A case of possible *Bacillus clausii* sepsis.

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Abstract

***Bacillus clausii* is a Gram-positive bacterium whose spores are widely used as probiotics. The term "probiotics" indicates live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. While their favourable effects make them a potential option in treating various pathological conditions, in some vulnerable people such as infants, patients with diabetes, leaky gut, malignancies and post-organ transplant convalescence, probiotics can turn into opportunistic pathogens, causing sepsis, endocarditis, pneumonia and liver abscess.**

To our knowledge, only four cases of *Bacillus clausii* associated septicaemia have been reported. Hereby we describe an event of sepsis that was possibly caused by this bacterium, since it occurred – after a surgical intervention – to a diabetic adult woman who was independently taking Enterogermina® (*Bacillus clausii* spore oral suspension), and no other bacteria or fungi were found on blood cultures, apart from B. clausii. Thanks to a broad spectrum anti-infective therapy, the clinical response of the patient was excellent.

Keywords: *Bacillus clausii*, Septicaemia, Enterogermina, Probiotics.

Introduction

Bacillus clausii is a Gram-positive bacterium whose spores are widely used as probiotics. The definition of "probiotics", initially provided by FAO/WHO (Food and Agricultural Organization/World Health Organization) and years later confirmed by ISAPP (International Scientific Association of Probiotics and Prebiotics), refers to live microorganisms that, when administered in adequate amounts, confer a health benefit on the host [1]. The favourable effects of probiotics documented in the scientific literature, make them a potential option in treating various pathological conditions, especially gastrointestinal disorders [2-4]. However, a recent review of existing meta-analyses concluded that not all types of their related use are evidence-based. More, in some vulnerable people such as infants, patients with diabetes, leaky gut, malignancies and post-organ transplant convalescence, probiotics can turn into opportunistic pathogens, causing sepsis, endocarditis, pneumonia and liver abscess [5].

As far as we know, only four cases of *Bacillus clausii* associated septicaemia have been reported [6-9], with one of these even being questioned [10].

Herereby we describe an event of sepsis possibly caused by this bacterium. It occurred after a surgical intervention, to a diabetic adult woman who was independently taking Enterogermina® (*Bacillus clausii* spore oral suspension) for about two weeks, with no other microorganisms growing on blood cultures, apart from *B. clausii*.

Case Report

In July 2020, a 50-year-old Albanian woman – resident in Italy for years – underwent a biological mesh placement for multiple recurring ventral hernia. Her past medical

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history was as follows: congenital solitary kidney, diabetes, hypothyroidism, morbid obesity, hypertension; previous umbilical hernioplasty; previous plastic of median ventral hernia; further laparotomy due to relapse, with removal of prosthetic mesh and VAC-therapy positioning.

On the sixth post-operative day, fever took over (38ºC). No abnormal findings on physical examination and vital signs. Laboratory tests revealed white blood cells (WBC) 9200/mmc, neutrophils (N) 7000/mmc, C-Reactive Protein (CRP) 23 mg/dL [cut-off:<0.5] and Procalcitonin (PCT) 0.1 ng/mL [cut-off:<0.5]. Computed Tomography (CT) scan of the abdomen showed widespread flogistic hypodensity and micro-collections at the abdominal wall, with hepatosplenomegaly.

After an unsuccessful attempt at piperacillin-tazobactam therapy, defervescence was obtained by using meropenem, with CRP dropping to 3.3 mg/dl. Meanwhile, blood cultures performed at the onset of the febrile problem, tested negative. Instead, microbiological analysis carried out on abdominal drainage fluid, documented the growth of Methicillin-Resistant *Staphylococcus Aureus* (MRSA) and multi-susceptible Pseudomonas aeruginosa. Piperacillin/tazobactam was thus re-introduced in place of carbapenem, with the addition of teicoplanin.

Nevertheless, a few days later, fever returned, with peak temperature of 40º C. Moreover, vulvar pain was present.

The gynecologist diagnosed vulvovaginitis and prescribed topical gentamycin plus oral fluconazole. A second collection of blood cultures (19th post-operative day), tested again negative, as well as those ones from the tip of central venous catheter (CVC). Same result also from urine culture.

