place in the management of TEN if given early in the disease and tapered promptly.[12] Corticosteroids are thought to act by having suppressive effects on the cytotoxic T lymphocytes and also inhibit interferon gamma mediated apoptosis. Moreover, they have pleomorphic effects on the immune system including inhibition of chemokines and numerous cytokines like TNF-alpha.[9]

IVIG on the other hand, is a highly purified Immunoglobulin G prepared from pooled plasma with trace amounts of Immunoglobulin A or Immunoglobulin M.[3] It possesses anti-Fas activity and inhibits keratinocyte apoptosis by blocking the binding of Fas – ligand to Fas receptors.[1] Additionally, IVIG has anti infective properties and also corrects protein and fluid

Table 3: Comparison of SCORTEN predicted mortality rates with actual mortality rates.

SCORTEN	Expected deaths (%)	Group A			Group B		
		No. of patients	Predicted deaths	Actual deaths	No.of patients	Predicted deaths	Actual deaths
0-1	3.2	0	0	0	2	0.06	0
2	12.1	7	0.84	0	7	0.84	0
3	35.3	9	3.17	0	6	2.118	0
4	58.3	1	0.58	1	3	1.749	3
5-7	90	1	0.9	0	0	0	0
Total		18	5.49	1	18	4.767	3

loss. Potential side effects include thromboembolism, aseptic meningitis, hemolysis, vasomotor symptoms and anaphylactic reactions but is generally well tolerated by patients who have adequate renal function.[13]

A number of retrospective and prospective studies have been conducted to examine the efficacy and safety of IVIG in TEN patients. Viard *et al*., Metry *et al*. and Tristani – Firouzi *et al.* found IVIG to have a beneficial effect in TEN whereas the study by Brown *et al.* and the EuroSCAR study demonstrated no benefit.[1,14-17] It seems impossible to draw a consensus regarding the effectiveness of IVIG in the absence of prospective, controlled, multi-centric trials. But one inference that may be drawn regarding the contrasting results is that Fas – Fas ligand interactions may not be the only mechanism of apoptosis active in TEN; other pathogenic mechanisms may be responsible for the damage. In view of the accumulating experimental evidence for the role of cytotoxic T lymphocytes in the destruction of the epithelium, there may be a rationale for the effectiveness of steroids in Stevens-Johnson Syndrome / TEN.[2]

In this context, combination therapy seems an attractive choice. Combining steroids with IVIG is a feasible option as they do not have a similar adverse effect profile, and may have a synergistic action targeting the different pathways of apoptosis active in TEN. Very few authors have studied the beneficial effects of combination of IVIG and steroids.[18,19] But the dose of IVIG used in most studies is around 2 g/kg. The increased cost takes high-dose IVIG out of reach of the common man in India. A study by Mangla *et al*. has proposed low-dose IVIG (0.05 - 0.1 g/kg/day for 5 days) to be a safe and effective treatment option in children.[4] Viard *et al*. found benefit with IVIG in a dose as low as 0.8 g/kg.[1] The dose used by us was a cumulative dose of 0.2–0.5 g/kg divided over 3 days and the approximate cost incurred by the patient was between ₹ 18,000-30,000 in contrast to approximately ₹ 1.5-2 lakh, which is the average cost of the high-dose regimen.

Based on the SCORTEN predicted mortality rate analysis, our study showed that the combination therapy significantly reduced the mortality rates. Steroids alone also reduced mortality, but not as significantly as in combination. Moreover, the combination therapy arrested the disease progression earlier than corticosteroids. The onset of epithelization was also faster. This indicates that corticosteroids could be tapered earlier and the total steroid dose could be reduced. Finally, it is also noteworthy that no serious adverse effects of either treatment modality were found in any of our patients.

We are not unaware of the limitations of our study. In view of the rarity of the disease and the small sample size expected, we did not go for a randomized study design. Also histopathological confirmation of all cases could not be performed. We intend for our study to be taken as a pilot project and hope that more researchers will conduct further elaborate trials to confirm or refute our findings.

In conclusion, our study supports the use of combination therapy with low dose IVIG and steroids in TEN. Even though treatment with steroids alone also has a definite role, our study indicates that combination therapy has a superior therapeutic effect when compared to steroids alone. As similar studies are lacking in the literature, more multi-centric randomized controlled trials are needed to confirm the findings of this study.

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AN AETIOPATHOLOGICAL STUDY OF EXFOLIATIVE DERMATITIS

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ABSTRACT

BACKGROUND

Erythroderma or exfoliative dermatitis is an inflammatory disorder in which erythema and scaling occur in a generalized distribution involving more than 90% of body surface. It is a reaction pattern of skin due to various pre-existing dermatoses, malignancy– cutaneous or internal. 100 clinically diagnosed cases of exfoliative dermatitis were included in this study.
The objectives of this study were- to evaluate clinical profile and aetiology of exfoliative dermatitis and to correlate histopathological findings with clinical diagnosis.

MATERIALS AND METHODS

100 clinically diagnosed cases of exfoliative dermatitis were included for this cross-sectional study, during a period of 18 months (from March 2014 to August 2015). A detailed history and clinical examination were done. Investigations including complete blood count, peripheral smear, urine routine examination, LFT, RFT, chest X-Ray, ECG, blood sugar, FNAC lymph node and skin biopsy were done in all patients. An approval from institutional review board for ethics committee and informed consent from all patients were obtained. All data was collected in a proforma and evaluated by using epidemiological investigative software SPSS.

RESULTS

Male to female ratio was 5:1:1. Mean age of patients was 57.7 years. 57% of patients were manual labourers. 82% of patients develop exfoliative dermatitis from pre-existing skin diseases and psoriasis was present in 42%. The interval between pre-existing skin disease and Erythroderma was 1 week to 1 year in 61% of patients. Drugs caused exfoliative dermatitis in 11% of patients. Lymphadenopathy was seen in 80% of cases. Anaemia was found in 61% of patients. LFT abnormality was noted in 48% of cases. Histopathology of skin correlated with clinical diagnosis in 51% of patients.

CONCLUSION

Erythroderma mainly a disease affecting persons of 40-70 yrs. Psoriasis is the common single disease causing exfoliative dermatitis. Histopathology helps in diagnosis only in 50% of cases.

KEYWORDS

Exfoliative Dermatitis, Skin Biopsy, Psoriasis.

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BACKGROUND

Erythroderma or exfoliative dermatitis is an inflammatory disorder in which erythema and scaling involving more than 90% of the body surface.[1] It is usually accompanied by other systemic manifestations resulting in hemodynamic and metabolic derangements.

Erythroderma is a morphological reaction pattern of skin to pre-existing dermatoses like psoriasis, atopic dermatitis, contact dermatitis, systemic skin conditions including malignancy and drug reaction. Pre-existing dermatoses or their therapy can result in erythroderma and this is the most common cause of Erythroderma in adults.[2,3,4,5,6,7] Psoriasis is the most common cause of exfoliative dermatitis amongst dermatological disorders.[2,7,8,9]

Irrespective of etiology the clinical features of erythroderma were almost identical. Thus, the importance of trying to find the etiology with special emphasis on histopathology, allowing early and appropriate intervention for each case.[10] The number of new erythroderma cases in dermatology department of government medical college Kottayam for 18 months (from March 2014 to August 2015) was 115 and we include first 100 patients who full filled inclusion and exclusion criteria in this study.

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MATERIALS AND METHODS

100 clinically diagnosed cases of exfoliative dermatitis were included in this cross-sectional study during the given period of 18 months (from March 2014 to August 2015). Patients were clinically evaluated with detailed history including the

occupation, socioeconomic status, onset, duration, evolution of disease, pre-existing dermatoses, aggravating /precipitating factors, previous treatment, personal history, family history and any associated disorder. A detailed clinical examination was carried out.

Extent of erythema and scaling were calculated according to the "Wallace's rule of nine". Changes in palms, soles and nail were noted; also, mucous membrane were examined.

Systemic examination was done, to detect clinical evidence of cardiac failure, hepatomegaly and any lung changes. Per rectal examination was done, in all old male patients and per vaginal examination in all married females. Investigations like haemoglobin, total and differential white cell count, erythrocyte sedimentation rate, peripheral smear for abnormal cell, urine routine examination, liver function test, renal function test, serum electrolytes, X-ray chest, ECG and blood sugar estimation were done. FNAC examination done in patients with significant lymph node enlargement and suspected cases of malignancy, skin biopsy was taken from all patients.

An approval from Institutional Review Board for Ethics Committee and informed consent from all patients who participated in the study were obtained. All data was collected on a proforma and evaluated by using epidemiological investigative software SPSS.

OBSERVATION AND RESULTS

100 patients were included in this study from March 2014 to August 2015. In these 83 were males and 17 were females. Male to female sex ratio was 5.12:1 Maximum patients (30%) were of 7th decade followed by 18% of 6th decade. Youngest patient was a 10 months old boy and the oldest was 89 years old man. Mean age of our patients was 57.7 years. Most of the patients in this study were manual labourers 57% followed by farmers with 17%. In majority of patients (63%) the duration of disease was <3 months. Minimum duration of 2 days was seen in a case of irritant contact dermatitis due to application of some Ayurvedic preparation and a case of drug reaction with amoxicillin. While maximum duration (12 years) was in a case of psoriatic erythroderma. 82% developed Erythroderma due to pre-existing dermatoses in which most common was psoriasis. Drug reaction was responsible for 11%, malignancy for 2% and rest 5% left without definite diagnosis as idiopathic. (Figure - 1 & 2)

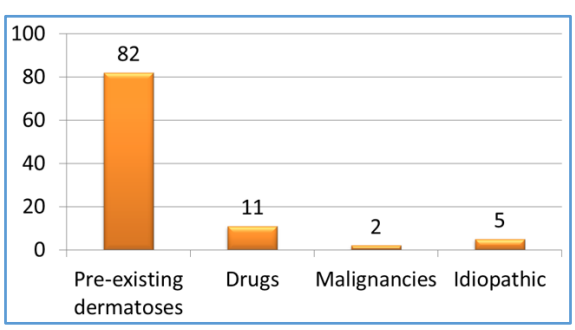

Figure 1. Aetiological Factors of Erythroderma

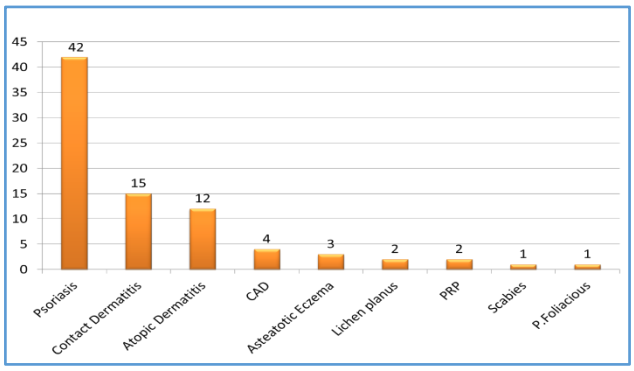

Figure 2. Types of Pre-existing Dermatoses

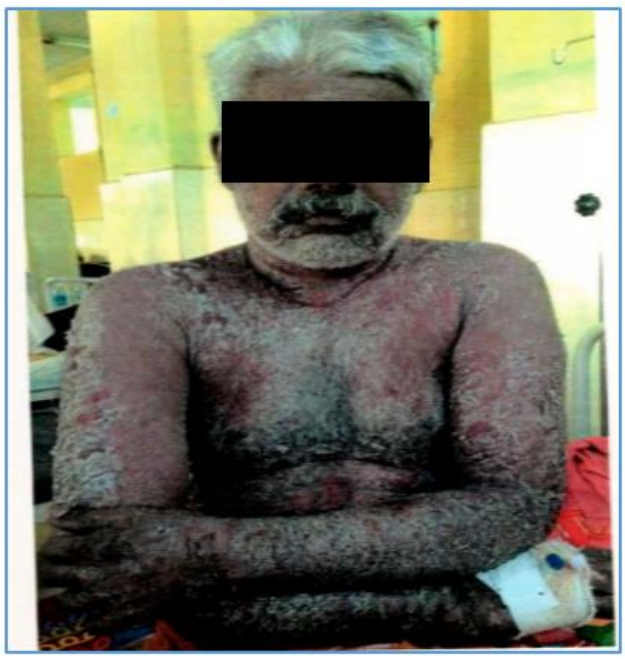

Figure 3. Erythroderma Secondary to Pustular Psoriasis

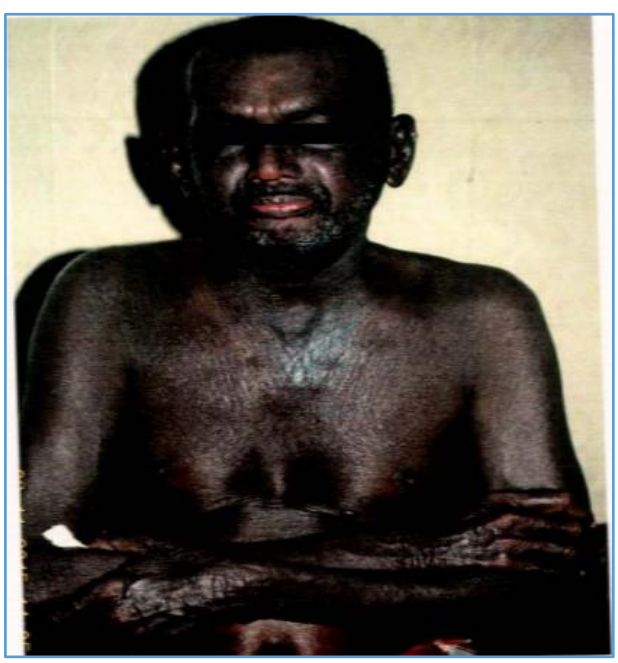

Figure 4. Erythroderma Secondary to Chronic Actinic Dermatitis

History of psoriasis was noted in 42% (Figure 3) contact dermatitis in 15%, and atopic dermatitis in 12%, chronic actinic dermatitis (CAD)/ Photodermatoses (Figure 4) in 4%, and asteatotic eczema in 3%, lichen planus in 2%, pityriasis rubra pilaris (PRP) in 2%, pemphigus foliaceus and scabies in 1% each. Time interval between PED and erythroderma was 1 week to 1 year in 61% patients with minimum of <1 week in 2% cases and maximum >10 years in 4%. Mean duration of this interval was 2.5 years. Total number of drug induced erythroderma patients were 11 and the most common drug causing erythroderma was Phenytoin sodium in 5 cases followed by INH and Dapsone 2 cases each and 1 case each of sodium valproate and penicillin's (amoxicillin + cloxacillin). 2 cases of malignancy were found in this study. One case each of CTCL and papillary carcinoma of thyroid. With our best efforts of thorough evaluation, we could not find out exact aetiology in 5 patients. History of AYUSH (Ayurvedic, Unani, Siddha, and Homeopathy) therapy, home remedies or other indigenous medication was present in 30%, infections in 18%, photo-exacerbation in 6%, drug intake was in 11%, drug withdrawal in 8%, irritant applications in 6%, stress and winter season in 2% cases each. Itching was present in 87%. Chills, rigor, malaise were present in 62%, fever in 58% and burning sensations in 4% cases.

Diffuse non-scarring hair loss was present in 21 cases, majority (9 cases) were of contact dermatitis followed by 8 cases of psoriasis while 2 cases from CAD and 1 each from atopic dermatitis and idiopathic. Most common finding on oral examination was dental carries in 54% cases, followed by mucosal changes (46%) white lacy pattern, hyper-pigmentations, atrophic glossitis, scrotal tongue and candidiasis. Nail changes were found in 71% of cases. Most common nail changes were longitudinal ridges in 63% cases. The specific nail change for psoriasis, oil drop sign was present only in 8 cases of psoriatic erythroderma. While other suggestive nail changes were pitting, subungual hyperkeratosis (SUHK) and onycholysis. Enlargement of lymph node were present in 80% cases, of these 30% cases had generalized lymphadenopathy and 50 % cases had localized involvement in inguinal and/or axillary group of lymph nodes.

