Concurrence of Human Immunodeficiency Virus Infection and Buruli Ulcer, A Neglected Tropical Disease in a Paediatric Patient – A Case Report

BENJAMIN TA[1] MSc, **OTROFANOWEI E**[1,2] **FMCP, BANJO AAF**[3,4] FMCPath, **AKINJO AO**[3,4] FMCPath

[1]Dermatology Unit, Department of Medicine, Lagos University Teaching Hospital
[2]Department of Medicine, College of Medicine, University of Lagos
[3]Department of Anatomic and Molecular Pathology, College of Medicine, University of Lagos
[4]Department of Anatomic and Molecular Pathology, Lagos University Teaching Hospital, Idi-Araba Lagos

Corresponding Author: Dr Benjamin Timilehin Anthony
Email address: Bentimilehin2014@gmail.com

Abstract

We present a case report on the co-existence of human immunodeficiency virus infection and a seemingly rare neglected tropical disease, Buruli ulcer, in a two-year-old female born to a mother living with HIV infection. This case report aims to sensitize clinicians and healthcare providers about Buruli ulcers, its risk factors (including HIV infection), the importance of prompt tissue diagnosis, and the benefits of multidisciplinary care for optimal case outcomes.

A two-year-old female retroviral-positive child of a mother living with HIV was referred to our facility because of a year's history of weight loss, a seven-month history of progressive abdominal swelling and a three-week history of a non-healing back ulcer. The back ulcer continued to increase in size despite receiving antimicrobial treatment and other supportive care from referral hospitals. However, a wound biopsy at our centre confirmed the diagnosis of a Buruli ulcer. She was managed non-operatively with nutritional support, wound dressing and antibiotics. The wound gradually reduced in size. The patient also demonstrated clinical improvement, as evidenced by weight gain and increased tolerance to physical effort. The doctors discharged her after a 42-day admission.

Although rare, Buruli ulcer is a neglected tropical disease that persists, and its presentation is protean. While Buruli ulcer has been reported in immunocompetent patients, it is much more prevalent in patients with suppressed immunity, as seen in this case report. A significant risk factor for acquiring Buruli ulcer, in this case, is HIV infection. It is, therefore, imperative to maintain a high index of suspicion when managing patients with non-healing ulcers and thoroughly investigating, as the seemingly low incidence of many of these NTDs may be due to underdiagnosis and underreporting.

Keywords: Buruli ulcer (BU); Human Immunodeficiency Virus (HIV); Neglected Tropical Disease (NTDs)

Concomitance d'une infection par le virus de l'immunodéficience humaine et d'un ulcère de Buruli, une maladie tropicale négligée chez un enfant, à propos d'un cas

Nous présentons un cas clinique concernant la coexistence d'une infection par le virus de l'immunodéficience humaine et d'une maladie tropicale négligée apparemment rare, l'ulcère de Buruli, chez une fillette de deux ans née d'une mère infectée par le VIH. Ce cas clinique vise à sensibiliser les cliniciens et les professionnels de santé à l'ulcère de Buruli, à ses facteurs de risque (dont l'infection par le VIH), à l'importance d'un diagnostic histologique et aux avantages d'une prise en charge multidisciplinaire pour un résultat optimal.

Une fillette de deux ans, séropositive pour le VIH et née d'une mère infectée par le VIH, a été orientée vers notre établissement en raison d'une perte de poids depuis un an, d'un gonflement abdominal progressif depuis sept mois et d'un ulcère du dos persistant depuis trois semaines. L'ulcère a continué de s'élargir malgré le traitement antimicrobien et les autres soins de soutien dispensés par les hôpitaux de référence. Cependant, une biopsie de la lésion réalisée dans notre centre a confirmé le diagnostic d'ulcère de Buruli. La prise en charge a été non chirurgicale, avec un apport nutritionnel, un pansement et des antibiotiques. La taille de

l'ulcère a progressivement diminué. L'état clinique de la patiente s'est également amélioré, comme en témoignent une prise de poids et une tolérance accrue à l'effort physique. Les médecins ont autorisé sa sortie après 42 jours d'hospitalisation.

