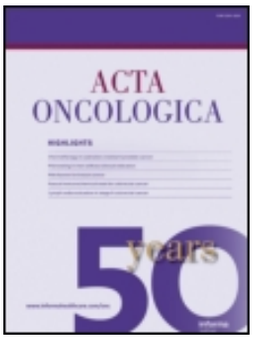

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LETTER TO THE EDITOR

Regression in cancer following fever and acute infection

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To the Editor,

Spontaneous regression (SR) in cancer has been an object of interest for a long time. Rare, unexpected and poorly understood regressions from cancer still occur, despite the advances in medicine. In particular, the phenomenon has been observed following fever and acute infections.

Based on recent observations in the clinic together with the improved understanding of tumor immunology, we argue that acute infections especially when accompanied by high fever can induce and facilitate an efficient antitumoral response, and may improve antitumor efficacy of immunotherapy.

We report two cases of remission from cancer observed shortly after an acute, febrile infection: one in the preleucemic condition myelodysplastic syndrome (MDS), later developing to acute myeloid leukemia (AML), and one in metastatic melanoma.

The first case was a young female patient who debuted with a week of high fever and signs of an infection. Laboratory results showed pancytopenia and elevated CRP. The patient was treated with broad-spectrum antibiotics whereafter the temperature normalized, but no causative agent of an infection could be detected. A bone marrow biopsy was taken showing hypoplastic conditions despite a clone of larger lymphocytes, but otherwise without convincing signs of malignancy. Less than a month after the admission the blood counts normalized without supply of blood products. Seven months later the patient was readmitted under the same clinical picture with high fever, pancytopenia and elevated CRP. Treatment with broad-spectrum antibiotics was initiated, but yet again, a specific infectious agent could not be detected. A new bone marrow biopsy was taken, this time surprisingly with immature blast cells filling up to 90% of the marrow, giving the diagnosis of AML. Five days after the second admission the fever resolved and the blood counts improved, being close to normal 25 days after the admission. As the bone marrow was still positive for malignant cells, the standard AML treatment was initiated. Retrospectively, when comparing the latest bone marrow biopsy with the biopsy taken seven months earlier, similar infiltration of immature, malignant cells could be identified. The count of immature blast cells in the first biopsy, however, was not high enough to meet the criteria of AML, but suggested that the patient initially had suffered from MDS. It seems likely that the patient underwent a complete remission of the MDS, and after relapsing and progressing to AML, experienced a partial remission as the hematological blood counts normalized, but with the bone marrow still being positive for malignant cells.

The second case was a previously healthy female patient diagnosed with metastatic melanoma shortly after the operation of a stage III nodular melanoma on her right ankle. Immunotherapy with interleukin 2 (IL2) and interferon-alpha (IFN) was initiated, being our standard treatment for metastatic melanoma. After two cycles of immunotherapy the first evaluation computed tomography (CT)-scan was performed, showing stable disease consisting of unchanged metastatic lymph nodes. The patient had tolerated therapy well with the expected IL-2 related flu-like symptoms and was therefore recommended two more cycles of immunotherapy. Shortly after the third cycle the patient developed an infection in the area where a central venous catheter had been removed three days before. High fever occurred with

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temperatures up to 40°C, and treatment with broad-spectrum antibiotics was initiated. Blood samples showed neutrophile leucocytosis and elevated CRP. Blood cultures were positive for *Staphylococcus aureus* and *S. epidermidis*. After a week the temperature normalized and the infection resolved. Immunotherapy was therefore continued as initially planned. After four series of IL2/IFN a new CT-scan was performed, surprisingly showing significant disease regression with substantial reduction of the metastatic lymph nodes. Due to the convincing response immunotherapy was continued with the next evaluation scan showing further disease regression. The patient then proceeded to treatment free observation with CT-scans performed regularly, still with no evidence of disease activity. Most likely the acute infection and the accompanying fever were at least partly responsible for the remission, as it is highly unusual for a patient to respond on immunotherapy first after four cycles of therapy, if there was no response after the first two.

Discussion

SR in cancer is considered a rare event [1–6]. In melanoma, a malignancy known for its particular immunologic potential, the rate of SR has been estimated to occur in about 1/400 patients [2], accounting for 11% of all reported cases of spontaneous tumor regression. SR of hematologic cancers, is a much rarer and often temporary event [7]. Less than 150 reports on SR in AML have been published between 1878 and 2004 [8]. Moreover, SR in MDS is sparsely reported, but has been observed, especially in children [9].

