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Clinical and radiological differentiation of COVID-19 pneumonia from non-COVID-19 atypical pneumonia

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Abstract:

BACKGROUND AND AIM: Atypical pneumonia involves viral and some bacterial microorganisms in etiology. As Coronavirus 2019 (COVID-19) is newly identified, the differences between coronavirus and other microorganisms causing atypical pneumonia have not been fully expressed yet. We aimed to make a clinical comparison of cases with COVID-19 and atypical pneumonia.

METHODS: "Non-COVID-19 atypical pneumonia" (non-COVID) group included patients with both radiological and clinical confirmation of atypical pneumonia by radiologists and clinicians. Patients with a positive polymerase chain reaction test formed "COVID-19 pneumonia" (COVID) group. Demographics, radiological, laboratory, and clinical features were recorded retrospectively.

RESULTS: A total of 177 patients (46 non-COVID and 131 COVID) were included. The mean age of the COVID group was significantly lower (p=0.040). Ground-glass density and peripheral involvement were more common in thoracic computed tomography of patients with COVID-19 (p=0.017 and p=0.019). Fever and fatigue in COVID (p<0.001 and p=0.040) and shortness of breath and gastrointestinal complaints in non-COVID group were significantly higher as presenting symptoms (p<0.001 and p=0.031). In biochemical tests, impairment in liver function tests in COVID-19 (p<0.001), impairment in kidney function tests, increased C-reactive protein (CRP) and procalcitonin (PCT) in non-COVID-19 patients were more common (p=0.003, p=0.042, and p=0.023, respectively). Serum PCT, CRP, and lymphocyte levels were significantly lower in cases with COVID-19 (p<0.001, p=0.048, and p=0.016). There was no significant difference in the prognosis of both groups (p=0.556).

CONCLUSIONS: With COVID-19 pandemic, there has been an increase in atypical pneumonia cases in which viral strains play a role. Symptomatic, laboratory, and radiological differences between two groups detected in our study may help in differential diagnosis especially in winter when atypical pneumonia is more common.

Keywords:

Atypical pneumonia, COVID-19, differential diagnosis

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Introduction

Community-acquired pneumonia (CAP), which is one of the most common acute infections, is a common cause of admission to the hospital and mortality. CAP is caused by various infectious pathogens, including viruses, typical bacteria, and atypical pathogens. Atypical pneumonia is caused by atypical organisms that are not detectable on Gram stain and cannot be cultured using standard methods.[1] These atypical pathogens include *Legionella* species, *Chlamydophila*, *Mycoplasma*, and viral microorganisms.

Viruses may cause 13%–50% of pathogen-diagnosed CAP cases as sole pathogens.[2] The most common types of viral pneumonia are those that develop secondary to influenza A and respiratory syncytial virus. These respiratory viruses usually follow seasonal patterns of activity (late autumn and early winter) and are most likely to cause pneumonia during those times.[3]

In late 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2), was identified to be the cause of viral pneumonia cases in Wuhan, China.[3] There has been a large number of cases of Coronavirus disease 2019 (COVID-19) pneumonia since March 2020 in Turkey during the pandemic.

As SARS-CoV-2 is a newly defined microorganism in the community, the differences between COVID-19 pneumonia and other factors causing atypical pneumonia have not been fully expressed yet. In this study, it was aimed to make a radiological and clinical comparison of past atypical pneumonia cases and COVID-19 pneumonia cases.

