ORIGINAL ARTICLE

Apical fibrosis was the most common incidental pulmonary finding in a familial Mediterranean fever cohort

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Abstract

Introduction Familial Mediterranean fever (FMF) is one of the common autoinflammatory diseases with multisystemic manifestation. Pleuritis is the only known pulmonary involvement of FMF; however, as far as we know, thoracic involvements in pleural, parenchymal, bronchial, and vascular structures have not been evaluated yet.

Method We included 243 consecutive FMF patients who applied to our clinic within the last 5 years and were requested to have a thorax CT for any reason and 122 trauma patients without any comorbidity. An experienced radiologist evaluated the thorax CT images blindly according to the relevant guidelines. We then presented the common incidental pulmonary and mediastinal findings on the thorax CT. Additionally, we compared patients with and without lung involvement according to demographic and disease-related parameters.

Results In our study, 167 of 243 patients (68.7%) had at least one of the pulmonary findings on their thorax CT. The most common pulmonary findings were apical fibrosis in 96 (39.5%) patients, parenchymal fibrotic changes in 48 (19.8%) patients, and a solitary parenchymal nodule smaller than 4 mm in 33 (13.6%) patients. All demographic, genetic, and disease-related characteristics, including the frequency of spondyloarthropathy, were similar in patients with and without pulmonary findings.

Conclusions We showed that the most common incidental pulmonary finding in our FMF cohort was apical fibrosis on thoracic CT. Our data did not show causality between FMF and apical fibrosis; therefore, more studies are needed to evaluate the frequency and clinical significance of apical fibrosis in FMF.

Key Points
- *More than two-thirds of familial Mediterranean fever (FMF) patients in our study group who underwent a thoracic scan for any reason had pulmonary and mediastinal findings on thorax computed tomography (CT).*
- *In our FMF cohort, the most common incidental pulmonary finding on their thorax CT was apical fibrosis.*
- *All demographic and disease-related characteristics, including the frequency of spondyloarthritis, were similar between patients with and without pulmonary and mediastinal findings.*

Introduction

Familial Mediterranean fever (FMF) is an autoinflammatory disease most commonly seen in the Mediterranean basin [1]. The main feature of the disease is recurrent polyserositis,

and in addition to serositis, systemic involvement may occur in FMF patients. Joint, enthesis, muscle, and skin findings are common manifestations of the disease [2]. Furthermore, vasculitis, neurological, thrombotic, ocular, and cochlear disorders have been demonstrated in FMF patients [3]; however, as far as we know, there is no data in the literature showing direct FMF-related lung involvement, except serositis [4].

Many of the systemic features are common in patients carrying the M694V mutation. [2, 5]. Features such as myalgia, persistent arthritis, spondyloarthropathy, and enthesitis are associated with persistent inflammation, high

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disease scores, and severe serositis attack features, as seen in M694V mutation carriers [6–9]. Thus, as expected, systemic involvement and associated persistent chronic inflammation may be associated with AA amyloidosis in FMF [10].

Various pulmonary involvements have been shown in autoinflammatory diseases. Serositis is the most common type of involvement. Additionally, parenchymal pulmonary features have been presented in some diseases such as adult-onset Still disease [11], deficiency of IL-1 receptor deficiency syndrome [12], and SAPHO syndrome [13]. Pulmonary vascular and peri-pleural parenchymal involvements or spondyloarthropathy-like involvements can be predicted as the cause of possible non-serous findings in FMF.

Our hypothesis in this study is that patients with FMF may have typical pulmonary serous or parenchymal findings. Here, we first evaluated the lung and mediastinal findings on thoracic computed tomography (CT) of FMF patients and a control group. We then evaluated demographic and disease-related factors associated with pulmonary manifestations in FMF.

Material and methods

We included adult FMF patients in our cohort who met the Tel-Hashomer Criteria [14]. First, we identified all consecutive FMF patients who presented within the 5-year period and had a thorax CT requested for any reason. We then excluded the patients if there is a history of malignancy, active infection, active tuberculosis, or tuberculosis history, active or history of coronavirus 19 disease (COVID-19), nursing and pregnancy, and rare conditions that may yield to a confusing result (i.e., asbestosis or lung operation sequelae). We also included healthy controls who underwent thoracic CT due to trauma. Here, all controls were matched with FMF patients in a 2:1 ratio by age and gender. In addition, none of the patients in the control group had any additional disease.

