Cutaneous Infections from Aquatic Environments

11

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Various skin disorders can develop after exposure to aquatic environments. Pathogenic organisms can be introduced through stings and bites, or wounds inflicted by aquatic life forms. In addition, preexisting wounds can be passively infected as a result of exposure to contaminated waters. Table 11.1 lists the pathogenic organisms most commonly associated with waterborne skin infections [1–3].

11.1 Infection by *Mycobacterium marinum*

Mycobacterium marinum lives in aquatic environments, where it causes disease in many poikilothermic fish species living in fresh- or saltwater; the organism has a wide geographic distribution in the water world [4]. It was first isolated in 1926 by Aronson from tubercles in various organs of marine fish found dead in the Philadelphia Aquarium [5]. This organism was identified as a causal agent of human disease only in 1951, when it was identified from skin lesions in swimmers in a contaminated swimming pool in the city of Orebro, Sweden [6]. The term "swimming pool granuloma" was coined to denote these lesions and the causal agent was classified as *M. balnei* [7], and then, when the two mycobacteria were later seen to be identical, as *M. marinum* (Fig. 11.1).

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Table 11.1 Skin infections by waterborne pathogenic organisms

Organism	Clinical features
Mycobacterium marinum	Swimming pool granuloma (very rare today)
	Fish tank granuloma (associated with aquariums, or in pet shop workers)
Mycobacterium ulcerans	Necrosis of dermis and subcutaneous tissue with ulceration (Buruli ulcer)
Rapidly growing mycobacteria	Post-surgical infections
	Skin and soft tissue infections
Erysipelotrix rhusiopathiae	Erysipeloid
Aeromonas species	Cellulitis, fasciitis
Chromobacterium violaceum	Macular lesions and abscesses
Edwardsiella tarda	Cellulitis, abscesses
Shewanella species	Deep ulcers and hemorrhagic blisters of legs
Vibrio vulnificus	Cellulitis
Streptococcus iniae	Cellulitis
Pseudomonas species	Swimmer's ear
	Hot tub folliculitis
	Trench foot

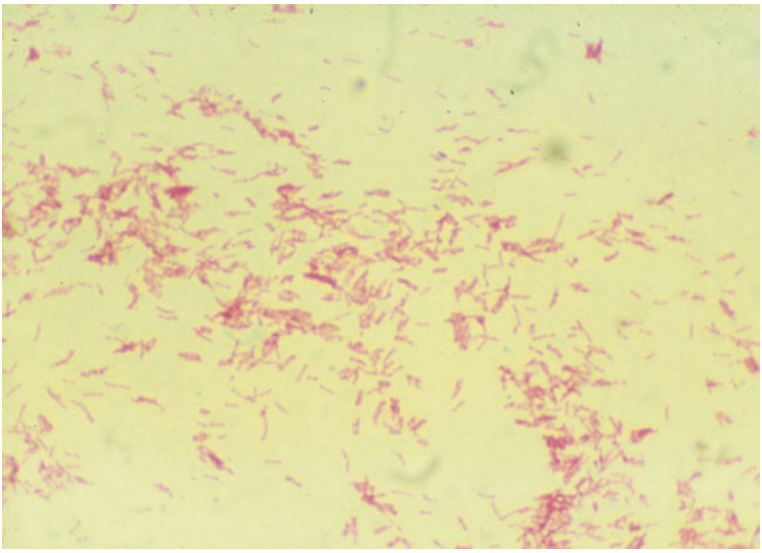


Fig. 11.1 *Mycobacterium marinum*

Lastly, in 1962 Swift and Cohen reported two cases of *M. marinum* infection from a tropical fish tank; the term "fish tank granuloma" was introduced at this stage [8]. Since those reports, "swimming pool granuloma" has essentially disappeared thanks to the introduction of proper chlorinization of this reservoir. Various other activities may implicate a potential risk, including cleaning household aquariums, skin diving [9], dolphin training [10] and a number of fishing and boating activities [11].

Table 11.2 Classification of mycobacteria

"Typical" mycobacteria
Mycobacterium tuberculosis
Mycobacterium bovis
Mycobacterium leprae
Nontuberculous mycobacteria
Group I (photochromogens)
Mycobacterium kansasii
Mycobacterium marinum
Mycobacterium ulcerans
Group II (scotochromogens)
Mycobacterium scrofulaceum
Mycobacterium flavescens
Group III (non chromogens)
Mycobacterium avium
Mycobacterium intracellulare
Mycobacterium xenopi
Mycobacterium triviale
Mycobacterium terrae
Group IV (fast growing)
Mycobacterium fortuitum
Mycobacterium abscessus
Mycobacterium chelonae

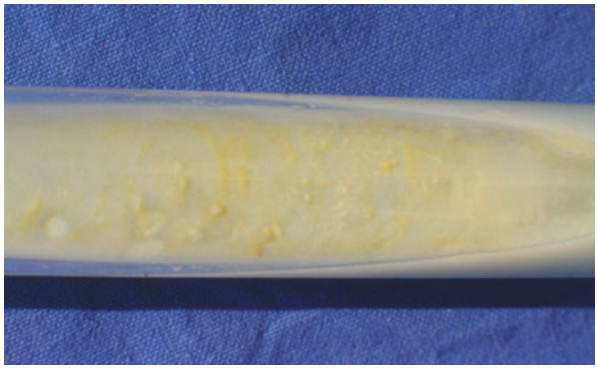


Fig. 11.2 Yellow photochromogenic colonies of *Mycobacterium marinum* in Löwenstein-Jensen culture medium

This mycobacterium belongs to the first of four groups in Runyon's classification (Table 11.2) [12]. It is photochromogenic (cultures turn yellowish-orange after photoexposure) (Fig. 11.2) and in culture medium (Löwenstein-Jensen) it grows slowly over 3–4 weeks at 30–32 °C rather than 37 °C. Thus, unless it is suspected and searched for in appropriate culture medium, the bacillus may not be identified [13–15]. *M. marinum* is alcohol- and acid-fast.

While endemic in fish, *M. marinum* infection in humans through contact with contaminated water or fish is comparatively rare [8, 16–32]. In a retrospective survey carried out in 21 Spanish laboratories from 1991 to 1998, 39 bacteriologically confirmed cases were noted [32]. Culture-confirmed *M. marinum* infection was reported in 66 patients from 1996 to 1998 in France, with an infection incidence of

about 0.04 cases per 100,000 inhabitants per year [33]. The annual incidence in the USA is 0.27 confirmed cases per 100,000 inhabitants [34].

In the last years, significant updates on the pathophysiology of *M. marinum* have been reported. A dynamic host-pathogen interaction has been shown: metabolically active bacteria are controlled by the host immune system and products of specific bacterial genes interfere with the host's effort to eradicate the bacteria. In more detail, the ESX-55 system of the mycobacteria is responsible for the secretion of various proline-proline-glutamic acid (PPE) and proline-glutamic acid (PE)-polymorphic GC-rich repetitive sequence (PGRS) proteins. Animal model studies suggest that such proteins interact with host immune components and possibly subvert critical innate immune pathways, establishing a moderate, persistent infection [35–39]. *In vitro* observations on infected human macrophages further suggest that these proteins strongly modulate the human macrophage response and actively suppress T-lymphocyte receptor signaling-dependent innate immune cytokine secretion, thus allowing bacterial survival [40]. In particular the PPE38 protein, expressed on the cell-wall surface, seems to be involved in bacterial surface properties such as cord formation, sliding motility and biofilm formation, as well as in the induction of pro-inflammatory cytokines in infected macrophages [39]. Additionally, some authors have presumed that these proteins are a source of antigenic variation which allows the pathogen to evade antigenic-specific host responses [38]. Given the above data, it is easy to understand why immune system impairment is a significant factor in the establishment of *M. marinum* infection at the pathogenic level [41].

Owing to the growth temperature of *M. marinum*, the infection is primarily localized at the coolest region of the body, which is the skin. Less commonly it involves deeper structures, such as joints, tendons and bones [42–45].

As already pointed out, dissemination of the infection more commonly occurs in immunocompromised hosts, like transplant recipients and subjects on corticosteroid therapy [46–49], while it is rarely reported in individuals with a relatively intact immunity [50, 51]. As of recent date, *M. marinum* infection has gained a relevant role as an opportunistic infection in patients treated with anti-tumor necrosis factor (TNF)-α or other biological drugs [52–56]. However, recent reports support a safe re-exposure to anti-TNF-α therapy after elimination of the bacteria through correct antibiotic therapy [57].

The infection is now linked in particular to activities such as maintenance of domestic aquariums, and is occasionally reported in occupational environments (among fishermen, laboratory technicians, workers in charge of maintenance of fish tanks at aquariums, zoos or pet shops), although one case was observed in an industrial plumbing mechanic with no direct aquatic exposure [23].

M. marinum invades the tissues through preexisting broken skin. The sites most commonly affected are the knees, elbows, arches of the feet and backs of the hands in swimming pool granulomas, and the backs of the hands in fish tank granulomas. One case of sporotrichoid infection of the face has also been reported, in a 2-year-old child, probably caught from fish in an aquarium [27].