Materials and Methods

There were two patient groups with pneumonia in the study. The patients with atypical pneumonia (non-COVID-19 atypical pneumonia) formed "non-COVID" group. Atypical pneumonia was diagnosed according to clinical and radiological examination results and the exclusion of alternative causes. A patient with prodromal period presence, extrapulmonary findings, and absence of typical signs of pneumonia (acute and severe start, the fever increasing with the chill trembling, pleuritic pain, purulent sputum, leukocytosis, PNL (polymorphonuclear leukocyte) dominance, signs of consolidation on physical examination, and/or lung lobar involvement on radiogram) was accepted to have atypical pneumonia.[4]

Patients with the term "atypical pneumonia" in the thorax computed tomography (CT) report in the last 2 years were detected from the radiology report archive. Patients found by this research were evaluated if they had clinically/microbiologically confirmation of atypical pneumonia in the hospital application at the time of CT scan. The diagnosis of non-COVID atypical pneumonia was confirmed by negative real-time polymerase chain reaction (RT-PCR) result for COVID-19 and a lack of findings supporting COVID-19 pneumonia in the thorax CT radiology report.

The second group included the patients who were diagnosed with COVID-19 pneumonia in March–April 2020 in our hospital. "COVID" group patients had both a positive PCR assay result and thorax CT report confirming the presence of COVID-19 pneumonia.

Pneumonia findings in thorax CT were evaluated according to the COVID-19 pneumonia imaging classification proposed by the Radiological Society of North America Expert Consensus Statement,[5] and the patients were divided into four categories: typical appearance, indeterminate appearance, atypical appearance, and negative for pneumonia.

Demographic information, symptoms at presentation, radiological findings, laboratory data, and clinical course were recorded retrospectively from the hospital records in these two groups.

Ethics approval

Ethics committee approval for the study was obtained from the local ethics committee of our hospital (Approval date and number: June 18, 2020/IRB #0745), and permission for the study was obtained also from the Ministry of Health of the Republic of Turkey. The requirement for informed consent was waived due to the retrospective design of the study.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences version 15.0 software (SPSS, Inc.; Chicago, IL, USA). Baseline characteristics including demographic data, presence of symptoms, radiological, and laboratory findings were summarized by descriptive statistics. The Chi-squared test and Fisher's exact test were used in the comparison of the frequency

rates of categorical variables between COVID and non-COVID groups. Student's t-test or the Mann-Whitney U test was used to compare the means of these two groups. P<0.05 was considered statistically significant.

Results

A total of 177 patients, 46 with a diagnosis of atypical pneumonia (non-COVID-19) and 131 with a diagnosis of COVID-19, were included in the study. Comorbid diseases, the most common of which are hypertension and diabetes, were found in 54.8% of the cases. The mean age of the patients was 54.22±16.90 years, with 94 men (53.1%) and 83 women (46.9%). Patients in the COVID group (52.68±16.31 years) had significantly lower mean age when compared with the non-COVID group (58.61±17.92 years) (p=0.040).

There were 15 asymptomatic patients in the COVID group. On the other hand, all patients with atypical (non-COVID) pneumonia had at least one symptom at the time of presentation. Fever and fatigue in the COVID (p<0.001 and p=0.040) and shortness of breath and gastrointestinal complaints (such as nausea, vomiting) in the non-COVID groups were significantly higher as presenting symptoms (p<0.001 and p=0.031, respectively). Demographics and presenting symptoms of COVID and non-COVID groups are shown in Table 1.

Radiological findings

Ground-glass opacity (GGO) was the most common radiological finding on thorax CT in patients with COVID-19. It was detected alone in 73.3%, while it was with consolidation and/or crazy paving in 24.4% of COVID-19 patients. Of 46 patients with atypical pneumonia, GGO was recorded in 28 (60.9%). Thorax CT also indicated other types of infiltrations, such as tree-in-bud opacities and multifocal consolidations (39.1%) in the non-COVID group.

