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Turkish Title: Sistemik sklerozlu hastaların tanı anında akciğer parankimi dışı toraks YÇBT bulguları

Turkish Running Head: Sklerodermada ekstraparenkimal HRCT bulguları

Title: Extra-parenchymal chest HRCT findings of patients with systemic sclerosis at the time of initial diagnosis

Running Head: Extraparenchymal HRCT findings in Scleroderma

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Introduction

Systemic sclerosis (SS), also known as scleroderma, is an autoimmune collagen vascular disease (CVD) and it causes abnormal collagen growth in tissues such as skin, lung, heart and digestive tract. SS usually characterized by swelling in the fingertips, joint pain and excessive tension and hardness of skin (1). Chest high-resolution computed tomography (HRCT) significantly increase the diagnostic sensitivity of lung involvement in SS (1-4). Also, mediastinal lymph node enlargement (MLNE), pleural disease or thymic enlargement may be seen in SS patients at any time during the illness (5-10). However, the extra-parenchymal findings of SS may change with medical treatment. For example, thymus gland size decreases in response to use of corticosteroids or immunosuppressants. However, the risk of MLNE and pleural disease (pleural effusion or thickening) increases because of the increased frequency of infection in patients using corticosteroids or immunosuppressants (11,12). To the best of our knowledge, there is no study that evaluates extra-parenchymal chest CT findings in newly diagnosed SS patients. Therefore, our aim was to evaluate the extra-parenchymal chest HRCT findings in newly diagnosed SS patients and compare with literature. We also aimed to demonstrate the relationship between the age at initial diagnosis and extra-parenchymal HRCT findings.

Methods

This single-center retrospective study received approval from our institutional local ethics committee.

Patients

The patients diagnosed with systemic sclerosis (SS) according to the criteria of the American Rheumatism Association (ARA) 1980 (13) or ACR/EULAR 2013 classification criteria (14) for SS, between January 2009 and August 2017 were retrospectively analyzed.

The SS patients who underwent HRCT scan within one month after the initial diagnosis were included in the study. The HRCT indications were positive respiratory symptoms. Patients with history of malignancy, esophageal-gastric surgery or smoking and patients with additional rheumatologic disease (such as rheumatoid arthritis, Sjögren syndrome) or patients with overlap syndromes (such as systemic sclerosis and Sjögren syndrome overlap syndrome) were excluded from the study. Patients without HRCT screening within one month after initial diagnosis were not included in the study.

High-resolution computed tomography (HRCT) scanning protocol and radiological evaluation

All HRCT scans were obtained in the supine position with using a multi-detector CT system (Brilliance 16; Philips Healthcare, Best, the Netherlands) with full inspiration and the following parameters: Kv, 140; mAs, 280; detector collimation, 16×0.8/0.4 mm; slice thickness, 1 mm; slice interval, 10 mm; field of view (FOV), 35 cm and matrix, 512 x 512. Expiratory scans at least three selected levels (aortic arch, 2 cm above the diaphragm and tracheal carina) were obtained.

The all HRCT images of the SS patients were evaluated by two radiologists by consensus. Axial HRCT images of the chest were evaluated in the lung window for the presence of distal esophageal dilatation (with a maximum esophageal diameter $\geq$ 9 mm). Also HRCT images were evaluated in the mediastinal window for the presence of thymic hyperplasia (TH) (increased thymic thickness with $\geq$ 13

mm), mediastinal lymph node enlargement (MLNE) (increased short-axis diameter with ≥ 10 mm), pleural or pericardial abnormalities (effusion or thickening).

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) for Windows (Version 19.0: SPSS Inc. IBM Corp, Chicago, IL, USA). Continuous and categorical data are reported as mean ± SD, frequency and percentage. Intergroup comparisons were performed using independent T-test or a Mann-Whitney U test for continuous variables. Spearman's correlation coefficients and univariate correlations were used to detect the relationship between continuous variables. $P < 0.05$ was considered to indicate statistical significance.

