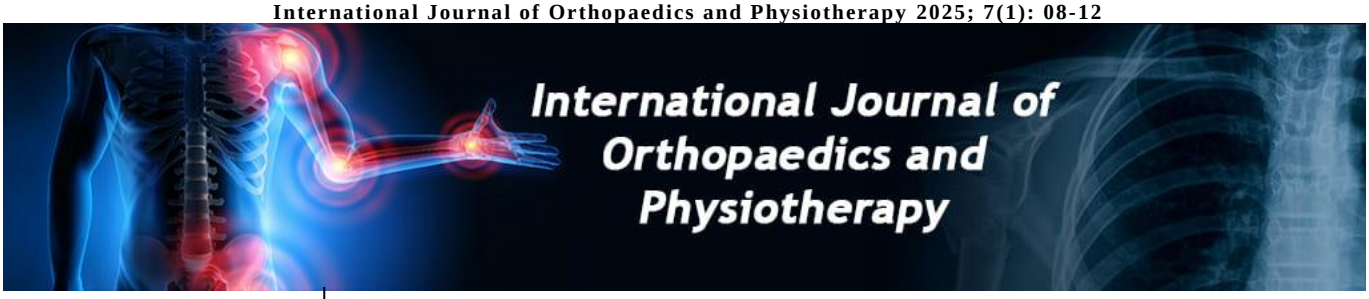

ISSN Print: 2664-8989
ISSN Online: 2664-8997
IJOP 2025; 7(1): 08-12
www.orthopedicsjournals.com
Received: 07-01-2025
Accepted: 12-02-2025

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Antiretroviral Therapy induced Charcot Neuroarthropathy, a descriptive case report

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DOI: https://www.doi.org/10.33545/26648989.2025.v7.i1a.31

Abstract
Charcot neuroarthropathy is a devastating joint condition that affects persons with neuropathy. With HIV/AIDS treatments prolonging the lives of these persons, it is likely that long-term sequelae of the disease will become more evident in the near future. Patients with this disease frequently develop peripheral neuropathy. A high index of suspicion must be raised in any patient with peripheral neuropathy of any cause and a red, hot, swollen, painful foot for Charcot neuroarthropathy to give these patients proper treatment to help prevent the devastating effects of Charcot Neuroarthropathy with its potential consequences including foot ulceration and amputation. We present a case of an individual with toxic polyneuropathy associated with antiretroviral therapy inducing Charcot Neuroarthropathy.

Keywords: Charcot Neuroarthropathy, HIV, Amputation, Antiretroviral Therapy

Introduction
HIV-sensory neuropathy associated with Charcot Neuroarthropathy is a debilitating complication in HIV patients with or without anti-retroviral treatment (ART). Common symptoms of HIV-SN include pain, decreased sensation, paresthesias, and dysesthesias in a symmetric stocking-glove distribution. While HIV-1 protein such as gp120 is implicated in HIV-SN (e.g. impaired large-diameter fiber), ART itself was recently shown to contribute to HIV-SN in HIV patients and impair nerve fiber conduction. Neuropathic arthropathy is a devastating joint condition that was first described by William Musgrave in 1703 as an arthralgia caused by venereal disease [1]. In 1868 Jean-Martin Charcot, a french neurologist, described a hypertrophic process of destructive arthritis in persons with syphilis and neuropathy (tabes dorsalis) [2]. The disease subsequently became known as Charcot joint disease or Charcot Neuroarthropathy. This condition is characterized by bony fragmentation, fractures, and subluxation/dislocation most typically in the midfoot, which frequently results in the characteristic rocker-bottom foot. This foot deformity can lead to bony prominences that can lead to plantar foot ulcerations, and in some cases osteomyelitis and amputation. Peripheral neuropathy has become the major neurological complication of HIV infection in the developed world [3]. There are two subtypes of peripheral neuropathy in persons with HIV: one type solely associated with HIV infection (primary HIV induced neuropathy) and the other type a toxic polyneuropathy associated with antiretroviral treatments [4]. Toxic polyneuropathy associated with antiretroviral treatments, is thought to occur from mitochondrial dysfunction from neurotoxicity of the antiretrovirals [5]. This neurotoxicity may be dose dependent and is estimated to occur in 15-30% of patients receiving these drugs [6]. Some researchers report that neuropathy from antiretroviral therapy may be more painful, rapidly progressing, and have a more abrupt onset as opposed to primary HIV induced neuropathy [7]. Highly active antiretroviral therapy (HAART) has been used for HIV infection, conferring lower viral loads, increased host immune function, and fewer opportunistic infections for HIV-positive patients.