FNAC was done in 17 suspected cases of malignancy out of which 8 showed reactive changes and remaining 9 cases showed lipomelanotic reticulosis (dermatopathic lymphadenopathy). These 8 patients with reactive changes were further investigated by lymph node biopsy; in them one case came as CTCL and was confirmed by skin biopsy also. In one case FNAC and biopsy was taken from hard thyroid swelling and result came as papillary carcinoma of thyroid. 87% cases had dependent pitting pedal oedema along with 12 cases of facial puffiness. Most common finding on haemogram was anaemia which was present in 61% cases, followed by eosinophilia in 54%, neutrophilia, leucocytosis and lymphocytosis were present in 47%, 25%, and 4% respectively. All the haemogram findings had no association to any specific aetiology.

5 cases showed atypical lymphocytes in peripheral smear and on further investigation one case came as CTCL. 23 patients were found to be diabetic on blood sugar testing. Urine- abnormal in 19% cases in which significant increased pus cells (>5 in no. in males and >10 in females) were in 8% cases, other findings were proteinuria and glycosuria in 4% cases each, while RBC casts were present in 3% cases. LFT were done in all patients. Abnormality seen in 48% cases in which most common was hypoproteinaemia in 39%, hypo-albuminaemia in 32%, while enzymes were raised in 10 cases in which most of the cases (8) were of drug induced Erythroderma and rest 2 were in erythrodermic psoriasis cases. Serum bilirubin was raised in 4 cases, out of which 3 were of drug induced erythroderma and there was no relation in hypo-proteinemia/ hypo-albuminemia in different aetiologies of erythroderma. Most common finding in RFT was raised serum creatinine in 15% cases, raised blood urea in 7%. Electrolyte imbalance was present in 18 cases. Out of which hyponatremia in 8%, hypokalaemia in 3%, and hypocalcaemia in 7% cases. LDH done in 17 suspected cases of malignancy and raised LDH was present in 9 cases. 1 case came as malignancy (CTCL) after further investigations. Endoscopy was done in 2 cases and one case came as Barrett's oesophagus. USG abdomen were done in 52 cases out of which fatty liver were in 7 cases, liver fibrosis in 2 cases, BPH in 10 cases, hepatomegaly in 9 cases, splenomegaly in 3 cases, ascites in 2 cases, 1 case each of renal agenesis and renal cyst. ECG was done in 43 cases in which slight abnormality seen in 7 cases. Skin biopsy was performed in all cases. Total 106 samples were examined (6 repeat biopsy taken from 6 suspected cases of malignancy and for IHC). Histopathology was correlated with clinical diagnosis in 51%. (Table 1 & 2).

H/P Findings	Number of Cases (%)
Psoriasis	31
CAD	2
LP	2
PRP	2
P.F.	1
DRUGS	4
Spongiotic dermatitis	17
Psoriasiform dermatitis	15
Malignancy	2
Non-specific dermatitis	24

Table 1. Histopathological Diagnosis

Erythroderma Aetiology	Clinical Diagnosis	Histopathological (h/p) Diagnosis	Positive Correlation of h/p with Clinical Diagnosis (in %)
Psoriasis	42	31	73
Contact dermatitis	15	4	26.66
Atopic dermatitis	12	3	25
CAD / Photodermatoses	4	2	50

Asteatotic Eczema	3		
CTCL/Other Malignancy		2	-
Lichen planus	2	2	100
PRP	2	2	100
Scabies	1	-	-
Pemphigus foliaceus	1	1	100
Drugs	11	4	36.36
Idiopathic	7	-	-

Table 2. Clinco Histopathological Correlation

DISCUSSION

ED is a distressing illness with high morbidity. In fully involved state, to identify its cause is very difficult and hence its management. It requires very detailed and prompt history, clinical and histological examination and other relevant lab investigations to know the etiology. 100 patients were studied in 18 months of period, male to female ratio among them were 5.12:1. Very high male: female sex ratios 11.27:1 and 14:1 were seen in Nicholas et al[11] and Hulmani et al[4] studies respectively. Lowest ratio 1: 0.38 was seen in the study of Sehgal et al.[2] Hence this study is similar with other studies regarding male preponderance. Males are mostly affected due to more exposure to predisposing environmental factors. In the present study, the maximum numbers of patients (30%) were in the 61-70 (7th decade) age group. Studies of Abraham et al,[12] Nicolas et al,[11] Sehgal et al,[2] Bharatiya et al[3] show maximum incidence in the age group of 50-59, which is almost similar to the present study. 57% of patients with ED were manual labourers including construction work, head load workers, painters, etc. These patients are likely to be subjected to maximum stress, exposure to sunlight, contact sensitization, infections, poor living conditions which may result in exfoliative dermatitis.

The duration of exfoliative dermatitis at the time of admission ranged from 2 days to 12 years. Most of the patients (63%) presented with duration of disease <3 months and 37% cases with duration >3 months. Bharatiya et al[3]; observed that 60.81% of patients had the duration of ED <3 months. This shows similarity with present study.

