Rare infective causes of chronic wounds

Although rare in the UK, there are certain types of infective organisms that can cause chronic wounds. In these circumstances, conventional wound care is rarely successful and the causative organism needs to be targeted with specific therapy. Often, these organisms are contracted abroad and may be seen in returning travellers or immigrants. In addition, patients who are immunosuppressed are at risk of opportunistic infections. Thorough patient assessment is key to establish a diagnosis, but a high index of suspicion may also be needed. This article describes three cases in which unusual infective organisms were the principal cause of chronic wounds.

Chronic wounds are characterised by a persistent inflammatory state, which impairs the physiological healing process. The presence of pathogens in the local wound environment is thought to contribute to this abnormal immune response (Martin and Nunan, 2015). Sometimes, rather than contributing to chronicity, pathogens can lead to cutaneous disease, including chronic wounds. In these circumstances, conventional wound care may not achieve healing, as the underlying cause of the wound has not been addressed. As such, an appreciation of these uncommon infections may be useful for the wound specialist.

Although rare in the UK, unusual infective causes of chronic wounds can be acquired abroad and so may be seen in returning travellers or immigrants from countries where these organisms are endemic. Alternatively, patients who are immunosuppressed are at higher risk of infection (Heinzelmann et al, 2002). In this group of patients, particularly those with immune deficiencies, infections may be opportunistic, i.e. rarely occur or only cause mild infections in immunecompetent individuals. An example is chronic granulomatous disease, an inherited primary immunodeficiency that is commonly associated with invasive fungal infections (Arnold and Heimall, 2017). In both of these circumstances, thorough patient assessment is required to trigger the appropriate investigations

that may establish a diagnosis. Certain factors in the patient's history and examination can prompt the clinician to suspect an unusual cause, for example, travel history, history of recurrent infections, associated systemic symptoms, atypical wound appearance or lack of response to conventional wound treatment. *Table 1* provides some examples of infections that can manifest with cutaneous complications, including chronic wounds. The typical features are described as well as the methods of diagnosis. Following this, we describe three cases that were treated in a complex wound clinic in the UK, unusual infective organisms were the principal cause of these chronic wounds.

CASE 1:
MYCOBACTERIUM TUBERCULOSIS

A 27-year-old man from Bangladesh presented with a non-healing wound above his left clavicle. Six weeks previously, he had attended the Emergency Department with a painful swelling in the supraclavicular region and feeling generally unwell. He underwent an incision and drainage of what was presumed to be an abscess and subsequently improved, however, the resulting wound failed to heal. He was otherwise fit and well and not on any regular medication. The wound was 2 cm by 1 cm, well-circumscribed and had adipose-like tissue in its base, with no surrounding cellulitis. The wound surface was curetted and samples were sent for

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Table 1. A description of the organisms that can cause cutaneous manifestations and the features that may help in their identification