The initial lesion, generally single, presents as a reddish or reddish-blue nodule, of a soft consistency and variable diameter, that may even be as large as 5–6 cm. Ulceration or colliquation may develop and the lesion will then rupture and exude pus, or else it may remain as a verrucous surface lesion. Multiple or disseminated

lesions on the trunk or limbs are rare [17, 20, 21], except in subjects with an immune deficiency. Sporotrichoid forms are frequently observed, with several nodules running along the lymphatic drainage lines. Mild involvement of regional lymph nodes is a rare possibility. The infection may resolve spontaneously within a few months, but generally persists for many years.

Concerning the histopathology, it is widely known that a histologic diagnosis of *M. marinum* infection can be difficult [58] because various aspects tend to vary according to the age of the lesion. In particular, a nonspecific inflammatory infiltrate may be observed in the first 6 months; after this period, a granuloma with epithelioid and multinucleated cells is much more likely [28, 59]. Various patterns can be observed: sarcoid-like granuloma, granuloma annulare, or rheumatoid-like nodules are frequent pictures [60–63]. Epidermal changes (hyperkeratosis, acanthosis, pseudo-epitheliomatous hyperplasia, intradermal neutrophilic abscesses and ulcerations), as well as dermal fibrosis (in chronic lesions) and small vessels proliferation are important findings that are generally present in such cases [58, 63]. In histological preparations, alcohol-acid-resistant bacilli can be identified using Ziehl-Neelsen or trichromic staining.

M. marinum infection does not confer immunity so re-infection is possible. The clinical history is very important for diagnosis, as well as identification of the mycobacterium by biochemical tests (Table 11.3), and molecular biology methods are a must. Intradermal tests with PPD prepared from *M. marinum* will be positive.

There is currently no consensus on the optimal treatment of *M. marinum* infection. Therapy is usually medical in nature, although adjunct surgical procedures, cryotherapy and electrodessication may be needed to control resistant or deeper infections. The duration of therapy varies widely in the literature, ranging from 2 to 12 months overall: most authors recommend extending treatment for 1–2 months following clinical resolution,. Spontaneous resolution is possible but rare; complete regression can take up to

Table 11.3 Differential features of some mycobacteria inducing skin lesions

Species	*M. tuberculosis*	*M. marinum*	*M. ulcerans*	*M. fortuitum*	*M. chelonae*
Growth rate	L	I	I	R	R
Optimal growth temperature	37 °C	30 °C	30 °C	37 °C	37 °C
Growth 25 °C	–	+	+	±	±
Growth 45 °C	–	–	–	–	–
Pigment	N	P	N	N	N
Niacin test	+	V	–	–	–
Reduction of nitrates	+	–	–	+	–
Tween hydrolysis (10 days)	±	+	–	+	V
Catalase 68 °C	–	+	+	+	+
Urease	+	+	–	+	V
Pyrazine amidase	+	+	–	+	+
Growth NaCl 5 %	–	V	–	+	V
Growth MacConkey Agar	–	–	–	+	+

Rate of growth = *R* (rapid: non >7 days); *I* (intermediate: 8–14 days); *L* (slow: more than 14 days)
Pigment = *N*: non photochromogenic; *P*: photochromogenic
V = variable

Table 11.4 Drugs most widely used in the treatment of *Mycobacterium marinum* cutaneous infection according to the literature [66]

Antimycobacterial agent	Dosage[a]	Duration
Minocycline	50–100 mg/2/die	2–6 months
Doxycycline	50–100 mg/2/die	4–5 months
Clarithromycin	250–500 mg/2/die	3–6 months
Ofloxacin	200–300 mg/2/die	1–2 months
Ciprofloxacin	250–500 mg/2/die	2–3 months
Rifampicin	600–900 mg/die	2–5 months
Rifamycin	250 mg im/2/die	2–5 months
Rifabutin	450–600 mg/die	2 months
Sulfamethoxazole plus trimethoprim	400 mg + 80 mg/2/die	1–2 months
Ethambutol hydrochloride	15–25 mg/kg/die	2–6 months
Isoniazid	5–10 mg/kg/die	1–2 months

[a]If unspecified, administration is per os

2 years [64]. Various antibiotics are reported as effective options but randomized controlled trials comparing different antibiotics regimens are lacking. Widely used molecules include tetracyclines (mostly minocycline and doxycycline), sulfamethoxazole plus trimethoprim, rifampicin, and ethambutol. Less common alternatives are clarithromycin, levofloxacin and amikacin [33, 41, 59, 65, 66]. Other drugs such as newer macrolides and fluoroquinolones (sparfloxacin) offer feasible approaches [33] (Table 11.4), even if both success and failure have been reported for each of these molecules. Monotherapy with minocycline, doxycycline and clarithromycin has proven successful in most cases, especially for superficial cutaneous infections. Combination therapy, often with clarithromycin plus rifampicin and/or ethambutol, is preferred for more severe forms characterized by deep tissues involvement.

11.1.1 Personal Experience [67]

From 1987 to 2011 we observed 15 patients with cutaneous *M. marinum* infection, 12 males (80%) and 3 females (20%; male to female ratio 4:1), of ages ranging from 15 to 55 years (mean: 39.9). The infection was occupational in 11 subjects (3 of them worked at institutional aquariums, 8 in shops selling aquariums) and extra-occupational in 4 patients (all of whom tended home aquariums). One of the latter four patients was in the 8th month of pregnancy at the time of observation [67].

Each patient had a documented history of former minor trauma, such as abrasion or a superficial wound, acquired while handling fish, shellfish, or alternatively caused by infected foreign bodies within the aquarium, like wood splinters or stones. The median incubation time after the traumatic inoculation was relatively long, ranging from 3 to 24 weeks (mean: 6.6). The interval between the lesion onset and our observation was in the range of 1–6 months (average 4.3 months).

Four patients (20.7%) presented with a single papulo-verrucous plaque (Figs. 11.3, 11.4, 11.5, and 11.6) and 11 (73.3%) had a sporotrichoid distribution of nodular lesions (Figs. 11.7, 11.8, 11.9, 11.10, 11.11, 11.12, 11.13, 11.14, 11.15,

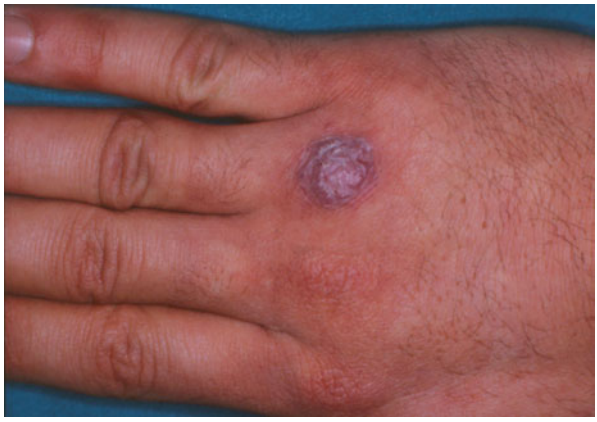


Fig. 11.3 Fish tank granuloma

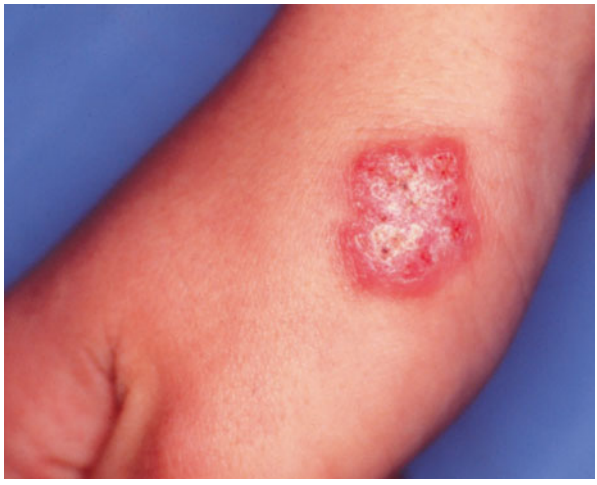


Fig. 11.4 Fish tank granuloma

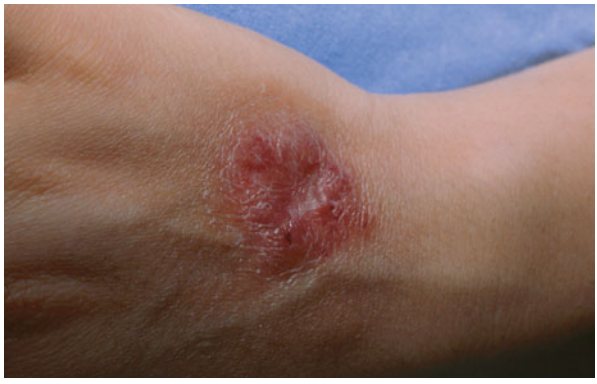


Fig. 11.5 Fish tank granuloma

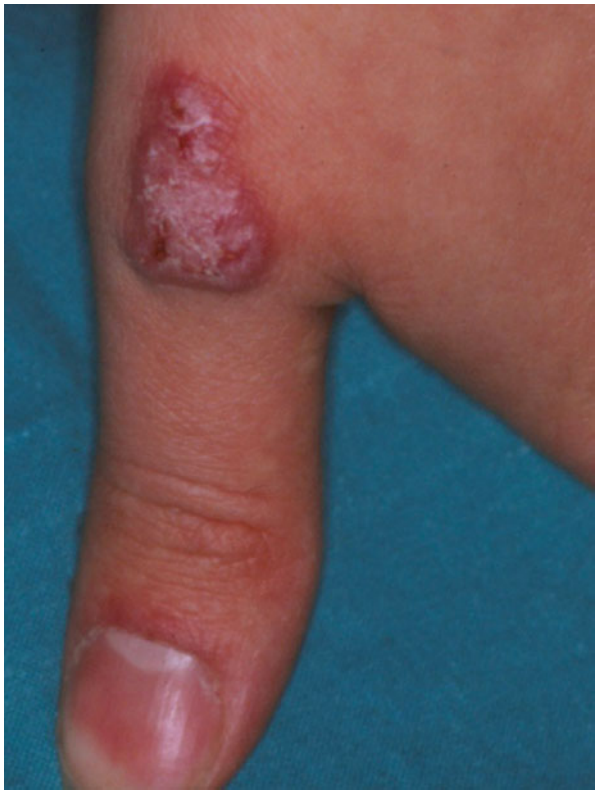


Fig. 11.6 Fish tank granuloma (Reproduced with permission from Bonamonte and Angelini [30])

