CASE REPORT

Cutaneous diphtheria complicated oncologic reconstruction surgery in osteosarcoma

Babak Abdolkarimi[1] | Ali Amanati[2] 🔵 | Gholamreza Bahoush Mehdiabadi[3]

[1]Pediatric Hematology-Oncology, Lorestan University of Medical Sciences, Khorramabad, Iran

[2]Professor Alborzi Clinical Microbiology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

[3]Pediatric Hematology-Oncology, Iran University of Medical Sciences, Tehran, Iran

Correspondence
Ali Amanati, Professor Alborzi Clinical Microbiology Research Center, Shiraz University of Medical Sciences, Shiraz 7193711351, Iran.
Email: ali_amanati_1356@yahoo.com

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Abstract

Diphtheria is an uncommon bacterial infection of the upper respiratory tract. We described a surgical site infection in a young adolescent female on maintenance chemotherapy. *Corynebacterium diphtheriae* was recovered from the wound, and she was treated with antibiotics and antitoxin. Cutaneous diphtheria should be considered in immunocompromised patients receiving chemotherapy.

KEYWORDS

Corynebacterium diphtheriae; infection, osteosarcoma, soft tissue; infection, surgical wound; tumor

1 | INTRODUCTION

Osteosarcoma (osteogenic sarcoma), as a primary malignant bone tumor, usually involves long bones of the extremities (more often the legs).[1] The incidence rates range between 4.6 and 6.8/year/million in a different race, with a 5-year overall survival rate of about 54%–68%.[2,3] The surgical site infections (SSIs) usually occur 4 weeks after surgery[4]; however, it may be delayed for about 5 months.[5] Chemotherapy, orthopedic surgical removal of the primary tumor (including limb-sparing excisions and partial or radical amputations),[6] with or without radiation therapy, is the standard treatment strategy for osteosarcoma.[7]

Post-operative infection in patients treated for osteosarcoma could affect the clinical response to chemotherapy and outcome. SSIs are usually associated with early failure of reconstructions with implants after bone tumor resection, which requires additional surgical interventions, long-term antibiotics treatment, delays in the treatment course, and infection-related mortality.[8] Like the non-oncologic patient, gram-positive bacteria such as *Staphylococcus aureus* and methicillin-Resistant *Staphylococcus aureus* (MRSA) are considered common causative agents; however, gram-negative bacteria, especially non-fermenters (including *Acinetobacter* species, and *Pseudomonas* species), are more prevalent pathogens in some reports.[9,10] Although *Corynebacterium diphtheriae* (*C. diphtheriae*) is a rare etiology for SSIs due to high vaccination rates,[11] oncologic patients may be susceptible to invasive forms of cutaneous diphtheria secondary to altered immune responses.[8] Cutaneous diphtheria is usually complicated pre-existing cutaneous lesions, including traumatic abrasions, surgical wounds, burns, insect bites, pyoderma, eczema, impetigo, and dermatitis, which causes a breach in the skin

surface[12,13]; however, it also could be appeared on previously healthy skin.[14] Cutaneous diphtheria rarely develops into an invasive disease in immunocompetent patients.[15] Here, we report a case of lower limb osteosarcoma complicated with post-surgical cutaneous diphtheria.

2 | CASE PRESENTATION

2.1 | Case history/examination

A 15-year-old female, a known case of right lower limb osteosarcoma with a history of reconstruction surgery after tumor resection, visited for SSI on April 01, 2021. She has a history of open reduction and internal fixation of the right tibia using a cadaveric bone graft in a rural setup elsewhere. During the 14th course of chemotherapy, she developed localized surgical site cellulitis, which progressed gradually to complete wound dehiscence after about 4 weeks. On admission, a large skin defect over the anterior aspect of the right tibia with an exposed black cadaveric bone (about 3 cm below the knee) was found (Figure 1). Despite primary surgical debridement, a progressive necrotic ulcer developed around the skin defect 3 weeks later.

2.2 | Differential diagnosis, investigations, and treatment

Wound culture and gram-stain from pus discharge, in addition to right tibia magnetic resonance imaging (MRI) with and without intravenous contrast injection performed for the investigation of osteomyelitis (Figure 2). C. diphtheriae was identified in the wound culture. Accordingly, intramuscular penicillin-G (1.2 million units/day), intravenous ciprofloxacin (500 mg/Q 12-h), and vancomycin (500 mg/Q 6-h) started. Horse serum diphtheria antitoxin (20,000 international units) infused

simultaneously during 4 h after skin sensitivity testing (Basredka method).[16] Diphtheria and tetanus (DT) vaccines also were injected. Throat and nasal swabs were taken from her family members. Chemoprophylaxis with erythromycin was also given to the family members.

