Comparison of typical and atypical computed tomography patterns regarding reversibility and fibrosis in pulmonary sarcoidosis

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Abstract:

PURPOSE: This study aims to investigate whether there is a significant difference between typical and atypical parenchymal patterns in the development of fibrosis, which is the most crucial factor affecting morbidity in pulmonary sarcoidosis.

METHODS: In our hospital, 145 cases with Siltzbach Types 2 and 3 sarcoidoses diagnosed by clinical, radiological, and histopathologic were retrospectively investigated. Perilymphatic nodules, accompanying mosaic attenuation, and interlobular septal thickening and central peribronchovascular bunch-like thickening on high-resolution computed tomography were assessed as typical. Solid nodules, galaxy finding, consolidation, ground-glass opacity, isolated mosaic attenuation, and interlobular septal thickening, and pleural fluid were accepted as atypical findings. Findings indicating fibrosis were fine and rough reticular opacity, traction bronchiectasis, volume loss, and cystic changes.

For the analysis of variables, SPSS 25.0 program was used.

RESULTS: Ten (16%) of the 61 cases with typical findings and 16 (19%) of the 84 with atypical findings developed fibrosis (P = 0.827). The mean age of cases with fibrosis was higher. With the cut-off of 50 years, sensitivity was 61.5%, and specificity was 68.9%. The highest fibrosis rate was in cases with ground glass pattern (n = 7/17), whereas higher reversibility rates were in those with miliary pattern (n = 9/12) and galaxy sign (n = 5/6).

CONCLUSION: The incidence of fibrosis is higher in the atypical group with no significant difference. The incidence of fibrosis differs in each atypical pattern, being highest in ground-glass opacity and lowest in the miliary pattern.

Keywords:

Atypical, computed tomography, fibrosis, pulmonary, sarcoidosis, typical

Sarcoidosis is a common multisystemic disease that is characterized by noncaseous epithelioid cell granuloma with unknown etiology. In this chronic inflammatory disease, the lung and the mediastinum are involved in approximately 90% of patients. Histopathologic findings are nonspecific. Diagnosis is made with clinical and radiological findings, histopathologic verification, exclusion of other infectious granulomatous diseases, and malignant causes. The primary imaging method for intrathoracic sarcoidosis is chest X-ray. However, high-resolution computed tomography (HRCT) is preferred for determining irreversible fibrosis and active inflammation in the lung.
Spontaneous regression or resolution occurs generally in the pulmonary sarcoidosis, but in 10%–20% of cases, diffuse fibrosis consequent to an ongoing chronic inflammatory reaction may occur. The factors causing fibrosis remain unknown; yet, fibrosis is known to increase morbidity and mortality. In most of the cases with improving sarcoidosis, mild fibrosis is observed around granuloma, but it limits itself focally and does not disrupt respiratory functions, whereas diffuse intense fibrotic reactions are causing permanent destruction and loss of parenchyma. Cases with fibrosis are commonly referred to as Siltzbach Stage 4 sarcoidosis in daily practice.

The most common radiological findings for intrathoracic sarcoidosis are bilateral hilar and parastracheal lymphadenomegaly, and micronodules of 2–4 mm in diameter located in peribronchovascular, interlobular, and subpleural zones. Parenchymal findings are predominant in the upper and central zones. Atypical HRCT findings are the alveolar pattern, consolidation, ground-glass opacity, miliary nodules, solid nodules larger than 1 cm, solid lesions with mass appearance, pleural effusion, mosaic attenuation, cavitary nodules, cavernoma, linear pattern, and tracheobronchial involvement. Cysts with honeycomb appearance, bullae, rough septal bands, structural distortion, volume loss, and traction bronchiectasis are irreversible and show fibrosis.

Atypical findings are essential for the diagnostic difficulty and the determination of morbidity. According to researches, the rate of irreversibility differs between the cases with typical and atypical patterns. Therefore, knowing the frequency of fibrosis-particularly in the atypical group—is essential for starting early treatment and reducing morbidity due to its prognostic importance. In this retrospective study, typical and atypical computed tomography (CT) patterns were divided into two separate groups, and rates of developing fibrosis were compared in each group. Further, the rates of reversibility, chronicity, and fibrosis of each pattern were investigated.

