

Reviewer 1

This manuscript is strictly related to clinical medicine and its molecular aspect is very limited as it essentially deals with two parameters related to the T cells.

We thank the reviewer for raising this question. Due to the scarcity of serial clinical samples, we had to focus our analysis on parameters that we had reasons to believe would be the most relevant for the therapy being used. Since the main objective of dendritic cell vaccination therapy is to induce an adaptive response, we chose to focus on CD4 as well as CD8 T cells, its two main axes. Furthermore, clinical data of the many immunotherapeutic approaches confirms that these cells, and especially CD8 T cells, are indeed the most relevant for treatment outcomes. In the manuscript, therefore, we evaluate and follow both the frequency and the phenotype of “all” T cells capable of recognizing the patient’s tumor during treatment, using a new approach that allowed for this broad analysis, which is usually not described in the literature.

In general, this is a well written manuscript clearly presenting all its aspects, but as a case report, its novelty cannot be generalized.

We thank the reviewer for this comment. We agree with the reviewer that, as a case report, the results cannot be generalized, and we attempted not to give that impression in the text. However, we think the results we observed and described are relevant and deserve publication, not only because of the clinical response itself, since the tumor nearly disappeared at a very late stage of the disease, but also because this clinical response was undoubtedly induced by vaccination and strongly dependent upon changes in CD4+ T cell activity, which predicted the recurrence. This point becomes even more relevant since CD4+ T cell responses are not usually investigated in most studies in the field. Thus, this illustrative case brings novel insights into the importance of the immunological response (and the involvement of its cell subpopulations) for tumor control and recurrence in GBM. To the best of our knowledge, this is the first clinical description of a correspondence between tumor activity and immunological response patterns depending on Th17 and CD4. A deeper understanding of the mechanisms underlying this response would pave the way for novel approaches either boosting Th1 or reducing Th17 activity, which could be translated into better clinical outcomes.

Moreover, the conclusion on the key role of CD4+Tcell phenotype in glioblastoma immunotherapy is unjustified.

While most work in cancer immunotherapy so far has focused mostly on the role of CD8+ T cells, we would like to point out that there is an important body of work showing that when both CD4+ and CD8+ T cells have been studied, an at least as significant role for CD4+ T cells has been reported, in cancer immunology as well as in transplantation and infectious diseases, and by extension, in the general physiology of the immune system. However, since this is a single case study, we have modified the text to describe the role of these cells more clearly but also to ‘tone down’ the claim of the key role of these cells in glioblastoma immunotherapy.

This manuscript should be submitted to a more clinically-oriented journal, e.g., MDPI Journal of Clinical Medicine or Cancers and not to IJMS.

While we agree with the reviewer that our manuscript could fit a more clinically oriented journal, we chose to submit it to IJMS’s special issue on Glioblastoma, since our main focus is the immune mechanisms behind the patient’s unexpected evolution

(during the response phase and recurrence), and not the clinical evolution itself. Immune response patterns are direct consequences of the body's molecular environment, so the immune response patterns throughout a patient's clinical history represent molecular changes that ought to be described and understood. In this manuscript, we describe a repertoire analysis tool that allowed us to detect and follow-up the patient's immune response patterns, thus revealing potentially relevant modifications in molecular configurations.