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NON-TOXIGENIC DIPTHERIA SEPTICEMIA IN DIABETIC FOOT: - THE RETURNING REAPER OF DEATH

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ABSTRACT

Corynebacterium diphtheria is an assassin of the past with near total eradication in view of extensive vaccination around the world. Usually presenting as a respiratory ailment, its pathogenesis is aided by the toxaemia instead of bacteraemia. Nevertheless, over the last 20-30 years, cutaneous forms of diphtheria have been increasing in trend affecting the immunocompromised in the form of an opportunistic infection. Although bacteraemia is a rare occurrence, it has been found to cause systemic sepsis with multi-organ involvement in the form of encephalitis, cardiomyopathy, endocarditis and osteoarthritis. Herein we present a rare case of right diabetic foot with uncontrolled glycaemic state in systemic sepsis presenting with Corynebacterium diphtheria as the causative organism with significant colony count.

KEYWORDS: ***Corynebacterium diphtheria, toxaemia, MODS, tellurite agar, jet black colony***

INTRODUCTION

Corynebacterium diphtheria comes under the group of aerobic, gram-positive, non-motile, non-spore-forming, non–capsulated, non-fastidious, club-shaped, differentially staining bacteria with a majority of the genome in the commensals and contaminant type. The most common presentation of this pathogen is respiratory diphtheria which is an exotoxin mediated ailment with the pathognomonic formation of obstructing pseudomembranes in various respiratory domains. Since pancontinental vaccination programs were carried out for this deadly disease with apt success, the prevalence of non-toxigenic strains has increased over time as the major contributor to disease causation [1]. Although conventionally diphtheria is considered a disease of toxemia and not that of bacteremia, there has been an increased incidence of cutaneous forms of the ailment causing necrotic or punched-out ulcerations with aggravated local morbidity. Hereby we present one of the rare instances of right diabetic foot locally complicated by a Corynebacterium infection with possible systemic sepsis.

CASEPRESENTATION

A 49-year-old man with uncontrolled non-compliant type 2 diabetes for 10 years developed a spontaneous onset bleb on the right foot plantar aspect for 5 days. The lesion ruptured and started outpouring the purulent material associated with severe pain and multiple fever spikes for 3 days. He also had extensive scaly lesions of skin all over his body including the scalp with poor oral hygiene. In addition, the patient had a sudden onset diminution of vision for 4 days with the development of occasional exertional dyspnoea and palpitations

On examination, he was febrile, pale, lethargic, and dehydrated with a significant tachycardia of 124 beats per min and blood pressure of 128/88 mm of Hg. He had extensive scaly skin lesions all over the body with utmost prominence on extensors of limbs, periumbilical, and groin regions. On oral examination, he had scattered white patches on the tongue with developing blackish pigmentation on the hard palate towards the uvula. On local examination, pus was actively pouring out from the right foot lesion with surrounding erythema, warmth, and induration with features of ascending cellulitis, all peripheral pulses were felt and no evidence of peripheral vascular disease was found. There is the presence of bilateral inguinal lymphadenopathy which was tender, firm, and non-suppurative.

Routine investigations revealed elevated counts of 26410 with normal liver function tests. Renal function tests

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revealed acute kidney injury with a creatinine of 1.6. The chest X-ray of the patient didn't reveal any abnormalities. A local X-ray of the right foot was normal with no evidence of osteomyelitis.

Local venous USG revealed no evidence of deep venous thrombosis with any extension of pus collection into the right knee joint capsule. Colour Doppler of the right limb does. He was planned for surgical debridement where all the pus pockets were laid open and drained. The tissue bit and pus aspirate were sent for culture and sensitivity. Immediate microscopic examination of pus aspirate on gram stain revealed club-shaped gram-positive bacilli in a cuneiform arrangement. And the exudate culture grew Corynebacterium diphtheria in significant colony counts. On further investigation, Echocardiography was suggestive of diastolic failure with mild pericardial effusion and an ejection fraction of 25-30%. Ophthalmoscopic examination revealed severe compromised visual acuity with bilateral values of 1/60 and ocular studies revealed the presence of CSME. The patient was kept on strict glycemic control with an HbA1c of 14.3 with injectable and oral anti-hypoglycemics.

The patient was initially started on intravenous antibiotics with ceftriaxone and metronidazole and was later on started on clindamycin as the exudate grew Corynebacterium. The patient was taken up for serial debridement with the evacuation of multiple pus pockets which led to the amputation of the middle three toes. The ascending cellulitis responded to the clindamycin and there was a symptomatic improvement. Strict glycemic control was maintained as the patient was going into continuous hypoglycemia. Anti-fungals were started for a differential of visceral tinea corporis and showed improvement in the overall control. The patient symptomatically improved and was hence discharged.

DISCUSSION

INCIDENCE

Diphtheria is generally a non-invasive disease trademarked by toxic septicemia but not bacteremia. The global incidence of this disease has substantially dropped owing to the excellent vaccination drive done against this ailment. Nevertheless, the disease remains autochthonous in many countries as of now with subclinical presentations. WHO recorded a pulsating count of around 16600 cases in 2018 with multiple outbreaks in pancontinental domains. India also envisaged outbreaks of respiratory diphtheria from 2011-to 2016[2]. As a major causality of childhood mortality in the pre-vaccine era, the resurgence in the form of small cohorts has been deemed due to the failure of healthcare systems and vaccination programs.

Predominantly it affects children less than 15 years of age with the majority of them falling in the unimmunized and the immunocompromised category. Bearing a malefic case fatality of 5-17% in the unvaccinated population [3], the cutaneous form of this ailment has been seen to be cropping up one and again in different parts of the world. Usually, a part of the nasal commensals' bio genome, colonization of the Corynebacterium species has been seen in endemic and non-endemic populations and the pretense of the vaccination reduces the potential lethality of the diphtheria invasiveness. Humans are the only known natural host for Diphtheria which is responsible for a spectrum of respiratory, cutaneous, and invasive infections. The majority are the non-toxigenic strains inoculation resulting in ocular diphtheria, 21-day cardiomyopathy, infective endocarditis, septic arthritis, and septic shock [1]. For over a century, only 58 documented cases have been seen in India from 1893 to 2003 due to apt vaccination coverage of around 78% [4].

PATHOPHYSIOLOGY

Pathophysiology of this ailment is centered on the diphtheria toxin [DT] being encoded by the DT [tox] gene with a lysogenic integration of the beta-prophage into the genome which confers the lethality to the organism. The regulation is controlled by siderophore-mediated iron uptake and the expression of the Haem oxygenase which causes the toxin to have divalent ion activators causing iron levels in the patient-a major confluent factor. However, in the near-century, most of the reported invasive infections have been caused by the non-toxigenic strains which connote adaptive lethality in the molecular structuring in the form of adhesins, hemagglutinins, and surface-exposed non-fimbrial proteins. The vaccination made against the organism was aspired to reduce the toxin mediating organisms with a coverage of around 78% has created a pressured natural requisition of secondary virulent factors in the forms of transposons or plasmids [5].

CLINICAL FEATURES

The invasive spectrum of causality usually includes myocarditis which has been associated with the major mortality with this ailment [60-70%]. In addition, it also affects the peripheral nervous system and results in irreversible neuropathy manifesting as palatal palsy, limb weakness, and requirement for mechanical ventilation. Ophthalmic diphtheria may result in direct corneal penetration with sudden onset blindness. Cutaneous form results in punched-out ulcerations, and dermal ichthyosis, and in rare instances it might mimic eczemas which make the diagnosis even more difficult. Multiple in vitro studies in ongoing research has postulated a zipper-like mechanism for this invasiveness trend for this systemic syndrome but the exact pathomechanism at the cellular levels remains ambiguous [6].

As in our case, the possible hypothesis would be the entry of the organism through the breach of the epithelial integrity at the site of a diabetic foot ulcer-causing local dermal lesion. This was followed by septicemia causing ocular and cardiac ailments in the form of blindness and cardio topographic abnormalities.

DIAGNOSIS

The window period between the infection and the symptom development can typically range from 1-10 days with a mean duration of 2-5 days. In the case of asymptomatic clinical status, the patients are still infective for around 4 weeks [7]. Pragmatic risk factors for the ailment would include

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lack of vaccination, a compromised immune system, a history of atopic dermatitis [eczema], congested and/or unsanitary living conditions, and travel to endemic areas. Prompt diagnosis in the case of diphtheria can be made clinically by the presence of pathognomonic pseudomembranous disease or evidence of systemic septicemia in the form of multi-organ involvement and lymphadenopathy.

