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Tropical ulcers: the first imported cases and review of the literature

Background: A tropical ulcer is a bacterial necrotizing disease of the skin, with an acute or chronic clinical course, caused by anaerobic bacteria, notably *Fusobacteria* spp. *Objectives*: We present six Italian tourists who acquired tropical ulcers in tropical and subtropical countries. *Materials & Methods*: Four males and two females acquired a skin ulcer during trips to Brazil, Malaysia, Fiji Islands, Zambia, Tanzania and India. In all patients, medical history, physical and dermatological examination, laboratory tests, bacteriological examinations and biopsy were carried out. *Results*: All patients were in good general health. All patients stated that the ulcer was caused by a trauma. No fever was reported. Neither lymphangitis nor lymphadenopathy were detected. The ulcer was located on a forearm in one patient, on a leg in two and on an ankle in three patients. All ulcers were malodorous and painful. Laboratory tests revealed mild leucocytosis and a mild increase in erythrocyte sedimentation rate and C-reactive protein. Results of bacteriological examinations revealed the presence of *Fusobacterium* spp. in five patients. Other bacteria were identified in all patients. Histopathological examination showed: necrosis of the epidermis and dermis; vascular dilatation; oedema in the dermis; massive infiltration with neutrophils, lymphocytes and histiocytes; and fragmented collagen bundles. No signs of vasculitis were observed. All patients were successfully treated with oral metronidazole (1 g/day for two weeks) and, according to antibiograms, with different systemic antibiotics. *Conclusion*: To our knowledge, these are the first cases of tropical ulcers reported in Western tourists

Key words: anaerobic bacteria, *Fusobacteria* spp., *Fusobacterium ulcerans*, tropical ulcer

Tropical ulcer (TU), or tropical phagedenic ulcer, is a bacterial necrotizing disease of the skin, with an acute or chronic clinical course, caused by anaerobic bacteria, notably fusobacteria.
To our knowledge, no cases of TU in Western tourists have been reported so far. In the period 2007-2019, we observed six Italian tourists who acquired the infection in different tropical and subtropical countries. A review of the literature from 1950 is included [1-77].

Patients and methods

The cases are comprised of four males and two females, with an age ranging from 31 to 57 years (mean age: 42.1 years), who acquired a skin ulcer during trips to Brazil, Malaysia, Fiji Islands, Zambia, Tanzania and India. All patients were tourists who went trekking in a savannah, forest or jungle.
All patients sought consultation from 10 days to six weeks after the appearance of the ulcer. According to medical history, the ulcer was preceded by a painful swelling; within a few days, it was followed by the appearance of a blister or a pustule. All patients had been previously, although unsuccessfully, treated at other centres with oral amoxicillin (two patients), ciprofloxacin (two patients), doxycycline (one patient), levofloxacin (one patient), topical gentamicin (five patients), and fusidic acid (one patient).
In all patients, past medical history, physical and dermatological examination, laboratory tests, bacteriological and mycological examinations, and biopsy for histopathological and direct immunofluorescence examinations were carried out. Arterial and venous colour Doppler ultrasound of the lower limbs was performed in all patients.

Results

All patients stated that the ulcer was caused by a trauma. All patients were in good general health. No fever was reported. Neither lymphangitis nor lymphadenopathy were detected. The ulcer was located on a forearm in one patient, on a leg in two and on an ankle in three patients (*table 1*). It was roundish, with a necrotic-purulent bed and well-defined

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Table 1. Patients' characteristics.

