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EDITORIAL

Bipartite Task of Immunity in Cancer Progression

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INTRODUCTION

The spontaneous regression and remission from malignancy was defined by Everson and Cole[1] as "the partial or complete disappearance of a malignant tumor in the absence of all treatment, or in the presence of therapy which is considered inadequate to exert significant influence on neoplastic disease."

Frequency of these cases is as low as 1 in 100,000 cancers.[2] The first ever case of spontaneous regression reported in the oral cavity was of Ki-1 anaplastic large cell lymphomas by Savarrio et al.[3] Koga et al[4] have reported a case of extranodal diffuse large B cell lymphoma of the upper gingiva, which had regressed spontaneously after biopsy. King et al[5] described a case of complete spontaneous regression of metastatic cutaneous melanoma with parotid and neck lymph node metastases.[6]

Everson and Cole proposed a justification for spontaneous regression implicating several mechanisms although the end outcome is either differentiation or cell death.[6] According to them, the factors or mechanisms accountable for spontaneous regression are ambiguous or unidentified in the light of subsisting knowledge but the mechanisms like immunologic action, elimination of carcinogens, trauma, hormones, irradiation, infection and/or fever, and drugs or chemicals may have probable association with this enigmatic phenomenon.[1] But the protocols strongly advocate that the immunologic reactions seem to be the best rationalization.[1] There are several case reports of spontaneous regressions from cancer occurring after a fever brought on by an infection,[2] to brace this causative connection. Thus, it has been suggested that the cell-mediated immunity is a crucial mediator in cancer regression.[7]

Malignant tumors are usually infiltrated by numerous immune cells. In their presence, the human immune system has dual functions to perform, which are defense and repair to maintain the integrity of the host.[8] The immune system is primarily recognized for its role in defense against foreign pathogens; however, it plays an equal substantial role in tissue repair. A tumor, being partly "self" and partly "foreign," can incite a reparative growth-promoting response from intratumoral leukocytes.[9] These immune cells can cause damage to the tumor cells. Leukocyte-induced damage, i.e., cytotoxic activity of these tumor-infiltrating leukocytes is expected to cause morphological changes in the tumor cells. But as the cytotoxic activity of these cells gets compromised, the tumor cells get rarely affected despite their close contact with the leukocytes.[8] They not only fail to inhibit growth, but also actively enhance tumor progression through their reparative functions. Thus, in the reparative mode, the immune system can promote tumor growth in its attempt to repair what it perceives as a sterile wound.[10] As observed in the wounds, chemokines and other cytokines which attract leukocytes are released by the proliferating tumor cells. There is an increased need for oxygen and nutrient supply for the multiplying cancer cells. Thus, an aberrant and injurious reparative response is engendered, where the immune system effectively supports tumor growth.[9]

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One of the characteristic features in many rapidly growing tumors is the presence of macrophages in large numbers. Macrophages contribute to the production, mobilization, activation, and regulation of all the immune cells. There is substantial evidence that monocyte/macrophages can differentiate into endothelial progenitor cells and fibroblasts. Tumor-derived fibroblasts have shown to stimulate tumor cells *in vitro*, which is generally not observed with normal tissue fibroblasts.[9,11] Thus, macrophages play a pivotal part in tumor stroma formation. Moreover, macrophages are abundant in areas of tumor cell proliferation, where evidence of macrophage-induced tumor cell killing is rare or absent.[9]

On the contrary, in acute infection, the defensive role becomes active and the cytotoxic cells start destroying the invading malignant tumor cells. There is generation of inflammatory products during this period, be it natural or simulated (Coley's toxins).[8,10] Hobohm[2] has recently observed that following cascade after injecting Coley's toxins, fever generates inflammatory factors with co-stimulatory activity, which activate resting dendritic cells, leading to the activation of anergic T cells that may be accomplished by a second process, where a possible physical damage of cancer cells leads to a sudden supply of cancer antigens to dendritic cells.[10] In other words, fever is a state in which body's own antigen recognition mechanism turns on to such a high level of activity that it becomes capable of recognizing cancer and microbial invaders. Specialized cells like the dendritic cells then communicate the identity of the pathogen to lymphocytes to establish active immunity against stealth diseases.[2,10]

Another type of cells is the macrophages, which also help in regression of the tumor by down regulating the production of several factors like platelet-derived growth factor and vascular endothelial growth factor. They are involved in matrix degradation and stimulation of blood and lymphatic vessel development.[12] They can also act by direct killing of tumor cells with the help of reactive oxygen and nitrogen metabolites. The Toll-like receptors expressed on macrophages and dendritic cells, an important mediator of the innate immune response, are involved in both the defense and repair mechanism. This underlines the delicate balance that exists between immune-mediated tumor growth and regression.[11,12] These receptors dictate the innate defensive reaction and characterize the reparative response.

Any immune response is associated with an assembly of cytokine cascades, which include tumor necrosis factor, interleukins, and interferons.[13] Thus, the occurrence of hypoxia or necrosis in a sterile neoplasm can release the factors that promote tumor growth; while the introduction of Coley's vaccine, or microbial infection, can shift the balance back toward a defensive immune response.

