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ORIGINAL

The prevalence of single pulmonary nodules as the first sign of COVID-19 pneumonia in CT scans of patients suspected to COVID-19

La prevalencia de nódulos pulmonares únicos como el primer signo de neumonía por COVID-19 en tomografías computarizadas de pacientes sospechosos de COVID-19

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Abstract

Background: The role of diffuse nodular lesions has been cited as a specific indication for COVID-19 progresiion and severity; however the place of single nodules in this role is quite ambiguous. The present study aimed to determine the prevalence of single pulmonary nodules as the first sign of COVID-19 pneumonia in CT scans of patients suspected to disease.
Methods: In this cross-sectional study, all consecutive patients suspected to COVID-19 referred and admitted to Imam Hussein Hospital in Tehran, Iran between February 20, 2020 and April 19, 2020 that assessed by CT scanning were prospectively assessed. All CT scans were interpreted by two independent high-experienced radiologists with high diagnostic agreement.
Results: In total, 5211 individuals suspected to COVID-19 were assessed by CT scanning in our center. Of those, the diagnosis of the disease was definitively confirmed in 1357 cases with the prevalence rate of 26.0%. Among the confirmed cases of the disease with CT positivity, 32 had single pulmonary nodules and therefore, the prevalence rate of single nodules to all initial suspected cases was revealed to be 0.6% and to all subjects with definitive diagnosis of disease with positive CTs to be 2.4%. The characteristics of nodules (size, type, or location) were independent to patients' age and gender.
Conclusion: The appearance of pulmonary single nodules may be predictive for early diagnosis and confirming COVID-19 disease in suspected cases.

Key words: COVID-19, single pulmonary nodules, COVID-19 pneumonia.

Resumen

Antecedentes: El papel de las lesiones nodulares difusas se ha citado como una indicación específica para la progresión y la gravedad de la COVID-19; Sin embargo, el lugar de los nódulos únicos en este papel es bastante ambiguo. El presente estudio tiene por objeto determinar la prevalencia de los nódulos pulmonares nódulos pulmonares únicos como primer signo de neumonía por COVID-19 en las TC de pacientes con sospecha de enfermedad.
Métodos: En este estudio transversal, todos los pacientes consecutivos con sospecha de COVID-19 remitidos e ingresados en el Hospital Imam Hussein Hospital de Teherán, Irán, entre el 20 de febrero de 2020 y el 19 de abril de 2020 fueron evaluados por TC prospectivamente. Todas las tomografías computarizadas fueron interpretadas por dos radiólogos independientes de gran experiencia con alta concordancia diagnóstica.
Resultados: En total, 5211 individuos con sospecha de COVID-19 fueron evaluados mediante TC en nuestro centro. De ellos, el diagnóstico de la enfermedad se confirmó definitivamente en 1357 casos, con una tasa de prevalencia del 26,0%. Entre los casos confirmados de la enfermedad con positividad en la TC, 32 tenían nódulos pulmonares únicos y, por tanto, la tasa de prevalencia de nódulos únicos en todos los casos iniciales sospechosos fue del 0,6% y en todos los sujetos con diagnóstico definitivo de la enfermedad con TAC positivo fue del 2,4%. Las características de los nódulos (tamaño, tipo o localización) fueron independientes de la edad y el sexo de los pacientes.
Conclusiones: La aparición de nódulos únicos pulmonares puede ser predictiva para el diagnóstico precoz y la confirmación de la enfermedad COVID-19 en los casos sospechosos.

Palabras clave: COVID-19, nódulos pulmonares únicos, neumonía por COVID-19.

Introduction

Pneumonia with an unknown cause was initially diagnosed in December 2019 in Wuhan, China and subsequent studies identified the new coronavirus as its related etiology[1-3]. This new virus called the coronavirus type 2 which causes severe acute respiratory syndrome or SARS-CoV-2 and thus, the resulting disease was named COVID-19 by the World Health Organization[4]. The virus is the seventh member of the Corona family of RNA viruses with envelope, along with other family viruses such as SARS and MERS. The first cluster of patients affected by the virus was identified among aquatic sellers in the city of Wuhan, and eventually the transfer from person to person was confirmed at the same time[5-7]. With the global spread of the virus, its count was reported as a pandemic in China and then in all countries[8]. Therefore, a large number of articles on clinical and epidemiological evidence were immediately published[9-11].

The diagnosis of COVID-19 disease was first determined by confirmation of coronavirus nucleic acid in the swap sample, sputum or respiratory secretions, or PCR on the patient's blood sample. However, the use of diagnostic kits was mostly time consuming. In addition, false negatives were gradually reported. Based on this, imaging tools, especially CT scans, were used to diagnose the severity and stages of the disease and were used with great precision, especially in assessing the severity of pneumonia caused by the virus[12,13]. In recent reports, between 70 and 80 percent of CT findings have been matched with clinical manifestations, and CT has been cited as an important and practical tool in the diagnosis and progression of the disease[14]. Accordingly, various manifestations of CT have been considered with the severity of the progression of the resulting pneumonia disease, and accordingly, five stages of the disease have been defined based on CT findings. In the ultra-early stage, single or multiple ground-glass opacities (GGO) can be seen along with GGO-coated nodules, patchy consolidations, and air-bronchogram signs; in the early stage, multiple GGO, patchy consolidation and increased thickness of the interlobular septum with interstitial edema, alveolar capillary congestion, and exudate fluid are seen; in rapid progression stage, the exacerbation of inflammatory lesions is seen in the form of consolidative opacities with air-bronchogram, which gradually change in size and density; in consolidation stage, their size and density decrease; and finally in the dissipation stage, the lesions may be more limited in number and extent, and only a limited number of consolidative opacities, reticular epithelium, and thickness of the introllobular septum may be observed[15].

