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Review Article

Spontaneous Regression of Oral Cancer: A Review

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Abstract

Spontaneous regression of some tumors is flimsy and inconceivable process. Nonetheless, it is observed in virtually all types of human cancer, Neuroblastoma, renal carcinoma being remarkable in number and a few reported cases of oral cancer. The induction of spontaneous regression involves multiple mechanisms which may either be differentiation, apoptosis and genetic crisis. But surpassed understanding of the process of spontaneous regression may include the indulgence of the possible and improved methods of treating and preventing cancer. The article gives an overview of the mechanisms involved in spontaneous regression and various reported cases of oral cancer.

Keywords: Spontaneous Neoplasm Regression;Oral Cancer;Head and Neck Neoplasms; Apoptosis;Recessive Genetic;Differentiation.

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Introduction

These days the world is heading towards various types of non-communicable diseases, which are known as modern epidemics. Among these modern epidemics cancer is the second commonest cause of mortality in developed countries. In the developing countries cancer in among the ten commonest cause of mortality.[1] Cancer is one of the most common causes of morbidity and mortality today, with more than 10 million new cases and more than 6 million deaths each year worldwide.[2]

More than 20 million persons around the world live with a diagnosis of cancer, and more than half all cancer cases occur in the developing countries. Cancer is responsible for about 20% of all deaths in high income countries and 10% in low-income countries. It is projected that by 2020 there will be every year 15 million new cancer cases and 10 million cancer deaths.[3] Oro-pharyngeal cancer is significant component of the global burden of the cancer. Incidence rates for oral cancer vary in men from 1 to 10 cases per 100,000 populations in many countries. In south-central Asia, cancer of the oral cavity ranks among the three most common types of cancer. In India, the age standardized incidence rate of oral cancer is reported at 12.6 per 100,000 population.[4,5]

Spontaneous regression of cancer is one of the most fascinating phenomena observed in medicine. It is generally regarded as inexplicable, although there are now some lab studies of regressed or regressing tumors, as well as new possibilities about their mechanisms.[6] Spontaneous regression of malignant disease has been defined as "the complete or partial disappearance of a malignant tumor in the absence of any treatment, or in the presence of therapy that is considered inadequate to exert a significant influence on neoplastic disease".[7,8] It is not usually associated with cure of malignant disease as most of the cases ultimately relapse. Spontaneous tumor regression is reported to occur in approximately one in every 1,40,000 cases of cancer and is one of the most tantalizing, heartwarming phenomenon.[9]

Spontaneous regression has been documented for many types of human cancers with majority in neuroblastoma, renal cell carcinoma, malignant melanoma and leukemia, including oral cancer. It was postulated that an intriguing but extremely effective mechanism was engaged in eradicating cancer cells after the development of advanced malignancy.[10,11]

History

Spontaneous regression was better fraternized as "Saint Peregrine Tumor" on the name of young priest "Saint Peregrine" at the end of 13th century. He had a large bone tumor which required amputation. He prayed immensely a night before the surgery. He awoke with absence of any tumor remnants.[12]

Reported Cases

The first case of spontaneous regression of a carcinoma of tongue was reported by Roxburgh D in 70 years old female patient in 1935.[7,13] Spontaneous regression of recurrent SCC of the tongue was reported by Oya R and Ikemura K in a 73 years old male. Without any specific therapy, the tumor gradually and spontaneously regressed, 4 months after the recurrence was diagnosed, and it had completely disappeared.[13]

Kurita M *et al* reported a case of spontaneous regression of cervical lymph node metastasis in a patient with nasopharyngeal squamous cell carcinoma of the tongue. The authors claimed that this may be the first case of squamous cell carcinoma undergoing spontaneous regression in which enhanced apoptosis was demonstrated quantitatively.[14]

First ever case of spontaneous regression of a neoplasm in the oral cavity of a subset of Non-Hodgkin's lymphoma known as ki-1 anaplastic large cell lymphoma was reported by Savarrio *et al*.[15]