The association between infections and SR in cancer has repeatedly been highlighted in the literature and has been observed among a diversity of different cancers [2,10,13–15]. The intensive work of Dr William Coley is maybe the most important in this context. In the late 19th century he began to treat cancer patients with a bacterial vaccine, later to be called "Coley's toxin". In the beginning he used live bacteria, but because of the obvious inconveniences related to this approach, he shifted to a heat killed vaccine consisting of a mixture of *Streptococcus pyogenes* and the gram negative bacteria *Serratia marcescens*. With this vaccine Coley could mimic an acute infection without the risks of a life-threatening infection [12,16]. A retrospective evaluation of the patients he treated reports a five-year survival rate of 44%, which is quite impressive considering the fact that the majority of the patients suffered from inoperable, advanced cancers, and that the treatment took place over a hundred years ago [16].

More recent work has focused on the exact immunologic mechanisms involved in the interplay between acute infections and neoplastic disease [14,17,18]. One of the key factors in this relation is believed to be pathogen-associated molecular patterns (PAMP) [14]. This group of various pathogens, which among others include lipopolysaccarides (LPS), a component of bacterial cell walls, interacts with Toll-like receptors (TLR) on various immune cells (T lymphocytes, dendritic cells and neutrophils). Binding of the TLRs by PAMPs results in activation of the transcription factor NF-κB, which is responsible for the production of proinflammatory cytokines crucial for the initiation of an effective and cytotoxic T cell response [18]. Most tumors are in some way recognized by the immune system as tumor infiltrating lymphocytes (TILs) have been observed within and around the tumor tissue in a variety of different cancers [14]. Under normal conditions, despite the presence of TILs, an efficient immune response against the tumor is avoided. During a bacterial infection, PAMPs are present in the tumor microenvironment and proinflammatory conditions are induced. This shift in the microenvironment, with the presence of proinflammatory mediators such as IL-1ß, TNF-α and IL-12 is believed to break the tolerating state of the immune system by inducing maturation of primarily dendritic cells which are crucial for the initiation of a cytotoxic T-cell mediated antitumor response [14].

The importance of fever during an acute infection, and the role of fever in tumor regression has been emphasized in several of the earlier as well as the more recent reports of SR in cancer [11–15]. Fever is a part of the acute phase response as well as the innate immune response, and is accompanied by a multitude of immunologic changes [3,5,6,11,19]. Following fever, especially in relation to an acute infection, an increase in proinflammatory cytokines like IL2, TNFα, and IFN can be observed. Moreover the cytotoxic potential of neutrophils, NK cells, and DCs are enhanced, and the differentiation of T cells is stimulated [7]. The result is a highly improved proinflammatory response with potent and cytotoxic effector cells able to defeat and to kill the threat of the organism [19]. In addition to the immunologic effects of fever, there is also the thermal aspect. Tumor cells are more fragile and vulnerable to heat with apoptosis taking place at lower temperatures compared to normal cells [2,14]. Necrotic or heat-stressed cancer cells can function as antigens and thereby generate an immune-stimulating environment [14]. The beneficial effect of hyperthermia in the treatment of cancer has also been recognized for a long time, but technical and practical inconveniences have restricted its use in the treatment of

metastatic disease. Taken together, it seems that the immunologic and postulated beneficial effects of an acute infection on neoplastic disease are accentuated by the induction of high temperatures and fever [2]. One could say that the immune system functions at its best under febrile conditions.

The phenomenon of SR in cancer is reported more rarely today compared to the first part of the 20th century [12]. In part, this can possibly be explained by the improved therapeutic possibilities in the field of cancer so that few patients today stay untreated which reduces the opportunity to observe the natural course of the disease as well as its interaction with an unaffected immune system. Moreover, modern anti-cancer therapies like radio- and especially chemotherapy are highly immunosuppressive making infections in cancer patients, when they do occur, less immunstimulatory [19].

Fever often occurs in conjunction with many modern cancer treatments, especially in immunotherapy. The symptom of fever is generally regarded as a simple and unwanted side-effect to be suppressed. Little attention is given that the fever reaction itself may have beneficial effects and might improve the efficacy of the ongoing treatment. A recent follow-up study by Ellegaard et al. evaluated the effect of the IL-2 induced fever in patients with metastatic melanoma treated with immunotherapy [20]. They demonstrated that temperature of 39.5°C or above was an independent factor for improved survival and objective tumor response.