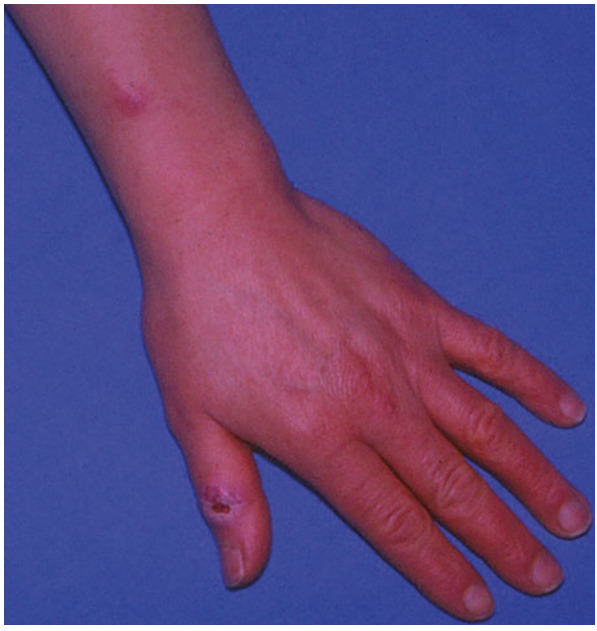


Fig. 11.7 Sporotrichoid fish tank granuloma

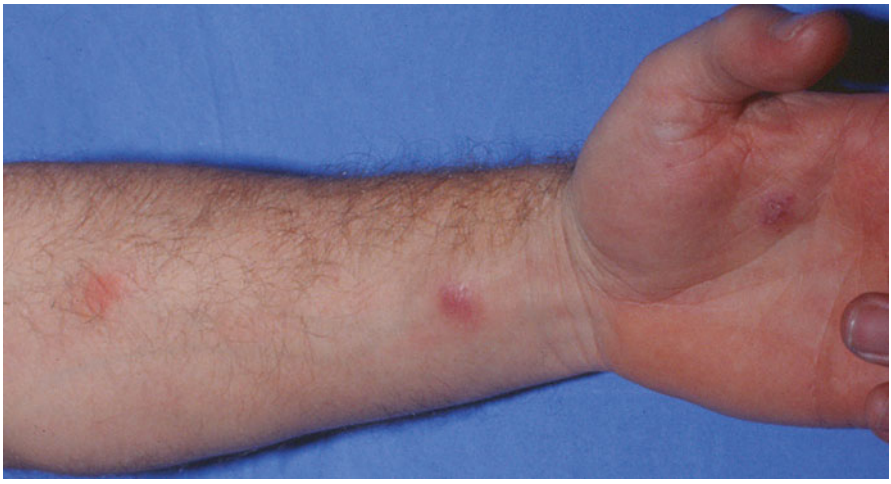


Fig. 11.8 Sporotrichoid fish tank granuloma

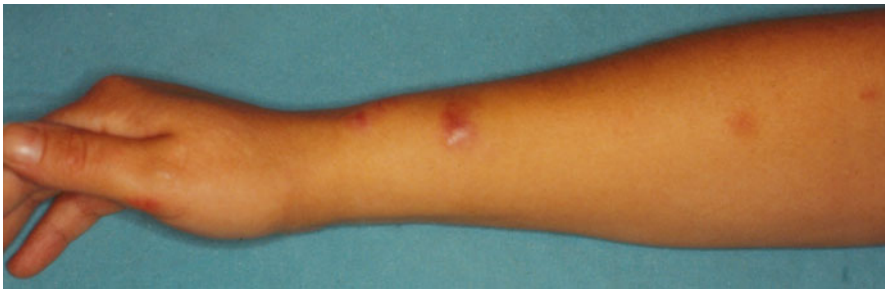


Fig. 11.9 Sporotrichoid fish tank granuloma

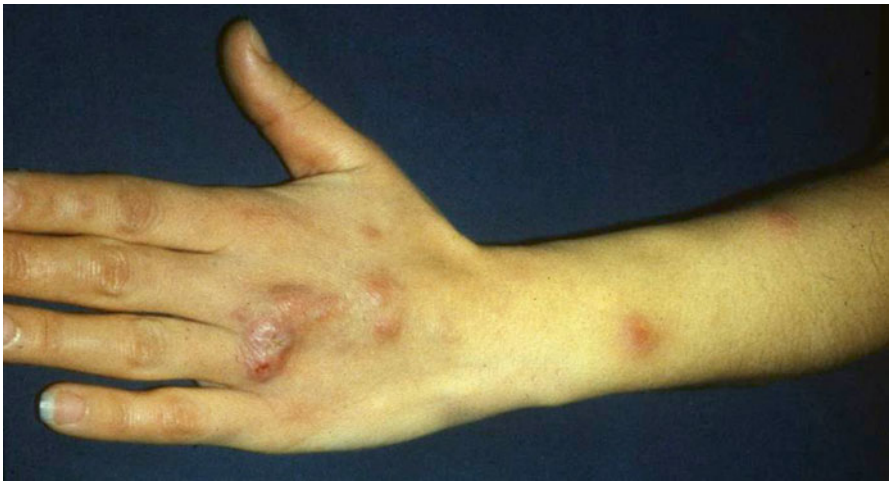


Fig. 11.10 Sporotrichoid fish tank granuloma

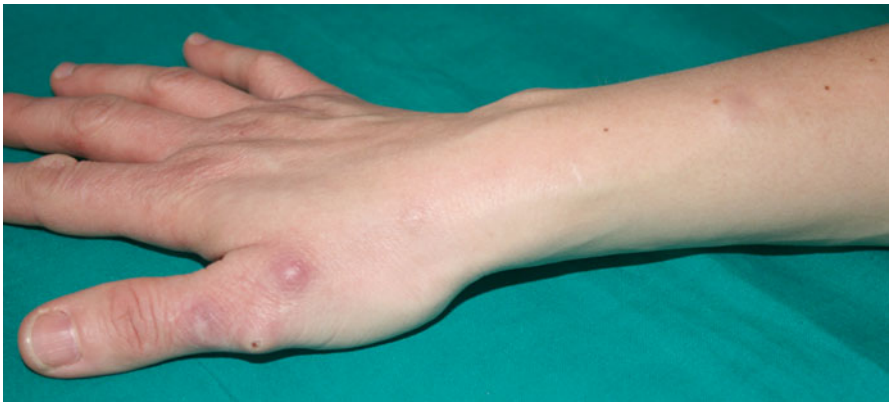


Fig. 11.11 Sporotrichoid fish tank granuloma

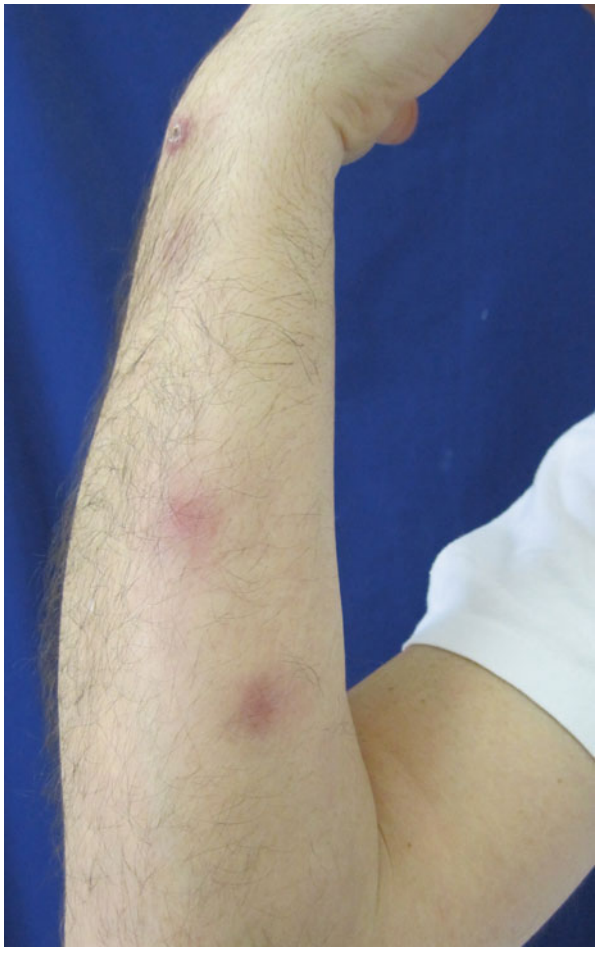


Fig. 11.12 Sporotrichoid fish tank granuloma

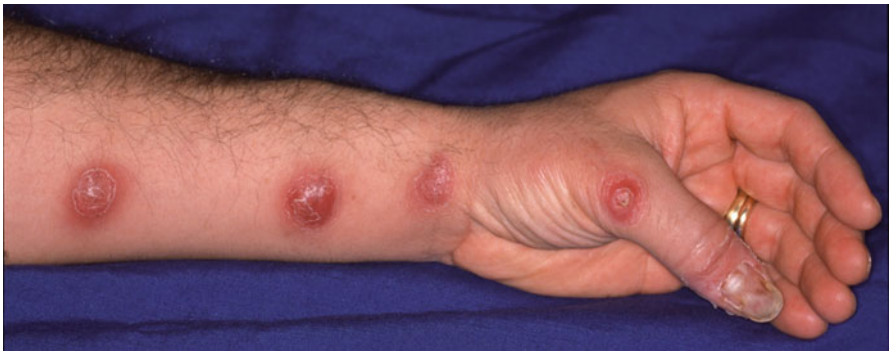
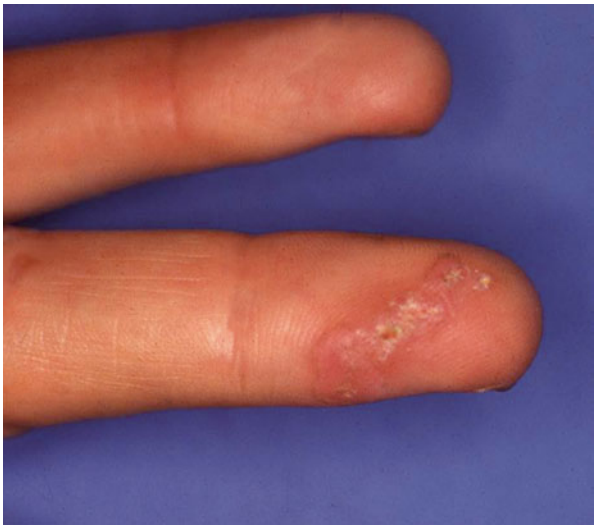


Fig. 11.13 Sporotrichoid fish tank granuloma (Reproduced with permission from Bonamonte and Angelini [30])

Fig. 11.14 Fish tank wound



11.16, and 11.17). The anatomic distribution was typically on the upper limbs, first involving the hand, fingers and dorsum (right hand in 13 cases, left hand in 2 cases), in 12 cases later spreading centripetally up the whole arm, trailing up lymphatic vessels. In 3 of these 12 sporotrichoid cases, the first observed lesions were ulcerated nodules that caused mild pain, unlike in the remaining cases, where the infection was painless. Associated systemic symptoms, localized adenopathy, deep structures involvement like tenosynovitis, bursitis, and arthritis, were not present in any of the 15 cases. All patients were immunocompetent and referred no history of transplantation or immunosuppressive therapy.

An interesting finding emerged from the history of the 12 sporotrichoid pattern cases: nodular lesions, arranged in rosary-like chains, appeared one after the other at regular 1–2 week intervals. Moreover, each lesions first involved the cutis deep structures, presenting as a prominence covered by healthy skin, and then later the overlapping epidermis was affected [67].

