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Improving the availability of reliable healthcare information on skin disorders

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Conflict of interests: None

Key words: Reliable healthcare information; skin diseases; advocacy; World Health Organization.

Imagine a world where every person has access to the reliable healthcare information they need to protect their own health and the health of others; where everyone is equipped with the knowledge to prevent, diagnose and manage disease – including skin disease. Currently we do not have such a world. Presentation and diagnosis are often delayed, with serious consequences for patients. Skin of colour can present additional challenges. For example, although people with skin of colour are less likely to develop melanoma than White people, they are more likely to have advanced melanoma by the time of diagnosis and hence are more likely to die from the disease. The availability of reliable information is important across all areas of health, including skin health.

Reliable healthcare information

Reliable healthcare information is the information people need to protect their own health and the health of others. It should be accurate, up to date and unbiased, reflecting, as far as possible, cumulative evidence that is based on robust research; it should be in the right language and format and at the right technical level; it should be relevant and applicable to the person's immediate situation (which is always changing) and the person should be empowered to differentiate it from the barrage of widely available misinformation. 'Reliable information' goes beyond looking something up in a book or website; it also includes knowledge from past exposure or experience. If a parent already knows that sunscreens can help prevent melanoma, this is an example of access to reliable information from past exposure or experience. If a health worker knows the various ways in which a melanoma can present, this also would be included.

Access to reliable healthcare information

Access to reliable healthcare information is a human rights issue. It is fundamental to safe and effective care through all levels of the health system and has been recognized by the United Nations as a determinant of the right to health. It is a prerequisite for global health equity. Healthcare Information For All (HIFA) and the New York Law School demonstrated that governments have a legal obligation under international human rights law to ensure that their populations have adequate access to reliable healthcare information, a responsibility that has been flouted with impunity by heads of state, as seen during the COVID-19 pandemic.

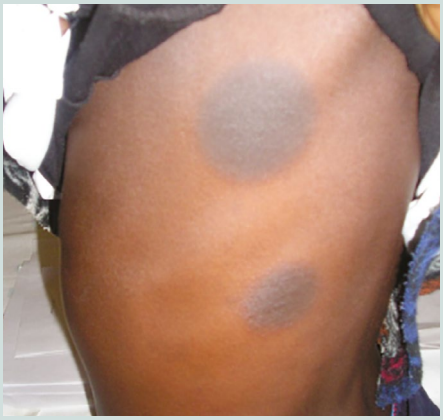
Millions of people die every year because of poor quality healthcare in the health system. Many more die or suffer needlessly because of poor care and poor healthcare decisions in the home, especially in low- and middle-income

Continued overleaf…

CASE REPORT

Fixed drug eruption from consumption of chicken

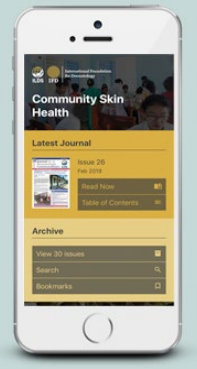
See page 25.



Community Skin Health App

The CSH App is available on both iOS and Android.

You can now have every issue at your fingertips, search the comprehensive archive for hot topics, bookmark your favourite articles and automatically get the latest issue delivered straight to your phone.



Contents

countries (LMICs). Remarkably little is known about the relative contributions of, say, access to essential medicines and access to reliable healthcare information.

How can we improve the availability of reliable information on skin disease?

The availability of reliable information on any area of health depends on the integrity of the global evidence ecosystem (Fig. 1). This comprises the work of researchers, publishers, systematic reviewers, guideline developers, creators of content for different audiences, people who help audiences to find the information they need (and differentiate it from misinformation) and, of course, those who access and apply information at any given time, whether patients, health workers or policymakers.

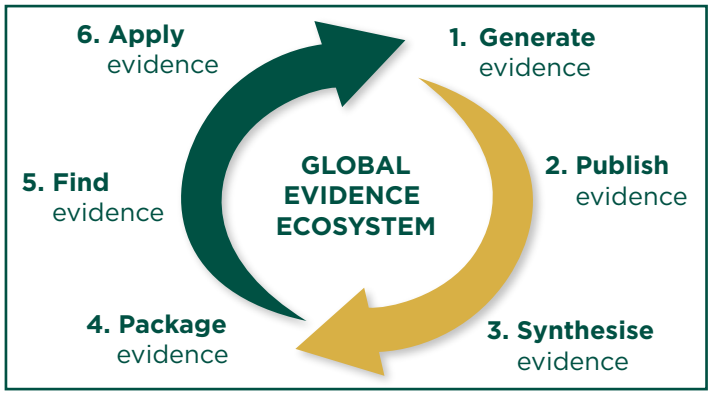


Fig 1. Global evidence ecosystem.

Three intrinsic weaknesses of the system were identified by Fiona Godlee, myself and others.[1] Our paper argued that it is not working, especially for people in LMICs, largely as a result of weaknesses in the system itself, poor communication and coordination among stakeholders in the system, poor understanding of information needs and how to meet them, and a lack of advocacy and high-level commitment to universal access to reliable healthcare information. We called on the World Health Organization (WHO) to champion the goal of universal access to reliable healthcare information. WHO encouraged us to take the lead. A year later we launched HIFA, a global campaign for a world where every person has access to the information they need to protect their own health and the health of others. HIFA is administered by a small non-profit organization called Global Healthcare Information Network (GHI-Net), based near Oxford, UK. *Community Skin Health* (initially under its previous title, *Community Dermatology Journal*) has been affiliated to HIFA since 2013.[2]

HIFA

HIFA is designed to strengthen communication, understanding and advocacy across the system. We were confident that we could make a difference, thanks to the recent emergence of group email communications that enable us to facilitate in-depth global discussions among thousands of people on a wide range of topics relating to information needs and how to meet them. Our approach is based on Wenger's 'community of practice' concept and, within weeks, enabled us to connect 1000 professionals representing all parts of the global evidence ecosystem. Our network continues to grow and we now have 20,000 members in 180 countries. Around 500 members have stepped up as volunteers: steering group members, country representatives, a social media team and project working groups. We currently have 20 projects that aim to promote communication and understanding among all HIFA members. We have moderated countless spontaneous discussions on topics relating to improving the availability and use of information. We have also supported many planned, deep-dive discussions, typically lasting 4–6 weeks and often leading to publication in peer-reviewed journals. Skin disease has not yet been addressed systematically and we would welcome the opportunity to do so.

We have developed and tested a database to collate experience about information needs and how to meet them, as expressed on the HIFA forums.

Advocacy

Resulting from our work, the World Medical Association, representing 10 million doctors, now has an official policy in support of universal access to reliable healthcare information, and has agreed our seven recommendations on the way forward. We are far too small to make a difference in such a big global health issue on our own, so we have built a community of 445 supporting organizations worldwide. Most importantly, we were granted official relations with WHO in 2022.

I am proud of the way that HIFA has grown organically over the years, with each achievement building on the last (see: https://www.hifa.org/about-hifa/achievements). It is the consistent delivery of achievements that is our greatest success. Our greatest failure is, paradoxically, our inability to fully implement our strategy because of limited resources such as in-house expertise in organizational development and fundraising. We continue to operate with only 1.4 staff (and hundreds of volunteers) and we are currently trying to recruit a second global health professional. We welcome offers of support and collaboration.

Reliable information on skin disease

Reliable information on skin disease depends on the integrity of the global evidence ecosystem, but there are further considerations for skin disease. Dermatological diagnosis relies on visual recognition; artificial intelligence (AI) is already being used to help diagnose melanoma, for example, based on a photograph. Typing a skin disease question into a chatbot such as ChatGPT is very likely to provide a coherent and reliable answer, at least in English. One limitation is that ChatGPT is entirely text based and does not handle images. As AI develops and the world's population is increasingly connected, it will become increasingly useful.

The role of WHO

The greatest opportunity that we are focusing on right now is for WHO to explicitly commit to the goal of universal access to reliable healthcare information. This would be a game changer. The concept is not new to WHO. Universal access is implicit in

its Constitution, published 75 years ago: 'The extension to all peoples of the benefits of medical, psychological and related knowledge is essential to the fullest attainment of health'. A May 2023 paper co-authored by the Deputy Director-General of WHO, Zsuzsanna Jakab, is titled: 'Universal health information is essential for universal health coverage'.[3]

For WHO to explicitly champion this goal, there needs to be a catalyst. HIFA has taken the first step by becoming a non-governmental organization collaborating officially with WHO in 2022. The next step is a global stakeholder consultation. The centrepiece is a global survey, targeting all stakeholders, especially publishers, which ran from 21 August to 15 October 2023. The survey is now completed and we are analysing the results with help from Digital Medic at Stanford University.

Our goal is to demonstrate massive public support for universal access, and to gather inputs from all stakeholders on how to accelerate progress and what more WHO can do.

Although the survey is completed, we continue to debate the issues on our discussion forums, which are free to join and available in English, French, Portuguese and Spanish: https://www.hifa.org/join

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2. Pakenham-Walsh N, Murdoch M, Lovell C. HIFA and *Community Dermatology Journal*. *Community Dermatol J* 2013; **9**:1.
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The above article repurposes some of the content of a recent Scholarly Kitchen article 21 August 2023:
https://scholarlykitchen.sspnet.org/2023/08/21/universal-access-to-reliable-healthcare-information-an-interview-with-neil-pakenham-walsh-of-hifa/

Letter to the Editor

Dear Editor,

I am very grateful for receiving the *Community Skin Health* teaching journals. Earlier this year our District experienced an outbreak of measles and a mother took her child to the hospital because of a skin condition. The clinician diagnosed 'measles'. The pharmacist, however, upon looking at the child disagreed with the diagnosis. I was consulted by the mother and arrived at the diagnosis of tinea corporis and tinea capitis. I therefore advised the mother to shave her child's head, and cloxacillin capsules, miconazole cream and griseofulvin tablets were prescribed. Six weeks later the fungal infection had cleared and the mother was very delighted. I have been sharing the *CSH* journal with a lot of staff. This is an indication that the journal is helping with management of skin conditions.

