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Clinical Studies

Cancer cachexia and chronic inflammation: an unbreakable bond

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We read with great interest the recent article by McGovern et al. [1] titled "Cancer cachexia: a nutritional or a systemic inflammatory syndrome?", where the authors hypothesise that systemic inflammation could play a crucial role in the genesis and maintenance of cancer cachexia, although it was mainly considered a simple nutritional disease until recently.

In agreeing with the authors' proposal, however, we believe it is worth highlighting that the role of systemic inflammation in cancer cachexia has been well documented, even if it has not been emphasised in recent years. Therefore, we believe that the authors' question can be answered with certainty: neoplastic cachexia is, indeed, an inflammation-induced disease. In particular, it is precisely in the understanding of the phases of the body's response to oncogenesis and neoplastic proliferation, i.e., the resistance and tolerance phases, that we can find the explanation that link specific/non-specific inflammation and the aetiopathogenesis of cancer cachexia (and of its characteristic symptoms, including anorexia, sarcopenia, anaemia and immunodepression).

As discussed in our recent paper [2], the evolution of the neoplastic disease begins with the failure of the resistance phase, where the body attempts to counteract cancer cells by activating specific immunity, which is followed by an increase in innate immunity, characterised by a macrophage-mediated chronic inflammatory response that promotes tumour growth and orchestrates an immune-suppressive status with lymphocyte exhaustion, thus favouring tumour escape. This second phase (the tolerance phase) is characterised by the "cytokine storm", which is induced by the uncontrolled proliferation of cancer cells, chronic activation of the monocyte-macrophage system, subsequent immunopathology involving necrosis, and the associated factors (especially HIF). The persistence of the cytokine storm is therefore the key event of the tolerance phenomena, likely reflecting an alternative defence strategy where symptoms typical of cachexia aimed at fighting tumour growth and minimising damage. From this perspective, cancer cachexia must be interpreted as an expression of the tolerance phase and a systemic inflammatory response-related syndrome.

Over the past decades, our research group has demonstrated the key role of systemic inflammation in cancer and cachexia. In 1998, we demonstrated a correlation between systemic inflammation—as evaluated based on the levels of C-reactive protein (CRP) and interleukin (IL)-6—and the efficiency of immune response in patients with advanced ovarian cancer. We showed that inflammation was correlated with the impairment of peripheral blood T-cell function in response to the blastic stimulus [3]. Then, in 2000 [4], we demonstrated how the poor nutritional status of patients with advanced cancer—as evaluated based on the circulating levels of leptin, a key marker of nutritional status and energy metabolism, was correlated with high levels of proinflammatory macrophagic cytokines (IL-6, IL-1 and tumour necrosis factor-α). Moreover, we affirmed the need, when we establish to use of immunotherapy, especially in patients with advanced stages of disease and cachexia, to combine it with anti-inflammatory drugs (such as MPA at high doses) and weekly chemotherapy [5].

One often-neglected aspect that explains the deductions of the authors is that the cachectic syndrome can manifest differently in neoplastic patients. Reversible cachexia—typical of many patients at the time of diagnosis—regress if the neoplasm is effectively counteracted by available antineoplastic therapies. In these cases, as the tumour burden—typically associated with a chronic inflammatory profile with high levels of proinflammatory cytokines and CRP, a high neutrophil–lymphocyte ratio, and high Glasgow Prognostic Scores—decreases, the same indexes of inflammation also decrease with response to treatment and the resolution of cachexia and its related symptoms [6]. Conversely, in patients with no longer curable disease, the evolution of cachexia is accompanied by increasing inflammation and the progressive worsening of nutritional status until death (irreversible cachexia). This has been demonstrated by us in patients with advanced ovarian cancer, in whom the terminal phase of the disease was accompanied by the highest levels of IL-6 and lowest levels of leptin [7].

These findings answer the initial question posed by McGovern et al., as confirmed by the indispensability of anti-inflammatory therapy for the multimodal treatment of cancer cachexia [8]. The authors correctly propose a comparison with COVID-19; the similarities between chronic inflammation, the evolution of ovarian cancer and its symptoms, and COVID-19 have been discussed recently by us [9]. Then, anti-inflammatory therapy can be used not only to treat the most commonly reported symptoms of cancer (such as weight loss and anorexia), but also allows to introduce other therapies (such as immunotherapy) to significantly prolong patient survival [10].

In conclusion, we consider of fundamental importance the highlights that you propose hypothesising an interpretation of neoplastic cachexia as a systemic inflammatory disease and the therapeutic implications of this assumption. Nevertheless, we emphasise that these topics have been discussed for decades and are supported by a body of literature devoted to these issues.

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DATA AVAILABILITY

Not applicable.

REFERENCES

1. McGovern J, Dolan RD, Skipworth RJ, Laird BJ, McMillan DC. Cancer cachexia: a nutritional or systemic inflammatory syndrome? Br J Cancer. 2022;127:379–82.
2. Maccio A, Sanna E, Neri M, Oppi S, Madeddu C. Cachexia as evidence of the mechanisms of resistance and tolerance during the evolution of cancer disease. Int J Mol Sci. 2021;22:2890.
3. Macciò A, Lai P, Santona MC, Pagliara L, Melis GB, Mantovani G. High serum levels of soluble IL-2 receptor, cytokines, and C reactive protein correlate with impairment of T cell response in patients with advanced epithelial ovarian cancer. Gynecol Oncol. 1998;69:248–52.
4. Mantovani G, Macciò A, Mura L, Massa E, Mudu MC, Mulas C, et al. Serum levels of leptin and proinflammatory cytokines in patients with advanced-stage cancer at different sites. J Mol Med. 2000;78:554–61.
5. Mantovani G, Macciò A, Lai P, Massa E, Massa D, Mulas C, et al. Results of a dose-intense phase 1 study of a combination chemotherapy regimen with cisplatin and epidoxorubicin including medroxyprogesterone acetate and recombinant interleukin-2 in patients with inoperable primary lung cancer. J Immunother. 2000;23:267–74.
6. Sanna E, Tanca L, Cherchi C, Gramignano G, Oppi S, Chiai MG, et al. Decrease in neutrophil-to-lymphocyte ratio during neoadjuvant chemotherapy as a predictive and prognostic marker in advanced ovarian cancer. Diagnostics. 2021;11:1298.
7. Macciò A, Madeddu C, Massa D, Astara G, Farci D, Melis GB, et al. Interleukin-6 and leptin as markers of energy metabolic changes in advanced ovarian cancer patients. J Cell Mol Med. 2009;13:3951–9.
8. Macciò A, Madeddu C, Gramignano G, Mulas C, Floris C, Sanna E, et al. A randomized phase III clinical trial of a combined treatment for cachexia in patients with gynecological cancers: evaluating the impact on metabolic and inflammatory profiles and quality of life. Gynecol Oncol. 2012;124:417–25.
9. Macciò A, Oppi S, Madeddu C. COVID-19 and cytokine storm syndrome: can what we know about interleukin-6 in ovarian cancer be applied? J Ovarian Res. 2021;14:28.
10. Macciò A, Madeddu C. Blocking inflammation to improve immunotherapy of advanced cancer. Immunology. 2020;159:357–64.

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ADDITIONAL INFORMATION

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