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Spontaneous tumor regression

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ABSTRACT

Spontaneous tumor regression is defined as spontaneous remission or disappearance of a tumor in the absence of any treatment. Activation of immune system has been found important in its pathogenesis. Further, spontaneous tumor regression appears to be associated with apoptosis, tumor microenvironment, and DNA oncogenic suppression. It can be observed in all types of tumors, most frequently in renal cell cancer, germ cell tumors, malignant melanoma, and neuroblastoma. It is crucial to understand this phenomenon in order to improve the immune treatments which are effective in neoplastic diseases.

1. Introduction

Spontaneous tumor regression was defined differently for many types of cancer by several researchers during the last century. Spontaneous regression is partial or complete disappearance of primary tumor tissue or its metastases in patients who have never been treated.[1,2] Its frequency is approximately 1 in every 60,000 to 100,000 cancer cases.[3] Everson divides the spontaneous regression into four categories: Primary tumor regression, metastatic tumor regression (primary focus is defined pathologically), metastatic tumor regression (no pathological diagnosis of primary tumor), radiologically-considered-metastasis tumor regression.[4] Although spontaneous cancer regression is defined as remission or disappearance of a tumor in the absence of any therapeutic intervention, today it is believed that this is caused by immunologically important events.

Spontaneous regression has been a phenomenon of many years historically and defined initially for acute infections.[5] It was called St. Peregrine tumor in the past. It was named after Peregrine Laziosi, a young priest, who lived in 12th century and had a tumor of tibia with a serious infection that progressed to skin, led to fracture, and required amputation. The tumor in the reported case was observed to disappear miraculously without leaving any scar while under physician supervision.[6] Spontaneous regression of malignant tumor has been attracting notice since the periods during which cancer treatments were quite limited. It may be observed in benign tumors as well as in primary malignant tumors and their metastases. Regression may occur in primary tumor and its metastases at the same time; however, primary tumor regresses, while its metastases may remain, as observed more often in renal cell cancer. Spontaneous regression typically occurs as a result of the activation of apoptosis caused by serious of events in the immune system and tumor microenvironment. It should be noted that no treatments must have been administered for spontaneous tumor regression. Those cases where metastases disappear following the treatment of primary tumors are also considered subject to the spontaneous regression. Primary factors affecting spontaneous regression include apoptosis, immune system activation, and particularly the microenvironment where matrix metallo-proteinases and angiogenesis are inhibited

2. Cancers with spontaneous tumor regression and their possible mechanisms

Spontaneous tumor regression may occur partially; however, this term is generally used for complete regression. Complete regression may occur in primary tumor and its metastases. When regression process begins in the tumor or one of its metastases, it accelerates relatively in other tumor tissues, and this process is observed most apparently in renal cell cancers. Spontaneous regression is associated with apoptosis, immune system, microenvironment and more or less with DNA oncogenic suppression.

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Spontaneous regression is relatively more often in testicular germ cell tumors. Spontaneous regression in testicular germ cell tumors is defined as “burned out testicular tumor”. This definition applies to the cases where scar tissue which is histologically similar to the primary tumor is detected while metastases are present. It was pointed out in a case by Prym for the first time in 1927.[7] In 1961, Azzopardi and Hoffbrand defined the term “burned out” in 17 cases with extra-gonadal germ cell testicular cancer.[8] Every extra-gonadal germ cell tumor is considered as “burned out testicular tumor” unless otherwise proven.[9] In these cases, hyper-echogenic areas identified in ultrasonographic examinations of the testicle demonstrate the scarring process developing with hemorrhagic necrosis and micro-calcifications of the tumor.[10] Spontaneous regression is observed more often in seminoma cases.[11] “Ghost tubule” may be observed in 60% of cases even if no tumors are demonstrated in these cases.[12] Approximately 10% of patients with metastatic testicular cancer are observed to have tumor regression in classical autopsy series.[13] For cases of partial or complete regression, survival difference is not known, and orchiectomy is not mandatory in regressed testicular tumors. However, many groups prefer orchiectomy in case of ultrasonographic changes in the atrophic testicle or cryptorchidism.[14] Even if systemic chemotherapy is successful in metastatic germ cell tumors, 50% of cases may have tumor cells in testicle.[15,16]

Spontaneous regression cases are observed often in melanoma and cutaneous basal cell cancers. Spontaneous regression is observed more easily in such cases as they are cutaneous. CDKN4 gene mutation, which contributes to the development of malignant melanoma, plays a significant role in spontaneous regression.[17] In such cases, immune system has a central role. A high incidence of CD4 T lymphocytes and Th1 cytokines is detected in regressed tumors.[18] In parallel, tumor-specific antibody and cytotoxic T cells are at a high level in peripheral blood.[19] A melanoma cancer cell expresses proteins with strong immunogenic effect, and these are considered as significant targets for MHC class II and cytotoxic T cells in particular. Spontaneous regression is observed more often especially in tumors with a high expression of Melan-A/MART1, gp-100, HLA A 0201 among these proteins.[20] Primary tumor and other melanocytic lesions may be exposed to spontaneous regression as a result of an immune reaction beginning in metastatic lymph node.[21] Kalialis et al reported that 76 cases were included in the literature since 1866 until today.[22] Maurer and Koelmel suggest that spontaneous tumor regression is associated with febrile attack in 21 of 68 regressed melanoma cases, and that it is linked to erysipelas in nine of them.[23] Tetanus, diphtheria, and BCG vaccines were responsive in malignant melanoma cases.[24] As a result of observation of spontaneous regression in melanoma, which is an immunogenic tumor and demonstration of its immunogenicity, immunotherapy studies have been accelerated and now targeting immune system has a central role.