However, it is important to note that due to the similar pathogenesis of COVID-19 with other pneumonias from other members of the coronavirus family, it is not possible to diagnose COVID-19 pneumonia solely on the basis of these findings[16,17]. In some recent studies, the role of single nodules, especially in cases with halo sign, has been cited as more specific indications for COVID-19[18,19]. Therefore, what assessed in the present was to determine the prevalence of single pulmonary nodules as the first sign of COVID-19 pneumonia in CT scans of patients with suspected disease.

Materials and methods

In this cross-sectional study, all consecutive patients suspected to COVID-19 referred and admitted to Imam Hussein Hospital in Tehran, Iran between February 20, 2020 and April 19, 2020 that assessed by CT scanning were prospectively assessed. On admission, baseline characteristics including demographic parameters and medical history were collected by interview and clinical manifestations were evaluated on admission by an emergency medicine physician. The results of a series of laboratory tests including the white blood cell count (WBC) (normal range 3.5-9.5×109/L), and lymphocytes (normal range 1.1-3.2×109/L)were recorded. All CT scans were performed by a single spiral CT (Siemens, Germany) and the radiographic images were interpreted by two independent high-experienced radiologists who were completely unaware of the diagnosis and therefore the agreement of the two radiologists was also assessed to obtain valid final diagnoses. The machine and the room were thoroughly disinfected after the examination of each patient. The images were analyzed for the following aspects: **1.** presence of single or multiple of pulmonary nodules; **2.** the type and size of nodules; **3.** how to spread nodules in the lungs; and **4.** the time of onset of pulmonary evidences on scans. The study endpoint was to determine the overall prevalence of single pulmonary nodules in patients with definitive diagnosis of the COVID-19 to all patients' population and also to suspected individuals. We also assessed the characteristics of single pulmonary nodules based on baseline parameters.

For statistical analysis, results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by frequency (percentage) for categorical variables. Continuous variables were compared using t test or Mann-Whitney test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the study groups. Categorical variables were, on the other hand, compared using chi-square test. P values of ≤ 0.05 were considered statistically significant. For the statistical analysis, the statistical software SPSS version 23.0 for windows (IBM, Armonk, New York) was used.

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Results

In the study period (from February 20, 2020 and April 19, 2020), in total, 5211 individuals suspected to COVID-19 were assessed by CT scanning in our center. Of those, the diagnosis of the disease was definitively confirmed in 1357 cases with the prevalence rate of 26.0%. Among the confirmed cases of the disease with CT positivity, 32 had single pulmonary nodules and therefore, the prevalence rate of single nodules to all initial suspected cases was revealed to be 0.6% and to all subjects with definitive diagnosis of disease with positive CTs to be 2.4%.

The characteristics of COVID-19 patients with single nodules in CTs are summarized in **table I**. The average age of patients was 38.09±12.93 years ranged 22 to 72 years and 22 cases (68.8%) were male. Regarding lobes involved, the most common lobes included right lower lobe in 43.8% followed by left lower lobe in 34.4%. The mean size of single nodules was 11.97±7.76mm widely ranged 2.0 to 30.0mm. Most of the nodules were ground-glass type (90.6%) and others were solid. The mean time between the onset of suspicious clinical symptoms and the onset of imaging evidences in CT was 2.28±1.14 days ranged 1.0 to 5.0 days. With respect to laboratory findings, the mean WBC count was 7.83±3.84/mm^3 that higher than 10.000/mm^3 in 4 cases (12.5%). Also, the mean lymphocyte count was 21.95±14.14%, higher than 60% only in one patient (3.1%). Within the follow-up time, the CT images turned to clear in 26 cases (81.2%), while the lesions progressed in residual subjects. Requiring hospitalization due to the worsening of symptoms was reported in 4 patients (12.5%) and ICU admission in one patient (3.1%). Only one case died within the following-up that resulted in overall death rate of 3.1%.

Table I: The patients' characteristics and CT findings in patients with lung single nodules.

