Listeria infection after treatment with alemtuzumab: a case report and literature review. Would antibiotic prophylaxis be considered?

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SUMMARY

Few cases of complicated infections with *Listeria monocytogenes* (LM) have been reported to date in patients with multiple sclerosis (MS) treated with alemtuzumab. Primary prevention strategies may be suggested in such patients to avoid infections. However, these may be ineffective because patients may already be carriers of LM. We report herein a case of bloodstream infection due to LM in a 25-year-old woman with MS treated with alemtuzumab. We searched the UMC/WHO Vigibase system for all reported cases of LM in patients treated with alemtuzumab and found 29 cases overall up to 21 July 2019. We also performed a literature review of MS cases with LM on alemtuzumab, in order to evaluate epidemiology, clinical characteristics, and outcome of this complication. Since the published cases (N=8) were mainly reported in recent years but more cases were found in the UMC/WHO Vigibase system (although not necessarily in patients with MS), we hypothesize that this complication is more frequent than currently believed and may become even more important in the future. Therefore, it is worth reaching a consensus on appropriate algorithms to stratify individuals by risk so as to implement targeted prevention strategies (whether primary or secondary).

Keywords: Listeria, alemtuzumab, multiple sclerosis.

INTRODUCTION

Alemtuzumab, an anti-CD52 monoclonal antibody, has been introduced as a treatment option for relapsing remitting multiple sclerosis (MS) and fludarabine-refractory chronic lymphocytic leukaemia (CLL) [1, 2]. It has been associated with several side effects, such as infusion reactions and potentially life-threatening infections, such as listeriosis by *Listeria monocytogenes* (LM) [3-5]. Few cases of LM sepsis and meningitis were already described [2, 6].

Listeriosis is a foodborne infection, caused by LM, a Gram positive bacterium, which can be easily acquired by introducing contaminated deli and dried meat or unpasteurized cheese and milk [4, 7]. This infection may be mild in immunocompetent hosts, with self-limiting fever, diarrhoea and abdominal cramps [4]. By contrast, in fragile patients such as those immunocompromised, the clinical course may be complicated by bloodstream and/or central nervous system (CNS) infections [8, 9].

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We herein report a case of a 25-year-old woman who developed LM bloodstream infection few days following alemtuzumab treatment. A systematic review of other cases reported in literature was performed. Also, we searched the Uppsala Monitoring Centre (UMC)/World Health Organization (WHO) Vigibase system for all reported cases of LM in patients treated with alemtuzumab.

CASE REPORT

A 25-year-old caucasic woman was diagnosed with relapsing-remitting MS in 2008 and has been followed up at the Unit of Neurology of the "Mater Domini" teaching Hospital in Catanzaro. Over years, she failed three lines of treatment: interferon (from 2008 to February 2012), beta-interferon (from March to August 2012), and fingolimod (from Jan-

Table 1 - Clinical characteristics and outcomes of the published cases of Listeria infection after treatment with Alemtuzumab

Authors, year	*No. patients*	*Gender and age (years)*	*Type of infection*	*Time between last infusion and onset of infection*	*Symptoms*	*Treatment and length*	*Time from admission to the start on an adequate antibiotic treatment*	*Outcome*	*Sequelae*
Wray S, et al., 2009*	1	F, 36	Meningitis	16 days after the last infusion	Fever, headache, abdominal pain	NA	NA	Favourable	NA
Rau A, et al., 2015	2	F, 47 F, 43	Meningitis Meningitis	The day after the last infusion Three days after the last infusion	Fever, headache, worsening of MS symptoms, photophobia Fever and headache	Ampicillin 21 days Ampicillin and gentamicin 21 days, then trimethoprim/ sulfamethoxazole as relapse prophylaxis for 4 weeks	1 8	Favourable Favourable	None None
Ohm S, et al., 2015*	1	F, 33	Sepsis	10 days after the last infusion	Fever and chills	Ampicillin for 14 days	NA	Favourable	NA
Holmoy T, et al., 2017	1	F, 50	Sepsis	Few hours after the third infusion	Nausea, fever, abdominal discomfort	Ampicillin and trimethoprim sulfamethoxazole, length NA	NA	Favourable	None
Haggerty P, et al., 2018	1	F, 35	Meningitis	Immediately after the fourth infusion	Leg tremors and headache, transient dysarthria, worsening of her chronic leg numbness	Ceftriaxone and 24 hours after ampicillin/ gentamicin	1	Favourable	Implanted ventricles-peritoneal shunt for hydrocephalus
Canham L, et al., 2018	1	F, 42	Meningitis	3 days from the last infusion	Diarrhoea, vomiting, general malaise, coma over hours	Amoxicillin 2 g every 4 hours	4	Unfavourable	Deceased on the day of the admission
Pappolla A, et al., 2019	1	M, 32	Meningitis	5 days after the last infusion	Fever, headache, abdominal pain	Penicillin for 3 weeks	6	Favourable	NA