The patient was kept on contact isolation until cultures from the throat, nose, and wound were negative. Evaluation of bone and subcutaneous tissue around the wound was done by ultrasonography and MRI. Osteomyelitis was ruled out by MRI, and the skin lesions improved, and repeat cultures did not have any growth of C. diphtheriae after about 2 weeks.

2.3 | Outcome and follow-up

Cadaveric bone was replaced with a metal prosthesis (Figure 3) after clinical improvement about 6 weeks after anti-diphtheria treatment (Figure 4). The patient's chemotherapy continued successfully without further complications.

3 | DISCUSSION

Surgical site infections may be a devastating complication with a substantial impact on morbidity and mortality. Systemic antibiotic therapy is an integral part of the treatment strategy intended to eradicate the infection; however, immunosuppression situations such as chemotherapy or atypical microbial and uncommon pathogens such as C. diphtheriae could affect the SSI clinical course outcome. The risk of SSI could be predicted using the musculoskeletal oncological surgery invasiveness (MOSI) index. The MOSI index could be predicted successfully by considering operation duration, blood loss, preoperative chemotherapy, and artificial materials.[17]

Surgical site infections could be classified as early, delayed, and late based on the time interval between surgery

FIGURE 1 Inflamed, necrotic lesion on the anterior aspect of the right tibia

FIGURE 2   Sagittal T_1WI, T_2WI, and fat-sat T_2WI show low-signal T_1WI and high heterogeneity signal T_2WI of the right tibia proximal metaphysis extend and involve epiphysis associated with periosteal reaction and adjacent soft tissue signal changes. On post-contrast images, heterogeneity enhancement at proximal metaphysis and adjacent soft tissue is defined. The findings were suggestive of the right tibia proximal metaphysis osteosarcoma
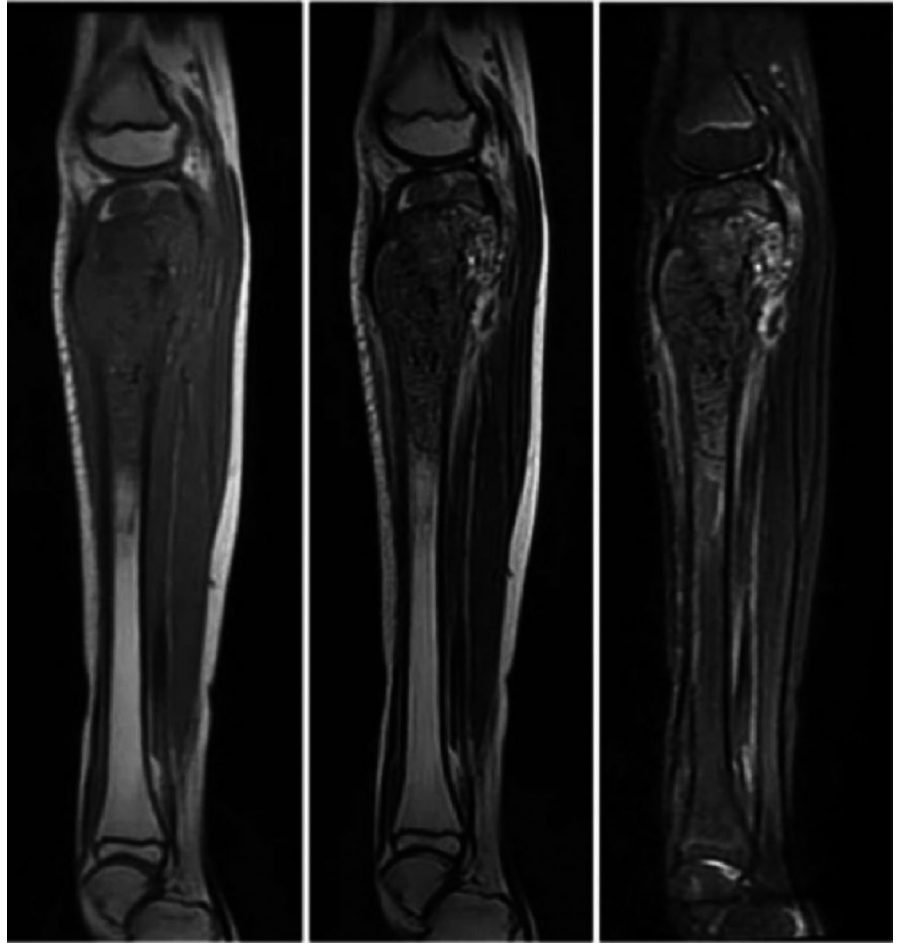
FIGURE 3   Plain X-ray of the right tibia before and successful cadaveric bone replacement with metal prosthesis 6 weeks after antibiotic therapy