Table 1: Eichenholz classification of Charcot neuroarthropathy with Shibata's modification

	Stage0 (prodromal period)	Stage1(development or fragmentation)	Stage2(coalescence)	Stage3 (reconstruction or reconstitution)
Clinical findings	-Loss of protective sensation -Erythema edema present	-Acutely erythematous and edematous with increased skin temperature -Pain may or may not be present -Ligamentous laxity	-Resolution of erythema, edema, increased skin temp	-Absence of inflammation -Stable examination
Radiographic findings	-Normal radiographs	-Osteopenia -Joint subluxations -Intra-articular fractures -Debris formation	-Resorption of debris -Healing of fractures -Sclerotic appearing bone	-Further repair and remodeling of bone -Reduced sclerosis. -Ankylosis of fragmented bone -Unstable fractures and dislocations may persist

Case Report

A 50-year old male was consulted to the orthopedic OPD for evaluation of infected, swollen and discolored right hallux. The patient denied a history of diabetes mellitus, syphilis (tabes dorsalis), cerebral palsy, leprosy, syringomyelia, spinal cord trauma and other CNS lesions but admitted to being HIV positive since 2001. He reported that he has been insensate for at least 10 years. He stated that, he is using Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets IP 50mg/300mg/300mg.

Physical examination revealed absent Achilles tendon reflexes bilaterally. Testing of ankle joint dorsiflexion, plantarflexion, inversion, eversion as well as the intrinsic musculature of the feet revealed a moderate decrease in strength bilaterally accompanied with complete sensory loss. No marked deformity was noted. Sharp/dull proprioception and temperature sensations were not tested. It should be noted that the patient also admitted experiencing subjective symptoms of peripheral neuropathy such as numbness, burning and tingling for which he has used gabapentin in the past.

Radiograph of the patient feet were obtained. The radiograph of the right hallux showed complete destructive distal and proximal phalanges accompanied with bony erosions as well as soft tissue swelling, demineralization of both phalanges. AP view of left hallux significantly showed hallux valgus deformity and bony erosions. Due to presence of suspected trauma it was decided to perform great toe amputation and the procedure was performed accurately. For further investigation specimen was sent to the pathology laboratory for histopathological analysis that revealed Extensive Benign Squamous Papillomatous Lesions- Toe with Koilocytic changes and associated Intense Acute and Chronic Inflammatory changes and Osteomyelitis.

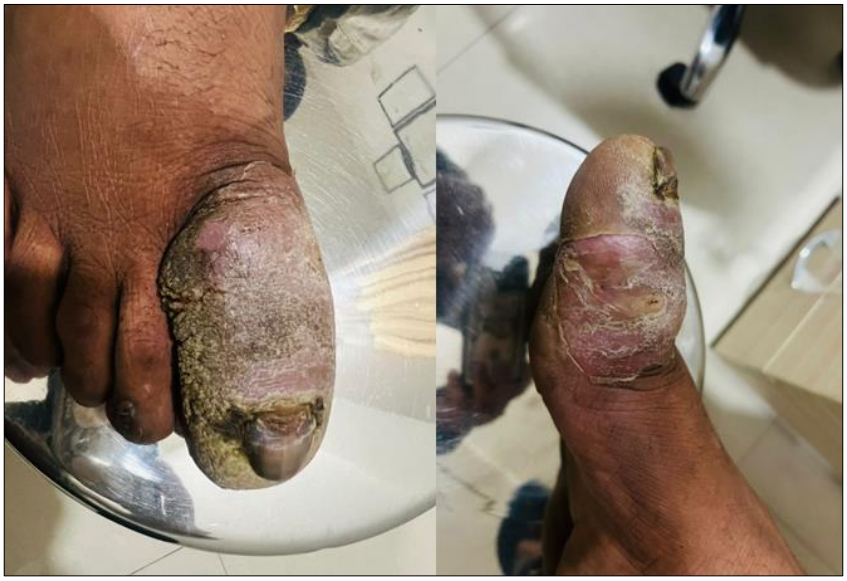


Fig 1: Clinical view of patient showing swollen, traumatic, discolored right hallux.

