Original Article

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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 regresssing spontaneously.

Spontaneous tumor regression is a phenomenon that has been observed for hundreds of years. Although mechanisms about spontaneous 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 number of 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-
Spontaneous regression of lung carcinoma

ated with tumor types like kidney cancer, cho-

avian epithelioma, neuroblastoma, and malig-nant 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 re-

ports of spontaneous regression of lung can-

cer. Here, we have comprehensively reviewed

14 cases of spontaneously regressed lung can-

cer 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 por-

trayed.

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 the literature were subse-

quently investigated for relevance. We includ-

ed only those articles that contained true spon-
taneous regression of lung cancer matching

the Everson and Cole criterion that is defined

as: 1) patients did not receiving any systemic

therapy (chemotherapy, radioablative techni-

cues, chemoembolization, surgery), 2) primary

malignancy was pathologically diagnosed, 3)

complete or partial disappearance of lung
cancer in patients' tissue that can be illustrat-
ed 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 fol-

low-up time lasted for 36 months (from 4 to

72 months). Among these cases (Table 1), four

patients had confirmed tumor metastasis in-

cluding lymph node metastases, brain metas-
tasis, 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 spontane-
ous lung cancer regression occurred mainly

under two physiologic circumstances (Table 2):

(1) with neurologic disorders; and (2) with

abnormal immunological disorders (Table 2).

There were neurological disorders in 6 pa-

tients and systemic immunological abnormali-
ties in 7 patients. In one patient, no obvious

physiologic events were found accompanied

by tumor regression [14]. As previously report-
ed, tumor regression may be an immune-medi-

ated event especially through inhibiting tumor
growth. Interestingly, among the patients suf-

fering with neurologic disorders, there were 3

patients with positive paraneoplastic neuronal

antibodies. Various specific neuronal antibod-

ies that are found in paraneoplastic neurologi-
cal syndromes (PNS) patients suggests that

PNSs are the consequences of cancers medi-

ated by immune responses against the tumor

[15], and characterized by poor overall outcome

[16].

The pathogenesis of the paraneoplastic syn-
drome in the nervous system is caused by the
tumor cells’ expressing the neural system anti-
gens 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 onco-
nearl antibody [17]. Due to antigenic similarity,

these onconeural antibodies and related onco-
nearl antigen-specific T lymphocytes inadvert-
tently attack components of the nervous sys-
tem, stimulating a range of immune responses

leading to immune-mediated neural syndrome

[17, 18]. The association of paraneoplastic syn-
drome with spontaneous tumor regression st-
rongly suggests that anti-tumor immune-medi-
ated responses are a potential mechanism for

the regression. PNS may promote an anti-tu-

mor immune response by affecting autoimmu-
nity in lung carcinoma. Meanwhile, the pre-

ence of the Hu antibody at diagnosis of small
cell lung cancer (SCLC) is a strong and indepen-
dent predictor of a complete response to treat-
ment, 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 pre-

ence of Hu-Ab is not associated with the prog-

dnosis of SCLC, but may reflect unknown cellular
### Spontaneous regression of lung carcinoma