and infection. The different treatment strategies may be considered according to the clinical manifestation, laboratory examination, and radiological findings described by Lin, T et al.[4] The recommended treatment approaches for SSIs are systemic antibiotics, debridement, bone-cement spacer placement, two-stage prosthesis revision, bone transposition, combined implantation of cement and prosthesis, and partial or radical amputation after limb salvage surgery for patients with osteosarcoma.[4] Non-infectious complications such as non-union of allograft
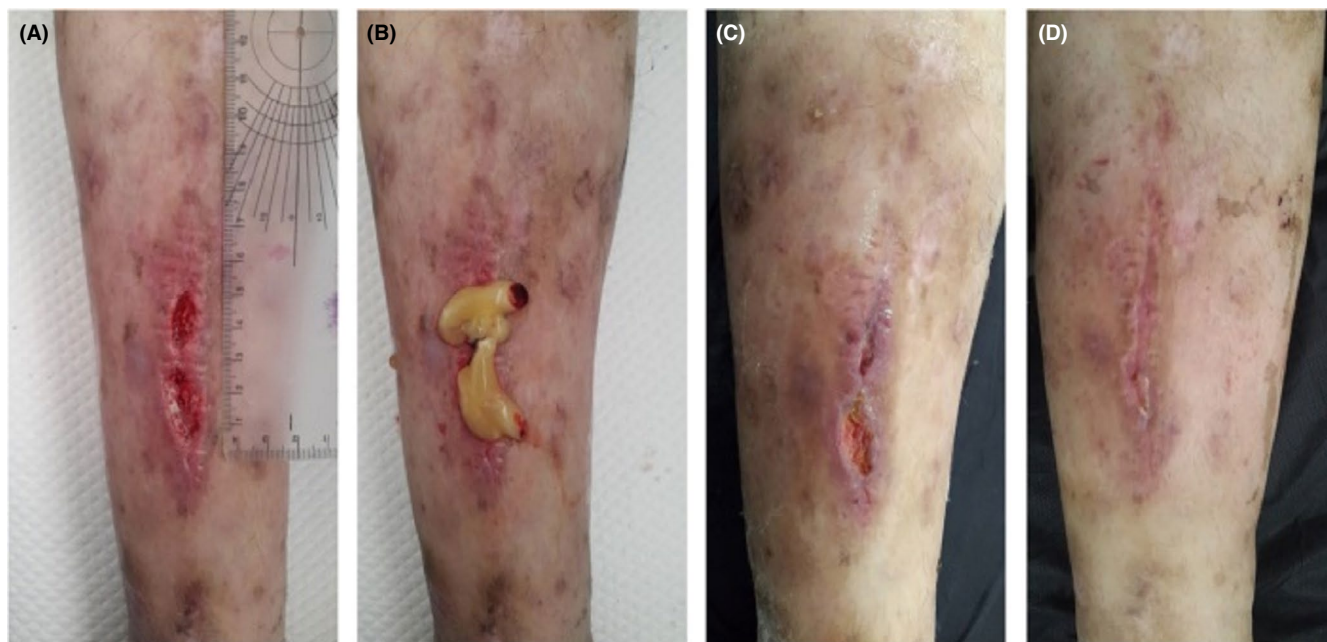
FIGURE 4 (a-d) Wound healing process during the treatment course with about 2 weeks intervals

bone, prosthesis looseness, and local recurrence of the primary tumor or secondary malignant lesions should be considered in the differential diagnosis of SSIs.[18]

