Original Article
Chance to rein in a cancer–Spontaneous regression of lung carcinoma (1988-2018): a 30-year perspective

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Abstract: Background: Spontaneous regression of tumor is an extremely rare phenomenon in the oncology field and even rarer for lung cancer. However, the underlying mechanism is poorly understood. Summarizing the available clinical information and the supposed mechanism shed new light on lung cancer therapy strategies in the new era of immunotherapy. Summary: We conducted a PubMed search using the retrieval tactics ("Lung Neoplasms" [Mesh]) AND "Neoplasm Regression, Spontaneous" [Mesh] for reports from 1988 to January 2018, and all references in the relevant literature were subsequently investigated for relevance. Using the criteria of Everson and Cole, 14 cases were finally defined as spontaneous regression and were reviewed in the research. Key messages: The information regarding patient characteristics, treatments, and follow-up has been summarized. In this review, we found that spontaneous lung cancer regression cases fall into two categories including: (1) neurologic disorders in 6 cases, half of whom suffered with paraneoplastic neurological syndromes (PNS) and (2) immunological reactions in 7 cases. Getting data on more spontaneous regression cases and more detailed information will definitely help us understand the mechanism for the body's surveillance system-cancer balance, creating a big chance to increase cancer immunotherapy.

Keywords: Spontaneous regression, lung carcinoma, paraneoplastic neurological syndrome, immunological reaction

Introduction

Lung cancer is one of the most fatal cancer types and the leading cause of cancer death among males [1]. Among females, lung cancer is the leading cause of cancer death in more developed countries, and the second cause of cancer death in less developed countries [2]. In 2015, more than 3 million cases of lung cancer and 1.7 million lung cancer-related deaths were documented across the globe [3]. For advanced local or metastatic disease, the five-year survival rate following diagnosis is roughly as low as 16% [4]. Almost all of the cancer patients will develop into later stages if no interference is applied; however there are indeed rare instances of lung cancer regressing spontaneously.

Spontaneous tumor regression is a phenomenon that has been observed for hundreds of years. Although mechanisms about spontane-ous regression have been assumed, they are still behind the veil. Spontaneous regression was defined as the complete or partial disappearance of a malignant tumor in the absence of treatment or in the presence of therapy considered inadequate to exert a significant influence on the disease by Everson and Cole in the 1960s [5, 6]. It is defined as partial or complete disappearance of a malignant tumor in patients' tissue that can be illustrated by pathologic examination. However, to qualify as spontaneous regression, this phenomenon must occur in the absence of any medical treatment [7], leaving a very limited numbernof cases to track possible mechanisms. In this paper, the mechanism of spontaneous regression is discussed using recent references.

Spontaneous tumor regression occurs in approximately one in every 140,000 cases of cancer [8]. Regression is more commonly associ-

ated with tumor types like kidney cancer, chorion epithelioma, neuroblastoma, and malignant melanoma [9]. In recent years, there have been some reviews of spontaneous regression of melanoma [10], thoracic malignancies [11], Merkel cell carcinoma [12], and hepatocellular carcinoma [13]. However, there are rare reports of spontaneous regression of lung cancer. Here, we have comprehensively reviewed 14 cases of spontaneously regressed lung cancer published from 1988 to 2018, containing small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), and an overview of possible mechanisms of regression is portrayed.

Methods

We conducted a PubMed search using the retrieval tactics ("Lung Neoplasms" [Mesh]) AND "Neoplasm Regression, Spontaneous" [Mesh] reported from 1988 to January 2018, and all references in theliterature were subsequently investigated for relevance. We included only those articles that contained true spontaneous regression of lung cancer matching the Everson and Cole criterion that is defined as: 1) patients did not receiving any systemic therapy (chemotherapy, radioablative techniques, chemoembolization, surgery), 2) primary malignancy was pathologically diagnosed, 3) complete or partial disappearance of lung cancer in patients' tissue that can be illustrated by pathologic examination. 14 cases were found in the research shown in **Table 1**.

Epidemiology

Observations regarding the epidemiology of spontaneous lung cancer regression have been reported since 1988. The review of 14 patients showed that the median age of the patients with spontaneous regression was 67.6 years (range: 44-88 years). Of the 14 patients, 64.3% (9/14) were male and the average follow-up time lasted for 36 months (from 4 to 72 months). Among these cases (**Table 1**), four patients had confirmed tumor metastasis including lymph node metastases, brain metastasis, and adrenal metastasis, but there were still two patients with complete spontaneous regression of lung cancer.