Results

Medical database analysis revealed a total of 101 patients were newly diagnosed with SS between January 2009 and August 2017. Among these patients, 4 patients with history of malignancy (2 breast, 1 lung, 1 rectum cancer), 9 patients with additional rheumatic disease or overlap syndromes (4 Sjögren syndrome, 2 rheumatoid arthritis, 2 dermatomyositis, 1 systemic lupus erythematosus) and 9 patients with smoking history were excluded from the study. In addition, 26 patients with >1-month interval between imaging and initial diagnosis, 2 patients with severe artifacts on HRCT. Totally, 51 patients (88.2% women)45 of 51] and 11.8% men [6 of 51]; mean age + STD, 49.2 years + 13.9; range 18 - 71 years) who met the appropriate conditions were included in the study. The median time between SS diagnosis and HRCT examination was 8 days (range: 1 - 23 days).

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The HRCT findings (thymic enlargement, MLNE, esophageal dilatation, pleural-pericardial abnormalities) and frequencies are shown in Table – 1 and 2. Also, correlations of variables are shown in Table - 3. The HRCT images of the patients are shown in Figure 1-4.

Four patients had pericardial effusion (7.8%). Pericardial thickening was not seen in any patient. Six patients (11.8%) had pleural abnormality, including effusion (n = 4), and focal pleural thickening (n =2).

There was no significant difference between male and female patients for thymic enlargement (p=0.699), MLNE (p=0.351), esophagus dilatation (p=0.699), pleural (p=0.699) and pericardial abnormalities (p=0.457).

Discussion

According to our results, esophageal dilatation (88.2%) is frequently found in SS patients with respiratory symptoms, at the time of initial diagnosis. Mediastinal lymph node enlargement and pleural abnormalities are significantly more common in patients with SS diagnosis at the late age.

Although the actual role of thymic abnormalities on imaging studies in SS patients is still unclear, the possible involvement of the immune-mediated SS pathogenesis at an early stage may be presumed (7, 8, 14). When the increased thymic thickness was accepted as a threshold value of greater than 13 mm, Colaci et al. (15) reported that the frequency of abnormalities in thymus size was 9.5% (19 of 200 patients) in SS patients with a mean 5 years (0-38 years) disease duration. Ferri et al. (7) found that, radiological thymic enlargement were correlated with SS disease duration and thymic enlargement more common in patients with short disease duration (≤ 5 years or > 5 years; P = 0.007). They were detected thymic enlargement in 9 of 34 cases (26%). We found that the thymic enlargement

was present in 11.8% (6 of 51) of patients with SS, at the time of initial diagnosis. In addition, studies showed that SS patients with thymic enlargement were found at a younger age. For this reason, it has been argued that thymic enlargement is due to insufficient involution of the thymus gland (16-18). In our study, although the mean age of cases with thymic enlargement was lower than that of without thymic enlargement, there was no statistically significant difference between the age of initial diagnosis and presence of thymic enlargement (44 vs 49.9 years; p=0.441). This may be due to a small number of cases in our study. In our study, unlike previous studies, the HRCT findings of newly diagnosed SS patients were evaluated. We suggest that the duration of the disease and the medications may cause thymic abnormalities. There is a need for more extensive studies in order to explain this situation.

Mediastinal lymph node enlargement (MLNE) has been reported to be a common finding in SS patients (9). In SS patients, Santos et al (5) demonstrated that, MLNE was present in 5 of 23 patients (21%), Yamakawa and colleagues (17) found that MLNE was seen in 20% (n=40), and Farrokh et al (18) found that 30% (n = 40) of SS patients had MLNE on HRCT. Wechsler et al. (19) and Garber et al. (20) found that, MLNE was present in %50 and 32% of SS patients, respectively. In those studies, examining the prevalence of MLNE, the duration of the disease and medical treatment were not considered (5,9,17-20). In our study, MLNE was present in 11.8% of newly diagnosed SS patients (n=51). The mean age of the patients with MLNE was significantly higher than those without MLNE (p=0.021). It is more likely that elderly patients have more SS disease duration and risk of infectious lung diseases than younger ones.