Most of the patients in both groups had multifocal, bilateral, and multilobar infiltrations. Lower lobe involvement was more common than upper lobe in COVID and non-COVID groups, but opacities appeared in both upper and lower lobes in most of the patients. However, CT abnormalities in COVID-19 pneumonia more frequently exhibited a peripheral predominance. In the radiological comparison, the presence of ground-glass density and peripheral involvement were found to be significantly higher in the COVID group (p=0.017 and p=0.019). Table 2 reveals

Table 1: Demographics of COVID and non-COVID groups

Demographics	COVID group (n=131)	Non-COVID group (n=46)	p
Gender			
Male	74	20	0.128
Female	57	26	
Mean age (years)	52.68±16.31	58.61±17.92	0.040*
Smoking history			
Yes	72	32	0.104
No	59	14	
Comorbidities			
Present	67	30	0.099
Not present	64	16	
Presenting symptoms	**COVID group (n=116)**	**Non-COVID group (n=46)**	**p**
Fever			
Present	61	6	<0.001*
Not present	55	40	
Cough			
Present	83	26	0.066
Not present	33	20	
Dyspnea			
Present	28	28	<0.001*
Not present	88	18	
Fatigue	39/77	8/38	0.040*
Myalgia	21/95	5/41	0.258
Gastrointestinal symptoms (nausea, vomiting, diarrhea)	4/112	6/40	0.031*

*: Statistically significant. The Chi-squared test and Fisher's exact test: if n<5. Student's t-test was performed for age. COVID-19: Coronavirus disease 2019

Table 2: Radiological CT findings in COVID-19 and non-COVID-19 pneumonia

Parameters	COVID group (n=131)	Non-COVID group (n=46)	p
Ground-glass opacities			
Present	128	28	0.017*
Not present	3	18	
Multifocal infiltrations			
Present	109	43	0.064
Not present	22	3	
Peripheral predominance			
Yes	83	20	0.019*
No	48	26	
Multilobar pneumonia			
Yes	85	35	0.189
No	46	11	
Bilateral infiltrations			
Present	107	37	0.852
Not present	24	9	

*: Statistically significant. The Chi-squared test and Fisher's exact test were performed. COVID-19: Coronavirus disease 2019, CT: Computed tomography

Figure 1: Lung CT image of a 55-year-old non-COVID-19 female patient. Peribronchovascular patchy alveolar infiltrations in the right lower lobe
CT: Computed tomography

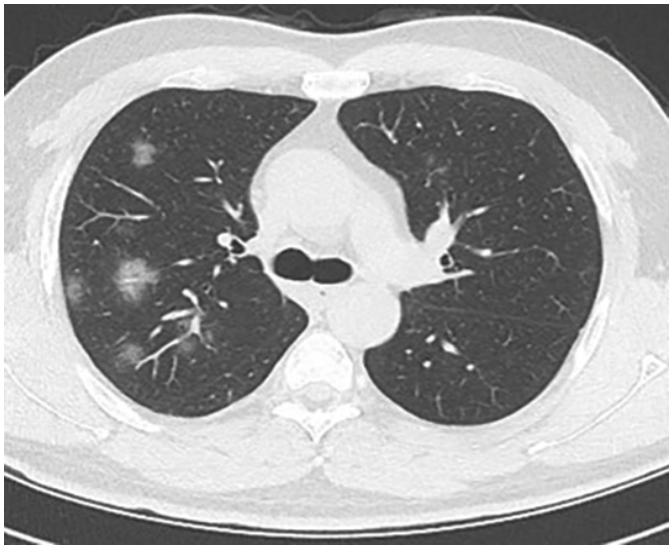

Figure 2: Lung CT image of a 40-year-old COVID-19 male patient. Peripheral predominant patchy ground-glass infiltrations

radiological CT findings in both groups. Figures 1 and 2 are examples of CT images for non-COVID-19 and COVID-19 pneumonia, respectively.

Vital signs and laboratory findings

Among the vital signs, the presence of hypotension was significantly more common in the patient group without COVID-19 (p=0.010). The presence of neutropenia in COVID (p=0.027) and anemia in non-COVID groups (p=0.001) was the pathological finding observed in the hemogram. The mean lymphocyte level in the COVID group (1425.0±682 mL^{-1}) was significantly lower than that in the non-COVID group (2014.6±1497 mL^{-1}, p=0.016).