Bien que rare, l'ulcère de Buruli est une maladie tropicale négligée persistante et dont la présentation est variable. Si des cas d'ulcère de Buruli ont été signalés chez des patients immunocompétents, sa prévalence est beaucoup plus élevée chez les patients immunodéprimés, comme le montre ce cas clinique. Dans ce cas, l'infection par le VIH constitue un facteur de risque important de contracter l'ulcère de Buruli. Il est donc impératif de maintenir une forte suspicion lors de la prise en charge des patients présentant des ulcères non cicatrisants et de procéder à des investigations approfondies, car l'incidence apparemment faible de nombre de ces maladies tropicales négligées pourrait s'expliquer par un sous-diagnostic et une sous-déclaration.

Mots-clés: ulcère de Buruli (UB), virus de l'immunodéficience humaine (VIH), maladies tropicales négligées (MTN)

Introduction

Buruli ulcer (BU) is a chronic debilitating necrotizing skin infection caused by Mycobacterium ulcerans, a prominent member of the Mycobacteriacae family. Buruli ulcers became noticeable in 1897 when Cook described the lesions, which Clancey and colleagues had earlier named following the emergence of the first large epidemic in Buruli County, Uganda.[1] Buruli ulcer is also known as Bairnsdale or Searles's ulcer in Australia and Kumusi ulcer in Papua New Guinea. First reported in 1948, currently, Buruli ulcers have been reported in over 34 countries with a predilection for tropical and subtropical climates.[2] Other nomenclatures for BU include Mossman or Daintree ulcer.

The prevalence of BU cuts across approximately 33 countries, primarily in tropical regions, with the highest frequency in Africa, particularly in the West African countries of Côte d'Ivoire, Ghana, and Bénin, ranging from 20 to 158 cases per 100,000.[3] Debacker et al.. published a higher detection rate for BU in the Zou region of Benin in 1999 than leprosy and tuberculosis. They observed the prevalence of osteomyelitis in more than 13% of the patients.[3]

There is a paucity of data on the epidemiology of BU in Nigeria. However, Marion et al. reported 51 cases of BU over a 45-year period since it became endemic in Nigeria in 1967.[4] Buruli ulcer affects all age groups, but children aged 5 to 15 are most commonly affected.[5] Buruli ulcer has been associated with Wetlands, but knowledge of its reservoir and vectors is limited.[6] Besides, no potent vaccine has been discovered for BU.[2]

Buruli ulcer was classified as a neglected emerging infectious disease by the WHO in 1988, following the re-emergence of cases. This development has prompted significant research into the disease conditions.[7]

Mycobacterium ulcerans is a slow-growing mycobacterium cultured in vitro at 29 to 33°C, capable of producing mycolactone, a cytotoxin that induces skin necrosis and ulceration.[8] In Japan, BU has been attributed to a subspecies of Mycobacterium ulcerans, specifically *M. ulcerans subsp. shinshuense*.[8]

While mycolactone causes tissue destruction and widespread cellular apoptosis, including that of immune cells, the host's activation of the angiotensin 2 receptor plays a key role in analgesia.[9] This could explain a common clinical manifestation of BU as a painless nodule. Consequently, immune paresis and cellular apoptosis result partly from the disruption of the intracellular Sec61 translocon or damage to the cytoskeleton of several different host cells, triggered by the activation of Wiskott-Aldrich syndrome proteins through a mechanism that impairs protein synthesis in the endoplasmic reticulum.[9]

Buruli ulcer is linked with Human Immunodeficiency Virus infection (HIV), and the WHO, in her technical update in 2020, remarked that HIV increases the risk for BU infection. Patients with BU are more likely to have an HIV infection than those without BU. Skin lesions in patients with coexistent BU and HIV often occur in multiple,

extensive and ulcerative lesions than those without HIV. The initial lesion, a painless nodule, usually breaks down after days to weeks, forming an ulcer with characteristic undermined edges. This ulcer painlessly progresses and is usually bereft of systemic symptoms, unlike most ulcers, unless a superimposed secondary bacterial infection is present.[10,11]

One-third of Buruli ulcer cases can resolve spontaneously. However, joint contractures and other musculoskeletal complications often result.[12] Furthermore, diagnostic conundrums often accompany BU among clinicians, as there are many mimics, including cellulitis, leprosy, leishmaniasis, pyoderma gangrenosum, tuberculosis, yaws, actinomycosis, and Kaposi sarcoma. Nevertheless, early case detection and treatment are crucial to controlling BU and preventing its associated morbidities. Röltgen et al. noted that confirmatory diagnostic tests for BU lack sufficient sensitivity and specificity and are most centralized. Thus, accessibility to patients living in remote rural areas becomes difficult.[2]