In the past, recognition of the organism was solely based on slide appearance, Albert stain findings, selective growth medium, and biochemical properties which have been expedited now because of automated methods like MALDI-TOF MS[5] with an accuracy of around 97-100% [6]. Toxin detection can be done with the aid of the Elek's gel precipitation test or PCR [5] for the detection of genomic identities like tox, dtxR, 16S ribosomal RNA [16S rRNA] RNA polymerase β subunit [rpoB], etc. In addition to this panel, bio typing can be done for speciation and MIC can be assessed using the VITEK-2 automated AST system. In our case, the patient's exudate culture grew a high count of diphtheria colony which was confirmed based on gram stain (Figure 1) and differential Albert stain (Figure 2). In addition, sub-culturation with potassium tellurite agar bore the characteristics of Jet black colonies that are diagnostic of Diphtheria (Figure 3). Moreover, the throat swab taken was negative for the same and hence the patient was ruled out as a perpetual carrier.

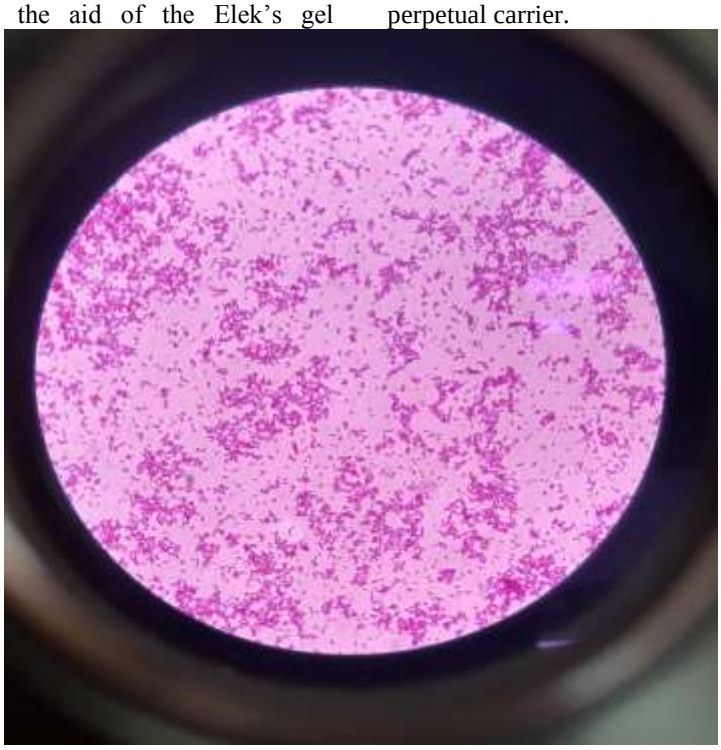

Figure 1: Gram stain showing gram positive bacilli arranged in V-in Y arrangements that resemble Chinese letters.

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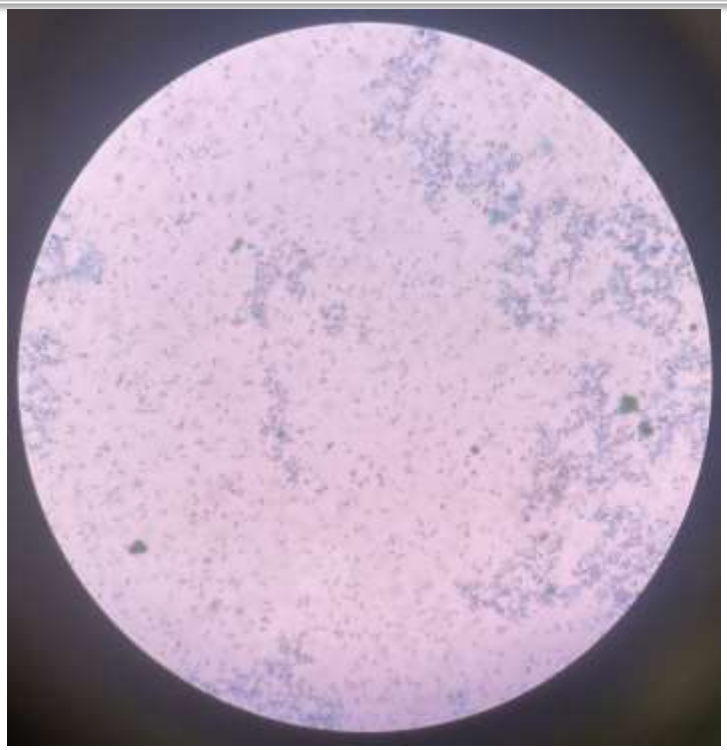

Figure 2: Albert stain showing metachromatic granules.

