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Thoracic high resolution computed tomography (HRCT) in asthma

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Key words

Asthma, HRCT, Remodelling, Bronchiectasis

Summary

Introduction: *High-resolution computed tomography (HRCT) is a widespread medical imaging method for the study of thoracic diseases. In asthma it is very useful particularly when it is difficult to achieve an effective control of disease, and in severe deterioration.* ***Aim:*** *It was intended to evaluate the imaging changes by HRCT in asthmatic patients and to assess the expression according to the symptoms and duration of disease.* ***Material and methods:*** *Thirty three patients from the Outpatient Department, with asthma classified in the different clinical severity stages according to GINA, were randomly included. They were submitted to HRCT (Somaton Plus-4, Siemens®). The lesions were classified in reversible (mucoid impaction, acinar pattern centrilobular nodules and lobar collapse) and irreversible (bronchiectasis, bronchial wall-thickening, sequellar line shadows and emphysema).* ***Results:*** *The 33 asthmatic patients (20 female) had an average age of 44.76±16.98 years and a mean disease evolution time of 23.39±14.83 years. 30% had mild persistent asthma, 43% moderate persistent asthma and 27% severe persistent asthma. All the patients were under inhaled corticotherapy. Only 6 patients had normal HRCT: 4 with mild persistent asthma (4 to 25 years of duration of disease) and 2 with moderate persistent (10 to 48 years of duration of disease). 81.81% of the patients had changes in HRCT, being the irreversible lesions the most frequent. The most important irreversible lesions were observed in severe asthma patients with longer duration of disease. All the patients with reversible lesions had also irreversible changes. Most of the bronchiectasis were centrally located and were found in severe asthma patients. Irreversible changes were identified in 3 patients with mild asthma and a maximum of 6 years of duration of disease.* ***Discussion:*** *HRCT findings were related with asthma severity and long lasting disease but there are some asthmatics that also present early abnormalities, even in milder forms. All the groups of asthmatic patients presented all types of imaging changes, including the irreversible ones. In asthma these changes can be the result of individual patterns of response to frequent exacerbations, leading to a persistent chronic inflammatory process that will determine airway remodelling, even in early stages of disease and/or mild asthma.*

Introduction

Bronchial asthma is characterised by reversible airflow obstruction and bronchial hyperresponsiveness (1, 2). It is a chronic inflammatory disease, where most patients can achieve complete reversibility with bronchodilators and/or anti-inflammatory medications (2, 3). However, in many asthmatics this inflammatory condition can be followed by healing that may result in an altered structure, due to the remodelling of the airways (3, 4). Structural changes can occur in central and peripheral small airways and are thought to result in an irreversible component of the airway obstruction seen in asthma and perhaps also in the development of airway hyperresponsiveness (1, 2, 5). Patients with an irreversible airflow obstruction can experience considerable morbidity and account for a high percentage of the health costs related to asthma (6).

The detection and quantification of airway remodelling have been based on histological examination (7). However, the development of high resolution computed tomography (HRCT) has provided a potential non-invasive technique for its measurement in vivo, even though the information that can be obtained from HRCT is essentially less detailed than that obtained on histological examination (6, 7).

With conventional chest radiography one can only evidence a limited number of abnormalities in asthmatic patients (8.

The dimensions of the central airway in patients with asthma can be assessed quantitatively by computed tomography (CT), but these measures are considered indirect measures of airway remodeling and analysis of the wall area or luminal area of small airways are beyond the spatial resolution of conventional CT9,10. Measures derived from full-expiratory scans by HRCT can indicate the presence of air trapping in asthma (2, 9, 11) and hyperlucency should identify hyperinflation (12). Subsequently, HRCT has been tried as an alternative procedure and some authors describe its potentiality in evaluating the airways in patients with asthma (2, 13). The HRCT scans of asthmatics patients have shown both decreased and increased bronchial lumen area, excessive airway narrowing in response to a variety of stimuli and airway wall thickening, in addition to mosaic perfusion and gas trapping on expiration (7).

