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[Case Report] Profound Symptom Alleviation in Long-Covid Patients After PAMP-Immunotherapy: Three Case Reports

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Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.

Abstract

Background

Long-Covid patients suffer from a range of symptoms with a largely varying degree of severity, including chronic fatigue syndrome (CFS), myalgic encephalomyelitis (ME), post-exertional malaise (PEM), postural orthostatic tachycardia syndrome (POTS), loss of smell and/or taste, cough, shortness of breath, headache, muscle ache, sleep disturbance, cognitive dysfunction, and depression.

Treatment

PAMP-immunotherapy was developed by one of us (UH), inspired by the old fever therapy a century ago, to treat cancer patients. Unintentionally, in three cases of Long-Covid, quick and profound symptom alleviation could be observed after only a few PAMP treatments.

Conclusion

PAMP-immunotherapy might be a treatment option for Long-Covid patients which is surprisingly brief, cheap, and effective.

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Keywords: Long-Covid, Post-Covid syndrome, PAMP-immunotherapy.

Introduction

Long-Covid / Post-Covid Syndrome

Long-Covid (LC), also named post-Covid syndrome (PCS), is defined as a syndrome diminishing quality of life and persisting more than 4 weeks after a Covid-19 infection (or vaccination), or symptoms occurring a couple of weeks after infection (or vaccination) and remaining persistent. Symptom duration, combination, and severity may vary extensively between patients; there is no uniform disease description. For instance, 32% of LC patients reported fatigue, and 22% reported cognitive impairment 12 weeks post-infection [1]. LC leads to health-related quality-of-life (QoL) reduction, with about 20% of patients reporting a severe reduction of QoL, 50% moderate, and 30% report mild PCS scores [2]. The LC set of more than 200 conditions affects at least 10% of Covid-19 infected individuals, with an estimate of 65 million afflicted individuals worldwide. The incidence can be subdivided depending on vaccination status and age at infection: LC afflicts 10-30% of non-hospitalized cases, 50-70% of hospitalized cases (mostly elders), and 10-12% of vaccinated cases. Symptoms can last for years and may even be lifelong [3]. Causal hypotheses include immunological effects such as persistent latent infection [4] and/or autoimmune disease trigger. In many cases, the severity of symptoms is so strong that patients are unable to work, and in cases of severe CFS, they even have to spend their lives in bed. Some preconditions favoring LC have been identified, such as type-2 diabetes, but one-third of LC patients have no known risk factors. It is often assumed that LC is a SARS-CoV-2 specific sequela; however, other viral infections, e.g., Ebola, may cause similar symptoms, in particular CFS [5].

Successful treatment of LC so far is an unmet medical need.

History of Fever Therapy in Cancer Patients

Inspired by observations from W. Busch in Germany[6], William Coley, in the years 1895-1936, used Streptococcal extracts to treat cancer patients, which led to numerous amazing cures. The molecular explanation, unknown to Coley, most likely was the activation of a strong innate immune response against cancer cells by bacterial ‘pathogen-associated molecular patterns’ (PAMP). It should be noted that most so-called ‘spontaneous regressions’ from cancer were preceded by a feverish infection. More details of these exciting results can be found elsewhere [7][8][9]. Cancer fever therapy later was overshadowed by X-ray and chemotherapy and is largely forgotten nowadays.

PAMP-immunotherapy

Following the gist of the Busch-Coley therapy, we developed a protocol for the treatment of cancer patients using approved PAMP-containing drugs off-label. This protocol was tested in cancer patients and refined under the legal label of an individual healing attempt (‘individueller Heilversuch’), which in Germany can be applied if the patient signs consent, the method is scientifically plausible, and adverse effects are known and predictable. We have seen numerous remissions (data not shown). If we focus on previously untreated patients without chronic preconditions, PAMP-immunotherapy turned

out to be inexpensive, safe, simple to apply, and, apart from usual flu-like symptoms, well-tolerated even if applied over longer periods.

Results

Case 1

Patient ARM, born in 1978, female, had depressive episodes in 2015 and 2017, a fibromyalgia diagnosis in 2017, and a diagnosis of arthritis at lumbar vertebra K5-S1 in 2019. She had 3 SARS-CoV-2 vaccinations. She presented at a university clinic in February 2022 with fibromyalgia symptoms including a whole-body pain score of 3-4/10, weakness, blood parameters largely normal, and overweight. No drugs were used at that time. She reported a SARS-CoV-2 infection in March 2022. Since the infection, POTS, pain, and weakness increased tremendously, leaving her in bed mostly all day and using crutches to walk. She visited the university clinic again in April 2022 and was diagnosed with CFS; muscle pain; joint pain; depression; POTS; constipation; obesity; elevated triglycerides, folic acid; reduced eosinophils, urine creatinine; EKG QTc 453; Canadian Bell score 20-30. Drugs consumed were morphine, an antidepressant, an antipsychotic, an antihypertensive, estradiol, progesterone, an asthma spray, and a laxative.

