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Charcot Neuropathic Osteoarthropathy with Hypoalbuminemia: A Case Report

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Abstract: ***Charcot neuropathic osteoarthropathy (CN), commonly referred to as the Charcot foot is a condition affecting the bones, joints, and soft tissues of the foot and ankle, characterized by inflammation in the earliest phase. We report a case of Charcot Neuropathic Osteoarthropathy of the ankle joint with hypoalbuminemia presenting as complications from poorly controlled Diabetes Mellitus. Charcot neuropathic osteoarthropathy is a debilitating condition which may lead to postural instability, gait disorder and osteomyelitis. Early diagnosis and proper treatment is beneficial to reduce the risk of further complications.***

Keywords: charcot osteoneuroarthropathy, charcot foot, diabetes mellitus, hypoalbuminemia**.**

1. Introduction

Charcot neuropathic osteoarthropathy (CN), commonly referred to as the Charcot foot, is a condition affecting the bones, joints, and soft tissues of the foot and ankle, characterized by inflammation in the earliest phase [1].

The Charcot foot has been documented to occur as a consequence of various peripheral neuropathies; however, diabetic neuropathy has become the most common etiology. Interaction of numerous component factors such as diabetes, sensory-motor neuropathy, autonomic neuropathy, trauma, and metabolic abnormalities of bone, may result in an acute localized inflammation that can lead to varying degrees and patterns of bone destruction, subluxation, dislocation, and deformity [1]. The hallmark deformity in Charcot Foot is midfoot collapse, described as a **"**rocker-bottom**"** foot [1].

2. Case Illustration

A 57 year old female came to ER with worsening fatigue over the past 48 hours. She denied any history of fainting nor did she experience any symptoms of giddiness. There were no complaints of nausea or vomiting, but she told the ER physician she ate almost nothing for the last 2 days. Any symptoms of increased body temperature, productive cough, difficulty in breathing, weight loss were also denied.

The patient had been admitted to Hospital two times in the past due to non-healing wound on her left foot; with the last admission was 1 month before current ER visit. She did not experience any pain on her left foot, however she could not stand with both her feet properly, she needed assistance to be able to walk.

Significant past medical history was uncontrolled Diabetes Mellitus since more than 10 years, the patient received rapid acting insulin treatment (4 International Units, every 8 hours by subcutaneous injection) after the last admission.

On physical examination, vital signs were normal, lung, heart, and abdominal examinations were normal. Distal extremity findings were rocker-bottom left foot deformity (Figure 1) and deep ulcer extending to tarsal bones without gangrenous toes (Wagner IV). No edema, increased temperature compared to surrounding area, or pain was found (Eichenholtz Stage III).

Routine laboratory findings were as follows : Hemoglobin 8, 3 g/dL, White Blood Cells 15.500 /µL, Hematocrit 28%, Thrombocyte count 589.000 /µL, AST 11 U/L, ALT 28 U/L, BUN 62 mg/dL, Serum Creatinine 1, 0 mg/dL, Natrium 134 mmol/L, Potassium 3, 7 mmol/L, Serum Albumin 1, 3 g/dL, Clotting and bleeding time within normal limits. HbA1c level was 6, 2%, peripheral blood smear showed Anemia due to chronic disease.

The patient underwent several radiograph examinations including chest and left foot X-Ray. Chest X-Ray result was unremarkable, while evidence of PIP joint digit III, IV, V destruction with bone debris and subchondral sclerosis at Proximal phalanges IV, V, metatarsal bones II, IV, V of the left foot were visible from AP and Oblique projection (Figure 2 and 3). Pencil point deformity on 4^{th} and 5^{th} left digits alongside with destruction of distal Tibia and Fibula, all the evidence leading to Osteomyelitis radiographic appearance and Charcot Joint deformity of the left foot.

