Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

En los hallazgos observados en la TAC de tórax, ambos pacientes presentan hallazgos típicos de neumonía por SARS-CoV-2 objetivándose alteraciones en el parénquima pulmonar con patrón en vidrio deslustrado bilateral (fig. 1), siendo difícil diferenciar el patrón visible en relación con el virus, del que podría ocurrir en relación con la infección por *Aspergillus*.

El interés de esta carta científica es llamar la atención sobre la infección vírica por SARS-CoV-2 y su posible coinfección pulmonar por *Aspergillus*. En los pacientes graves ingresados por neumonía producida por este virus, es importante realizar cultivos micológicos de muestras respiratorias con el fin de identificar coinfecciones y valorar la existencia de API de forma precoz e iniciar tratamiento. Por otra parte son pacientes que pueden beneficiarse de tratamiento con esteroides sistémicos a dosis elevadas y con inhibidores de la IL-6 (tocilizumab) y por tanto será importante identificar aquellos pacientes con aspergilosis pulmonar para evitar complicaciones derivadas de estos tratamientos. En estos pacientes debe de realizarse un diagnóstico precoz y estrategias de tratamiento y deberían realizarse estudios multicéntricos para definir mejor la incidencia y evolución.

Bibliografía

1. Gangneux JP, Bougnoux ME, Dannaoui E, Cornet M, Zahar JR. Invasive fungal diseases during COVID-19: we should be prepared. J Mycol Med. 2020;6:100971, http://dx.doi.org/10.1016/j.mycmed.2020.100971.
2. Blaize M, Mayaux J, Nabet C, Lampros A, Marcelin AG, Thellier M, et al. Fatal invasive Aspergillosis and Coronavirus disease in an immunocompetent patient. Emerg Infect Dis. 2020;26(7.). Doi: 10.3201/eid2607.201603.
3. Koehler P, Cornely OA, Böttiger BW, Dusse F, Eichenauer DA, Fuchs F, et al. Covid-19 associated pulmonary aspergillosis. Mycoses. 2020;63:528–34.
4. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan China: a single centered, retrospective, observational study. Lancet Respir Med. 2020, dx.doi.org/10.1016/S2213-2600(20)30079-5.
5. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan China: a descriptive study. Lancet. 2020;395:507–13.
6. Schauwvlieghe A, Rijnders BJA, Philips N, Verweij R, Vanderbeke L, van Tienen C, et al. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. Lancet Respir Med. 2018;6:782–92.
7. He F, Deng Y, Li W. Coronavirus disease 2019 (COVID-19): what we know? J Med Virol. 2020:14, http://dx.doi.org/10.1002/jmv.25766.
8. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunologic features in severe and moderate Coronavirus disease 2019. J Clin Invest. 2020:137244, doi: 10.1172/JCI137244.
9. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;piiS2213–2600:30079–85, doi: 10.1016/S2213-2600(20)30079-5.
10. Lescure FX, Bouadma L, Nguyen D, Parisey M, Wicky PH, Behillil S, et al. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. Lancet Infect Dis. 2020;piiS1473–3099, 30200-0. doi: 10.1016/S1473-3099(20)30200-0.
11. Huang L, Zhang N, Huang X, Xiong S, Feng Y, Zhang Y, et al. Invasive pulmonary aspergillosis in patients with influenza infection: A Retrospective study review of the literature. Clin Respir J. 2019;13:202–11.
12. Garcia-Clemente M, Martín-Iglesias L, Enríquez-Rodríguez AI, Iscar-Urrutia M, Madrid-Carbajal C, López-González FJ. Invasive aspergilosis as a complication of influenza virus H3N2 infection. Arch Bronconeumol. 2020;56:406–8.
13. García-Vidal C, Barba P, Arnan M, Moreno A, Ruiz-Camps I, Gudiol C, et al. Invaseve aspergilosis complicating pandemic influenza A (H1N1) infection in severely immunocompromised patients. Clin Infect Dis. 2011;53:e16–9.
14. Bermejo-Martín JF, Martín-Loeches I, Rello J, Antón A, Almansa R, Xu L, et al. Host adaptative immunity deficiency in severe pandemic influenza. Crit Care. 2010;14:R167.
15. Wauters J, Baar I, Meersseman P, Meersseman W, Dams K, de Paep R, et al. Invasive pulmonary aspergillosis is a frequent complication of critically ill H1N1 patients: A retrospective study. Intensive Care Med. 2012;38:1761–8.

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https://doi.org/10.1016/j.arbres.2020.06.028

The Reversed Halo Sign and la COVID-19: Possible Histopathological Mechanisms Related to the Appearance of This Imaging Finding

El signo de halo invertido y la COVID-19: Posibles mecanismos histopatológicos relacionados con la aparición de este hallazgo radiológico

Dear Editor:

COVID-19, the infection caused by the SARS-CoV-2 virus, typically present with fever, cough, dyspnea, and myalgia, and the infection may cause severe pneumonia. Most of the patients with COVID-19 have mild disease symptoms. However, few patients can develop acute respiratory distress syndrome (ARDS) and other complications, including thrombotic phenomena.