No. of patients	Sex	Age	Countries in which the ulcer was acquired	Location
1	f	37	Brazil	Left leg
2	m	57	Malaysia	Right forearm
3	m	38	Fiji Islands	Right ankle
4	f	44	Zambia	Left ankle
5	m	31	Tanzania	Left leg
6	m	46	India	Left ankle

borders. In five patients, the borders were surrounded by an erythematous halo, and in one patient, borders were surrounded by crusts and scales (*figures 1-4*). All ulcers were malodorous and painful. Laboratory tests revealed mild leucocytosis and a mild increase in erythrocyte sedimentation rate and C-reactive protein. Results of bacteriological examinations are reported in *table 2*. It was impossible to perform polymerase chain reaction for *Fusobacterium* spp. Mycological examinations were negative. In all cases, histopathological examination revealed: necrosis of the epidermis and dermis; vascular dilatation; oedema in the dermis; massive infiltration with neutrophils, lymphocytes and histiocytes; and fragmented collagen bundles. No signs of vasculitis were observed. A histopathological diagnosis of non-specific ulcers was made. In four patients, Gram-positive ($n = 3$) and Gram-negative ($n = 1$) bacteria were detected. Results of direct immunofluorescence were negative. Arterial and venous colour Doppler ultrasound of the lower limbs was normal in all patients. All patients were treated with oral metronidazole (500 mg/twice daily for two weeks) and, according to antibiograms, with amoxicillin (one patient), ceftriaxone (one patient), ciprofloxacin (two patients), erythromycin (one patient) and tetracycline (one patient). In addition, all patients were treated with 0.05% sodium hypochlorite (2-3 compresses/day) and paraffine bandages.

Complete remission was observed within four to six weeks. Follow-up (≥nine months) was negative.

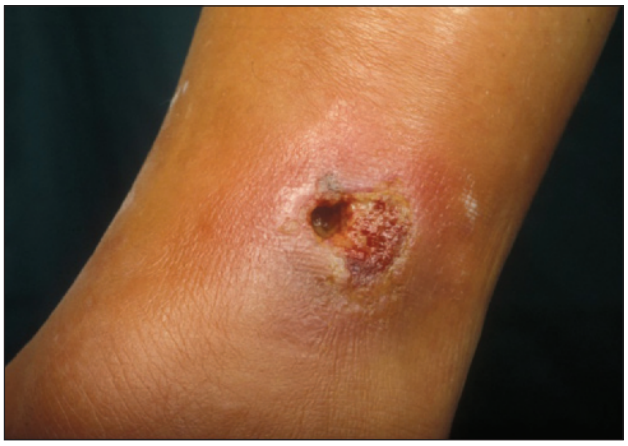

Figure 1. Patient 1. TU on the left leg.

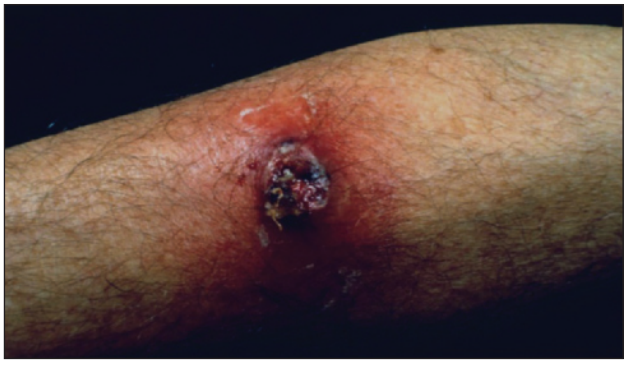

Figure 2. Patient 2. TU on the right forearm.

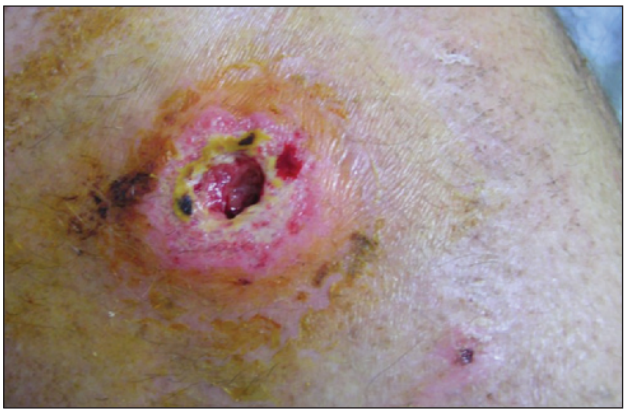

Figure 3. Patient 5. TU on the left leg.