Commonly used laboratory tests for BU include microscopic detection of acid-fast bacilli (AFB) in stained smears from clinical specimens, PCR targeting the *M. ulcerans*–specific insertion sequence (IS) element IS2404 of the DNA (the most sensitive and specific method, thus considered the gold standard), and histopathology of sections from the affected tissue. Another method is the primary cultivation of the mycobacteria.[2] The currently available pharmacotherapy for BU includes rifampicin, streptomycin and clarithromycin.[2]

Case Presentation

The patient was a 2-year-old girl with retroviral disease diagnosed 15 months prior and adherent to antiretroviral therapy (Lamivudine and Abacavir). She presented with a year's history of gradual unintentional weight loss, painless abdominal swelling of 7 months and a 3-week history of a gradually increasing ulcer on her back. Her mother said the ulcer began as a small, painless boil that gradually increased in size before developing into an ulcer. There was an associated high-grade fever, which resolved shortly after she was given some parenteral broad-spectrum antibiotics from the initial healthcare facility she was taken to, but the ulcer did not resolve. Instead, it grew larger and wider, and she was referred to our facility. Her birth was uneventful except that she was born to a mother living with AIDS who had been on ART for about 7 years. She met all her developmental milestones in a timely fashion.

Significant examination findings at the presentation were multiple furuncles on the face and head. The child weighed 7.5 kg (3 SD below the mean). She was dyspnoic with a respiratory rate of 55/m; breath sound was vesicular. SPO2 on room air was 100%. The heart rate was 144 beats per minute, and only the first and second heart sounds were audible. The back examination revealed an ulcer that extended from the left scapular region to the posterolateral chest wall (24 cm by 18 cm), as shown in Figures 8 and 9. The edges were undermined, and the inferior third was covered by necrotic tissue. The floor of the ulcer had pale granulomatous tissue, and the surrounding skin was indurated.

The Mantoux test and Chest radiograph showed no evidence of tuberculosis. The wound swab for microscopy, culture, and sensitivity was not remarkable; however, the wound smear for acid-fast bacilli and PCR was not performed. Blood culture did not yield any growth. The fungal culture was not done due to financial constraints.

Her blood work was remarkable for leukocytosis of 16,700/mm2 and anaemia of 20.4%. CD4 was 961cells/mm2. Blood chemistry results showed mild hyponatremia at 131mmol/L, hypokalemia at 3.21mmol/L, and hyperchloremia at 107mmol/L. Other findings were hypoproteinemia of 51.9mg/dl and hypoalbuminaemia of 22.9mg/dl.

The histopathology findings from a tissue specimen from a wound biopsy showed foreign body-type giant cells within the dermis. There was also a necrosis focus in the deep dermis. The edge of the subcutaneous fat showed a focus of stratified squamous epithelium.

The wound biopsy shows acanthosis of the epidermis with a focus of parakeratosis overlying an

area of hypogranulosis. The dermis shows periadnexal, perivascular, and perineural inflammatory cell infiltrates comprising lymphocytes, plasma cells, histiocytes, and neutrophils. The inflammation extends into the subcutaneous fat. There are foreign body-type giant cells within the dermis. There are also foci of necrosis in the deep dermis. The edge of the subcutaneous fat shows a focus of stratified squamous epithelium with overall features consistent with buruli ulcer (BU). (Figure 1-5).

She was managed by a multidisciplinary team comprising Paediatricians, burns and Plastic surgeons, dermatologists, the DOTS Team, medical microbiologists, and dietitians.

The wound at the back reduced gradually in size. Her effort tolerance also improved. She was discharged after 40 days of admission, having shown remarkable improvement and gained 2.5kg during her stay. The back wound closed fully eight months post-discharge.

Discussion

Buruli ulcer is a chronic, debilitating, neglected tropical disease of the skin caused by Mycobacterium ulcerans, the third most common microbe affecting immunocompetent hosts among the Mycobacteriaceae family, after Mycobacterium tuberculosis and Mycobacterium leprae.[1] We reported an occurrence of BU in an immunocompromised female toddler born to a retroviral-positive mother.

