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Spontaneous Regression of Endobronchial Carcinoid Tumor

Sindhaghatta Venkatram, MD, FCCP, Nupur Sinha, MD,†*
Hafiz Hashmi, MD,† Masooma Niazi, MD,‡
*and Gilda Diaz-Fuentes, MD, FCCP**

Summary: **Spontaneous regression (SR) of cancer refers to partial or complete disappearance of a malignant tumor in the absence of treatment or in the presence of therapy, which is considered inadequate to exert a significant influence on the growth of neoplastic disease. SR is a very rare phenomenon in primary lung cancers. Follow-up of these patients is generally either by imaging or bronchoscopy. We present a patient with SR of an endobronchial carcinoid, followed by serial bronchoscopies and biopsy over a 24-month period.**

Key Words: carcinoid, neuroendocrine, endobronchial, tumor, regression

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CASE REPORT

A 67-year-old African American woman was evaluated for abnormal computed tomography (CT) scan of the chest in February 2013 after finding incidental pulmonary nodules in an abdominal CT. The patient denied any respiratory or constitutional symptoms or use of illicit drugs. She was a chronic active smoker with a 40 pack-year history. There was no family or personal history of cancer or occupational exposure to toxins. Physical examination was entirely normal.

Chest CT on February 2013 showed focal right perihilar consolidation suspicious for malignancy (Fig. 1A). Flexible fiberoptic bronchoscopy revealed an endobronchial lesion at the orifice of the right middle lobe (Fig. 2A). Histopathology of endobronchial biopsies revealed a carcinoid tumor. Immunostains were positive for synapthophysin and chromogranin (Fig. 3).

In May 2013, the patient finally agreed for lobectomy of the right middle lobe; a preoperative bronchoscopy showed decrease in the size of the endobronchial lesion. Spontaneous regression (SR) of the tumor was suspected and the procedure was cancelled.

The patient underwent serial follow-up bronchoscopies (Table 1); she was able to quit smoking, and she remains asymptomatic. There have been no changes in medications, no new vaccinations, no over-the-counter medication use, and no dietary changes elicited during follow-up. Repeated chest CT scans performed on May and November 2013 and November 2014 remain stable with no new findings (Figs. 1B–D).

DISCUSSION

Spontaneous regression of cancers (SRC) was described by Drs Everson and Cole in their classic editorial in *Journal of the American Medical Association* 1959.[1] They defined SRC as the partial or complete disappearance of a malignant tumor in the absence of treatment or in the presence of therapy, which is considered inadequate to exert a significant influence on the growth of neoplastic disease. History of SRC is detailed in Table 2.

SRC is rare in thoracic malignancies; a review of SRC in thoracic cancers found 5 of 76 (6.5%) cases of true primary thoracic malignancy.[5] Neuroendocrine tumors with SRC have been described in the gastric and pelvic carcinoid, with only 1 case of carcinoid of the lung reported in the English literature, and this was associated with pregnancy.[6] The cases of SRC have generally been confirmed by serial imaging and/or bronchoscopy and rarely at autopsy. Our patient had carcinoid tumor of the lung followed up over a 2-year period, which showed both bronchoscopic and pathologic resolution of the tumor.

The main hypothesis for SRC is some form of immunomodulation. Causes for B-cell or T-cell modulation include infection and hormonal

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From the *Division of Pulmonary and Critical Care Medicine; ‡Department of Pathology, Albert Einstein College of Medicine, Bronx Lebanon Hospital Center; and †Division of Pulmonary and Critical Care Medicine, Bronx Lebanon Hospital Center, Bronx, NY.

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Reprints: Sindhaghatta Venkatram, MD, FCCP, Division of Pulmonary and Critical Care Medicine, Albert Einstein College of Medicine, Bronx Lebanon Hospital Center, 1650, Selwyn Ave, Apt 12 F, Milstein Building, Bronx, NY 10457 (e-mail: onevenkat@yahoo.com).

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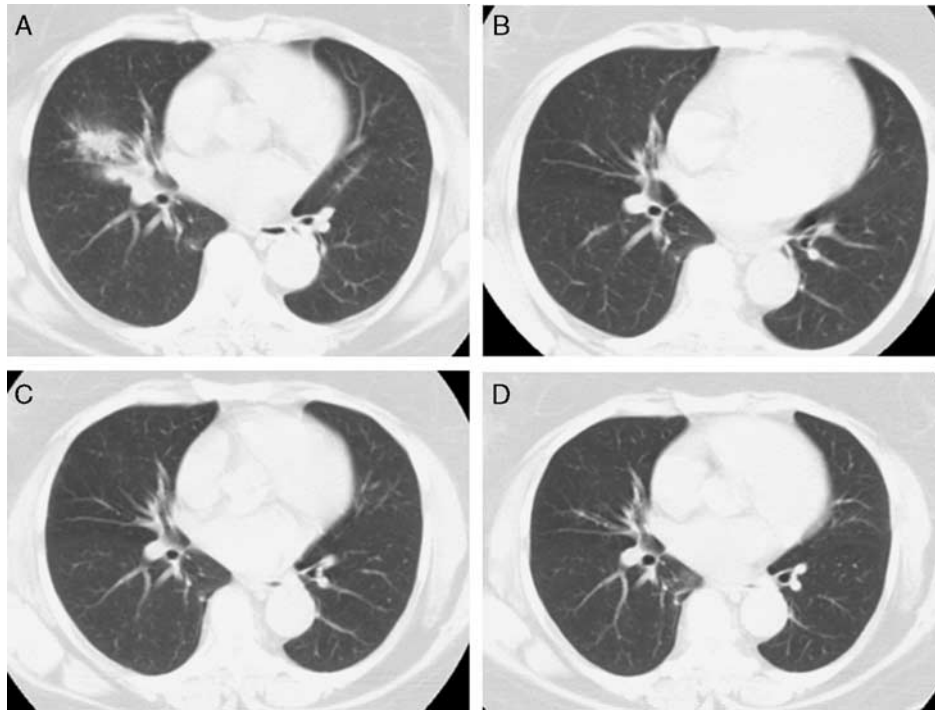

FIGURE 1. Chest computed tomography showing (A) right perihiliar infiltrate. Resolution of infiltrates (B) 3 months, (C) 9 months, and (D) 21 months later.

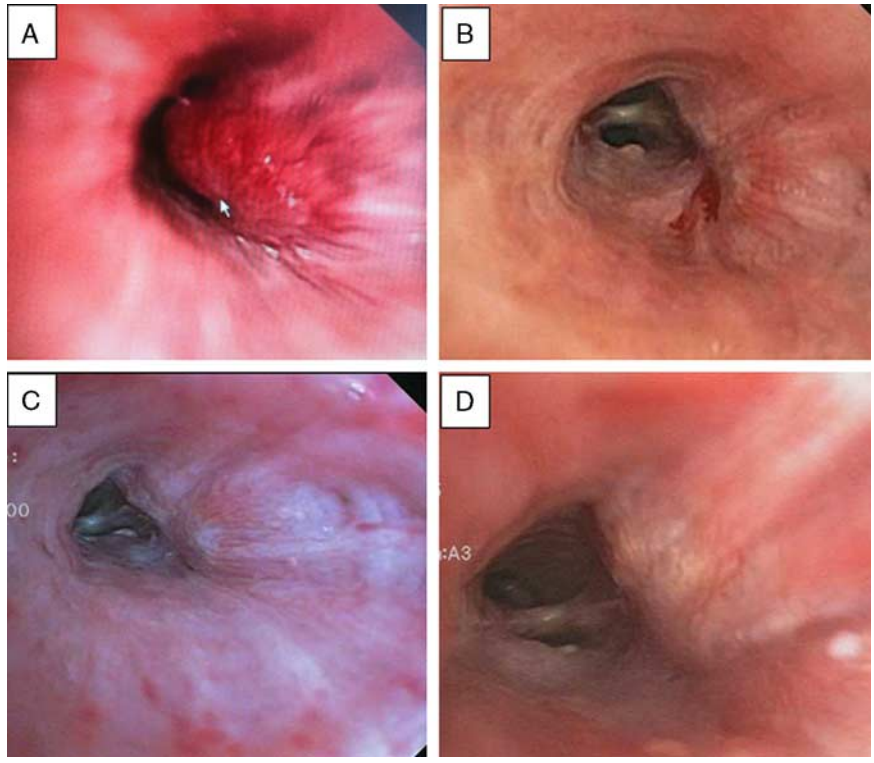

FIGURE 2. A, Bronchoscopic view showing tumor obstructing the right middle lobe. B, C, and D, Resolving endobronchial lesion up to 23 months later.

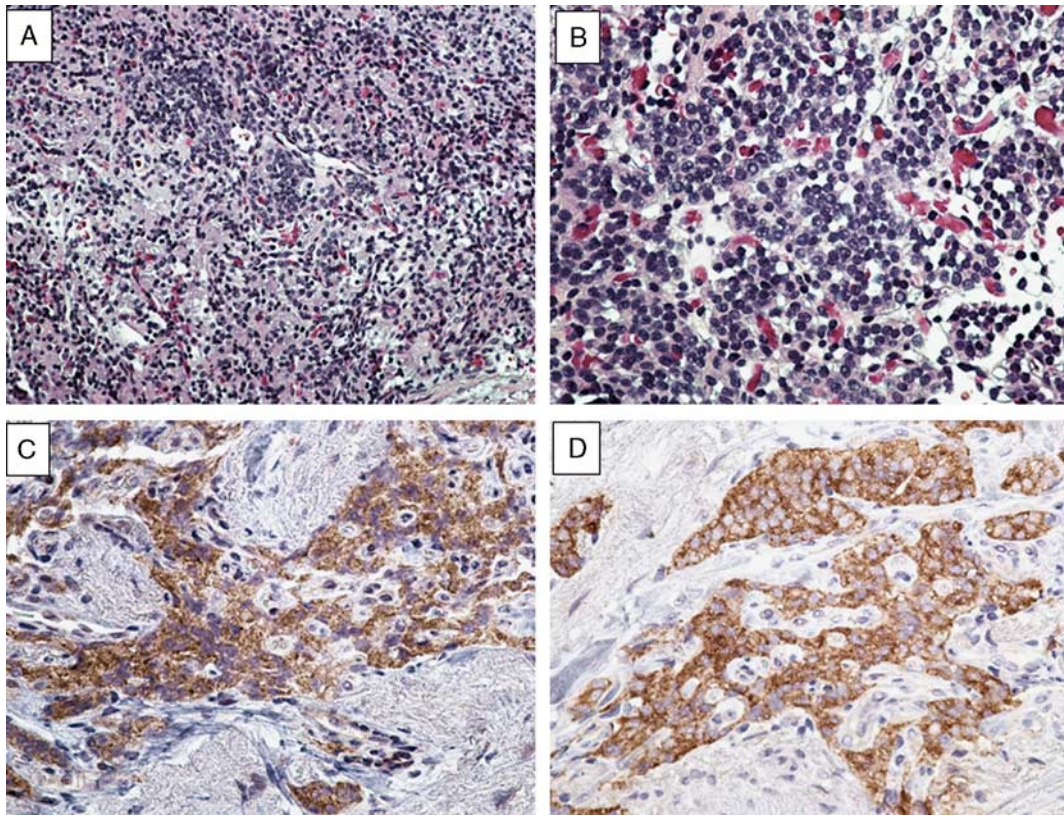

FIGURE 3. A and B, Carcinoid tumor showing monotonous round cells with finely granular chromatin, arranged in an organized pattern (A: H&E stain ×10) (B: H&E stain ×40). C, Tumor cells are immunopositive for chromogranin-A and (D) positive for synaptophysin (H&E stain ×40). H&E indicates hematoxylin and eosin.

and paraneoplastic syndromes. In the pre-chemotherapy era, some cases were associated with infections, which led to the development of vaccines to promote immunity. The best known of these "Coleys toxins" were used in patients with sarcomas, melanomas, lymphomas, and carcinomas.[7] The immunotherapy of cancer has made significant strides due to improved understanding of the underlying principles of tumor biology and immunology. Immunotherapy research has focused on the discovery of tumor antigens (TAs) that could confer specificity to immune cells that detect and destroy cancer cells. The first successful identification of TAs recognized by T cells occurred in 1991, with identification of multiple TAs in a variety of solid tumors.[3] Of a variety of TAs, immunologic checkpoint blockade with antibodies that target cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and the programmed cell death protein 1 pathway (PD-1/PD-L1) has demonstrated promise