Methods

For this study, permission was obtained from the scientific research board of our hospital (March 19, 2018, 2377 number). In 2009–2017, 353 sarcoidosis cases diagnosed with clinical, radiological, and histopathologic findings in our hospital were retrospectively researched. The clinical practice guideline accepted by the American Thoracic Society in the diagnosis of sarcoidosis disease was taken as reference. One hundred forty-nine cases with only mediastinal involvement (Type 1, according to Siltzbach), 59 cases with an only pulmonary radiograph (cases in which remission or fibrosis cannot be decided because the radio-pathological process continues) or with fibrosis on first attendance were excluded from the study. All 145 patients included had a preliminary diagnosis of sarcoidosis clinically and radiologically and definite diagnosis through the histopathological examination of the specimens obtained by transbronchial needle aspiration from mediastinal or hilar lymph nodes, superficial lymph node dissection, transbronchial or endobronchial lung biopsy, or skin biopsy. In each patient, forced vital capacity (FVC%), forced expiratory volume (FEV%), and diffusing capacity of the lung for carbon monoxide (DLCO%) values were measured at the time of initial diagnosis, and the results were classified, as usual, obstructive type respiratory failure (ObsRF), and restrictive respiratory failure (RestRF).

The lung parenchyma was evaluated with HRCT images with a slice thickness of 1–1.5 mm and an interval of 1–1.25. First, two radiologists experienced in thoracic radiology (4 and 10 years) held a joint meeting and provided consensus for the identification, naming, and typical-atypical distinction of CT patterns. Then they examined the CT scans independently to identify the main patterns at the first images. As a third step, they decided on the reversibility, stability, or fibrosis of the lesions in the follow-up CT scans. Finally, a conclusion was made by comparing CT patterns with clinical and functional data for all cases. Interobserver agreement as to the identity of the main CT pattern was determined using the kappa statistic.

The parenchymal lesions determined at the time of initial diagnosis or overtime were divided into two groups as typical or atypical findings. Typical findings were peribronchovascular, subpleural, perifissural, perilymphatic micronodules between 2 and 4 mm that were more widespread in the upper and central zones with accompanying smooth or nodular interlobular septal thickening. We have included mosaic attenuation ushering perilymphatic nodules into the typical group.

We have considered alveolar infiltration as seen on-air bronchograms, diffuse or focal ground-glass opacity, consolidations, common miliary nodules, solid nodules larger than 1 cm, solid lesions with mass appearance, pleural fluid and thickening, pure mosaic attenuation, cavitary nodules, cavernoma, bronchial stricture, and atelectasis and tracheal involvement as atypical. Predominant lower lobe involvement was included in the atypical group [Figure 1]. Parenchymal conglomerate nodules with satellite nodules and typical galaxy appearance were in the atypical group.

Regardless of the follow-up period, lesions that disappeared entirely or almost completely were
considered reversible [Figure 1a and b]. Initially absent, but later developing fine or rough reticular opacity, distortion of bronchovascular structures, traction bronchiectasis and bronchiectasis, cysts with honeycomb appearance, and volume loss observed during follow-up were accepted as fibrosis [Figure 2a and b]. In these patients, pulmonary function tests and clinical correlation were achieved. The patients’ test results at the time of the first diagnosis and their follow-up results with or without treatment were compared.

Perihilar peribronchovascular mass-like irreversible thickening was included in the focal fibrosis group. The irreversibility of the lesions was confirmed after a follow-up period of at least 12 months regardless of whether treatment was given.

We used the SPSS 25.0 (IBM Corporation, Armonk, New York, NY, United States) program for the analysis of variables. A comparison of quantitative data from two independent groups used the independent samples t-test and the Mann–Whitney U-test. A comparison of categoric variables used the Pearson Chi-square test. Sensitivity and specificity rates were investigated with the receiver operating curve analysis. The multiple logistic regression test determined the cause-outcome correlations according to typical-atypical response categorized age variables. Quantitative variables are shown as mean ± standard deviation, minimum/maximum, and median values. Categoric variables are shown as n (%). Variables were investigated at the 95% confidence level with a P value below 0.05 accepted as significant. The kappa statistic was used for interobserver agreement.

Results

In a total of 145 intrathoracic sarcoidosis cases with pulmonary parenchymal involvement, only 2 cases were Siltzbach Type 3, and the others were Type 2. Type 2 cases had right lower paratracheal and subcarinal and/or bilateral hilar lymphadenomegaly and hilar involvement was bilateral, except for 1 case. The demographic characteristics of the patients are shown in Table 1. A total of 145 cases had a mean age of 46.08 ± 13.35 years (range: 19–84). Of the 145, 56% (89/158) were female, and 44% (69/158) were male. The average age for typical and atypical groups were 42.8 and 47.4 years (P = 0.041), respectively. The gender distribution was not significantly different between both groups. Our mean follow-up period was 49.7 ± 26.8 months (range: 12–120). In the typical (50.3 ± 27.2) and atypical group (49.2 ± 27.2), follow-up times were similar.

34.4% of the patients with typical findings and 44.2% of the atypical group received treatment, and the difference between the two groups was not significant (P = 0.232). While RFT was normal in 60% of the patients at the time of initial diagnosis, ObsRF was found in 10% group and RestRF in 30%. In the typical and atypical two groups, a significant difference was found in FVC% and FEV1%
Table 1: The comparison of patients with typical and atypical parenchymal findings in terms of age, gender, treatment status, respiratory function test results during the initial diagnosis, FVC%, FEV1%, and DLCO values, follow-up periods, reversibility of lesions and fibrosis development rates

|                | Total (n=145) | Typical (n=61) | Atypical (n=84) | P  |
|----------------|--------------|---------------|----------------|----|
|                | Mean±SD. (Min/Max) | Mean±SD. (Min/Max) | Mean±SD. (Min/Max) |    |
| Age            | 45.51±12.51 (20-82) | 42.85±14.87 (20-82) | 47.44±10.12 (22-88) | 0.0411 |
| Gender         |              |               |                |    |
| Female         | 103 (71)     | 39 (37.9)     | 64 (62.1)      | 0.138p |
| Male           | 42 (29)      | 22 (52.4)     | 20 (47.6)      |    |
| Fibrosis       |              |               |                |    |
| No             | 119 (82.1)   | 51 (83.6)     | 68 (81.0)      | 0.827p |
| Yes            | 26 (17.9)    | 10 (16.4)     | 16 (19.0)      |    |
| Treatment      |              |               |                |    |
| No             | 86 (59.3)    | 40 (65.6)     | 46 (54.8)      | 0.232p |
| Yes            | 59 (40.7)    | 21 (34.4)     | 38 (45.2)      |    |
| RFT            |              |               |                |    |
| Normal         | 87 (60.0)    | 46 (75.4)     | 41 (48.8)      | 0.003p |
| ObstRF         | 15 (10.3)    | 2 (3.3)       | 13 (15.5)      |    |
| RestRF         | 43 (29.7)    | 13 (21.3)     | 30 (35.7)      |    |
| FVC%           |              |               |                |    |
| First          | 82 (74/92)   | 85 (79/93)    | 79 (67/90.5)   | 0.007u |
| FEV1%          |              |               |                |    |
| First          | 81 (72/91)   | 84 (79/94)    | 78.5 (64.5/89) | 0.003u |
| DLCO%          |              |               |                |    |
| First          | 60 (50.5/65.5)| 60.5 (53/64)  | 60 (46/68)     | 0.597u |
| Reversible     |              |               |                |    |
| No             | 60 (41.4)    | 22 (36.1)     | 38 (45.2)      | 0.308p |
| Yes            | 85 (58.6)    | 39 (63.9)     | 46 (54.8)      |    |
| Time (month)   | 48 (30/72)   | 48 (36/72)    | 43 (26.5/72)   | 0.317 |

Respiratory function test: RFT, Obstructive type respiratory failure: ObstRF, Restrictive type of respiratory failure: RestRF. *Independent Samples t-Test (Bootstrap), †Pearson Chi-Square Test (Exact), ‡Pearson Chi-Square Test (Monte Carlo), §Mann whitney test (Monte Carlo), SD.: Standard deviation, Q1: Percentile %25, Q3: Percentile %75