Another common finding in SS patients is esophageal involvement. Esophageal involvement is common in SS and it can occur from 58 to 80% in different studies (9,21,22). Vonk and collagues (21)

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reported that, esophageal dilation in patients with interstitial lung disease suggests a diagnosis of SS with a high sensitivity and specificity on HRCT (63% and 88%, respectively). In our study, we demonstrated that esophageal dilation is a frequent HRCT finding in SS patients at the time of initial diagnosis, with a rate of 88,2% (45/51).

It has been reported that pleural abnormalities are rarely present in SS patients. Pleural abnormalities may be seen as, diffuse or focal pleural thickening, pleural effusion, and pseudo-plaques (22). Farrokh et al. (18) reported that pleural abnormality was present in 30% of patients (12 of 40) with SS and they found 4 patients had pleural effusion, 8 patients had pleural thickening. Yamakawa et al (17) found that, pleural abnormality (thickening or effusion) was present in 10% of SS patients (n=40). Pleural effusion in SS patients is an uncommon finding that requires a complete evaluation to exclude different causes of pleural effusion such as heart failure, side effects of medication and pneumonia (23). Similar to Yamakawa et al (17), we also detected 11.8% of SS patients had pleural abnormalities on HRCT. We also found that, as expected, the age of the patients with pleural abnormality was significantly higher than the age of the patients without pleural abnormality ($p = 0.002$). This may be due to; elderly patients are more likely to develop empyema or hemothorax than younger patients. Also, pleural abnormality may occur due to long disease duration or due to heart failure in the elderly.

This study has some limitations. First, the HRCT images were evaluated by two observers by consensus so the differences between the observers could not be assessed. Second, it was a retrospective study that involved a relatively small number of cases. Third, there was also sampling bias since only patients with positive respiratory symptoms were included in the study. So, we could not evaluate the extra-parenchymal chest CT findings in patients without respiratory symptoms.

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Finally, we did not have histopathological findings, and we could not make a radiological- histopathological comparison.

Conclusion

Despite these limitations, our study suggests that esophageal dilatation is frequently found in SS patients with respiratory symptoms at the time of initial diagnosis. Mediastinal lymph node enlargement and pleural effusion are more common in newly diagnosed SS patients at the late age, probably due to long disease duration and advanced age.

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Figure Legends:

Figure 1. A 42-years-old woman with systemic sclerosis. Axial HRCT image obtained during deep inspiration shows ground-glass opacity areas (arrowheads). Also, distal esophageal dilatation is seen (black arrow).

Figure 2. A 56-years-old woman with systemic sclerosis. Axial HRCT image shows right para-tracheal lymph node enlargement with a 14 mm short axis.

Figure 3. A 48-years-old woman with systemic sclerosis. Axial HRCT image obtained during deep inspiration shows pericardial effusion with a 9 mm thickness.

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Figure 4. A36-years-oldman withsystemicsclerosis. Axial HRCT image Show sthymicen largement with a 21 mm thickness (white arrows).

Table 1. HRCT findings in patients with systemic sclerosis (SS).

HRCT Finding	Yes n(%)	No n(%)
Thymic Enlargement	6 (11,8%)	45 (88,2%)
MLNE	6 (11,8%)	45 (88,2%)
Esophagus dilatation	45 (88,2%)	6 (11,8%)
Pleural abnormalities	6 (11,8%)	45 (88,2%)
Pericardial abnormalities	4 (7,8%)	47 (92,2%)

HRCT: High-resolution computed tomography, MLNE: Mediastinal lymph node enlargement, n: number of patients

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Table 2. Comparison of HRCT findings in systemic sclerosis patients according to mean age of the patients

HRCT Finding	Yes	No	*P* value
	Mean Age	Mean Age	
Thymic Enlargement	44 years	49.9 years	0.441
MLNE	61.3 years	48.6 years	0.021
Esophagus dilatation	50.2 years	41.8 years	0.166
Pleural abnormalities	64.8 years	47.1 years	0.002
Pericardial abnormalities	62 years	48.1 years	0.054

HRCT: High-resolution computed tomography, MLNE: Mediastinal lymph node enlargement, n: number of patients, $p<0.05$ means statistical significance.

