

# COVID-19 pneumonia with ARDS and secondary haemophagocytic lymphohistiocytosis: a case report

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## ABSTRACT

Although most people with COVID-19 have mild to moderate symptoms; some people may experience worsened symptoms, such as pneumonia, acute respiratory distress syndrome (ARDS) and respiratory failure. Here we reported a case of COVID-19 pneumonia with ARDS and secondary haemophagocytic lymphohistiocytosis (sHLH). A 44-year-old man presented to the emergency department with a history of cough, fever, sore throat, and muscle ache. The patient transferred to Chest Diseases Department, with a diagnosis of COVID-19 pneumonia. Oseltamivir, hydroxychloroquine, azithromycin, low molecular weight heparin (LMWH) and favipravir added to the treatment. Tocilizumab started after endotracheal intubation. In general, we saw improvement in respiratory values and vital signs. Administration of LMWH to the patient may have prevented the development of coagulopathy. In conclusion, using HFO system and using low tidal volume according to ARDS net protocol, using optimal PEEP/FiO<sub>2</sub> ratio, paying attention to keeping driver pressures low may be beneficial for the clinical improvement of the disease.

**Keywords:** COVID-19, respiratory failure, pneumonia, ARDS, tocilizumab

COVID-19 is the infectious disease caused by the most recently discovered coronavirus. This new virus and disease were unknown before the outbreak began in Wuhan, China, in December 2019. COVID-19 is now a pandemic affecting many countries globally. The most common symptoms of COVID-19 are fever, dry cough, and tiredness. Some people become infected but only have very mild symptoms. Most people (about 80%) recover from the disease without needing hospital treatment. Around 1 out of every 5 people who gets COVID-19 becomes seriously ill and develops difficulty breathing [1].

## CASE PRESENTATION

A 44-year-old man presented to the emergency de-

partment with a history of cough, fever, sore throat, and muscle ache. He had no history of use medications, smoking and alcohol. On physical examination, no abnormalities were found. Clinical examination revealed a temperature of 38°C, a pulse rate of 112 beats per minute, a blood pressure of 120/80 mm Hg. He had rare inspiratory rales in the basal lungs. No feature was detected in other system examinations. Laboratory results were as follows: white blood count count (WBC) of 6.8 L×10<sup>3</sup>/uL (normal 5.2-12.4 L×10<sup>3</sup>/uL), a hemoglobin (Hgb) of 13.8 g/dL (normal: 12-18 g/dL) and a platelet count of 240×10<sup>3</sup>/uL (normal: 130-400×10<sup>3</sup>/uL), C-reactive protein of 19.4 mg/dL (normal: 0.5-0.9 mg/dl), ferritin 518 (normal 12-300 ng/mL), D-dimer of 631µg/L, INR of 0.96 (normal: 0.8 to 1.1) and procalcitonin of < 0.12 ng/ml (normal: 0.00-0.05 ng/ml).

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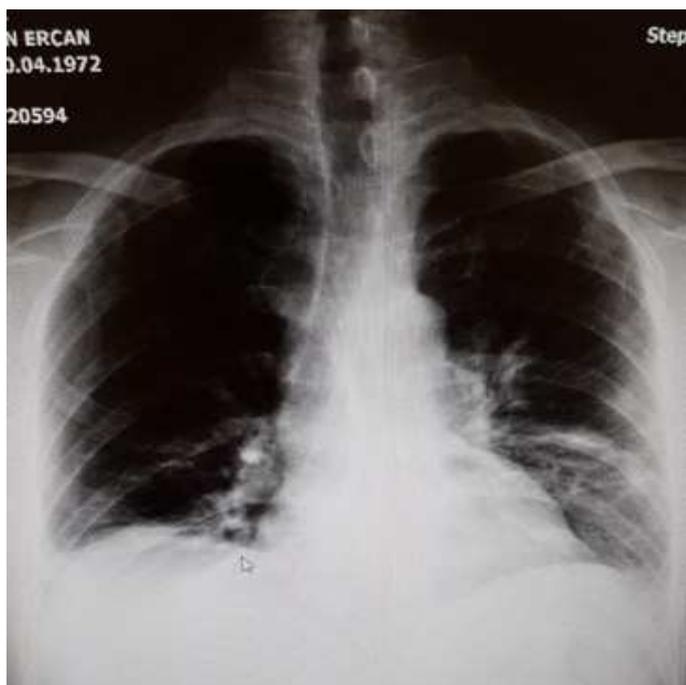
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There was more peripheral density increase in the left lung lower zone on chest radiograph (Fig. 1). There were multiple ground-glass areas in the thorax CT, mostly in both lower lobes and peripheral regions (Fig. 2). The patient transferred to Chest Diseases Department, with a diagnosis of COVID-19 pneumonia. Hydroxychloroquine 2×400 mg (bolus), azithromycin 1×500 (bolus), influenza pneumonia, oseltamivir 2×75 mg and LMWH treatment at prophylactic dose were administered to the patient. The PCR sample taken from the patient twice; although the first was negative, the second test was evaluated as positive. On the 5th day of hospitalization, the general condition deteriorated and the patient's SpO<sub>2</sub> decreased to 83% despite 3 L/minute oxygen inhalation by face mask. The leukocyte, platelet, ferritin, D-dimer, CRP and INR values were increased, and the lymphocyte and hemoglobin values were decreased (Table 1). The patient's control chest x-ray showed an increase in heterogeneous density in both middle and lower zones of the lung. We observed worsening in the first radiograph compared to the other (Fig. 3). The patient was taken to the intensive care unit because of the his current findings, and favipravir 2×1600 mg (bolus) and piperacilin-tazobactam 3×4.5 g and levofloxacin 1×750 mg were added to his current treatment. As the patient's oxygen saturation was low, high flow oxygen

therapy (HFO) was started (40 L/ min flow and FIO<sub>2</sub> 100%). On day 10 of hospitalization the patient was intubated and connected to the mechanical ventilator (Table 2) (Fig. 4) (respiratory rate of 42 breaths per minute, oxygen saturation of 80%, increased leukocyte, D-dimer, ferritin, CRP and procalcitonin values, worsening arterial blood gas values and worsening on chest x-ray).

The patient's symptoms were moderately compatible with ARDS (PEEP / FiO<sub>2</sub> = 123). Therefore, MV was applied to the patient with low tidal volume (4-6 ml/kg), low plateau pressure (< 30 cm H<sub>2</sub>O), low drive pressure (< 15 cm H<sub>2</sub>O) and optimal PEEP/FiO<sub>2</sub> values in accordance with the ARDS net protocol. The patient was started to be followed up in VC-SIMV mode with a dose of 0.02-01 mg/kg/h with midazolam (Table 3). As the patient's clinical and laboratory values were compatible with secured hemophagocytic lymphohistiocytosis (sHLH), tosilizumab (400 mg+400 mg) treatment was started in addition to the current treatment. On the 15th day of hospitalization (on the 5th day of intubation) respiratory values (Table 2) and laboratory values (Table 1) of the patient improved. Regression was observed on the chest X-ray of the patient (Fig. 5). Upon improvement in the general condition of the patient, his sedation was reduced and discontinued. The patient was extubated according



**Fig. 1.** Hospitalization Chest X-ray



**Fig. 2. a-**Hospitalization thorax CT.

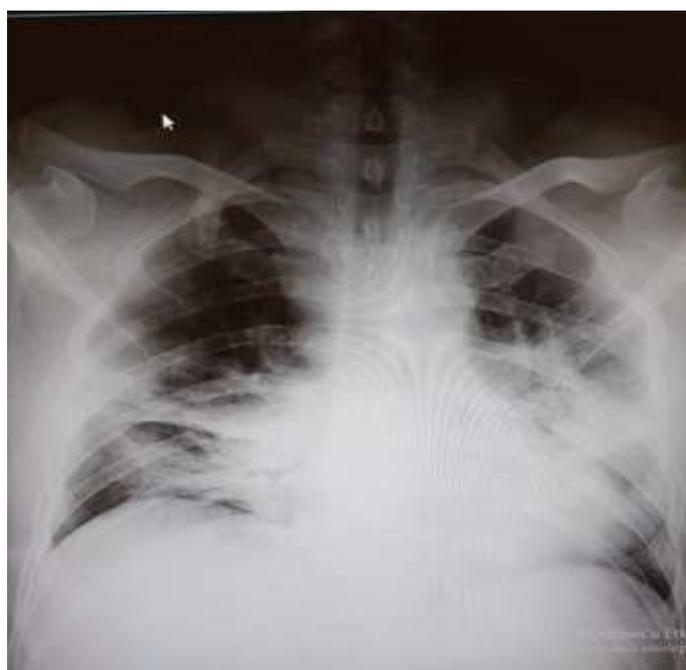
**Table 1. Laboratory results of the patient**