The aim of this study was to evaluate the imaging changes by HRCT in asthmatic patients and to assess their relationship with the clinic and the duration of disease.

Methods

Subjects: The patients were selected from our outpatient department. During 33 consecutive weeks we selected the first adult asthmatic patient that had a scheduled appointment each Monday. All the patients were non-smokers, with previous clinical and functional diagnosis of asthma, according to the GINA criteria (14). They should be under appropriate optimized therapy, according to clinical severity. Demographic and clinical data such as age, duration of disease, medication used and severity of disease were taken into account. Allergic sensitizatisation was defined by positive skin-prick tests to common aeroallergens (Leti, Spain) and/or serum specific IgE levels higher than 0.35 kU/L for at least one allergen.

Only the patients without respiratory infections or exacerbations of asthma in the last month were selected for this study. Written informed consent was obtained from all the subjects.

HRCT image acquisition: CT scans were performed using a single detector device (Somaton Plus 4; Siemens, Erlangen, Germany). Two sets of 15 to 20 images (according to the size of the patient's thorax) were acquired at full inspiration. The scans were performed on the whole lung using a sequential mode (1 mm section thickness at 20 mm increment intervals), in order to get images from the apices to the diaphragm. CT scans were performed using the following parameters: 120 kV, 200 mAs, pitch 1,0 and 0.5 to 1 second rotation time.

The images were reconstructed using a high spatial resolution algorithm and visualized with a window setting of 1500 Hounsfield units (HU) width and -700 HU level.

The scans were sequentially interpreted by two radiologists that did not have any previous knowledge about the chest X-ray and the clinical severity of the disease. Both internal and external diameters of the apical bronchus of the right upper lobe were measured in order to evaluate the agreement between the 2 observers. Consensus reading was regarded as the average of the two observer's measurements.

The following lesions were taken into consideration for the proposal of analysis: reversible and irreversible, and classified from mild to severe (+ to +++). Several HRCT scan abnormalities were annotated: reversible lesions as mucoid impaction, acinar pattern and lobar collapse, and irreversible forms of damage as bronchiectasis, bronchial wall thickening, sequellar line shadows and emphysema (4).

All the data was collected and analyzed, in order to iden-

tify possible relationships between the changes in HRCT and clinical characteristics of the patients.

Statistical analysis: Statistical analysis was performed with SPSS 15.0 (2006 SPSS Inc, Chicago, Ill, USA). Distribution of frequencies was obtained for the different groups of patients. Additionally, average and standard deviation were calculated for quantitative variables. Association between allergic sensitization and abnormal HRCT scans was evaluated by chi-square tests (Pearson or Fisher's exact test). Differences between patients with more than one irreversible lesion and those with only one as well as patients with more than one reversible lesion and those with only one were analysed by Mann-Whitney U test. Significance was considered for a p value less than 0.05.

Results

Thirty-three patients were included, 20 female and 13 male. The mean age of the sample was 44.76±16.98 years old and the mean duration of disease was 23.39±14.83 years old. According to the clinical classification 30% of the sample had mild persistent, 43% moderate persistent and 27% severe persistent (Table 1). Allergic sensitization was present in 24:33 patients (house dust mites=16; grass pollen=7; mites and grass pollen=2).

All the subjects were under optimized therapy, according to clinical and functional severity, namely inhaled corticosteroids. No patient was under immunotherapy or were previously submitted to this treatment. No one had systemic corticosteroids therapy in the last 6 months either.

Table 2 shows the clinical and radiological characterization of the patients. A full concordance of imaging results interpretation was obtained from the two imagiologists.