Portaels et al. remarked that BU is the least understood of the three notable microbes in the Mycobacteriaceae family and remains to be elucidated in terms of its modes of transmission.[1,6] In this case report, immunosuppression from HIV could have been responsible for the susceptibility of this child to BU. It has also been published that consumption of unprotected water from swamps, Vaccination with M. Bovis BCG vaccine and place of residence were associated with increased risk of BU.[3]

Raghunathan et al.'s case-control study in Ghana showed that BU was associated with penetrating skin trauma and waddling in a river. However, there was no significant association with HIV co-infection.[13] As earlier reported, the age of occurrence of BU is 5-15 years.[5] Debacker et al. found the highest incidence of BU in the age brackets of less than 5 years and 45 years or older among patients with BU in Benin.[3] In this case report, the patient developed BU at a younger age of two years. This early onset of disease could be immunosuppression from HIV infections.

Also captured in this case report is the low awareness of BU ulcers among patients, their relatives, and healthcare providers, who often misuse antimicrobials to treat ulcers originating from BU. As reported by Aujuolat et al. and Renzaho et al., the awareness of BU is low, and patients perceive the disease as God-inflicted or as a result of the consumption of pond water, swimming in rivers, waddling in swampy areas, witchcraft and curses.[14,15]

It is, therefore, imperative to further educate the general public and healthcare professionals on the importance of maintaining a high index of suspicion in treating ulcers, especially those that fail to heal despite appropriate wound care and antimicrobial interventions.

This case report also highlights some of the dilemmas that patients and caregivers face, especially in a developing world like Nigeria, where poor referral mechanisms are evident, as evidenced by multiple referrals before reaching a tertiary Centre. During the process of inter-hospital referrals, considerable time and energy are wasted. Furthermore, mismanagement of such cases is likely to occur. Additionally, care for a patient with BU is multidisciplinary, as illustrated in this patient. This is only feasible in tertiary institutions, especially in a developing world like Nigeria.

Conclusion

This case report underscores the incidence of a neglected but noticeable tropical disease, BU, in a two-year-old retroviral-positive child of a retroviral-positive mother. The perceived low incidence of BU in many countries might be due to underreporting. Clinicians are to treat non-healing wounds with a

high index of suspicion. Besides, with concerted efforts among healthcare professionals in a multi-specialist setting, improved case outcomes from BU are high. Strong public health advocacy and education are needed to reduce the burdens of NTDs, such as BU.

Ethical Consideration: Informed consent was obtained from the patient's primary care provider and next of kin, the mother. She showed great interest in the published case and sent us pictures of the child from home several months after discharge.

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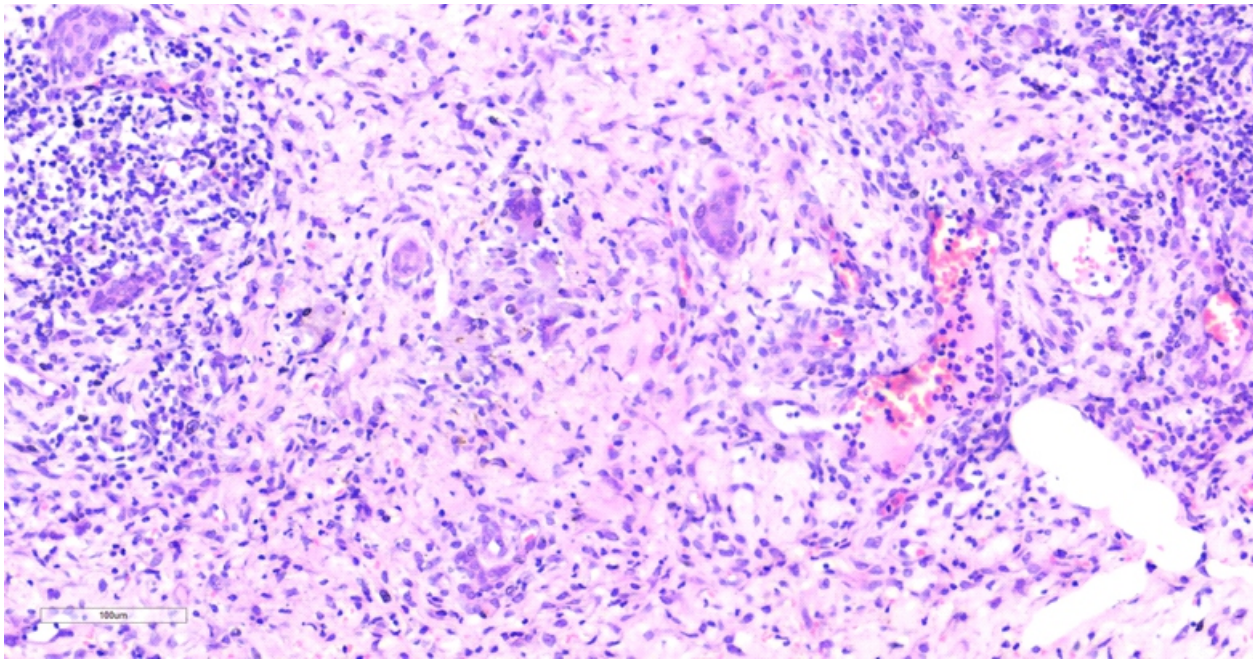