Year	Author	Reported Cases
1935	Roxburgh D	Carcinoma of tongue
2004	Oya R and Ikemura K[13]	Recurrent SCC of tongue
2007	Kurita M *et al*[14]	Cervical lymph node metastasis in a patient with nasopharyngeal squamous cell carcinoma of tongue
1999	Savarrio *et al*[15]	Non Hodgkins lymphoma of oral cavity
2001	King *et al*[17]	Metastatic cutaneous melanoma with parotid and neck lymph node metastasis
2003	Koga *et al*[16]	Extra nodal malignant lymphoma with a diffuse bucco-lingual swelling on the left maxillary gingiva in the incisor region
2004	Heibel H *et al*[18]	Highly malignant B-cell Non-Hodgkin's lymphoma with primary manifestation in the oral cavity

Regression of extra nodal malignant lymphoma in 78 years old female with a diffuse bucco-lingual swelling on the left maxillary gingiva in an incisor region was claimed by Koga *et al*.[16] A case of complete spontaneous regression in metastatic cutaneous melanoma with parotid and neck lymph node metastasis was reported by King *et al*.[17]

A case of complete spontaneous remission of a histopathologically supported highly malignant B-cell Non-Hodgkin's lymphoma with primary manifestation in the oral cavity was presented by Heibel H *et al*. This regression, which has showed no signs of recurrence for more than 18 months, occurred following a diagnostic biopsy and without any therapeutic intervention.[18]

Mechanisms

Contingent Role of Cytotoxic Immune Response: As explained by Beyer-Garner[19] and others cytotoxic immune response plays a key role in regression of some tumors. Interleukin (IL-18) stimulates T-cell and natural killer cell activities and is associated with interferon (IFN)-γ production that can induce anti-tumor immune responses.[9] Tumor-associated antigens that may be targets for CD8+T cells include viral antigens, melanocyte differentiation antigens and cancer testis antigens. Expression for the cancer testis antigen, NY-ESO-1 has been shown to induce both humoral and cellular immune responses and is associated with a high rate of regression.[20] The observation that autoimmune manifestations may occur concomitantly with spontaneous tumor regression also depicts that regression may be immune-mediated.[21]

Genetic crisis - A possible reason: Spontaneous regression may present a process of terminal differentiation or may be related to vascular compromise. Genomic instability is another mechanism for tumor regression.[22] Telomerase is related with cellular immortality and tumorigenesis. Inhibition of telomerase may result in genomic crisis and tumor regression.[23] In neuroblastoma, high levels of telomerase activity correlate with poor outcome, whereas telomere shortening correlates with tumor regression.[24]

Apoptosis: Spontaneous regression of solitary cutaneous mastocytomas has been shown to be related to apoptosis.[25] Programmed cell death is involved in spontaneous regression and differentiation of neuroblastoma and may be related to expression of a variety of cell death-related proteases.[26] Spontaneous regression of some neuroblastomas is associated with a form of *ras*-mediated programmed cell death

that is caspase cascade-independent (non-apoptotic).[27]

Spontaneous regression attributable to antiangiogenic factors: Angiogenesis is imperative for the development of many tumors and antiangiogenic factors are promising agents in the treatment of cancer. The humanized monoclonal antibody bevacizumab exerts an effect on vascular endothelial growth factor and improves survival in metastatic colorectal cancer, suggesting that antiangiogenic therapy can have a meaningful clinical effect.[28] Ornithine decarboxylase (ODC) over expression is associated with the formation of spontaneous skin carcinomas in some transgenic mice. ODC stimulates dermal vascularization. Treatment with difluoromethylornithine, an inhibitor of ODC, causes a decrease in blood vessel count and regression of the tumors.[29]

Cytokines: These are proteins produced by many cell type; principally activated lymphocytes and macrophages. Cytokines implicated in spontaneous regression of tumors include:

a. Tissue inhibitors of matrix metalloproteinase (TIMPs): TIMPs block tumor metastasis by inhibiting invasion of the basement membrane or by restraining tumor angiogenesis.[22]
b. Tumor necrosis factor (TNF): Stoelcker *et al* demonstrated that TNF reduces $XV\beta_3$ an integrin mediated endothelial cell adhesion in-vitro resulting in detachment and apoptotic cell death. The endothelial destruction is the effector mechanism, thus indicating the endothelium as the target for TNF induced tumour necrosis.[30]
c. Transforming growth factor (TGF-β): Corallini A demonstrated that over expression of $TGF\beta_1$ inhibits angiogenesis and causes formation of a fibrotic wall around tumor thus inducing tumor necrosis.[31]
d. Secreted Protein Acidic and Rich in Cysteine (SPARC) (also known as Osteonectin, BM40 and 43kd protein): This is an intracellular calcium binding glycoprotein. Its biologic function is variable in human cancers. Its suppression results in significant decrease in tumorigenesis of melanoma cells which is one of the tumor that regresses spontaneously.[32]