Thanks!

Andrew Chulu, Retired Clinical Care Officer, Chinsali Hospital, Chinsali District, Zambia.

Shining a spotlight on skin neglected tropical diseases

Highlights from the ILDS-WHO Mini SkinNTD Summit in Dar Es Salaam, Tanzania on 20 September 2023 can be found at #NNN2023 Conference.

This important gathering brought together over 90+ passionate participants representing the 12 dynamic working groups born from the WHO Global Meeting on Skin Neglected Tropical Diseases (skin NTDs) in March 2023.

The summit provided a valuable platform for the working groups to delve into priority activities, chart progress and tackle the challenges faced in implementing integrated skin NTD initiatives at the national level.

This event was made possible because of the collaboration between the WHO and ILDS and it was facilitated by the NNN Skin Cross Cutting Group.

WHO staff and NNN Skin Cross Cutting Group


Breakout session of the working groups

Reactions in leprosy

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Conflict of interests: None.

Key words: Leprosy; Hansen disease; multi-drug therapy; type 1 reaction; type 2 reaction; Lucio phenomenon; aetiopathology; treatment.

Introduction

In our recent paper, in *Community Skin Health*, we discussed the diagnosis and management of leprosy.[1] Here we discuss, in more depth, leprosy reactions, which are a major clinical challenge in treatment. Leprosy reactions are episodes of exacerbated inflammation and may cause nerve damage leading to permanent disability. Reactions may occur before, during or after antimycobacterial treatment. Although reactions belong to the normal course of untreated leprosy, treatment can prevent or precipitate reactions. There are three types of reactions:

- type 1 leprosy reaction (T1R) or reversal reaction (RR);
- type 2 leprosy reaction (T2R), also referred to as erythema nodosum leprosum (ENL); and
- Lucio's phenomenon, a rare type of reaction that occurs most commonly in patients from Central America.

T1Rs may occur in borderline leprosy (borderline tuberculoid [BT], borderline borderline [BB] and borderline lepromatous [BL] leprosy) and tends to develop early in the course of infection. It develops gradually and takes weeks or even months before there are noticeable problems but, occasionally, a severe reaction may occur overnight. T2Rs occurs in multibacillary leprosy, BL and lepromatous leprosy (LL), and typically develops later in the course of the disease. Both T1Rs and T2Rs can occur in BL leprosy, even at the same time. Lucio's phenomenon particularly occurs in diffuse LL.

A T1R (or upgrading reaction) can be triggered when cell-mediated immunity (CMI) suddenly increases, after starting HIV treatment, after pregnancy or after discontinuing immunosuppressive drugs. A T2R may be triggered by vaccination, anaemia, anxiety and intercurrent infections such as tuberculosis, ulcers or intestinal parasitic infections. Lucio's phenomenon may be triggered by sudden cold weather after high environmental temperature.

The diagnosis of leprosy reactions relies completely on the expertise of healthcare workers as currently no laboratory tests are available to predict their development. Lack of awareness and knowledge among healthcare providers may lead to diagnostic delay resulting in nerve damage. It is important to diagnose reactions early and treat them appropriately to prevent unnecessary disability.

In this paper, we will discuss the pathophysiological mechanisms, clinical diagnosis and management of T1Rs, T2Rs and Lucio's phenomenon.

Type 1 leprosy reaction

Signs and symptoms:

T1Rs usually involve the nerves and skin, but occasionally may also affect the liver and joints. Skin damage often accompanies nerve damage but can also precede or follow nerve damage. Clinically, a reaction may be suspected when there is increased inflammation of pre-existing skin lesions in patients with borderline leprosy. Hypopigmented or slightly erythematous macules become red and swollen (Fig. 1) and occasionally can ulcerate (referred to as 'Lazarine leprosy') (Fig. 2). New lesions may suddenly appear in previously clinically unaffected skin (Fig. 3). Sometimes extensive oedema may affect the extremities or face (acroedema), especially in patients with BL (Fig. 4). Patients may complain of a burning or stinging sensation in the skin lesions together with pain in the extremities or face and loss of strength and/or sensory perception (Fig. 5).

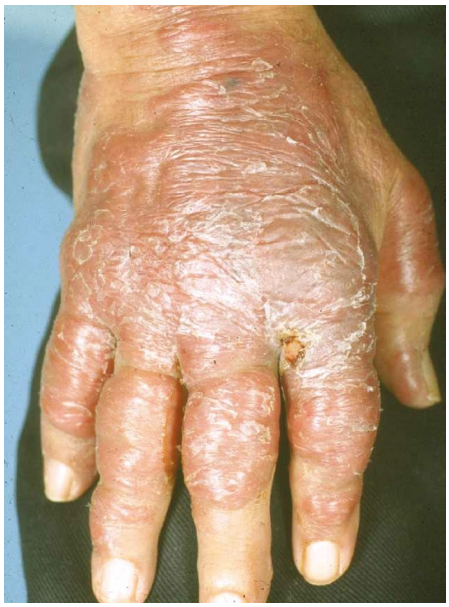

Fig 1. Erythematous swelling in type 1 reaction.

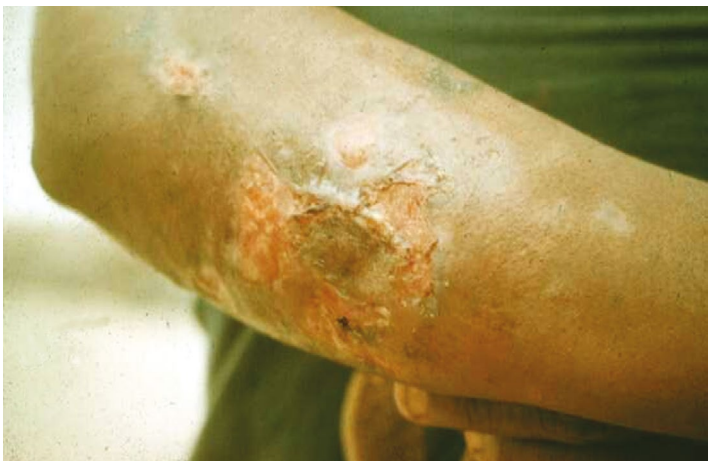

Fig 2. Type 1 reaction, ulcerated lesion.

The peripheral nerve trunks may become swollen and sensitive in specific places. The Tinel sign is a test to demonstrate neuritis; gently tapping on the nerve causes a tingling sensation ('pins and needles') in the distribution of that nerve. Loss of strength can occur in the eyelids, face, hands and feet. Patients may suddenly drop things from their hands or stumble while walking. Vision loss is one of the major disabilities and must always be prevented. Minimal nerve damage

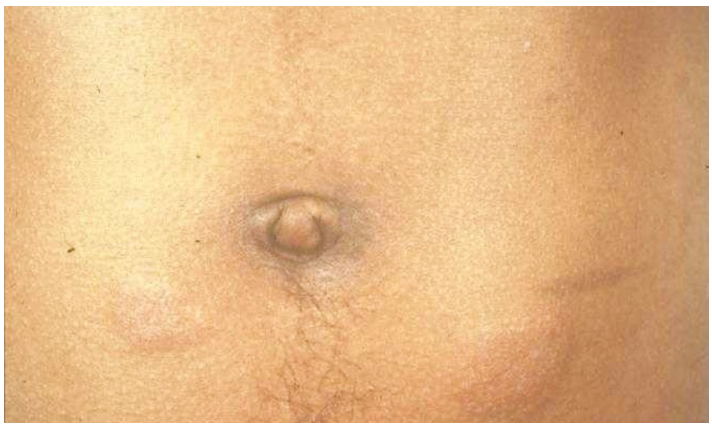

Fig 3. New type 1 lesions in previously unaffected skin.

may go unnoticed when a patient is asked to close his or her eyes tightly. In order to detect a T1R early in the face, the patient should be asked to close both eyes gently. A slight movement of the eyelid and/or minimal opening at closure may herald further damage from a T1R (Fig. 6).

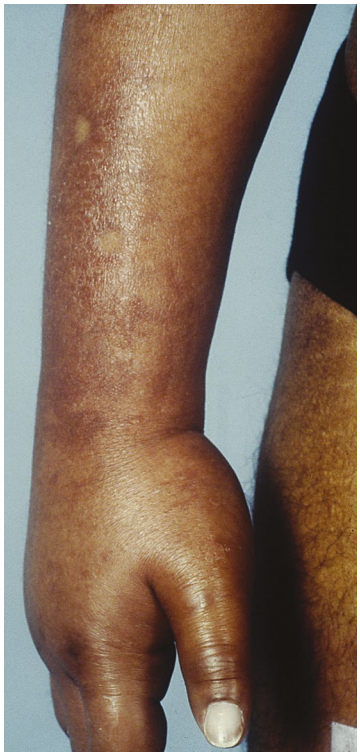

Fig 4. Extensive oedema affecting arm in patient with borderline lepromatous.