Figure 1: Micrograph showing mixed inflammatory cells composed of lymphocytes, plasma cells and neutrophils. Foreign body-type giant cells within the dermis at 200x magnification.

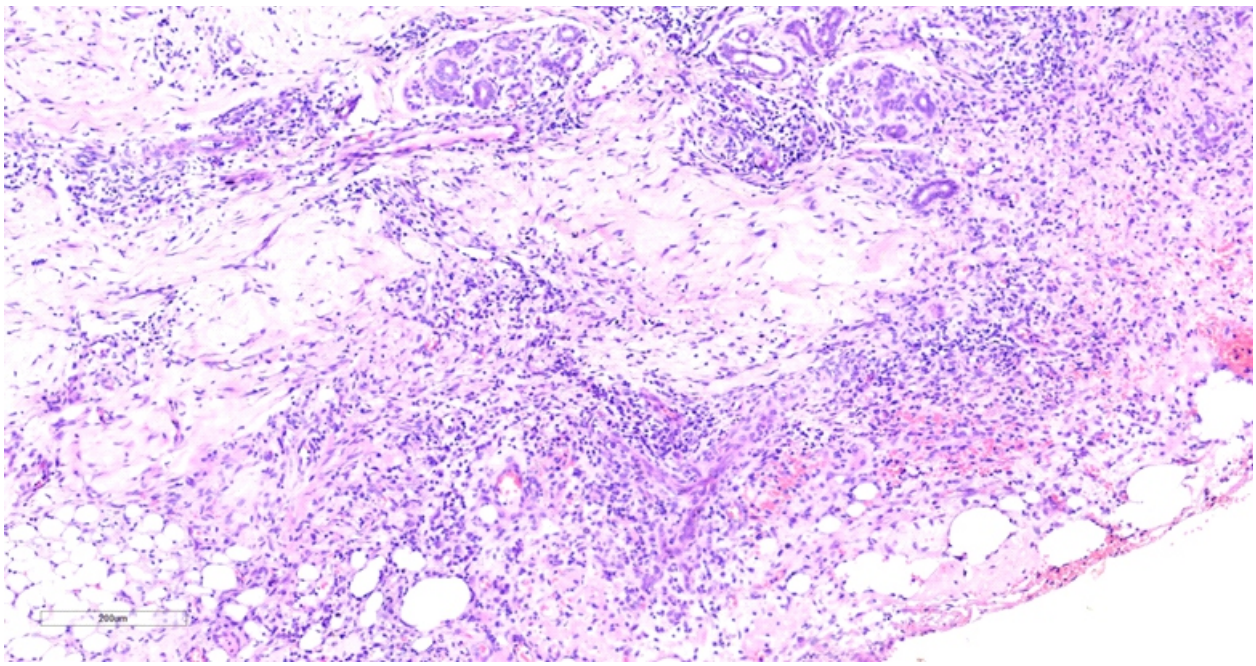

Figure 2: Micrograph showing mixed inflammatory cells around blood vessels and eccrine glands in the dermis and extending to the subcutaneous tissue at x 100 magnification