Shortest duration of 2 days was seen in a case of irritant contact dermatitis due to application of some Ayuvedic preparation and a case of drug reaction with amoxicillin. While maximum duration was in a case of psoriatic Erythroderma. Mean duration of erythroderma in this study was 1.59 years. This is almost similar to 1.44 years of one recent study done by Sudho et al[8] from South India. In the study by Abraham et al[12] (1963) mean duration was 5 years showing a wide range in duration of illness. Many of the patients get initially treated with self-medication and indigenous medicines which often result in worsening of the condition. In this study, 82% of the cases developed Erythroderma due to pre-existing dermatoses. Present study is similar to other studies done by Hasan et al[6] (42%), Shegal et al[2] (52.50%), Akhyani et al[9] (59.80%), Pal et al[7] (74.40%) regarding the most common etiology of Erythroderma pre-existing dermatoses. While study done by Nicholas et al[11], drug reaction was the major factor. Psoriasis was the most common etiology among pre-existing dermatoses (42%). Hasan et al[6] study showed psoriasis as an etiology in 10%, Bandyaopadhyay et a1[13] in 33.33% cases, Pal et al[7] in 37%. 15% of cases in this study were due to contact dermatitis. Similar finding was noted in the study done by Kondo et al,[10] where 15.58% exfoliative dermatitis cases were due to contact dermatitis. In this study, 12% of cases of ED were due to atopic dermatitis. Akhyaniet al[9] had 13.4% of ED due to atopic dermatitis; Hasan et al[6] had 14% cases due to atopic dermatitis, which almost correlate with this study. In this series 4% cases were due to CAD/Photodermatoses which is almost comparable to studies of Botella et al[14] (5.4%) and exact correlate with Hasan et al[6] who had (4%)cases due to this. The present study showed 2% of cases due to PRP which is similar to the observations made by Pal et al[7] study (2.2%). While some other studies showed slightly higher incidence of Erythroderma due to PRP like 5.33% in Bandyaopadhyay et al[13] and 8.2% in Akhyani et al[9] study. Asteatotic eczema was present in 3% cases which was correlate with study of Hasan et al[6] with 2% cases. Lichen planus was present in 2% cases which were almost similar to Rymet al.[15] Pemphigus foliaceous was present in 1% cases. Different studies have showed higher incidence of PF as a cause of ED as compared to this study, 4% in Sudhoet al,[8] 5.33% in Bandyaopadhyay et al,[13] 5.6% in Pal et al[7] and 6.25% in Rym et al[15] study.

Scabies as a cause of ED was present in 1% case. This is almost correlate with studies done by Rym et al[15] (1.25%) and Bandyaopadhyay et al[13] (1.33%). Drugs as a cause of erythroderma were found in 11%. This was exactly match with study done by Rymet al[15] (11.25%). Out of 11 cases in this study of which maximum 5 cases were due to phenytoin induced,2 cases each of INH and Dapsone while one case each of sodium valproate and penicillin's (amoxicillin + cloxacillin). Sehgal et al[2] (1986) & Bharatiya et al[3] (1995) noted INH& Kondo et al[10] (2006) observed sulfone induced erythroderma. In this study only 2 cases found as cause of erythroderma, one case each of CTCL and papillary carcinoma of thyroid. This finding is almost correlate with several Indian studies done by Bandyaopadhyay et al[13] (2.67%), Sudhoet al[8] (4%) Bharatiya et al[3] (4.35%). Abraham et al[12] had 8% of erythroderma cases due to lymphomas/leukaemia. Nicholas et al[11], Botella et al[14]noted 21% & 12.5% cases of malignancy respectively in their studies, In 5% of patients of this study, an etiological diagnosis could not be reached. This study showed correlate with one study done by Sudho et al[8] (8%) from South India. Maximum number of idiopathic cases was observed in western study by Abraham et al[12] (46.53%) and Indian study by Bandyaopadhyay et al[13] (21.33%). This study showed pruritus of varying intensity in most of the cases

(87%), chills and rigor in 62% of cases and fever in 58% cases. Pal et al[7] noted pruritus in 86% and chills in 64.4% which is almost comparable to the results in the present study. Non-cicatricial diffuse hair loss of varying degree was noted in 21% of cases with maximum cases from contact dermatitis followed by psoriasis. The results are comparable with that of Pal et al[7] & Nicolis et al[11] studies.

Most common finding on oral examination was dental carries in 54% cases, followed by other non-specific changes like hyper-pigmentations, atrophic glossitis, scrotal tongue and candidiasis. In this study mucosal involvement was present in46% cases this is near to study done by Pal et al[7] (36.6%). Nail changes of various types were found in 71% of cases. Most common nail changes were longitudinal ridges in 63% cases. 29% cases were having shiny nails. Pal et al[7] study (80%) almost has the same results. Other changes are coarse pitting, subungual hyperkeratosis (SUHK) and nail destruction due to onycholysis.

Enlargement of lymph node were present in 80% cases, of these 30% cases had generalized lymphadenopathy and 50% cases had localized involvement in inguinal and/or axillary group of lymph nodes. Nicholas et al[11] and Sigurdsson et al[16] have almost the same observation (71%). 87% cases had dependent pitting pedal oedema along with 12 cases of facial puffiness. Involvement compared to the studies of Sigurdsson et al,[16] Bharatiya et al.[9] Anaemia was noted in 61% cases (Hb<12 mg% in Males, Hb<11gm% in Females) Leucocytosis in 21% patients, eosinophilia in 45%, hypoproteinaemia in 39%. Percentage of anaemia in this study is similar to Nicolis et al,[11] Sehgal et al[2] and Pal et al[7] studies Increased total leukocyte count is seen almost in the same manner as with Hasan et al[6] and Pal et al[7] study.