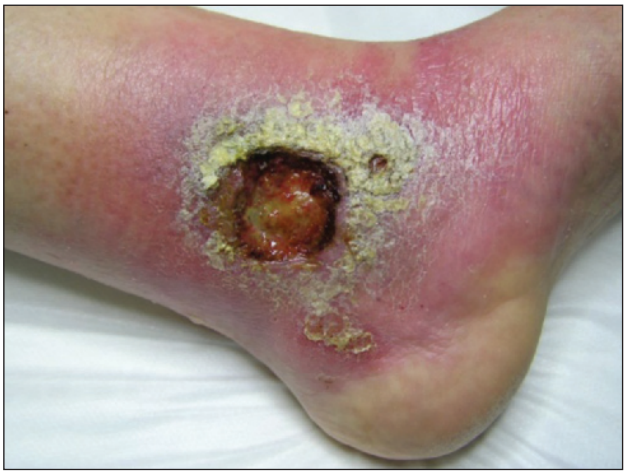

Figure 4. Patient 6. TU on the left ankle.

Discussion

Historical notes

Literature on TUs before 1950 is abundant. However, it is very often misleading; in fact, ulcerative diseases of the skin acquired in tropical and subtropical countries were often diagnosed as TUs, but were actually ulcerative pyodermas, such as ecthyma, or cutaneous diphtheria, ulcers caused by mycobacteria, such as Buruli ulcer, treponematoses, post-traumatic ulcers with bacterial superinfections and cutaneous leishmaniasis.
An additional complication is represented by the fact that TU was previously referred to by numerous names, including Naga sore, phagedena, phagedenic ulcer, tropical phagedena, tropical phagedenic ulcer, ulcère phagédénique des pays chauds and ulcus tropicum [13, 49]. To this list, it is also necessary to add other terms related to specific geographic locations: Massaua ulcer in Eritrea, Sarnes ulcer in the Congo, Zanzibar ulcer in Tanzania, Mozambique ulcer in Mozambique, Aden or Yemen ulcer in the Arabian peninsula, Cochin sore in India and Annam, and Indochina ulcer in South-East Asia [13].

Aetiopathogenesis

In the past, several bacteria were considered as possible aetiological agents of TUs. These include: cocci, diphtheroids, fusiform bacilli (*Bacillus fusiformis*, *Bacillus hastilis, Fusobacterium fusiforme* and *Fusobacterium plauti-vincenti*) and spirochaetes (*Spirochaeta schaudinni, Treponema vincentii* [previously named *Borrelia vincentii*] and *Spirochaeta vincenti*) [8, 12, 18, 24, 35]. In the past, *Staphylococcus aureus* or *Staphylococcus albus* and *Borrelia vincentii* with fusiform bacilli were consistently reported to be predominant in the rainy season, and *Corynebacterium* spp. and *S. aureus* or *S. albus* predominant during the dry season [2].
The aetiology of TU was clarified by means of fundamental epidemiological, clinical, bacteriological and histopathological studies by Adriaans, Drasar, Hay and Robinson [48, 50, 55, 56, 58-62]. The results of their studies may be summarized as follows:

(1) Anaerobes are always present, together with aerobes or facultative anaerobes, particularly in early phases.
(2) Fusobacteria are most frequently isolated, in particular *Fusobacterium ulcerans* (which has been identified in mud collected in areas where patients with TU were living). This strain differed from other *Fusobacterium* spp. by its morphology, biochemical profile and soluble cellular proteins, as determined by polyacrylamide gel electrophoresis [61]. Two morphological types of *F. ulcerans,* NCTC 12111 and NCTC 12112, on the basis of slightly different biochemical properties, were subsequently detected [62]. Both strains of *F. ulcerans* induced a marked cytotoxic effect *in vitro* on a range of tissue culture cell lines [62]. Also, *F. nucleatum* was considered as possible aetiological agent of TU [63].
(3) Spirochaetes were identified in material examined by light and electron microscopy, but were not cultured.

