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Original Article

Incidental pulmonary nodules in children: characteristic features and clinical course

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ABSTRACT

Background. There exists insufficient information about the natural course of incidental pulmonary nodules (IPN) determined on tomography in children. The aim was to determine the characteristic features and factors affecting the course of IPN.

Methods. This retrospective study included patients who presented at the Pediatric Pulmonology, Allergy & Immunology Section of Akdeniz University Hospital between January 2014-2020, and were determined with pulmonary nodules on high-resolution computed tomography (HRCT). The patients were separated into two groups as those with a nodule decreased in size or which had disappeared on the follow-up HRCT (Group 1) and those with a nodule which had remained at the same size (Group 2). These two groups were compared in respect to demographic data, nodule size and characteristics, and accompanying findings on HRCT.

Results. A total of 177 nodules were determined in the 66 patients included in the study. A follow-up HRCT was taken within mean 16.29±11.38 months in 27 patients. In these patients, 78 nodules were determined on the initial HRCT. On the follow-up, twelve of the nodules were seen to have shrunk or disappeared compared to the initial images, 66 had remained the same size, and none had grown. The mean age of the patients in Group 1 was statistically significantly lower than that of patients in Group 2 ($p<0.001$). The rates of an accompanying mosaic attenuation pattern ($p<0.001$) on HRCT and subsolid density ($p=0.011$) of the nodules in Group 1 were statistically significantly higher compared to Group 2 and the rate of calcification content was statistically significantly lower ($p=0.002$). No suspicious or confirmed malignancy was observed in any case throughout the mean follow-up period of 38.33±16.5 months after the initial HRCT.

Conclusions. The young age of patients, subsolid structure of nodules, calcification content and the presence of an accompanying mosaic attenuation pattern on HRCT, could be useful factors in the estimation of size in the follow-up of nodules.

Key words: pulmonary nodule, incidental nodule, HRCT.

Pulmonary nodule is defined as a rounded or irregular opacity, well or poorly defined, which measures up to 3 cm in diameter on radiological imaging.[1] The causes of pulmonary nodules in pediatric patients include infections (e.g. tuberculosis, histoplasmosis), sarcoidosis, vasculitis (e.g granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis), hypersensitivity pneumonitis, lymphomatoid granulomatosis, primary lung malignancies, and cancers with pulmonary metastases (wilms tumour, osteosarcoma and ewing sarcoma).[2] There is no clear relation between malignancy and nodule size.[3]

The widespread use of high-resolution computed tomography (HRCT) for pediatric patients has increased the frequency of

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incidental determination of pulmonary nodules. This creates a challenging decision-making situation for clinicians. When it is considered that there may be an accompanying infection, immune deficiency disorder, malignancy or congenital airway malformations in pediatric cases determined with pulmonary nodules, it must be determined whether or not the nodule is incidental.[4] Pulmonary nodules may be an important indicator of metastasis in children with known malignancy, and incidental pulmonary nodules determined in cases with no underlying malignancy are generally considered benign.[5,6]

As a result of concerns regarding radiation exposure, there exists insufficient information about the frequency, characteristics and natural course of incidental pulmonary nodules (IPN) determined on tomography in children, and there are no general rules that can be formulated in the management of these nodules.[4,7,8] Therefore, adult guidelines are usually used for children with pulmonary nodules. To be able to determine the applicability of using these guideline recommendations in pediatric cases, it is extremely important to evaluate the course of IPN determined in children.[4,7]

The aim of this study was to examine the demographic data of pediatric cases determined with IPN on HRCT and to determine the characteristic features and factors affecting the course of the nodules.

Material and Methods

Study design and setting

A retrospective screening was made of the results of patients aged <18 years who presented at the Pediatric Pulmonology, Allergy & Immunology Section of Akdeniz University Hospital between January 2014 and January 2020, and were determined to have pulmonary nodules on HRCT, which was performed for various reasons. Patients were excluded from the study if they had any known malignancy, congenital lung disease, immune deficiency disorder, cystic fibrosis, rheumatological disease, fungal infection, latent tuberculosis infection/tuberculosis disease, or any findings of lower respiratory tract infection clinically or radiologically and also diagnosed with these diseases after HRCT with microbiological examinations (bronchoalveolar lavage or sputum culture), immunological (tuberculin skin test and/or interferon gamma release assay) and other laboratory tests.

Approval for this retrospective study was granted by the Ethics Committee of Akdeniz University (decision no:421, dated: 06/12/2020).