Only 6 out of 33 patients had HRCT without changes (Table 1). These patients had a mean age of 35.83±17.99 years and 16.50±17.22 years of duration of disease. From these patients, 4 had mild persistent (duration of disease 10.25±9.88 years; 4 to 25 years) and 2 moderate persistent asthma (duration of disease 29.00±26.87 years; 10 and 48 years). The other 29 patients (81.81%) showed abnormalities, as outlined in Tables 1 and 2; the mean age of these patients was 46.74±16.44 years, with a duration of disease of 24.93±14.15 years. Despite a higher frequency of abnormal HRCT scans in atopic patients compared to non atopic (20 versus 7 patients), these differences had no statistical significance (p=0.533).

The most common irreversible lesion was bronchial wall thickening (69.7%), followed by bronchiectasis (45.5%), sequellar line shadows (30.3%) and emphysema (24.2%) (Figures 1 and 2).

Bronchial wall thickening was found in 88.9% of the patients with severe persistent, in 78.6% with moderate persistent and in 40% of the mild persistent asthma patients.

In the majority of patients, the bronchiectasis were centrally located (86.7%). These patients had mostly severe forms of ashtma. Nonetheless, 2 patients with mild persistent asthma had also bronchiectasis. These lesions were present in 77.7% of the patients with severe persistent, 42.9% of the moderate persistent patients and in 20% of those with mild persistent asthma.

Ten patients had sequellar line shadows shown by HRCT. This lesion was found in 66.7% of patients with severe

Table 1 - Summary of the radiological lesions, according to the asthma severity classification.

		Mild persistent	Moderate persistent	Severe persistent	Total
Total of patients		10	14	9	33
Irreversible lesions	Bronchial wall thickening	4	11	8	23
	Bronchiectasis	2	6	7	15
	Sequellar line shadows	0	4	6	10
	Emphysema	0	4	4	8
	Total of patients				26
Reversible lesions	Acinar pattern	1	3	2	6
	Lobar collapse	1	3	2	6
	Mucoid impaction	0	1	0	1
	Total of patients				7
Normal		4	2	0	6

Table 2 - Clinical and imaging characterization of the patients. Asthma classification: MiP=mild persistent; MoP=moderate persistent; SP=severe persistent. Sensitization: HDM=house dust mites. P=pollens. N=study without changes. Reversible lesions: MI=mucoid impaction ; AP=acinar pattern; LC=lobar collapse. Irreversible lesions: Br=Bronchiectasis (C=Cylindrical, V=Varicose, Q=Cystic); BWT=bronchial wall thickening; SLS=sequelar line shadows; Em=Emphysema (C=Centrolobular, P=Paraseptal, B=Bullous. UL-R: right upper lobule. Ling.=Lingula)

Patient	Gender	Age	Disease	Classification	Atopy	Sensitization		Reversible lesions			Irreversible lesions			
	(Years)	(Years)	(Years)			HDM	P	MI	AP	LC	Br	BWT.	SLS	Em
1	F	50	30	MiP	Yes	Yes	No					+		
2	F	40	25	MiP	Yes	No	Yes	N	N	N	N	N	N	N
3	M	28	21	MiP	Yes	No	Yes				C, V			
4	F	24	12	MiP	Yes	No	Yes					+		
5	F	23	6	MiP	Yes	No	Yes	N	N	N	N	N	N	N
6	M	21	6	MiP	Yes	Yes	No	N	N	N	N	N	N	N
7	M	22	5	MiP	Yes	Yes	No					+		
8	F	19	5	MiP	No	No	No		+	UL-R	C, V			
9	F	23	4	MiP	Yes	Yes	No	N	N	N	N	N	N	N
10	F	54	2	MiP	Yes	Yes	No					+		
11	F	68	48	MoP	No	No	No	N	N	N	N	N	N	N
12	F	61	46	MoP	No	No	No				C, V		+	+
13	F	55	45	MoP	Yes	No	Yes			+		++	++	
14	F	46	40	MoP	Yes	Yes	No		+	+	C, T, V	+++	++	+
15	F	43	30	MoP	No	No	No					+		
16	M	51	30	MoP	No	No	No					+		
17	M	70	26	MoP	No	No	No			Ling.		+	++	
18	F	38	23	MoP	Yes	Yes	No	+	+	+	C, V	++		
19	M	18	17	MoP	Yes	Yes	No				C, V	++		
20	F	17	16	MoP	Yes	Yes	Yes					++		
21	F	65	17	MoP	No	No	No				V	+		
22	F	57	11	MoP	Yes	No	Yes					+		
23	M	40	10	MoP	No	No	No	N	N	N	N	N	N	N
24	F	36	8	MoP	Yes	No	Yes		+		V	++		
25	M	75	60	SP	Yes	Yes	No				C, V	+	+	C
26	M	51	45	SP	Yes	Yes	No				C	+		C, B
27	F	44	33	SP	Yes	Yes	No						+	
28	M	48	30	SP	Yes	Yes	No				Q, V, C	++	+	
29	M	51	29	SP	No	No	No				C	+		
30	M	61	29	SP	Yes	Yes	No		+		C	+	+	
31	M	58	25	SP	Yes	No	Yes				C	+	+	
32	F	60	23	SP	Yes	Yes	No		+	UL-R	T, C, V	+	+++	P
33	F	60	15	SP	Yes	Yes	No					+		+