We used both the International Severity Scoring System for FMF (ISSF) [15] and Pras [16] scores for evaluating the severity of the disease. ISSF scores range from 0 to 10, where 10 is the most severe. Patients can be classified as either severe disease (≥ 6), moderate disease (3–5), or mild disease (≤ 2) according to ISSF scores. In this study, we divided the patients into severe-moderate (≥ 3) and mild disease (≤ 2), and we recorded patients' demographic parameters, disease-related features (age, FMF duration, attacks properties, other FMF related symptoms, frequency of spondyloarthropathy, attacks in last 3 months, sites involved per attack, amyloidosis, daily colchicine dosage, *MEFV* mutations if available, IL-1

blocker treatment, and colchicine resistance), smoking, pulmonary disease history, and comorbidities (hypertension, hypothyroidism, hyperthyroidism, cardiovascular diseases, coronary artery diseases, cerebrovascular diseases, chronic renal disease, chronic obstructive pulmonary disease, diabetes mellitus). We also recorded the reason for ordering a thorax CT. Charlson Comorbidity Index was used to evaluate the weight of the comorbidity [17]. We applied Assessment of Spondyloarthritis (SpA) International Society (ASAS) criteria for diagnosing peripheral and axial SpA [18]. All laboratory data were obtained from the medical center's medical database at the time of the evaluation.

Colchicine resistance is defined as patients who continue to have one or more attacks per month despite receiving the maximum tolerated dose for at least 6 months [19] and/or ongoing subclinical inflammation.

Among the patients with eligibility criteria, 147 of patients had *MEFV* mutations. We classified the patients as homozygous, heterozygous, compound heterozygous, and negative according to the *MEFV* mutation.

We evaluated lung involvement in FMF and healthy controls with thorax CT. All thorax CT images were retrospectively obtained from the medical center's medical database. A radiologist (TB) with >20 years of experience in the evaluation of thoracic scans reviewed thoracic CTs blindly. Here, we reported the thoracal CT findings according to relevant guidelines [20, 21]. These parameters are interstitial lung disease, ground glass opacities, honeycomb appearance, interstitial fibrosis, mosaic attenuation, alveolitis, parenchymal nodules, pleural effusion, pleural changes, pneumothorax, bronchial changes, bronchiectasis, emphysema, atelectasis, pulmonary air cysts, increased broncho vascular markings, mediastinal lymphadenopathy, increased pericardial fat, pericardial effusion, cardiomegaly, apical fibrosis, fissure nodule, pleural nodule, and parenchymal fibrotic changes.

All CT examinations in our center were performed with three scanners (128-section Philips ingenuity and 16-section Toshiba Alexion). The main scanning protocol was as follows: tube voltage, 120 kVp; tube current modulation, 120–380 mA; detector configuration, 64×0.625 mm or 16×0.625 mm; rotation time, 0.5–0.7 s; slice thickness, 5 mm; and pitch, 0.984. Reconstruction kernel was lung with a thickness and an interval of 0.625 mm. All images were reviewed in both lung (width, 1200 HU; level, −700 HU) and mediastinal (width, 350 HU; level, 40 HU) settings.

This study was approved by the Local Research Ethics Committee and carried out in compliance with the Helsinki Declaration.

Statistical analyses

Statistical analyses were carried out using SPSS Version 25.0 (SPSS Inc., Chicago, IL, USA). To determine if the data were normally distributed, the Kolmogorov-Smirnov test was performed. Since the parameters did not distribute normally, comparisons of the continuous variables and categorical variables were performed by the Mann-Whitney U test and chi-square test, respectively. Descriptive statistics were presented by numbers (with %) for categorical variables and median (with 25–75%) for numerical variables. P-value lower than 0.05 was considered as statistically significant.

Results

Two hundred ninety-six FMF patients in our cohort underwent a thoracic CT scan over a 5-year period. Two hundred forty-three (82.0 %) were included in the study according to the inclusion and exclusion criteria (Fig. 1). Here, 167 of 243 patients (68.7%) had at least one of the pulmonary findings on thorax CT, the median age of the patients was 40.0 (30.0–48.0) years, and 159 (65.4%) of 243 patients were female. Peritonitis was the most common symptom among patients. Of the 243 patients, 26 (10.7%) had amyloidosis at the time of study, 54 (22.3%) patients had colchicine-resistance/intolerance, and 25 (10.5%) were receiving IL-1 blocker therapy. Clinical and demographic features of familial Mediterranean fever patients are shown in Table 1.