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Table 3. Correlations of variables.

HRCT Finding	1	2	3	4	5
1. Thymic Enlargement	1	-0,13	0,13	-0,13	-0,11
2. MLNE	-0,13	1	0,13	0,62**	0,35*
3. EsophagealDilatation	0,13	0,13	1	0,13	0,11
4. PleuralAbnormality	-0,13	0,62**	0,13	1	0,35*
5. Pericardial Abnormality	-0,11	0,35*	0,11	0,35*	1

*p < 0.05, **p < 0.01, MLNE; mediastinal lymph node enlargeme

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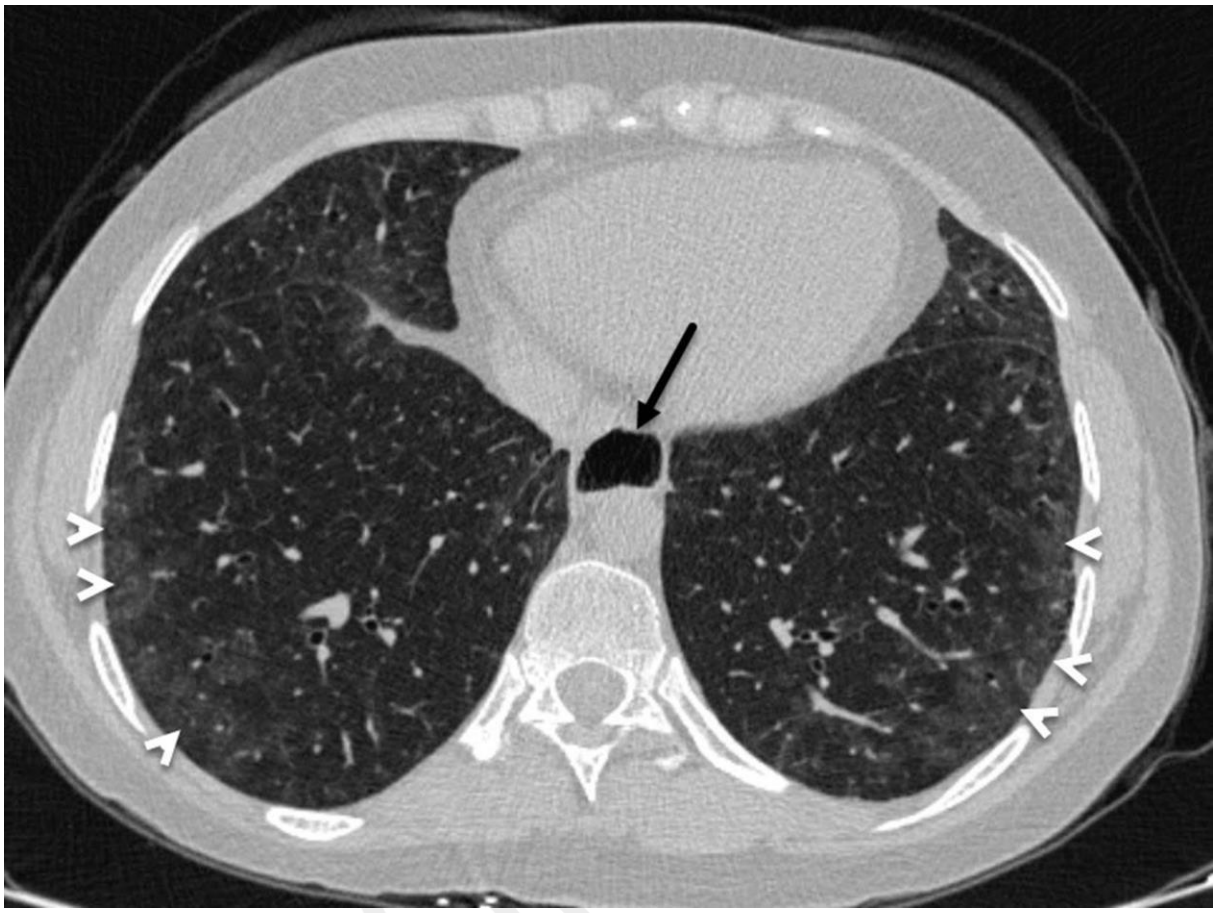