Parameters	Day 1 (hospitalization)	Day 5 (HFO)	Day 10 (IMV)	Day 13 (IMV)	Day 17 (O2)	Day 20 (Room)
Leukocyte* ( $\times 10^3/\mu\text{L}$ )	6800	13000	15800	7000	7200	8100
Lymphocytet# ( $\times 10^3/\mu\text{L}$ )	2	1	0.59	0.71	1.86	2.68
Hb# (g/dL)	13.8	11.8	9.6	8,3	10,3	11.2
Platelets	240000	350000	546000	377000	354000	283000
Ferritin*	518	673	710	612	654	733
Fibrinogen# (mg/dL)	417	398	372	358	276	209
D-dimer* ( $\mu\text{g/L}$ )	631	1090	6390	2430	1867	443
Troponin (ng/L)	< 10	< 10	< 10	< 10	< 10	< 10
INR*	0.96	1.12	1.7	1,8	1.4	0.99
CRP* (mg/L)	19.4	144	171	25	12	< 3
Procalcitonin* (ng/ml)	< 0.12	0.8	1.3	0.32	< 0.12	< 0.12
ALT (u/L)	26	58	46	82	105	129
AST (u/L)	30	33	44	58	83	55
CK (u/L)	134	128	136	140	142	143
LDH u/L	278	329	341	422	310	258
Triglyceride (mg/dL)	256	260	302	384	414	551

The parameters marked \* showed a positive correlation with the progression of the disease, and a positive correlation with the # marked parameter.



**Fig. 2. b-Hospitalization thorax CT.**



**Fig. 3. Intensive care hospitalized chest X-ray (Day 5 of hospitalization).**

to the weaning protocol on the 17th day of hospitalization and 7 days after intubation. The patient was transferred to the chest service. Patients' laboratory values (Table 1) and chest x-ray result found normal (Fig. 6). The patient was discharged with a prophylactic dose of LMWH.

**DISCUSSION**

The vast majority of COVID-19 patients presented with lymphocytopenia (83.2%), whereas 36.2% had thrombocytopenia, and 33.7% showed leukopenia, increased values of CRP (75-93% of cases), LDH (2-92% of cases), ESR (up to 85% of cases) and D-dimer

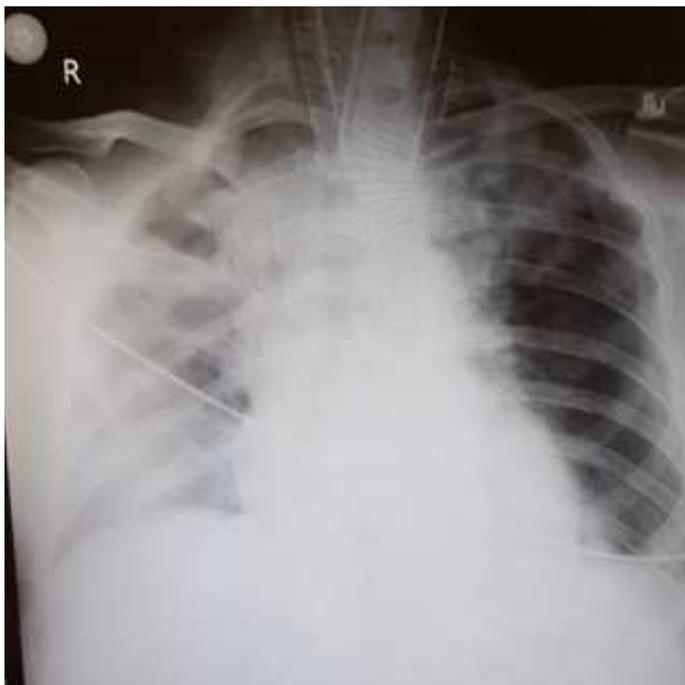
**Table 2. Respiratory values of the patient**

