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ABSTRACT

Objectives: *Listeria monocytogenes (Lm)* is a foodborne human pathogen responsible for severe infection, including septicemia, neurolisteriosis, maternal-fetal and focal infections. Little is known about *Lm*-associated respiratory tract or lung infections.

Methods: Retrospective study of culture-proven cases of *Lm* pleural infections and pneumonia reported to the French National Reference Center for *Listeria* from January 1993 to August 2016.

Results: Thirty-eight consecutive patients with pleural infection (n=32), pneumonia (n=5), or both (n=1) were studied. 71% were men. Median age was 72 (range 29–90). Two patients presented with concomitant neurolisteriosis. All patients but one reported at least one immunosuppressive condition (97 %), with a median number of 2 (range, 0–5), including 29% (8/28) with current exposure to immunosuppressive therapy and 50% (17/34) with ongoing neoplasia. Seventy-five percent (21/28) reported previous pleural or pulmonary disease. Antibiotic therapy mostly consisted in amoxicillin (72%), associated with aminoglycoside in 32%. Chest tube drainage was performed in 7/19 (37%) of patients with empyema. Twenty five percent (7/30) of patients required intensive care management. In-hospital mortality reached 35% and occurred after a median time interval of 4 days (range, 1–33). Three patients had recurrence of empyema (time interval of 1 week to 4 months after treatment completion). Altogether, only 13/31 patients diagnosed with *Lm*-respiratory infection (42%) experienced uneventful outcome at 2-year follow-up.

Conclusion: *Lm* is a rare but severe cause of pneumonia and pleural infection in older immunocompromised patients, requiring prompt diagnosis, adequate management and follow-up.

INTRODUCTION

Listeriosis is a major foodborne infection caused by *Listeria monocytogenes* (*Lm*), a Gram-positive bacillus. Listeriosis incidence is estimated around 3 to 6 cases per million in Europe and the United States (1, 2). The 3 main invasive forms are isolated septicemia, neurolisteriosis and maternal-neonatal infections (3, 4). Non-maternal invasive infections are mostly reported in older immunocompromised patients with a mortality rate above 30%, despite antibiotic therapy (5). Aside from these typical presentations, other localized infections have been described, such as bone and joints, urinary tract, skin, bile and eye infections (6-10). Pleural and lung involvements have also been reported as isolated cases within cohorts of patients with listeriosis or as small series of 2 – 7 cases (11-15, 16 , 17, 18 , 19). The clinical presentation, microbiological characterization and outcome of *Lm*-associated pulmonary tract infections remain poorly characterized.

We studied all *Lm*-associated pulmonary tract infection cases reported to the French National Reference Center for *Listeria* (NRC, Institut Pasteur) over a 23-year period (1993 to 2016). We report here the results of the detailed study of this rare clinical entity by analyzing its clinical and microbiological features and outcome.

PATIENTS AND METHODS

Data collection – Surveillance of human listeriosis in France is based on both mandatory reporting of cases (monitored by *Santé Publique France*, the French public health agency) since 1999) and voluntary submission of *Lm* strains to the NRC. The exhaustiveness of this reporting is estimated at 87% (1).

All cases reported in France from January 1993 until August 2016 with mention of "pneumonia", "lung infection", "respiratory tract infection", "pleuropneumonia infection", "pleural effusion", "thoracic empyema" or "parapneumonic effusion" were included. Fourteen

cases reported before the mandatory reporting began were also collected. Clinicians and microbiologists in charge of the patients were contacted, and medical charts analyzed according to a pre-established checklist containing epidemiological, clinical and biological data as well as treatments and follow-up information relevant to both *Lm*- and respiratory infections (5, 20).

Case definition – Cases were classified as lung and/or pleural infection. A case of *Lm*-pleural infection was defined as a patient with acute respiratory symptoms, accompanied with pleural effusion and isolation of *Lm* by culture of a pleural sample. A case of *Lm*-pneumonia was defined as a patient with acute respiratory symptoms, and an acute infiltrate on a chest radiograph or auscultatory findings consistent with pneumonia and either a lower respiratory sampling (broncho-alveolar lavage or protected specimen brush) isolating *Lm* or a concomitant culture positive blood sample in the absence of any other respiratory pathogen documented, in according to international criteria (20, 21). Diagnoses of central nervous system infection or peritoneal infection were based on concomitant positive cerebrospinal fluid or peritoneal fluid culture, respectively. Pleural fluid was classified as exsudate when protein concentration was above 30 g/L and transudate when it was below 30 g/L.