Patient data

Data related to patient age, gender, indications for HRCT and smoking/exposure to cigarette smoke, were retrieved from the hospital records system (MIA MED, 1.0.1.3295). Some patients had control HRCT: the decision was made on a case-by-case basis by the responsible physician using clinical judgment. The patients were separated into two groups, one with patients with a nodule which decreased in size or had disappeared on the follow-up HRCT (Group 1) and another comprised of patients with a nodule which had remained at the same size (Group 2). These two groups were compared in respect to demographic data, indications for HRCT, exposure to smoking, nodule size and characteristics, accompanying findings on HRCT, as well as interval between the two HRCT examinations. The clinical follow-ups of the patients in respect to findings or suspicion of malignancy after HRCT, were evaluated from the hospital records system.

CT Technique

The CT examinations were performed with 128-detector multidetector CT devices (Somatom Definition Edge, GERMANY). All chest CT studies were performed with the following parameters: 1) 0.625 mm collimation; 2) weight-based kilovoltage and tube current; 3) high-speed mode; 4) pitch equivalent of 1.0–1.5. A slice thickness of 0.5 mm was used to reconstruct the data set for review. All CT images were evaluated using a picture archiving and communication system (PACS; Sectra Workstation IDS7; Sectra AB, Linköping, SWEDEN) and standard soft tissue (level, 40–50 Hounsfield units [HU]; width, 400-450 HU) and lung (level, -450 to -550 HU; width, 1,600 – 1,800 HU). PACS allowed multiplanar (e.g., coronal and sagittal reformation) imaging, which was used routinely for the evaluation.

Image review

Two radiologists with experience evaluating pulmonary nodules on CT studies, (A.K. 15 years of experience in radiology; A.E., 13 years of experience in radiology) independently reviewed the lung parenchyma on the CT images using a PACS Workstation, and the final decision was made in consensus.

Maximum intensity projection (MIP) images were used to identify pulmonary nodules. All visualized pulmonary nodules were counted. First, perifissural nodules and parenchymal pulmonary nodules were identified and evaluated separately. The size, density, shape, and contour characteristics of the pulmonary nodules were evaluated and recorded. On axial CT images, the long and short axis diameters of the pulmonary nodule were totalled and averaged as in the Fleischner guidelines and recorded. Pulmonary nodule shape was characterized as round, ovoid, rectangular or triangular. Pulmonary nodular margins were described as regular or irregular. Attenuation was assessed as solid or subsolid. The lobe in which the pulmonary nodule was located was recorded, and whether the pulmonary nodule contained cavitation or calcification. The pulmonary nodules were subsequently compared on follow-up CTs and recorded.

Statistical Analysis

Data obtained in the study was analysed statistically using the SPSS v. 23.0 software. Descriptive statistics were stated as number and percentage or mean, standard deviation, median, 25th and 75th percentile, minimum and maximum values. In the analysis of categorical data, the Fisher's Exact test was applied if the expected value was <5 in >20% of cells and the Pearson Chi-square test if <20%. Conformity of the data to normal distribution was assessed with the Shapiro Wilk test. In the analysis of the difference between two groups, the Mann Whitney U-test was used when the data did not show normal distribution. A value of $p<0.05$ was accepted as statistically significant.

Results

A total of 394 HRCT images of 286 patients were evaluated and pulmonary nodules were determined in 90 (31.46%) patients. Of these, 24 were excluded from the study because of known malignancy (n=4), immune deficiency disorder (n=6), a diagnosis of cystic fibrosis (n=6), and clinical-radiological findings of lower respiratory tract infection (n=8). Thus, analysis was made of the data of 66 patients, comprising 42 (63.63%) males and 24 (36.36%) females. The most common indication for HRCT was treatment-resistant asthma (n=22, 33.33%), followed by chronic cough (n=21, 31.81%), determination of abnormality on plain radiographs (n=16, 24.24%) and recurrent pneumonia (n=10, 15.15%) (Table I). None of the patients smoked, whereas 12 (18.18%) were exposed to cigarette smoke.

A total of 177 nodules were determined in the 66 patients included in the study, at mean 2.68±2.79

Table I. Indications for HRCT.