Another early sign of a T1R is whether hands and feet feel moist or have newly formed dry patches. The appearance or enlargement of dry areas is often the first sign of an incipient reaction. However, patients with a T1R, unlike patients with a T2R, are not sick. The diagnosis of an early T1R can easily be missed as some patients have remarkably few signs and symptoms. To facilitate early diagnosis and treatment, objective clinical parameters are important. These include mapping (drawing) of skin lesions, which may be considered tedious but is well worth it, and careful assessment of nerve function by voluntary muscle testing (VMT) and graded sensory testing (GST), graded because they have stimuli of different defined strengths so that sensory changes can be measured on the same site.[2,3]

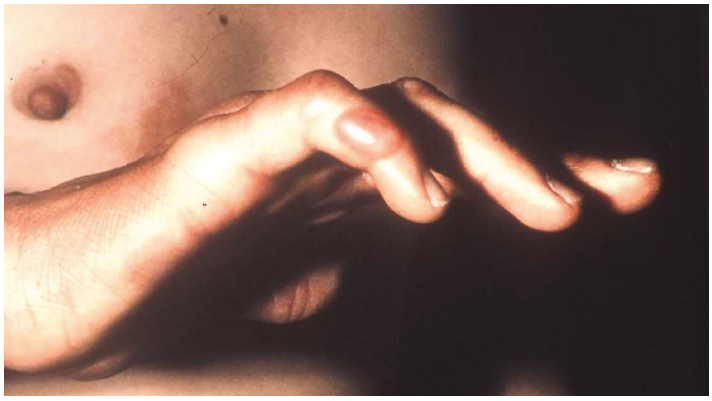

Fig 5. Burn because of sensory loss.

Laboratory testing:

So far, laboratory tests have little additional value to diagnose leprosy reactions. Antibodies against *Mycobacterium leprae* antigens, including phenolic glycolipid 1 (PGL-1) and leprosy immune diagnostic 1 (LID 1), are of no diagnostic significance,[4] nor are tests of CMI. A new promising development is a transcriptomic signature (mRNA from host and mycobacteria) that can show the development of a T1R up to 2 weeks before clinical signs.[5]

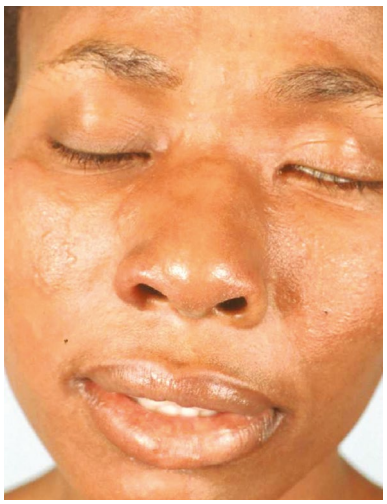

Fig 6. Impaired closure of eyes in type 1 reaction.

Immunology and pathology:

Histopathology of T1R lesions shows a delayed hypersensitivity reaction. Only mild extracellular oedema with some proliferation of fibroblasts is seen in an early lesion, with an increased number of lymphocytes in the leprosy granuloma. Later, there is a further increase in oedema and a change in the cellular composition in and around the epithelioid cell granulomata because of an influx of mainly $CD4^+$ T-(helper) lymphocytes ($CD4^+$ T cells), especially of the T helper cell (Th)1 class.[6] During a T1R and when it diminishes, the relative number of $CD8^+$ T cells (suppressor/cytotoxic) increases. The importance of the $CD4^+$ T cells is supported by the observation that leprosy and especially T1Rs can occur when patients co-infected with HIV and *M. leprae* are treated with effective antiretroviral therapy. The $CD4^+$ T cells then increase and a T1R occurs as an immune reconstitution inflammatory syndrome.[7] Human nerves and skin have been shown to share several antigenic determinants with *M. leprae* (Fig. 7).[8] Many of those epitopes are located on heat shock proteins (HSPs).[8] This can be demonstrated in macrophages and epithelioid cells of other granulomatous diseases such as sarcoidosis, necrobiosis lipoidica and granuloma annulare. It can therefore be theorized that T1R is an autoimmune disease.[9]

Treatment:

This is based on the understanding of immunopathology: a delayed-type hypersensitivity reaction to *M. leprae* antigenic determinants. A logical approach is to reduce the number of stimulating determinants with chemotherapy while simultaneously suppressing the cell-mediated immune response. Dapsone, an important component of multiple drug therapy (MDT), when administered at a dose of 50 mg or higher, has a suppressive effect on the occurrence of T1Rs.[10] In most settings, prednisone is the drug of choice, as it immediately reduces oedema, is immunosuppressive and reduces post-inflammatory scarring. Azathioprine, ciclosporin,[11] methotrexate and biologicals, such as infliximab, have also been shown to be effective.

The duration of immunosuppression should be long enough to cover the period during which the antigenic load can activate the CMI response.[12] For patients with BT leprosy, this is 2–6 months; for patients with BB 4–9 months; and for some patients with BL up to 1 year or even longer. The crucial starting dose of prednisone appears to be between 25 mg and 40 mg daily, depending on the type of leprosy; 40 mg in BT and 25 mg in BL. A higher dose is given in patients with BT compared with patients with BL because the CMI against *M. leprae* determinants is less strong in BL. A higher initial

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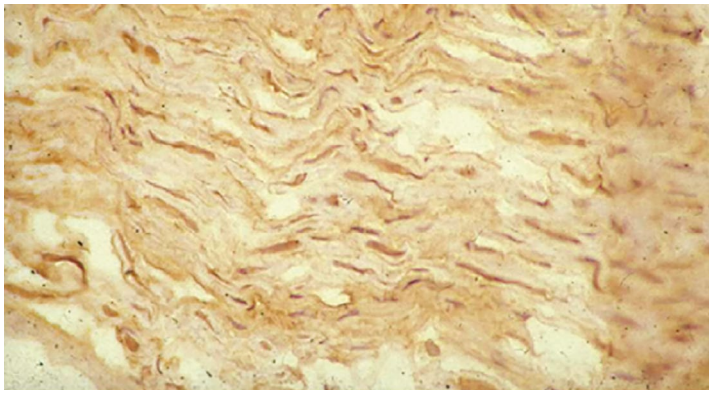

Fig 7. Cryostat section of a healthy nerve. Immunoperoxidase staining with monoclonal antibody against heat shock protein 65 kDa of *Mycobacterium leprae* (magnification x 400).

dose may reduce oedema, especially at the beginning of treatment, but it does not improve the long-term outcome. After 1–3 months of clinical follow up, the prednisone dose can gradually be reduced to 15–20 mg/day. The steroid dose should not be reduced too quickly, otherwise there is the risk of a relapse of the reaction. When 10 mg is reached, treatment can be stopped within 2 weeks. GST and VMT may guide prednisone tapering. GST has been found the most sensitive.[3] Before initiating and during corticosteroid therapy, screening and preventative measures include:

- bone protection; women and older adults are at greater risk of osteoporosis;
- gastric protection;
- monitor blood pressure;
- check for diabetes (fasting glucose or haemoglobin A_{1c} [HbA_{1c}]) and monitor during treatment;
- eyes; check for cataracts and raised intraocular pressure;
- examine skin for features of fungal infection.

The World Health Organization (WHO) tablet blister packs are difficult to obtain. The packs contain only 2 months' supply of prednisone, in dosages of 15–20 mg and consequently doses get tapered down quickly within 1 month, which for most T1Rs is too short and this may cause the reaction to flare up again. This flare represents an exacerbation rather than a new reaction.[13] It is worth considering prophylactic antihelminthic treatment before initiating immunosuppressive therapy, as screening measures are unreliable. Serious side-effects of prednisone during treatment of a T1R are not commonly observed, except in patients receiving high doses.

When one or two nerves do not respond during effective anti-reaction treatment, it can be assumed that there is 'venostatic oedema' and nerve decompression surgery should be considered as soon as possible in a referral centre, at the latest within 3 months.[14] The surgery should be performed while the patient is on steroids as this prevents postoperative oedema and reduces postoperative scarring. It should be noted that although most leprosy surgeons are convinced of the positive effect of nerve release, other clinicians consider the evidence to be insufficient.

Type 2 leprosy reaction

Signs and symptoms: ENL describes the most common manifestation of this reaction (an eruption of tender red papules and nodules) that develops within hours to days and lasts for several days to weeks. The patient feels unwell, has fever, may have granulocytosis and often has albumin in the urine. The papules and nodules are red to purple in fair-skinned patients (Fig. 8) and skin coloured (Fig. 9) or dark blue-red in dark-skinned patients. When they disappear, they leave behind a grey-blue lesion resembling a bruise in fair-skinned patients and a deep bluish-brown or black discolouration in dark-skinned patients. The resolving lesions usually flake slightly. Active and fading lesions may be present at the same time. Occasionally, the lesions coalesce and become plaques. Both plaques and nodules may ulcerate.

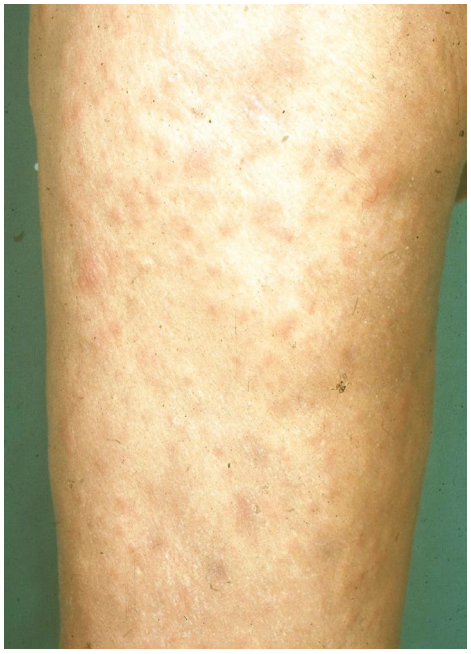

Fig 8. Erythema nodosum leprosum in fair-skinned patient.

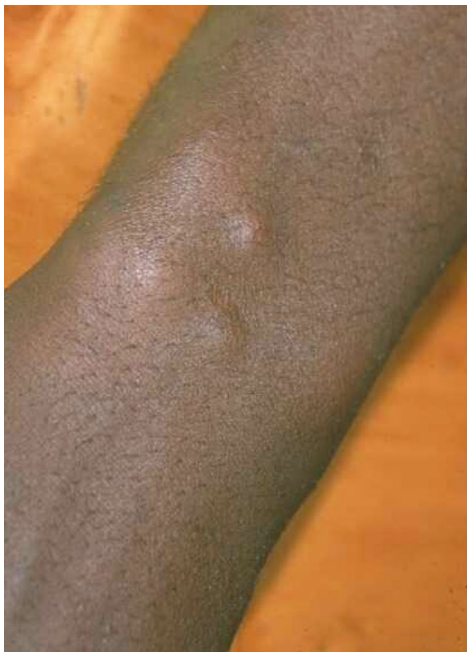

Fig 9. Skin-coloured lesions in skin of colour.

