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Early Access
Case Report

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Synchronous multiple neuroendocrine primary lung cancer with endobronchial extension in a never smoker - An unusual manifestation

Vinay V[1], Sushil Kumar Munjal[2], Jitendra Kumar Saini[3], Gaurav Kumar Singh[4], Shibani Modi[5], Alpana Srivastava[6]

[1]Department of Pulmonary, Critical Care and Sleep Medicine, All India Institute of Medical Sciences (AIIMS), Patna;

[2]Chest Physician (SAG);

[3]Chest Specialist (Grade-SAG) and Head of Thoracic Oncology Clinic, National Institute of Tuberculosis and Respiratory Diseases (NITRD), New Delhi;

[4]Senior Resident, National Institute of Tuberculosis and Respiratory Diseases (NITRD), New Delhi;

[5]Post Graduate Trainee, National Institute of Tuberculosis and Respiratory Diseases (NITRD), New Delhi;

[6]Senior Pathologist, Department of Pathology, CORE Diagnostics, Delhi, India;

Corresponding author: Vinay V, Room 412, Hostel 10, All India Institute of Medical Sciences (AIIMS), Patna, Bihar, INDIA – 801507.

Tel. +91-9740451097.

E-mail: docvinayv@gmail.com

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Key words: Multiple Primary Lung Cancer, Synchronous Lung Cancer primaries, neuroendocrine tumor, diagnostic challenge.

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Consent for publication: the patient's written informed consent to use his personal data for the publication. All authors agree to the content of the manuscript.

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Abstract

Synchronous Lung Cancer primaries (SLC) are uncommon, with diverse underlying histology, constituting only a small proportion. The scarcity also poses a challenge in formulating a standardized diagnostic approach. Consequently, the diagnostic and staging challenges for SLC are heightened, particularly when the tumors are located on opposite sides of the chest.

We report an exceptionally rare phenomenon in synchronous multiple primary lung cancers with simultaneous occurrence of two neuroendocrine tumors with endobronchial extension, small cell carcinoma and typical carcinoid tumor. Immunohistochemistry proved valuable in confirming the diagnosis. Given the poor prognosis associated with such cases, an accurate diagnosis is crucial for determining appropriate treatment options.

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Introduction

Multiple Primary Lung Cancer (MPLC) is characterized by the occurrence of two or more primary malignancies either simultaneously or sequentially within the lungs of a same patient. Martini and Melamed established strict criteria for categorizing multiple lung tumors. MPLC is further categorized into simultaneous MPLC (sMPLC) when occurring in <6 months and metachronous MPLC (mMPLC) when occurring in ≥6 months. The classification as multiple requires histologically distinct tumors, and in cases of identical histology, it is imperative to rule out intrapulmonary metastasis and neoplastic invasion of lymphatics.[1] Synchronous neuroendocrine lung cancers are infrequent, we describe a case exhibiting two neuroendocrine tumors simultaneously which are independent primary lung cancers with distinct histological characteristics.

Case Report

A 40-year-old male presented with fever for 1 month and hemoptysis for 7 days. He also had loss of appetite. The patient is a non-smoker and had no pertinent history of occupational exposures or infections. He reported that none of his family members had a history of lung disease. The patient was referred to our centre suspecting tuberculosis, given India's status as an endemic country for the disease. On presentation, he was alert and conscious responding to commands, heart rate was 114 bpm, BP 116/78 mmHg, respiratory rate 20/min, peripheral saturation of 97%. The physical examination showed no signs of pallor, icterus, finger

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clubbing, or palpable lymphadenopathy. Auscultation revealed decreased air entry in the right upper zone and left lower lung zone. Heart sounds were normal and no added sounds were heard. Abdominal examination did not reveal any hepatosplenomegaly. Sensory and motor system examination was normal.