The disease presents challenging clinical, pathophysiological, laboratory, and histopathological aspects that have been the subject of research in practically all countries in the world. This complexity of aspects also applies to imaging findings.

High-resolution chest CT is the most effective radiological examination for the evaluation of lung involvement by COVID-19. The predominant CT findings of COVID-19 pneumonia are multifocal, bilateral, peripheral, and basal-predominant ground-glass opacities, often with round and/or oval morphology and/or consolidation. The crazy-paving pattern may also be observed, particularly when the disease progresses. These CT findings are not specific to COVID-19; similar results can be obtained for other infectious and non-infectious diseases. Nonetheless, normal chest CT findings do not exclude this diagnosis.[1–3]

Another tomographycal finding recently related to COVID-19 pneumonia is the reversed halo sign (RHS). This sign is defined as a focal rounded area of ground-glass opacity surrounded by a complete or near-complete ring of consolidation observed on chest computed tomography,[4] has been reported in association with a wide variety of clinical entities, including infectious and noninfectious diseases.[5,6] The presence of the RHS in patients with COVID-19 has been reported,[1,7–10] with a highly variable incidence among published studies. Bai et al.[7] reported that the RHS was present in 5% of 219 patients, whereas the incidence was much lower in other

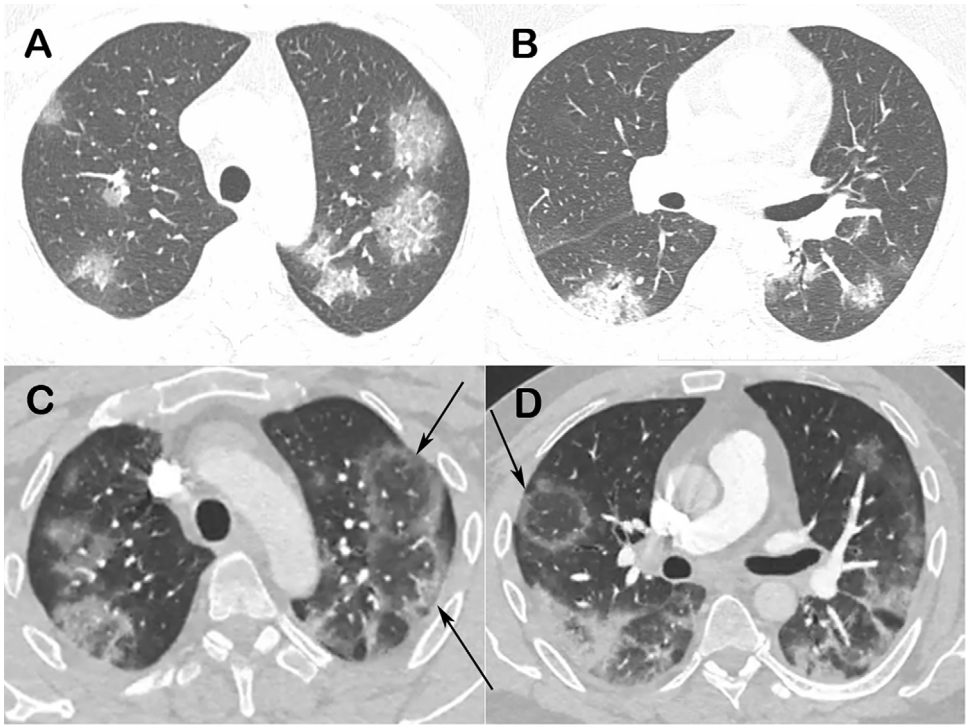

Fig. 1. Chest computed tomography images of a 48-year-old man with confirmed COVID-19 pneumonia. Images obtained at the levels of the upper (A) and lower (B) lobes 2 days after symptom onset show bilateral round and oval ground-glass opacities. Enhanced images (C and D) obtained at the same levels as A and B 3 days later show multiple reversed halo signs (arrows) in both lungs.

casuistic studies; Bernheim et al.[1] observed the RHS in only 1 of 121 patients, and Ai et al.[3] did not report the presence of the sign in any of their 1014 patients. Although some authors have reported the appearance of the RHS in later stages of the disease, during the evolution of the pulmonary infectious process,[1,2] other authors have described its presence in the first days after symptom onset.[8,9]

Recently a 48-year-old man presented to our hospital with a 5-day history of fever, cough and myalgia. He reported having systemic arterial hypertension and type 2 diabetes mellitus.

On admission, the patient was in good general condition; he was tachypneic, his body temperature was 38.2 °C, and cardiac and pulmonary auscultation was normal. Laboratory tests showed a normal blood cell count, erythrocyte sedimentation rate of 96 mm/h (normal = 0–10 mm/h), C-reactive protein level of 19 mg/L (normal = 0.3–10 mg/L), and unremarkable lactate dehydrogenase, creatine phosphokinase, and liver function findings. Blood gas analysis yielded normal findings (O_2 saturation = 96%).