Name and Organism(s)	Occurrence	Risk factors	Clinical features	Diagnosis
Buruli ulcer* *Mycobacterium ulcerans* (Blaney, 2015)	Tropical: W Africa, Australia, Japan, S America	Rural wetlands, manual farming, or residing in an endemic region	A chronic painless skin ulcer, with undermined edges and a pale necrotic base, typically on the lower extremities healing with hypertrophic or keloid scarring. Bone and joints may be involved and contractures can develop. Often found in adolescent and young adult men	Biopsy for histology, Ziehl-Neelsen stain, specific mycobacterial culture and molecular diagnostics
Diphtheria *Corynebacterium diphtheriae, C. ulcerans, C. pseudotuberculosis* (Tiwari, 2015; Moore et al, 2015)	Globally in under-vaccinated populations; currently SE Asia, particularly India	Non- or under-immunised individuals residing in, or visiting an endemic region	A painful, non-healing chronic ulcerating lesion following the history of a minor laceration, with oedema, erythema and a greyish membrane. Super-infection with *Staphylococcus aureus* or Group A streptococcus leads to impetiginous lesions and spreading cellulitis. Cutaneous disease is highly infectious, leading to traditional pharyngeal disease in non-immune contacts	Bacteriological culture from ulcer samples, clearly stating clinical and travel history
Leishmaniasis* *Leishmania* protozoa (species varies according to "Old world" or "New world" acquisition) (Dagne and Jannin, 2015; Chiodini and Manser, 2013)	**"New world"** Mexico, C + S America **"Old world"** parts of Asia, N Africa, Middle-East, Mediterranean littoral, etc	Rural, forested regions, visitors from non-endemic countries, sandfly bites due to contact with vectors such as rodents, sloths, marsupials, domestic dogs, etc	A macule progressing to an enlarging papule and painless ulcer at the site of a sandfly bite. Exposed surfaces are most affected (face, arms, legs). Spontaneous healing can occur in months, but often lesions can persist for a year or more. Some untreated *Leishmania* species can progress to destructive mucosal lesions, causing facial disfigurement, called espundia, especially from the "New World"	Biopsy for histology to visualise intracellular parasites (amastigotes) and in viral transport medium for reference-centre molecular diagnostics
Melioidosis* *Burkholderia pseudomallei* (Blaney, 2015; Gibney et al, 2008)	Tropical + sub-tropical: Asia, N Australia, Pacific Islands, India, etc	Contact with soil and water in endemic regions, e.g. rice farming, especially following rainy season. Military personnel, construction workers, eco-/adventure-tourists, laboratory workers. High-risk comorbidities for infection, e.g. diabetes, cirrhosis, alcoholism, malignancy, etc	Single to multiple lesions, typically ulcers without purulence, associated with prior abscess formation. There is an absence of surrounding cellulitis. Lower extremities are mostly affected, but lesions can be found in any region. Dormancy has been reported to be as long as 62 years, so past travel history is notable. Regarded as a potential biological weapon	Bacteriological culture from ulcer samples, clearly stating clinical and travel history. The laboratory should be warned if considered likely due to inhalational risk
Mycetoma Bacterial: *Nocardia brasiliensis,* Fungal: *Madurella mycetomatis, Trematosphaeria grisea, Pseudoallescheria boydii, Falciformispora senegalensis* (Bower et al, 2015; Hogade et al, 2011)	Tropical and sub-tropical regions: Saharan and sub-Saharan Africa, India, C + S America and Australia	Agricultural and outdoor workers, especially barefoot exposure to soil, immunosuppression or underlying malignancy	Painless, enlarging subcutaneous nodules, eventually leading to sinus tracts with bony involvement causing deformity and loss of function. Typically found unilaterally on the foot or lower extremity, very occasionally elsewhere. Often in young adult men	Microscopy of purulent material may reveal causative organism in "granules". Biopsy for histology and specific fungal and actinomycete culture. Imaging helps assess the extent of infection
Blastomycosis* + Paracoccidioidomycosis* *Blastomyces dermatidis + Paracoccidioides brasiliensis* (Roy, 2015; Harris, 2015)	N + C + S America	Occupational and agricultural exposure to dust and soil, especially in woods, waterways and sheds. Immunosuppression	Multiple erythematous papules develop into verrucous, crusted or ulcerated lesions, which spread slowly. Found on the face or distal extremities and can mimic cutaneous leishmaniasis. These are often accompanied with constitutional symptoms of weight loss and fever. Much more common in men than women	Microscopy of biopsy may reveal characteristic yeasts, and specific fungal culture may yield the pathogen, confirmed by molecular diagnostics. The laboratory should be warned if considered likely due to inhalational risk
Tuberculosis* Mycobacterium tuberculosis complex (Raviglione and Getahun, 2015; Fontanilla et al, 2011)	Globally, but especially in non-industrialised countries, sub-Saharan Africa, Asia, Eastern Europe	Residence in an endemic region, extremes of age, HIV co-infection, other immunosuppression, diabetes mellitus, alcoholism, illicit drug use, cattle farming	Slowly progressive, painless swelling of a lymph node or occasionally multiple lymph nodes, reaching up to 10 cm in diameter, infrequently complicated by a draining sinus. The node is typically painless and not erythematous. There may be concomitant symptoms of constitutional or pulmonary tuberculosis	Excision biopsy or needle aspiration for histology, which should yield noncaseating granulomata and acid-fast bacilli. Tissue for culture may provide a rapid diagnosis using molecular diagnostics followed by traditional culture