#### Table 1. Clinical characteristics of lung carcinomas spontaneous regression

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Age</th>
<th>Sex</th>
<th>Metastasis</th>
<th>Regression</th>
<th>TNM</th>
<th>Pathologic examination</th>
<th>Pathologic diagnosis</th>
<th>Associated treatments or health conditions</th>
<th>Follow-up (month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68</td>
<td>M</td>
<td>None</td>
<td>Complete regression</td>
<td>Stage I</td>
<td>CT-guided fine needle aspiration biopsy</td>
<td>Poorly differentiated pulmonary adenocarcinoma</td>
<td>Unknown</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
<td>F</td>
<td>N/A</td>
<td>Complete regression</td>
<td>N/A</td>
<td>Fine-needle transbronchial biopsy</td>
<td>Non-small cell lung cancer</td>
<td>Anti-Hu Antibody Syndrome</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>81</td>
<td>F</td>
<td>Lymph node metastases</td>
<td>Partial regression</td>
<td>T2N3M0</td>
<td>Ultrasound-guided biopsy</td>
<td>Moderately differentiated squamous cell carcinoma</td>
<td>Essiac tea</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>M</td>
<td>Brain and adrenal glands and metastases</td>
<td>Partial regression</td>
<td>N/A</td>
<td>Biopsies of both the adrenal gland and lung</td>
<td>Poorly differentiated non-small-cell carcinoma</td>
<td>HAART (AIDS)</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>F</td>
<td>N/A</td>
<td>Complete regression</td>
<td>N/A</td>
<td>Bronchoscopy biopsy</td>
<td>Small cell lung cancer (SCLC)</td>
<td>Lower respiratory tract infection (fever and cough with yellowish sputum)</td>
<td>132</td>
</tr>
<tr>
<td>6</td>
<td>71</td>
<td>M</td>
<td>N/A</td>
<td>Complete regression</td>
<td>N/A</td>
<td>Bronchoscopy biopsy</td>
<td>Squamous cell carcinoma</td>
<td>Pulmonary tuberculosis</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>71</td>
<td>M</td>
<td>None</td>
<td>Complete regression</td>
<td>cT4N0M0</td>
<td>Thoracoscopy</td>
<td>Poorly differentiated adenocarcinoma</td>
<td>Anti-NY-ESO-1 immunity</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>N/A</td>
<td>F</td>
<td>N/A</td>
<td>Complete regression</td>
<td>N/A</td>
<td>Bronchoscopy</td>
<td>Atypical cells suggestive of SCLC</td>
<td>Ataxic sensorimotor neuropathy with mild weakness (intravenous immunoglobulin and intravenous methylprednisolone and subsequent oral corticosteroid)</td>
<td>18 DEATH for Neurologic disorder</td>
</tr>
<tr>
<td>9</td>
<td>88</td>
<td>M</td>
<td>N/A</td>
<td>Complete regression</td>
<td>N/A</td>
<td>Sputum cytology</td>
<td>Squamous cell carcinoma</td>
<td>Tiapride for the treatment of senile mental illness</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>69</td>
<td>F</td>
<td>Partial regression</td>
<td>cT1N2M1</td>
<td>CT-guided needle biopsy</td>
<td>Lung adenocarcinoma</td>
<td>Immunological CD8+ T cell</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>60</td>
<td>M</td>
<td>None</td>
<td>Complete regression</td>
<td>N/A</td>
<td>Biopsy specimen</td>
<td>Small cell lung cancer (SCLC)</td>
<td>Paraneoplastic neuronal antibodies</td>
<td>72</td>
</tr>
<tr>
<td>12</td>
<td>61</td>
<td>M</td>
<td>None</td>
<td>Complete regression</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Hu-antibody positive</td>
<td>12 and Death for Her neurological state progressively deteriorated</td>
</tr>
<tr>
<td>13</td>
<td>50</td>
<td>F</td>
<td>Lymph node metastases</td>
<td>Complete regression</td>
<td>N/A</td>
<td>Bronchoscopy examination</td>
<td>Small cell lung carcinoma (SCLC)</td>
<td>Hepatitis B cell strain</td>
<td>72 months and died for hepatocellular carcinoma</td>
</tr>
<tr>
<td>14</td>
<td>61</td>
<td>M</td>
<td>Adrenal metastasis</td>
<td>Complete regression</td>
<td>N/A</td>
<td>Needle aspiration</td>
<td>Squamous cell carcinoma</td>
<td>Auditory hallucinations (treated with amitriptyline and perphenazine)</td>
<td>24</td>
</tr>
</tbody>
</table>
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-

<table>
<thead>
<tr>
<th>Neurologic disorder</th>
<th>Immunological reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paraneoplastic neuronal antibodies [34, 38]</td>
<td>Essiac tea [35]</td>
</tr>
<tr>
<td>Ataxic sensorimotor neuropathy [36]</td>
<td>HAART (AIDS) [26]</td>
</tr>
<tr>
<td>Senile mental illness [37]</td>
<td>Lower respiratory tract infection (fever and cough with yellowish sputum) [20]</td>
</tr>
<tr>
<td></td>
<td>Anti-NY-ESO-1 immunity [29]</td>
</tr>
<tr>
<td></td>
<td>Massive infiltration of CD8+ lymphocytes [31]</td>
</tr>
<tr>
<td></td>
<td>Hepatitis B virus [25]</td>
</tr>
</tbody>
</table>
Sporaneous regression of lung carcinoma should be further investigated in every detail.

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Disclosure of conflict of interest

None.

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Spontaneous regression of lung carcinoma


Spontaneous regression of lung carcinoma