The lesions frequently occur along the extensor side of the arms and thighs, on the trunk and face, but may occur elsewhere. They differ in their distribution from the erythema nodosum lesions that occur during sarcoidosis or tuberculosis, chlamydia, yersinia or streptococcal infection that have a typical predilection for the shins. Sometimes the lesions can be palpated more easily than seen. The lesions may feel firm and palpation is often painful for the patient. They often extend into the deeper layers of the dermis and into the subcutaneous fat. 'Ellis' and 'Ryrie' tests are positive (see below). Other manifestations of T2Rs have also been reported: the so-called erythema multiforme type commonly seen in Brazil, but also reported with increasing prominence in other parts of the world (Fig. 10). Some patients present with superficial bullous ulcerative skin lesions (Fig. 11) associated with high fever, malaise and oedema.

In T2Rs, the skin is not the only organ involved. Painful enlargement of lymph nodes, liver and spleen may occur, as well as episcleritis and iridocyclitis (cave glaucoma). Lymph node involvement can lead to oedema of the extremities, especially the legs. In men, epididymo-orchitis can be seen. Nerves and joints can become swollen and tender. Periostitis, tenosynovitis and myositis are also observed. Glomerulonephritis may also be present, which may also lead to

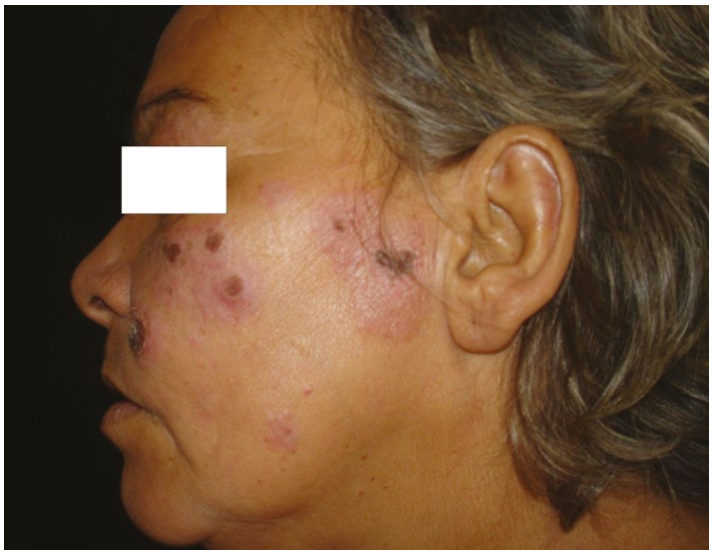

Fig 10. Type 2 reaction. Facial lesions resembling erythema multiforme.

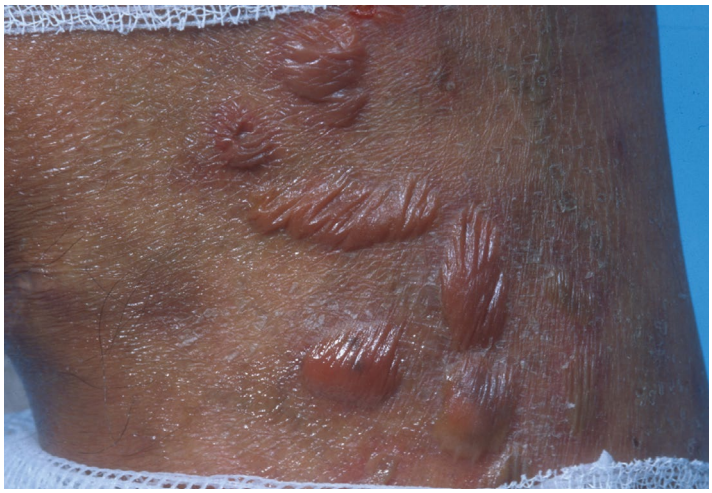

Fig 11. Bullous lesions in type 2 reaction.

oedema. Even peritonitis has been seen. As BL and LL are more generalized diseases, any organ or tissue may be involved in T2Rs with the central nervous system as a possible exception.

A T2R usually occurs in episodes, lasting from only a few days to 1 to 2 weeks. Over 95% resolve spontaneously within 1 month.[15] Some patients, however, experience intermittent lesions lasting months or even years. In a few patients, the condition may become chronic, the most serious complications of leprosy requiring long-term treatment with prednisone that may even lead to death.[16] Although T2Rs may occur in untreated patients, 50–60% of treated patients with LL will also develop one or more reactions. When diagnosed early, only 10–15% of patients with multibacillary leprosy experience a T2R, which is often mild; in more advanced disease 30–40%. The occurrence and severity of a T2R appears to be related to the progression of the disease before MDT is started.

Laboratory testing: In contrast to T1Rs, laboratory tests may be of some help including granulocytosis, high erythrocyte sedimentation rate (ESR) and sometimes proteinuria.

Immunology and pathology: In the initial T2R lesions there is a slight increase in the number of lymphocytes, especially around blood vessels. Most of these infiltrating cells are $CD4^+$ Th2 cells.[15] When the reaction continues, the number of $CD4^+$ Th2 cells increases further and exceeds the number of $CD8^+$ cells that normally make up the majority in a LL lesion. Plasma cells in ENL lesions, stimulated by interleukin (IL)4-producing cells, produce antibodies against *M. leprae* antigenic determinants. These antibodies react with the antigens ubiquitous in LL (BL and LL) and, when not phagocytized by a macrophage, form immune complexes.[15-17] These induce complement activation and a clinical T2R (Fig. 12). Antigen, IgG, IgM, complement and IL-4 mRNA have been shown in the tissues. IL-4 is important because it is a B-cell stimulator, increases HLA-DR expression and is a growth factor for mast cells. When the T2R response is active, polymorphonuclear granulocytes dominate the picture, some natural killer cells are also seen, as well as a greater number of mast cells. The involvement of both immune complexes and CMI has been demonstrated in peripheral blood.

An unknown stimulus → influx of CD4 Th2 cells into the tissues
↓
IL4 and others → CD4 and CD8 cytotoxic cells → inflammation and destruction
↓
B cells→ plasma cells → antibody production
↓
Antigens in the tissues → immune complexes
↓
Complement activation
↓
Granulocyte chemotaxis
↓
Tissue destruction

Fig 12. Immunopathogenesis of type 2 leprosy reaction. IL, interleukin; Th, T helper cell. Adapted from Naafs.[18]

Differentiation between T1R and T2R: It is often difficult to distinguish T1Rs from T2Rs. They can even occur together or one after the other. Some physical signs can help with the differential diagnosis. A T2R is a generalized disease that can involve other organs such as joints and lymph nodes in addition to skin and nerves. The patient may be ill (usually not during a T1R), may have an elevated temperature and ESR, and may even have proteinuria. The skin lesions in T2Rs are usually tender but in a T1R they are not. Lesions in a T1R may have a loss of sensation compared with the surrounding skin, whereas in a T2R this is usually not the case. When palpating the lesions, a T2R plaque consists of confluent papules and nodules, whereas in T1Rs the lesions are more homogeneous. Both T2R and T1R lesions can ulcerate, but a slit-skin smear from a T2R lesion shows predominantly polymorphs, whereas that from a T1R lesion shows lymphocytes. In addition, two 'old tests' can help. The Ryrie test involves stroking the sole of the foot with the back of a reflex hammer, which in a T2R produces a burning pain that can also be noticed when the patient walks, as if walking on hot coals. Another test is the Ellis test, which involves squeezing the wrist. This causes a painful response in T2Rs that does not occur during T1Rs unless the radial cutaneous nerve is tender.[19]

Treatment: Since T2Rs are mostly episodic and self-limiting, many treatments have mistakenly been assessed as therapeutic.[13] Treatment of a T2R is less straightforward than for a T1R. As with T1Rs, the antigenic load should be reduced, preferably with WHO-MDT. Clofazimine (Lamprene®), one of the components of multibacillary MDT, has been shown to suppress T2Rs. The

Continued overleaf…

prevalence of T2Rs appears to have decreased since its introduction. Mild ENL with only a few erythematous papules and no other organs involved usually causes little damage, although the patient may feel uncomfortable. In these patients, the symptoms are treated with mild analgesic and anti-inflammatory drugs such as aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs). Although the event will subside spontaneously, prostaglandin-suppressing drugs can help ease the reaction. If the reaction, however, is more severe and involves fever, leucocytosis and involvement of other organs, additional treatment is required. When the reaction involves joints (arthritis), a combination of an NSAID and antimalarials (chloroquine or hydroxychloroquine) is often effective.

In severe cases of T2Rs with orchitis, iridocyclitis or neuritis with worsening nerve function, corticosteroids or thalidomide should be considered, or perhaps both drugs, especially when there is acute nerve involvement. The dose depends on the severity of the symptoms. A high initial dose of 60–120 mg prednisone for approximately 3 days is required to reduce oedema, as T2Rs are complement-mediated. The prednisone can then be tapered down within 1 month resembling the natural duration of most T2Rs. If the T2R recurs during the tapering process, the initial dose should be restarted and then tapered down again. Prednisone therapy has been shown to be very effective, although at high dosage has numerous side-effects, especially in patients with chronic or recurrent T2Rs. Steroid dependence is a major challenge and should be prevented.