Figure 1

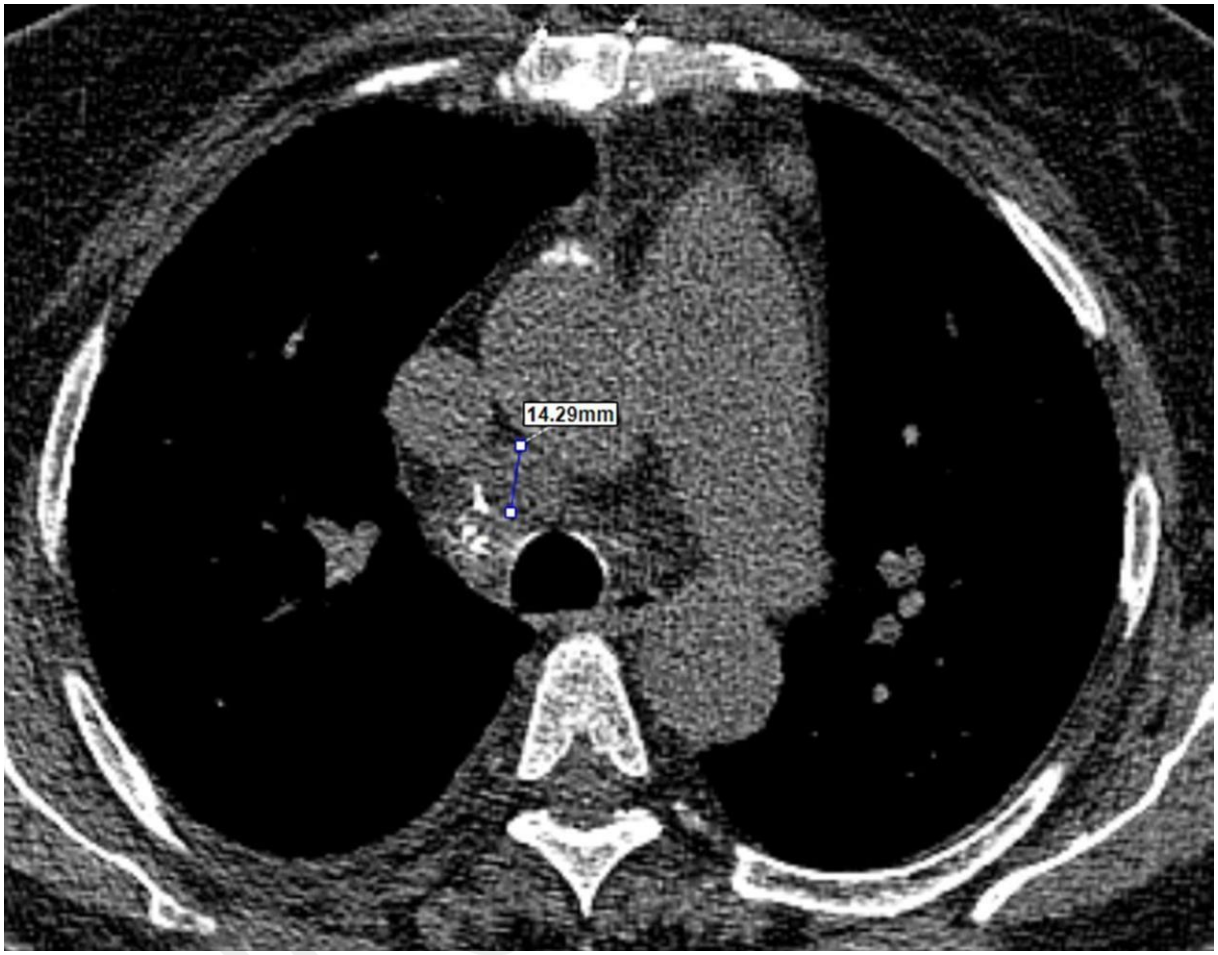