Tumor Suppressor Genes: These anti-oncogene protein products also play important role in tumorigenesis; they include p53 gene and Retinoblastoma (Rb) gene. They act by inhibiting and preventing mitosis such that tumor cells do not complete the cell cycle.[33]

Hypoxia: Low oxygen levels that occur in the core of tumors lead to necrosis of the tumor cells, which may cause the tumor to implode.[33,34]

Stress*:* High stress may raise levels of natural steroids and cause temporary regression of tumor. Mild to moderate stress increases the production of proteins that help repair body cells including those in the brain and enables them to work at peak capacity.[35]

Other contrivances for spontaneous regression: Patients pleasurably incur the regressions, but at the same time this feature also makes it more challenging and expensive for investigators to prove that a new treatment has clinical benefit, which is essential to boon the progress against the disease.[35] Some of the theories accorded are:

1. Immune response against tumors may be produced by immune recognition of the tumor cells.
2. Viruses may infect lymphoma cells as they do other lymphocytes and thus make them more recognizable to other immune cells. This could be the mechanism behind the measles vaccine, which is being studied in clinical trials for lymphoma.
3. Transient or short-term fluctuations in the size of lymph nodes could be accounted for inflammation and not related to tumor progression or regression. If inflammation is caused by immune system activity against the tumor, real regression may happen as well for some people.[35]

Conclusion

Neoplastic transformation is related to the expression of oncogenes, production of growth factors and inactivation of tumour suppressor genes. Spontaneous regression may be mediated by the immune response, apoptosis, antiangiogenesis, terminal differentiation, or genomic crisis. It is generally recognized that growth rates of different types of cancers varies greatly and also the growth rate of specific type of

cancer varies widely in different patients. A complex interplay of mechanisms is involved in tumor growth and tumor regression. Better understanding of these mechanisms may give us a better ability to predict tumor behavior and for effective cures.

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References

1. Khandekar SP, Bagdey PS, Tiwari RR. Oral cancer and some epidemiological facts: A hospital based study. Indian J Com Med 2006;31(3):157-9.
2. World Health Organization. The world health report 2004: changing history. Geneva: WHO; 2004.
3. Peterson PE. Oral Cancer prevention and control-the approach of the world health organization. Oral Oncol 2009;45(4):454-60.
4. Stewart BW, Kleihues P, editors. World cancer report. Lyon: WHO international agency for Research on Cancer; 2003.
5. Petersen PE. The world oral health report 2003: continuous improvement of oral health in the 21st century- the approaches of the WHO global oral health Programme. Community Dent Oral Epidemiol 2003;31(1):3-24.
6. Osler W. The medical aspects of carcinoma of the breast, with a note on the spontaneous disappearance of secondary growth. Am Med 1901;17(19):63-6.
7. Everson TC, Cole WH. Spontaneous regression of cancer: preliminary report. Ann Surg 1956;144:366–83.
8. Fujiwaki R, Sawada K. Spontaneous regression in recurrent epithelial ovarian cancer. Arch Gynecol Obstet 2007;275(5):389-91.
9. 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.
10. Zheng C, Willinghan MC, Hicks AM, Alexander-Miller MA, Howard TD, Hawkins GA, et al. Spontaneous regression of advanced cancer: Identification of a unique genetically determined, age-dependent trait in mice. PNAS 2003;100(11):6682-7.
11. Papac RJ. Spontaneous regression of cancer: Possible mechanisms. In Vivo 1998;12(6):571-8.
12. Pack GT. Saint Peregrine, O.S.M. - The patron saint of cancer patients. CA Cancer J Clin 1967;17(4):181-2.
13. Oya R, Ikemura K. Spontaneous regression of recurrent squamous cell carcinoma of the tongue. Int J Clin Oncol 2004;9:339-42.
14. Kurita M, Hirano K, Ebihara S, Takushima A, Harii K, Fujino T, Fujioka Y. Spontaneous regression of cervical lymph node metastasis in a patient with nasopharyngeal squamous cell carcinoma of the tongue: possible association between apoptosis and tumor regression. Int J Clin Oncol 2007;12(6):448-54.
15. 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;35(6):609-13.
16. Koga M, Kusukawa J, Hayabuchi N. Spontaneous regression of extra nodal malignant lymphoma occurred in the gingiva. Oral Oncol 2003;39(3):323-4.
17. King M, Spooner D, Rowlands DC. Spontaneous regression of metastatic melanoma of the parotid gland and neck lymph nodes: A case report and review of the literature. Clin Oncol 2001;13(6):466-9.
18. Heibel H, Knödgen R, Bredenfeld H, Wickenhauser C, Scheer M, Zöller JE. Complete spontaneous remission of an aggressive non-Hodgkin's lymphoma with primary manifestation in the oral cavity. Leuk Lymphoma 2004;45(1):171-4.
19. Bayer-Garner IB, Ivan D, Schwartz MR, Tschen JA. The immunopathology of regression in benign lichenoid keratosis, keratoacanthoma and halo nevus. Clin Med Res 2004;2:89-97.
20. Jager D, Jager E, Knuth A. Vaccination for malignant melanoma: Recent developments. Oncol 2001;60:1-7.