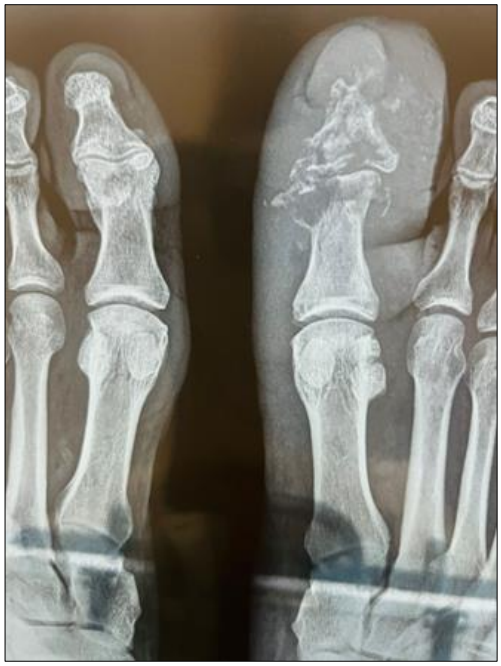
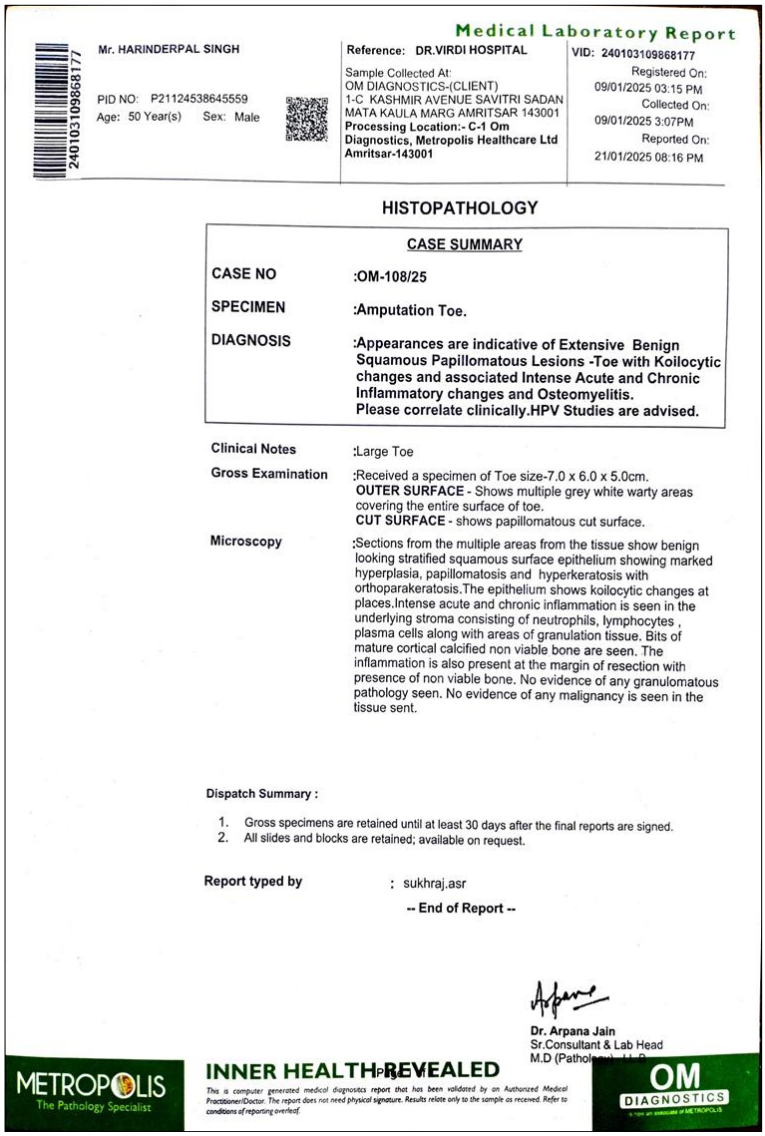


Fig 2: Radiograph: AP view depicting destructive and fragmented distal and proximal phalanges of right hallux and noted bony erosions of left hallux



Medical Laboratory Report

Mr. HARINDERPAL SINGH
PID NO: P21124538645559
Age: 50 Year(s) Sex: Male

Reference: DR.VIRDI HOSPITAL
Sample Collected At:
OM DIAGNOSTICS-(CLIENT)
1-C KASHMIR AVENUE SAVITRI SADAN MATA KAULA MARG AMRITSAR 143001
Processing Location:- C-1 Om Diagnostics, Metropolis Healthcare Ltd Amritsar-143001

VID: 240103109868177
Registered On: 09/01/2025 03:15 PM
Collected On: 09/01/2025 3:07PM
Reported On: 21/01/2025 08:16 PM

HISTOPATHOLOGY

CASE SUMMARY

CASE NO :OM-108/25
SPECIMEN :Amputation Toe.
DIAGNOSIS :Appearances are indicative of Extensive Benign Squamous Papillomatous Lesions -Toe with Koilocytic changes and associated Intense Acute and Chronic Inflammatory changes and Osteomyelitis. Please correlate clinically.HPV Studies are advised.

