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Review Article

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Spontaneous Regression of Lung Carcinoma: An Essential Review

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Abstract

Lung cancer is the second leading cause of cancer in both males and females in the United States, as it has been estimated that 200,000 new cases will appear in males and females in the U.S, accounting for 14% of new cancers. Lung cancer accounts for 25% of cancer fatalities and has the lowest survival rates. Cancer Spontaneous Regression (SR) is defined as either partial or complete, and temporary or permanent, disappearance without appropriate treatment for the disease, and is a very rare phenomenon of unknown mechanism. The exact incidence of cancer SR is unknown. 176 cases of cancer SR have been reported from 1900 to 1964 with an assessed incidence of 1/ 60,000-100,000 cancer patients, whereas another research found total 15 cases from 1954 to 1997, and more recently 741 cases of SR of malignant diseases in the literature between 1900 and 1987 have been recorded. SR cases concerned several types of malignancies such as lymphoma, leukemia, retinoblastoma, neuroblastoma, melanoma, choriocarcinoma, renal, bladder, and breast cancer, and represented 69% of all SR cases, whereas lung cancer SR only observed in 2.6% of all patients with SR. A few cases reported that SR is an extremely rare biological event in primary lung cancer, and in particular, SR of non-small cell lung cancer (NSCLC) has been scarcely reported. The SR incidence of advanced NSCLC is relatively low, as approximately 20 cases were recorded from 1950 to 2004, and no more than 15 new cases have been reported in the last 12 years. 10 articles describing NSCLC SR between 1997and 2018 have also been observed. Currently, 17 well-documented case reports of lung cancer SR concerning NSCLC and small cell lung cancer (SCLC) have been described. A total of 25 cases of lung cancer were identified between 1987and 2020. Squamous cell carcinoma (SQCLC) accounted for 10 cases, followed by NSCLC not otherwise defined and adenocarcinomas. The pathogenesis of SR cancer is poorly understood, however recent investigations revealed the role of immunological mechanisms, consequently indicating possible therapy options by specific immunotherapy in the future.

It has also been supposed that there may be an immunological association between the stimulus of the biopsies and the SR. Recent researches have shown that immunological reaction can be initiated by trauma to an anatomic location. In some

cases the tumor SR became evident only after the tissue biopsy, observation that leads to the option that immune response to the surgical procedure seems to be a plausible contributor to the SR. Para-neoplastic sensorimotor neuropathy (PNS) has been suggested as a mechanism of SCLC and NSCLC SR. Specific anti-neuronal auto-antibodies, anti-Hu antibodies, react both to the tumor and nervous system, in patients with sensorimotor neuropathy, and this inflammatory response has been associated with the antitumor immune response. Many cases of SCLC SR have been escorted by neurological symptoms, but no neurological abnormalities were observed. However, the real association between PNS, Hu-antibody and SR of lung cancer still needs to be clarified by further evidence. It has also been recorded that bronchoscopy contributed to SR of lung cancers. Diverse case reports have recorded patients with advanced, poorly differentiated NSCLC (highly expressing programmed death ligand-1 [PD-L1]) that progressed despite multiple cycles of chemotherapy but then spontaneously remitted, patients with lung squamous cell carcinoma who experienced SR following biopsy without other therapeutic intervention, and patients with lung adenocarcinoma that spontaneously remitted. Almost all case reports described SR of an untreated lung cancer and were diagnosed and histologically confirmed.

Keywords: Non-Small Cell Lung Cancer; Small Cell Lung Cancer; Spontaneous Regression; Immunologic Response; Biopsy

Abbreviations: SCLC: Small Cell Lung Cancer, SR: Spontaneous Regression, SQCLC: Squamous Cell Lung Cancer, NSCLC: Non-Small Cell Lung Cancer, IPF: Idiopathic Pulmonary Fibrosis, TB: Tuberculosis, PNS: Para-neoplastic Neurological Syndromes, HAART: Highly Active Antiretroviral Therapy, SPM: Specialized Pro-resolving Mediators, TNF-A: Tumor Necrosis Factor-Alpha, IFN-Γ: Interferon Gamma

Introduction

The spontaneous regression (SR) of cancer is defined as either partial or complete, and temporary or permanent, disappearance in the absence of anticancer therapy or with inadequate treatment for cancer control **[1-8].** However, to describe as SR, this phenomenon must occur in the absence of any medical treatment **[9]**, leaving a very limited number of cases to detect possible mechanisms.