21. Renno T, Lebecque S, Renard N, Saeland S, Vicari A. What's new in the field of cancer vaccines? Cell Mol Life Sci 2003;60:1296-310.
22. Elston DM. Mechanism of Regression (Guest editorial). Clin Med Res 2004;2(2):85-88.
23. Kim NW. Clinical implications of telomerase in cancer. Eur J Cancer 1997;33:781-6.
24. Hiyama E, Hiyama K, Nishiyama M, Reynolds CP, Shay JW, Yokoyama T. Differential gene expression profiles between neuroblastomas with high telomerase activity and low telomerase activity. J Pediatr Surg 2003;38:1730-4.
25. Inoue T, Yoneda K, Kakurai M, Fujita S, Manabe M, Demitsu T. Alteration of mast cell proliferation/apoptosis and expression of stem cell factor in the regression of mastocytoma - Report of a case and a serial immunohistochemical study. J Cutan Pathol 2002;29:305-12.
26. Nakagawara A, Nakamura Y, Ikeda H, Hiwasa T, Kuida K, Su MS, et al. High levels of expression and nuclear localization of interleukin-1 beta converting enzyme (ICE) and CPP32 in favorable human neuroblastomas. Cancer Res 1997;57:4578-84.
27. Kitanaka C, Kato K, Ijiri R, Sakurada K, Tomiyama A, Noguchi K, et al. Increased Ras expression and caspase-independent neuroblastoma cell death: Possible mechanism of spontaneous neuroblastoma regression. J Natl Cancer Inst 2002;94:358-68.
28. Sparano JA, Gray R, Giantonio B, O'Dwyer P, Comis RL. Eastern Cooperative Oncology Group Portfolio of Clinical Trials. Evaluating antiangiogenesis agents in the clinic: the Eastern Cooperative Oncology Group Portfolio of Clinical Trials. Clin Cancer Res 2004;10:1206-11.
29. Lan L, Trempus C, Gilmour SK. Inhibition of ornithine decarboxylase (ODC) decreases tumour vascularization and reverses spontaneous tumors in ODC/Ras transgenic mice. Cancer Res 2000;60:5696-703.
30. Stoelcker B, Ruhland B, Bluethmann H, Luther T, Mannel DN. Tumour necrosis factor induces tumour necrosis via Tumour Necrosis Factor Receptor Type-1 expressing endothelial cells of the tumour vasculature. Am J Pathol 2000;156(4):1171-5.
31. Corallini A. Tumour-host interaction mediates the regression of BK virus-induced vascular tumour in mice: Involvement of Transforming growth factor β. Carcinogenesis 2003;24(9):1435-44.
32. Serra M, Morini MC, Scotlandi K, Fisher LW, Zi'ni N, Colombo MP. Evaluation of Osteonectin as a diagnostic marker of osteogenic bone tumors. Hum Path 1992;23:1326-31.
33. Mellors RC. Growth characteristics of tumor cells: Available from http://www.Neoplasia 2005.htm
34. Oluwole O, Samaila M. Spontaneous Tumour regression. Int J Pathol 2009;8(1):18.
35. Vivek PK. Understanding the possible mechanisms of spontaneous regression of oral cancer. J Oral Maxillofac Pathol 2007;11:1-4.

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