TABLE 1. Timeline of Evolution of the Carcinoid

Date	Bronchoscopic Findings	Histopathologic Findings
June and August 2013	Decrease in size of right middle lobe endobronchial lesion as compared with prior bronchoscopy (Figs. 2B, C)	Not performed
May 2014	No endobronchial lesion seen	Endobronchial biopsies at the former site of lesion revealed nests of neuroendocrine cells, without mitotic activity or necrosis. Tumor cells positive for synaptophysin and chromogranin antibodies
January 2015	Sustained resolution of lesion	Endobronchial biopsies at the former site of lesion revealed no evidence of malignancy (Fig. 2D)

TABLE 2. Selected Studies Reporting Spontaneous Resolution of Tumor

Year	Author	Findings	Reference
1325	Unknown	Spontaneous resolution of tumor (SRC) called St Peregrine tumor after regression of a bone tumor in a young priest called Peregrine	
1875	Campbell de Morgan	Occasional regressions and remissions of cancers after postoperative infections, particularly streptococcal infection—erysipelas	2
1891	William B. Coley	"Coleys Toxins" 1891 to 1931: Coley injected >1000 cancer patients with bacteria or bacterial products and reported excellent results in SRC, especially in bone and soft-tissue sarcomas	3
1959	T.C. Everson and W.H. Cole	Identified 112 cases with probably SRC that had adequate documentation and histologic diagnosis of malignancy. SRC was most commonly seen in neuroblastoma (25 cases), choriocarcinoma (14 cases), carcinoma of the kidney (11 cases), malignant melanoma (10 cases), soft-tissue sarcoma (9 cases), and carcinoma of the bladder (7 cases)	1
1990	G.B. Challis and H.J. Stam	Identified 741 cases from 1900 to 1987 that fitted the SRC definition. Nine cancers accounted for up to 70% of cases and included kidney, neuroblastoma, malignant melanoma, choriocarcinoma, bladder, retinoblastoma, lymphoma, leukemia, and breast cancer	4

SRC indicates spontaneous regression of cancer.

in a variety of malignancies. PD-1 receptor is an inhibitory T-cell receptor that is engaged by its 2 known ligands, PD-L1 and PD-L2, which play a pivotal role in the ability of tumor cells to evade the host's immune system. Blockade of interactions between PD-1 and PD-L1 enhances immune function. In a report on neuroendorine carcinoma cancer, 18.5% showed PD-L1 expression in tumor-infiltrating macrophages and 48% showed PD-1-positive lymphocytes.[8] It is possible that host response to infection may exhibit cross-reactivity to TAs resulting in SRC. We wonder whether antibodies blocking PD-1 and/or PD-L1 are seen in patients with SRC.

Immunological stimulation by trauma with the use of Nd-YAG laser irradiation, ethanol injection, transbronchial lung biopsy, and surgery has been associated with SRC.[9–11] Smith[12] reported SRC of the lung with incomplete surgical resection, and surgical trauma was described as the potential cause in 71 of 176 cases of SRC described by Cole.[9] Bronchoscopy contributing to SR of lung cancers has been described as well.[13]

Hirano et al[14] reported an association of paraneoplastic syndrome with SR of small cell cancer; 3 of 8 cases had paraneoplastic sensory neuropathy. Anti-Hu, anti-Yo, and anti-Ri antibodies can be found in patient with paraneoplastic sensory neuropathy, and they exhibit cross-reactivity to both tumor and nervous tissue.[14]

This is the first report of SRC of a carcinoid tumor followed up during a 2-year period with serial bronchoscopy and biopsies until complete resolution was demonstrated. Although SRC remains an enigmatic event for patients and treating physicians, caution is advised when discussing this phenomenon. To quote the immortal words of Everson and Cole: "the remote possibility of SRC may be of some psychotherapeutic value in offering hope to patients and relatives of patients with "incurable cancer." The simple thought that regression of a cancer might be possible will change the patient's attitude from that of complete despair to that of hopeful toleration. The professionals should use knowledge of this phenomenon in an endeavor to comfort the patient and relatives in the trying days of terminal cancer. With proper precaution the physician can do this without being guilty of offering "false hopes." Close monitoring of the tumor with serial imaging and ideally pathologic confirmation is mandated if this pathway is chosen.

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