She started PAMP-immunotherapy in October 2023. After 12 days and three PAMP applications, she could walk without crutches into the physician's office and reported (in her own words): "Contrary to expectations, the therapy is already working very well. I hardly expected that. In fact, since the first injection and the changes I have noticed in my body, fibromyalgia flare-ups with the corresponding severe pain have been extremely reduced. I haven't used morphine once since then. I am able to keep going for a whole day with very few breaks in between. That was unimaginable 3 weeks ago. I couldn't do anything on my own at the time; I was just bedridden and full of pain, exhausted and listless. For the first weekend in a long time, I was able to cook, have visitors, and even drive a car. The CFS is also significantly reduced. My husband and daughter see the old me coming back." Four weeks after the PAMP treatment began, the antidepressant dosage was reduced by one third. Morphine, laxatives, and asthma spray were dropped. She still took antihypertensive, antipsychotic, and hormone drugs. However, this benefit was not completely durable. Tiredness and fibromyalgia pain returned partially a few weeks later, leading to an overall smaller improvement compared to the other two cases, who had no severe prior disease. Results are summarized in Table 1, which reflects the state 7 weeks after treatment began.

Case 2

Patient JS, born in 1954, male, slim, had LC symptoms since May 2022. Treatment started at the end of January 2023 and ended after 6 applications in March 2023. The patient reported a pronounced symptom improvement. The improvement lasted until manuscript preparation in December 2023 and appears durable.

Case 3

Patient RJH, born in 1963, female, slim, had LC symptoms since the 3rd vaccination in November 2021; no medicines or treatments, no prior chronic disease. PAMP treatment started in January 2023. She reported substantial improvement after four weeks and four PAMP applications. Her personal final statement was, “I am significantly more resilient.” The improvement lasted until manuscript preparation in December 2023 and appears durable.

Questionnaire

Patients were requested to fill out a symptoms questionnaire before PAMP treatment and after symptom relief. Patient JS filled out the initial questionnaire in retrospect. Results are summarized in Table 1.

Table 1. Symptom severity was compared before and after PAMP treatment using a questionnaire consisting of 14 questions. Severity was assessed on a scale of four stages: (1) not at all, (2) a little, (3) marked, and (4) strong. For each question, three numbers were recorded: symptom severity before treatment, after treatment, and the difference (0 indicating no improvement). If the symptom severity before treatment was rated as 1 (not at all), it was excluded from the calculation of improvement.

	Patient ARM	Patient JS	Patient RJS
Number of PAMP treatments until marked symptom improvement	3	4	4
Length of PAMP treatment until marked symptom improvement (weeks)	4	6	4
1. Shortness of breath	4-3=1		2-1=1
2. Lack of muscular power	4-3=1		4-1=3
3. Cough			
4. Tachycardia	4-4=0		3-2=1
5. Tiredness	4-4=0	3-2=1	4-2=2
6. Muscle or joint pain	4-3=1		3-2=1
7. Smelling or tasting problems	4-3=1		4-4=0
8. Balance or motor skill problems	4-3=1	3-1=2	4-2=2
9. Problems to concentrate during reading or to formulate longer sentences	4-3=1	2-1=1	2-2=0
10. Headache	2-2=0		
11. Sleep disturbance	4-4=0	3-2=1	
12. Avolition/motivation problems	3-3=0		2-2=0
13. Problems to control feelings	3-1=2		
14. Anxiety	2-2=0		
Improvement	9/47=20%	5/11=46%	18/28=36%

Discussion

Before we discuss PAMP-immunotherapy for LC patients, let’s take a brief look at the development of PAMP-immunotherapy in cancer, both in Coley’s time and today. PAMP-immunotherapy of cancer takes months. Unlike in

Coley's time, nowadays bacterial extracts can hardly pass regulatory hurdles for drug approval. In the quest to bring Coley's successes in cancer treatment into the present, we thought about means for a substitute for the bacterial extracts used by Coley and his contemporaries. By searching the list of approved drugs in Germany ("Rote Liste") and interrogating medical contacts, we aimed at finding approved drugs for potential off-label use in cancer therapy which, according to the patient information leaflet, contained pathogenic extracts or substances and where body temperature elevation was mentioned as one of the known side effects. In these cases, we presume that PAMP substances are contained in the drug.

This can be repeated, in principle, in any country. Within the EU, drugs approved in one country can be prescribed in any EU country. If those drugs cannot be found on a local pharmaceutical market, as a substitute, ordinary vaccines—which we did not test—might as well serve the function of PAMP-immunostimulation. Many vaccines are known to contain PAMPs. As an example, the yellow fever vaccine is one of the most effective vaccines ever made. It may provide protection for more than three decades [10]. The yellow fever vaccine contains several PAMPs which address at least six Toll-like receptors [11]. As another example, BCG is approved for the treatment of bladder cancer and might be tested in PAMP-immunotherapy. It should be noted that live attenuated vaccines may, in principle, be more effective compared to inactivated vaccines [12].