Thalidomide seems to be the drug of choice but it is not easily accessible and is even prohibited in many endemic settings. It is extremely effective and possibly even safer than prednisone.[20,21] Thalidomide has several side-effects that usually do not warrant stopping the drug. Teratogenicity is a well-known side-effect which limits its use. Neuropathy is likely to be more common than reported as it is probably masked by leprosy neuropathy. The mechanism of action of thalidomide is still unclear. Thalidomide is given at a dose of 100–300 mg per day for a few days and then tapered to a dose of 50–100 mg to prevent the recurrence of T2Rs.[17] Pentoxifylline is claimed to have a strong anti-tumour necrosis factor (TNF)-α effect and thus might be expected to have an anti-T2R effect. However, even though TNF-α is even more present in T1Rs, neither thalidomide nor pentoxifylline has any effect on T1Rs. Pentoxifylline reduces leg oedema during T2Rs effectively, however, in a comparative study, it was found to be inferior to thalidomide.[22] Biologicals, like infliximab and etanercept, have been reported to be helpful in treating T2Rs as well, although they are less accessible for resource-poor settings. A multicentre randomized controlled trial is currently underway to examine the efficacy of methotrexate in the management of T2Rs (NCT03775460).[23]

Recurrent T2Rs: Clofazimine is used to reduce the severity and frequency of T2Rs. It is given as a dose of 100–300 mg per day. Recently, methotrexate was shown to be effective in weaning patients off steroids, provided steroids are only given during an active T2R. No steroids should be given in the period between T2R episodes, only methotrexate. Immunotherapy with bacillus Calmette-Guerin (BCG) can reduce the frequency and severity of T2Rs. This was also shown for *M. vaccae*, *M. w* and the ICRC bacilli (JL Stanford, personal communication 1987 and Zaheer *et al*.[24]). More research should be done on the mechanisms involved in this phenomenon.

Lucio's phenomenon

Strictly speaking, this is an occlusive disorder of blood vessels rather than a primarily inflammatory reaction. It may present in patients with diffuse LL, especially from Central America, who have an extremely high bacillary index (BI). They may have multiple stellate purpuric patches, angular infarcts and gangrene, a few with overlying haemorrhagic bullae and deep jagged necrotic ulcers and

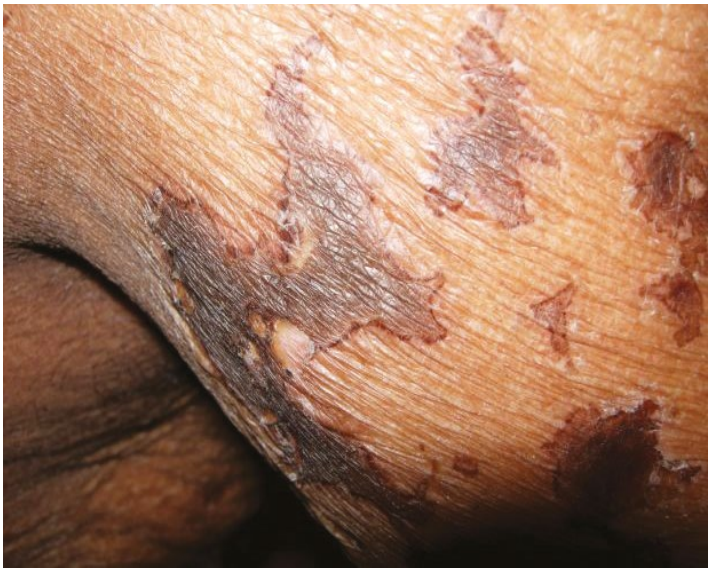

Fig 13. Stellate purpuric patches and angular infarcts in Lucio's phenomenon.

purpuric patches (Fig. 13). It may develop quickly and has a high mortality rate.[25] Apart from an extremely high BI score on slit-skin smear, specific laboratory tests are not available to diagnose Lucio's phenomenon.

Histopathologically, Lucio's phenomenon presents as an infarction in the skin, when huge numbers of bacilli are blocking the venous return in the small venules. This condition is only seen in untreated

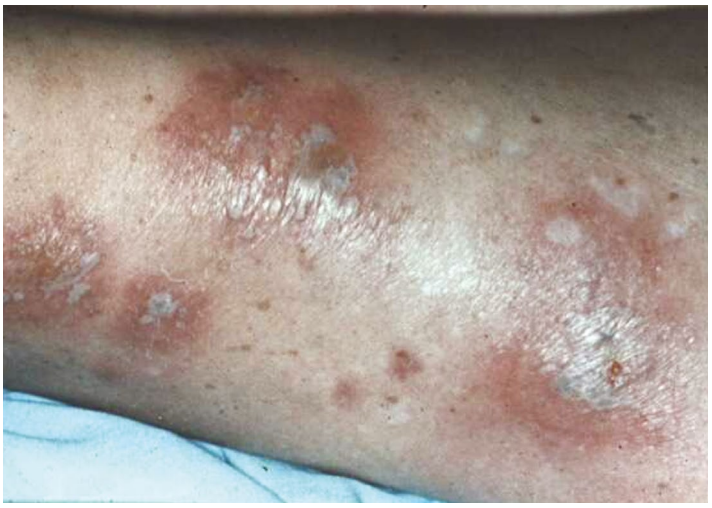

Fig 14. Ulcerating erythema nodosum leprosum.

diffuse LL. Some researchers believe that a special strain, *L. lepromatosis*, is responsible. Lucio's phenomenon is often confused with ulcerating ENL (Fig. 14). It is treated with MDT that contains an effective antibiotic (e.g. rifampicin).

Conclusion

This is a brief summary of the diagnosis and treatment of leprosy reactions. The next paper in this series will be an explanation of the physical damage to nerves after a reaction has occurred and neuropathic pain that may persist even once the disease is under control.

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CASE REPORT

Fixed drug eruption from consumption of chicken

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Funding: None.

Key words: Fixed drug eruption; chicken; co-trimoxazole; sulfonamides.

Case report

An 8-year-old boy presented to the skin outpatient clinic with a history of recurrent, hyperpigmented lesions on the upper left arm (Fig. 1) and trunk (Fig. 2) for the past 6 months. The skin lesions were initially erythematous plaques, sometimes with vesicles or bullae within the lesions. With time they would become hyperpigmented and then start fading before another attack would occur. Each recurrence would be preceded by an itching and burning sensation within the lesions.

There was no history of drug intake associated with the eruption of the lesions. Further discussion with the mother into a possible cause of what was clinically a fixed drug eruption (FDE), revealed that when the child ate chicken the lesions erupted. They had to stop him from eating chicken but, as it was a special treat, they would sometimes allow him to eat it and each time the reaction would recur.

It was agreed that the mother would find out from the neighbour, from whom she usually bought the chicken, whether co-trimoxazole (a combination of sulfamethoxazole and trimethoprim), the current local poultry treatment preference, was part of the management of sick chickens. During the next visit, it was confirmed that the chickens that the neighbour rears are treated with co-trimoxazole when sick.

Discussion

Antibiotics are used extensively in many branches of farming and are considered to be important animal food additives included in commercial feeds.[1–3] They are used to treat active infections in animals and birds. Antibiotics are also used prophylactically to prevent infections in animals and birds kept under unnatural profit-driven conditions of overcrowding and high density. More concerning is their inappropriate use as feed additive 'growth factors' and feed proficiency enhancers of dubious effectiveness.[1,3] As a consequence, antibiotics can end up as residues

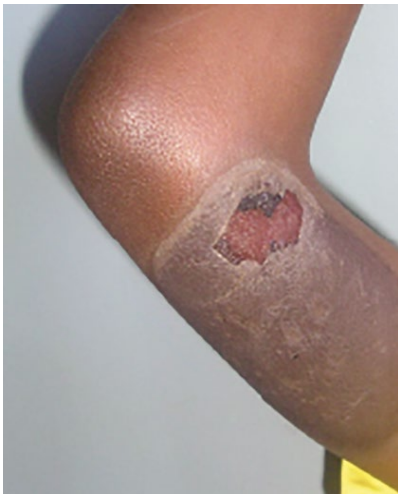

Fig 1. Early, well-demarcated, purple, bullous lesion on the right upper arm. The bulla has ruptured leaving an erosion.

Continued overleaf…

Fixed drug eruption from consumption of chicken

in foodstuffs such as milk, eggs and meat. Cooking does not necessarily eliminate the residual drugs in these products because of the thermostability of the antibiotics.[4]

The presence of these residues in foods may cause mild to severe adverse reactions in consumers.[4] The reactions can be because of direct toxicity and allergic reactions or indirect effects through microbe resistance to antibiotics. Most reported reactions are related to beta-lactam antibiotic residues, especially penicillin and cephalosporins. They include rashes such as urticaria, erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis, and conditions such as anaphylaxis, serum sickness, thrombocytopenia, haemolytic anaemia, vasculitis, acute interstitial nephritis and hepatitis among others.[4]

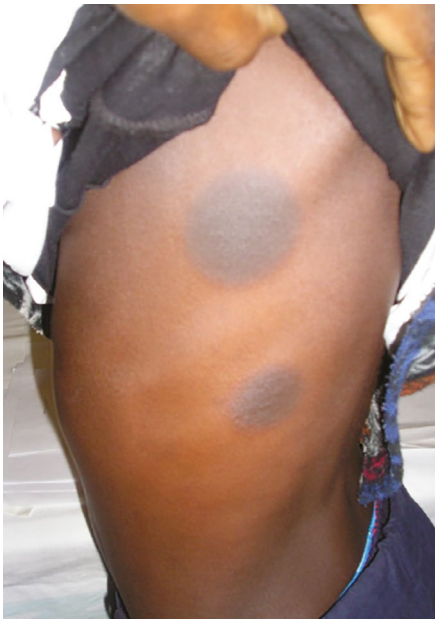

Fig 2. Well-demarcated, round hyperpigmented macules with a rim of erythema on the trunk, classic of an active fixed drug eruption.