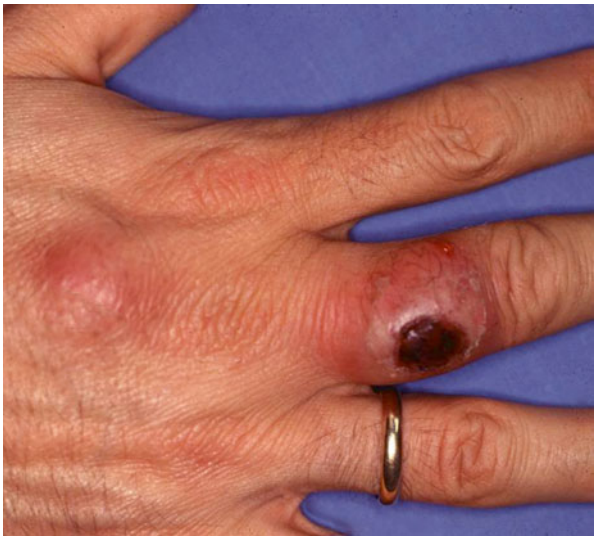


Fig. 11.15 The same case as in Fig. 11.14. Sporotrichoid fish tank granulomas, one with an ulcerative evolution (Reproduced with permission from Bonamonte and Angelini [31])

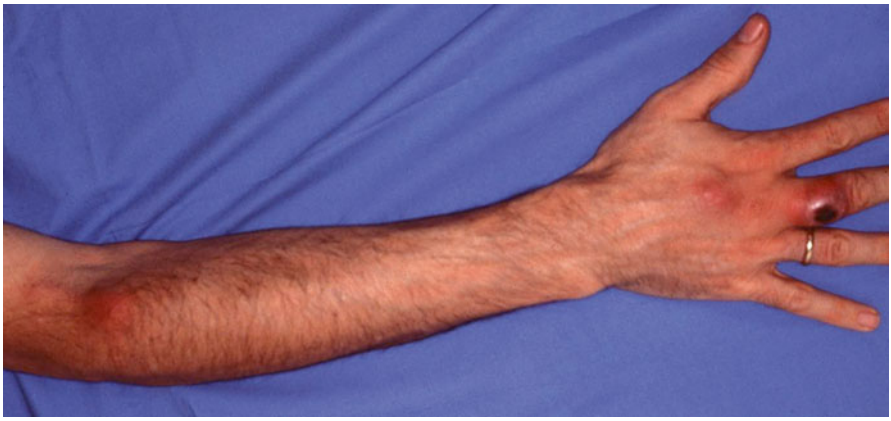


Fig. 11.16 The same case as in Fig. 11.14 with sporotricoid granulomas

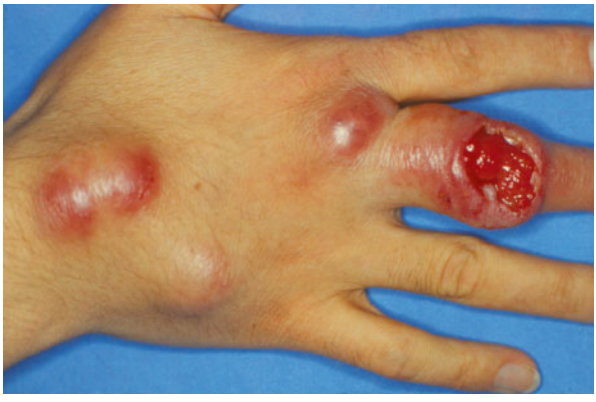


Fig. 11.17 Sporotrichoid fish tank granulomas with an ulcerative evolution

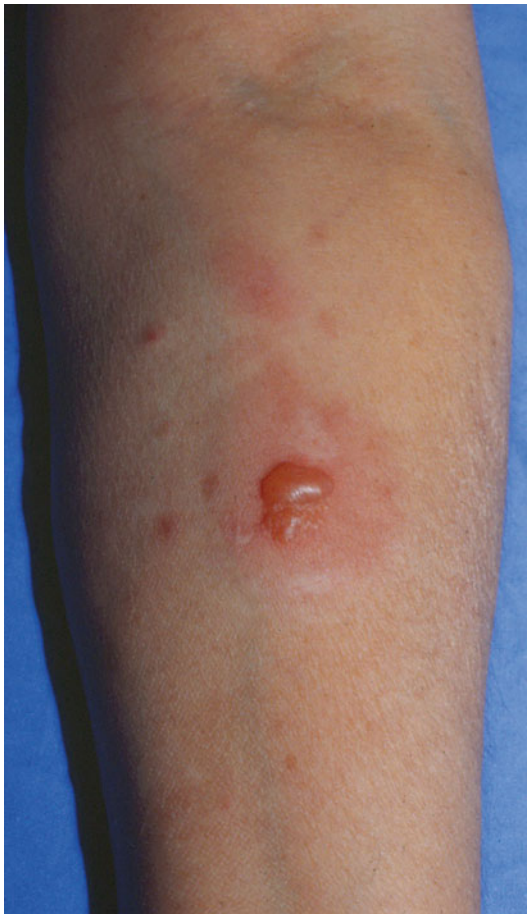


Fig. 11.18 Strongly positive reaction to PPD from *Mycobacterium marinum*

Culture tests of skin biopsy fragments in Löwenstein-Jensen at 30 °C indicated *M. marinum* growth in 13 of our 15 cases (93.3 %); according to the literature, positive rates of cultures range from 70 to 80 %. However, in the two culture-negative cases, the history, intradermal skin tests with PPD of *M. marinum* and PCR tests were positive, lesions were classic sporotrichoid, and minocycline therapy was efficacious. Culture in Löwenstein-Jensen at 37 °C yielded negative results in each case. In all cases PPD skin tests resulted strongly positive for *M. marinum* (Fig. 11.18); the lesions featured an induration area measuring 10–15 mm in diameter, and were moderately positive for *M. tuberculosis* (Fig. 11.19) [67]. Even if none of our patients had a history of a positive tuberculin skin test result, the positive PPD results could be interpreted as cross-reactivity, consistent with studies showing a close genome relationship between *M. marinum* and *M. tuberculosis* [68]. Deep tissue involvement was not revealed in any of our cases, likely because of the brief time lag between the disease onset and the clinical diagnosis. In 7 of the 15 patients the PCR test was performed, yielding positive results in each instance.