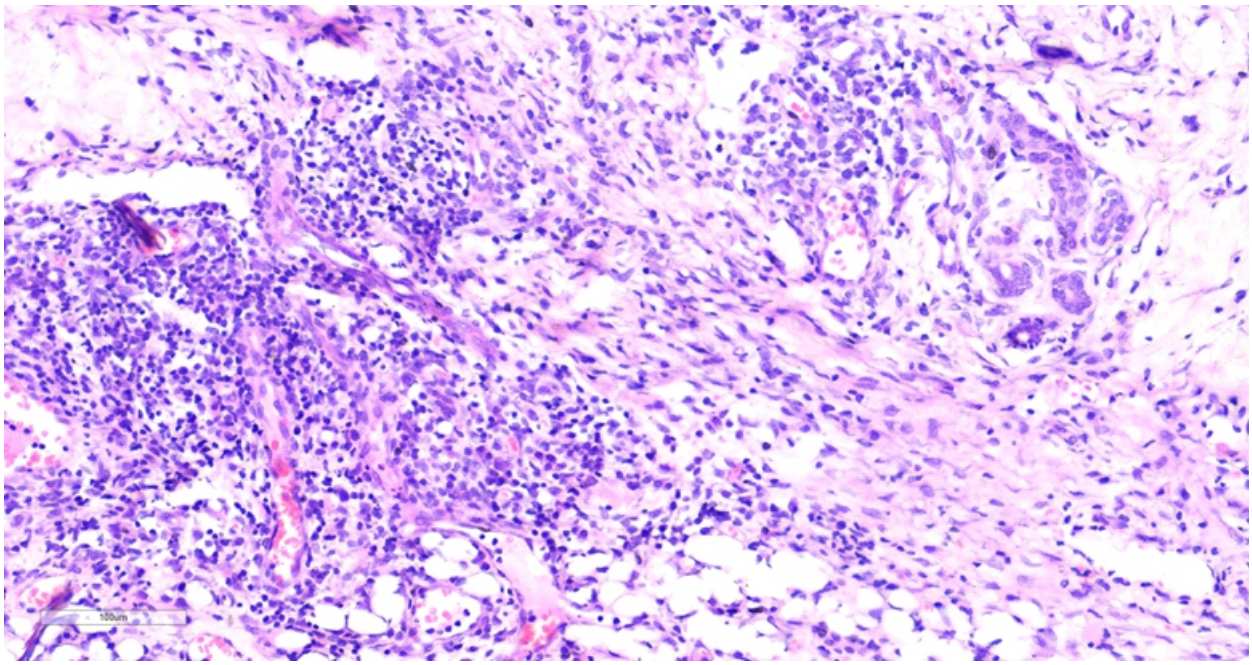

Figure 3: Micrograph showing mixed inflammatory cell infiltrate within the dermis and subcutaneous tissue at X 200 magnification