Peripheral Smear was done in all cases. 5 cases showed atypical lymphocytes. On further investigation one case came as CTCL. Abraham et al[12] had diagnosed 4 cases of leukaemia in their study after peripheral smear and bone marrow examination of 30 cases.

Histopathological results of clinically diagnosed dermatoses, like PRP, lichen planus and pemphigus foliaceus were 100% co-related. Pal et al,[7] Botella et al[14] noted that biopsy helped to detect pemphigus foliaceus, PRP, as in this study. In the rest of the cases the result came as psoriasis (31%), nonspecific dermatitis (24%), Spongiotic dermatitis (17%), Psoriasiform dermatitis (15%), photo dermatitis (2%), and drug (4%). Pal et al[7] also noted that nonspecific and Spongiotic dermatitis picture of histopathology predominant in Erythroderma so this study also correlates with this view.

In 51% cases histopathology was well correlated with clinical diagnosis. This correlation is almost similar to Bandyaopadhyay et al[13] study (52%). Pal et al[7] noted that in 27.7% of clinically diagnosed cases had correlation with skin biopsy. In 49% of cases no histologic correlation was obtained. Most of such cases were eczemas and few cases due to psoriasis. Because the histological feature of these often become non-specific in erythrodermic stage.

CONCLUSION

Erythroderma is a disease mainly affecting persons between 40-70 years old. Pre-existing dermatoses and their treatment are the most common causes among these; psoriasis is the common single dermatoses in the aetiology. Both endogenous and exogenous eczemas are other major group of dermatoses causes erythroderma followed by drugs. In full blown and chronic cases, the aetiology is often obscure. Detailed history, clinical & laboratory examination will help some extent to identify the cause.

Histopathological examination if performed early, preferably after subsidence of acute stage and repeatedly from multiple sites may help to identify and confirm the aetiology in around 50% of cases. Majority of histopathological reports were non-specific dermatitis, spongiform dermatitis and Psoriasiform dermatitis. Even though in about 10-20% of patients, aetiology remains unknown, continued follow up and repeated investigations are necessary in these patients.

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Tropical medicine rounds

Mycetoma-like chromoblastomycosis: a diagnostic dilemma

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Abstract

Mycetoma and Chromoblastomycosis are subcutaneous fungal infections caused by pigmented fungi. They are common in the tropics and subtropics and are usually acquired through minor trauma or abrasion in the skin. Here, we report a pregnant woman who presented with an indurated swelling around the ankle joint with multiple discharging sinuses which was clinically diagnosed as a case of mycetoma. But on further investigating, histopathology and fungal culture were suggestive of Chromoblastomycosis caused by *Fonsecaea pedrosoi.* This unusual mycetoma like presentation of chromoblastomycosis has not been previously reported in literature and may be attributed to the altered immune status in pregnancy. Treatment was initiated with Terbinafine 250 mg daily and patient showed excellent response within 6 months of therapy.

Conclusion This unusual clinical scenario should alert physician about the need to be vigilant of the atypical presentations of well-known dermatological conditions, especially in special situations like pregnancy.

Introduction

Mycetoma is a chronic suppurative granulomatous disease affecting the skin and subcutaneous tissue which is common in the tropics and subtropics. It was John Gill who first described the clinical features of the disease in the year 1842 in Madurai[1], the city after which it was named Maduramycosis. It includes two main groups – Actinomycetoma caused by aerobic actinomycetes and Eumycetoma caused by true fungi[2]. We report a very rare and unusual case of mycetoma-like presentation caused by *Fonsecaea pedrosoi* which is a common causative agent of chromoblastomycosis.

Case report

A 24-year-old primigravida in her 7th month of gestation attended the dermatology outpatient clinic with a rapidly enlarging painful swelling on the right ankle of 2 months duration. There was no history of any preceding trauma or surgical procedures. Patient had no comorbidities. The lesion continued to increase in size causing considerable discomfort to the patient despite antibiotic therapy and surgical debridement.

Examination revealed a diffuse indurated swelling around the ankle joint with sparing of the anterior part (Fig. 2a,b). There were multiple papules and nodules with sinuses draining serosanguinous and purulent material on the surface. Regional lymph nodes were not enlarged. Systems were within normal limits. Based on the above clinical picture, we made a presumptive diagnosis of Mycetoma and did further investigations.

Routine blood and urine examinations, radiograph of right ankle and chest showed no abnormalities. No grains were identified from the discharge obtained from a saline dressing kept overnight and a KOH smear showed no organisms. Pus culture revealed no bacterial growth. Biopsy from the area showed numerous neutrophilic microabscesses and tuberculoid granuloma with giant cells and lymphocytes. Numerous thick-walled brownish spherical sclerotic bodies were present both inside and outside the giant cells suggesting the picture of chromoblastomycosis (Fig. 1a). No grains or fungal hyphae could be seen. Specimens were also sent for fungal and mycobacterial culture. Within 3 weeks, culture in Sabouraud's dextrose agar showed olive gray colonies with jet black in reverse (Fig. 1b); and lactophenol cotton blue mount of the same showed septate branching hyphae with sympodial (*Rhinocladiella*) and acropetal (*cladosporium*) type of conidiation typical of *Fonsecaea pedrosoi* (Fig. 1c).