Table 2: Distribution of lesions according to CT Patterns, number and rates of reversible and stable lesions in each pattern, and the rate of fibrosis

| Pattern                  | n     | Fibrosis | Reversible | Stable |
|--------------------------|-------|----------|------------|--------|
| Solid nodule             | 35    | 4        | 0.11       | 21     | 0.60  | 10   | 0.29 |
| Interlobular septal thickening | 34    | 10       | 0.29       | 13     | 0.38  | 11   | 0.32 |
| Mosaic attenuation       | 21    | 5        | 0.24       | 7      | 0.33  | 9    | 0.43 |
| Consolidation            | 19    | 5        | 0.26       | 12     | 0.63  | 2    | 0.11 |
| Peribroncovascular thickening | 14   | 5        | 0.36       | 3      | 0.21  | 6    | 0.43 |
| Ground glass opacity     | 17    | 7        | 0.41       | 8      | 0.47  | 2    | 0.12 |
| Miliary opacities        | 12    | 1        | 0.08       | 9      | 0.75  | 2    | 0.17 |
| Bronchial sticure        | 7     | 2        | 0.28       | 1      | 0.14  | 4    | 0.57 |
| The galaxy sign          | 6     | 1        | 0.16       | 5      | 0.83  | 0    |      |
| Mass lesion              | 4     | 0        | 1          | 1      | 0.25  | 3    | 0.75 |
| Lower lobe involvement   | 17    | 3        | 0.18       | 9      | 0.53  | 5    | 0.29 |
| Pleural effusion         | 10    | 2        | 0.20       | 6      | 0.60  | 2    | 0.20 |
| Cavity                   | 1     | 1        |            |        |       |      |      |
| Perilenfatic nodules     | 74    | 13       | 0.18       | 44     | 0.59  | 14   | 0.28 |
| Typical                  | 61 (%42) | 10       | 0.16       | 38     | 0.62  | 13   | 0.22 |
| Atypical pattern         | 84 (%58) | 16       | 0.19       | 42     | 0.50  | 26   | 0.31 |

values (P < 0.05). However, the difference between DLCO values was not found to be significant, according to the P value [Table 1].
Table 3: The Comparison of Patients with and without fibrosis in terms of age, gender distribution, whether they received treatment or not, results of pulmonary function tests at the time of the first diagnosis and the last time, FVC%, FEV1%, and DLCO values and the difference between them and the duration of follow-up

|                | No (n=119) | Yes (n=26) | P     |
|----------------|------------|------------|-------|
| Age            |            |            |       |
| Mean±SD. (Min/Max) |    |            |       |
| Age (n (%))    | 44.52±12.37 (20-82) | 50.04±12.35 (23-68) | 0.034*
| Gender         |            |            |       |
| Female         | 85 (82.5)  | 18 (17.5)  | 0.999p
| Male           | 34 (81.0)  | 8 (19.0)   |       |
| Age            |            |            |       |
| <50.5          | 82 (68.91) sp | 10 (38.46) | 0.006*
| >50.5          | 37 (31.09) | 16 (61.54) ss | 3.5 (1.5-8.5) or
|                |            |            |       |
| AUC (SE)       | 0.656 (0.063) | P=0.013    |       |
| Atypical       |            |            |       |
| No             | 51 (83.6)  | 10 (16.4)  | 0.827p
| Yes            | 68 (81.0)  | 16 (19.0)  |       |
| Treatment      |            |            |       |
| No             | 78 (65.5)  | 8 (30.8)   | 0.002*
| Yes            | 41 (34.5)  | 18 (69.2)  |       |
| RFT            |            |            |       |
| Normal         | 76 (63.9)  | 11 (42.3)  | 0.044*
| ObstRF         | 13 (10.9)  | 2 (7.7)    |       |
| RestRF         | 30 (25.2)  | 13 (50.0)  |       |
|                | Median (Q1/Q3) | Median (Q1/Q3) |       |
| Time (m)       | 42 (27/60) | 72 (48/84) | 0.003*
| FVC%           |            |            |       |
| First          | 83 (76/95) | 74.5 (62/84) | <0.001*
| Last           | 90 (79/100) | 71.5 (56/87) | <0.001*
| Difference (first-last) | 6 (-6/14) | 0 (-8/5) | 0.030*
| P for first-last | 0.001*   | 0.669* |       |
| FEV1%          |            |            |       |
| First          | 82 (74/93) | 74 (63/84) | 0.029*
| Last           | 87 (76/99) | 75 (64/87) | 0.001*
| Difference (first-last) | 4 (-3/13) | 0 (-12/10) | 0.141*
| P for first-last | <0.001*  | 0.866* |       |
| DLCO%          |            |            |       |
| First          | 60 (53/66) | 53 (46/63) | 0.080*
| Last           | 64.5 (53/83) | 38.5 (23/60) | <0.001*
| Difference (first-last) | 1 (-5/14) | -12 (-18/0) | 0.001*
| P for first-last | 0.083*   | 0.012* |       |