Biopsies were taken in all subjects. Epidermal changes were present in 46.6 % of cases and included hyperkeratosis (three cases), acanthosis (seven cases) pseudoepitheliomatous papillomatosis (four cases) and lymphocyte exocytosis (two cases). We demonstrated superficial and/or deep dermal involvement in every case. A tuberculoid granuloma, with lymphocytes, histiocytes, neutrophils, giant cells but no sign of central caseation (Figs. 11.20 and 11.21),

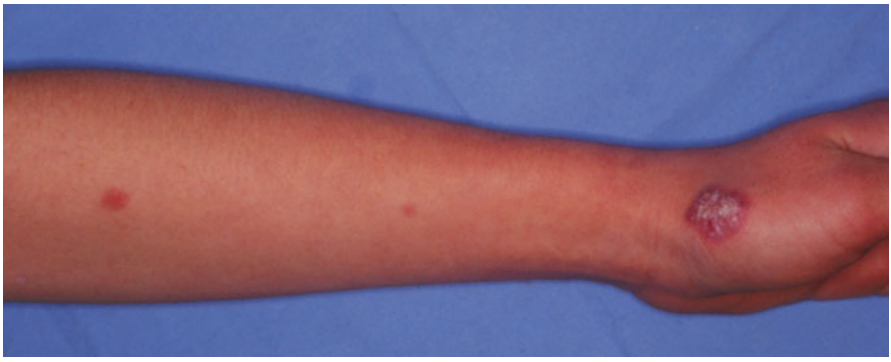


Fig. 11.19 Fish tank granuloma with intensely positive PPD to *Mycobacterium marinum* and weakly positive PPD to *Mycobacterium tuberculosis*

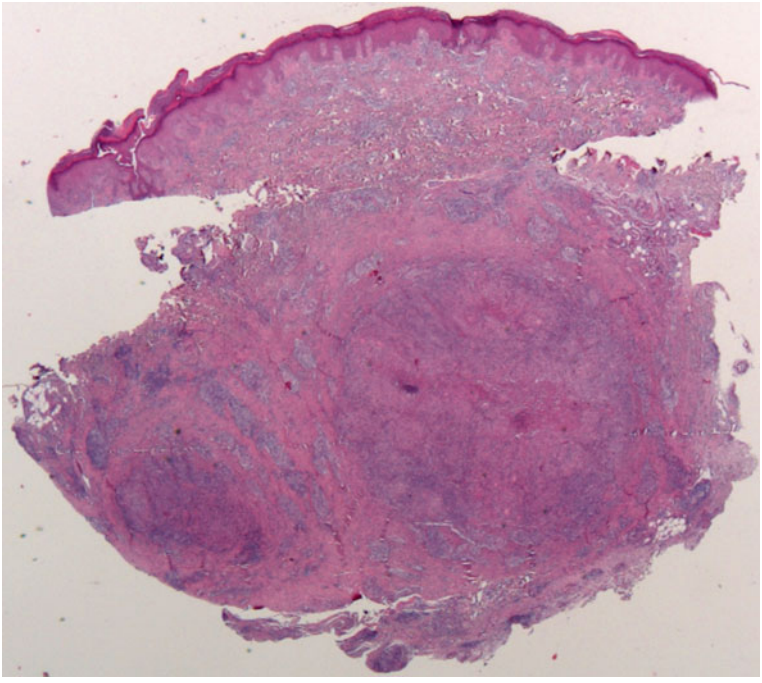


Fig. 11.20 Granulomatous inflammation of deep dermis and subcutaneous tissue (Hematoxylin-eosin – ×10) (Reproduced with permission from Bonamonte and Coll. [67])

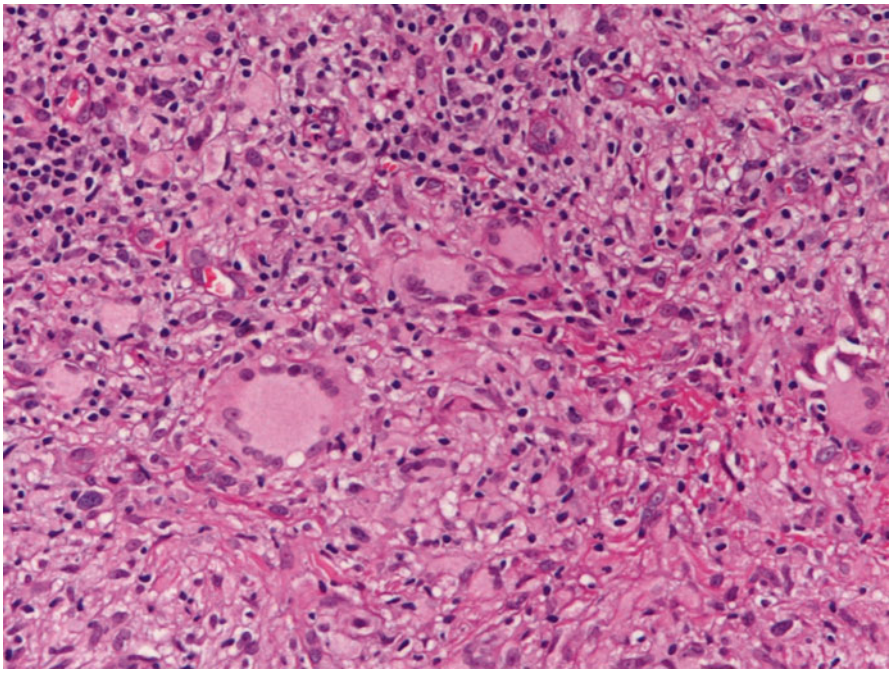


Fig. 11.21 Tubercoloid granulomatous infiltrate with lymphocytes, hystiocytes, and giant cells (Hematoxylin-eosin – ×100) (Reproduced with permission from Bonamonte and Coll. [67])

was found in one case (6.7 %), in which the sampled lesion was 5 months old. In the remaining 14 cases, in which histology was performed on lesions that were 3–12 weeks old, a nonspecific dermo and/or hypodermic mononuclear-cell (lymphocytes, histiocytes, plasma cells) infiltrate was evidenced, with little or no tendency towards a tubercular-like granuloma formation (Fig. 11.22). Other observed features included dermal fibrosis (one case) and mild blood vessels proliferation (three cases). Ziehl-Neelsen stain highlighted acid-fast bacilli only in the histologically demonstrated tuberculoid granuloma case (6.7 %). Additional laboratory tests, done for differential diagnosis purposes in particular with other mycobacteria, fell into the normal or negative range in every case [67].

We collected two dead aquarium fishes for testing purposes: notably, acid-fast bacilli were present in Ziehl-Neelsen stained sections from the two examined aquarium fishes and PCR was also positive in the single fish tested.

As to treatment, 13 patients responded completely to minocycline monotherapy 100 mg twice daily in 2–3 months. In one patient, who had already been treated with sulfamethoxazole plus trimethoprim for 30 days with no apparent benefit, the infection finally resolved after a switch to isoniazid (600 mg/die) and rifampicin (900 mg/die) for 2 months. Mean duration of treatment was 2.7 months. It should be noted

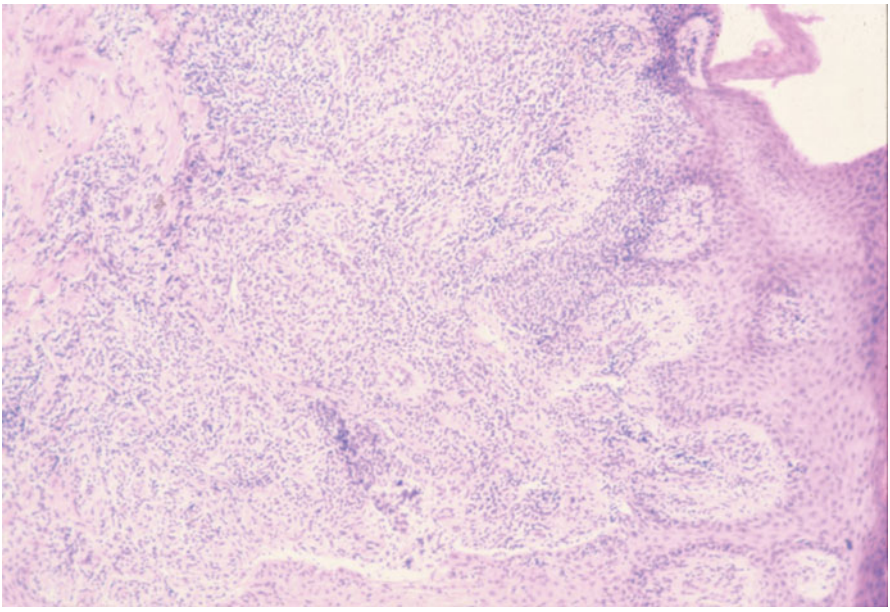


Fig. 11.22 Aspecific granulomatous infiltrate (Hematoxylin-eosin – ×40)

that therapy, that was antiobiogram-guided in all patients, was continued for at least a month after lesions clearance. None of the patients required surgical debridement. In the 8th months pregnant patient, regardless of the antibiogram sensitivity to tetracyclines, we did not administer the drug, given the well-known contraindications. Other viable options were either ineffective, as per antibiogram, or unfit for use during pregnancy. However, a spontaneous regression of the infection was observed through weekly follow-up, with complete resolution 1 month post-partum. End of follow-up in all the patients ranged from 12 months to 2 years and did not reveal relapse in any case [67].