Immunosuppressive conditions were defined as reported previously (22): daily alcohol uptake >3 glasses/day, cancer, congenital immune deficiency, diabetes, cirrhosis, hemodialysis for end-stage kidney disease, bone marrow transplantation, solid organ transplantation, hematological malignancies, pre-existing lymphopenia, pre-existing neutropenia, giant cell arteritis, systemic lupus erythematosus, rheumatoid arthritis, spondyloarthritis, inflammatory bowel disease, other auto-immune disease, asplenia, HIV infection, age > 70 years, prescription of corticosteroids and prescription of other immunosuppressive treatments in the last 5 years.

***Listeria monocytogenes* characterization** – Species identification of all *L. monocytogenes* clinical isolates was performed using the API-*Listeria* identification microgallery (bioMérieux, Marcy l'Etoile, France). Until December 2016, all *Lm* isolates were analyzed by Pulse Field

Gel Electrophoresis (PFGE) using a standardized protocol (23); and since January 2015, genome sequencing is routinely performed in parallel or in replacement of PFGE (24). Multilocus sequence typing (MLST) clonal complexes (CCs) (25) were either deduced from PFGE profiles as previously described (n = 30; (22)) or extracted from genome assemblies using the BIGSdb-*Lm* platform (http://bigsdb.pasteur.fr/listeria) when the genome was available or when the CC could not be deduced with confidence from PFGE profiles (n = 8; (26)).

Samples were all collected as a part of the National surveillance of listeriosis. The study was classified as retrospective observational and therefore exempted of Institutional Review Board approval by an appropriate local ethical Committee (Comité de Protection des Personnes Ile de France II) on the 4th July 2017, according to the French legislation.

RESULTS

Clinical cohort – Among the 7,911 human cases for which a clinical *Lm* strain was collected between January 1993 and August 2016 in France, 38 involved patients with *Lm*-associated respiratory infections (0.5%). They included 32 pleural infections, 5 pneumonias and both in one case. Distribution of reported cases was stable over time.

Epidemiological characteristics – The main features of the 38 patients are presented in Table 1. Median age was 72 (range, 29 – 90) and 24% of the patients (9/38) were older than 80 years. All but one patient reported at least one immunosuppressive comorbidity (37/38, 97%), with 12 patients reporting ≥ 3 (12/38, 32%). Among the 20 patients with neoplasms; 17 had ongoing neoplasia (17/34, 50%) and 3 were considered in remission (3/34, 9%). Seventy five percent of patients (21/28) reported preexisting respiratory tract or pleural diseases, including chronic obstructive or restrictive disease, pulmonary arterial hypertension, neoplasia, past pleural effusion or pleural tuberculosis sequelae.

Clinical characteristics – The main symptoms are detailed in Table 2. Clinical presentation was non-specific, with most patients reporting fever (13/20, 65%) and dyspnea (14/27, 52%). Two patients had concomitant documented neurolisteriosis, including one with also *Lm*-associated peritoneal infection. Another patient reported simultaneous pleural and peritoneal *Lm* infections. A patient had both pleural and peritoneal effusion, with *Lm* only evidenced in pleural fluid (culture of peritoneal fluid was negative).

Microbiological features – By definition, all pleural infections had *Lm* evidenced in pleural fluid cultures (32/32, 100%); of them, 6 also exhibited positive blood cultures (6/32, 19%). One patient had *Lm* isolated from broncho-alveolar lavage, pleural, peritoneal and cerebrospinal fluids (but not in blood culture) and was diagnosed with *Lm* pneumonia and pleural empyema. Among the 5 cases with *Lm*-pneumonia, one had *Lm* cultured from the distal protected brush sample and 4 from concomitant blood cultures (with no significant pathogen evidenced from sputum or blood culture cultures). No resistance toward main antibiotics for listeriosis treatment was evidenced (amoxicillin, ampicillin, cotrimoxazole and gentamicin) (27). Isolates belonged to hypervirulent clonal complexes (CCs) in 26% of cases (CC1, 2, 4 and 6, 10/38), hypovirulent CCs in 16% (CC9 and 121, 6/38) or to other CCs in 58% (22/38). This matched the overall CC distribution among human clinical isolates in France during the same period (data not shown) (22).