Parameters	Day 1 (hospitalization)	Day 5 (HFO)	Day 10 (IMV)	Day 13 (IMV)	Day 17 (O2)	Day 20 (Room)
Respiratory rate (Lt / min)	18	28	42	20	19	16
PH		7.49	7.37	7.48	7.46	
PCO2 (mmHg)		30	60.2	38	39	
PO2 (mmHg)		96	74	63,8	67	
HCO3 (mEq/L)		25	31	29	28	
O2 sat (%)	92	97	80	91	95	97
Lactate (mmol/L)		1.4	2.1	1.2	1.1	
PaO2/FiO2		118	123	116	167	320
FiO2 (%)		100	60	55	40	Room

**Table 3. Monitored values in patient's ventilator follow-up**

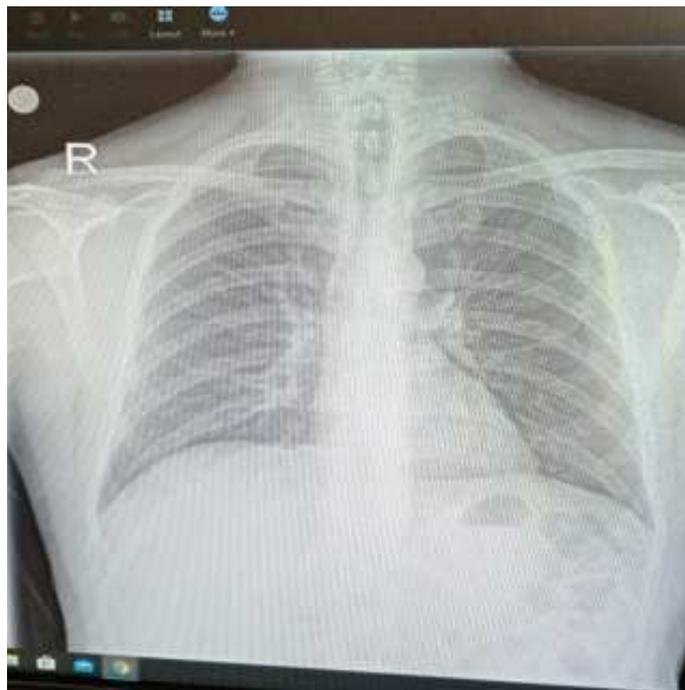
	Day 10 (IMV)	Day 13 (IMV)	Day 17 (O2)
MODE	VC-SIMV	VC-SIMV	VC-SIMV
FiO2	60	55	40
PaO2/FiO2	123	116	167
VT	400	400	400
T isn	1.5	1.5	1.5
PEEP (cmH20)	15	12	5
Support Pressure (cmH20)	20	18	10
Insp, flow (L/min)	45	50	45
MVE (L/min)	12.3	8.9	7.3
VTE (ml)	420	370	372
RR	18	18	18
TOTAL RR	22	20	19
Plateau Pressure (cmH20)	27	24	16
Drive Pressure (cmH20)	12	12	11
Resistance	16.4	10	8.4
Dynamic Compliance (mL/cmH2O)	70	94	103

VT = tidal volume, Ti = inspiration time, PEEP = positive end expiratory pressure, MVE = minute ventilation, VTE = vital capacity RR = number of breaths



**Fig. 5.** Chest x-ray (transferred from the intensive care unit to the service-Day 17 of hospitalization).

(36-43% of cases), as well as low concentrations of serum albumin (50-98% of cases) and hemoglobin (41-50%) [6-8]. Increased white blood cell count, increased neutrophil count, decreased lymphocyte count, decreased albumin, increased LDH, ALT, AST, bilirubin, creatinine, cardiac troponins, D-dimer, prothrombin time, procalcitonin and CRP values. In our case, leukocyte, CRP, procalcitonin, ferritin, INR, triglyceride, D-Dimer values increased as disease progression increased. The lymphocyte count and hemoglobin values of the patient decreased as the disease progressed (Table 1). In our case, AST, ALT, LDH, CK, fibrinogen, platelet values did not correlate with the patient's progression. In addition, the patient's increased triglyceride values did not reach normal values despite the patient's clinical and radiological regression. During hospitalization, a nasopharyngeal swab was taken 2 times with an interval of 48 hours, and a real-time PCR test was performed, but a negative result was found. The first rapid antibody test on the 5th day of hospitalization was negative. The second rapid antibody test was found positive. It is known that viral load is high in nasopharyngeal secretions during the first week. In a study, 63% of nasal swabs and 32% of pharyngeal swabs were detected [9]. However, in real time PCR tests, many factors such as sample sample