FDE because of residual antibiotics in food was suggested by Han in his correspondence[5] on a report by Zhang *et al.*[6] of a case of FDE caused by alcohol binges in China. A further case of FDE because of doxycycline and erythromycin in food, namely pork and fish, was reported by Won-Suk Lim *et al.*[7]

FDE is a common cutaneous adverse drug reaction. Anderson and Lee report that FDE was first described by Bourns in 1889 and Brocq is credited for assigning the name 'éruption érythémato-pigmentée fixe'.[8]

FDE has distinct clinical characteristics making differentiation from other drug reactions relatively easy. It is a muco-cutaneous reaction that characteristically recurs at the same site(s) with repeated exposure to the causative agent. Lesions can be single or multiple, localized or generalized, tender or pruritic, well-demarcated, rounded or oval, erythematous oedematous plaques or bullae and red, purple or hyperpigmented macules/plaques with or without a ring of erythema. FDE is usually asymptomatic but may be itchy or painful. Over the next few days and weeks, the surface may become scaly or crusty before peeling off, and the colour fades to leave brown, or in darker skin, blackish post-inflammatory hyperpigmentation. This post-inflammatory hyperpigmentation tends to be more prominent in skin of colour.

The hands and feet, eyelids and anogenital areas are common sites. Lesions on the oral mucosa are usually found on the lips, tongue and hard palate. FDE may recur at the same site but new lesions may also develop on re-exposure to the precipitating agent.

It is not often misdiagnosed by dermatologists, but finding the cause is often difficult and challenging, requiring good collaboration between the practitioner and the patient or patient's caregiver.

Patients may not be aware that a drug, dietary supplement, over-the-counter medication, or, in rare cases, food can be the cause of the skin problem. They may be convinced that an insect, especially a spider or a rove beetle within the subtribe *Paederinae*, is the culprit or that they have been cursed. Careful history-taking is required to ascertain whether anything was eaten or drunk that could be temporally related to the onset of the eruption. If medication is implicated, patients often report ingestion of episodically taken treatments, such as painkillers, antibiotics or laxatives as culprit drugs.

Here we have presented a case report about an individual with an FDE from consumption of chicken meat; the chickens were frequently exposed to sulfonamide and co-trimoxazole for treatment and prophylaxis.

Our patient was diagnosed as having an FDE secondary to sulfonamide and trimethoprim residue in poultry. The association of the lesion and consumption of chicken had been noted by the family, but they did not know about the association with the antibiotic residue in the chicken meat. Detailed history-taking lead to the identification of the cause of the FDE.

Antibiotics are used for the treatment of bacterial infections in chicken farming in Kenya and as feed additives for poultry and livestock health maintenance. Sulfonamide and trimethoprim are among the commonest drugs used for animal food supplementation, possibly because sulfonamides are considered growth promoters in poultry. Studies from Kenya by Muriuki *et al.* in 2001[9] and Shitandi and Sternesjö in 2004[10] reported tetracycline and β-lactams in beef, liver, kidney and milk. In a study of chicken farming in peri-urban Nairobi, Muthuma *et al.*[11] confirmed that broiler chicken meat contained sulfonamide residues supporting our conclusion that sulfonamides present in chicken meat are the cause of the FDE in our patient.

Conclusion

This patient's case has demonstrated that residues of antibiotic used in veterinary medicine and in animal food production should be considered as a cause of FDE.

Acknowledgements

I wish to express my gratitude to the patient for consenting to the use of their case and photos for the purposes of this article. A special thank you must go to Emeritus Professor Gail Todd, University of Cape Town and Professor Ben Naafs for their expert input, constructive criticism and guidance during the writing of the article.

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Fixed drug eruption – a photo gallery

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A range of fixed drug eruption (FDE) presentations

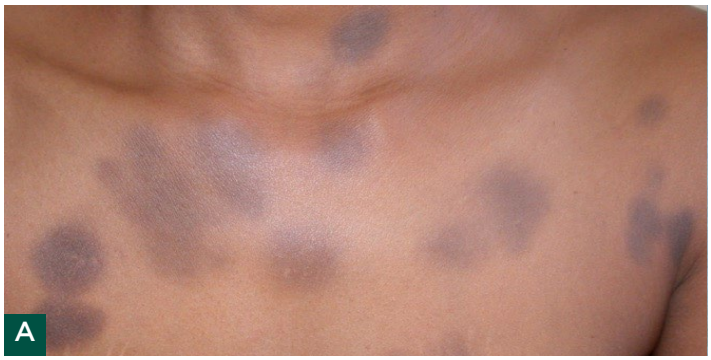
A. Resolved FDE. Well-defined round postinflammatory hyperpigmented macules.

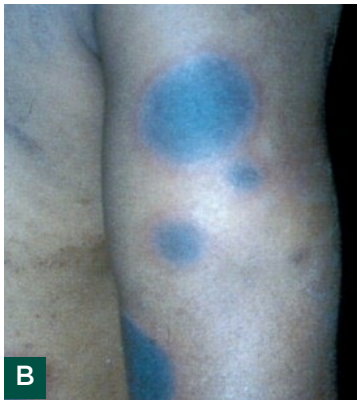
B. Active recurrent FDE. Well-defined round postinflammatory hyperpigmented macules with rim of erythema.

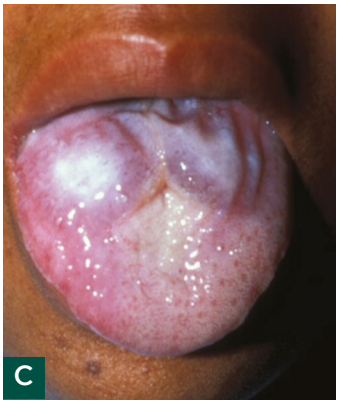
C. Active new bullous FDE of tongue. Well-defined round blisters.

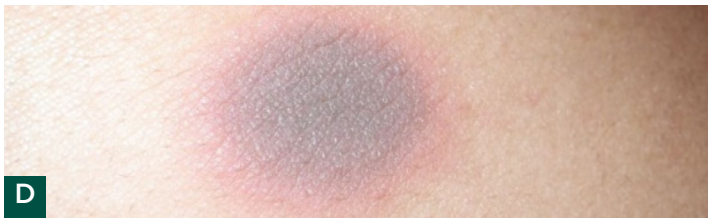
D. Active recurrent FDE. Well-defined round postinflammatory hyperpigmented macules with rim of erythema.

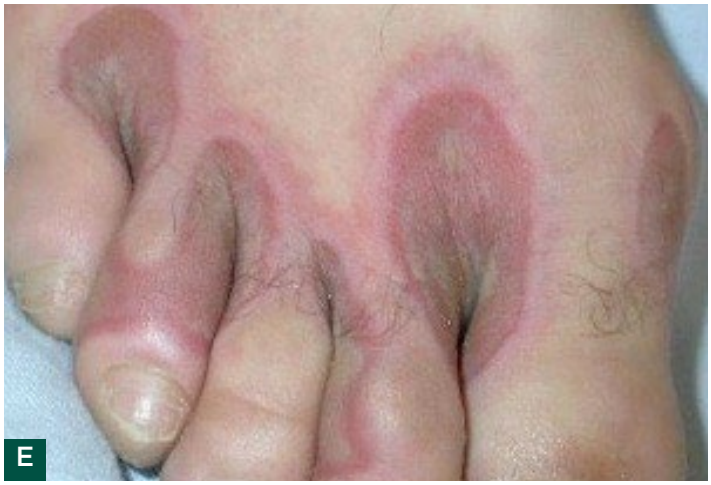
E. Active new bullous FDE. Well-defined erythema with central epidermal necrosis and blisters.









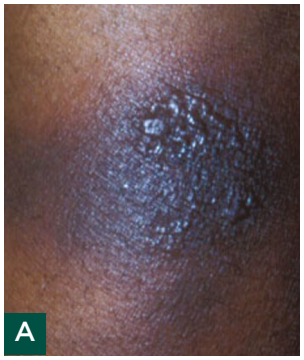


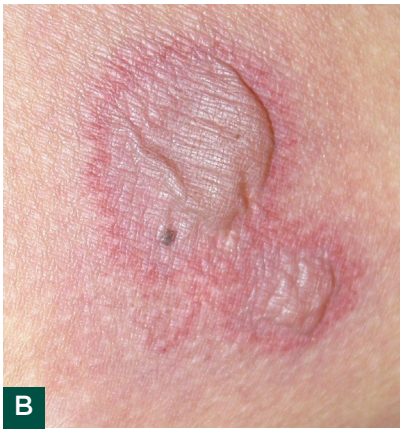
A range of bullous FDE presentations

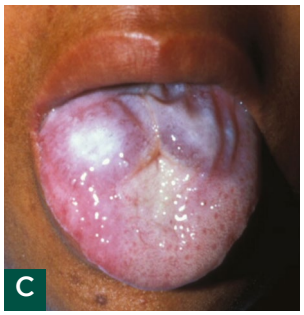
A. Active recurrent bullous FDE. Well-defined round postinflammatory hyperpigmented plaque with vesico-bullae.