Clinical Notes :Large Toe
Gross Examination :Received a specimen of Toe size-7.0 x 6.0 x 5.0cm.
OUTER SURFACE - Shows multiple grey white warty areas covering the entire surface of toe.
CUT SURFACE - shows papillomatous cut surface.
Microscopy :Sections from the multiple areas from the tissue show benign looking stratified squamous surface epithelium showing marked hyperplasia, papillomatosis and hyperkeratosis with orthoparakeratosis.The epithelium shows koilocytic changes at places.Intense acute and chronic inflammation is seen in the underlying stroma consisting of neutrophils, lymphocytes , plasma cells along with areas of granulation tissue. Bits of mature cortical calcified non viable bone are seen. The inflammation is also present at the margin of resection with presence of non viable bone. No evidence of any granulomatous pathology seen. No evidence of any malignancy is seen in the tissue sent.

Dispatch Summary :
1. Gross specimens are retained until at least 30 days after the final reports are signed.
2. All slides and blocks are retained; available on request.

Report typed by : sukhraj.asr
-- End of Report --

Dr. Arpana Jain
Sr.Consultant & Lab Head
M.D (Patho

METROPOLIS The Pathology Specialist
INNER HEALTH REVEALED
This is computer generated medical diagnostics report that has been validated by an Authorized Medical Practitioner/Doctor. The report does not need physical signature. Results relate only to the sample as received. Refer to conditions of reporting overleaf.
OM DIAGNOSTICS

Fig 3: Histopathology revealed Extensive Squamous Papillomatous Lesions

Discussion

Over the past two decades, HIV infection has been transformed from a rapidly progressive fatal disease to a chronic illness. With the use of HAART and the prolonging of lives of patients with HIV/AIDS, more long-term complications of this disease will likely become more evident, Reports exist of rhabdomyolysis and myopathy in patients taking raltegravir and dolutegravir, so patients require monitoring for increases in creatine phosphokinase (CK). Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs) are known to cause mitochondrial toxicity that may present as peripheral neuropathy and lactic acidosis that can be fatal. Some NRTIs may also cause bone marrow suppression, anemia, and lipodystrophy. Tenofovir is typically well tolerated but may cause kidney injury or decreased bone mineral density. Other medications require consideration in patients with a history of renal impairment (eGFR less than 60 mL/min/1.73m) or osteoporosis. Discontinuation of tenofovir formulas will warrant clinical and laboratory monitoring of hepatic function because discontinuation may cause an acute exacerbation of HBV. Peripheral neuropathy is a well-known adverse effect associated with nucleoside reverse transcriptase inhibitors (NRTIs). Peripheral neuropathy is one of the most frequent side effect that occurs during therapy with some nucleoside reverse transcriptase inhibitors, mainly zalcitabine (ddC), didanosine (ddI) and stavudine (d4T). The study of Gordana Dragovic and Djordje Jevtovic reported that out of 112 patients, Peripheral neuropathy developed in 32 patients, who complained of neurological symptoms with manifestation of nerve conduction abnormalities, electric abnormalities, pain, and paresthesia with or without clinical abnormality with the lowest incidence rate (IR) for peripheral neuropathy of 0.13 per 100 person-years was found in the didanosine group while the highest IR was in the didanosine+stavudine group that was 0.18 per 100 person-years.

Moreover a study from Malawian cohort reported that 56% of patients have developed peripheral neuropathy while receiving stavudine Therapy. A sudden increase in redness, warmth, swelling in the limb of a patient with peripheral neuropathy should raise a high index of suspicion for Charcot neuroarthropathy. As patients with HIV/AIDS are surviving longer with HAART, it is likely that the incidence of patients with HIV neuropathy and Charcot neuroarthropathy will also increase. The case highlights the long term adverse effect of antiretroviral therapy inducing Charcot neuroarthropathy. Long-lasting immunosuppression in HIV-positive individuals placed on HAART may have exceeded a critical threshold for developing HPV-related disease, and cannot be reversed with treatment where HPV-specific immunity is not recovered completely after the immune system is restored with HAART. Meanwhile as per biomechanics of foot the great toe plays a crucial role in maintaining balance and providing stability while walking or running. This condition can have significant implications for mobility and functional abilities. Without the great toe, individuals may experience difficulties in walking, running, and maintaining proper posture. Balance may be compromised, leading to an increased risk of falls and injuries. Additionally, the loss of the great toe can affect overall structure and alignment of the foot, potentially causing long-term complications such as foot deformities and chronic pain. Rehabilitation restores functionality and improve quality of life. Physical therapy may also be recommended to strengthen the surrounding muscles and improve balance and coordination. We hope it will serve as a useful reminder to clinicians when dealing with such presentations.

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How to Cite This Article
Kaur P. Prospective study on the functional and radiological outcome of open reduction and plating for intraarticular fractures of the Calcaneum. International Journal of Orthopaedics and Physiotherapy. 2023;5 International Journal of Orthopaedics and Physiotherapy. 2025;7(1):08-12.