Working diagnosis for this patient were Type 2 Diabetes Mellitus, Charcot foot of the left ankle, Anemia due to chronic disease, and hypoalbuminemia

Surgical consultation was done and surgical debridement was planned. Intravenous Cefoperazone 1 gram q12h was given since day one, two Packed Red Cells were transfused, patient received 4 Units of subcutaneous Rapid Acting Insulin q12h initially, but stopped on the 4^{th} day of admission due to hypoglycemia, for correction of hypoalbuminemia, a total of 9 flasks of 20% human albumin were given before and after surgical debridement, increasing the serum albumin level to 2, 3 - 2, 5 g/dL throughout treatment duration.
Patient underwent surgical debridement successfully with no serious complications (figure 4) and discharged with scheduled follow-up appointment to internal medicine and

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surgical outpatient clinic.



Figure 1: Left foot, Rocker-Bottom Deformity



Figure 2: Left foot radiography, Oblique Projection



Figure 3: Left foot radiography, AP and Lateral Projection



Figure 4: Left foot after debridement, surgeon in charge made an opening at dorsal region for wound cleaning purposes

3. Pathophysiology

3.1. The Charcot Foot in Diabetes

In 1966, Eichenholtz published a staging of CN, based on clinical and radiographic findings [41] (Table 1 [41]).

The pathogenesis of Charcot foot is mediated through a process of uncontrolled inflammation in the foot. When a bone is fractured, the release of pro inflammatory cytokines such as tumor necrosis factor-a and interleukin-1b leads to increased expression of the polypeptide receptor activator of nuclear factor-k B ligand (RANKL) from local cell types [1].

RANKL triggers the synthesis of the nuclear transcription factor nuclear factor-kb (NF-kb), stimulating osteoclasts maturation. At the same time, NF-kb prompts the production of the glycopeptide Osteoprotegerin (OPG) from osteoblasts, working as an antagonist of RANKL [3]. OPG acts as a decoy receptor for RANKL, reducing osteoclastogenesis by binding to RANK receptor on osteoclasts [3], demonstrating its osteoprotective effect (Fig.5 [42]). Interleukin 1 (IL-1) promotes osteolysis through up-regulating RANK system and increases the proliferation of osteoclasts precursors [40].

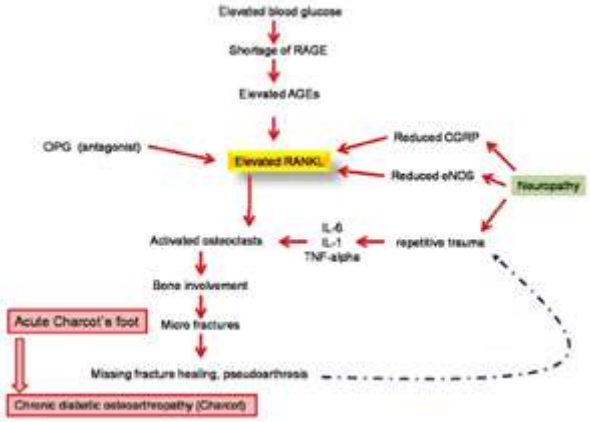


Figure 5: Patophysiology of Diabetic Osteoarthropathy, showing role of RANKL-OPG System [42]

In a person who develops acute Charcot foot, the loss of pain sensation from peripheral neuropathy allows for uninterrupted ambulation with repetitive trauma. Currently

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there are no reported cases of CN developing in the absence of neuropathy. It has been suggested that this repeated event generates continual production of pro inflammatory cytokines, RANKL, NF-kb, and osteoclasts, thus leads to continuing local osteolysis [2].

The diagnosis of Charcot foot is based on clinical and radiographic examinations. Diagnostic clinical findings include components of neurological, vascular, musculoskeletal, and radiographic abnormalities [3].

Cardinal signs of inflammation are crucial since inflammation plays a key role in the pathophysiology of CN. Edema, erythema, warm extremity on palpation, and more than a 2^0C difference in local temperature in comparison to the contralateral extremity are characteristic symptoms of active CN. Distinguishing CN from phlegmon with osteomyelitis or from acute gout [5] could be confusing, particularly since pain occurs in only 50% ofneuropathy cases [6].

Radiography is the primary modality of choice in confirming structural damages in CN, mostly due to its low cost and availability [1]. Changes on the X-ray are usually delayed and have low sensitivity [7].“Classic 5Ds” radiographic manifestations for the diagnosis of Charcot Neuropathic Osteoarthropathy are Distension of joints, Dislocation of joints and bones, Debris of bones, Deorganisation of joints and bones, and Density rise of bones [42].