Cancer SR is divided into four categories, as follows, primary tumor regression, metastatic regression (primary focus is diagnosed pathologically), metastatic tumor regression (no pathological diagnosis of primary tumor), and radiologically considered metastasis tumor regression **[6].**

Cancer patients who refused treatment and "survived" despite the fact that they did not receive a specific therapy and were still in a good condition. Some of those patients have experienced recurrent cycles of spontaneous remission and relapse **[10],** showing that further spontaneous remissions of untreated malignant tumor might occur.

The SR of cancer is a phenomenon that has been observed and reported for several years by scientists such as oncologists, hematologists, pathologists, and researchers **[11].** Everson in one of his publications in1968, clearly defined this phenomenon and he also emphasized the fact that these cases of cancer were all diagnosed by histopathological examination of a tissue biopsy **[12].** SR of cancer occurs very rarely, approximately1 in 100,000 cases **[7]**, or1 in every 140,000 cases of cancer **[9].** Similar articles showed that the incidence of cancer SR is about 1 in 60,000 to 100,000 patients with cancer **[3,5,13].** Several case reports described SR of various cancers, including renal cell carcinoma, leukemia/lymphoma, non-Hodgkin's lymphoma, chronic lymphoid, leukemia, melanoma, neuroblastoma, thoracic malignancies **[14]**, Merkel cell carcinoma **[15]**, and hepatocellular carcinoma **[7,16-20].** Melanoma, neuroblastomas, renal cell carcinoma, and lymphoma were more common **[16]**, as have shown relatively high incidences of SR **[7].** SR of primary malignant lung tumors is a rare occurrence **[1,21,22]**, especially in the case of squamous cell lung cancer (SQCLC), very few reports in the literature to date **[20]** in the case of small cell lung carcinoma (SCLC) **[12]** and is extremely rare in patients with non-small cell lung cancer (NSCLC) **[5,13,14,18,23-37].**

15 case reports of lung cancer SR from 1954 to 1997 have been described **[13]**, 20 cases of NSCLC SR were reported from 1950 to 2004 **[3,5,13]**, and14 cases of spontaneously regressed lung cancer published from 1988 to 2018 and concerned mainly NSCLC than SCLC cases **[37].** Spontaneous regression (SR) of cancer has an unclear pathogenesis **[1,7].** Immunological and cytokine repair processes, modulated immunological response following systemic infection, interruption of immune-suppression therapy, immune reconstitution in HIV patients, psycho-immunological mechanisms induced by causative factors, such as infection, fever, drugs, radiation, and trauma, which includes surgery, hormones, pregnancy, and carcinogens, tumor inhibition by cytokines or growth factors, elimination of carcinogenesis, tumor necrosis, apoptosis, surgical trauma (operation or biopsy), epigenetic mechanisms, telomerase inhibition, psycho-neurological factors, suspension of exogenous carcinogens, differentiation of malignant cells into benign ones, induction of differentiation, hormonal mechanisms, psychoneuro-immunological factors, angiogenesis inhibition or paraneoplastic sensorimotor neuropathy have been considered as part of this mechanism **[2-4,7,11-13, 21, 25, 28,31,37-51]**.

Especially, cancers regression often occurs simultaneously with infections such as influenza, hepatitis, tuberculosis, and others **[52,53]**.

SR of lung cancer cases

Enough researches have reported SR in cases of primary lung cancer **[1,3,34,50]**. Kumar et al. reported only two cases of primary lung cancer from 1951 to 2008 that met the definition of Everson and Cole **[14]**, whereas the same authors investigated 47 SR of cancers, and lung cancer was only one of the 47 cases, five years after underwent thoracotomy and biopsy **[1]**.

Neuroendocrine tumors with SR have been described in only one case of lung carcinoid **[54]**. Challis and Stam **[20]** stated 25 cases, whereas O'Regan and Hirshberg **[55]** mentioned eight case reports of lung cancer SR.

Everson and Cole **[19]** reported only two cases, Lowy **[56]** recorded four cases in the medical literature up to 1984 and reported a case of SR in a patient with metastatic SCLC, in spite of its worldwide high incidence.

A total of 25 cases were identified between 1987 and 2020. SQCLC cases accounted for 10 cases, followed by NSCLC not otherwise defined (n= 6) and adenocarcinomas (n= 6). All except three cases with SR observed in the primary tumor, whereas the SR was complete in seven cases and partial in 15. From cases where data was available, two cases experienced local relapse and one, distant relapse, and each of these cases had SR observed in the primary tumor **[57]**. The majority of SR of NSCLC cases involved SQCLC, and most reports showed SR of advanced NSCLC with no treatment **[25,30]**. A similar study **[27]** reported a case of supposed SQCLC that demonstrated SR after biopsy of a mediastinal lymph node, but the investigators did not receive tissue from the lung tumor itself. The authors also described a limited number of primary lung cancer SR cases. Similarly, in a current research Ariza-Prota et al. also stated a SR case after biopsy in a case with metastatic SQCLC in a patient that was refused to receive anticancer treatment **[58]**.

Seven cases had SQCLC and only three were extensive stage SQCLC which did not received any type of treatment. These cases showed SR duration of two, five, and twelve years, respectively. A case of SR of advanced SQCLC that progressed after a 5th round of chemotherapy, regressed after interrupting the chemotherapy, and maintained SR for over one year **[23]**.

A rare case of a 79-year-old male with advanced SQCLC whose tumor spontaneously regressed with no active treatment was recorded by Park et al. **[34]**. Another rare case report of a patient with NSCLC who exhibited SR of the primary and metastatic lesions without receiving treatment was also recorded by Ryoko Ogawa et al. **[32]**. The authors described a case with metastatic poorly differentiated NSCLC whose tumors regressed after the biopsy of a cervical lymph node metastasis and the primary lesion. It has been suggested that the invasive procedure triggered an immunologic stimulus resulting in subsequent regression. Esplin et al. described a case of a patient with primary SQCLC, stage T1M0N0, that demonstrated SR after biopsy with no additional therapeutic intervention by the medical therapeutists or lifestyle change by the patient **[59]**. Heon Sung et al. reported a rare case of complete spontaneous remission in an elderly patient with SCLC **[60]**. Masaki

Yamamoto et al. examined two SR cases of NSCLC with different clinical outcomes **[61]**.

The SR incidence of advanced NSCLC was relatively low, as approximately 20 cases were recorded from 1950 to 2004 **[23]**, and no more than 15 new cases have been reported from 1954 to 1997**[13]**. Ten articles describing NSCLC SR between 1997 and 2018 have also been recorded **[62]**. The authors also presented a case of a male who experienced SR of biopsy-proven NSCLC that clearly regressed over a six-month period without intervention and was for a long time, more than 13 months, post-biopsy without evidence of active disease. Currently, 17 well-documented case reports of lung cancer with SR, 10 NSCLC and 7 SCLC cases have been described **[5,13,18,22,24,25,27,30,31,35,40,47,63-67]**.

In another report, Marques et al. **[28]** examined 17 cases of SR in lung cancer, 10 of which concerned NSCLC. They also recorded 19 cases of SR in NSCLC since the 1990s. Other studies recorded that only four of the 19 reported cases had long-term outcomes that showed a recurrence-or progression-free period of five years or more, and they also reported a variety of follow-up periods, ranging from two to 31 months **[13,18,27,68]**.

In most cases, advanced-stage cancer existed, or poor lung function even in case of early-stage cancer. Various standards of complete or partial regression were observed, as the primary lesion disappeared, but the metastatic lesion remained or both the primary and metastatic lesions remained after regression, or the primary lesion remained, but the metastatic lesion disappeared. For the mentioned reasons, it is difficult to identify long-term outcomes after SR. An alteration in tumor size is one of the most important indicators for assessing the malignant potential of a tumor in all lung cancer screening guidelines.

The SR of NSCLC has also been reported in a patient who presented with an anti-Hu antibody peripheral neuropathy. The lung neoplasm was confirmed by biopsy. 12 months later the neuropathy had progressed but there was no evidence of the tumor on CT imaging **[35]**.

Another study described a case of a patient with lung adenocarcinoma exhibiting SR of a scalp metastasis **[69]**. Remarkably, the scalp metastatic lesion SR developed after one month after performing biopsy of the scalp tumor and the regression of the primary lung lesion also developed one month after performing a trans-bronchial biopsy **[69]**.

In another report a case of a 74-year-old female diagnosed with advanced poorly differentiated NSCLC that spontaneously remitted after failure of multiple courses of chemotherapy **[70]**. Menon et al. described the first case in the literature of SR of metastatic NSCLC in the setting of immune reconstitution in an HIV positive individual **[18]**.

Hwang et al**. [26]** presented a rare case of NSCLC in a patient with Idiopathic Pulmonary Fibrosis (IPF) whose tumor spontaneously regressed without treatment. Moreover, lung cancer SR is extremely rare especially in patients with NSCLC occurring on IPF **[26]**.

Possible mechanisms for lung cancer SR

Lung cancer is the second leading cause of cancer in both males and females in the U.S. It has been estimated that 200,000 new cases will appear in males and females in the United States accounting for 14% of new cancers. Lung cancer accounts for 25% of cancer fatalities and has the lowest survival rates **[71]**. Similar researches stated that lung cancer is one of the most fatal cancer types and the leading cause of cancer death among males **[72]**, whereas among females, lung cancer is the leading cause of cancer death in more developed countries, and the 2nd cause of cancer death in less developed countries **[73]**. In 2015, more than 3 million cases of lung cancer and 1.7 million lung cancer-related deaths were described worldwide **[74]**. The five-year survival rate following diagnosis is approximately as low as 16% for advanced local or metastatic disease **[75]**. The majority of lung cancer patients will be deteriorated and develop into later stages if no treatment is applied. However, rare cases of lung cancer SR have been detected.

The precise mechanism of SR is controversial. Recent articles have recorded a possible influence of various mechanisms, including immune mediation, tumor inhibition by cytokines, chemokines or growth factors, hormonal influence, elimination of carcinogenesis, angiogenesis inhibition, immunological response, telomerase inhibition, psycho-neuro-immunological response, tumor necrosis, epigenetic mechanisms, apoptosis, and induction of differentiation **[2,7,13,21,45]**. Although tumor SR may be an immune-mediated phenomenon especially through inhibiting tumor

growth, the mechanism underlying cancer SR remains controversial as already mentioned **[37]**. It has been suggested an anti-tumor immune-mediated response as a potential mechanism for SR, and due to its very rare incidence, only a few cases with a long period of SR in SCLC cases have so far been described **[47,56,76]**.

In lung cancer, the immunologic reaction is the most logical mechanism for SR. Moriyama et al. **[77]** reported that HLA class I antigen and CD8-positive lymphocytes are increased in lung cancer tissue and suggested that these lymphocytes might be cytotoxic to tumor cells. Regarding to lung cancer, changes in the immunological environment of the tumor that can influence both oncogenesis and regression have been recorded. Scheider et al. showed an accumulation of regulatory T cells in lung adenocarcinoma and metastatic lymph nodes, leading to a local decrease of antitumor immune response by natural killer cells **[78]**. Iwakami et al. reported an infiltration of CD8-positive lymphocytes in SCLC that regressed spontaneously, indicating that T cell-mediated cytotoxity is a possible mechanism of SR in lung cancer **[79]**. Isobe et al. demonstrated an integrated immune response consisting of immunoglobulin G (IgG) antibodies, CD4 and CD8 T cells against a NY-ESO-1-expressing NSCLC experiencing SR **[80]**.

A systemic reaction, such as an immune reaction to tumors, could be a possible causative mechanism. However, no reports indicating immunoreaction-mediated SR in patients with NSCLC have been carried out. NY-ESO-1 antigen was initially identified in esophageal cancer by serological expression cloning using autologous patient serum and recorded that it was a cancer/testis antigen that is expressed in cancer and testis, but not in normal adult somatic tissues **[81,82]**. This antigen is a vaccine and immunotherapy candidate. NY-ESO-1 has already been examined in diverse experimental studies in more than 30 clinical trials worldwide, and its main characteristic focused on its capacity to induce spontaneous antibody and T-cell responses in a rate of cancer patients **[83]**. Similarly, another article recorded that SR is a result of an immune system process associated with the tumor's microenvironment and oncogenic expression **[84]**. Nakamura et al. **[31]** similarly suggested that immunological reaction to specific antigens such as NYESO-1 is a possible mechanism of SR in lung cancer.

A recent study showed that better survival was observed among patients with lung cancer with tuberculosis (TB) than among patients without TB **[85]**.

A case of left-sided hemichorea associated with anti-SOX1 (SOX1-Ab) and-CV2/CRMP5 (CV2/ CRMP5-Ab) antibodies with a 7-year interval free of disease progression of SCLC has been described **[86]**.

Previous researches revealed a relatively high incidence of para-neoplastic neurological syndromes (PNS) associated with SR of cancer. Para-neoplastic syndromes have been shown to be associated with lung cancer, and the patients produce a tumor-targeting antibody, the onconeural antibody in order to deal with cancer **[87]**. Due to antigenic similarity, these onco-neural antibodies and related onco-neural antigen-specific T lymphocytes accidentally attack components of the nervous system, stimulating immune responses resulting in immune-mediated neural syndrome **[87,88]**. The association of para-neoplastic syndrome with tumor SR strongly suggested 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 cancer cases.

The Hu antigens are normally expressed throughout the central and peripheral nervous system. In SCLC cases, one of these antigens, Hu-D, may also be expressed by tumor cells. Although the exact pathogenesis is unclear, it is thought that when this occurs the Hu antigens are recognized by the immune system as ‘non-self’ triggering the para-neoplastic response **[89]**.

The Hu antibody is directed against RNA-associated neuronal proteins and is known to cause para-neoplastic encephalomyelitis/sensory neuronopathy syndrome, mostly when associated with SCLC **[90]**. Moreover, the presence of the Hu antibody at diagnosis of SCLC is a potent 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 **[91]**. It is hypothesized that tumor expressing Hu antigen can enhance anti-tumor immunity and increase chemo-sensitivity **[47]**. However, it has been found that the presence of Hu-antibody

was not associated with SCLC prognosis but may reflect unknown cellular immune responses, induce nervous system syndrome, and improve tumor outcome **[92]**.

Anti-Hu antibodies indicate an underlying neoplasm in 88% of cases, and 81% of these were SCLC cases **[93]**. SCLC patients with no clinical para-neoplastic syndrome had anti-Hu antibodies in their serum in approximately 17% of cases **[91,94]**. These antibodies are responsible for a wide range of neurological para-neoplastic syndromes, such as Lambert-Eaton syndrome, cerebellar ataxia, limbic encephalitis, polyradiculopathy, opsoclonus-myoclonus syndrome and, most frequently, sensory neuropathy (54%) **[93,95]**. A previous case reported tumor SR associated with anti-Hu antibodies in patients with histologically proven SCLC, as was confirmed by a biopsy of a supraclavicular node. The clinical course showed that the patient developed a progressive para-neoplastic syndrome with high titers of anti-Hu antibodies. A chest x-ray revealed almost complete dilution of the neoplasm prior to starting chemotherapy **[96]**. It is obvious that the real association between PNS, Hu-antibody and lung cancer SR still needs to be clarified by further investigation.

