INTRODUCTION

The spontaneous regression and remission from malignancy was defined by Everson and Cole 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. The first ever case of spontaneous regression reported in the oral cavity was of Ki-1 anaplastic large cell lymphomas by Savarrio et al. Koga et al have reported a case of extranodal diffuse large B cell lymphoma of the upper gingiva, which had regressed spontaneously after biopsy. King et al described a case of complete spontaneous regression of metastatic cutaneous melanoma with parotid and neck lymph node metastases.

Everson and Cole proposed a justification for spontaneous regression implicating several mechanisms although the end outcome is either differentiation or cell death. 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. But the protocols strongly advocate that the immunologic reactions seem to be the best rationalization. There are several case reports of spontaneous regressions from cancer occurring after a fever brought on by an infection, to brace this causative connection. Thus, it has been suggested that the cell-mediated immunity is a crucial mediator in cancer regression.

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. 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. 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. 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. 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.
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/macro-
phages 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, mac-
rophages 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 genera-
tion of inflammatory products during this period, be it
natural or simulated (Coley’s toxins).8,10 Hobohm2 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
in 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 recep-
tors 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 introduc-
tion 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 remis-
sion 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 spontane-
ous 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.

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