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Dear Editor,

Scobie *et al.* recently reported a 10-year review of non-pregnant listeriosis cases in England[1]. No case of cutaneous listeriosis was reported in this large cohort of 1,357 patients. Aside gastro-enteritis and invasive infections (septicemia, neurolisteriosis and maternal-neonatal infections), *Listeria monocytogenes* (*Lm*) can also be responsible for other focal infections, including bone and joint infection, biliary, pulmonary, or urinary tract infections[2]. Skin infections have also been reported before, either as a part of disseminated infection in neonates —a condition known as "*granulomatosis infantiseptica*"— or as an occupational disease of veterinarians and farmers[3]. Cutaneous listeriosis include a multistep process starting from erythematous lesions, which become nodular and pustular within 2-5 days after contact of intact skin with infected fluids, such as animal secretions[3,4].

In France, surveillance of human listeriosis is based on mandatory reporting of cases since 1999 and voluntary submission of strains to the French National Reference center for *Listeria* (NRC). The exhaustiveness of this reporting is estimated around 87%[5]. In this context, we retrospectively studied all consecutive culture-proven *Listeria*-associated skin and soft tissue infections reported to the NRC from January 1994 to December 2018). All cases with the mention of "cutaneous", "nodular", "pustular", "skin" or "soft tissue" infections were included. Medical charts were reviewed and clinical bacterial isolates sequenced.

Species identification was carried out with API-Listeria microgallery (bioMérieux, Marcy l'Etoile, France) before January 2017, and thereafter with MALDI-TOF mass spectrometry as described[6]. Hemolysis tests were performed at 37°C for 24h on horse blood agar. Genome sequencing was performed as described[7]. PCR serogrouping, multilocus sequence types (MLST) and core genome MLST (cgMLST) profiles were deduced from genome assemblies using the BIGSdb-*Lm* platform (https://bigsdb.pasteur.fr/listeria)[8].

Among 7,294 human cases collected between 1994 and 2018 in France, 16 involved patients with *Listeria*-associated skin/soft tissue infections (0.2%). Of them, 11 (11/16, 69%) were male. Median age was 62 years (range: 8 – 93); 4 patients (4/16, 25%) were more than 80 years old. Only 5 patients reported immunosuppressive comorbidity (lung cancer (n=2), cirrhosis (n=1), diabetes mellitus (n=1), Rituximab therapy (n=1)) (5/16, 31%). Lesions consisted in single skin abscesses (n=11), cellulitis (n=3) or single nodular lesions (n=2). Three patients reported fever (3/16, 19%). Skin lesions involved legs (n=7/15, 47%), arm/hands (n=5/15, 33%), or the face (n=3/15, 20%). When performed (n= 5), all blood cultures were negative. No patient reported any other *Listeria* localization, in particular no concomitant neurolisteriosis or gastro-enteritis. Environmental exposure was only reported in one farmer patient. No other patient reported any contact with animals, farms, hay or contaminated silage. No preexisting skin abrasion was reported.

Lm was grown from skin samples in 15 cases; *Listeria seeligeri* was identified in one case. One *Lm* isolate from 1994 could not be grown from the culture collection and was therefore not sequenced. All sequenced *Lm* isolates belonged to different cgMLST types (Figure 1), indicating that these cases were unrelated microbiologically, and that a large variety of strains can be responsible for cutaneous listeriosis. 5/14 *Lm* isolates (36%) belonged to hypervirulent clonal complexes (CC1 and CC4)[9]. No acquired resistance toward the main antibiotics for listeriosis treatment was evidenced (amoxicillin, ampicillin, trimethoprim/sulfamethoxazole or gentamicin).

All patients received antibiotic therapy against *Lm*, for a median of 12.5 days (range, 7 – 21): amoxicillin/piperacillin 12/16, 75%, cotrimoxazole in 1/16, 6.3% and was not reported in 3 cases. Nine of them with abscesses also benefited from local drainage (9/16, 56 %). All patients experienced full recovery.

So far, only 26 cases of skin and soft tissue infections have been reported since 1957, as case reports or small series of less than 6 cases[4]. This series of 16 cases is, to our knowledge, the largest on this rare entity. Importantly, most published cases were reported before 1995 and before the implementation of current animal and food safety regulation[4]. At that time, cutaneous listeriosis appeared as an occupational hazard involving veterinarians or farmers exposed to infected secretions. Our case series, starting in 1994, captured a different picture of the disease. Indeed, in sharp contrast to previous reports that involved immunocompetent patients with massive occupational exposure, only one patient reported environmental (animal) exposure, whereas all other cases had no identified source of infection, but rather reported classical risk factors for listeriosis, namely older age and immunosuppressive comorbidities[10]. Although no local trauma was reported, skin infections may result from direct local inoculation rather than hematogenous dissemination, considering the constant absence of concomitant bacteremia, and of any other localization of infection, as well as the favorable evolution under relatively low dose amoxicillin (3g/d), much lower than recommended regimens for systemic listeriosis. The source of infection could be either contact with contaminated material, in case of infections of the limbs, or chronic fecal carriage, in case of perineal abscesses, as reported in bovine mastitis[11].

The main limitation of this work is its retrospective nature, although cases were prospectively reported as part of national surveillance. One could also not exclude under-diagnosis and under-reporting of this rare presentation, as most empiric antibiotic therapy targeting skin pathogens would be effective against *Lm* and lead to complete resolution, most infections remaining therefore likely undetected.

Altogether, these results underline the wide array of infections associated with *Listeria monocytogenes* and the favorable outcome of this very rare clinical entity.

Figure Legend

Figure 1. Single linkage clustering based on the cgMLST profiles of 14 *Listeria monocytogenes* isolates collected between 1994 and 2018 from patients' skin (1 isolate from 1994 could not be sequenced). The percentage of cgMLST profile similarities between isolates (based on 1748 genes) are indicated at branch nodes. The details on the molecular typing results, skin lesion and body location (when available) are provided in the adjacent column.

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