*(abstract at the European Committee for treatment and Research, Dusseldorf and Barcelona in 2009 and 2015, respectively). F = Female, M = Male.

uary 2013 to 2015). From December 2015 to March 2018, she was treated with natalizumab. This drug was discontinued for the high risk of developing progressive multifocal encephalopathy (PML) due a high titre of anti-JC virus antibodies. Therefore, following eligibility criteria, neurology consultant decided to switch her to alemtuzumab.

From 17th to 21st September 2018, she received alemtuzumab infusions. No short-term side effects were observed during or immediately after infusions, and the patient was discharged.

After 4 days from the last infusion, she developed sore throat, productive cough and high-grade fever. For the worsening of symptoms and the onset of headache, she was admitted at the Unit of Infectious and Tropical Diseases on 28th September 2018. She did not present any comorbidity, and her past medical history was unremarkable. She did not have known allergies or intolerance and conducted a healthy life style.

At the physical examination, she did not show any abnormal findings. Temperature was 38.2°C, blood pressure 120/70 mmHg, heart rate 101 beat per minute and oxygen saturation 98%. She was clinically stable; there were no signs of meningeal inflammation or other neurological signs, apart from headache. A cranial computerised tomography (CT) scan was immediately performed, but it did not show any significant findings. Chest X-rays results were normal, as well as abdominal ultrasound. Chest high-resolution CT and cardiac ultrasound results came back as negative. Table 1 shows the results of microbiological tests that were prescribed. Complete blood count showed mild anaemia (9.8 g/dL, normal value 12-16 g/dl), white blood count 5.830 x 10^3 mmc, with 85.8% neutrophils and 2.4% lymphocytes. Protein C reactive and procalcitonin levels were 25.5 mg/dL (normal value <5 mg/dL) and 0.05 ng/mL (normal value <0.05 ng/mL), respectively.

As soon as microbiological and cultural samplings were performed, an empiric intravenous (i.v.) antibiotic treatment with levofloxacin and ceftriaxone was started. On positive blood cultures, multiplex polymerase chain reaction (PCR) was performed (Biofire® FilmArray®, bioMérieux diagnostics, Italy). It came back in few hours as positive for LM. By contrast, serology for LM was negative. Thereafter, levofloxacin and ceftriaxone were then switched to ampicillin 12 g/day and gentamicin 5 mg/kg/day. Symptoms recovered after 2 days, with a complete resolution of fever and normalization of inflammatory indexes. The i.v. antibiotic treatment with ampicillin and gentamicin lasted 2 weeks with an apparent complete resolution of the symptoms. Moreover, new blood cultures were negative. Therefore, the patient was discharged on the October 11th, 2018 with advice to continue oral antibiotic treatment with amoxicillin 3 g/day until October 19th. Three days after discharge, the patient had relapsing headache and fever, so she was readmitted on October 17th. Ampicillin and gentamicin were therefore restarted i.v. and continued until November 5th, 2018 when she was discharged in good conditions.

Literature review and results for the UMC/WHO database

As at July 21st, 2019 42 cases of listeriosis were notified and registered in the UMC/WHO (Vigibase) surveillance system in association with alemtuzumab treatment [10]. Among these cases, MS was reported as indication for alemtuzumab in 29, CCL was reported in 1, and for 12 cases no specific indications were reported. We reviewed all published cases as at the same date, by searching the PubMed database for the keywords "alemtuzumab" AND "multiple sclerosis" AND "listeria" OR "listeriosis". Clinical characteristics and outcomes of the published cases are summarised in Table 1. Most represented demographic features were female gender (7/8, 87.5%) and adult age. Median age was 39 years (range: 32-50). The median time to symptoms onset after alemtuzumab infusions was 5 days (range: 0-16 days). In most cases (6/8, 75%), there was a CNS involvement.