persistent and in 28.6% of the moderate persistent asthma patients. None of the asthmatics with mild persistent form showed this lesion.
Concerning emphysema, no mild persistent asthmatic presented this lesion, however it was found in 28.6% of the moderate persistent patients and in 44.4% of those with severe persistent asthma.
The most important irreversible lesions were more common in patients with severe and long-lasting asthma. Three patients with mild asthma and duration of disease lesser than 6 months had irreversible lesions: 2 with bronchial wall thickening, one with central bronchiectasis and another one with varicose bronchiectasis. The patients with more than one irreversible lesion were older and had a longer duration of disease, than those with only one: 53.31±14.12 versus 37.18±15.29 years (p=0.009) and 29.88±13.89 versus 17.73±11.61 years (p=0.064), respectively. At least two irreversible lesions were more frequently found in atopic patients than in non atopic (12 patients versus 4 patients), (p=0.081).
Reversible lesions were less common than the irreversible ones. Moreover, all patients with reversible lesions had also irreversible abnormalities. Patients with more than one reversible lesion had a mean age of 40.75±17.11 years and duration of disease of 22.75±14.29 years. Those with only one reversible lesion had a mean age of 55.50±14.39 years, with a mean duration of disease of 27.00±15.17 years. These differences were not statistically significant.

Figure 1 - HRCT scan image of a patient with varicose and cystic bronchiectasis, sequellar line shadows and emphysema

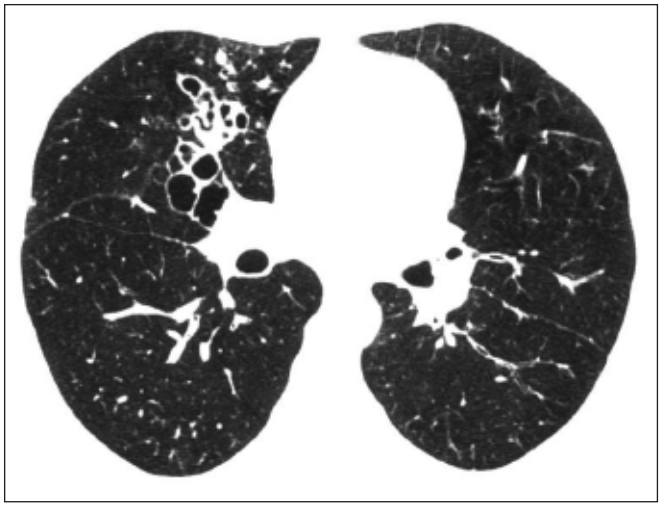
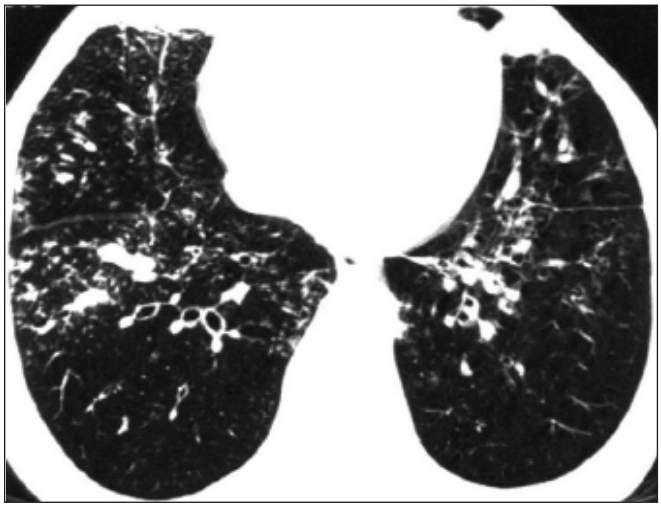