A chest x-ray was performed and it showed opacity in right upper zone and left lower zone (Figure 1). The routine complete blood count, liver function and kidney function tests including electrolytes were within normal limits. Electrocardiogram was normal. The sputum bacterial culture and sensitivity test, KOH mount, and CBNAAT all produced normal results. Contrast ENHANCED CHEST THORAX (CECT) showed soft tissue density mass (5.7x3.6x5.4 cm) in the para-mediastinal aspect of Right Upper Lobe (RUL) with endobronchial extension. The lesion appears to encase the segmental branch of the right upper lobe bronchus with area of distal collapse and consolidation with multilocular cystic changes (Figure 2A). An additional endobronchial soft tissue mass (1.2x1.4 cm) was identified in Left Lower Lobe (LLL) with distal collapse of basal segments while sparing the superior basal segment with area of distal consolidation (Figure 2C).

Bronchoscopy was performed, a fungating growth was visualized protruding from right main bronchus (Figure 2B), accompanied by a lobulated mass in the LLL (Figure 2D). Histopathological Examination (HPE) of RUL mass revealed small dark blue cells infiltrating connective tissue suggestive of Small Cell Lung Carcinoma (SCLC) (Figure 3) while HPE of the LLL uncovered tumor cells with rounded to oval morphology, granular eosinophilic

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cytoplasm, and nuclei displaying speckled chromatin indicative of a carcinoid tumor (Figure 4). Definitive confirmation of both tumors was achieved through Immunohistochemistry (IHC). Cells from the RUL mass exhibited positivity for CD-56, while being negative for CD-45 and LCA, confirming SCLC (Figure 3). Conversely, cells from the LLL mass demonstrated positivity for synaptophysin, chromogranin, and ki-67 was 1.5%, confirming a diagnosis of typical carcinoid (Figure 4). Whole-body 18F-NOTA-[1-Nal 3]-octreotide (NOC) scan showed RUL mass with SUV max of 9.0 and LLL mass with area of distal consolidation showing heterogeneous tracer avidity of SUV max-1.5. No significant tracer avid mediastinal adenopathy noted by size or metabolic criteria (Figure 5). Contrast enhanced Magnetic Resonance Imaging (MRI) of the brain was normal. Thus, a definitive diagnosis of synchronous multiple neuroendocrine lung cancer was established. Following a tumor board discussion, it was decided to initiate a treatment regimen involving cisplatin and etoposide chemotherapy targeting SCLC followed by cryo-debulking of carcinoid tumor assessing his performance status.

Discussion

Synchronous Multiple Primary Lung Cancer (sMPLC) is defined as two or more lung tumors detected at the same time without a tumor-free period in ipsilateral or contralateral lung. It was initially documented by Beyreuther in 1924, with reported proportions ranging widely from 0.2% to 6.2%.[2] Martini and Melamed outlined the most widely acknowledged diagnostic criteria for sMPLC. According to their classification: i) tumors should be physically distinct

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and separate; ii) the histological types are categorized as either different or the same, but located in different segments, lobes, or lungs.

This encompasses situations in which tumors arise from carcinoma *in situ*, lack carcinoma in common lymphatics, and exhibit no extrapulmonary metastases at the point of diagnosis.[3] These standards continue to be the prevailing criteria used in current clinical research. In 2016, the International Association for the Study of Lung Cancer (IASLC) established clear criteria for classifying lung cancers with multiple localizations into four patterns: sMPLC, multifocal ground-glass/lepidic lung cancers, primary lung cancer with separate tumor nodules (intrapulmonary metastasis), and pneumonic-type lung cancer. This classification involves a comprehensive evaluation of clinical, imaging, histologic, and genetic factors. Following the TNM 8th edition lung cancer classification, if neoplastic lesions are within the same lobe as the main tumor, they are categorized as T3; if in a different lobe but on the same side-T4; and if on a contralateral side-M1a. Distinguishing between a multi-center lung cancer and a primary tumor in a different organ becomes challenging when there is more than one primary lung tumor.[4] Roughly 60% of sMPLC consist of squamous cell carcinomas, with 60% of these instances demonstrating tumors of identical histologic type.[5] Trousse *et al.* demonstrated that the presence of SCC in combination constituted 28.8% among 125 study patients with sMPLC.[6] In sMPLC, distinguishing separate primary sites is easy with differing histological features, but challenging with morphologically similar tumors. Genetic analysis is now a widely used diagnostic tool for overcoming this challenge.[7]

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The treatment strategy for multiple malignant lung tumors is pivotal, given the differences in prognosis and the need to distinguish between sMPLC and lung metastases. When treating MPLC, clinicians can choose from three approaches: employing a treatment modality for both cancers, prioritizing the more aggressive cancer in treatment, or exploring two separate treatment plans.[8] Currently, diverse treatments for sMPLC include medical therapy, Surgery, Stereotactic Ablative Radiation (SABR), immunotherapy, and ablation techniques. While the surgical approach continues to be the primary treatment method, there is a notable absence of prospective randomized controlled trials with a substantial sample size. Since majority of early-stage sMPLCs were observed to derive no additional benefit from post-operative adjuvant therapy, especially those with intrapulmonary metastases (T3, T1a), surgery remains a crucial intervention for most sMPLC patients.[9] Primarily, the current preferred treatment for MPLC involves surgical resection combined with either chemotherapy or radiotherapy.[10] As per the Clinical Practice Guidelines for Small Cell Lung Cancer (SCLC) treatment by the European Society for Medical Oncology, individuals with T1-4, N0-3, M0 tumors, and in a favorable performance status should undergo combined chemotherapy and thoracic radiotherapy.[11]

Studies suggest synchronous cancers carry a less favorable prognosis than metachronous cancers.[5,12] In the meta-analysis by Nye *et al*., it was revealed that 64% of stage I SMPLC patients experienced more favorable outcomes, achieving a 5-year overall survival rate of 62%. Although these results were less favorable when compared to stage I solitary lung cancer, they surpassed outcomes for intrapulmonary metastatic diseases. This emphasizes the significance of early sMPLC detection, not only to decrease the occurrence of lymphatic or hematogenic

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metastases and address treatment challenges but also to manage the disease at an early stage, thereby augmenting the therapeutic effectiveness of surgical interventions. Collectively, a majority of sMPLC patients are diagnosed early, and surgical treatment can result in favorable long-term survival outcomes. The extent of lung resections leads to varying degrees of loss of lung function, with a more significant decline observed when combining thoracic surgery with Chronic Obstructive Pulmonary Disease (COPD). Therefore, it is crucial to conduct a pre-operative clinical assessment to choose the appropriate surgical technique, with Forced Expiratory Volume in One Second (FEV1) serving as a predictor of post-operative complications.[13] In a recent meta-analysis by Tie H, combined survival rates at 1, 2, 3, and 5 years were 86.8%, 71.7%, 62.9%, and 44.9%, respectively.[2] Age, gender, smoking history, FEV1, tumor size, and lymph node status play crucial role as prognostic factors in sMPLC post-surgery.[2] In our case, considering the favorable performance status of the patient, the treatment was specifically targeted at small cell lung cancer. It involved chemotherapy and prophylactic whole-brain radiotherapy followed by cryo-debulking of the carcinoid tumor.

Conclusions

Discerning sMPLC from pulmonary and extrapulmonary metastases and infections is imperative. Evaluating the patient's clinical features thoroughly and staging is crucial in determining the therapeutic approach in sMPLC. Currently, there are no established guidelines for the treatment protocol in such cases, necessitating personalized care and a multidisciplinary approach.

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Figure 1. Chest radiograph (Posteroanterior view) reveals two opacities, one in right upper zone and another in left lower zone.

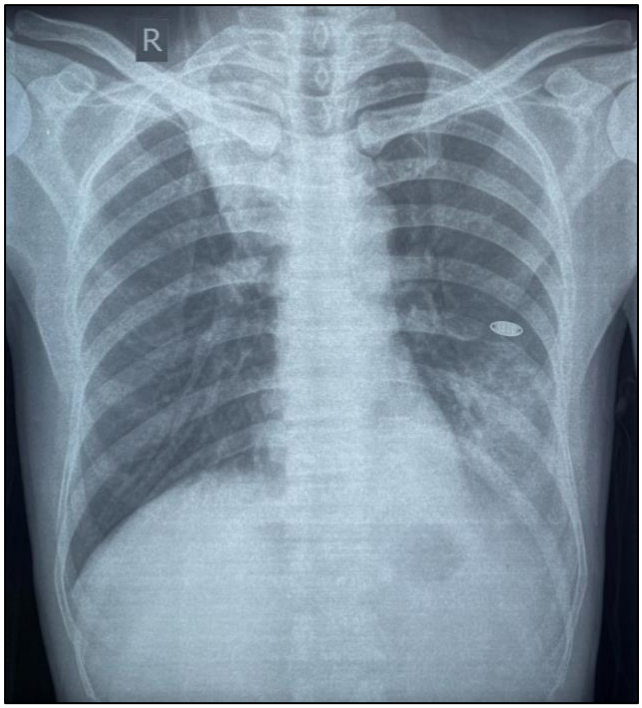

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Figure 2. CECT thorax showing soft tissue density mass in the para-mediastinal aspect of right upper lobe with endobronchial extension. **A)** coronal view and an endobronchial soft tissue mass in left lower lobe with distal collapse of basal segments while sparing the superior basal segment **(C) (**coronal view). **B)** bronchoscopy revealing fungating growth in right main bronchus and a well lobulated mass in the left lower lobe while sparing the superior basal segment **(D)**

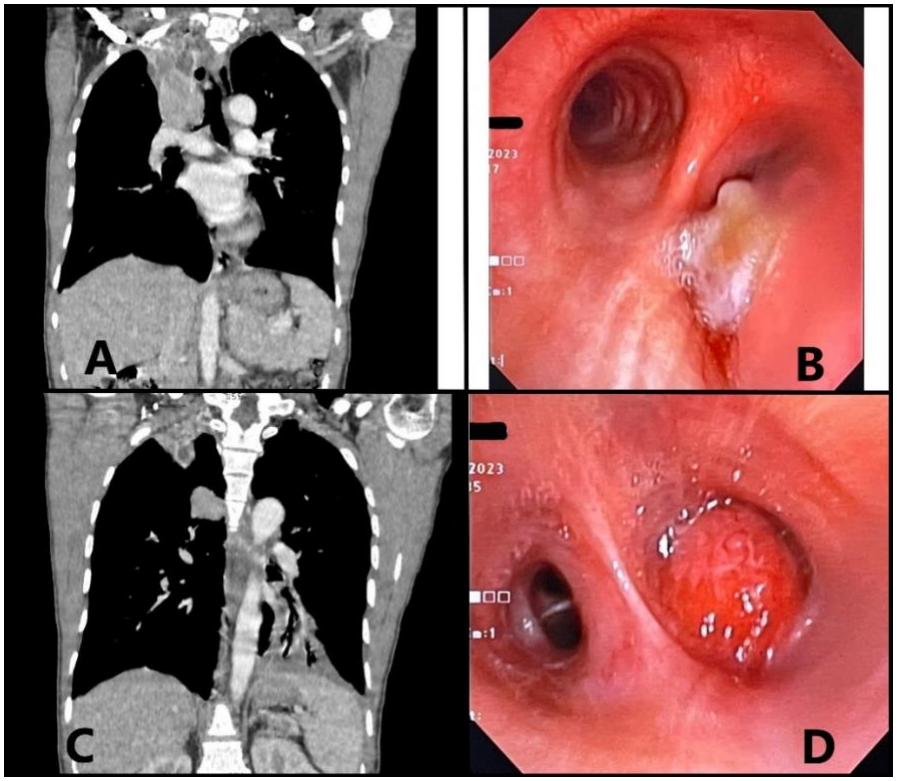

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Figure 3. Histopathological examination of the right upper lobe mass showing infiltration of connective tissue by small dark blue cells, as seen in figure 3A at 10x magnification and figure 3B at 40x magnification. The cells show positivity for CD-56 **(C)** while testing negative for CD-45 **(D),** confirming small cell lung carcinoma.

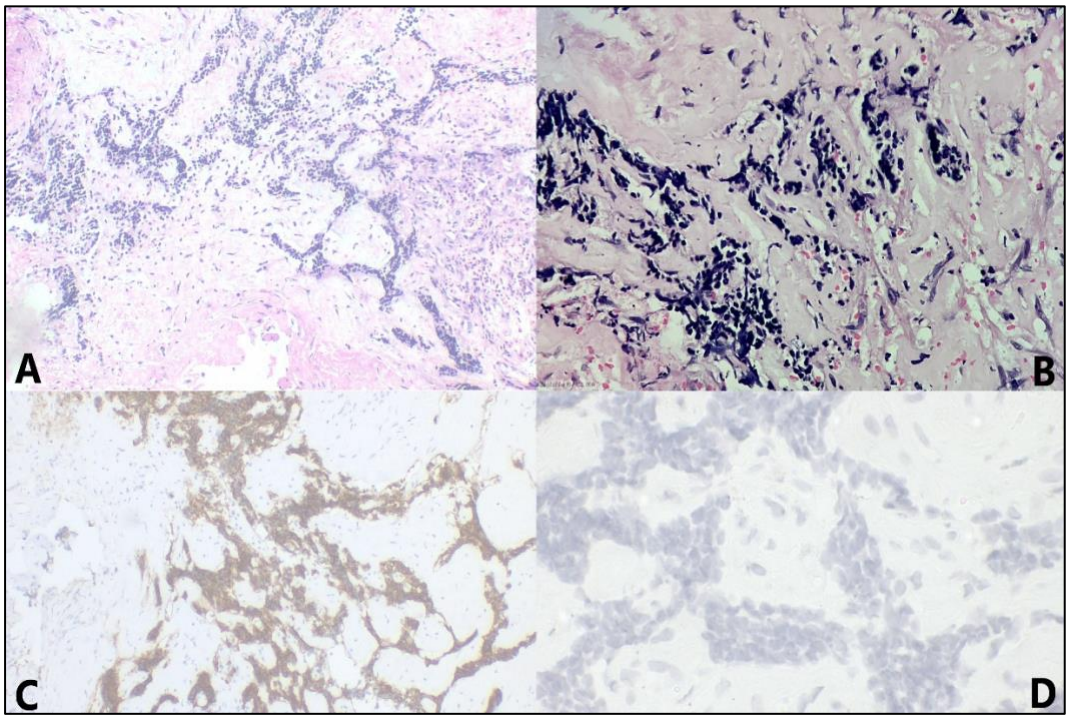

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Figure 4. Histopathological analysis of the left lower lobe mass reveals tumor cells with rounded to oval morphology, granular eosinophilic cytoplasm, and nuclei exhibiting speckled chromatin. These cells are organized in groups and tubules, displaying a clear perivascular arrangement, as depicted in Figure 4A. Notably, the cells exhibit positivity for synaptophysin (Figure 3B), chromogranin (Figure 3C) and a ki-67 index of 1.5% (Figure 3D), confirming typical carcinoid.

