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1 ***Listeria monocytogenes*-associated respiratory infections: a study of 38 consecutive cases**

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16

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18

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27 **ABSTRACT**

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

31 **Methods:** Retrospective study of culture-proven cases of *Lm* pleural infections and pneumonia
32 reported to the French National Reference Center for *Listeria* from January 1993 to August
33 2016.

34 **Results:** Thirty-eight consecutive patients with pleural infection (n=32), pneumonia (n=5), or
35 both (n=1) were studied. 71% were men. Median age was 72 (range 29–90). Two patients
36 presented with concomitant neurolisteriosis. All patients but one reported at least one
37 immunosuppressive condition (97 %), with a median number of 2 (range, 0–5), including 29%
38 (8/28) with current exposure to immunosuppressive therapy and 50% (17/34) with ongoing
39 neoplasia. Seventy-five percent (21/28) reported previous pleural or pulmonary disease.
40 Antibiotic therapy mostly consisted in amoxicillin (72%), associated with aminoglycoside in
41 32%. Chest tube drainage was performed in 7/19 (37%) of patients with empyema. Twenty five
42 percent (7/30) of patients required intensive care management. In-hospital mortality reached
43 35% and occurred after a median time interval of 4 days (range, 1–33). Three patients had
44 recurrence of empyema (time interval of 1 week to 4 months after treatment completion).
45 Altogether, only 13/31 patients diagnosed with *Lm*-respiratory infection (42%) experienced
46 uneventful outcome at 2-year follow-up.

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

50

51 INTRODUCTION

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

63 We studied all *Lm*-associated pulmonary tract infection cases reported to the French
64 National Reference Center for *Listeria* (NRC, Institut Pasteur) over a 23-year period (1993 to
65 2016). We report here the results of the detailed study of this rare clinical entity by analyzing
66 its clinical and microbiological features and outcome.

67 PATIENTS AND METHODS

68 **Data collection** – Surveillance of human listeriosis in France is based on both mandatory
69 reporting of cases (monitored by *Santé Publique France*, the French public health agency) since
70 1999) and voluntary submission of *Lm* strains to the NRC. The exhaustiveness of this reporting
71 is estimated at 87% (1).

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

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

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

90 Immunosuppressive conditions were defined as reported previously (22): daily alcohol uptake
91 >3 glasses/day, cancer, congenital immune deficiency, diabetes, cirrhosis, hemodialysis for
92 end-stage kidney disease, bone marrow transplantation, solid organ transplantation,
93 hematological malignancies, pre-existing lymphopenia, pre-existing neutropenia, giant cell
94 arteritis, systemic lupus erythematosus, rheumatoid arthritis, spondyloarthritis, inflammatory
95 bowel disease, other auto-immune disease, asplenia, HIV infection, age > 70 years, prescription
96 of corticosteroids and prescription of other immunosuppressive treatments in the last 5 years.

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

100 Gel Electrophoresis (PFGE) using a standardized protocol (23); and since January 2015,
101 genome sequencing is routinely performed in parallel or in replacement of PFGE (24).
102 Multilocus sequence typing (MLST) clonal complexes (CCs) (25) were either deduced from
103 PFGE profiles as previously described (n = 30; (22)) or extracted from genome assemblies
104 using the BIGSdb-*Lm* platform (<http://bigsdb.pasteur.fr/listeria>) when the genome was
105 available or when the CC could not be deduced with confidence from PFGE profiles (n =
106 8; (26)).

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

111

112 **RESULTS**

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

117 **Epidemiological characteristics** – The main features of the 38 patients are presented in Table
118 1. Median age was 72 (range, 29 – 90) and 24% of the patients (9/38) were older than 80 years.
119 All but one patient reported at least one immunosuppressive comorbidity (37/38, 97%), with
120 12 patients reporting ≥ 3 (12/38, 32%). Among the 20 patients with neoplasms; 17 had ongoing
121 neoplasia (17/34, 50%) and 3 were considered in remission (3/34, 9%). Seventy five percent
122 of patients (21/28) reported preexisting respiratory tract or pleural diseases, including chronic
123 obstructive or restrictive disease, pulmonary arterial hypertension, neoplasia, past pleural
124 effusion or pleural tuberculosis sequelae.

125
126 **Clinical characteristics** – The main symptoms are detailed in Table 2. Clinical presentation
127 was non-specific, with most patients reporting fever (13/20, 65%) and dyspnea (14/27, 52%).
128 Two patients had concomitant documented neurolisteriosis, including one with also *Lm*-
129 associated peritoneal infection. Another patient reported simultaneous pleural and peritoneal
130 *Lm* infections. A patient had both pleural and peritoneal effusion, with *Lm* only evidenced in
131 pleural fluid (culture of peritoneal fluid was negative).