Figure 2

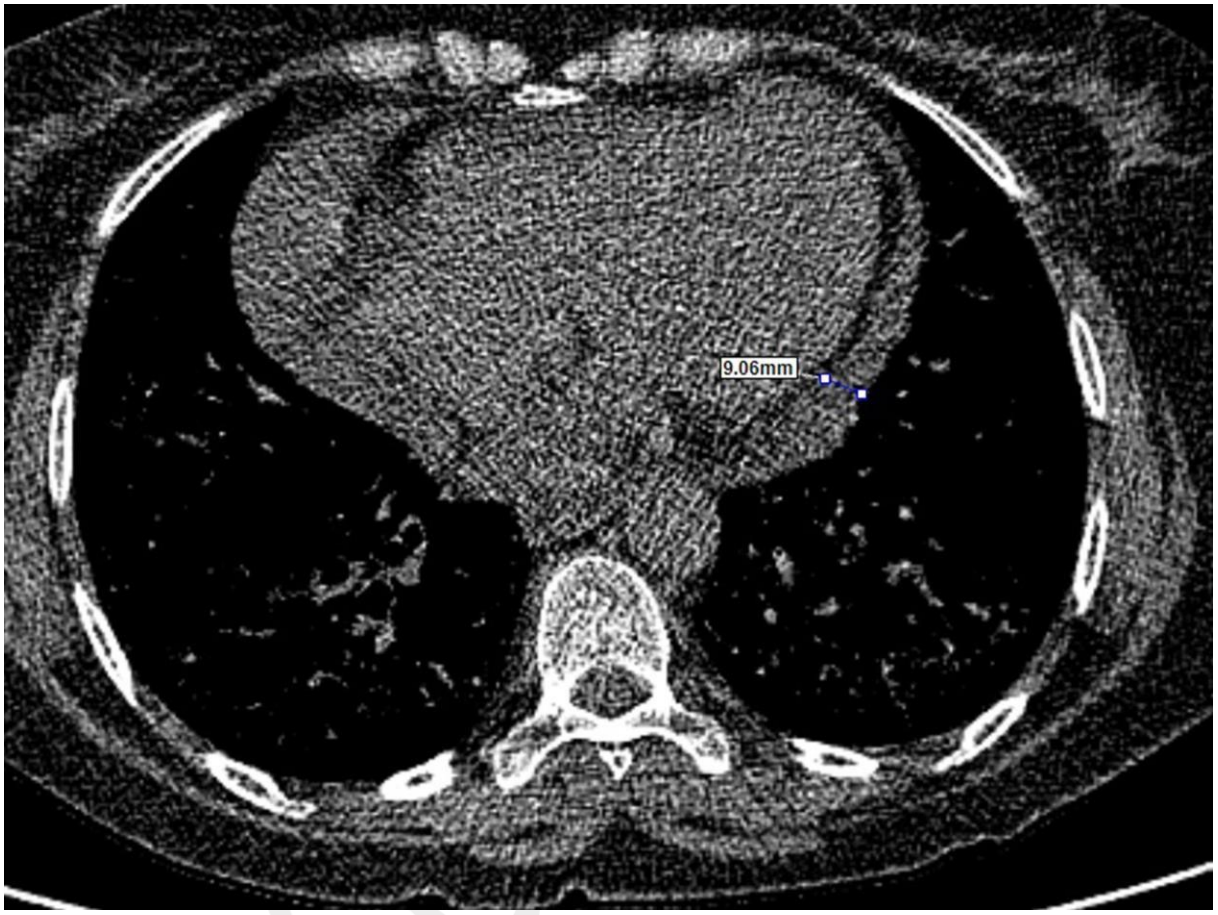

Figure 3