In conclusion, the diagnosis of *M. marinum* infection relies on a detailed history, as well as microbiologic and PCR-based investigations. From a preventive point of view, the use of adequate concentrations of free chlorine in swimming pools, spas and hot water tubs is advisable, as recommended by the Center for Disease Control and Prevention [69, 70]. Furthermore, fish tank-related infection may be prevented by the use of waterproof gloves during maintenance and by the appropriate care of skin lesions on the upper limbs [71]. For the latter, however, chlorine derivatives show a limited activity against mycobacteria [72], whereas phenol, formaldehyde and glutaraldehyde derivatives are effective.

Recently, fish tank water sterilization by UV filters, which easily inactivate mycobacteria, has been introduced on the market, and a vaccine against *M. marinum* infection in fish has also been designed [73, 74].

11.2 Infection by *Mycobacterium ulcerans*

This disease is essentially cutaneous, even if it can be accompanied by bone involvement. It is characterized by the presence of ulcers with an undermined border and indolent course. No general signs are present. Due to its notable frequency in one region of Uganda, Buruli, it is better known as the Buruli ulcer, as instanced on the World Health Organization (WHO) Consulting Group web site: www.who.int/buruli. In the literature, the infection has also been reported by other eponyms: Bairnsdale ulcer (referring to the first focus, in Australia), Kakerifu ulcer and Kasongo ulcer (for the foci in Congo), and Kumusi ulcer (foci in New Guinea-Papuasia) [75].

After tuberculosis and leprosy, infection by *M. ulcerans* is the third most common mycobacterium infection in immunocompetent individuals [76]. In 1977, WHO recognized the infection as an important emerging disease, and in 1998 a world campaign to fight the infection was launched.

The disease had first been recognized as a specific entity in 1937 in Bairnsdale, South-East Australia, and the first Australian observations were published in 1948 [77], when a new alcohol-acid-resistant bacillus was isolated from the borders of cutaneous ulcers, that grew in culture at temperatures ranging between 30 and 33 °C, named *M. ulcerans* [78]. The first African report was in Uganda, and in 1972 the name Buruli ulcer was proposed [75]. The infection was then reported in many inter-tropical nations, Africa, South-East Asia (Malaysia, Indonesia, India, Sri Lanka, China), Latin America (Mexico, Peru, French Guyana) and Oceania (New Guinea-Papuasia) [79–86].

On numerous occasions, infection by *M. ulcerans* appeared 2–3 years after a severe ecological perturbation. It manifests as circumscribed endemic foci around aquatic systems (rivers, lakes, irrigation systems, marshes). *M. ulcerans* takes up to 6–12 weeks to grow at temperatures of 25–33 °C. Many conventional decontaminants can render the organism non viable, while the best culture media of the species must include egg yolk or a reduced oxygen tension. Molecular biology techniques have been developed to make a rapid identification of the organism [14].

Children over the age of 2 years, male or female, are the most frequently affected, likely because they have not yet developed an antimycobacterial immunity, as well as being more prone to contact with germs while playing. In adults there is a prevalence in women. Cases reported in tourists in endemic zones suggest a geographic risk as well as the need for conditions favoring the introduction of the mycobacterium into the organism: skin microtrauma, bites or stings by aquatic insects, bites by fish, wounds from shellfish claws, although never in marine saltwaters [75].

After an incubation of 6–12 weeks, the infection presents as one or more subcutaneous cold, well circumscribed nodules that do not adhere to the deep skin planes and are indolent and only mildly pruriginous. The legs are most commonly affected and less frequently, the arms. In children, the face and trunk can also be involved. Some forms can be extremely severe, showing an edematous onset, and are termed fulminant. They manifest as a hard, hot edema affecting a limb segment. The lesions

evolve slowly, the nodules fluctuate and ulcerate within 4–6 weeks. The ulceration is characteristic, featuring rounded or polycyclic margins while the base is covered by an adherent greyish-yellow patina that, when cleaned, appears granulomatous and erythematous. The ulcer margins are thickened, devitalized and undermined. There is generally only one ulcer but sometimes satellite, communicating ulcers can form around it. The lesions extend horizontally and can affect the entire limb, penetrating deep down to the muscles and tendons. These ulcers are painless or only slightly painful, and paradoxically, the patient's general conditions are good, with no fever nor loco-regional adenopathy.

The disease evolves over three phases: the above-described deep, horizontal extension, that lasts several months, is followed by a non uniform stabilization phase, while in the third and last phase there will be centripetal scarring. A superimposed infection of the lesions can occur, and it also poses a risk of tetanus. Even if this skin mycobacteriosis is not considered fatal, it can cause disabling scars, with tendon retraction, anchylosis, post-scarring lymphedema; amputation of the limb could even be necessary. In some disease foci a bone infection is also reported (osteomyelitis and even bone necrosis), that develops as a result of contiguity with the skin lesions or through the bloodstream [87].

The histology of the nodular and ulcerative lesions is peculiar. It initially reveals a necrotic eosinophilic vasculitis penetrating down to the deep derma and hypoderma; ischemia progressively affects the epidermis, and blistering appears, originating the ulceration process. During the ulcerative phase, the hyperplastic epidermis tend to become deeply invaginated, while a lymphohistiocytic infiltrate appears in the derma. The hypoderma is affected by the same massive eosinophilic necrosis and arteriovenous thrombosis may occur. In necrotic zones, Ziehl-Neelsen or auramine staining demonstrates the mycobacteria. In the chronic phase there will be a granulomatous infiltrate, with macrophagic epithelioid and giant cells. Finally, fibrohyalinose will replace the necrosis and lead to healing.

A direct search for the mycobacterium in the lesions is possible only in 30–65 % of cases, whereas the same search on biopsy samples seems to be more sensitive. Culture is also frequently negative, whereas gene amplification tests are rapid and sensitive.

M. ulcerans is the only mycobacterium that secretes a toxin with strong cytotoxic and immunosuppressive properties against the T lymphocytes. This same toxin, mycolactone, also inhibits local macrophagic phagocytosis, which explains the weak inflammatory reaction in the course of extensive necrosis.

Medical treatment offers no benefit in the case of extensive ulcerations [76]. Preulcerative lesions can be successfully treated by surgical excision, followed by monotherapy with rifampicin or heat therapy. Post-surgical antimycobacterial treatment can prevent relapse of the infection and metastases. However, many antimycobacterial agents are inefficacious; to control complications of the ulcers, rifampicin and clarithromycin are valid drugs. The ulcerations can be treated by superficial debridement and subsequent skin grafting [76].

The administration of the BCG (Bacillus of Calmette and Guérin) vaccine can confer some immunity also to infection by *M. ulcerans*: in fact, it has been noted that the disease incidence is notably reduced in vaccinated children. It should be borne in mind that *M. ulcerans* has a phylogenetic but not phenotypic affinity to *M. marinum* [88].

11.3 Infection by Rapidly Growing Mycobacteria

Rapidly growing mycobacteria (RGM) are known to cause cutaneous and subcutaneous infections as well as pulmonary, extra-pulmonary and systemic/disseminated disease. The main source of RGM is drinking water [89]. They can also be isolated from rivers and lakes, seawater, waste water from hospitals, animal drinking troughs, hot drinking water distribution systems, raw milk and soil [90]. It should be noted that RGM are robust bacteria, that are resistant to the standard disinfectants (e.g., chlorine) used in water treatment processes and in the hospital setting [91].

11.3.1 *Mycobacterium abscessus*

The most common source of the infection is tap water. An easy access point for this mycobacterium is also any skin piercing (e.g., tattooing) [92].

The skin infected by *M. abscessus* is erythematous, edematous, hot and painful; blisters and pustules can also be present, together with fever, chills, muscle aches, and a general feeling of malaise. Post-traumatic wound infections cause localized abscesses that can give rise to sporotrichoid pictures via a rising lymphatic spread [93]. Even if they are rare, infections by *M. abscessus* have been reported in fish handlers or individuals exposed to saltwater [94, 95], yielding sporotrichoid pictures similar to those of *M. marinum*.

The infection is diagnosed on a search for the bacillus in culture or molecular amplification tests. In localized infections, clarithromycin can be administered. This same antibiotic, together with azithromycin, is elective treatment also for disseminated forms, even if the risk of potential resistance makes it wise to combine these with other drugs such as amikacin, imipenem or cefoxitin.

11.3.2 *Mycobacterium fortuitum*

The onset of primary cutaneous and soft tissue infection due to *M. fortuitum* is most often following post-traumatic and surgical wounds, mesotherapy injections, venous catheterization in a healthcare setting, and at injection sites [96–100].