B. Active new bullous FDE. Well-defined erythema with central blisters.

C. Active new bullous FDE of tongue. Well-defined round blisters.



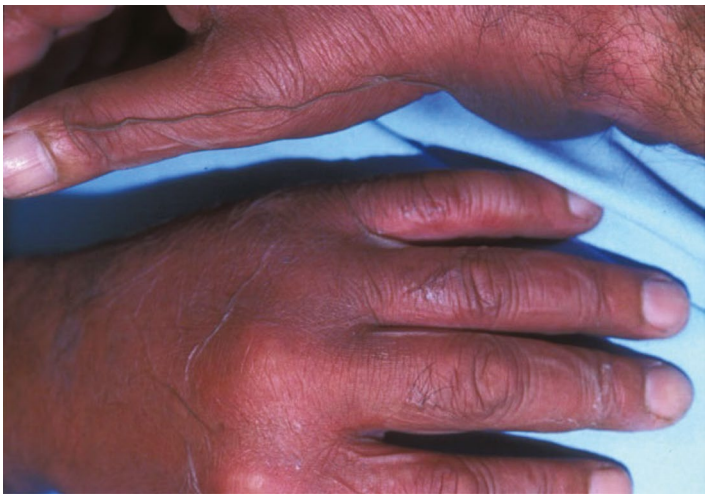


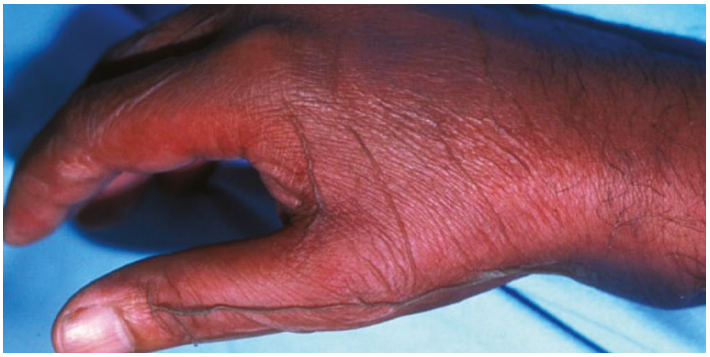


Bullous FDE from over-the-counter medication

Localized bullous FDE. Well-defined purple patches of epidermal necrosis with blisters and positive Nikolsky sign.

Occurred with each exposure to phenolphthalein laxative.





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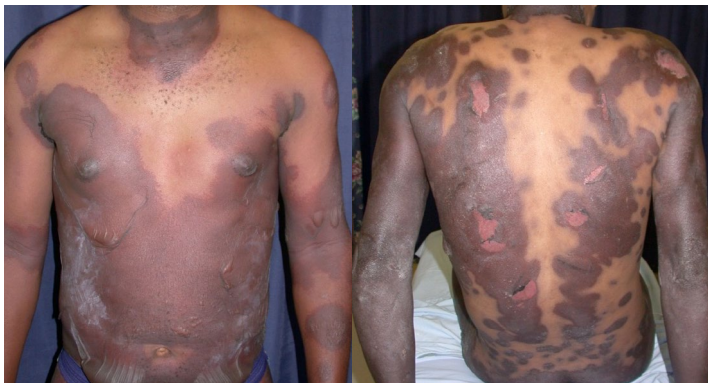
A range of bullous FDE presentations

Generalized bullous FDE. Well-defined purple/red patches and plaques of epidermal necrosis, with blisters and erosions and a positive Nikolsky sign.



A range of inactive FDE presentations

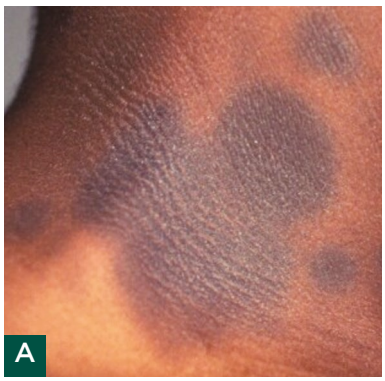
A. Resolved FDE. Well-defined round postinflammatory hyperpigmented macules.

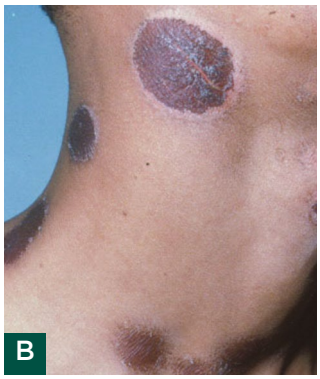
B. Resolved FDE. Well-defined round plaques of desquamating dry epidermal necrosis.

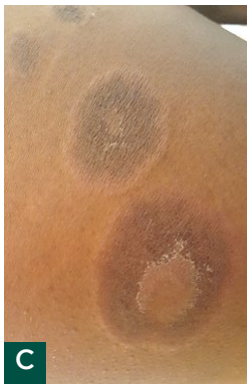
C. Resolved FDE. Well-defined annular plaques with central hyperpigmented desquamating skin.

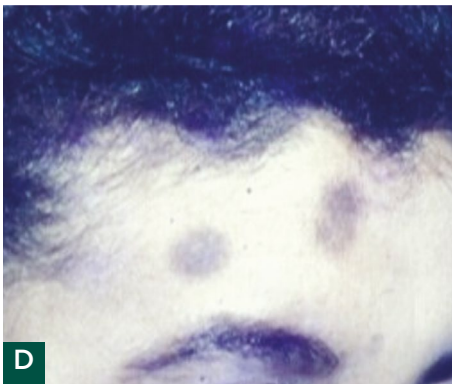
D. Resolved FDE. Well-defined round postinflammatory hyperpigmented macules.

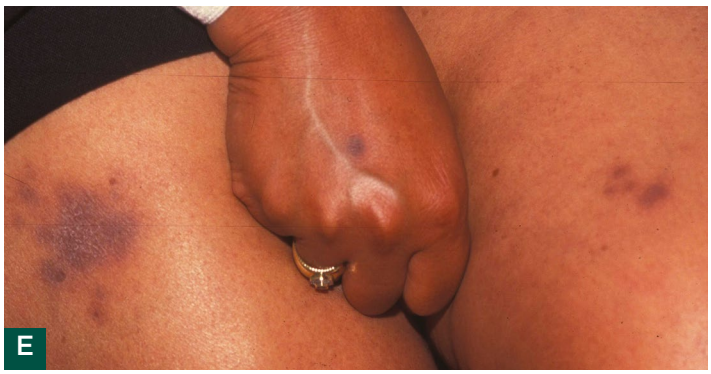
E. Resolved FDE. Well-defined round postinflammatory hyperpigmented macules.









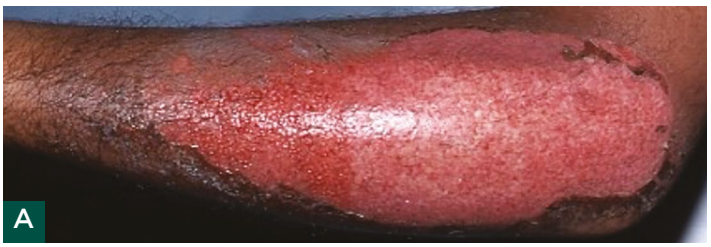


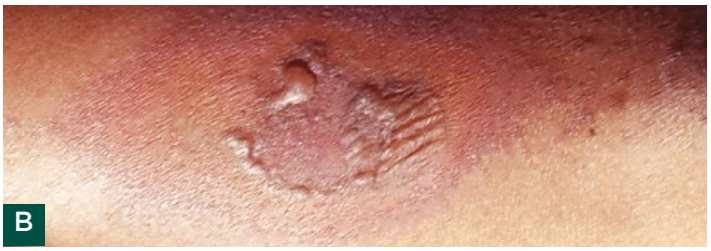
Occupational bullous FDE

A. Localized bullous FDE. Well-defined purple patches of epidermal necrosis and erosions.

B. Localized bullous FDE. Well-defined purple patches of epidermal necrosis and bullae.

Occurred with each assignment of a pharmaceutical worker to the morphine/codeine manufacturing unit.





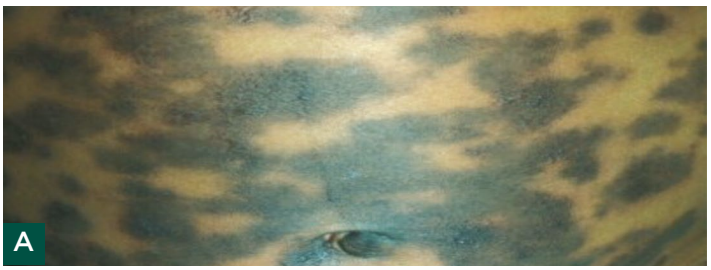
Iatrogenic bullous FDE with complications

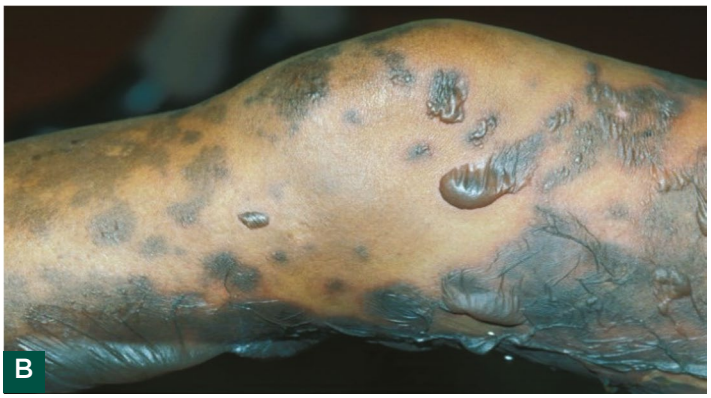
A. Early active recurrent FDE. Well-demarcated hyperpigmented macules and patches, some with rim of erythema on torso.

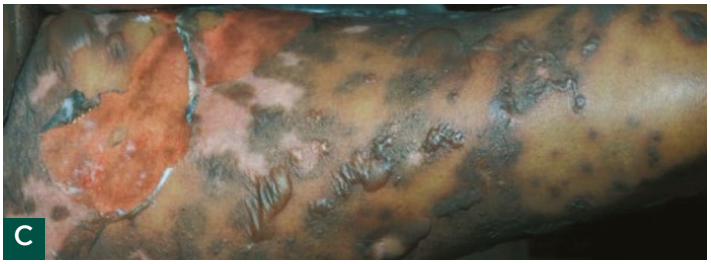
B. Active recurrent FDE. Well-demarcated hyperpigmented and purple macules and patches rimmed with erythema and blistering.

C. Complicated recurrent active FDE. Well-demarcated hyperpigmented and purple macules and patches rimmed with erythema and central blistering and erosions. Depigmentation complication.