One hundred twelve trauma patients without comorbidities were included in the study. Eighty (65.5%) of these patients were women. In addition, the median age of the controls was found to be 40.0 (30.0–48.0) years, the same
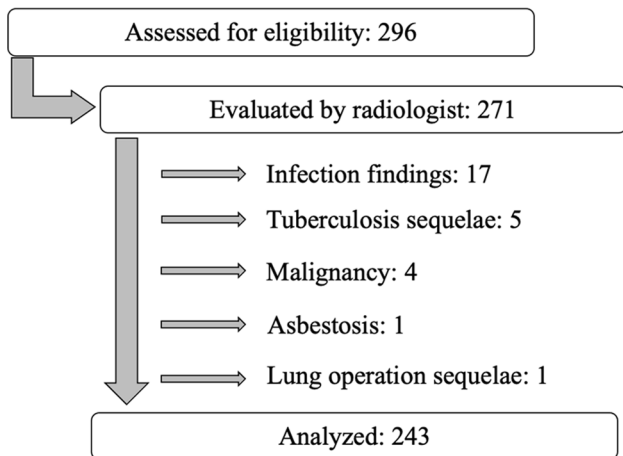

Fig. 1 Diagram of eligibility

Assessed for eligibility: 296

Evaluated by radiologist: 271

Infection findings: 17

Tuberculosis sequelae: 5

Malignancy: 4

Asbestosis: 1

Lung operation sequelae: 1

Analyzed: 243

Table 1 Clinical and demographic features of familial Mediterranean fever patients (n: 243)

Age (years)	40.0 (30.0–48.0)
Male/female (n)	84/159
Disease duration (years)	17.0 (10.0–26.0)
Smoking (%)	79 (32.5)
Comorbidity score	0 (0–2.0)
Pulmonary diseases (%)	38 (15.6)
Amyloidosis (%)	26 (10.7)
Spondyloarthropathy (%)	44 (18.1)
MEFV mutations (%)*	
Homozygote	39 (26.5)
Compound heterozygote	51 (34.7)
Heterozygote	47 (32.0)
Negative	10 (6.8)
Attack features	
Peritonitis (%)	213 (87.7)
Fever (%)	160 (65.8)
Pleuritis (%)	99 (40.7)
Musculoskeletal signs (%)	158 (65.0)
Chronic arthritis (%)	19 (7.8)
Erysipeloid rash (%)	35 (14.4)
Attack frequency (last 3 months)	0 (0–1.0)
Attack duration (days)	1.0 (0–3.0)
ISSF score	1.0 (0–2.0)
Pras score	4.0 (3.0–6.0)
Treatment	
Colchicine dosage (mg/day)	1.5 (1.0–1.5)
IL-1 blockers (%)	25 (10.5)
Colchicine resistance/intolerance (%)	54 (22.3)
Reason for thorax CT**	
Chest pain	37 (26.8)
COVID-19 suspicion	23 (16.6)
Screening	20 (14.4)
Chronic cough	17 (12.3)
X-ray abnormalities	10 (7.2)
Dsypnea	8 (5.7)
Trauma	7 (5.0)
Other	16 (11.5)

ISSF, international severity score for FMF; *CT*, computerized tomography

*MEFV mutation result is available in 147 patients

**Reason for requesting thorax CT is available in 138 patients

as the FMF patients. Of 147 patients with a *MEFV* mutation, the most common mutations were M694V (53.1%), R202Q (30.7%), and M680I (17.4%). Furthermore, 38 of the patients had history of pulmonary diseases; 28 (11.5 %) had chronic obstructive pulmonary disease; and 10 (4.1%) had asthma. Also, 9 (3.7%) patients had pleural effusion in their medical history.

We were able to determine the reason thoracic CTs were requested for 138 (56.7%) patients. The most common causes were chest pain in 37 (26.8%) patients, suspected COVID-19 in 23 (16.6%) patients, and screening in 20 (14.4%) patients. The reasons for requesting thoracic CT are shown in Table 1.

In this study, the most common pulmonary findings on the thorax CT were apical fibrosis in 96 (39.5%) patients, parenchymal fibrotic changes in 48 (19.8%), and a solitary parenchymal nodule smaller than 4 mm in 33 (13.6%). In addition, apical fibrosis in 24 (19.7%) patients, parenchymal nodules smaller than 4 mm in 11 (9.0%) patients, and pleural nodules and parenchymal fibrotic changes in 9 (7.4%) patients were the most common lung findings in control patients. Moreover, the frequency of parenchymal nodules smaller than 4 mm, pleural nodule, cardiomegaly, mosaic attenuation, and ground glass opacity were similar between the groups. All other pulmonary findings were more common in the FMF group. The radiological features of familial Mediterranean fever patients with lung involvement and controls are shown in Table 2. In addition, SpA frequency was similar among the patients with or without apical fibrosis (p=0.38).