Age as an independent variable. Sensitivity and specificity are shown with the ROC curve. Respiratory function test: RFT, obstructive type respiratory failure: ObstRF, restrictive type of respiratory failure: RestRF. *Independent Samples t-Test (Bootstrap), P Pearson Chi-Square Test (Exact), Fisher Freeman Halton Test (Monte Carlo), or Odds Ratio (%95 Confidence interval), Roc Curve Analysis (Youden index J - Honley & McNell), AUC: Area under the ROC curve, ss Sensitivity, sp Specificity, Mann whitney test (Monte Carlo), Wilcoxon Signed Ranks Test (Monte Carlo), SD.: Standard deviation, Q1: Percentile %25, Q3: Percentile %75 SE: Standard Error, SD.: Standard deviation

cases are shown in Table 2. The pattern of predominant solid nodules larger than 1 cm suggesting metastasis or granulomatous infection was the most common (35%). The dominant interlobular septal pattern, which indicates pulmonary edema or lymphangitic metastasis, was the 2nd most common finding, and the rate of fibrosis development was 29% (10/34). The highest fibrosis rate among all patterns developed in the ground glass pattern (41%, 7/17). After the galaxy finding (5/6), the highest reversibility was seen in the miliary pattern, which mimicked miliary tuberculosis or pneumoconiosis. In cases of evident central peribroncovascular thickening, the fibrosis rate was also high (36%, 5/14) [Figure 3]. In four instances characterized by sarcoid lesions in the form of mass, fibrosis did not develop, and the lesion regressed in 3 cases. Mosaic attenuation was isolated or predominant in 21 cases, and the findings were stable in 41%. Mosaic attenuation accompanying typical perilymphatic nodules was included in typical results.

Regression was observed in 34% of 145 cases. Lesions regressed in 38 of 61 cases (62%) with the typical pattern.
and 42 of 84 cases (50\%) with the atypical pattern. In general, reversibility was higher than the typical group [Table 3].

Fibrosis developed in 16 cases (19\%) dominated by atypical patterns. In 61 cases with typical findings, 16.4\% had fibrosis (P = 0.827). The difference was not significant when looking at gender among the factors that may affect fibrosis development (P = 0.999). The average age of patients with fibrosis was higher (44.5/50 P = 0.034) [Table 3]. Statistical analysis determined the age of 50.5 years as the cut-off for the independent variable in typical and atypical differentiation. Typical pattern incidence increases by 3.5 (1.5–8.5) times under the age of 50.5 (odds ratio: 3.5 [1.5–8.5], area under the curve [standard error]: 0.656 [0.063]; P = 0.013) [Table 3]. The rate of treatment was highest in the atypical group with fibrosis (69\%). RestRF was observed in 50\% of the patients who developed fibrosis. Follow-up time was longer in patients with fibrosis [Table 3]. The FVC\% and FEV1\% and DLCO\% values of the patients are shown in detail in Table 3. In cases with fibrosis, the changes support the diagnosis, and the difference is significant (P < 0.005). The interobserver agreement for recognizing the main CT pattern was good (κ = 0.67, P = 0.035).

**Discussion**

Thoracic sarcoidosis has been called “the great mimic” in the radiology literature. Mediastinal involvement may mimic many diseases such as lymphoma and tuberculosis, but the use of histopathological diagnostic methods such as transbronchial biopsy in almost every patient makes the diagnosis easier. Since lung biopsy is not preferred unless mandatory, the biggest challenge is the nonspecific pulmonary involvement with a broad spectrum. Atypical findings in pulmonary sarcoidosis were previously described by many researchers. Among these, there were studies using chest X-rays. However, we used the HRCT images of patients as a basis for their high reliability in the diagnosis of fibrosis.