Meanwhile, CRP and PCT respectively rose to 13.9 mg/dL and 1.3ng/mL, with WBC still in range (6500/mmc). No abnormal findings on physical examination, vital signs and chest x-ray. No vegetations on both transthoracic and transesophageal echocardiography. A further CT scan of the abdomen, revealed reduction of the flogistic hypodensity above mentioned. HIV, Widal-Wright and Quantiferon test were negative. Same result for 1-3 Beta D Glucan assay, Leishmania and West-Nile Virus serology. Due to persistence of temperature rise, in agreement with the Infectious Disease (ID) consultant, the following changes were made: discontinuation of piperacilln/tazobactam, resumption of meropenem, start of oral metronidazole and switch to intravenous fluconazole. Teicoplanin was also continued. Unfortunately, this change didn't affect body temperature, since fever remained. However, on the side of phlogosis indices, PCT almost reached normalization (0.6ng/mL), with CRP 17.3 mg/dL and WBC 7000/mmc. The woman underwent a surgical revision, which didn't document significant alterations (the fascia was intact; there were no signs of collection in the abdominal soft tissues; the skin was left open). In the meantime, news came from the laboratory: as a matter of fact, blood cultures of 32th and 34th post-operative day, tested positive for *Bacillus Clausii*, which was identified by Gram microscopic examination, colony morphology in pure culture, and MALDI-TOF ("Matrix Assisted Laser Desorption Ionization-Time of Flight") assay.

Following an in-depth medical history led by the ID specialist, it emerged that the patient had been independently taking Enterogermina® (*Bacillus clausii* spore oral suspension) for two weeks. The intake of the probiotic, amounting to four billion spores per day, was thus immediately stopped. Furthermore, the ID consultant decided to broaden the spectrum of anti-infective therapy, mainly including drugs active against *Bacillus Clausii*: that's how daptomycin, clindamycin and ciprofloxacin were introduced. At the same time, fluconazole was replaced by caspofungin. Lastly, meropenem was continued and teicoplanin – under way for fourteen days – concluded. All of these provisions finally led to defervescence, as well as drastic reduction of PCR and definitive normalization of PCT (respectively: 17.3 → 1.4 mg/dL; 0.6 → 0.09 ng/mL).

Meanwhile, it emerged that *Bacillus clausii* had grown only in two of twelve blood culture bottles (six collected on the 32th post-operative day, and six on the 34th), making its pathogenic value not clear. Nevertheless, because of scant literature on this microorganism, the ID specialists suggested to continue the treatment, and asked the lab for an antibiogram to be performed. The microbiologist could test only a limited number of antibiotics – using Kirby Bauer disc diffusion – indeed without providing breakpoints, since not covered by EUCAST or CLSI. However, the collective impression was that of sensitivity of the bacterium to all the molecules analysed (meropenem, vancomycin, ciprofloxacin, daptomycin, linezolid), with the exception of clindamycin. This antibiotic was therefore discontinued.

The patient also underwent body global tomoscintigraphy (PET), which detected only mild and nonspecific signs of inflammation, mainly at the surgical site. After having ascertained the negativity of new control blood cultures, anti-infective treatment with meropenem, daptomycin, ciprofloxacin and caspofungin was concluded within the following three weeks (the duration of therapy was extended as a precaution, due to the particularity of the case). Subsequent clinical and laboratory check-ups, tested satisfactory.

Discussion

As far as we know, only four cases of *Bacillus clausii* associated septicaemia have been reported [6-9], with one of these even been questioned [10].

We faced an event of sepsis, occurred to a surgical and diabetic patient who was independently taking the probiotic supplement Enterogermina® (*Bacillus clausii* spore oral suspension) for two weeks. Since her blood cultures tested positive for *Bacillus clausii*, which was identified by Gram microscopic examination, colony morphology in pure culture and MALDI-TOF assay, we thought that the ongoing problem was caused by this bacterium, and ordered the immediate discontinuation of the probiotic (our patient also had diabetes, a possible risk factor for probiotics-related issues [5]). As soon as it became evident that the microorganism had grown only in two of twelve culture bottles (six collected on the thirty-second post-operative day, and six on the thirty-fourth), we felt somewhat less confident in our hypothesis. However,

defervescence, drastic reduction of PCR and normalization of PCT, were achieved after the introduction of daptomycin, ciprofloxacin and clindamycin, with the first two ones representing a good option against *B. Clausii*, according to the sensitivity test performed by our laboratory. Furthermore, this treatment led to negativization of follow-up blood cultures. We therefore assume that the etiology of this septic episode could be traced back to *Bacillus Clausii*. This, in a context of bacterial translocation –namely the passage of viable bacteria from gastrointestinal to extraintestinal sites, including bloodstream – as contemplated by the specific literature [11-13].

Conclusion

We faced an event of sepsis which was possibly caused by *Bacillus clausii*, since it occurred – after a surgical intervention – to a diabetic patient who was independently taking the probiotic supplement Enterogermina® (*Bacillus clausii* spore oral suspension), and for no other bacteria or fungi grew on blood cultures apart from *B. Clausii*. Thanks to a broad spectrum anti-infective therapy, the clinical response of the patient was excellent.

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