Anti-Hu para-neoplastic syndromes, such as cerebellar ataxia or peripheral neuropathy, might be the first clinical manifestation of human malignancies **[95]**. In some cases, the determination of malignant disease that was responsible for these para-neoplastic syndromes was difficult or impossible. Moreover, the disease would be difficult to be identified and the patient could die of neurological complications, whereas SCLC remains nearly undetectable at minimal tumor burden **[95]**.

It can be hypothesized that patients with anti-Hu antibodies without demonstrable lung cancer are those for whom immunity against the disease may have reduced the tumor to an undetectable level. The development of a para-neoplastic syndrome as the presenting reaction of an underlying SCLC explains why anti-Hu antibodies are associated with earlier tumor stage and prolonged survival **[91,93]**.

A recent report also suggested that anti-Hu antibodies are associated with increased chemosensitivity **[93].** Pujol et al. **[35]** reported that anti-Hu antibody syndrome is associated with SR of NSCLC.

A case report suggested that the immunology of Hu antibody para-neoplastic syndrome itself could partially explain the better response rate usually associated with treatment of patients with lung cancer who present with a high serum Hu antibody level. The possibility of achieving a complete response was more than five times greater for Hu antibody-positive versus Hu anti-body-negative patients (95% odds ratio, 5.4). In contrast with SCLC, complete remission among patients with NSCLC is a rare event, particularly long-term remission **[35]**.

The pathogenesis of the para-neoplastic syndrome in the nervous system is caused by the tumor cells' expressing the neural system antigens which cross-immunize with the nervous tissues, resulting in neural system dysfunction **[37]**. Hirano et al. reported an association of para-neoplastic syndrome with SR of SCLC, and three of eight cases showed para-neoplastic sensory neuropathy. Anti-Hu, anti-Ri, and anti-Yo antibodies can be found in patient with para-neoplastic sensory neuropathy, and they exhibit cross-reactivity to tumor and nervous tissue simultaneously **[22]**.

Another case report focused on an elderly female who developed a lung neoplasm histologically confirmed as SCLC. The patient developed a para-neoplastic sensory neuropathy with high titers of anti-Hu antibodies, and the lung tumor regressed with no evidence of neoplasia on radio imaging (CT and PET) or bronchoscopy **[65]**.

Para-neoplastic sensorimotor neuropathy has been suggested as a mechanism of SCLC SR **[65,96]**. Specific anti-neuronal autoantibodies react with the tumor and nervous system, in patients with sensorimotor neuropathy, and this inflammatory response is associated with the antitumor immune response. 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 some patients with positive para-neoplastic neuronal antibodies. Various specific neuronal antibodies that are found in para-neoplastic neurological syndromes (PNS) patients suggested that PNSs are the consequences of cancers mediated by immune responses against the tumor **[97]** and characterized by poor overall outcome **[98].** Three case reports of SR of SCLC patients with para-neoplastic anti-neuronal antibodies have been recorded

[76].

A similar report described a 71-year-old female with a left pulmonary nodule on CT. However, bronchoscopy was normal. She developed a sensory neuropathy with associated anti-Hu antibodies, and an assumed diagnosis of SCLC with para-neoplastic sensory neuropathy was made. Within 4 months she had radiological evidence of complete resolution of the lung tumor without any active treatment **[76]**.