Indication	Number of patients (%)
Treatment-resistant asthma	22 (33.33%)
Chronic cough	21 (31.81%)
Determination of abnormality on direct radiography	16 (24.24%)
Recurrent pneumonia	10 (15.15%)
Unexplained shortness of breath	1 (1.51%)
Hemoptysis	1 (1.51%)
Finger clubbing	1 (1.51%)
Nasal polyp	1 (1.51%)

(range, 1-13) nodules per patient. Nodule localisation was 89 (50.28%) parenchymal and 88 (49.71%) perifissural, some 173 (97.74%) nodules were solid and four (2.25%) of them had subsolid density. Calcification was present in 26 (14.68%) nodules and cavitation in one (0.56%) nodule. The most common indication for HRCT in the cases with calcified nodules was treatment-resistant asthma (51.6%), followed by chronic cough (41.9%) and in the cases with subsolid density nodules, it was treatment-resistant asthma (50%) and recurrent pneumonia (50%). The nodule margins were regular in 165 (93.22%) and irregular in twelve (6.77%). The nodules were most often located in the right lung upper lobe (49 nodules, 28%), followed by the left lung lower lobe and the right lung lower lobe (Fig. 1).

In twenty (30.30%) patients, there were additional findings accompanying the nodule on HRCT; linear atelectasis in thirteen patients, mosaic attenuation pattern in eleven, and air cyst in one. In patients with mosaic attenuation, the most common indication for HRCT was treatment-resistant asthma (45.4%), followed by recurrent pneumonia (27.3%) and chronic cough (18.2%), respectively.The mean nodule diameter was 3.11±1.31 mm (range, 1.30-7.10 mm), and a weak positive correlation was determined between mean nodule size and age (r=0.219, p=0.003). The mean nodule diameter was determined as 3.83 ± 1.34 mm in the right lower lobe, 2.99 ± 1.16 mm in the right upper lobe, 2.93 ± 1.15 mm in the right middle lobe, 2.90 ± 1.63 mm in the left upper lobe, and 2.79 ± 1.12 mm in the left lower lobe. The mean diameter of nodules localised in the right lower lobe was determined to be statistically significantly higher than that of the other lobes (p<0.0001). No statistically significant difference was determined between mean nodule diameter according to gender, perifissural location, and parenchymal location (p=0.21, p=0.12, p=0.12, respectively).

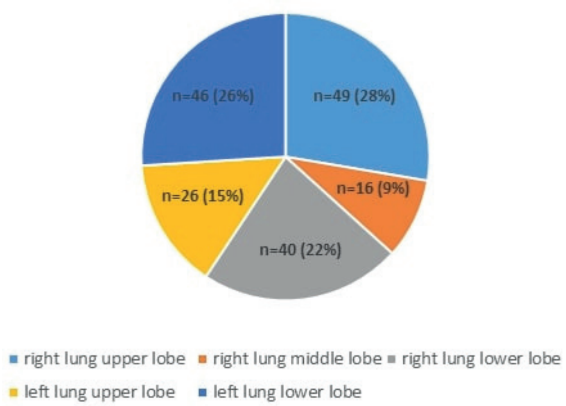

Fig. 1. Localisation of the nodules.

A single nodule was present in 34 (51.51%) patients and multiple nodules were present in 32 (48.48%). No statistically significant difference was determined between the presence of single or multiple nodules according to age, gender, exposure to cigarette smoke, indication for tomography and accompanying findings on tomography.

A follow-up HRCT was present in the system for 27 (40.90%) patients, taken at mean 16.29±11.38 months (range, 6-50 months) after the first imaging. On the first HRCT of these 27 patients, there were 78 nodules present with a mean diameter of 3.67±1.53 mm (1.50-7.10 mm). On the follow-up HRCT examination, twelve (15.38%) of the nodules were seen to have shrunk (n=2) or disappeared (n=10) compared to the initial images, 66 (84.61%) had remained at the same size, and none had grown. No suspicious or confirmed malignancy was observed in any case throughout the mean follow-up period of 38.33±16.5 months after the initial HRCT.

Comparisons between Group 1 and Group 2

The mean age of the 27 patients with a follow-up tomography was 10.24±4.26 years (1-17 years). The mean age of the patients in Group 1, where nodules had shrunk or disappeared (4.50 ± 2.65 years), was statistically significantly lower than that of patients in Group 2, where nodules had remained the same (11.29 ± 3.63 years) (p<0.001) (Table II).

The rate of subsolid density of the nodules and mosaic attenuation pattern accompanying the

Table II. Factors affecting nodule size during follow-up.