Discussion

Dematiaceous or pigmented fungi cause a variety of subcutaneous fungal diseases – Mycetoma, chromoblastomycosis, and pheohyphomycosis being important among them. Mycetoma presents as a chronic indurated swelling with discharging sinuses usually involving the lower extremities. The hallmark

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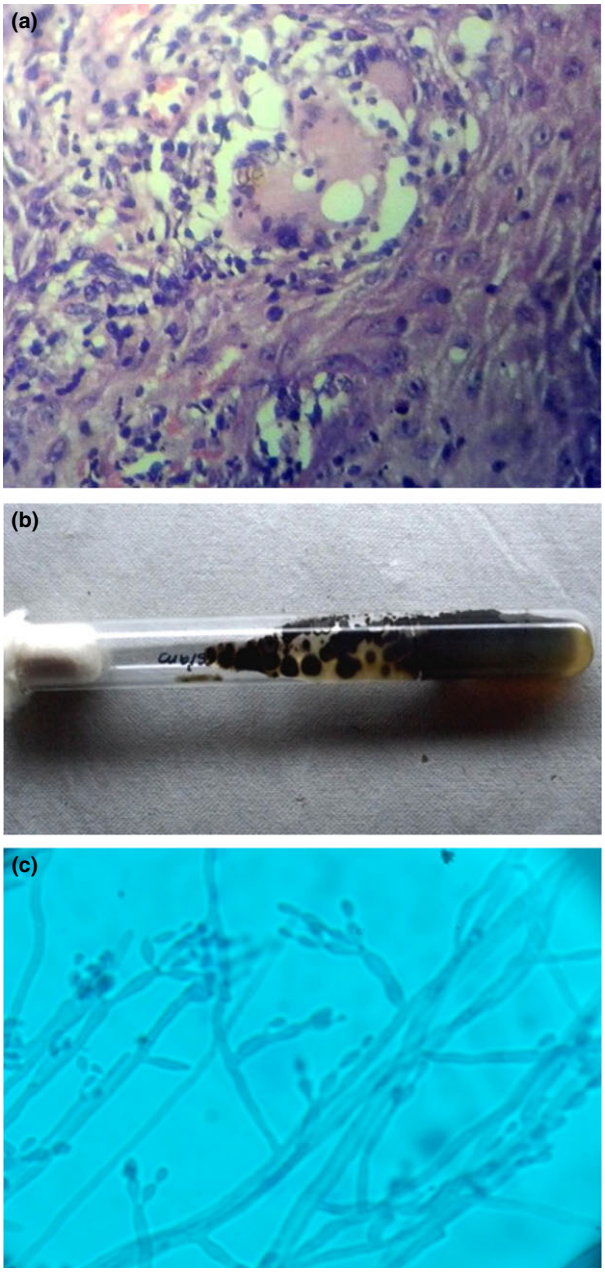

Figure 1 (a) Skin biopsy showing granuloma in the dermis with Langhans Giant cell containing sclerotic body (H&E; × 40). (b) Gray-black velvetty colonies on tube culture with a jet black reverse, (c) microscopy showing septate hyphae with sympodial and acropetal type of conidiation (lactophenol cotton blue mount, ×40)

triad of the disease is tumefaction, fistulization of the abscess and extrusion of colored grains[3,4]. Grains, also known as sclerotia, are aggregates of the fungal hyphae or bacterial filaments, sometimes embedded in tough, cement-like material[5]. It extends slowly invading the subcutaneous tissue, fat, ligaments, muscle, and bone. The infection is not self-curing and, if untreated, leads to massive lesions, which may in the end necessitate surgical amputation[6]. *Madurella mycetomatis, Madurella grisea, pseudallescheria boydii, leptosphaeria senegalensis, and Acremonium* are some of the important fungal agents causing eumycotic mycetoma, whereas *Nocardia, Actinomadura, and Streptomyces* are common agents causing actinomycotic mycetoma. Histologically, there is chronic inflammatory reaction with suppurative granuloma formation and granules containing either thick-walled septate hyphae as in eumycotic mycetoma or fine branching interlacing filaments as in actinomycotic mycetoma.

Chromoblastomycosis, on the other hand presents as a hypertrophic verrucous plaques at sites prone to trauma commonly on feet, legs, arms, face, and neck[7]. It may ulcerate or develop atrophy and scarring. Satellite lesions are produced by scratching and there may be lymphatic spread to adjacent areas. It can also present in varied morphologies like nodular, tumoral, cicatritial, plaque, and verrucous.[8–10] The common causative agents include *Fonsecaea pedrosoi, Cladophialophora carrionii, Phialophora verrucosa*, *Rhinocladiella aquaspersa,* and *Fonsecaea compacta*. Irrespective of the species, the pathogen can be demonstrated as deeply pigmented thick-walled muriform or sclerotic bodies. They are seen either in giant cells or neutrophilic abscesses in histopathology[11]. Demonstration of muriform body in scrape smear, histopathology or in aspiration cytology is diagnostic of Chromoblastomycosis.[12]