132 **Microbiological features** – By definition, all pleural infections had *Lm* evidenced in pleural
133 fluid cultures (32/32, 100%); of them, 6 also exhibited positive blood cultures (6/32, 19%). One
134 patient had *Lm* isolated from broncho-alveolar lavage, pleural, peritoneal and cerebrospinal
135 fluids (but not in blood culture) and was diagnosed with *Lm* pneumonia and pleural empyema.
136 Among the 5 cases with *Lm*-pneumonia, one had *Lm* cultured from the distal protected brush
137 sample and 4 from concomitant blood cultures (with no significant pathogen evidenced from
138 sputum or blood culture cultures). No resistance toward main antibiotics for listeriosis treatment
139 was evidenced (amoxicillin, ampicillin, cotrimoxazole and gentamicin) (27). Isolates belonged
140 to hypervirulent clonal complexes (CCs) in 26% of cases (CC1, 2, 4 and 6, 10/38), hypovirulent
141 CCs in 16% (CC9 and 121, 6/38) or to other CCs in 58% (22/38). This matched the overall CC
142 distribution among human clinical isolates in France during the same period (data not shown)
143 (22).

144 **Laboratory and radiological findings** – Biological data are detailed in Table 2. All but one
145 patient exhibited blood leukocytes cell count above 10,000/mm³ (median leucocytosis of
146 14,580/mm³); all patients exhibited blood C-reactive protein levels \geq 100mg/L when performed
147 (n=11, median value of 192 mg/L). No difference in blood leukocyte count or C-reactive protein
148 level was found between patients with or without pleural infection (data not shown). Pleural
149 fluid characteristics were available for 20 patients with *Lm*-associated pleural infection. Pleural
150 fluid was described as serous effusion in 6/20 patients (30%), cloudy or purulent in 11/20 (55%)

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

156 **Treatment and follow-up** – Median follow-up was 8 months (range, 1–160). Treatment and
157 evolution data are detailed in Table 3. Seven patients required intensive care (7/30, 25%),
158 including mechanical ventilation in the context of acute respiratory distress in 3 cases (3/30,
159 10%). One patient died in the hours following admission before *Lm* was identified and
160 antimicrobial therapy prescribed, all others received active antibiotherapy (amoxicillin,
161 amoxicillin-clavulanate, aminoglycoside, cotrimoxazole and fluoroquinolones). Median
162 antibiotic reported duration was 14 days (range, 1– 42). Chest tube drainage was performed in
163 9/19 cases with pleural infection (47%). Among the 31 patients with follow-up data available,
164 11 in-hospital deaths were reported, including 8 attributed to ongoing *Lm* infection (11/31
165 (35%), with 1/5 pneumonias (20%), and 10/26 pleural infections (38%)). Median time interval
166 between the diagnosis procedure and death was 4 days (range, 1 – 33).

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

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

177

178

179 **DISCUSSION**

180 Here we studied the characteristics of *Lm*-respiratory infections in a large series of 38
181 consecutive patients over a 23-year study period. To our knowledge, only 16 pneumonias and
182 23 empyemas have been reported over the past 40 years, either as isolated case reports or small
183 series of 2 to 7 cases (11-15, 16 , 17, 18 , 19). Only one patient had pleural localization in a
184 review of 64 invasive cases (16); in another series of 102 kidney transplanted patients with
185 listeriosis, 7 reported *Lm*-related pneumonia (7%, 5 deaths) (28). This study is therefore to our
186 knowledge the largest on this rare entity, and the only one examining detailed clinical and
187 microbiological data. Its main limitation is its intrinsic retrospective nature, that hampered the
188 exhaustiveness of the collection of epidemiological and clinical data, although cases were
189 reported in a prospective manner in the context of the national surveillance of listeriosis.
190 Another limitation is a possible under-reporting of atypical *Lm* infections, especially when *Lm*
191 is not retrieved from the blood or cerebrospinal fluid, although the exhaustiveness of mandatory
192 reporting has consistently been estimated around 87% in the last 30 years through
193 capture/recapture studies, with isolate sent to the NRCL for above 95% of declared cases (1,
194 29). Four pneumonia cases had *Lm* only evidenced in blood cultures, we can therefore not
195 exclude the possibility of a *Lm*-bacteremia occurring in the context of a pneumonia due to
196 another pathogen or of an acute respiratory distress syndrome. We chose to classify them as
197 *Lm*-associated pneumonias, as they were considered as such by clinicians after adequate work-
198 up did not evidence any other pathogen, furthermore clinical presentation was in line with
199 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

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

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

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

259

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

266

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269

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