The general role of infection has also been examined as a possible risk factor of lung cancer SR. Three cases with SR of lung cancer from 1988-2018, were described and the possible reasons for the regression were lower respiratory tract infection **[47]**, pulmonary TB **[40]**, and hepatitis B virus **[99]**. Menon et al. **[18]** reported that possible factors connected with tumor regression include anti-retroviral treatment and immune recovery through highly active antiretroviral therapy (HAART) **[18,100]**. A report by Heard et al. showed that early remission of cervical intraepithelial lesions appeared in HIV patients after antiretroviral therapy **[101]**. Those findings suggested that immune recovery from an deteriorated condition may cause SR of tumors. Increasing evidence suggested 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 influence prognosis. The mechanisms of immunologic reactions produce a stronger than normal response leading to recovery of lung cancer, the stimulus of which may be an infection caused by TB **[40]**, viruses **[18,31,99]** or any other events that affect the lung **[102]** and make lung cancer unable to escape the immune response. Moreover, the massive infiltration of CD8+ lymphocytes **[4]** was associated with a better prognosis compared to cases without CD8+ infiltration in lung cancer cases **[103]**. Several cases of poorly differentiated lung cancer escorted by leukemoid reaction have been described **[104-106]**. Inflammation is physiologically self-limiting, as the acute inflammation is terminated by activated neutrophils generating specialized pro-resolving mediators (SPM), such as protectins, lipoxins, resolvins, and maresins, which are derived from essential fatty acids **[107,108]**. In vitro evidence showed that SPM controls innate and adaptive immunity by reducing the generation of inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interferon gamma (IFN-γ) and memory B-cell antibody production **[109,110]**. Based on the association between cancer progression and inflammation, increased cellular proliferation in poorly differentiated cancer might quaintly induce the suppression of tumor growth via SPM, leading to cancer SR.

Lung cancers incur SR less frequently, probably because they have a tendency to be less immunogenic **[111]**. However, it has been recorded **[112]** lung cancer SR cases after incomplete surgical resection. Cole **[7]** suggested surgical trauma as the possible cause in 71 of 176 cases of SR cancer. Surgical trauma, such as bronchoscopic biopsy, could especially result in SCLC SR **[56,113]**, whereas bronchoscopy has also been contributed to SR of lung cancer cases **[114]**. An unusual case described by Kappauf et al. and presented a metastatic bronchogenic cancer with metastasis to the abdominal wall **[13]**. The cancer showed complete remission after biopsy, without pyretic infection or conventional cancer therapy, after an excisional biopsy with incomplete resection, a rare event, as there are few cases that document SR following metastasis. Gladwish et al. described a case report of a patient with SR of stable IIB NSCLC after receiving an herbal remedy (essiac tea) **[25]**, showed an anti-proliferative effect on cancer cells at elevated concentration in vitro **[115]**. Chung et al. also reported the case of a NSCLC patient with SR who received herbal medication during and after chemotherapy **[23]**. Orostachys japonicas is a flowering plant with anti-cancer effects on human gastric cancer cells **[116]**. An in vivo model study also proposed the role of Orostachys japonicus in enhancing immunity by increasing immune cell spread and immunity-related cytokines production **[117]**.

It is still controversial whether dietary supplements have anti-cancer effects, but many cancer patients take additional vitamin or mineral supplements after cancer diagnosis **[118]**. Beetroot (Beta vulgaris) is of interest because it contains betanin and betalains. One in vitro study reported these nanoparticles biosynthesized from Beta vulgaris extract had an antitumor effect on lung cancer **[119]** and another in vitro study showed Beta vulgaris root extract had antitumor effects on lung cancer in mice **[120].** In this case, the patient started

to consume beet juice after his cancer diagnosis, he did not receive chemotherapy or take other herbal supplements. However, scientific conclusions cannot be drawn on how cancer SR was associated with the consumption of beetroot juice **[121].**

Conclusion

The SR of a cancer is possible, is a well-documented phenomenon in the literature, and is very rare in case of lung cancer. Although the pathogenesis and the precise mechanism of SR is unknown, the alteration of immunity might be an explanation, as the importance of immunity in lung cancer control is essential. An immune response could be a reasonable explanation for the observed SR mainly in cases the patients received no treatment. Moreover, because the tumor regression became evident after the tissue was biopsied in many cases, the patient's immune response to the surgical procedure seems to be a plausible factor in the appearance of SR in the primary lung cancer. It is possible that the immune system of the patient activated by the needle core biopsy as an important mechanism of SR. Similarly with surgical trauma, beetroot intake may play some role in tumor regression, but the precise mechanism is unknown. Consequently, the main challenge would be identified the exact nature of the mentioned triggers in spontaneous remission of SCLC and NSCLC cases. Identifying the mechanism underlying this phenomenon would be important and would help in the development of targeted immunotherapies that could serve as treatment options for cancer patients.

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