In our case, although the clinical presentation showed close resemblance to mycetoma, typical granules were not demonstrated which pointed against a diagnosis of mycetoma. Diagnosis of chromoblastomycosis was confirmed through histopathology which showed sclerotic bodies and fungal culture which demonstrated the causative agent *Fonsecea pedrosoi.*

The reason for such an altered presentation may be related to the underlying immunological mechanism. It is assumed that genetic susceptibility of the host, virulence of the organism, and host immunity are important factors determining the clinical and histological presentation of the disease. Tsuneto et al.[13] have enumerated the role of HLA-A29 A in susceptibility to Chromoblastomycosis. Though the first line of defense against fungi are the dendritic cells, studies have shown that the immunological response in chromoblastomycosis is primarily T-cell mediated. In 2003, D'Ávila et al.[14]suggested that patients presenting with verrucous plaques have Th2 immunological response characterized by suppurative granulomas with several fungi cells, while those with erythematous atrophic plaques have a Th1 response associated with tuberculoid granulomas and few fungi cells within the lesions. According to Mazo etal[15], severe forms of the disease are associated with high levels of IL-10 and low IFN-γ, whereas mild forms are associated with low levels of IL-10 and higher IFN-γ, thereby indicating a crucial role of IFN-γ and CD4 + T lymphocytes in the immune response against chromoblastomycosis.

Pregnancy is associated with immunosuppression often subjecting the patient to increased risk of infection. There is a shift

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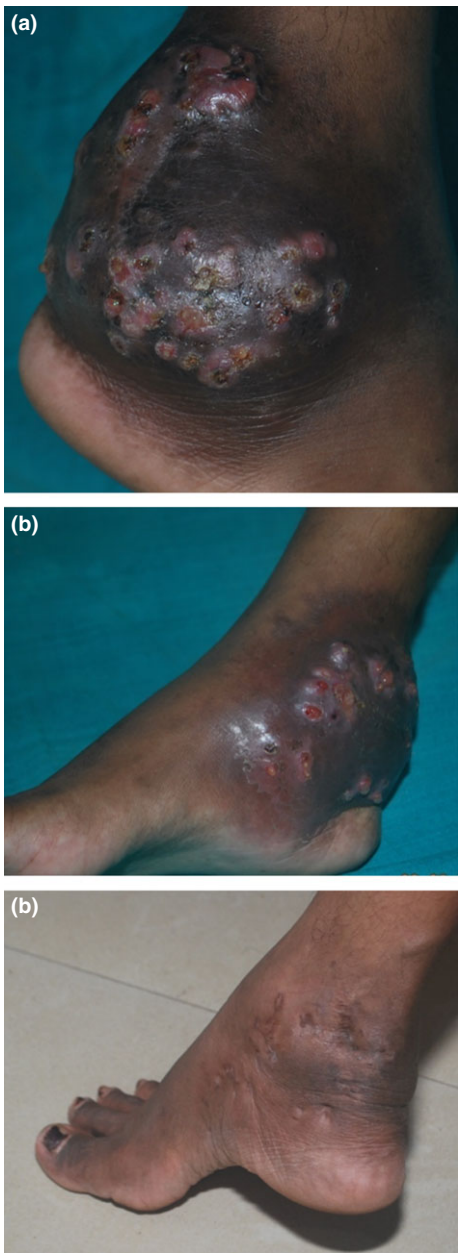

Figure 2 (a & b) Indurated swelling with multiple discharging sinuses around right ankle. (c) After 6 months of treatment with Terbinafine

in the immunological profile toward Th2 response in pregnancy with elevated IL-10 levels[16] and it would be reasonable to postulate that this shift in immunological profile accounted for the severe form of the disease with deeper tissue involvement and rapid progression of the condition.

Dematiaceous fungi are increasingly being recognized as an important pathogen in human infections especially in the past few decades. A case of Disseminated Phaeohyphomycosis because of *Exophiala spinifera* during pregnancy was reported by Ricardo et al.[17] and a case of concurrent mycetoma and chromoblastomycosis was reported by Murthy et al.[18], but a mycetoma-like presentation of chromoblastomycosis is yet to be reported. It is said that Chromoblastomycosis and pheohyphomycosis represent two poles of a spectrum of disease caused by pigmented fungi[19]. So, we assume that the spectrum of diseases caused by dematiaceous fungi has no strict boundries and a mycetoma-like presentation may be induced by F.pedrosoi during immunosuppression. Interestingly, *Exophiala jeanselmei* is a black fungi which is known to cause all the three conditions[6].

Both itraconazole and terbinafine have been used successfully in the treatment of chromoblastomycosis. Potassium iodide is another effective drug for chromoblastomycosis caused by *F.pedrosoi*. The therapeutic responses to Itraconazole and Terbinafine are thought to be better if the causative agent is *C.carrionii*[15]. Other options include surgical excision, cryotherapy, local application of heat, and CO_2 laser vaporization. They are useful only in smaller lesions. Our patient was treated with terbinafine 250 mg daily in the postnatal period and she showed an excellent response within 6 months (Fig. 2c).

Conclusion

This unusual clinical setting reiterates the need to be vigilant about the atypical presentations of well-known dermatological conditions, especially in special situations like pregnancy. It also emphasizes the need for appropriate investigations in every case even if the diagnosis seems straight forward. Being a case report, our findings have limitations and we need further reports to confirm the new findings.

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