Renal cell cancer has an incidence frequency of 3–5% among all types of cancer, and spontaneous regression is observed considerably more with an incidence frequency of 1% compared to other types of cancer.[25,26] Tumors with spontaneous regression may be accompanied by an intra-tumoral hemorrhage or renal vein embolism.[27,28] Von Hippel Lindau (VHL) gene is crucial in development of renal cell carcinoma. However, genetic or epigenetic alterations of VHL gene have not been certain yet in spontaneous regressed tumors. Most types of cancer with spontaneous regression are associated with nephrectomy; however, this relation has not been reported in most researches.[29,30] Growth factors and some apoptosis-related molecules are released as a result of the resection of primary tumor. Such molecules prevent the progression of cancer, and immune system is activated with antigens of cancer cells.[31] Immune system has been considered effective in regression since the first spontaneous regression was identified in patients with renal cell cancer.[32] Activation of immune system with infections or autoimmune diseases leads to spontaneous regression in RCC cases as well as in other tumors. Pulmonary metastases regressed as a result of psoriasis exacerbation in the patient with psoriasis and metastatic RCC.[33]

Spontaneous regression in breast cancer is rarely observed in literature, and it was reported in 41 patients in a spontaneous regression research consisting of 741 patients.[34] Number of cases has considerably decreased in recent years since effective treatments began to be administered in breast cancer, and consequently, only 3 cases were reported after 1987.[35–37] In one of the reported cases, spontaneous regression developed following an arm fracture while regression was observed in the primary tumor and metastatic lymph node following a steroid treatment in the other case. Presence of increased natural killer cells were noted in the biopsy performed for the latter. In the third case, spontaneous regression developed during the preoperative period of a patient receiving insulin therapy. No increase in natural killer cells, which was detected in the other case, was observed in the biopsy; however, an increase in the number of particularly CD4 and CD8 positive T cells was observed. Massive necrosis and granulation in metastatic lymph node were reported during postoperative examination of this case. CD3 positivity is observed more often in lymph nodes and metastases compared to primary tumor, and these cells are effective in tumor necrosis development.[38] In breast carcinoma cells, T-cell-mediated activation of apoptosis through Fas–Fas Ligand, TNFα-TNFα receptor and perforin-granzyme mechanism of killing exists in tumor regression.[39] p53 Gene activation is a well-known pathway in apoptosis process. It may or may not depend on transcription, and this pathway is active in approximately 50% of cases in breast cancer.[40] This mechanism works more actively in hormone-receptor-positive breast cancer cases.[41] Spontaneous regression was reported in a limited number of cases which were monitored by mammography.[42]

Spontaneous regression cases are rarely seen in colon cancer. The reason may be that urgent treatment is typically administered in such patients following the diagnosis of colon tumor. Only 11 cases were reported in a research reviewing cases between 1900 and 2005.[43] Only three cases have been published since 2005. The underlying mechanism of spontaneous regression could not be clarified as it is rarely observed in colon cancers. In a study conducted by Abderezzaq, severe sepsis and prolonged fever history were considered to contribute to regression.[43] Miyamoto researched anti-tumor response related to immune system in “in vivo” models, and 40% regression was obtained in stage I-II colon cancer.[44] Tomiki et al identified regrowth in tumor following spontaneous remission caused by tumor resection.[45]

Neuroblastoma is the most frequent extracranial tumor in childhood. It is seen in childhood tumors at the rate of 8–10% across the USA and Europe.[46,47] Spontaneous regression may occur before it is clinically detected. Good responses may be obtained through chemotherapy and spontaneous remission may be observed in children younger than eighteen weeks while prognosis for children older than 18 weeks is poor.[48] Spontaneous regression is observed more often when compared to other tumors; however, no certain prevalence can be provided. ALK and PHOX2B genes diagnosed in neuroblastoma exist at the rate of 80% especially in hereditary neuroblastoma.[49] Trk-neurotrophin receptors are important in development of neuroblastoma and afterwards. High Trk-A is receptor for neural growth factor (NGF), and its increased expression marks good prognosis. Trk-A and Trk-C induce apoptosis. Trk-B and brain-derived neurotrophic factor (BDNF) expression marks poor prognosis.[50,51] Increase in expression of Trk-A receptors is associated with regression development of tumor.[52] The response of host