In biochemical tests, impairment in liver function tests (LFTs) (elevation of ALT or AST) was found to be significantly higher in the COVID group (p<0.001), while impairment in kidney function tests (elevation of creatinine), increased C-reactive protein (CRP), and procalcitonin (PCT) were more common in patients with other atypical pneumonia (p=0.003, p=0.042, and p=0.023). Both serum PCT (0.13±0.03 ng/mL) and CRP (43.3±26.4 mg/L) values in the COVID group were lower than those in the non-COVID group (PCT: 1.1±0.46 ng/mL, CRP: 62.5±41.4 mg/L), which were statistically significant (p<0.001 and p=0.048, respectively).

Seventeen patients in the COVID and 7 patients in the non-COVID groups were being treated in the intensive care unit (p=0.703). There was no significant difference in prognosis in both pneumonia groups: 13 patients with COVID-19 pneumonia (9.9%) and 6 patients with atypical (non-COVID-19) pneumonia (13%) died in the hospital (p=0.556). There were no parameters associated with mortality in both groups. The relationship between vital signs and laboratory findings in COVID and non-COVID groups is shown in Table 3.

Discussion

Although COVID-19 is the first diagnosis that comes to mind in most cases with pneumonia during the pandemic period, other causes of pneumonia should not be ignored in the differential diagnosis. Larici et al.[6] reported that viruses and atypical pathogens formed 13.3% of infectious diseases evaluated in the differential diagnosis with COVID-19. Our results demonstrated 46 patients with atypical pneumonia in the last 2 years. It means that the possibility of atypical pneumonia should be considered in the diagnostic process of the patients with suspected COVID-19 pneumonia.

Fever and fatigue were found to be significantly higher in COVID-19 pneumonia as presenting symptoms according to our results. The most common symptoms at the onset of COVID-19 include fever and fatigue.[7] Fatigue is a nonspecific symptom that can be seen in all types of pneumonia. Fever in COVID-19 has been described as low grade (axillary temperature >37.5°C),

Table 3: Vital signs and laboratory findings in COVID and non-COVID groups

Parameters	COVID group (n=131)	Non-COVID group (n=46)	p
Tachypnea			
Yes	18	3	0.144
No	113	43	
Tachycardia			
Yes	7	4	0.226
No	124	42	
Hypotension			
Yes	17	15	0.010*
No	114	31	
Lower oxygen saturation level			
Yes	18	10	0.302
No	113	36	
Neutropenia			
Present	12	0	0.027*
Not present	119	46	
Lymphopenia			
Present	29	6	0.223
Not present	102	40	
Thrombocytopenia			
Present	35	6	0.076
Not present	96	40	
Anemia			
Present	10	15	<0.001*
Not present	121	29	
Hyponatremia			
Present	42	10	0.272
Not present	89	36	
Impairment in liver function tests			
Present	43	1	<0.001*
Not present	88	45	
Impairment in kidney function tests			
Present	12	12	0.003*
Not present	119	34	
Increased C-reactive protein			
Present	96	40	0.042*
Not present	35	6	
Increased procalcitonin			
Present	33	25	0.023*
Not present	98	21	

*: Statistically significant. The Chi-squared test and Fisher's exact test were performed. COVID-19: Coronavirus disease 2019

intermittent, and of prolonged duration.[8] According to the British Thoracic Society, fever (higher than 38.5°C) is suggestive of bacterial rather than viral pneumonia.[9] It is hard to say that fever is a specific initial symptom to distinguish COVID-19 pneumonia from other atypical pneumonia. However, suspicious contact history with a COVID-19 patient and characteristic features of fever may help in the differential diagnosis.

Shortness of breath and gastrointestinal complaints were significantly higher as presenting symptoms in the non-COVID group in our study. Shortness of breath is a possible symptom of both COVID-19 and non-COVID pneumonia; it may sign the diffuse distribution of the lung. Gastrointestinal involvement is typical for *Mycoplasma* and *Legionella* in the atypical pneumonia group.[10] However, gastrointestinal symptoms such as nausea and diarrhea were relatively uncommon (lower than 5%).[8] Therefore, gastrointestinal symptoms may be helpful in differentiating atypical pneumonia from the one due to COVID-19.