Laboratory and radiological findings – Biological data are detailed in Table 2. All but one patient exhibited blood leukocytes cell count above 10,000/mm^3 (median leucocytosis of 14,580/mm^3); all patients exhibited blood C-reactive protein levels ≥ 100mg/L when performed (n=11, median value of 192 mg/L). No difference in blood leukocyte count or C-reactive protein level was found between patients with or without pleural infection (data not shown). Pleural fluid characteristics were available for 20 patients with *Lm*-associated pleural infection. Pleural fluid was described as serous effusion in 6/20 patients (30%), cloudy or purulent in 11/20 (55%)

or hemorrhagic in 3/20 (15%). It was classified as an exsudate in 14/20 cases (70%), with a predominance of polymorphonuclear cells in 8/14 cases (57%). Radiological data were detailed for 6 patients with pneumonia (5 with pneumonia alone and one patient with concomitant pleural infection). Pneumonia was described as a focal consolidation involving either a lower lobe (4/6), 2 lower lobes (1/6) or 2 lungs (1/6).

Treatment and follow-up – Median follow-up was 8 months (range, 1–160). Treatment and evolution data are detailed in Table 3. Seven patients required intensive care (7/30, 25%), including mechanical ventilation in the context of acute respiratory distress in 3 cases (3/30, 10%). One patient died in the hours following admission before *Lm* was identified and antimicrobial therapy prescribed, all others received active antibiotherapy (amoxicillin, amoxicillin-clavulanate, aminoglycoside, cotrimoxazole and fluoroquinolones). Median antibiotic reported duration was 14 days (range, 1– 42). Chest tube drainage was performed in 9/19 cases with pleural infection (47%). Among the 31 patients with follow-up data available, 11 in-hospital deaths were reported, including 8 attributed to ongoing *Lm* infection (11/31 (35%), with 1/5 pneumonias (20%), and 10/26 pleural infections (38%)). Median time interval between the diagnosis procedure and death was 4 days (range, 1 – 33).

Among the 20 patients with clinical cure, 3 relapses were reported within one week to 4 months after antibiotic completion. All relapses were reported in patients with initial empyema. They included one early relapse 7 days after treatment completion that required pleural drainage and prolonged antibiotics and 2 other clinical relapses without bacteriological confirmation, respectively 3 and 4 months after treatment completion. These 2 episodes could not be microbiologically documented: one patient died before thoracentesis and the other received preemptive antibiotics before the collection of purulent pleural fluid. Another 4 cases died within 2-year follow-up, as a consequence of their underlying conditions (neoplasia or

cirrhosis). Altogether, only 12/31 (39%) were alive and did not report any relapse within 2-year follow-up.

DISCUSSION

Here we studied the characteristics of *Lm*-respiratory infections in a large series of 38 consecutive patients over a 23-year study period. To our knowledge, only 16 pneumonias and 23 empyemas have been reported over the past 40 years, either as isolated case reports or small series of 2 to 7 cases (11-15, 16 , 17, 18 , 19). Only one patient had pleural localization in a review of 64 invasive cases (16); in another series of 102 kidney transplanted patients with listeriosis, 7 reported *Lm*-related pneumonia (7%, 5 deaths) (28). This study is therefore to our knowledge the largest on this rare entity, and the only one examining detailed clinical and microbiological data. Its main limitation is its intrinsic retrospective nature, that hampered the exhaustiveness of the collection of epidemiological and clinical data, although cases were reported in a prospective manner in the context of the national surveillance of listeriosis. Another limitation is a possible under-reporting of atypical *Lm* infections, especially when *Lm* is not retrieved from the blood or cerebrospinal fluid, although the exhaustiveness of mandatory reporting has consistently been estimated around 87% in the last 30 years through capture/recapture studies, with isolate sent to the NRCL for above 95% of declared cases (1, 29). Four pneumonia cases had *Lm* only evidenced in blood cultures, we can therefore not exclude the possibility of a *Lm*-bacteremia occurring in the context of a pneumonia due to another pathogen or of an acute respiratory distress syndrome. We chose to classify them as *Lm*-associated pneumonias, as they were considered as such by clinicians after adequate work-up did not evidence any other pathogen, furthermore clinical presentation was in line with previous reports (17, 18 , 19) and good subsequent evolution was reported under amoxicillin-