A basic examination is an X-ray of the talus and the weight bearing foot in the anteroposterior and dorsoplantar lateral projection. During the initial stage the X-ray finding can be negative or only minor bone infractions and joint in congruence are present. In a developed stage fractures and subluxations or luxations are clearly observed. The X-ray finding depend s on the specific type of CN. In a typical rocker bottom deformity a plantar dislocation of the navicular andcuboid bone is visible. The calcaneal inclination angle is reduced and the talo-first metatarsal angle is broken in advanced stages [1].

3.2. Human Serum Albumin in Diabetic Population

Human serum albumin (HSA) is the most abundant plasma protein synthesized in the liver. HSA constitutes over half of the total plasma protein, a concentration of 35-50 g/L, in a healthy individual [8].

Albumin is the major soluble proteins constituent of the circulatory system, it possesses numerous physiological and pharmacological functions [4]. One of its main functions is to regulate plasma osmotic pressure between the blood and tissues and it is chiefly responsible for maintenance of blood pH. Another very important role of HSA is that it also functions as a transport molecule. This role is based on albumin, unequal ability to bind a variety of exogenous and endogenous compounds, such as metal cations, fatty acids, amino acids and diverse drug molecules [9]. HSA is also proposed to serve an antioxidant function in vascular compartment because of its scavenging of reactive oxygen and nitrogen species that are generated by basal aerobic metabolism as well as produced at increased rates during inflammation [10], [11].

A notable physiological function of serum albumin is the maintenance of the redox state of the extracellular milieu via the mercapt-nonmercapt conversion. Albumin is known to have a set of various beneficial functions, not limited to oncotic pressure regulation and binding and transport capacities for a wide variety of metabolites, including therapeutic drugs [12], [13]. For this reason, albumin plays an important role in drug disposition and efficacy [14]. However, the most important property of albumin is its major antioxidant activity in a circulatory system which constantly subjected to powerful oxidative stress [15]. *In vitro* oxidation of amino acid residues leads to protein degradation, aggregation and cross-linking [16].

In diabetes, the circulating albumin level is depressed. A 30-40% fall in the rate of albumin synthesis in uncontrolled diabetic patients as well as in perfused livers of diabetic can be restored by *in vivo* insulin; based on a marked decline in transcription of albumin mRNA. Albumin degradation and relative extra vascular distribution volume are decreased about 35% in diabetics [17].Other features of diabetes are the effects of non-enzymatic glycation of circulating albumin; two laboratories almost concurrently reported non-enzymatic glycation of serum albumin [18], [19].

Possible sources of oxidative stress in diabetes include auto-oxidation of glucose, shifts in redox balances, decreased tissue concentrations of low molecular weight antioxidants(for example, reduced glutathione and vitamin E) and impaired activities of antioxidant defence enzymes such as superoxide dismutase and catalase [20].

Elevated serum glucose level induced mitochondrial overproduction of ROS (Reactive Oxygen Species) [21] and abnormal activation of NAD(P)H oxidase [22], are thought to be the main sources of ROS in hyperglycemic condition, while persistent hyperglycemia also decrease radical scavenging by manganese superoxide dismutase [23] and the glutathione redox cycle. Hence, chronic oxidative stress is proposed to be the culprit of diabetic complications.

Table 1: Eichenholtz Classification for Charcot Neuropathic Osteoarthropathy [41]

Stage	Radiographic Finding	Clinical Finding
I Development	Osteopenia, osseus fragmentation, joint subluxation or dislocation	Swelling, erythema, warmth, ligamentous laxity
II Coalescence	Absorption of debris, sclerosis, fusion of larger fragments	Decreased warmth, decreased swelling, decreased erythema
III Reconstruction	Consolidation of deformity, fibrous ankylosis, rounding and smoothing of bone fragments	Absence of warmth, absence of swelling, absence of erythema, fixed deformity

The etiology of oxidative stress in diabetes arises from a number of mechanisms such as excessive oxygen radical production from auto-oxidation of glucose [24], glycated proteins and glycation of anti-oxidative enzymes, which limit their capacity to detoxify oxygen radicals [25]. Additionally, two other mechanisms have been suggested as

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being responsible for oxygen radicals generation in diabetes. First, high glucose levels might stimulate cytochrome P450-like activity by excessive nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) produced by glucose metabolism [26]. Second, ketosis, a hallmark of Type 1 Diabetes in particular, could increase oxygen radical production in diabetic patients [27].