**Fig. 6.** Chest X-ray, Discharged (Day 20 of hospitalization)

quality, collection time of clinical samples, and transfer in unfavorable conditions affect the test results. Rapid antibody testing may be negative when performed at an early stage. Positivity rates are maximum 5-14 days after symptoms begin. However, antibody formation may not be the same in every patient. Real-time PCR is the gold standard in the diagnosis of the disease. However, it may show false negativity in the early stage of the disease [10, 11]. It should be borne in mind that in the early stage of the disease, limited frosted glass can not be seen on the chest radiograph. Sensitivity of chest radiography is reported between 30-60% [12]. In this case, chest x-ray showed an increase in heterogeneous density in the left lung lower zone with peripheral location (Fig. 1). However, this image is not specific for COVID-19 pneumonia. Therefore, our patient received a non-contrasted thorax CT. In the thorax CT, multiple frosted glass opacities were noted in all bilateral lung areas, mostly peripheral and in the lower lobe. In the studies conducted, the sensitivity of the real-time PCR test at the early stage of the disease was 71%, and the sensitivity of Torak CT was 98% [10, 11] Consolidation, cobblestone view, air bronchogram, vascular enlargement, bronchial dilatation, halo sign, inverse halo sign, nodules, air bubble (air-bubble), subpleural and parenchy-

mal bands were seen in cases of COVID-19 pneumonia in the literature [13-16]. Progression of consolidation and expansion to the upper lobes, development of pleural or pericardial fluid, development of lymphadenopathy, bronchiectasis, halo sign, cavitation development, and pneumothorax are poor prognostic factors. In our case, radiological progression was observed from the 5th day of hospitalization and the consolidation extended to both apical regions (Fig. 3 and 4). The majority of people infected with COVID-19 are asymptomatic, 14% of patients are hospitalized and 5% of them need intensive care [1]. Currently, there is no vaccine or antiviral treatment for COVID-19. Current treatments are given to prevent the entry of the virus into the cell, reduce its replication and suppress the increased inflammatory response [17]. We applied hydroxychloroquine treatment to the patient since his hospitalization. Because studies have shown that hydroxychloroquine reduces binding of the virus to angiotensin-converting enzyme 2 (ACE2) receptor and reduces the spread of the virus [18]. In addition, it has been shown that chloroquine is effective in preventing the development of the patient's pneumonia, shortening the disease duration and PCR negation [19]. We started Oseltamivir treatment. Because it was determined that 4.3% of COVID-19 patients can have influenza infection at the same time. However, differentiation of influenza pneumonia and COVID-19 pneumonia is not possible radiologically [20]. We started azithromycin as an initial treatment for our patient. Because it is known that macrolides have anti-inflammatory properties such as down regulation and adhesion molecules inhibition, as well as antibacterial properties of proinflammatory cytokines [21]. Therefore, it is thought to be used in COVID-19 pneumonia [22]. Finally, we started a prophylactic dose of LMWH in our patient. Because in COVID-19 infection, there are studies showing that patients with high D-dimer values and severe pictures can be complicated by thrombosis and that such cases are mortal. In autopsy studies, vasculitis, small vessel occlusion, and thrombotic microangiopathy were observed in these patients [23-25]. LMWH treatment reduces the risk of mortality [26]. As a result, we started treatment with oseltamivir, hydroxychloroquine, azithromycin and LMWH. We added favipiravir to the current treatment due to the clinical, laboratory and radiological progress monitoring of the patient. Because favipiravir