*These are caused by category 3 pathogens, meaning that they are an infection risk to laboratory staff and therefore can only be processed in containment level 3 laboratories
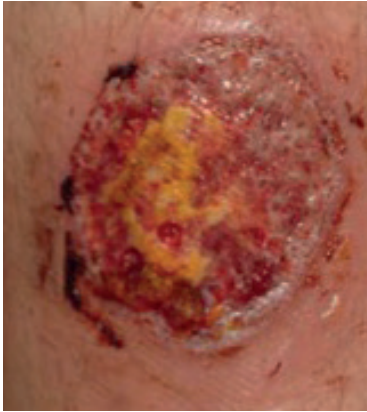
Figure 1. Wound on the posterior aspect of the lower leg. Well-defined raised borders are typical of cutaneous leishmaniasis. Classically, lesions begin as a papule at the site of the sandfly bite, which enlarges and eventually ulcerates. Wounds are not usually painful unless there is secondary bacterial infection. Multiple wounds are common and occur on exposed sites of the body such as the face, arms and legs

culture, which was positive for *Mycobacterium tuberculosis* (fully sensitive). A chest X-ray was normal. Blood tests were also normal, apart from slightly raised inflammatory markers (ESR 19, CRP 8). He was referred to the local Tuberculosis Unit and commenced on rifampicin, isoniazid, pyrazinamide, ethambutol and pyridoxine, which was reduced to dual therapy after two months. He received six months of treatment and during this time the wound fully healed.

This was a case of lymph node tuberculosis, often referred to as scrofula. *M. tuberculosis*, an acid-fast, aerobic bacillus, is typically associated with pulmonary infection, however, 15–30% of cases are extra-pulmonary, affecting any organ, but most commonly the lymph nodes (Dheda et al, 2016). Occurrence is worldwide, but highest incidence regions are sub-Saharan Africa, Central Asia and Eastern Europe; one-third of the global population is believed to be infected with *M. tuberculosis* (Dheda et al, 2016). Mycobacterial infection of the soft-tissues occurs following incision or spontaneous sinus development of an underlying lymph node, or due to primary cutaneous inoculation, and typically causes a chronic painless ulcer with undermined edges and a necrotic white or yellow base. This reflects the histopathological finding of incomplete caseous necrosis, recruitment of giant cells and granuloma formation (Dheda et al, 2016). Culture should be used in conjunction with histopathology to confirm the diagnosis and to provide essential antimicrobial susceptibility information (molecular methods are increasingly being used to speed up the time to diagnosis) (Fontanilla et al, 2011). Increasing antimicrobial resistance is a worldwide threat, with rising rates of untreatable tuberculosis, but for fully sensitive cases the combination of rifampicin, isoniazid, pyrazinamide and ethambutol remains the standard of care (Fontanilla et al, 2011).

CASE 2: *LEISHMANIA DONOVANI*
A 30-year-old man presented with painful bilateral lower leg ulcers that started after he returned from a holiday to Tunisia. He could not recall sustaining any injuries or insect bites during his trip. He was otherwise fit and well. He had three wounds, the

largest measured 15 cm by 5 cm. The wound edges were well-defined and the bases were sloughy *(Figure 1)*. Following biopsies and tissue cultures from the wounds, he was diagnosed with cutaneous leishmaniasis, caused by *Leishmania donovani.* He was treated with intravenous sodium stibogluconate, and two out of the three wounds healed rapidly. The largest wound, however, remained static. An element of venous disease was suspected and he, therefore, commenced compression bandaging, followed by class II stockings. The wound gradually improved and healed over two years later.