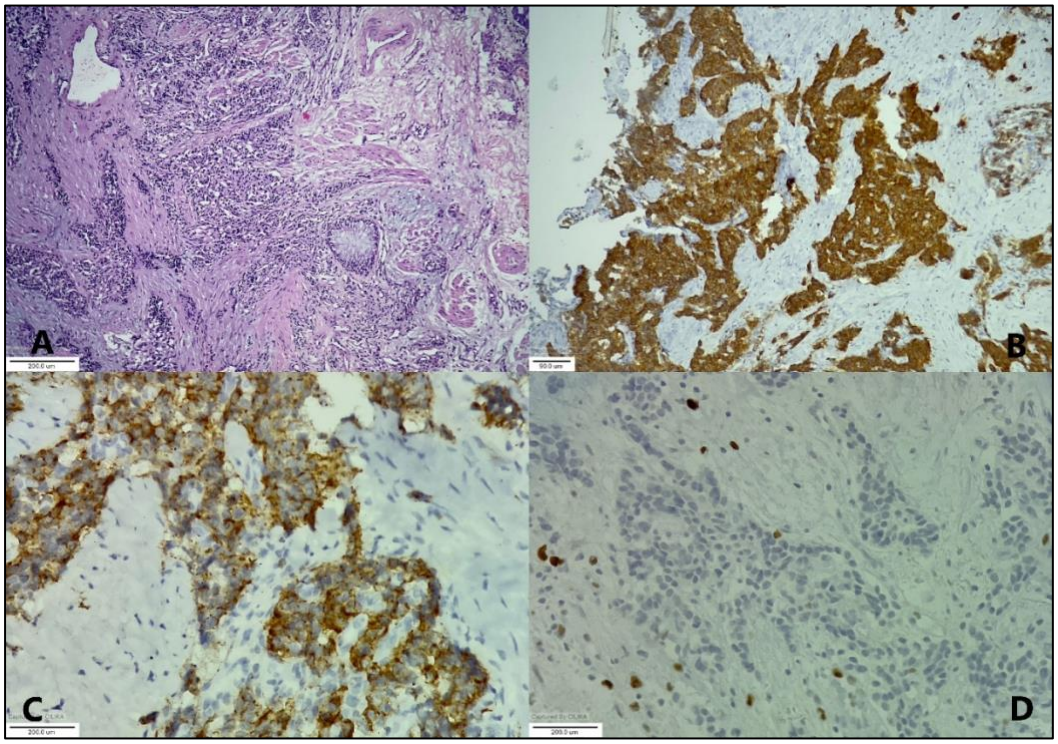

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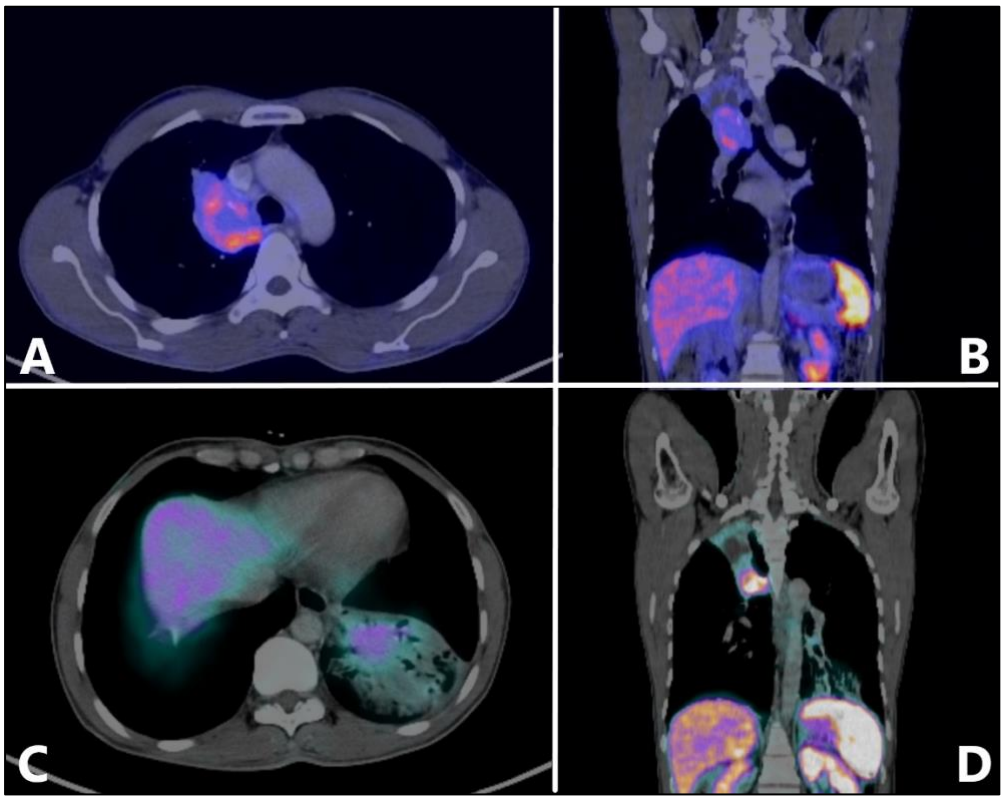
Figure 5. Whole-body 18F-AIF-NOTA-[1-Nal 3]-octreotide (NOC) scan showing RUL mass with SUV max of 9.0**; A)** axial view; **B)** coronal view and left lower lobe mass (SUV max-1.5) with collapse **; C)** axial view; **D)** coronal view.



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