	Group 1	Group 2	p
Age (years), mean ± SD	4.50 ± 2.65	11.29 ± 3.63	<0.001
Gender, male/female	11/1	50/16	0.446
The time between the two CT examinations (months)*	15.50 ± 12.82	13.89 ± 8.48	0.786
Indication for first HRCT; abnormality on chest x ray, n (%)	2 (16.66)	29 (43.93)	0.110
Indication for first HRCT; treatment-resistant asthma, n (%)	4 (33.33)	14 (21.21)	0.457
Indication for first HRCT; chronic cough, n (%)	2 (16.66)	15 (22.72)	0.99
Indication for first HRCT; hemoptysis, n (%)	3 (25)	4 (6.06)	0.069
Indication for first HRCT; recurrent pneumonia, n (%)	3 (25)	4 (6.06)	0.069

*Values presented as mean±SD

nodule on HRCT in Group 1 was statistically significantly higher compared to Group 2 (25% vs 1.51%, p=0.011, and 50% vs 1.51%, p<0.001, respectively) and the rate of calcification and solid density of the nodules was statistically significantly lower (0% vs. 18.8%, p=0.002 and 75% vs. 98.48%, p=0.011, respectively) (Table III). No statistically significant difference was determined between Group 1 and Group 2 in respect of mean diameter, lobe localisation, gender, perifissural/parenchymal localisation, shape, margin features, exposure to cigarette smoke, single or multiple nodes, indication for HRCT and time interval to follow-up HRCT.

Discussion

The aim of this study was to investigate the characteristic features of IPN determined in children and to ascertain the factors affecting

Table III. Characteristics of pulmonary nodules on the first HRCT in cases with follow-up HRCT.

	Nodules shrank or disappeared on the follow-up HRCT (n=12)	Nodules remained at the same size on the follow-up HRCT (n=66)	p
Mean diameter (mm)*	2.95 ± 1.37	3.80 ± 1.54	0.068
Location in right upper lobe, n (%)	6 (50.00)	15 (22.72)	0.059
Location in right middle lobe, n (%)	0 (0.00)	4 (6.06)	0.050
Location in right lower lobe, n (%)	1 (8.33)	21 (31.81)	0.088
Location in left upper lobe, n (%)	1 (8.33)	12 (18.18)	0.361
Location in left lower lobe, n (%)	4 (33.33)	14 (21.21)	0.282
On HRCT, accompanying linear atelectasis, n (%)	5 (41.66)	18 (27.27)	0.322
On HRCT, accompanying mosaic attenuation pattern, n (%)	6 (50)	1 (1.51)	<0.001
Round shape, n (%)	6 (50)	34 (51,51)	0.99
Oval shape, n (%)	6 (50)	32 (48.48)	0.99
Regular margins, n (%)	10 (83.33)	56 (84.84)	0.99
Irregular margins, n (%)	2 (16.66)	10 (15.15)	0.99
Containing cavitation (n)	0 (0)	1 (1.51)	0.99
Containing calcification, n (%)	0 (0)	12 (18.18)	0.002
Perifissural nodule, n (%)	6 (50)	40 (60.60)	0.536
Parenchymal nodule, n (%)	6 (50)	26 (39.39)	0.536
Solid density, n (%)	9 (75)	65 (98.48)	0.011
Subsolid density, n (%)	3 (25)	1 (1.51)	0.011

the course of the nodules. The results revealed that the size of pulmonary nodules determined at a young age shrank at a higher rate during follow-up. A subsolid density of the nodules and mosaic attenuation pattern accompanying the nodule on HRCT, were determined to be important factors in regards to shrinkage or the disappearance of the nodule during follow-up, whereas calcification content was significant in regards to remaining at the same size.

The mean age of the patients where nodules were seen to have shrunk or disappeared on the follow-up HRCT, was statistically significantly lower than the mean age of those where nodules had remained the same. This is thought to be associated with younger children contracting viral infections more often and that no clinically infectious conditions were determined. As there is a high probability of the disappearance of nodules determined at a young age and radiation exposure increases the risk of the development of cancer[9,10], it can be considered that follow-up tomography should not be applied at a very young age.

According to the guidelines recommended by Westra et al.[8] for the follow-up of incidental nodules determined in children, the probability of malignancy is very low when IPN determined in asymptomatic children have a solid structure with the classic benign features (fat/popcorn calcification, peripheral location, elongated, pleural tag, uniformly calcified). In another study by Westra et al.[4], ground glass opacities were reported to be secondary to infection or inflammation and there was a very low possibility of being an indicator of malignancy in asymptomatic pediatric cases with no known malignancy. In the current study, malignant characteristics were not observed in any of the solid or subsolid nodules during the follow-up period of mean 38.33±16.5 months. The majority of the nodules determined in this study were of solid structure (97.74%). The nodules that had shrunk or disappeared on the follow-up HRCT were determined to be of subsolid character at a statistically significantly higher rate, than the nodules that stayed at the same size. This suggested that in asymptomatic pediatric cases, there was a much higher probability of regression during follow-up of IPN of subsolid character determined in clinical practice, and there was no need for follow-up HRCT.