Leishmania protozoa are obligate intracellular parasites of humans and other mammals, transmitted through the bite of female sandflies (Chappuis et al, 2007). The disease is endemic to regions supporting the sandfly life cycle, principally Asia, Africa, the Americas and the Mediterranean littoral (Chappuis et al, 2007). Syndromes following infection are cutaneous, mucocutaneous and visceral leishmaniasis ("kala-azar"); each is associated with specific species of *Leishmania* (Chappuis et al, 2007). The lesions of leishmaniasis typically heal spontaneously after many months, however untreated mucocutaneous and visceral leishmaniasis are associated with progressive disfiguring nasopharyngeal destruction or ultimately fatal hepato-splenomegaly respectively, both taking several years to develop (Reithinger et al, 2007). Incubation from bite to cutaneous lesions or visceral symptoms is typically many months to several years. Diagnosis is based on the histological finding of amastigotes (nonmotile, intracellular parasites) from stained specimens of cutaneous, bone marrow, spleen, liver or lymph node tissues; with molecular methods on tissues used to speciate the leishmania (Chiodini and Manser, 2013). *L. donovani* is one of the causative agents of visceral leishmaniasis, making treatment mandatory, and options include pentavalent antimonials (such as sodium stibogluconate), amphotericin B and miltefosine (Reithinger et al, 2007).

CASE 3: *ASPERGILLUS FUMIGATUS*
A 26-year-old Venezuelan man presented with non-healing wounds on his back. Seven months previously, he had undergone a video-assisted thoracoscopic drainage of a right empyema, and following this, the port entry site failed to heal.

Figure 2. Wounds on the posterior chest wall at the port entry sites created during a video-assisted thoracoscopy. The wounds are relatively small with no suggestion of a communication with the chest cavity

The fluid drained from the chest at that time grew *Aspergillus fumigatus.* He was underweight and had previously undergone a right thoracotomy for a mass in his chest as a child in Venezuela (the exact nature of this was unclear). The wounds were 1cm by 1cm with friable, unhealthy granulation tissue suggestive of localised infection (*Figure 2*). There was no sign of communication with the chest cavity. He had mildly raised inflammatory markers (ESR 19, CRP 12) and radiological investigation was not suggestive of residual infection in the chest cavity. Multiple wound swabs were positive for *A. fumigatus*. Following the initiation of itraconazole and co-trimoxazole, there was a rapid improvement in his wounds and healing was achieved in two months. He was later diagnosed with X-linked chronic granulomatous disease (CGD), a disease of impaired phagocytosis by granulocytes leading to a greatly exaggerated risk of specific infections.

Aspergillus spp. are ubiquitous moulds found throughout the environment and across the globe, particularly in decaying vegetation and compost piles (Patterson et al, 2016). Of the 180 species, *A. fumigatus* is most commonly associated with human disease (Patterson et al, 2016). Because of the ubiquity of this organism, occurrence of disease is as an opportunistic infection; risk factors include prolonged neutropenia, corticosteroid treatment, organ transplantation, HIV-infection and CGD. The variety of clinical syndromes caused by this infection range from hypersensitivity reactions to aggressive angioinvasive disease (Patterson et al, 2016). The usual focus of infection is the lungs and primary cutaneous infection is rare, requiring immunosuppression and traumatic introduction of the organism (Patterson et al, 2016). Treatment is with debridement wherever possible, correction of the immune defect and antifungal agents (itraconazole, voriconazole or amphotericin B). In CGD, *A. fumigatus* is the most common cause of opportunistic infection, usually affecting the lungs and chest wall (Arnold and Heimall, 2017). Prior to the use of azole antifungals, it was a major cause of mortality in these patients (Arnold and Heimall, 2017).

CONCLUSION

An understanding of the many potential causes of chronic wounds, including possible infective organisms, is important for accurate diagnosis and successful treatment. Thorough patient assessment, including background, travel history and systemic symptoms may point to an unusual infection such as leishmaniasis. In the above cases, standard wound care did not lead to healing and appropriate systemic antimicrobial treatment was required. Although rare in the UK, in cases of non-healing wounds with an atypical history or appearance, infective causes should be considered. **WUK**

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