DISCUSSION

The overall prevalence of listeriosis after alemtuzumab among patients with MS was estimated to be about 0.26%, and female gender was most represented in the cases published so far [11-13]. So, not unexpectedly, our patient was a female, also probably because MS occurs more frequently among females. Currently, prevalence of MS is reported with a female to male ratio of up to 3.5:1, and it dramatically increased in females over the last 50 years [14]. Among cases reported in Table 1, female gender appeared to be slightly over-represented (87.5%) if compared with prevalence of MS among women (about 70%). This could be due to different reasons. It can be hypothesised

that women present some characteristics, which increase the risk of infection. Moreover, on the Vigibase system, rate of adverse events is higher in women than in men treated with alemtuzumab (59% vs. 31%) [15]. However, it cannot be excluded that underreporting of cases of LM among males could have played a role to produce this discrepancy.

Timing of onset of symptoms deserves also to be discussed. Several patients (including ours) develop symptoms related to listeriosis in few hours or days from alemtuzumab infusions (Table 1).

Alemtuzumab, which was recently warned for the high risk of infections and the occurrence of unexplained stroke events, induces a massive CD8 T cell depletion [3, 16-18]. These are the main cells involved in protection from Listeria infections [18]. So, it is possible that Listeria starts to replicate when immune system is at its nadir, especially in patients who are already carriers. Some authors, indeed, suggested that patients who are carriers of the bacterium in the gut may develop listeriosis when concomitant immunosuppression should occur [19-21]. This could be particularly true for patients described by Haggerty et al. and Holmoy et al. who developed symptoms in few hours from last infusion, as well as in our patient [5, 6]. In this patient, no specific food risk factors were present in her behavioural history, so this further supports the fact that she was already a carrier. By contrast, this hypothesis is not supported in other cases where the reported median incubation period for invasive listeriosis is longer (mean 11 days) [22, 23]. In these cases, acquired infection seems to be more likely.

In order to reduce the risk of listeriosis, literature data suggest that patients treated with alemtuzumab should avoid ingestion of uncooked/undercooked meats, soft cheeses and unpasteurised dairy products for at least one month after treatment [24]. However, in patients who are already carriers of the infection, this is obviously not useful. Therefore, in these cases, prophylaxis may be advocated in order to reduce the likelihood of reactivation (secondary prophylaxis). The importance of preventing infection and reactivation is underlined by observation that delay of diagnosis and inappropriate empirical antibiotic treatment have been shown to be independent predictors of mortality especially among patients with CNS involvement [25]. For these reasons, and since the lethality rate of invasive listeriosis can be very high (up to 40%), a prophylaxis treatment with oral amoxicillin or cotrimoxazole, in particular during the first days after alemtuzumab therapy, could represent a possible strategy to prevent the development of invasive listeriosis. Preventive strategy with cotrimoxazole is advocated in the United Kingdom [26]. However, randomised and controlled studies are necessary to understand whether an antibiotic prophylaxis would prevent severe LM-related condition. Indeed, from this point of view, data are quite scarce and there are not official guidelines or clinical trials that specifically evaluated and validated the efficacy of antibiotic treatment vs. behavioural prevention strategies, but only expert opinion (often case reports) are available [5, 6, 21, 26].

Clearly, general prophylaxis for all patients could increase the risk of overtreatment, so it would be useful to understand if there are any specific patient related characteristics that increase the risk of developing LM infections among patients with SM treated with alemtuzumab, and if there are biomarkers that can identify and predict this risk. So, targeted prophylaxis could be in place. Unfortunately, it is not easy to evaluate LM carrier status, since shedding of the bacterium in the stools is short and intermittent and PCR is quite expensive [17, 18]. Moreover, serology is unreliable and not recommended for diagnosis of past or acute listeriosis because sensitivity is reported to be low, although this datum comes from old studies [27]. Indeed, in our case, serology was negative.

In conclusion, listeriosis remains a quite severe condition in patients with MS treated with alemtuzumab. Further studies on risk assessment and prevention strategies are required.

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Authors' contributions statement

MM collected clinical data, did literature review, wrote the manuscript, and was involved in the clinical follow-up of the patient. BS, GG, FS, PV, AG were involved in the clinical follow-up of the patient. PV, SB and AG were responsible of the neurological management of the patient and revised the manuscript. AG, QA, MCL and GM were involved in microbiological tests and re-

vised the manuscript. SR kindly revised our manuscript for the sake of English language and style. EMT and TC supervised the final version of the manuscript, apart from following the infectious disease management of the patients.

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Conflict of interest
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