All demographic, clinical, genetic, and therapeutic features of FMF patients with and without lung involvement on thorax CT were similar, seen in Table 3. There was no difference in *MEFV* mutation characteristics between FMF patients with and without lung involvement (Table 4), and the frequency of lung involvement did not differ significantly between patients with and without major exon 10 mutations (M694V, V726A, and M680I) (p=0.39).

Furthermore, mild disease according to ISSF scores was present in 188 (77.4%) of FMF patients, with the incidence of lung involvement being similar among FMF patients with mild or moderate-to-severe disease (p=0.08).

Discussion

In this study, to evaluate common lung findings on thorax CT of FMF patients, we found that the most common finding was apical fibrosis. In addition, none of the clinical, demographic, genetic, and disease-related parameters was associated with these findings.

Systemic involvement is not uncommon in auto inflammatory diseases, and many diseases in this class have cutaneous, auditory, ophthalmic, neurological, cardiopulmonary, abdominal, musculoskeletal, and vascular manifestations [22]; however, pulmonary involvement is not a predominant feature of autoinflammatory diseases, except in serositis. As far as we know, pulmonary and mediastinal involvement and thorax scan findings have not been studied sufficiently in the literature. We first focused on thorax CT findings requested

Table 2 Radiologic features of familial Mediterranean fever patients and controls on thorax CT (%)

	FMF patients n=243	Controls n=112	p
Apical fibrosis	96 (39.5)	24 (19.7)	**<0.001**
Parenchymal fibrotic changes	48 (19.8)	9 (7.4)	**0.002**
Parenchymal nodule (≤4mm)	33 (13.6)	11 (9.0)	0.20
Pulmonary air cyst	22 (9.1)	0 (0)	N/A
Pleural changes	21 (8.6)	2 (1.6)	**0.009**
Bronchiectasis	21 (8.6)	3 (2.5)	**0.02**
Emphysema	19 (7.8)	0 (0)	N/A
Parenchymal nodule (>4mm)	16 (6.6)	0 (0)	N/A
Mediastinal lymphadenopathy	16 (6.6)	0 (0)	N/A
Pleural nodule	15 (6.2)	9 (7.4)	0.66
Parenchymal multinodular	14 (5.8)	0 (0)	N/A
Cardiomegaly	14 (5.8)	2 (1.6)	0.07
Atelectasis	13 (5.3)	0 (0)	N/A
Bronchial changes	10 (4.1)	0 (0)	N/A
Fissure nodule	9 (3.7)	0 (0)	N/A
Mosaic attenuation	8 (3.3)	3 (2.5)	0.75
Ground glass opacity	7 (2.9)	2 (1.6)	0.47
Pleural effusion	6 (2.5)	0(0)	N/A
Increased pericardial fat	6 (2.5)	0 (0)	N/A
Pericardial effusions	4 (1.6)	0 (0)	N/A
Alveolitis	3 (1.2)	0 (0)	N/A
Interstitial lung disease	2 (0.8)	0 (0)	N/A
Interstitial fibrosis	2 (0.8)	0 (0)	N/A
Increased broncho vascular markings	2 (0.8)	0 (0)	N/A
Pneumothorax	1 (0.4)	0 (0)	N/A
Cavitary lesion	1 (0.4)	0 (0)	N/A
Pulmonary thromboembolism	1 (0.4)	0 (0)	N/A
Honeycomb appearance	0 (0)	0 (0)	N/A

(Data are given with n with %) p<0.05 is shown bold

for any reason in FMF patients. The most common incidental thoracic CT findings in these patients were found to be apical fibrosis, followed by parenchymal fibrotic changes, and solitary parenchymal micronodules.

In FMF, some clinical and laboratory parameters are associated with severe disease. M694V carriers often have severe disease, especially in the homozygous individual, with multisite involvement during attacks and a high risk of amyloidosis [23]. Standing myalgia and enthesitis are related to severe presentation of the disease [8, 9]; however, in our study, none of the patient and disease-related parameters was associated with pulmonary findings on thorax CT.