In recent years, it was suggested that HRCT should be the first and only method for diagnosing, staging, and following sarcoidosis. Newer data indicate that specific HRCT findings may be associated with critical prognostic outcomes, such as increased mortality.

There are many articles on fibrosis and reversibility in pulmonary sarcoidosis. The difference of this study from others is to investigate whether there is a difference in the incidence of fibrosis development over time between typical and atypical CT patterns as two separate groups.

With terminology still widely used among clinicians and radiologists, the main subject of this study is whether there is a significant difference between typical and atypical parenchymal findings regarding the transition from Siltzbach Stages 2 and 3 to Stage 4. In the literature, spontaneous remission rates were reported to be 40\%–70\% for stage 2 sarcoidosis and 10\%–20\% for Stage 3. The numerical order in staging is not valid for the course and progression of the disease. It is known that each group may pass to a different stage at very different rates. Regardless of the stage, 34\% regression in all cases was consistent with the literature. Our mean follow-up periods were 50.3 and 49.2 months to confirm regression, and the shortness of the time was not thought to be a problem since the lesions were entirely or partially regressed. Brauner et al. followed up 20 patients with CT for 3 months after the response to corticosteroid treatment and reversibility. Also, the follow-up period of 10 cases was <2 years. In the study of Murdoch and Müller investigated reversibility, the follow-up time of 18 patients, ranged between 4 and 49 months.

Our rate of atypical pulmonary pattern in HRCT was 58\% and higher than the typical pattern. In the related literature, it is nearly 20\%. However, this study was
not planned as an incidence study covering all cases of sarcoidosis. Interobserver differences were the most crucial problem in the differentiation of typical and atypical lesions. There were no specific criteria.\[^{2,3,6,11}\]

The compliance rate between the two radiologists who conducted the study was 75%. As expected, the rate of atypia was higher in the less experienced radiologist. The correct diagnosis rate depends entirely on experience. In radiology practice, atypical lesions mean the radiologist is diverted from an essential diagnosis to other diagnoses. Here, the problem is atypical patterns which do not resemble sarcoidosis at first, misleading to other diseases such as tuberculosis, pneumoconiosis, lymphangitic or hematogenous metastasis, and mass lesions. For example, mosaic attenuation was reported at high rates of 90%,\[^{6}\]

Our rate was 20% (31/158) because if it accompanied typical perilymphatic nodules, we considered these cases as typical. Isolated or predominant findings were accepted as atypical. A similar situation was present for solid nodules. A few solid nodules accompanying typical findings were not accepted as atypical. Patients with atypical parenchymal findings and bilateral hilar and mediastinal lymphadenomalagaly primarily suggest sarcoidosis. Therefore, none of these patients should be considered atypical. The question was whether these patients were typical or atypical. In this study, we ignored mediastinal involvement and accepted them as atypical. All these details affected the typical and atypical case rates. However, the critical point was parenchymal lesions resulting in fibrosis.

When we consider atypical morphologies one by one, we see that they show a different prognostic course. For example, in alveolar sarcoidosis, which occurs with the combination of interstitial granulomas, but suggests air space pathologies due to air bronchograms, the fibrosis rate is 26% (the rate given for these lesions was not found in the literature).\[^{2}\]

The presence of sarcoid granuloma in the form of solid nodules larger than 1 cm with smooth or irregular contours and interstitial granuloma, leading to on-air consolidation bronchograms, were atypical findings for lesions.\[^{3}\]

In the literature, rates of 2.4%–4% and 15%–20% were reported.\[^{1,3}\]

A large portion of solid nodules was reversible.\[^{6}\]

In our research, the reversibility rate was highest in this group (n = 50/158). If there were satellite nodules, a “galaxy appearance” was formed. Galaxy finding is generally defined as irreversible, but we observed that lesions disappeared in 5 of 6 cases.\[^{3,6}\]

However, in chronic sarcoidosis, it is a separate clinical entity than fibrosis. Only 1 case developed fibrosis, and this case also showed an interlobular septal thickening.