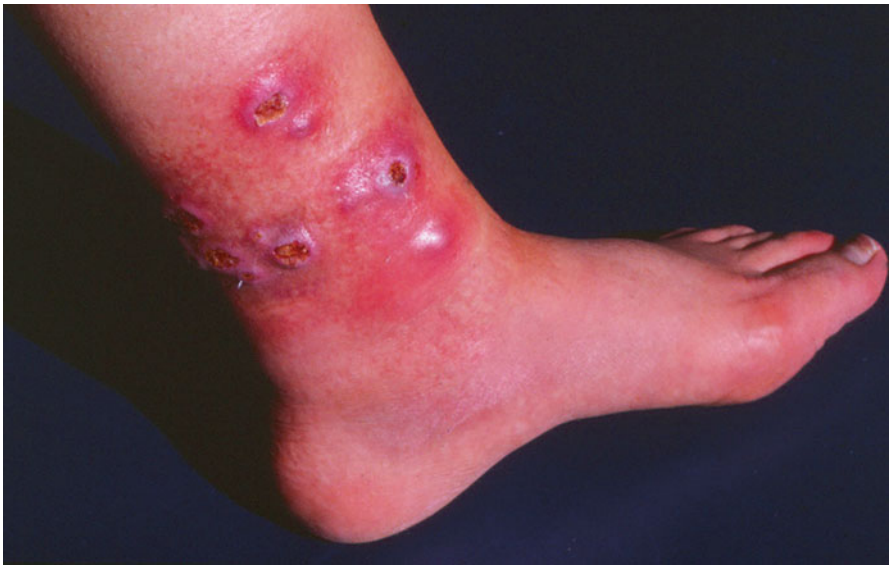


Fig. 11.23 Erythemato-ulcerative nodules from *Mycobacterium fortuitum*

Typically, the infection begins with erythematous-papulous lesions, that progress within weeks or months to purplish, fluctuating, painful nodules that evolve to ulcers (Fig. 11.23). Satellite adenopathy is rare.

Infection by *M. fortuitum* generally has a chronic, progressive course, although a spontaneous regression is sometimes observed. *In vitro s*usceptibility tests are important for treatment decision making. The most active drugs are macrolides (clarithromycin), quinolones, and sulfonamides but at least 4 months of therapy, with at least two agents, will be needed. Surgical drainage is indicated in cases of extensive disease and abscess formation.

11.3.3 *Mycobacterim chelonae*

Contaminated water is a natural reservoir and source of infection in man. *M. chelonae* prevalently infects immune-impaired subjects, such as HIV/AIDS patients. Cutaneous infections have been observed in hemodialysis and peritoneal dialysis patients, kidney and liver transplant patients, and individuals with tattoos [14]. The skin manifestations are like those induced by *M. fortuitum* (Fig. 11.24).

M. chelonae isolates show resistance to cefoxitin but are susceptible to clarithromycin, tobramycin and imipenem. However, susceptibility *in vitro* is not always correlated with a treatment efficacy *in vivo*. The choice of antibiotics (several drugs in combination), the treatment duration and the clinical outcome will depend on the host immunity status. Excision and drainage of the skin abscesses is a valid aid.

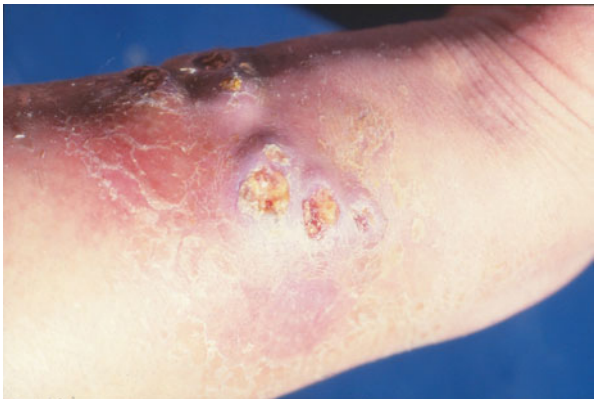


Fig. 11.24 Erythemato-ulcerative nodules from *Mycobacterium chelonae*

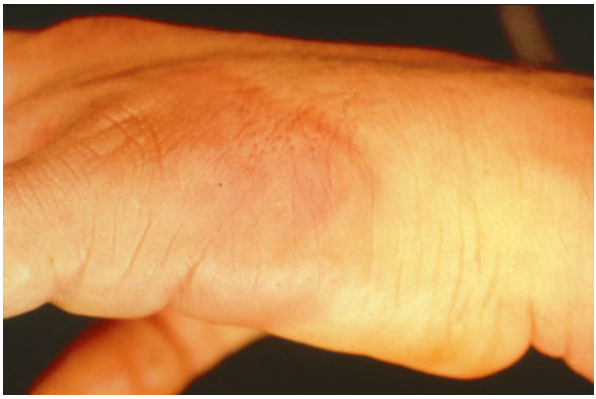


Fig. 11.25 Erysipeloid: erythematous raised lesion with centrifugal extension

11.4 Erysipeloid

This dermatitis, also known by the name of Baker-Rosenbach's erysipeloid, is an acute, rarely chronic infection induced by *Erysipelothrix rhusiopathiae,* the aetiological agent of "swine erysipelas" [101, 102]. *E. rhusiopathiae* is a Gram-positive, non spore-producing and non mobile bacillus, which usually has long filaments. It can survive in the environment for long periods and also lives in the sea. The infection is common not only in pigs but also in horses, chickens, ducks, sheep, turkeys and other animals and in salt- and freshwater fish. Although it is widespread all over the world in animals, man rarely contracts it. Most of the cases reported were occupational, being most often observed in fishermen and butchers. It has also been described in housewives pricked by fish or chicken bones.

The onset of erysipeloid is generally in the late summer when animal infections are most common. About 3 days after contagion, the puncture zone develops a dark erythematous raised area with an irregular centrifugal extension and distinct, raised polycyclic margins (Fig. 11.25). The sites most commonly involved are the hands and forearms but all exposed areas may be affected. In 10% of cases, fever

develops; pricking and itching sensations and pain may also be present. The area affected will spread wider over the following days and reach a maximum diameter of 10 cm. It resolves spontaneously in 2–3 weeks without any desquamation or suppuration phenomena [103–106].

Apart from this modest, localized form, a generalized skin condition can be observed in rare cases, as well as systemic forms complicated by septicaemia and endocarditis. Differential diagnosis must be made with erysipelas, a febrile streptococcal infection that spreads rapidly, and with cutaneous leishmaniasis [107, 108]. The disease does not confer immunity and re-infections are therefore possible. The bacterium responsible can be cultured from a biopsy sample obtained from the margins of the skin lesions, or from peripheral blood in systemic forms. However, isolation and identification is still not easy as the organism lies deep in the skin and culture (enriched with blood and incubated in an atmosphere containing 5–10 % CO_2) times are rather long. Some progress has recently been made in molecular approaches for diagnosis and for taxonomic and pathogenic studies of *Erysipelothrix.* Two different PCR techniques for diagnosis of the swine infection have also been described, one of which has been successfully used in human samples [109].

E. rhusiopathiae is sensitive *in vitro* and *in vivo* to penicillins, cephalosporins, tetracyclines (chlortetracycline, oxytetracycline), quinolones, clindamycin, erythromycin, imipenem and piperacillin. It is resistent to vancomycin, chloramphenicol, gentamicin, streptomycin, and trimethoprim-sulfamethoxazole. First choice drugs are penicillin and cephalosporins: a 7-day course is appropriate, and a clinical improvement is seen already after the first 2–3 days of treatment [101].

11.5 Infected Wounds

Seawater is a dilute suspension of bacteria, many of which are harmful to man and can cause various infections (external otitis, gastroenteritis, pneumonia). Wounds from any causes occurring in the sea can therefore easily become infected. The microorganisms isolated from infected wounds include bacteria present in seawater (vibriones, *Pseudomonas*, *Aeromonas* species, *Chromobacterium violaceum, Edwardsiella tarda, and Shewanella* species) and bacteria from normal skin flora (staphylococci, streptococci) [3].

11.5.1 *Aeromonas* Species

Aeromonas species (in particular *A. hydrophila*), that are Gram-negative rods found in warm, fresh and brackish waters worldwide as aquatic animal commensals and pathogens, give rise to wound infections typically occurring also after marine injuries from animals such as alligators, fish, snakes, or from freshwater leech bites [110, 111].

The body parts affected are generally the extremities or other regions immersed in contaminated waters during the warm months. Within 24 h, the wounds show

erythema, edema and purulent exudation. This may be followed by fever and chills and the onset of invasive infections, including necrotizing fasciitis, necrotizing myositis, and osteomyelitis in immunocompromised patients.

Most *Aeromonas* species are resistant to penicillins and first-generation cephalosporins. In addition to drainage and debridement of the wound, the infection must be treated with a combination of an aminoglycoside and either a fluoroquinolone or a third-generation cephalosporin.

11.5.2 *Chromobacterium violaceum*

This is an aerobic, Gram-negative bacillus widely distributed in soil and water in tropical and subtropical regions [112]. The bacillus grows rapidly in the usual culture media, producing purple colonies; strains of non pigmented *C. violaceum* are rarer, but the two forms may coexist in the same infection. The entry point is generally a wound or a fish bite, after exposure to brackish or stagnant water. The wound will become purulent, with a bluish exudate and regional swelling, usually of an extremity. In a few days, the onset of invasive septicemia can be observed, especially in immunocompromised subjects, with high fever and macular disseminated skin lesions that evolve to abscesses. Treatment is with aminoglycosides, fluoroquinolones, tetracyclines, imipenem, and trimethoprim plus sulfamethoxazole. The bacillus is resistant to penicillins and cephalosporins [3, 112].