Occurred with each exposure to phenytoin in the emergency room for epileptic seizures.







Prevalence of cutaneous manifestations and their associated factors among patients with chronic kidney disease in Mnazi Mmoja Referral Hospital, Zanzibar

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Key words: Cutaneous manifestation; haemodialysis; chronic kidney disease; Zanzibar.

Abstract

Background: Cutaneous manifestations are common in all stages of chronic kidney disease (CKD), particularly in end-stage renal disease when they have a prevalence of 50–100%. Management of patients with CKD is difficult in low-income countries because of the high cost of dialysis. The skin changes can vary according to the stage of the disease.

Objectives: To determine the prevalence of cutaneous manifestations and their associated factors among patients with CKD stages III to V.

Methods: A cross-sectional study of patients with CKD was performed from September to October 2021 at Mnazi Mmoja Referral Hospital, Zanzibar. Data were collected using a questionnaire and any skin manifestations were diagnosed by a dermatologist.

Results: Eighty-six patients with CKD participated in the study with a median age of 50 years (interquartile range 39–60), of whom 49 (57%) were on haemodialysis and 37 (43%) were receiving conservative management. Seventy patients (81%) had at least one skin problem. The most common skin disorders were xerosis (severe dry skin with scaling, 71%), pruritus (49%) and pallor (27%). Half and half nails (23%) and xerostomia (43%) were the commonest nail and oral presentations, respectively. Decreased sweating and dry skin were factors observed in 28% and 70% of patients, respectively, and the association with dry skin was significant ($P<0.001$). Neither haemodialysis treatment nor the stage of CKD (stage III, IV or V) were significantly associated with cutaneous manifestations in this study.

Conclusions: Cutaneous manifestations in CKD were common at our centre, in keeping with previous studies. Physicians caring for patients with CKD on dialysis need to be aware of cutaneous complications.

Introduction

Chronic kidney disease (CKD) is when the glomerular filtration rate (GFR) is <60 ml/min. A GFR <15 ml/min denotes end-stage renal disease (ESRD). There are five stages of CKD based on the GFR.[1] The cutaneous manifestations have been classified as specific disorders such as renal pruritus, acquired perforating dermatosis, nephrogenic systemic fibrosis, calciphylaxis, porphyria cutanea tarda and pseudoporphyria, and non-specific features including xerosis, pigmentary changes, skin infections, uraemic frost, nail changes, hair changes and mucosal alterations.[2] These usually develop as kidney function continues to deteriorate.[1]

Previously reported factors associated with cutaneous manifestations in CKD are haemodialysis, a high level of uraemic nitrogen, calcium and phosphate levels, diabetes mellitus, hypothyroidism, hepatitis and liver diseases, malignancies, HIV infection, secondary hyperparathyroidism, alcohol consumption, medications such as furosemide, naproxen, tetracycline, amiodarone, isotretinoin, nalidixic acid and steroids, decreased sweating, peritoneal dialysis and dry skin.[1,3]

Globally, cutaneous manifestations are common in all stages of CKD particularly in ESRD, where the prevalence is 50–100%.[3] In sub-Saharan Africa, the prevalence of skin manifestations was 89% amongst 120 patients with CKD in Ibadan, Nigeria.[4] To the best of our knowledge, in East Africa, including Tanzania, no study has been reported so far on cutaneous manifestations in patients with CKD, despite several publications looking at the association between CKD, diabetes mellitus and hypertension in patients on haemodialysis.[5] The aim of this study was to determine the prevalence of cutaneous manifestations and associated factors among patients with CKD at Mnazi Mmoja Referral Hospital, Zanzibar.

Methods

Participants: This hospital-based cross-sectional study was conducted from September to October 2021. Patients with CKD stages III–V attending the Mnazi Mmoja Hospital nephrology clinic and dialysis unit were invited to participate. This is a teaching hospital located in Zanzibar, Tanzania, making it a convenient centre for sampling.

Data collection methods/tools: After the purpose of the study had been explained and consent obtained, data were collected through interviews and physical examination. A structured questionnaire was used to collect demographic information and data such as stage of the disease, investigation results, treatment modalities and examination findings. The preliminary evaluation was done by an investigator and a dermatologist diagnosed any cutaneous manifestations, using a checklist in which the skin diseases were grouped as follows: colour changes (such as pallor); xerosis (grade 0, grade 1, grade 2); infectious diseases; nail changes; hair changes and mucosal involvement.

Statistical analysis: The Statistical Package for Social Science version 20.0 for Windows (SPSS) was used for analysis. Descriptive analysis was carried out to assess characteristics of the sample.

Ethical consideration: Ethical clearance number ZAHREC/04/ST/SEP/2021/79 was obtained from Zanzibar Health Research Institute

Continued overleaf…

and permission to conduct the study was granted by Mnazi Mmoja Hospital.

Results

Eighty-six patients with CKD were interviewed and examined; the median age was 50 years with an interquartile range of 39–60 years. Most patients (*n*=36, 42%) were in the age group 36–55 years. The male to female ratio was 1:1. Over two-thirds (*n*=70, 81%) came from Unguja, the largest, most densely populated island in Zanzibar. Seventy (81%) individuals had at least one cutaneous manifestation. Of the patients, 49 (57%) were on haemodialysis and 37 (43%) were receiving conservative management.

Types of cutaneous manifestations in CKD: The most common skin problem was xerosis (*n*=61, 71%) followed by pruritus (*n*=42, 49%) and pallor (*n*=23, 27%). Only two patients with palmoplantar keratoderma and three with acquired perforating dermatosis were recorded. Xerostomia (*n*=37, 43%) and half and half nails (*n*=20, 23%) were the commonest oral and nail changes, respectively. The most reported hair abnormalities were scalp hair loss (*n*=13, 15%) and brittle, lustreless hair (*n*=5, 6%, Table 1). Oral changes were observed in 50% of patients (*n*=43).

Factors associated with cutaneous manifestations: Dry skin (*n*=60, 70%) and decreased sweating (*n*=24, 28%) were the most common factors in this group of patients with CKD and the association with dry skin was significant (Chi-squared, $P<0.001$). Cutaneous manifestations were not significantly associated with haemodialysis treatment or the stage of CKD (Stage III, IV or V) (Table 2); although they were commoner in older patients (56–75 years) compared with those who were younger (15–55 years), this was not statistically significant (Chi-squared, $P=0.054$). Furthermore, none of the following associated factors were found to be statistically significant: high urea level in patients not on haemodialysis; high levels of urea or creatinine after haemodialysis; cardiovascular disease; diabetes mellitus (data not shown).

Discussion

Prevalence of cutaneous manifestations: Our finding of a prevalence of 81% of ≥1 cutaneous manifestation in patients with CKD is similar to that found in a Nigerian study that identified a prevalence of 89% in 107/120 patients.[4] This may be a reflection that both studies were performed in a secondary care setting. However, our findings are lower than a study from San Juan city, USA,[3] which found a prevalence of 100%, perhaps because all their patients were on dialysis with more advanced CKD.

Type of manifestation: Xerosis (71%) and pruritus (49%) were the most common cutaneous presentations in our study. Two studies from India[6,7] reported broadly similar findings of between 40% and 90% for both xerosis and pruritus and in a study from Nigeria pruritus was the commonest feature (61%).[4]

Oral changes were observed in 50% of patients, the most common being xerostomia (43%); we observed scrotal tongue in 8% and teeth marking on the tongue in 2%. In an Indian study oral changes were similar but less common, e.g. xerostomia in 12%.[8] Oral changes were reported in only 24%, with no cases of xerostomia, in a smaller series of 101 patients from Iran.[9]

Conclusion

Cutaneous manifestations in CKD are common. Our findings are comparable with studies from other centres across the globe, although neither the association with haemodialysis treatment nor the stage of CKD (Stage III, IV or V) were statistically significant

Table 1. Demographic and dermatological findings in 86 patients with chronic kidney disease attending Mnazi Mmoja Referral Hospital, Zanzibar between September to October 2021.

Characteristic	n	%
Age group, years		
15–35	19	22
36–55	36	42
56–75	31	36
Sex		
Female	43	50
Skin changes		
Pallor	23	27
Hyperpigmentation	18	21
Dermatitis	8	9
Xerosis	61	71
Pruritus	42	49
Purpura	1	1
Ecchymosis	1	1
Yellow skin	1	1
Acquired ichthyosis	1	1
Dyshidrotic eczema	1	1
Palmoplantar keratodermas	2	2
Malar rash	1	1
Acquired perforating dermatosis	3	3
Oral changes		
Xerostomia	37	43
Angular cheilitis	2	2
Teeth marking	2	2
Scrotal tongue	7	8
Oral candidiasis	3	3
Nail changes		
Half and half nail	20	23
Nail dystrophy	9	10
Onycholysis	9	10
Onychomycosis	5	6
Beau line	5	6
Nail clubbing	1	1
Longitudinal melanonychia	2	2
Absence of lunula	6	7
Onychogryphosis	2	2
Onychorrhexis	4	5
Hair changes		
Scalp hair loss	13	15
Brittle lustreless hair	5	6

Table 2. Factors associated with cutaneous manifestations in patients with chronic kidney disease (CKD) (n=86).

Characteristic	Cutaneous manifestations		X^2-test	P-value
	Yes	No		
Decreased sweating			–	–[a]
Yes	24	0		
No	46	16		
Dry skin			30.5	<0.001
Yes	58	2		
No	12	14		
Haemodialysis			1.1	0.25
Yes	38	11		
No	32	5		
CKD stage			0.3	0.87
III	11	3		
IV	7	1		
V	52	12		

[a]Zero value means X^2 test is not appropriate

in our study. Physicians should be aware of the high prevalence of skin manifestations in patients with CKD. A careful history and skin examination is recommended for patients with CKD because the cutaneous manifestations can cause discomfort and lower quality of life, especially in those with comorbidities.

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