Apical fibrosis can be found in a variety of pulmonary pathologies, and tuberculosis is the most common etiology of apical fibrosis, especially in developing countries. Other possible causes include aspergillosis, allergic alveolitis, ankylosing spondylitis, sarcoidosis, histiocytosis,

Table 3 Demographic, clinical, genetic, and therapeutic features of FMF patients with and without pulmonary/mediastinal involvement

	With pulmonary/mediastinal involvement (n: 167)	Without pulmonary/mediastinal involvement (n: 76)	P
Age (years)	41.0 (31.0–50.2)	39.0 (27.0–46.75)	0.15
Male/female (n)	57/110	27/49	0.83
Disease duration (years)	18.0 (10.0–27.0)	18.0 (4.0–27.0)	0.60
Smoking (%)	56 (33.5)	23 (30.2)	0.44
Comorbidity score	1.0 (0–2.0)	0 (0–1.7)	0.26
Pulmonary diseases (%)	28 (16.8)	10 (13.2)	0.47
Amyloidosis (%)	19 (11.4)	7 (9.2)	0.61
Spondyloarthropathy (%)	30 (18.0)	14 (18.4)	0.93
Attack features			
Peritonitis (%)	146 (87.4)	67 (88.2)	0.87
Fever (%)	115 (68.9)	45 (59.2)	0.14
Pleuritis (%)	68 (40.7)	31 (40.8)	0.99
Musculoskeletal signs (%)	111 (66.5)	47 (61.8)	0.48
Chronic arthritis (%)	11 (6.6)	8 (10.5)	0.28
Erysipeloid rash (%)	24 (14.4)	11 (14.5)	0.98
Attack frequency (/3 month)	0 (0–1.0)	0 (0–1.0)	0.24
Attack duration (days)	2.5 (1.5–3.5)	3.0 (2.0–4.0)	0.12
ISSF score	1.0 (0–3.0)	1.0 (0–2.0)	0.16
Pras score	4.0 (3.0–6.0)	5.0 (3.0–6.0)	0.65
MEFV mutations* (%)			
Homozygote	26 (15.6)	13 (17.1)	0.64
Compound heterozygote	38 (22.8)	11 (14.5)	
Heterozygote	32 (19.2)	15 (19.7)	
Negative	9 (5.4)	3 (3.9)	
Treatment			
Colchicine dosage (mg/day)	1.5 (1.0–1.5)	1.5 (1.0–2.0)	0.36
IL-1 blockers (%)	17 (10.2)	8 (10.5)	0.93
Colchicine resistance (%)	43 (25.7)	11 (14.5)	0.05

*MEFV mutation result is available in 147 patients

(*ISSF*, international severity score for FMF)

silicosis, and pneumoconiosis [24, 25]. In normal pulmonary physiology, the apex of the lung is relatively more ventilated and less lymphatic perfused compared to other parts of the lungs. This makes apices vulnerable to inhalation of the toxic substance or airborne pathogens such as tuberculosis [26]. Moreover, mechanical stress is highest at the apex as the chest wall is relatively immobile in this region. Increased mechanical pressure is associated with fibrotic changes in the lung. Ankylosing spondylitis often presents with increased limitation of the chest wall due to ankylosis of the thoracic spine. This is associated with increased mechanical stress and the associated increased risk of apical fibrosis [27]. In our cohort, approximately 40% of patients had apical fibrosis. Here, the frequency of spondylitis was similar in patients with and without apical fibrosis. Although we excluded patients with known or active tuberculosis, as Turkey is an endemic country for tuberculosis, tuberculosis may be the likely cause of the

high incidence of apical fibrosis in our cohort; however, in a previous study conducted in the Turkish population, apical fibrosis was not found as an incidental thoracic CT finding [28].

The second most common pulmonary finding in our cohort was nonspecific pulmonary parenchymal fibrotic changes. These are nonspecific thickening or scaring of the parenchymal ultrastructure. None of our cohort's changes was compatible with any specific and progressive pulmonary fibrotic disease. Those changes can be seen in normal aging lung [29], drug related [30], sequel of infection or acute respiratory syndrome [31, 32], or some autoimmune diseases, such as systemic sclerosis and rheumatoid arthritis [33]. Here, we believe that this finding was mainly an incidental observation related to the sequel of nonspecific infections.