The drugs we identified do not contain live pathogens. We started cautious dose escalations in cancer patients under the legal label of an individual healing attempt ("Individueller Heilversuch"). Starting from a minimal dose applied subcutaneously, we continued, depending on tumor location and size, to escalate the dose on a daily basis i.v., i.m., i.t., p.t., or s.c. Once a maximal body temperature elevation above 38°C was achieved and body temperature declined to normal within one day, we transitioned from dose finding to treatment every two or three days, in close agreement with Coley's practice. As a note of caution, in a few cases, against the explicit recommendation in our treatment leaflet, dose escalation was skipped by the respective physician for unknown reasons. This might lead to unexpected and erratic fever courses. Therefore, and because the treatment dose determined by dose escalation may markedly differ from patient to patient, we regard dose escalation as mandatory. During treatment, tiny dose adjustments may be required to keep temperature elevation constant. This treatment schema turned out to be inexpensive and safe [9]. The main adverse events were flu-like symptoms.

Beneficial effects of PAMP-immunotherapy in LC patients JS and RJS were found by happenstance and were not expected. At the time of these findings, neither author was engaged in clinical trials ongoing in university networks. We tried to connect with working groups within those networks; however, those working groups are heavily engaged in clinical trials using new drugs. So, we attempted to approach and inform our circle of physicians interested in PAMP-immunotherapy for cancer, as well as LC patient interest groups, which led to the recruitment of additional LC patients. Other than cancer patients, LC patients reported symptom alleviation after only a few PAMP applications in a relatively short time.

Mechanistically, the reasons for PAMP-immunotherapy benefits in LC patients are largely obscure. There are indications that SARS-CoV-2 may drive the immune system into a highly deranged state, particularly regarding the crosstalk between

innate and adaptive immune responses [13]. Among the numerous findings indicating immune dysfunction are exhausted SARS-CoV-2-specific CD8+ T cells [13], memory cell, dendritic cell, and naive B-cell repertoires; on the other hand, activated innate immune cells and B-cells. Patterns of cytokines are altered compared to normal [3]. Levels of autoantibodies and markers of inflammation may be elevated [13][14].

At present, there is no clear picture of which of these observations are primary or secondary events, i.e., causal or downstream.

So, we are left to engage in speculation about the mechanisms induced by PAMP-immunotherapy in LC patients. In general, at the heart of a successful immune response to pathogens such as SARS-CoV-2 is the activation of dendritic cells (DC) by, in this case, viral PAMP plus viral antigen. In COVID-19 patients, plasmacytoid dendritic cells (pDC) are often downregulated [15]. A pre-stimulated innate immune response may prevent SARS-CoV-2 infection in elders[16]. Upon proper DC activation, DCs become licensed to activate downstream events such as the activation and expansion of T- and/or B-cells. PAMPs are the most potent activators of DCs. Hence, it is not implausible to hypothesize that PAMP-immunotherapy may funnel and streamline a proper immune response against latent viruses. Swank et al. recently found that 12 months post-infection, in 22 out of 37 LC patients, SARS-CoV-2 spike antigen could be detected, as opposed to none in 26 non-LC patients [17]. Thus, latent persistent infection is demonstrated in at least a fraction of LC patients. On a side note, in two cases of chronic borreliosis, which is caused by latent infection by Borreliae hidden in cartilage, we could observe a profound alleviation of symptoms after a few PAMP applications as well (data not shown).

Activation of DC occurs indiscriminately of the specific PAMP applied. Although we use PAMPs of bacterial origin, this may induce an adaptive immune response against cancer cells as well as viruses; the final immunostimulatory response target is merely dependent on the particular antigen(s) involved in DC activation. Coley suggested that cancer treatment success correlated with the degree of body temperature elevation during treatment. One explanation for this observation might be that DC activation is more prominent under fever conditions [18]. Similar to Coley's old experiments, the induction of fever is one of the aims of PAMP-immunotherapy.

The evolutionary old mechanism of fever might induce a reset back to a more coordinated immune function, involving both activating and damping effects.

Our findings should be substantiated by an approved clinical trial, including immunological investigations comparing pre- and post-treatment stages, in particular with respect to IL-6, TNF-alpha, CRP [14].

Interested groups are invited for formal collaboration.

Statements and Declarations

Conflict of Interest

The authors declare no conflict of interest.

Funding

This research did not receive any funding.

Consent For Publication

Written informed consent to publish/present these cases was obtained from the patients. Patients were still accessible at the time of manuscript preparation. Participants did not receive any form of payment or reimbursement for their participation.

Ethical Approval

PAMP-immunotherapy treatments were done in Germany under the legal framework of “Individueller Heilversuch” (individual healing attempt), which can be applied when all of the following conditions are valid: the patient has given signed consent; there is no known healing procedure available; the treatment is safe; the treatment has a scientific rationale; the main purpose of the intervention is healing. The last point is more precisely defined as ‘if the act of treatment is not guided by accompanying interests in formal scientific research.’ In Germany, for an individual healing attempt, an ethics committee consultation is not required [19].

Authors’ Contribution

UH (ORCID iD: 0000-0003-0918-5614) developed the treatment concept and wrote the manuscript (conceptualization, formal analysis, writing), RG and HP applied PAMP-immunotherapy to Long-Covid patients (investigation).

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