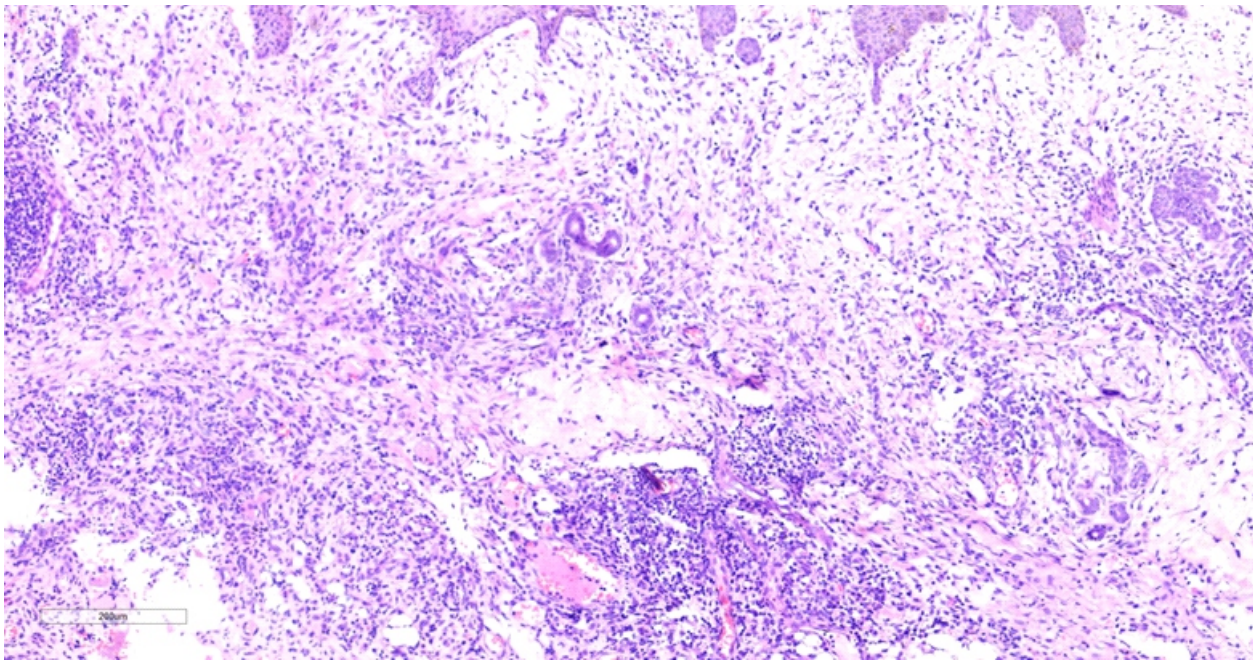

Figure 4: The Micrograph shows moderate to intense mixed inflammatory cell infiltrate within the dermis. The lower part of the rete pegs of the epidermis is seen at the top of the micrograph. X100magnification

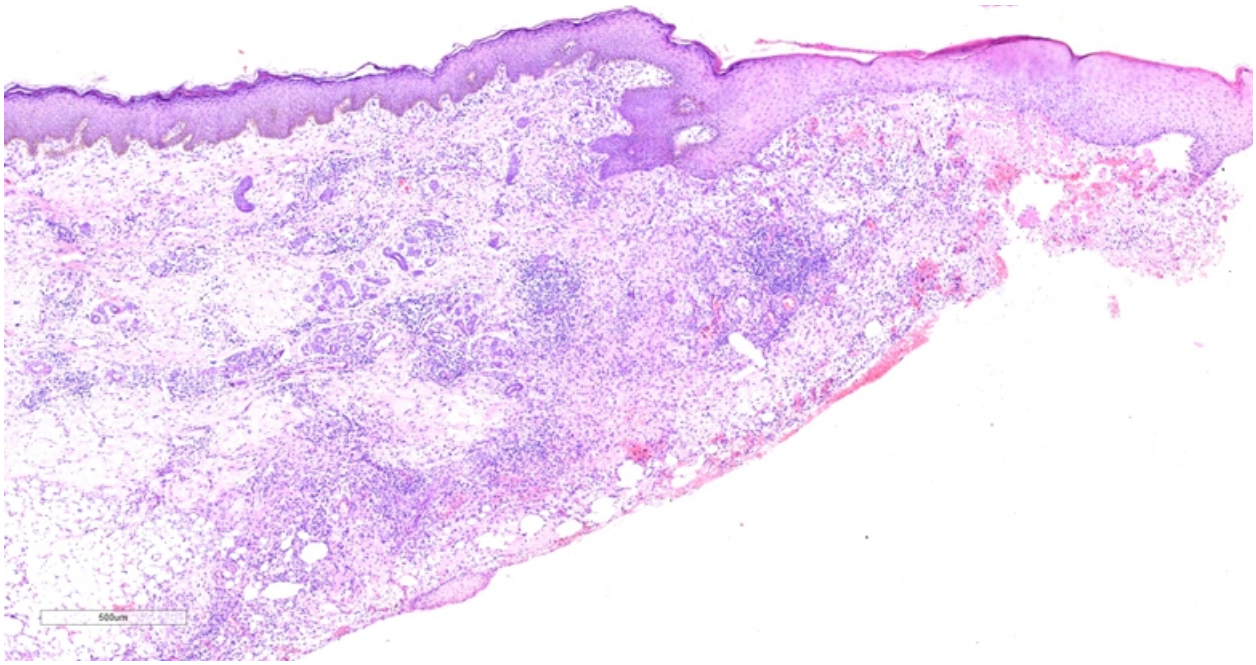

Figure 5: Micrograph showing the epidermis, dermis and subcutaneous tissue with acanthosis of the epidermis and moderate to intense mixed inflammatory cell infiltrate in the dermis and extending to the subcutaneous tissue at x 40 magnification