In a study by Adriaans *et al*. [55], coliforms were present in 60% of aerobic cultures, coagulase-negative staphylococci in 30%, streptococci in 15% and *S. aureus* in 1.6%. In anaerobic cultures, fusobacteria were present in 35% of cases, anaerobic cocci in 23%, bacteroides in 20%, propionibacteria in 4.1% and *Veillonella* spp. in 0.8%. The aetiology of TU is similar to that of cancrum oris (noma) or foot rot in sheep, a mixed bacterial infection leading to ulcers of the oral mucosa or skin.

Epidemiology

TU has been observed in several countries. In Africa: Senegal [42], Gambia [45, 47, 55, 58, 66], Liberia [2], Ghana [3, 4, 7, 8, 11], Nigeria [18, 29, 30, 35], Cameroon [28], Ethiopia [19], Somalia [76], Congo [32], Uganda [22], Kenya [5, 10], Tanzania [6, 51, 53], Zambia [49, 55, 58, 60, 70], Malawi [57], Zimbabwe [65], Namibia [44] and South Africa [12, 27]. In Asia: Israel [14], India [41, 46, 55, 58-60] and Indonesia [16]. In Oceania: Papua New Guinea [24, 55, 58-60, 63, 64], Fiji Islands [59], Cook Islands [26, 43] and Kiribati [54]. In America: Haiti [39], Dominican Republic [72] and Jamaica [1]. Our Brazilian case is the first reported from South America.
Epidemics occurred in 1976 in the Cook Islands [43], in 1989 in Zimbabwe (1.680 cases over a 14-month period) [65] and in 1997 in Djibouti [75].
TU occurs more frequently in males [18, 43, 65, 71, 74]. In a study carried out in Ethiopia, only 3% of patients were females [19]. However, in a study performed in Zambia, both genders were equally affected [49]. Children and adolescents are mainly affected [43, 49, 58-60, 63-65, 70, 71, 74]. Simultaneous cases within households are uncommon [49].

Risk factors

General predisposing factors have been considered in the pathogenesis of TU, including a hot humid climate [39, 65, 71, 75] and exposure to mud or slow-moving fresh water [60, 71].
Individual risk factors include: malnutrition [18, 19, 27, 29, 35, 37, 39], although this was not confirmed by all authors [49, 60, 71, 74]; drepanocytosis [28]; abnormalities in blood circulation [24]; pellagra [37]; trauma [24, 27, 39, 43, 59, 74], including sport injuries [69]; animal bites and stings [43]; burns [43]; lack of personal hygiene [24]; and walking barefoot [49]. In a study performed in Nigeria, trauma occurred in 63% of patients and mosquito bites in 26% [18]. As previously mentioned, in all our patients, the ulcer was caused by a trauma.

Clinical picture

The ulcer may be followed by a papule [59, 60] or a pustule [49]. The ulcer is often single; 80% of patients had a single lesion in the previously cited Nigerian study [18], 71% in a study carried out in the Cook Islands [43], and 75% in a study performed in Zambia [49]. The ulcer is usually roundish, with a purulent-necrotic, malodorous bed and well-defined borders. It is often accompanied by more or less severe pain [71, 74]. Although the hands [71], arms [43], thighs [43] and knees [6, 18, 43] may be affected, the legs

Table 2. Bacteriological results, therapy and outcome.