Discussion

The patients vary in terms of age, associated treatments, and clinical courses. The mecha-

nism of spontaneous lung cancer regression is obscure. By this review, though with a limited number of cases, we observed that spontaneous lung cancer regression occurred mainly under two physiologic circumstances (**Table 2**): (1) with neurologic disorders; and (2) with abnormal immunological reactions (**Table 2**). There were neurological disorders in 6 patients and systemic immunological abnormalities in 7 patients. In one patient, no obvious physiologic events were found accompanied by tumor regression [14]. As previously reported, tumor regression may be an immune-mediated event especially through inhibiting tumor growth. Interestingly, among the patients suffering with neurologic disorders, there were 3 patients with positive paraneoplastic neuronal antibodies. Various specific neuronal antibodies that are found in paraneoplastic neurological syndromes (PNS) patients suggests that PNSs are the consequences of cancers mediated by immune responses against the tumor [15], and characterized by poor overall outcome [16].

The pathogenesis of the paraneoplastic syndrome in the nervous system is caused by the tumor cells' expressing the neural system antigens which cross-immunize with the nervous tissues, leading to neural system dysfunction. To cope with the developing cancer, the patient produces a tumor-targeting antibody, the onconeural antibody [17]. Due to antigenic similarity, these onconeural antibodies and related onconeural antigen-specific T lymphocytes inadvertently attack components of the nervous system, stimulating a range of immune responses leading to immune-mediated neural syndrome [17, 18]. The association of paraneoplastic syndrome with spontaneous tumor regression strongly suggests that anti-tumor immune-mediated responses are a potential mechanism for the regression. PNS may promote an anti-tumor immune response by affecting autoimmunity in lung carcinoma. Meanwhile, the presence of the Hu antibody at diagnosis of small cell lung cancer (SCLC) is a strong and independent predictor of a complete response to treatment, and even a low titer can be used as a predictor of tumor response to treatment and longer survival [19]. It is speculated that tumor expressing Hu antigen can enhance anti-tumor immunity and increase chemosensitivity [20]. However, there are also reports that the presence of Hu-Ab is not associated with the prognosis of SCLC, but may reflect unknown cellular

Table 1. Clinical characteristics of lung carcinomas spontaneous regression

	Ref.	Age	Sex	Metastasis	Regression	TNM	Pathologic examination	Pathologic diagnosis	Associated treatments or health conditions	Follow-up (month)
1	Cafferata, MA [14]	68	M	None	Complete regression	Stage I	CT-guided fine needle aspiration biopsy	Poorly differenti-ated pulmonary adenocarcinoma	Unknown	48
2	Pujol, JL [34]	75	F	N/A	Complete regression	N/A	Fine-needle transbronchial biopsy	Non-small cell lung cancer	Anti-Hu Antibody Syndrome	18
3	Gladwish, A [35]	81	F	Lymph node metastases	Partial regression	T2N3M0	Ultrasound-guided biopsy	Moderately differ-entiated squamous cell carcinoma	Essiac tea	18
4	Menon, MP [26]	44	M	Brain and adrenal gl and metastases	Partial regression	N/A	Biopsies of both the adrenal gland and lung	Poorly differenti-ated non-small-cell carcinoma	HAART (AIDS)	60
5	Lee, YS [20]	70	F	N/A	Complete regression	N/A	Bronchoscopy biopsy	Small cell lung cancer (SCLC)	Lower respiratory tract infection (fever and cough with yellowish sputum)	132
6	Choi, SM [24]	71	M	N/A	Complete regression	N/A	Bronchoscopy biopsy	Squamous cell carcinoma	Pulmonary tuberculosis	10
7	Nakamura, Y [29]	71	M	None	Complete regression	cT4N0M0	Thoracoscopy	Poorly differentiated adenocarcinoma	Anti-NY-ESO-1 immunity	5
8	Mawhinney, E [36]	N/A	F	N/A	Complete regression	N/A	Bronchoscopy	Atypical cells suggestive of SCLC	Ataxic sensorimotor neuropathy with mild weakness (intravenous immunoglobulin and intravenous methylprednisolone and subsequent oral corticosteroid)	18 DEATH for Neurologic disorder
9	Asada, M [37]	88	M	N/A	Complete regression	N/A	Sputum cytology	Squamous cell carcinoma	Tiapride for the treatment of senile mental illness	4
10	Haruki, T [31]	69	F		Partial regression	cT1N2M1	CT-guided needle biopsy	Lung adenocarcinoma	Immunological CD8+ T cell	14
11	Darnell, RB [38]	60	M	N/A	Complete regression	N/A	Biopsy specimen	Small cell lung cancer (SCLC)	Paraneoplastic neuronal antibodies	72
12	Darnell, RB [38]	71	M	None	Complete regression	N/A	N/A	N/A	Hu-antibody positive	12 and Death for Her neurological state progressively deteriorated
13	Nakano, T [25]	50	F	Lymph node metastases	Complete regression	N/A	Bronchoscopy examination	Small cell lung carcinoma (SCLC)	hepatitis B cell strain	72 months and died for hepatocellular carcinoma
14	Sperduto, P [39]	61	M	Adrenal metastasis	Complete regression	N/A	Needle aspiration	Squamous cell carcinoma	auditory hallucinations (treated with amitriptyline and perphenazine)	24

