Monitoring the Pathogen-Specific Antibody Response in Periprosthetic Joint Infection – Kinetics and Implications for Treatment Strategies

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INTRODUCTION: Periprosthetic joint infections (PJIs) are a severe complication of arthroplasty and are associated with significant morbidity and mortality, posing an immense financial burden on healthcare systems. PJIs are most commonly caused by microorganisms introduced during surgery, but also through contiguous spread from an adjacent site or hematogenous dissemination. Microbiological culture is the gold standard for pathogen identification and diagnosis of PJI. However, culture diagnostics are time consuming and can be falsely negative, resulting in protracted or failed pathogen identification, thus delaying optimal antimicrobial therapy. We hypothesize that the pathogen-specific immune response to PJI reflects the infection process, provides clinically relevant information regarding infection course, and has the potential to optimize PJI diagnosis and antimicrobial therapy.

METHODS: We conducted a prospective matched cohort pilot study with 13 patients undergoing two-stage septic revision arthroplasty (PJI patients) and 11 control patients undergoing aseptic revision arthroplasty (Non-PJI patients). An institutional review board approval was obtained prior to commencement of this study (Nr. BB 036/20). We developed a custom high-throughput multiplex quantitative bead-based array for the simultaneous measurement of antibody responses against 32 pathogens commonly associated with PJI (Infection Array; IA). Patient material and clinical data were collected at multiple standardized time points around the explantation and reimplantation surgeries. To study long-term and acute antibody production, pathogen-specific antibody binding was measured in both the patients' sera and in cell culture supernatants of their peripheral blood cells (medium enriched for newly-synthesized antibodies; MENSA), respectively. Over the course of this pilot study, the IA was used to measure pathogen-specific antibody responses in 267 serum and 528 MENSA samples.

RESULTS: The IA was able to trace the dynamics of the pathogen-specific humoral immune response in all patients. In 8 of 13 (62%) PJI patients serum antibody titers against selected pathogens declined over the course of treatment. In six out of these eight PJI patients, serum antibodies were directed against staphylococci and streptococci. On the other hand, no changes in antibody titers were observed in 9 of 11 (82%) Non-PJI patients over a time course of 41 – 365 days. Using MENSA, we were able to measure the acute pathogen-specific antibody secretion by plasmablasts of the peripheral blood. Using that approach, we observed transient antibody production against numerous pathogens, predominantly staphylococci, streptococci and *C. acnes*, in 12/13 (92%) PJI patients, but also in all Non-PJI patients. Notably, *C. albicans* triggered an acute antibody production in 12/13 (92%) PJI patients, often within 5 – 11 days after surgery (8/13 PJI patients), and in 7/11 (64%) Non-PJI patients.

DISCUSSION: In PJI and Non-PJI patients, our host-oriented approach using the IA provided novel insights into the individual antibody response during the course of the disease. Serum antibody kinetics indicated that most PJI patients had chronic joint infections that resolved with therapy. The MENSA results confirmed these findings, and also showed that the immune system is constantly fighting off infectious agents, so that many invasive episodes do not manifest with clinical symptoms. Notably, the MENSA-based IA showed transient antibody responses to *Candida albicans* in most patients after surgery, suggesting that surgery and/or the accompanying extensive antibiotic therapy cause fungal invasion. Thus, IA is a valuable high-resolution serological tool to study the immunoproteomic footprint of infectious pathogens during the course of PJI. Our method provided a new tool to monitor the efficacy of PJI treatment and revealed new facets of the pathophysiology of PJI. Larger patient numbers are needed to evaluate the potential of IA for PJI diagnosis.

CLINICAL RELEVANCE: In the future, immunoproteomic analysis of the patients' acute and long-term antibody responses to pathogens may complement the standard diagnostic portfolio in PJI. The host-oriented approach may help to monitor the success or failure of PJI treatment for optimal patient follow-up, and guide clinicians to timely interventions and adaptation of the treatment strategy.

GRAPHICAL ABSTRACT: