

1 **Skin infection by *Corynebacterium diphtheriae* and *Streptococcus pyogenes*: an**
2 **unusual association**

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23 **Keywords**

24 Skin infection

25 Co-infection

26 Travelers

27 Diphtheria

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29 **Palabras Claves**

30 Infección Cutánea

31 Co-infección

32 Viajeros

33 Difteria

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45 *Dear Editor*

46 *Corynebacterium diphtheriae* is a noncapsulated, club-shaped facultative
47 anaerobic Gram-positive bacilli. Opportunistic or cutaneous co-infection caused by
48 this microorganism, especially non-toxigenic strains, has become important in
49 travellers [1]. The skin lesions are generally ulcerative with a torpid and nonspecific
50 evolution, which usually appear after a bite or minor trauma [2]. These infections
51 have a low incidence [3], which is why this microorganism is often not considered as
52 the first etiological diagnosis, so in many of the cases can be unnoticed. A study of
53 two cases of infection by *C. diphtheriae* and *Streptococcus pyogenes* was
54 performed. The microorganisms were isolated from swabs of wound exudates and
55 were identified by mass spectrometry (MALDI-TOF MS, Bruker©) and were
56 confirmed with the amplification and sequencing of the 16S rRNA gene. Diphtheria
57 toxin was performed by PCR [4].

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59 **Case 1**

60 A 28-year-old man with a recent travel history to Philippines attended for an
61 incised wound on the back of the left foot of 15 days of evolution, with signs of
62 cellulitis. The case was oriented as cellulitis and started intravenous treatment with
63 ceftriaxone 1g for 5 days and linezolid 600 mg for 3 days, after that the treatment
64 were change to oral azithromycin for one week. In culture, *S. pyogenes* and
65 *C.diphtheriae* were isolated. Antibiotic susceptibility testing (AST) was performed
66 and both microorganisms were susceptible to penicillin and erythromycin. Diphtheria
67 toxin was negative. The patients evolving favourably and subsequently decided to
68 administer a booster of diphtheria vaccine.

69 **Case 2**

70 A 32-year-old man, with a recent travel history to Southeast Asia for 2
71 months. Attended for a traumatic wound in the heel and erythematous and crusted
72 lesions of 2-3 cm in the right leg. Physical examination reveals a peripheral pustule
73 with inflammation of an inguinal node without signs of cellulitis in the peripheral skin.
74 The case was oriented as skin infection by biting of overinfected arthropods.
75 Serology was requested for Dengue, Chikungunya and culture. *S. pyogenes* and
76 *C.diphtheriae* were isolated. AST was performed and both microorganisms were
77 susceptible to penicillin and erythromycin. Serologies for Dengue and Chikungunya
78 were negative. Treatment with oral erythromycin 500 mg every six hour for 14 days
79 was started, contact study was carried out and reinforcement of the diphtheria
80 vaccine was administered. Diphtheria toxin was negative; the patient was evaluated
81 for 2 weeks, showing resolution of both traumatic wound and satellite lesions.

82 Cutaneous infection by *C. diphtheriae* is uncommon, tends to be of torpid
83 evolution and produce nonspecific lesions, so clinical suspicion is low. In recent
84 years this infection has been linked mainly with travellers to endemic areas including
85 Southeast Asia, some countries such as Cambodia, India, Indonesia, Malaysia, New
86 Guinea, Philippines, Thailand, Brazil and others [5] [6]. A study in Vancouver reports
87 37 cases of cutaneous diphtheria for non-toxigenic strains [8] which demonstrates
88 the high distribution of these strains. In Europe, the data was based mainly on
89 patients with a recent travel history [7], except in some Eastern European countries,
90 which are considered an endemics areas [2].

91 Other risk factors for the infection included population with low
92 socioeconomic resources, alcohol abuse, drugs, HIV infection, hepatitis, cirrhosis,
93 [8] [3]. Identification of Gram positive bacilli colonies may be considered in some
94 cases as non-pathogenic microbiota by the genus of *Corynebacterium*, and

95 presence of *C.diphtheriae* may be misidentified. In these cases we can apply the
96 MALDI-TOF MS, it's an easy technique and effective cost [2].

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98 Co-infection is a common clinical presentation. *S. pyogenes*, *Staphylococcus*
99 *aureus*, methicillin-resistant *S. aureus*, *Arcanobacterium haemolyticum* and species
100 of coagulase-negative staphylococci [8] are the more frequently association. In 2016
101 a third case of cutaneous diphtheria was also reported where colonies of *A.*
102 *haemolyticum* were also isolated in a 50-year-old patient with a recent travel history
103 to Guinea Bissau and mimicking pyoderma gangrenosum [9].

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105 Benzylpenicillin and macrolides were considered first line treatment in cases
106 of diphtheria, but in 2015 the first case of *C. diphtheriae* resistant to penicillin was
107 published in a cutaneous infection by a non-toxicogenic strain in the United Kingdom
108 [10] However, benzylpenicilin continue to be the first option for treatment in case of
109 diphtheria. In our cases the both strains and both *S.pyogenes* were susceptible to
110 penicillin and erythromycin. In Spain in 2015, the first case of diphtheria was
111 reported since 1986, in a 6-year-old unvaccinated child, who progressed
112 unfavourably and died after one month of medical treatment. However, in relation to
113 cutaneous diphtheria, no previous reports have been found.

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115 The number of travellers continues to increase in Spain and Europe, which
116 can increase the incidence of these mixed infections. The recent travel history
117 should be recognized as an epidemiological data to highlight not only the clinical
118 diagnosis but also the microbiological one.

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