The course of treatment should include deliberately infecting the cancer patients with a tropical disease. It is the need of the hour to standardize spontaneous remission as a treatment option in oral cancer therapeutics. The available knowledge of this dual role of immunity should be exploited in treating oral cancer as well as potentially malignant disorders.[14] The shift in the oral microflora because of induced infection can prove to be an area for future research.[15]

Cannibalism has become a well-known phenomenon in some benign and malignant lesions of oral cavity, including oral cancer.[16-19] This mysterious phenomenon involves engulfment of one cancer cell by another. It has been thought that nutrition plays a role in expression of this cannibalistic behavior in cancer cells. Hypothetically, eating one cancer cell by another should reduce the tumor load, a phenomenon very much similar to the spontaneous regression of cancer. It would be interesting to focus the future research on the aforementioned aspects to bring more clarity to their association.

Though the concept of spontaneous remission is still at a very primitive stage of development, clinical trials can lead us to some assenting conclusions. Though it is a tiny cue in an intricate jigsaw of cancer progression and a simple, quick and pain-free revival from cancer might just cultivate into the norm.

REFERENCES

1. Everson TC, Cole WH. Spontaneous regression of cancer. Philadelphia (PA): JB Saunders & Co; 1968.
2. Hobohm U. Fever and cancer in perspective. Cancer Immunol Immunother 2001 Oct;50(8):391-396.
3. Savarrio L, Gibson J, Dunlop DJ, O'Rourke N, Fitzsimons EJ. Spontaneous regression of an anaplastic large cell lymphoma in the oral cavity: first reported case and review of the literature. Oral Oncol 1999 Nov;35(6):609-613.
4. Koga M, Kusukawa J, Hayabuchi N. Spontaneous regression of extranodal malignant lymphoma occurred in the gingiva. Oral Oncol 2003 Apr;39(3):323-324.
5. King M, Spooner D, Rowlands DC. Spontaneous regression of metastatic malignant melanoma of the parotid gland and neck lymph nodes: a case report and a review of the literature. Clin Oncol (R Coll Radiol) 2001;13(6):466-469.
6. Pakhamode VK. Understanding the possible mechanisms of spontaneous regression of oral. J Oral Maxillofac Pathol 2007;11(1):2-4.
7. Lucey DR, Clerici M, Shearer GM. Type 1 and type 2 cytokine dysregulation in human infectious, neoplastic, and inflammatory diseases. Clin Microbiol Rev 1996 Oct;9(4):532-562.
8. Hoption Cann SA, van Netten JP, van Netten C, Glover DW. Spontaneous regression: a hidden treasure buried in time. Med Hypotheses 2002 Feb;58(2):115-119.
9. Hoption Cann SA, van Netten JP, van Netten C. Dr William Coley and tumour regression: a place in history or in the future. Postgrad Med J 2003 Dec;79(938):672-680.

10. Jessy T. Immunity over inability: the spontaneous regression of cancer. J Nat Sci Biol Med 2011 Jan;2(1):43-49.
11. Van Netten JP, Ashmed BJ, Cavers D, Fletcher C, Thornton IG, Antonsen BL, Coy P, Brigden ML. Macrophages and their putative significance in human breast cancer. Br J Cancer 1992 Jul;66(1):220-221.
12. Kataki A, Scheid P, Piet M, Marie B, Martinet N, Martinet Y, Vignaud JM. Tumor infiltrating lymphocytes and macrophages have a potential dual role in lung cancer by supporting both host-defense and tumor progression. J Lab Clin Med 2002 Nov;140(5):320-328.
13. Oettgen HF. Biological agents in cancer therapy: cytokines, monoclonal antibodies and vaccines. J Cancer Res Clin Oncol 1990;116(1):116-119.
14. Sarode SC, Sarode GS, Karmarkar S, Tupkari JV. A new classification for potentially malignant disorders of the oral cavity. Oral Oncol 2011 Sep;47(9):920-921.
15. Dagli N, Dagli R, Darwish S, Baroudi K. Oral microbial shift: factors affecting the microbiome and prevention of oral disease. J Contemp Dent Pract 2016 Jan 1;17(1):90-96.
16. Sarode GS, Sarode SC, Karmarkar S. Complex cannibalism: an unusual feature in oral squamous cell carcinoma. Oral Oncol 2012;48(2):e4-e6.
17. Sarode SC, Sarode GS, Kulkarni M, Patil S. Endocytosis of keratinocytes in oral squamous cell carcinoma: expression of phagocytic markers. Transl Res Oral Oncol 2016: doi:10.1177/2057178X15618551.
18. Sarode SC, Sarode GS. Neutrophil-tumor cell cannibalism in oral squamous cell carcinoma. J Oral Pathol Med 2014 Jul;43(6):454-458.
19. Sarode SC, Sarode GS, Chuodhari S, Patil S. Non-cannibalistic tumor cells of oral squamous cell carcinoma can express phagocytic markers. J Oral Pathol Med 2016 Sep 3: doi:10.1111/jop.12500.