Mean age, year	38.09 ± 12.93
Male gender	22 (68.8%)
Involved lung lobes	
RLL	14 (43.8)
LLL	11 (34.4)
RUL	3 (9.4)
LUL	3 (9.4)
RML	1 (3.1)
Mean size of single nodule, mm	11.97 ± 7.76
Type of single nodule	
Ground-glass	29 (90.6)
Solid	3 (9.4)
Mean time between clinical and CT signs, day	2.28 ±1.14
Laboratory parameters	
Mean WBC count, /mm^3	7.83 ± 3.84
Mean lymphocyte count, %	21.95 ± 14.14
Mean HS-CRP	94.66 ± 87.08
Follow-up events	
CT changes	
Cleared	26 (81.2%)
Lesion progressed	6 (18.8%)
Hospitalization	4 (12.5%)
ICU admission	1 (3.1%)
Disease-related death	1 (3.1%)

The characteristics of the single nodules as well as disease outcome in men and women are presented in **table II** indicating no difference across the two genders. We did not reveal any significant association between patients' age and the study parameters of involved lung lobes (p=0.636), size of the nodule (p=0.463), type of nodule (p=0.223), the time between clinical and CT signs (p=0.885), WBC count (p=0.316), lymphocyte count (p=0.399), and HS-CRP level (p=0.814). the mean age in the subgroups with progressed and unchanged CT feature was 44.83±19.82 years and 36.54 ± 10.74 years respectively indicating no difference (p=0.160). Also, the mean age for the hospitalized and outpatient groups was 42.75±20.32 years and 37.43±11.94 years respectively with no statistical difference (p=0.450).

Table II: The CT findings in men and women.

Item	Men	Women	P value
Involved lung lobes			0.958
RLL	10 (45.5)	4 (40.0)	
LLL	7 (31.8)	4 (40.0)	
RUL	2 (9.1)	1 (10.0)	
LUL	2 (9.1)	1 (10.0)	
RML	1 (4.5)	0 90.0)	
Type of nodules			0.164
Ground-glass	21 (95.5)	8 (80.0)	
Solid	1 (4.5)	2 (20.0)	
Size of nodules	12.86 ± 8.66	10.00 ± 5.12	0.342
Time between clinical	2.27 ± 1.24	2.30 ± 0.94	0.951
and CT signs, day			
Mean WBC count, /mm³	8.24 ± 4.36	7.18 ± 3.17	0.650
Mean lymphocyte count, %	24.66 ± 16.70	17.60 ± 8.56	0.404
Mean HS-CRP	106.80 ± 98.28	74.43 ± 78.98	0.648
Lesion progressed	3 (13.6)	3 (30.0)	0.346
Hospitalization	2 (9.1)	2 (20.0)	0.572
ICU admission	1 (4.5)	0 (0.0)	0.999
	0 (0.0)	1 (10.0)	0.313

Discussion

Along with the appearance of ground-glass opacities, patchy consolidations, and air-bronchogram, the presence of multiple nodules with halo signs is a main evidence of definitive diagnosis of COVID-19, however based on our clinical experiences, some patients who were suspected to this infection have been found with the appearance of single pulmonary nodules as the initial manifestation. In other words, early appearing single nodules in lung CT scanning may be diagnostic in pulmonary involvements and thus the predictive for disease progression. In our survey, 2.4% of all positive CT images were appeared as single nodules. It was also found that the pointed nodules were observed in lower lung lobes, the size of nodules widely varied, and most were ground-glass types. Interestingly, some authors obtained similar results to our survey. As shown by Lomoro et al[20], the most common findings in patients' CT were bilateral ground-glass and multi-lobar opacities in 59.5% and patchy consolidations in 35.7%, diffuse fibrosis at 50%, subpleural lines at 35.7%, air-bronchogram sign at 26.2%, and single pulmonary nodules in 2.4%[20]. However most studies suggested diffuse and multiple pulmonary nodules as the prominent imaging sign of COVID-19. As indicated by Meng et al[21], 58 asymptomatic patients with COVID-19 pneumonia were evaluated by CT. At the time of admission, they had no clinical or laboratory symptoms. ground-glass opacities were confirmed in 94.8% of cases, and within the first few days, 27.6% of patients were marked. Other pathological changes in CT were also observed in 17% of patients during hospitalization, including bilateral diffuse nodules. In some other researches, single nodule was not found in CT scan. In a 2020 study by Zhou et al[22], 62 patients with COVID-19 pneumonia were evaluated with CT. Diffuse multiple pulmonary lesions were observed in 83.9% of patients without any evidence of single nodules. In another study by Li et al in 2020[23] on 131 COVID-19 cases, in only one patient, evidence of a single pulmonary nodule was seen as a sign of pneumonia[23]. In a study by Guan et al[24], 53 patients with COVID-19 underwent thin-section CT. Overall, CT in 88.7% of patients showed abnormal lesions. Meanwhile, the involvement of both lungs in 78.7% was reported, however single or multiple nodules were not observed in any of the patients. Based on the literatures, between 3 and 13 percent of patients with COVID-19 can be detected by multifocal solid nodules or halo-marked nodules, but appearance of single nodules is rare[25]. We believe that in most cases, the first nodular manifestations in CT scanning of such patients are as single pulmonary nodules that may gradually progress to diffuse multi-nodular lesions. Therefore, by discovering such singles nodules in suspected patients, the predicting positive cases for coronavirus type-2 infection can be possible, however confirming the predicting role of single pulmonary nodule for early predicting the disease should be reassessed in large patients'population.

Conflict of interest

Authors do not have any conflict of interest to declare.

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