Hypoalbuminemia is found to have correlation with ketosis in patient with Diabetes Mellitus. One study concluded the prevalency of ketonuria was 48% in hypoalbuminemic subjects compared to 30% in those with normoalbuminemia (OR: 2.15; 95% CI: 1.26–3.57; □ = 0.004).Serum albumin concentration was found to be negatively correlated with HbA1C (□ = −0.293, □< 0.001) [28].

Insulin is an important regulator of albumin synthesis. This has been corroborated by impaired liver production of albumin during insulin deficiency and a 10% increase in daily albumin synthesis after insulin infusion in diabetic individuals [29].In clinical practice, an association between hypo albuminemia and insulin deficiency may explain the increased mortalityrate in hyperglycemic individuals with low serum albumin concentration [30].

Diabetic patients with low serum albumin concentration were prone to ketosis, as evidenced by a higher prevalence of ketonuria and a trend towards increased ketonemia in this population. Therefore, hypo-albuminemia may be a useful marker of ketosis risk, which in turn suggests underlying insulin deficiency [28]. Serumalbumin concentration may indirectly show a diabetic individual's insulin reserve and thus serve as an indirect indicator of glycemic control [28]. Moreover, a negative correlation was observed between serum albumin concentration andHbA1C.Other studies involving diabetic outpatients have demonstrated similar findings [31], [32], serum albumin has been validated as a measure of disease severity in the Acute Physiology and Chronic Health Evaluation scoring system [33].

Hypoalbuminemia is linked with worse clinical outcomes, including increased complications and reduced short-term and longer-term survival rate in critically ill patients. A meta-analysis of 90 cohort studies that had evaluated hypoalbuminemia as a prognosticbio marker in acutely ill patients, each 10 g/l decrease in serum albumin concentration was associated with a 137% increase in the odds of death, an 89% increase in morbidity, and a 71% increase in length of hospital stay [34].

4. Treatment

4.1. Charcot Foot Management

Treatment options are available including conservative / medical treatment and surgical. The medical treatment of CN is aimed at offloading the foot, treating bone disease, and preventing further foot fractures. Treatment guidelines are largely based on professional opinion rather than the highest level of clinical evidence due to limited randomized-control trials [1].

Offloading at the acute active stage of the Charcot foot is the most important management strategy and could arrest the progression to deformity [1]. This method is based on immobilisation and the complete absence of weight bearing for the affected extremity in the active stage. There are various opinions concerning the type of immobilisation and the period of non weight bearing for the foot [39].

The most common immobilisation used is a total contact cast (TCC) changed three days after the initial application and then every week [1]. The recommended length of fixation varies from six weeks to three months followed by a change of orthosis [39]. Similarly, the recommended period without any weight bearing varies—starting from weight bearing during application of TCC to the usage of a wheelchair as a preventive means against overloading the other extremity [37]. It is recommended six to eight weeks of TCC and a wheelchair with subsequent change for individual orthosis fixing the affected segment and at the same time preventing tibial rotation, thus enabling only axial weight bearing (a so-called frame orthosis) [38].

Surgical approach for CN is generally been advised for resecting infected bone (osteomyelitis), removing bony prominences that could not be accommodated with therapeutic footwear or customorthoses, and repair deformities that could not be successfully accommodated with therapeutic footwear [1].

Surgery has generally been avoided during the active inflammatory stage because of the perceived risk of wound infection or mechanical failure of fixation [1]. Most case series have focused on reconstruction of the deformity by reduction and arthrodesis using standard methods of internal fixation [1].

Foot reconstruction, resection of bonyprominences, and major amputations are considered for the surgical treatment [39]. Major below-knee amputation is considered in severe peripheral vascular disease, severe bone destruction (including osteomyelitis), or in case of failed past surgical attempts [39]. Bony prominences resection might be useful isolated prominences, including conditions where orthotic or prosthetic measures failed to show favourable outcome, but in stable plantigrade foot [39]. Because of the poor bone quality, expert opinion has advised an extended period of nonweight bearing after surgery to account for the poor bone healing and inherent weakness of the underlying osseous structures [1].