is a purine analogue with RNA-dependent RNA polymerase inhibitor (RBRI) and it can be effective in COVID-19 infection just as it is in SARS and MERS since it contains the SARCoV-2 virus RBRI [27]. However, despite the favipiravir treatment given, our patient still showed progression. Chen et al. [28] have been reported that abnormal AST and ALT following treatment with favipiravir. We considered secondary hemophagocytic lymphohistiocytosis (sHLH) due to; worsening of breathing, moderate ARDS, continued radiological progression, decreased lymphocyte and hemoglobin values, increased ferritin, D-dimer, triglyceride level and we started to tosilizumab treatment. In studies conducted in China, secondary hemophagocytic lymphohistiocytosis (sHLH) similar picture was observed in COVID-19 patients [8]. This may be due to the fact that the virus activates CD4 + T lymphocytes after entry into the cell, leading to the formation of T helper (Th), and the activation of inflammatory cytokines by activating the release of IL-6 from monocytes and macrophages through GM-CSF and other inflammatory cytokines [17]. Since our patient had bilateral lung infiltration in the last week and PaO<sub>2</sub>/FiO<sub>2</sub> ratio was 123, we accepted it as medium ARDS according to Berlin definition [29]. Our patient had bilateral lung infiltration in the last week and PaO<sub>2</sub>/FiO<sub>2</sub> ratio was 123, and we accepted our patient as middle ARDS according to Berlin definition [29]. We used a volume-controlled mode for our patient. We used the low tidal volume (6 ml/kg), optimal PEEP/FiO<sub>2</sub> ratio according to the ARDS network table. We tried to comply with the targets of plateau pressure (PPLAT) < 30 cmH<sub>2</sub>O, pH > 7.30, pO<sub>2</sub> > 60 mmHg and spO<sub>2</sub> > 90. Studies show that compliance and shunt fraction may differ from ARDS in patients who develop and intubate with COVID-19 pneumonia. Thorax CT findings of different severity were observed in patients with the same PaO<sub>2</sub>/FiO<sub>2</sub> ratio. Symptom onset and radiological involvement of patients may not be compatible with ARDS in all cases. Therefore, it may be beneficial to continue patients with HFO as much as possible without intubation. Gattinoni et al. [30, 31] (Explained hypoxia in 3 different mechanisms in patients with COVID-19 pneumonia.) These are dysregulation in pulmonary perfusion, microthrombus in lung parenchyma, non-cardiogenic pulmonary edema. For this reason, they divided the patients into two groups, H and L fen-

type. The main problem in the L phenotype is perfusion dysregulation and microthrombus. Therefore, patients with this phenotype do not respond to high PEEP, recruitment therapy and pron position. In patients with H phenotype, elastance was high and compliance was low. Therefore, high PEEP can respond to recruitment therapy and pron position. Patients can switch from the L phenotype to the H phenotype [30, 31]. Considering the air resistance and dynamic compliance values in our case, it fits the L phenotype. Therefore, high PEEP, recruitment therapy, prone position and neuromuscular blockade were not required.

## CONCLUSION

Approximately 14% of confirmed cases developed severe disease, while the grand fatality rate was 4.2%. No pharmaceutical products have yet been shown to be safe and effective for the treatment of COVID-19. Current treatments are provided to prevent the entry of the virus into the cell, reduce replication and suppress the increased inflammatory response. We gave our patient primarily oseltamivir, hydroxychloroquine, azithromycin, LMWH treatment. However, we added favipravir upon progression. Due to the suspicion of cytokine storm, we started early treatment of tocilizumab. In general condition, respiratory values and vital signs of our patient improved. We observed radiological regression in a short time. Administration of LMWH to the patient may have prevented the development of coagulopathy. Using HFO system and not rushing for intubation, using low tidal volume according to ARDSnet protocol, using optimal PEEP/FiO<sub>2</sub> ratio, paying attention to keeping driver pressures low may be beneficial for the clinical improvement of the disease.

## Authors' Contribution

Study Conception: HÖ, MT, EÜ; Study Design: HÖ, MT, EÜ; Supervision: HÖ, MT, EÜ; Funding: HÖ, MT, EÜ; Materials: HÖ, MT, EÜ; Data Collection and/or Processing: HÖ, MT, EÜ; Statistical Analysis and/or Data Interpretation: HÖ, MT, EÜ; Literature Review: HÖ, MT, EÜ, NAI; Manuscript Preparation: HÖ, MT, EÜ, NAI and Critical Review: HÖ, MT, EÜ, NAI.

## Informed consent

Written informed consent was obtained from the patient for publication of this case and any accompanying images.

## Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

## Ethical approval

This study was approved by the Ethics Committee of Erzincan University.

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