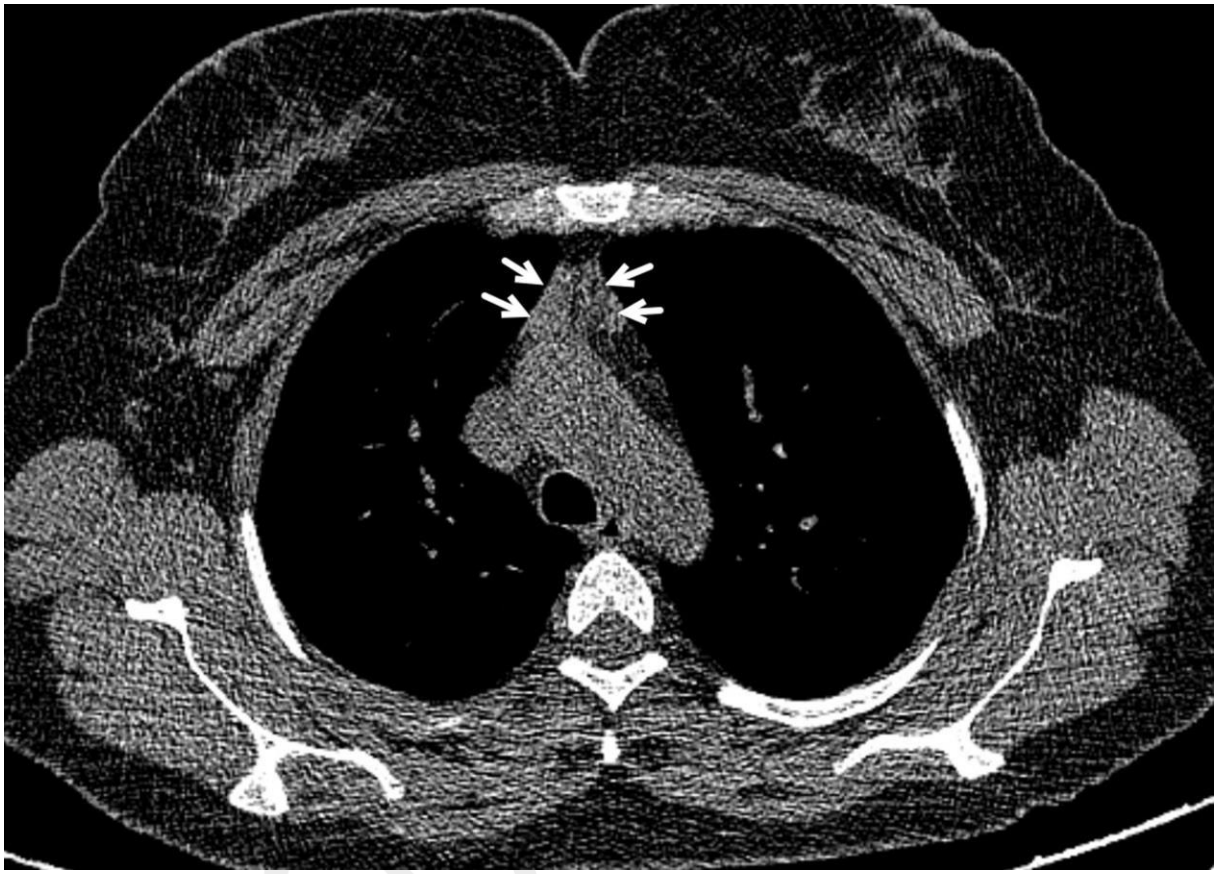

Figure 4