200 therapy in 4/5 cases. This was in agreement with international guidelines that classify such
201 cases with clinical and radiological evidence of pneumonia and blood documentation (30).
202 Important conclusions can be drawn from this study. First, *Lm*-associated respiratory infections
203 occurred in older patients mostly combining 2 conditions: (*i*) immunosuppression, including
204 ongoing neoplasia, reported in 97% and 59%, respectively; and (ii) pre-existing lung/pleural
205 disease, reported in 75%. Immunosuppressive conditions are indeed a major risk factor for
206 respiratory infections (31) and for listeriosis, evidenced in 93% of non-maternal cases in the
207 French listeriosis cohort MONALISA of 818 cases (5). The high proportion of ongoing
208 neoplasia (solid organ cancers and haematological malignancies) and immunosuppressive
209 drugs exposure has long been identified as a major risk factor for invasive listeriosis; as it has
210 been reported in 44% of non-maternal cases in the French MONALISA cohort (5) and in 8/9
211 cases with *Lm*- associated pleural empyemas reviewed by Mazzulli *et al*. in 1991 (11). *Lm*-
212 associated respiratory infections involved mostly men (71%), in line with previous observations
213 evidencing a male predominance in patients with invasive listeriosis (32) and in those with
214 respiratory infections (20).
215 The high proportion of patients with pre-existing lung and pleural conditions (75%,
216 mostly lung neoplasms and diseases responsible for recurring pleural effusions) had not been
217 evidenced before and might reflect specific pathophysiological features. Indeed, *Lm* is a
218 foodborne pathogen, responsible for bacteremia upon active crossing of the intestinal barrier
219 (33). Lung tissue lesions and/or inflammation may facilitate *Lm* access from the blood to alveoli
220 or from the parietal pleural capillary to the pleural space (34, 35). Haematogenous seeding is
221 the most likely scenario for respiratory *Lm* infections, which is a foodborne pathogen that
222 reaches the brain, the placenta, as well as bones and joints via the haematogenous route (8, 36,
223 37). Bronchogenic seeding appears less likely. Pathogens associated with bronchogenic
224 infections are often residents of the pharyngeal cavity; involved in sinusitis or bronchitis, which

have not been reported so far for *Lm* to our knowledge nor in our large series of 38 cases over a 23-year period (20). These are typically responsible for pluri-microbial empyemas, with frequent anaerobes involvement, in contrast with *Lm*-associated pleural infections, where *Lm* is constantly the only isolated microorganism (35). Bronchogenic parapneumonic effusions and empyemas may develop as a consequence of protracted pneumonias, which was reported in only one *Lm*-associated pleural infection (35). Trans-diaphragmatic infection after peritoneal infection appears as a rare occurrence, as concomitant peritoneal infection was documented only in 2 cases, with no evidence for abdominal infection or peritoneal fluid infection in the other 36 cases.

Lm-associated respiratory infections exhibit distinct clinical features: 35% of patients were afebrile at diagnosis, in line with the frequent lack of fever reported in old and/or immunocompromised patients with lower respiratory tract infections (20). The most important feature of *Lm*-associated respiratory infections is their marked severity, highlighted by the frequent need for intensive care management (25%), high in-hospital mortality (35%), recurrence rate in pleural infections and 2-years post-hospitalization mortality (15% and 25% of surviving patients, respectively). In-hospital mortality appears twice higher than the mortality rates reported in bacterial pneumonias (4 – 18% at one month as reviewed by Prina *et al*. (20)) but in line with the highest mortality rates reported in patients with severe opportunistic respiratory tract infections due to *Legionella* (35% (38)) or in immunocompromised patients with purulent pleural infection (empyema) (5 – 40%, reviewed in (35)). In-hospital mortality for *Lm*-respiratory infection reaches levels recorded for neurolisteriosis (5). Patients underlying conditions account most likely at least in part in this very poor outcome, in line with the elevated post-hospitalization mortality rate (5/31, 16%). The lack of available data hampers a detailed analysis of management strategies, especially treatment duration and expected benefits of chest drainage in *Lm*-empyema. However, this

study underlines the importance of considering *Lm* when a Gram-positive bacillus is evidenced in a respiratory sample. Third-generation cephalosporins, which might be considered in preemptive treatment of lower tract infections, are intrinsically ineffective and should not be proposed when listeriosis is suspected (39). Amoxicillin is the key antimicrobial for *Lm* in clinical practice; it should be combined with gentamicin despite the modest lung diffusion of aminoglycoside, as the combination exhibits a synergistic effect that overcome the weak bactericidal effect of antibiotics on *Listeria sp* (39). Extra-pulmonary tract *Lm* localization should systematically be looked for, as it is reported in 8% of the cases of this series. Indeed, neurolisteriosis requires specific management with higher betalactamin dosage (12).

In conclusion, *Lm* is responsible for pleural infections and pneumonias in older patients with immunosuppression and pleural/pulmonary underlying disease – a profile of patients that is poised to expand. *Lm*-associated respiratory infections likely reflect high host vulnerability; and are associated with high morbi-mortality in the range of other major invasive forms, namely bacteremia and neurolisteriosis. *Lm* should be considered as an important, although rare, opportunistic pathogen for pleural infections and pneumonias.

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