Pulmonary solitary or multiple nodules of various sizes were also one of the most common chest CT findings in our cohort. More than one-third of patients have at least one

Table 4 MEFV mutation features of FMF patients with or without pulmonary/mediastinal involvement

	With pulmonary/mediastinal involvement (*n*: 105)	Without pulmonary/mediastinal involvement (*n*: 42)	*p*
M694V	54 (51.4)	22 (52.3)	0.92
M680I	21 (20.0)	4 (9.5)	0.09
R202Q	30 (28.5)*	14 (33.3)**	0.79
V726A	12 (11.4)	4 (9.5)	0.65
V722M	1 (0.9)	0	N/A
R761H	4 (3.8)	1 (2.3)	0.61
A744S	1 (0.9)	0	N/A
E148Q	12 (11.4)	8 (19.0)	0.28
F479I	1 (0.9)	0	N/A
P369S	2 (1.8)	2 (4.6)	0.58
R408Q	1 (0.9)	1 (2.3)	0.52
S339F	1 (0.9)	0	N/A
E167D	1 (0.9)	0	N/A
K695R	0	1 (2.3)	N/A

(Data are given with *n* with %)

*22/30 (73.3%)

**10/14 (71.1%) patients have additional mutations to R202Q

type of nodule, and the differential diagnosis of pulmonary nodules varies. Here are neoplasms; infections; congenital anomalies; autoimmune diseases such as rheumatoid arthritis, sarcoidosis, and vasculitis; and finally many benign conditions [34]. We did not evaluate the possible etiologies of the nodules in this study; however, none of the patients had pathological imaging features [35].We assume that the etiology of these pulmonary nodules in the FMF cohort is benign.

Lymphadenopathy pleural and bronchial findings are also common in our cohort. The possible cause of pleural involvement is expected to be directly related to serositis due to FMF [4]. The imaging features of bronchial changes were consistent with chronic sequelae. Likewise, lymphadenopathies in our cohort had benign radiologic appearance.

Since thorax CT scans were requested according to the pulmonary symptoms of the patients, the frequency of some findings such as alveolitis, pulmonary thromboembolism, and pneumothorax was found higher than expected.

We included the control group from trauma patients in our study. Although apical fibrosis is also the most common pulmonary finding in controls, the frequency of apical fibrosis is significantly higher in FMF patients compared to controls. In addition, most thoracic CT findings were more common in FMF patients. We thought that the higher rate of comorbidity in FMF patients compared to controls, frequent pleural involvement in FMF, and the fact that the study was conducted in a tertiary

health center may be the main reason for this difference. Incidental thoracic CT findings have been previously evaluated in the literature. In a study where incidental findings on thorax CT requested for pulmonary thromboembolism were presented, pulmonary nodules and lymphadenopathy were found to be the most common findings [36]. In another study, which presented incidental pulmonary findings in abdominal CT scans performed for subjects from a similar population as our cohort, atelectatic changes, asbestosis, pleural effusion, and pulmonary nodules were detected [28]. And, in other studies, pulmonary nodules are the most frequent incidental finding in thorax CT scans [37, 38].

We believe that the most striking finding of the study is the high frequency of apical fibrosis in our FMF cohort; however, our data are insufficient to demonstrate a causal link between FMF and apical fibrosis. We also showed that the frequency of SpA, which is one of the etiologies of apical fibrosis and is frequently observed in FMF, is similar in patients with and without apical fibrosis. And, although tuberculosis is endemic in Turkey, apical fibrosis was not found as a common coincidental pulmonary finding in the Turkish population [28]. Further studies would be worth considering that re-examine our findings and evaluate the possible cause-effect relationship between FMF and apical fibrosis.

Although we found thoracic CT abnormalities in many patients, most of these pathologies were incidental. Our main purpose in this study was not to guide clinicians to have a thoracic CT scan of all FMF patients, and instead to guide clinicians that some thoracic CT findings are common in FMF and avoid unnecessary further procedures. Our study has several limitations. First, it was a retrospective cross-sectional study and thoracic CTs were requested for pulmonary complaints unrelated to FMF. Second, control group patients were selected from trauma patients only. Finally, the study was conducted in a tertiary medical facility where more complex patients were admitted.

In conclusion, more than two-thirds of our FMF patients had pulmonary findings on thorax CT requested for different pulmonary symptoms. Here, apical fibrosis is the most common finding and is not associated with SpA. Further studies should be performed to evaluate the possible causal link between FMF and apical fibrosis.

design of the work; or the acquisition, analysis, or interpretation of data for the work; RD: made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; SYO: provided contributions to collection/processing, review the article before submission scientifically besides spelling and grammar, and supervision; MET: writer, plan methodology to reach the conclusions, and review the article before submission scientifically besides spelling and grammar

Data availability The dataset analyzed during the current study is available from the corresponding author on reasonable request.

Declarations

Disclosures None.

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