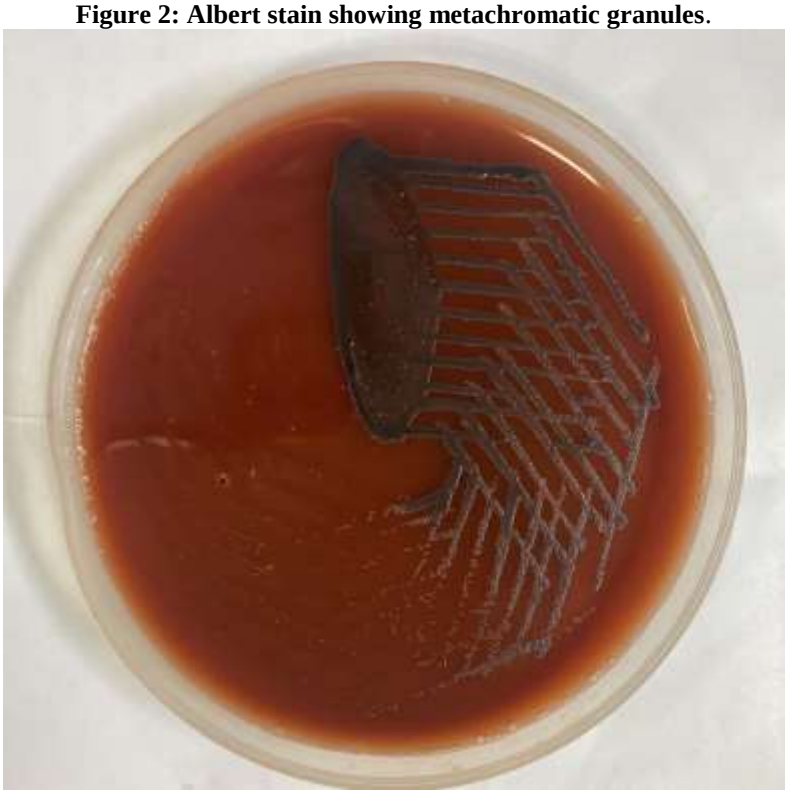

Figure 3: Potassium Tellurite agar showing Jet black colonies suggestive of Corynebacterium Diptheriaea.

TREATMENT

In general, the mainstay of treatment is the prompt administration of DAT which contains the equine antibodies against diphtheria toxin and therefore neutralizes the vapid progression. As per clinical guidelines, recommended antibiotics include oral penicillin V or erythromycin, parenteral benzyl penicillin, or erythromycin if the patient is unable to swallow. Azithromycin can be used as an alternative or even clindamycin has been seen to be preferred as it has been speculated to have anti-toxin activity in the form of a production blocker and antidote [8]. The patient should be isolated and a minimum duration of 2 weeks should be served

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to ensure complete eradication. In case of systemic complications, myocarditis can be dealt with carnitine supplementation or prophylaxis of erythromycin with streptomycin combination has been reported [9]. In case of the irreversible neuropathy, treatment is just conservative. In rare instances, the patient may encounter cardiorespiratory collapse and might require extraordinary measures in the form of intubation and mechanical ventilation, and nasogastric feeding for heightened survival [10]. All in all, increasing the vaccination coverage from the reported 78% to a complete 100% would confer total protection to the whole Indian population reducing the tenacity of carriers and any possible patients in the future.

In our case, the patient was started immediately on clindamycin with other adjunct high-end intravenous antibiotics to give broad-spectrum coverage. The patient was kept on strict input-output monitoring as he had initial features of systemic involvement. Systemic antifungals were also started because of extensive tinea involvement. Nutrition up-gradation and strict glycaemic control were done to maintain anabolic homeostasis with adequate fluid management. The patient gradually improved and was hence discharged with no further complications in the next 2 months of follow-up.

CONCLUSION

In a nutshell, although lethal, diphtheria is a preventable disease that can be mitigated in the form of vaccinations. Moreover, being a life-threatening ailment, it requires prompt detection, rapid treatment, and intensive care as and when required. With adequate coverage also, the disease still lurks in both the developed and the developing world, and increasing awareness about its intermittent resurgence needs to be addressed urgently. Clinicians must maintain a high degree of suspicion for rapid detection and affirmative assessment of non-toxigenic strains dominating the causality spectrum.

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