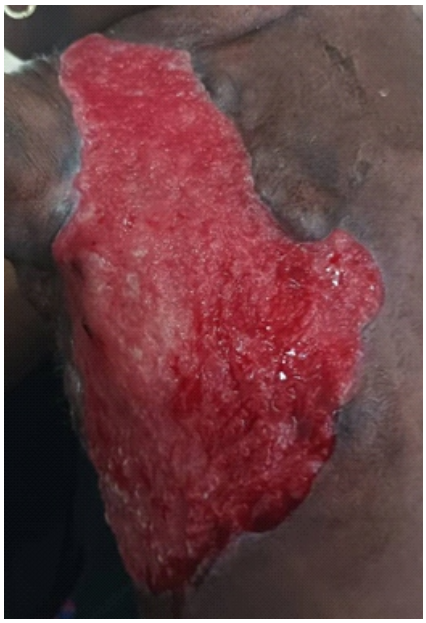

Figure 6: The ulcer at presentation. An ulcer extending from the left supra-scapular region to the posterolateral chest wall. The edges are undermined, and the inferior one-third is covered with necrotic tissue. The floor had granulation tissue and indurated skin.

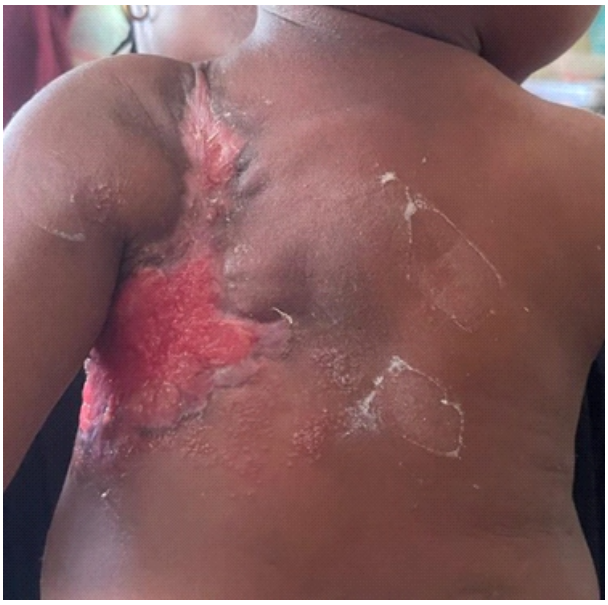

Figure 7: Four months post-discharge. The back ulcer is shrunken in size compared to the ulcer at presentation. However, there is an area of granulation tissue with overhanging edges in the inferolateral region of the scapular region.

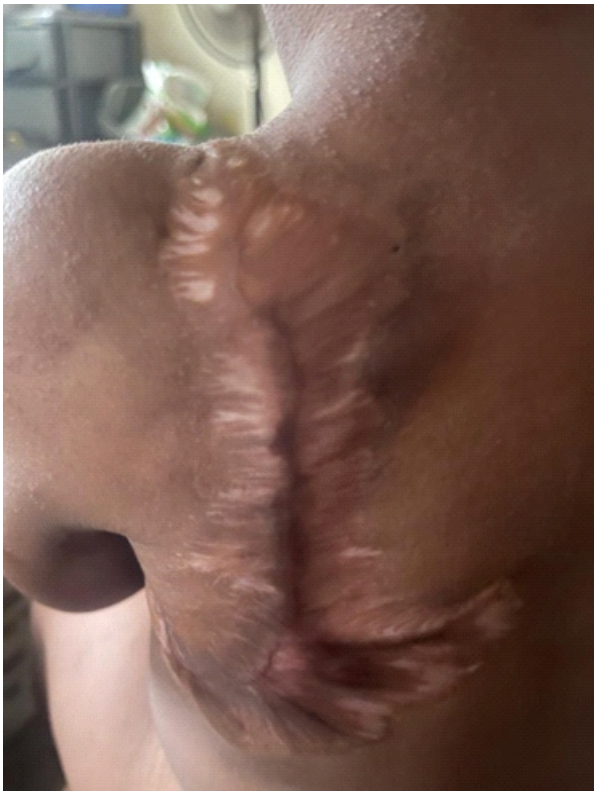

Figure 8: An extensive scar extending from the left suprascapular area to the subscapular region.