GGO was found to be the most common CT finding in both COVID and non-COVID groups in our study. In addition, the occurrence of GGO was significantly more frequent in patients with COVID-19 (only GGO: 73.3%) when compared with atypical pneumonia (50%). GGO has been one of the main thorax CT findings in COVID-19 pneumonia, especially in the early stage of the disease.[6] It was reported that GGO was more frequent in the COVID pneumonia group, whereas the patchy consolidations were more common in the non-COVID pneumonia group.[11] But according to some studies, GGO was found to be the most frequent radiological pattern in viral pneumonia cases.[12,13] Although ground-glass areas are observed at a higher rate in COVID-19 pneumonia, it is not considered a determining finding in the differential diagnosis of COVID and non-COVID groups because it can also be seen frequently in atypical pneumonia cases.

Thorax CT showed mostly multifocal, bilateral, and multilobar opacities in our study, but these opacities appeared significantly more in the peripheral areas of the lung in the COVID group. The typical imaging features of COVID-19 pneumonia consist of multiple patchy opacities in both lungs with a predominant peripheral distribution according to many studies.[11,14,15] Infiltration commonly begins in the perihilar region and spreads toward the periphery of the lung field in atypical pneumonia.[16] Therefore, the peripheral distribution of the lesions in the early stage may be a radiological difference between COVID-19 and other atypical pneumonia.

A higher rate of neutropenia was detected in the COVID group in our study. While lymphopenia has been reported as a common finding in COVID-19, particularly in severe cases, neutropenia has been rarely reported.[17] The neutrophil count is generally normal in non-zoonotic atypical pneumonia but neutropenia may be seen in

some types of viral pneumonia.[9] As there were only 12 patients with neutropenia in the COVID group (but no patient in the non-COVID group), it does not seem to be an important parameter in distinguishing these two pneumonia groups.

Another finding observed in the complete blood counts was anemia in the non-COVID group. Although COVID-19 patients with anemia were more susceptible to death according to some articles, anemia is not a common blood disorder in COVID-19.[18] Hemoglobin level was found to be higher in patients with PCR positive test results in one study.[19] There were more patients with comorbidities in the non-COVID group, so that can be the reason for a high anemia prevalence in our patients with atypical pneumonia. Our results revealed a significantly lower lymphocyte level in the COVID group. Recent studies revealed a decreased lymphocyte count, especially in the early stage of COVID-19.[20] The lymphocyte count could also be used as an indicator for identifying patients who may develop severe COVID-19.[21] However, there was no association between lymphocyte count and mortality in our study.

In biochemical tests, impairment in LFTs was found to be significantly higher in the COVID patient group. Abnormal transaminase levels have been reported frequently in hospitalized COVID-19 patients. A review of the literature showed that 46% of admitted COVID-19 patients had elevated plasma aspartate aminotransferase (AST) and 35% had elevated alanine aminotransferase (ALT) levels on admission.[22] On the other hand, elevated LFTs may suggest *Mycoplasma pneumoniae* or *Legionella pneumophila* in the atypical pneumonia group.

We found that there were more patients with renal impairment (increased creatinine level) in the non-COVID group. As atypical pneumonia is a syndrome with extrapulmonary manifestations, renal involvement may be a parameter suggesting "atypical" microorganisms.[9]

Among patients with confirmed SARS-CoV-2 infection, a significant number of patients were encountered with acute renal dysfunction.[23] Direct cytopathic effects of SARS-CoV-2 on kidney tissue and cytokine-mediated damage may be possible mechanisms of renal impairment in COVID-19 pneumonia. Our study showed that there was acute renal dysfunction in approximately 35% of non-COVID-19 and 10% of COVID-19 patients, which means attention should be paid to renal dysfunction in the presence of both COVID-19 and atypical pneumonia.