Table 2. Possible reasons for lung carcinomas' spontaneous regression

Neurologic disorder	Immunological reaction
Paraneoplastic neuronal antibodies [34, 38]	Essiac tea [35]
Ataxic sensorimotor neuropathy [36]	HAART (AIDS) [26]
Senile mental illness [37]	Lower respiratory tract infection (fever and cough with yellowish sputum) [20]
Auditory hallucinations [39]	Pulmonary tuberculosis [24]
	Anti-NY-ESO-1 immunity [29]
	Massive infiltration of CD8+ lymphocytes [31]
	Hepatitis B virus [25]

immune responses, induce nervous system syndrome, and improve tumor outcome [21]. Thus, it seems that the real relationship between PNS, Hu-antibody and spontaneous regression of lung cancer still needs to be clarified by further evidence.

Cancer regression is long known but underinvestigated because of its rare incidence. Notably, the regression of cancers often occurs simultaneously with infections including hepatitis, influenza, tuberculosis, and others [22, 23]. In the 3 cases with spontaneous regression of lung cancer from 1988-2018, we found that the possible reasons for the regression in lung cancer are lower respiratory tract infection [20], pulmonary tuberculosis [24], and hepatitis B virus [25] (**Table 2**). Meanwhile, Menon et al. [26] reported that possible factors connected with tumor regression include antiretroviral treatment and immune recovery through highly active antiretroviral therapy (HAART) [26, 27]. A report showed that early remission of cervical intraepithelial lesions appeared in HIV patients after antiretroviral therapy [28]. These suggest that immune recovery from an impaired condition may cause spontaneous regression of tumors. There is now increasing evidence that congenital and adaptive immune cells interact in the lung tumor microenvironment, and the structural and functional association between local immunity and the components of the tumor microenvironment can affect prognosis. The mechanisms of immunologic reactions produce a stronger than normal response resulting in recovery of lung cancer (**Table 2**), the stimulus of which may be infection caused by tuberculosis [24], viruses [25, 26, 29] or any other events that influence the lung [30] and make lung cancer unable to escape the immune response. Also, massive infiltration of CD8+ lymphocytes [31] are associated with a better prognosis compared to cases without CD8+ infiltration in lung cancer patients [32].

Growing evidence points to an immune imbalance for cancer development and progression. From this mini review, it seems immune factors are the cause for spontaneous cancer regression. In certain physical conditions, cancer patients are able to survive for a long period with stable cancer. For cervical intraepithelial neoplasia (CIN), spontaneous regression occurs more frequently and there is a greater chance for regression before irreversible cancer develops [33]. Therefore, it is very interesting and important to explore the mechanisms orchestrating tumor spontaneous regression. Here, by "spontaneous", it only means the cancers regress without receiving traditional treatment procedures like surgery, chemotherapy and radiotherapy, and there must be some internal or external factors that switch off the tumor progression. Spontaneous regression can involve two different processes, including to reverse the precancerous lesions or to shrink the existing tumors, at least achieving patients' long-term survival with a stable cancer, while saving aggressive chemotherapy or radiotherapy procedures. In an era of immunotherapy development, it is even more important to figure out the decisive power behind the cancer immune system. The real factors curbing tumor development and initiating tumor regression remain unknown, and even the factors predicting immunotherapy efficacy still are in an immature stage. This review about lung cancer spontaneous regression sheds light on the task to fight cancer. A major limitation of this study is its retrospective design, but a prospective analysis for spontaneous regression of lung malignancies is impossible, as they are so rare. The mechanism of this event is still a mystery. The two major physical abnormalities connected to lung cancer spontaneous regres-

sion should be further investigated in every detail.

Disclosure of conflict of interest

None.

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