11.5.3 *Edwardsiella tarda*

This is a Gram-negative rod of the family of Enterobacteriaceae, that is well known as a fish pathogen. Various cases of skin wounds that have evolved to abscesses after exposure to seawater have been described, especially after a catfish sting [113, 114]. As well as surgical drainage, treatment of all extra-intestinal cases relies on intravenous injection of a combination of Gram-negative anti-bacilli agents.

11.5.4 *Shewanella* Species

These are Gram-negative saprophytic bacteria that belong to the normal microflora of the marine environment in temperate and tropical regions worldwide. In culture they produce yellowish-brown mucoid colonies that emit hydrogen sulfide.

The most common clinical manifestations are deep ulcers, hemorrhagic blisters, generally on the legs, together with otitis externa, otitis media, and bacteremia. The ulcers can evolve to necrotizing fasciitis and osteomyelitis, while an ensuing septicemia is associated with endocarditis and meningitis. Pneumonia, cholecystitis, and peritonitis can follow the aspiration or ingestion of seawater. Triggering causes include trauma in seawater, the ingestion of raw seafood, preexisting ulcers on the legs, and immune system impairment [115].

Molecular amplification tests (PCR) are needed for a correct diagnosis. *Shewanella algae* is resistant to penicillins and first- and second-generation cephalosporins. Most species are sensitive to aminoglycosides, third-generation cephalosporins, and fluoroquinolones. In cases of invasive forms, a combination of several drugs is recommended, administered intravenously for 2 weeks followed by 2–4 weeks of oral therapy.

11.5.5 *Vibrio vulnificus*

This is a Gram-negative bacterium (of the Vibrionaceae family), that is pathogenic and highly virulent. It can cause three different types of infection: acute gastroenteritis from eating raw or under-cooked shellfish, invasive septicemia after ingesting raw shellfish (especially oysters), and necrotizing wound infections following marine injuries [3, 116].

Vibrio vulnificus is a halophilic, rod-shaped, motile bacterium that often flourishes in warm seawater estuaries, or brackish environments with a salinity of 0.5–2.5 % [117]. It is usually observed in temperate or subtropical seacoast regions or countries, such as the United States and East-Asia. Skin infections are uncommon, generally occur in the summer months, and are potentially fatal. Man is predisposed for several reasons, including occupational and recreational exposure to fish and shellfish (*V. vulnificus* can be isolated in the gut of oysters and other shellfish, and of fish that inhabit oyster reefs).

A necrotizing skin infection or septicemia following a marine injury, or the ingestion of, or exposure to raw seafood or seawater, especially in the summer months, should prompt suspicion of an *V. vulnificus* infection [3]. Aspirate from the skin lesions and blood cultures can demonstrate the characteristic bacillus. Antibiotic treatment must be instituted immediately due to high case fatality rates (CFR): a 24 h delay in starting therapy has been associated with a 33 % CFR and delays of more than 72 h with a 100 % CFR [118].

The US Centers for Disease Control and Prevention (CDC) recommend third-generation cephalosporins, specifically ceftazidime, plus doxycycline as the initial empiric treatment in suspected cases. In children, in whom doxycycline and quinolones are contraindicated, and in cases of antibiotic sensitivities, aminoglycosides and trimethoprim plus sulfamethoxazole can be used. Early surgical debridement of the wound and monitoring for compartment syndromes are indicated and help to reduce the mortality rate.

11.5.6 *Streptococcus iniae*

This Gram-positive beta-hemolytic is recognized to be a major fish pathogen that can cause outbreaks of invasive disease in farm-raised fish.

The first human cases of *S. iniae* invasive infections were reported in 1996 in subjects who had recently prepared fresh, whole, farm-raised fish [119]. The patients had handled live or freshly killed fish, and developed cellulitis within 16–24 h of an

injury incurred while handling the fresh fish, especially tilapia. In all cases the *S. iniae* isolates were sensitive to various antibiotics, such as aminoglycosides, cephalosporins, macrolides, penicillins, and trimethoprim plus sulfamethoxazole [119].

11.5.7 General Management of Marine Injuries

All traumas and even minor abrasions incurred in a seawater environment should be regarded as potentially contaminated by the commonest sea microbes, such as the *Vibrio* species. All wounds must be treated with normal sterile saline solution. Devitalized tissues must be surgically excised. Foreign bodies must be removed. Wounds should be left open to heal by secondary intention. Tetanus prophylaxis is indicated after all marine injuries [3].

Travelers with known risk factors for more severe marine infections, including those with open wounds, liver disease, an impaired immune system, diabetes mellitus, hematological disease, and AIDS, should be warned of the risk of contracting a marine infection after exposure to sea fish, seawater, live or freshly killed seafood, and ingesting raw or undercooked seafood, especially oysters. Travel medicine practitioners should be alert to the risk of onset of infection after an injury sustained in seawater, especially *V. vulnificus* in the Gulf of Mexico, *C. violaceum* in the Western Pacific, and *Shewanella* species in the Mediterranean and Western Pacific. Antibiotic treatment should be instituted at the first clinical signs of impetigo, cellulitis, erysipelas, pyodermas or necrotizing soft tissue infections [3].

11.6 *Pseudomonas* Dermatitis

Pseudomonas dermatitis has been reported after exposure to contaminated water in heated swimming pools, whirlpools, and hot tubes, or related to wearing a diving suit, or leg waxing [120–130]. Other pathogenic events for this dermatitis that are probably underestimated are exposure during a shower/bath [131, 132], or to contaminated bathing sponges or bathing suits [133].

In the majority of cases the causal agent is *Pseudomonas aeruginosa*, a Gram-negative, asporogenic, aerobic, mobile bacillus. It can survive at temperatures ranging from 4 to 42 °C, but not at pH values below 4.5. The most frequently reported serotypes are 0:9 and 0:11 and, less frequently, 0:4 and 0:8 [120–123, 132]. Major reservoirs include freshwater and humid terrains, but it may also be present on plants and in artesian wells. *P. aeruginosa* does not generally belong to the normal skin flora because it is unable to withstand dryness [134]. A simple occlusion does not seem to foster the growth of skin colonies of *P. aeruginosa*, whereas they can grow after prior hydration and then occlusion of the skin, bringing on skin manifestations [135].

The water temperature, pH and chlorine content are important factors for the development of skin infections, since *P. aeruginosa* can survive in warm and alkaline waters, that are physical-chemical conditions with lower chlorine levels [136, 137].

Usually, the dermatitis presents as maculous, pruriginous, follicular and papulopustular lesions on the lateral surface of the trunk, in the axillary folds, hips, buttocks, and suprapubic region. The onset of the lesions occurs a few hours or days after exposure, and they may show a pale green fluorescence under Wood's lamp [138]. Owing to the release of exotoxins, the skin eruptions can be accompanied by general signs such as malaise, fever, nausea and vomiting, diarrhea, painful otitis, a sore throat and sore eyelids, painful swelling of the mammary glands with axillary adenopathy [130, 132]. The affliction is usually self-limiting and resolves in 7–15 days. A case of "whirlpool-dermatitis" with "hot hands" has recently been reported: a 15-year-old boy suffered the onset of painful nodules on the palms and pustules on the forearms, 2 days after bathing in a new whirlpool. In children and adolescents such nodular lesions can also involve the soles of the feet ("hot foot syndrome") [139]. In immunosuppressed subjects, the infection can evolve to ecthyma gangrenosum, with nodules or progressive cellulitis [140, 141]; if untreated, it may persist for 2 weeks or more.

From the pathogenic standpoint, the typical skin distribution of the eruption can be explained by a possible specific apocrine tropism of *P. aeruginosa* [140] or, in cases linked to wearing a diving suit, by hydration and occlusion mechanisms [127]. Apart from the possible apocrine tropism of the bacterium, some authors believe that an occlusive enhancement during the hours after exposure, linked to wearing clothes that normally adhere to the typical sites of the eruption, can transform a superficial infection into manifest disease [132]. It is well documented in literature that not all members of a family exposed to the same water will develop the disease [132, 142]. A relapse may occur in cases of continued exposure.

Differential diagnosis of *Pseudomonas* dermatitis must be made with insect stings, other infectious folliculitis forms and scabies. The bacillus can be isolated in wells and tap water, kitchen sinks, bidets, showers, and the deep end of swimming pools.

Should the eruption persist, or severe general symptoms develop, and in immunesuppressed subjects, antibiotic treatment must be administered: the first-line antibiotic is ciprofloxacin 0.5–1 g daily. In children and adolescents ciprofloxacin is not recommended but piperacillin 4 g/tazobactam 0.5 g twice daily can be prescribed [139]. In milder cases, topical use of antibiotics, such as gentamycin or polymyxin may be sufficient [130].

Apart from the clinical forms reported above, *P. aeruginosa* can induce other skin infections such as balanitis, omphalitis, "green nail syndrome", as well as wound infections [143].

For prevention purposes, pool maintenance staff should have an adequate knowledge of appropriate chlorine and pH levels and monitor them daily. The free chlorine residual level must be 0.6 mg/l or higher with a pH of between 7.2 and 7.8, or 1.5 mg/l or higher with a pH of between 7.8 and 8.2. To eliminate *Pseudomonas*, some authors recommend hyperchlorination, with a chlorine residual level maintained at 5 mg/l or higher for at least 72 h [123]. In Germany, the Federal Environment Agency publishes special hygiene requirements for public bathing establishments and their surveillance: for whirlpools, for example, a free chlorine content of 0.7–1 mg/l and a pH value of 6.5–7.8 are required [130].

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