Our results revealed significantly higher CRP levels in non-COVID patients. The use of CRP has not been shown to accurately differentiate between bacterial and viral etiology of pneumonia in previous studies.[24] It is known that CRP levels may be higher in the early stage of COVID-19, generally reflecting the extent of lung lesions and disease severity. García Vázquez et al.[25] demonstrated that patients with atypical pneumonia (especially *Legionella*) had higher CRP levels than those with pneumonia of any other etiology, independently of severity of infection. As CRP is usually high in both types of pneumonia, it may not be a parameter to be used alone for differential diagnosis.

The mean PCT level was significantly higher, and the PCT was found to be above normal limits in more people in the non-COVID group according to our results. PCT value was found to remain within reference ranges in patients with noncomplicated SARS-CoV-2 infection; any increase may reflect bacterial coinfection or the development of a severe form of the disease.[26] As PCT is an increasing biomarker in bacterial infections than in viral infections,[27] it is not surprising that the atypical pneumonia group including some bacterial organisms such as *Legionella* and *Mycoplasma* had a higher rate of positive PCT results. Therefore, this has led to PCT being used as a guide to distinguish between atypical and COVID-19 pneumonia.

The mean age of non-COVID patients was found statistically higher than the one of COVID-19 pneumonia patients. Atypical pneumonia can be seen more commonly in younger patients. In fact, one of the criteria for atypical pneumonia in the Japanese Respiratory Society guidelines is to be younger than 60 years of age.[28] COVID-19 pneumonia is also a common condition in young people. According to an Italian study, the mean age of non-COVID-19 patients was found to be higher than that of COVID-19 patients,[29] which is compatible with our study data.

There was no significant difference in the prognosis of both pneumonia groups in our study. There has been low morbidity and mortality in the majority of patients with atypical pneumonia, and death is usually associated with secondary infection and underlying comorbid disease.[30] There are only a few studies comparing the mortality in COVID-19 and non-COVID-19 patients. Di Mitri et al.[29] demonstrated that the non-COVID-19 pneumonia group

showed a higher, but not statistically significant hospital mortality rate, which is similar to our study results.

There were a few limitations in this study. First, the number of patients with atypical pneumonia was not as high as the ones with COVID-19. This is due to the low frequency of atypical pneumonia cases in the community. Second, there were only a few patients with confirmation of atypical pneumonia by nucleic acid-based molecular techniques. Most of the patients with atypical pneumonia had the diagnosis by clinical, nonspecific laboratory and radiological findings, and the exclusion of alternative causes. Although the diagnosis of patients in the COVID group was confirmed by RT-PCR of nasopharyngeal or oropharyngeal swabs, a single PCR negativity in the COVID (–) group may not confirm the diagnosis of non-COVID atypical pneumonia. There may be false-negative results. Confirmation by repeat PCR was not performed, which can be considered another limitation.

Conclusion

With the COVID-19 pandemic, there has been an increase in cases of atypical pneumonia in which viral strains play a role. It is thought that the symptomatic, laboratory, and radiological differences between COVID-19 pneumonia and non-COVID-19 atypical pneumonia detected in our study may help in differential diagnosis especially in winter when other atypical pneumonia factors are also observed frequently.

Conflicts of interest
There are no conflicts of interest.

Ethics Committee Approval
The study was approved by the İzmir Katip Çelebi University Non-interventional Clinical Research Ethics Committee (No: 745, Date: 18/06/2020).

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Authorship Contributions
Concept – O.T.; Design – O.T.; Supervision – O.T.; Funding – O.T.; Materials – O.T.; Data collection &/or processing – O.T.; Analysis and/or interpretation – O.T., Ş.K., A.H.Ç., B.S.; Literature search – O.T.; Writing – O.T.; Critical review – O.T.

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