Figure 2 - HRCT scan image of a patient with mucoid impaction and bronchial wall-thickening



Discussion

We studied non smoker asthmatic patients, in order to establish a relationship between the clinical severity, duration of disease and lesions detected by HRCT. The previous chest X-ray results obtained for all the patients did not allowed to suspect the morphological abnormalities showed by HRTC. The majority of the mild and moderate asthmatic patients had normal images on chest X-ray, and only the patients with severe forms or long lasting asthma showed bronchial wall thickness features.
The prevalence of abnormal HRCT scans in our study was higher, comparing to similar reports from other groups; perhaps the degree of differentiation of our outpatient clinic can explain this disparity. In a sample of 31 asthmatic adult patients with clinical and functional worsening of disease submitted to chest radiographies and thorax HRCT scans, Rimondi et al. found abnormal HRCT scans in 61% of the patients (15). Vignola and coworkers in a study of 30 asthmatic patients and 12 patients with chronic obstructive pulmonary disease described 70% of abnormal HRCT scans among asthmatic patients (16). Paganin and colleagues found 71.9% of abnormal HRCT scans, in a study with 57 asthmatic patients8. A study with 48 asthmatic patients, undertaken by Lynch et al., described a higher abnormality rate than our results, with 92% of the sample with abnormal HRCT scans (17).
We found all types of imaging changes in all groups of patients, including the irreversible ones, although the

most severe lesions were more frequently found in asthmatic patients with the worst clinical impairment and longer duration of disease. There are some previous studies that corroborate our findings. Awadh and co-workers described that all groups of patients with near fatal attack of asthma, even those with moderate and mild asthma had greater airway wall thickening than the normal subjects (13). In the same study they found a greater airway wall thickening in the patients with the most severe symptoms comparing with those with milder forms (13). In a study comparing patients with near fatal, mild-to-severe asthma, and healthy controls Lee YM et al did not found significant differences in the bronchial wall thickening between the different groups of patients (18).

We found a high frequency of irreversible lesions among different groups of asthmatic patients even in those with milder forms. All patients with abnormal HRCT scans presented irreversible lesions. These severe injuries were present in 81.81% of our sample, being the most frequent bronchial wall thickening, followed by bronchiectasis, sequellar line shadows and emphysema.

Regardless of the majority of our patients being atopic, the presence of HRCT scan abnormalities were not related with allergic sensitization. Other groups found similar results (9, 19).