Patchy or diffuse ground-glass opacity is formed by combining many small granulomas surrounding alveolar septa or small veins, not by alveolitis or fibrosis was reported by approximately 40% (16%–83%) and to be largely reversible in the literature.\[^{2,5,17}\]

We observed it at much lower rates (11%), and in 47% of our cases, regression was observed.\[^{6,14}\]

Unlike other research, the fibrosis development rate was the highest at this pattern (41%). In 34 cases with predominant interlobular septal thickening, 10 developed fibrosis. The highest rate was in this group. Interlobular septal thickening is one of the 4 essential findings affecting prognosis on the CT activity score.\[^{17}\]

One of the often findings is bronchial stenosis and atelectasis. It develops due to endobronchial granuloma or peribronchial lymph node compression (7 cases).

Parenchymal fibrosis developed in only two patients; others became chronic. The incidence of pleural fluid on pulmonary radiography is 0.7%–10%. Granuloma locates in the pleura. Fluid accumulates due to lymphatic blockage.\[^{13,16,19,20}\]

In ten of our cases, pleural effusion was observed, with parenchymal fibrosis observed in two cases [Figure 4]. Those two cases also had interlobular septal thickening and mosaic attenuation in the parenchyma.

Since we did not encounter a cavity nodule mimicking granulomatosis with polyangitiis described by Armengol et al., we could not be evaluated.\[^{13}\]

Lower lobe predominance is rarely seen in sarcoidosis. In 2 of our 10 cases (Matsui et al. identified it in 9 of 113 cases), fibrosis developed during follow-up. It is controversial whether this result is meaningful regardless of the morphological pattern. However, it has been investigated because it is usually among the atypical findings in the literature.\[^{14}\]

Necrosis and cavitation seen in <1% of cases were seen in only one of our patients. Evaluating the evaluation of this lesion can only be considered a case report\[^{2,4}\] [Figure 5a and b].

For the diagnosis of fibrosis, detection of bronchovascular distortion, traction bronchiectasis, reticular opacities, and volume loss in the HRCT examination, and the detection of RestRF in RFT were considered sufficient.\[^{4,7,20}\]

RestRF was not detected in all patients with fibrosis (50%). However, there was a decrease in FVC%, FEV1% and DLCO% values, and this difference observed after the first diagnosis was statistically significant [Table 3].

Depending on the width of the areas with fibrosis, a different rate of impairment in respiratory function is expected. It is also necessary to score for this. Respiratory failure was not detected in patients with mass-form fibrosis and peribronchovascular thickening in a limited area. Lung biopsy was performed in only 2 of our cases.

In the related literature, HRCT is considered sufficient without a histopathologic examination in deciding for fibrosis, and the duration of the follow-up period loses its importance after the lesions appear.\[^{20}\]

The controversial subject here is the follow-up duration of the patients we consider stable. The optimal follow-up...
period should be at least 2–5 years to confirm the stability and development of fibrosis, which is correlated with chronicity.[20] In our study, the mean follow-up period was 4 years, although it was 12 months in 3% of the patients owing to complete resolution. Ideally, even these cases should have been followed up for at least 5 years. Follow-up time is a limitation of our study due to its retrospective design.

The fibrosis rate in patients with typical pulmonary sarcoidosis findings (16.4%) appeared different from the incidence in the atypical group (19%), but this was not statistically significant (P = 0.827). When we look at the other factors affecting fibrosis development, the mean age of patients with fibrosis was higher. With the cut-off value of 50 years obtained in our data, the sensitivity was 71%, and specificity was 65.4%. Forty-one percent of our patients received treatment. The rate of treatment is higher in patients with fibrosis (P = 0.002). The incidence of fibrosis development in all our cases, independent of medicine, was 18%, which complies with the literature.

The limitations of this study are that it is retrospective, fibrosis is diagnosed only with HRCT, is not multi-centered, and the follow-up time is short in some patients. The role of treatment as an independent variable should be further studied with standard protocols. Scoring for fibrosis is also essential in determining prognosis.

Conclusion

The incidence of atypical patterns causing diagnostic difficulty in pulmonary sarcoidosis is considerably high. They may occur more often than typical findings, as in our study. The prevalence of fibrosis differs in each atypical pattern, being highest in ground-glass opacity and lowest in the miliary pattern. The development of fibrosis is comparable between the typical and atypical patterns. Furthermore, older age is associated with atypical patterns and fibrosis.

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Conflicts of interest
There are no conflicts of interest.

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