The frequency of calcification of IPN determined in children has been reported in previous studies to be 10.7-19%.[7,11] Although the nodule calcification of IPN determined in children generally shows a benign character, it can be an indicator of malignant character in cases with malignancy.[12,13] In the current study, calcification was determined in 14.68% of the IPN and none of these nodules were seen to have shrunk or disappeared on the follow-up HRCT, which was consistent with the literature. This finding shows that in the clinical follow-up of calcified nodules, it must be kept in mind that they can remain stable without shrinkage.

There are few studies that have reported the prevalence of pulmonary nodules in children with no malignancy and the frequencies are in a wide range of 33 to 75%.[6,7,11] In the current study, the pulmonary nodule prevalence was determined to be 31.46%, and the mean diameter of the nodules determined was 3.11±1.31mm (range, 1.30-7.10mm), similar to findings in the literature.[6,7,11] In a study by Renne et al.[7] which examined 131 pulmonary nodules determined on tomography and taken because of trauma, nodules <5mm were reported to be determined more often in children with no malignancy. Alves et al.[11] evaluated a total of 225 pulmonary nodules in 99 pediatric patients applied with HRCT because of pectus excavatum and pectus carinatum, and reported at the end of a 2-year clinical follow-up period that there was a very low possibility of nodules ≤6mm being pathological. That no malignant course was seen in our study during follow-up was thought to be due to the mean nodule diameter being below these limits. In a recent review of the literature, Liang et al.[14] stated that a conservative recommendation would be that children with unexpected solid pulmonary nodules smaller than 5 mm in the absence of a malignancy, should not require dedicated follow-up CT scans unless there is an underlying clinical concern requiring further follow-up.

Previous studies have reported that the majority of incidental nodules determined in children are located in the lower lobes[7,11] and no relationship has been determined between nodule diameter and the lobe, as per where it is located.[11] In contrast to the literature, the most common site of localisation in the current study was the right lung upper lobe and the diameter of nodules located in the right lung lower lobe, was determined to be statistically significantly higher than that of nodules in other lobes. This difference in data shows that localisation and nodule diameter cannot be used in the prediction of whether or not the nodule is incidental.

In the current study, there were found to be mean 2.68±2.79 (range, 1-13) nodules per patient, and there were multiple nodules in 48.48% of the patients. The frequency of multiple nodules in IPN in children has been reported to be between 5% and 19%.[6,7] It has been reported that multiple nodules, large nodules and nodules not completely benign in character (non-calcified, non-perifissural) can be seen in children with no malignancy.[6] The relatively higher rate of multiple nodules in the current study compared to literature was thought to be associated with the difference in definitions. While two or more nodules were defined as multiple nodules in the current study, other studies have defined multiple nodules as the presence of four or more nodules. Therefore, there is a need for consensus on the definition of multiple nodules to be able to attain standardisation of the data.

There are very few studies in literature related to the course of the size of IPN determined in children. In a study of 36 pediatric patients, Assefa et al.[15] evaluated the data of 22 patients with nodules >4mm on follow-up tomography taken at 3-12 months; they reported that 54% of the pulmonary nodules remained at the same size, 19% shrank, and 27% disappeared. In the current study, 12 (15.38%) of the 78 nodules were seen to have shrunk (n=2) or disappeared (n=10) compared to the initial images, 66 (84.61%) had remained at the same size, and none had grown. Control HRCT ranged from 6 to 50 months that showed wide variation, so the possibility of disappearance of some pulmonary nodules in the late course is the limitation of our study. To the best of our knowledge, our study included the highest number of IPN determined in children and the longest clinical and radiological follow-up period.

In conclusion, the results of this study demonstrated that IPN of varying dimensions and character are frequently seen in childhood and throughout a 3-year clinical follow-up period, no malignancy developed. Although there is scant data in literature, these findings suggest that the likelihood of IPN determined in healthy children being primary lung cancer or findings of extrathoracic malignancy, is so low as to be negligible[16] and as routine tomography follow-ups can lead to the harmful effects of radiation exposure, the follow-up recommendations for adults are not valid for children. Nodules determined on HRCT, especially at a young age, with a subsolid density, calcification content and the presence of an accompanying mosaic attenuation pattern, could be significantly useful factors in the estimation of size in the follow-up of nodules.

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Ethical approval

The study was approved by the ethics committee of Akdeniz University (decision no:421, dated: 06/12/2020).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: AB, AEB, AB, AK; data collection: AB, AK,AE, SD, TK, DFU; analysis and interpretation of results: AB, AEB; draft manuscript preparation: AB, AEB,AK, AB. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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