Bronchial wall thickening is the result of airway remodelling. It is considered an irreversible structural abnormality in asthmatic patients (8, 18, 20), and can be responsible for irreversible airflow obstruction and an increase in airway responsiveness (2). The airway wall thickness results from mucosal infiltration with inflammatory cells, smooth muscle hypertrophy, deposition of connective tissue, and mucous gland hyperplasia (13). It has been demonstrated that these structural changes can occur not only in the central, but also in the peripheral small airways (2, 21). Other studies have been suggesting an association between asthma severity and bronchial wall thickness (6, 13). Bronchial wall thickening was the most frequent irreversible lesion detected by HRCT in our study (69.7% of the patients). This finding is corroborated by the results of other studies, where this lesion was the most common, but with different prevalence rates: 44% (Park et al.) (22) and 92% (Lynch et al.) (17).

Bronchiectasis is recognized as an important cause of respiratory morbidity, particularly in developing countries (23). We found bronchiectasis in 45.5% of our sample, mainly centrally located and mostly in patients with severe asthma. This percentage was lower than the data obtained by other groups. Rimondi et al. reported this abnormality in 53.8% of the patients (15). In 1992, Paganin and co-workers observed bronchiectasis, mostly cylindrical, in 37 of 57 asthmatic patients (8). Another classic study, undergone by the Lynch group, found a prevalence of 77% of bronchiectasis among a group of 48 asthmatic patients (17).

Another irreversible lesions found in our study were the sequellar line shadows, present in 30.3% of our sample; we did not found this lesions in patients with mild asthma. Patients with this radiological pattern had a longer duration of disease. Harmanci et al. correlated this radiological pattern with the duration of asthma, in a group of 160 asthmatic patients (24).

The less frequent irreversible lesion was emphysema; nevertheless it was observed in almost a quarter of the sample. This injury had been associated with severe asthma in the past, but only recently its role in asthma was well established; the use of HRCT scans, providing a high degree of anatomical detail, was helpful in determining this association (25).

In our sample, the irreversible lesions were dominant in early-onset than in late-onset asthma. We also found this type of severe abnormalities in younger patients and in those with short duration of disease, suggesting an early appearance of lesions.

In addition, patients with more than one lesion had a longer duration of disease; however one patient from the group of moderate persistent asthma and the longest disease evolution time had a normal HRCT scan.

We stress that some patients (ex. 7, 8 and 10) with mild forms of asthma and with reduced duration of disease have already irreversible lesions. Probably this could represent an expression of distinct phenotypes of asthma not discriminated by a classical clinical classification.

Eight patients were studied 5 years later with another HRCT scan (data not published). All of them were regularly observed in the outpatient department. Two patients changed their clinical severity pattern from moderate to mild and from severe to moderate, respectively. We found an increase of imaging abnormalities, with one patient presenting cylindrical bronchiectasis, despite the excellent clinical evolution and another one with a previous normal CT scan, showing brochiectasis, in spite of the maintenance of the same clinical severity.

The abnormalities described in our patients are probably related to the remodelling process. The parenchymal and airway changes that become irreversible throughout the long course of the disease, as structural changes can occur early during the course of disease (16, 26). In the past, Pa-

ganin et al. demonstrated the reversibility of the remodelled airways, after antiasthmatic therapy, with mucoid impaction, acinar patterns, and lobar collapse considered reversible lesions; however, lesions as bronchial wall thickness, bronchiectasis, and emphysema were described irreversible (8, 20). A more recent study illustrated bronchial wall thickening as partially reversible, after intensive anti-inflammatory therapy; however air trapping was not improved18. It seems that bronchial wall thickening is reversible when submucosal inflammation or oedema predominates, and irreversible when the airways are remodelled extensively (18).

As outlined before, we believe that morphological abnormalities occur earlier at the beginning of the disease, probably delayed by anti-inflammatory therapy. Perhaps, there are individual genetic factors, not yet clarified, that enhances or limits the remodelling and the severity of asthma. It seems that the HRCT findings are related with asthma severity and long lasting disease but there are some asthmatics that also present early abnormalities, even in milder forms. So this technique has a role in the management of the asthmatic patients, namely for the early identification of bronchiectasis that need a convenient therapeutic approach.

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