Taking poor bone quality and the presence of neuropathy into considerations, in long-term healing, the so-called super construction principles for reconstructions have been established: (a) extending arthrodesis beyond the affected area on surrounding joints, (b) bone resection for mild shortening of the foot, enabling satisfactory repositioning of the deformity without exorbitant tension of soft tissues, hence helping prevent secondary ischemia, (c) utilization of the strongest possible implant which can be tolerated, and (d)introduction of an implant that can maximize mechanic stability [43].

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4.2. Hypoalbuminemia Correction

Nearly all studies of albumin administration actually combine a degree of resuscitation with a degree of supplementation/maintenance of serum albumin. As a resuscitation fluid, the main benefit of albumin will be from its impact on oncotic pressure, resulting in a temporary raise in intravascular volume. As supplementation, effects on oncotic pressure are also important, potentially reducing the risk of interstitial edema, but some of albumin's other actions, such as transport and antioxidant effects, may also become important [34].

In a pilot RCT of 100 hypoalbuminemic critically ill patients who were randomized either to receive 300 ml of 20% albumin solution on the first day and then 200 ml/day if the serum albumin concentration remained <30 g/dl or to receive no albumin, Dubois and colleagues reported that organ function(using Sequential Organ Failure Assessment score) improved better in the albumin-treated patients (P = 0.03) [30]; these patients also had a less positive fluid balance (P =0.04) [34].

The meta-analysis of nine prospective controlled trials on correcting hypoalbuminemia in acutely ill patients mentioned earlier suggested that complication rates were reduced inpatients who achieved serum albumin concentrations >30 g/l after albumin administration [35]. As a result, the ALBIOS study protocol stipulated that albumin administration should be titrated to maintain serum albumin ≥ 30g/l [36].

In our case, the patient was admitted with a stage III Charcot Neuropathic Osteoarthropathy, complicated by a low serum albumin level (1, 3g/dL). Taking the clinical findings and radiographic findings into consideration, a surgical reconstruction might be useful due to foot unstability (non plantigrade foot) [39]. Major amputations should only be done when other means of surgical attempts failed to achieve a mechanical stability, or if the foot becomes gangrenous. However, since our hospital has limited facility and instruments, arthrodesis or super construction was not possible, surgical debridement to prevent further infection was done instead. Such low serum albumin level may reflect insulin defiency and poorly controlled glucose level in this patient. Prolonged hyperglycemic condition may lead into oxidative stress, lowering serum albumin level even more, therefore increasing the risk of ketosis. Albumin administration was commenced since day 2 during admission. Nevertheless, the serum albumin level remains below 3g/dL, possibly due to low oral protein intake. A serum albumin level follow-up will likely be beneficial to decide the need of albumin supplementation, all to reduce the risk of mortality in this patient.

5. Conclusion

Charcot Neuropathic Osteoarthropathy is a condition resulting from uncontrolled inflammation commonly seen in patients with Diabetes Mellitus, presenting as complications resulting from poorly controlled blood glucose resulting in neuropathy, repeated trauma in extremity, and deformity in affected joint. This case reflects a Charcot Neuropathic Osteoarthropathy in adult female with poorly controlled Diabetes Mellitus, complicated by a very low level serum albumin. Even though it was not ideal, the available surgical treatment measure was done to prevent secondary infection, a condition that may progress to worse outcome.

Early recognition and diagnosis is beneficial to prevent further damage to already deformed or inflamed joint. Various treatment modalities are available; including medical and surgical methods, with offloading in affected joint is the most important initial treatment. Surgical manipulations on the affected limb may be considered according to clinical and radiographic findings, and it may produce better mechanical stability. Hypoalbuminemia may present as a feature from chronic inflammation or as a sign of insulin deficiency. Although no optimal serum albumin level especially in critical illness is defined, it is necessary to maintain serum albumin level within normal range in patient with potentially severe infection for better patient outcome.

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