No. of patient	Bacteriological results	Therapy	Outcome
1	*Fusobacterium* spp.; *Streptococcus pyogenes*	Metronidazole (1 g/day for 14 days) Erythromycin (3 g/day for 10 days)	Complete remission within 4 weeks
2	*Fusobacterium* spp.; *Staphylococcus aureus*	Metronidazole (1 g/day for 14 days) Amoxicillin (3 g/day for 10 days)	Complete remission within 4 weeks
3	*Fusobacterium* spp.; *Staphylococcus aureus*	Metronidazole (1 g/day for 14 days) Ceftriaxone (2 g/day for 10 days)	Complete remission within 4 weeks
4	*Corynebacterium* spp,; *Staphylococcus epidermidis*	Metronidazole (1 g/day for 14 days) Tetracycline (2 g/day for 14 days)	Complete remission within 4 weeks
5	*Fusobacterium* spp.; *Pseudomonas aeruginosa*	Metronidazole (1 g/day for 14 days) Ciprofloxacin (750 mg/day for 14 days)	Complete remission within 6 weeks
6	*Fusobacterium* spp.; *Serratia marcescens*	Metronidazole (1 g/day for 14 days) Ciprofloxacin (750 mg/day for 14 days)	Complete remission within 6 weeks

[6, 12, 13, 17, 19, 23, 29, 39, 43, 44, 46, 47, 49, 55, 60, 63, 71, 72, 74, 76, 77], ankles [6, 13, 23, 24, 43, 49, 72] and feet [6, 12, 13, 18, 20, 29, 37, 41, 60] are more frequently involved.

Complications

Complications are represented by squamous cell carcinomas in long-standing ulcers [17, 39, 42, 60, 71] and soft tissue sarcomas (three cases of leiomyosarcoma, two of extraskeletal osteosarcoma, one of malignant fibrous histiocytoma and one of myxoid liposarcoma in the study by Fletcher [57]). In all these cases, the ulcers were clinically similar to squamous cell carcinoma [57]. Inflammatory periostitis [17, 37] and fracture [37] were also reported. Both hepatitis B surface antigen and e antigen were detected in exudates from TUs: TU can be a source of hepatitis B [45, 54, 66].

Histopathology

The histopathological picture is characterized by necrosis of the epidermis and dermis, dermal oedema, vascular dilatation, infiltration with neutrophils and lymphocytes and fragmented collagen bundles [56].

Differential diagnosis

This includes: ulcerative pyodermas, such as ecthyma; ulcers due to *Haemophilus ducreyi*, cutaneous diphtheria; ulcers caused by mycobacteria, such as Buruli ulcer; treponematoses such as yaws; post-traumatic ulcers with bacterial superinfections; cutaneous leishmaniasis; ulcers caused by arterial or venous insufficiency; and pyoderma gangrenosum. The latter was excluded in our patients according to the medical history, recovery by means of antibiotics and long negative follow-up.

Therapy

In patients with malnutrition, the role of diet is important [1, 18, 19, 47].
Some topical antiseptics and antibiotics have been used in the past: povidone-iodine [46], sulphonamides [2], chlortetracycline [8, 12], oxytetracycline [11], framycetin [46], and even papaya [32].
Among oral antibiotics, sulphonamides [2], nitrofurazone [46], chlortetracycline [3], oxytetracycline [7] and chloramphenicol [4, 9] have been used. Before the use of metronidazole, penicillin was largely used [6, 39, 43, 64], as well as procaine in oil and aluminum monostearate [14] or associated with polymyxin b sulphate [20]. Metronidazole was first used in 1968 in a double blind trial versus placebo [36]. It can be considered as the most effective therapy for TUs [41]. Intra-arterial or subcutaneous or intra-muscular acetylcholine has also been suggested [19].
Skin grafting is sometime necessary [5, 6, 22, 42, 51, 64, 74]. Some cases of amputation have been reported [74].

Prevention

Wearing suitable footwear and long trousers is an adequate preventive measure. Among those with TUs in a study in Zambia, few patients wore shoes and only a quarter reported wearing knee-length trousers at some time [49]. Prompt diagnosis and appropriate treatment of wounds reduce the likelihood of penetration of infection and subsequent progression. ■

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