Based on these recent data from patients and the scientific literature we suggest that acute infections especially when accompanied by high fever may facilitate and enhance clinically relevant antitumoral immune responses. We call for more studies and clinical trials that can investigate the possible therapeutic value of pro-inflammatory conditions and fever in cancer.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Challis GB, Stam HJ. The spontaneous regression of cancer. A review of cases from 1900 to 1987. Acta Oncol 1990;29: 545–50.

[2] Hobohm U. Fever therapy revisited. Br J Cancer 2005; 92:421–5.

[3] Muller CI, Trepel M, Kunzmann R, Lais A, Engelhardt R, Lubbert M. Hematologic and molecular spontaneous remission following sepsis in acute monoblastic leukemia with translocation (9;11): A case report and review of the literature. Eur J Haematol 2004;73:62–6.

[4] Papac RJ. Spontaneous regression of cancer. Cancer Treat Rev 1996;22:395–423.

[5] Rohdenburg G. Fluctuations in the growth energy of malignant tumors in man, with especial reference to spontaneous regression. J Cancer Res 1918;3:193–225.

[6] Stephenson HE Jr, Delmez JA, Renden DI, Kimpton RS, Todd PC, Charron TL, et al. Host immunity and spontaneous regression of cancer evaluated by computerized data reduction study. Surg Gynecol Obstet 1971;133:649–55.

[7] Kleef R, Jonas WB, Knogler W, Stenzinger W. Fever, cancer incidence and spontaneous remissions. Neuroimmunomodulation 2001;9:55–64.

[8] Maywald O, Bucheidt D, Bergmann J, Schoch S, Ludwig WD, Reiter A, et al. Spontaneous remission in adult acute myeloid leukemia in association with systemic bacterial infection-case report and review of the literature. Ann Hematol 2004;83: 189–94.

[9] Marisavljevic D, Rolovic Z, Ludoski-Pantic M, Djordjevic V, Novak A. Spontaneous remission in adults with primary myelodysplastic syndromes: Incidence and characteristics of patients. Med Oncol 2005;22:407–10.

[10] Papac RJ. Spontaneous regression of cancer: Possible mechanisms. In Vivo 1998;12:571–8.

[11] Hobohm U. Fever and cancer in perspective. Cancer Immunol Immunother 2001;50:391–6.

[12] Hoption Cann SA, van Netten JP, van Netten C, Glover DW. Spontaneous regression: A hidden treasure buried in time. Med Hypotheses 2002;58:115–9.

[13] Chang WY. Complete spontaneous regression of cancer: Four case reports, review of literature, and discussion of possible mechanisms involved. Hawaii Med J 2000;59:379–87.

[14] Hobohm U, Stanford JL, Grange JM. Pathogen-associated molecular pattern in cancer immunotherapy. Crit Rev Immunol 2008;28:95–107.

[15] Hoption Cann SA, Gunn HD, van Netten JP, van Netten C. Spontaneous regression of pancreatic cancer. Case Rep Clin Pract Rev 2004;5:293–6.

[16] Wiemann B, Starnes CO. Coley's toxins, tumor necrosis factor and cancer research: A historical perspective. Pharmacol Ther 1994;64:529–64.

[17] Kamposioras K, Pentheroudakis G, Pectasides D, Reiter A. Malignant melanoma of unknown primary site. To make the long story short. A systematic review of the literature. Crit Rev Oncol Hematol 2011;78:112–26.

[18] Speeckaert R, van Geel N, Vermaelen KV, Lambert M, Van Gele M, Speeckaert MM, et al. Immune reactions in benign and malignant melanocytic lesions: Lessons for immunotherapy. Pigment Cell Melanoma Res 2011;24:334–44.

[19] Hoption Cann SA, van Netten JP, van Netten C. Acute infections as a means of cancer prevention: Opposing effects to chronic infections? Cancer Detect Prev 2006;30:83–93.

[20] Ellegaard M, Bastholt L, Jakobsen AH, Donskov F, Schmidt H. Interleukin-2-induced fever in relation to objective tumor response and survival in patients with metastatic melanoma. J Clin Oncol 2010;28:15s. [Abstract]