Invasive diphtheria infections have declined in developed and developing countries due to effective immunization programs.[19] Most of the reported cutaneous diphtheria is post-traumatic with sure primary immunization.[12] Cutaneous diphtheria is frequently reported in the tropics and subtropical regions. The typical manifestation of cutaneous diphtheria is chronic non-healing ulcers developing over weeks to months.[20] The lesions usually begin as vesicles or pustules, progressing to multiple punched-out lesions covered with a pseudomembrane. The common sites include the lower legs, feet, and hands.[21] Bacterial coinfection, most notably with *S. aureus* and *S. pyogenes*, is very common, which might mask the *Corynebacterium* spp., leading to delay in diagnosing cutaneous diphtheria similar to this case.[22] Wollina et al. reported that a 91-year-old female patient presented a 2-year history of an enlarging forehead lesion with exudation and bleeding, suspicious of squamous cell carcinoma.[23] Histology ruled out the suspected diagnosis; however, the microbiology culture and polymerase chain reaction assay identified non-toxic *C. diphtheriae*.[23] Kolios reported two cases with cutaneous diphtheria infection presenting with disseminated skin nodules and ulceration.[24] Also, cutaneous diphtheria could be mimicking pyoderma gangrenosum.[25] These lesions usually occur in immunocompromised patients.[26] Infection with *Corynebacterium ulcerans* perfectly mimic cutaneous diphtheria, and consequently, all *Corynebacterium* spp. should be identified to the species level and possibly analyzed for toxin production. It is highly recommended to send the cultures to a reference laboratory to confirm species and toxigenicity.[25] In the face of waning herd immunity over time, the cutaneous carriage of this pathogen could risk the occurrence of outbreaks in close clusters.[12] Predisposing factors the spread include poverty, overcrowding, poor hygiene, frequent traumatization of unprotected skin, and insect bites.[27]

Clinical suspicion of cutaneous diphtheria depends on morphological and epidemiological features, and definitive diagnosis depends on culturing the organism. In this case, the wound culture was polymicrobial, including *S. aureus*, *S. pyogenes*, and *Corynebacterium* spp. Penicillin or erythromycin is usually considered to be the first-line treatment of nontoxigenic cutaneous diphtheria.[28]

In addition to culture, MALDI-TOF MS (matrix-assisted laser desorption/ionization-time of flight mass spectrometry), Elek immunoprecipitation test, and real-time polymerase chain reaction (RT-PCR) for *tox* gene could be used to confirm the diagnosis.[29] Enzyme Immunoassay (EIA), using monoclonal antibody to fragment A of the exotoxin, is highly accurate and could improve diagnosis in false-negative the Elek and RT-PCR test.[30] Since the differential diagnosis of malignant skin lesions such as squamous cell carcinoma (SCC) should be considered for non-healing chronic ulcers, the histopathologic examination is encouraged for definite diagnosis and rule outing non-infectious etiologies.

Once cutaneous diphtheria is suspected, specific antitoxin should be administered promptly (within the first

48 h of symptoms) to neutralize free toxin to reduce mortality and prevent disease progression.[31]

C. diphtheriae is susceptible to a wide range of antimicrobials, including β-lactams, erythromycin, ciprofloxacin, tetracycline, chloramphenicol, gentamicin, trimethoprim-sulfamethoxazole, and rifampin. However, penicillin and erythromycin are the drugs of choice when there is no contraindication (history of hypersensitivity reactions and pre-existing cardiac arrhythmia), and there is no concern regarding penicillin and macrolide-resistant strains.[32,33]

Active immunization against diphtheria should be undertaken during convalescence from diphtheria because the disease does not necessarily confer immunity.[34]

In a study conducted among patients with osteosarcoma, chronic localized infections (but not systemic infection) were determined in 4.8% of patients. The proximal tibia was reported as the common SSI location in infected patients. More amputations were necessitated in infected patients due to uncontrolled infection.[35]

Diphtheria is a vaccine-preventable disease; however, many pediatric cancer patients are not current with their vaccines or may not have protective serum concentrations of antibodies against diphtheria despite previous routine immunization.[36,37] All cancer patients should be encouraged to update their immunization schedules based on age, vaccination history, and chemotherapy status.[38,39]

4 | CONCLUSION

To conclude, cutaneous diphtheria could be missed due to nonspecific clinical presentation. So, any chronic non-healing ulcer should arouse the suspicion of rare etiologies such as cutaneous diphtheria. Skin ulcers not responding to conventional antibiotic treatment should be investigated for uncommon organisms such as *C. diphtheriae*. Finally, it is strongly recommended that all pediatric cancer patients be current with DT vaccines, especially those with solid tumors.

AUTHOR CONTRIBUTIONS
BA involved in study concept and design. BA, AA, and NHM involved in drafting the manuscript. BA and AA involved in critical revision of the manuscript for valuable intellectual content.

ETHICAL APPROVAL
The ethics committee approved the study protocol at Lorestan University of Medical Sciences. The study protocol conformed to the ethical guidelines of the 1975 Helsinki Declaration.

CONSENT
We have written informed consent obtained from the child's parents after the explanation of the report.

DATA AVAILABILITY STATEMENT
All data generated or analyzed during this study are included in this published article.

ORCID
Ali Amanati https://orcid.org/0000-0001-9173-2853

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