Real-time reverse-transcription polymerase chain reaction of a nasopharyngeal sample tested positive for the SARS-CoV-2, confirming the diagnosis of COVID-19. A chest computed tomography obtained 2 days after symptom onset showed bilateral ground-glass opacities (Fig. 1A and B). A new CT performed 3 days later demonstrated multiple RHS (Fig. 1C and D).

Hydroxychloroquine and symptomatic medication were administered. The patient recovered uneventfully, with the disappearance of symptoms and normalization of laboratory tests. He was discharged after 14 days in an asymptomatic state.

To understand RHS formation, an understanding of the pathogenesis of lung injury is very important. Although few reports on the histopathological characteristics of COVID-19 have emerged to date, early stages of organization (fibroblast proliferation) have been observed to follow initial diffuse alveolar damage.[11,12] Potential courses of this typical response to lung injury are known; if the stimulus for injury is removed and the basement membranes are intact, then the intraluminal fibroblastic tissue is remodeled into the interstitium or removed by the fibrinolytic system, and the normal architecture is re-established. If the stimulus for injury persists and the integrity of the basement membranes has been lost, then the alveoli collapse, their basement membranes fuse, fibroblast activation persists, and the self-reinforcing formation of organizing fibroblastic tissue progresses to fibrosis.[13] In COVID-19 cases, the predomination of fibroblastic tissue organization and development of fibrosis have been observed after the first week of the symptom onset. This process can be characterized as organizing pneumonia, which appears histologically as organizing fibroblastic plugs of spindle-shaped cells in a pale-staining matrix.[13] Also, presence of alveolar exudative inflammation, interstitial inflammation, fibrin exudation and alveolar hemorrhage has been described, and can compose the appearance of ground glass opacities seen in the RHS.[14,15] Consistently, histopathological examination of a transthoracic-needle lung biopsy sample from a patient who died 3 weeks after COVID-19 diagnosis showed diffuse alveolar damage in the organizing phase, with intra-alveolar fibrinous exudates, interstitial fibrosis, intra-alveolar fibrous plugs and organizing fibrin at most foci.[12]

This finding suggests that the disease course of COVID-19 might be similar to those of other viral infections, with early progression to organizing pneumonia and presentation of the RHS.

Conflicts of interests

The authors declare that they have no conflicts of interest to express.

Bibliografía

1. Bernheim A, Mei X, Huang M, Yang Y, Fayad ZA, Zhang N, et al. Chest CT findings in Coronavirus Disease-19 (COVID-19): relationship to duration of infection. Radiology. 2020;20:200463, http://dx.doi.org/10.1148/radiol.2020200463.
2. Simpson S, Kay FU, Abbara S, Bhalla S, Chung JH, Chung M, et al. Radiological society of North America expert consensus statement on reporting chest CT

findings related to COVID-19 endorsed by the society of thoracic radiology, the American College of Radiology, and RSNA. Radiol Cardiothorac Imaging. 2020;2, http://dx.doi.org/10.1148/ryct.2020200152.
3. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology. 2020;26:200642, http://dx.doi.org/10.1148/radiol.2020200642.
4. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner society: glossary of terms for thoracic imaging. Radiology. 2008;246:697–722, http://dx.doi.org/10.1148/radiol.2462070712.
5. Marchiori E, Zanetti G, Escuissato DL, Souza AS Jr, Meirelles GD, Fagundes J, et al. Reversed halo sign: high-resolution CT scan findings in 79 patients. Chest. 2012;141:1260–6, http://dx.doi.org/10.1378/chest.11-1050.
6. Godoy MC, Viswanathan C, Marchiori E, Truong MT, Benveniste MF, Rossi S, et al. The reversed halo sign: update and differential diagnosis. Brit J Radiol. 2012;85:1226–35, http://dx.doi.org/10.1259/bjr/54532316.
7. Bai HX, Hsieh B, Xiong Z, Halsey K, Choi JW, Tran TML, et al. Performance of radiologists in differentiating COVID-19 from viral pneumonia on chest CT. Radiology. 2020;10:200823, http://dx.doi.org/10.1148/radiol.2020200823.
8. Huang P, Liu T, Huang L, Liu H, Lei M, Xu W, et al. Use of chest CT in combination with negative RT-PCR assay for the 2019 novel coronavirus but high clinical suspicion. Radiology. 2020;295:22–3, http://dx.doi.org/10.1148/radiol.2020200330.
9. Xu R, Du M, Li L, Zhen Z, Wang H, Hu X. CT imaging of one extended family cluster of corona virus disease 2019 (COVID-19) including adolescent patients and "silent infection". Quant Imaging Med Surg. 2020;10:800–4, http://dx.doi.org/10.21037/qims.2020.02.13.
10. Wu Y, Xie Y, Wang X, Longitudinal CT. Findings in COVID-19 pneumonia: case presenting organizing pneumonia pattern. Radiol Cardiothorac Imaging. 2020;2:e200031, http://dx.doi.org/10.1148/ryct.2020200031.
11. Dolhnikoff M, Duarte-Neto AN, de Almeida Monteiro RA, Ferraz da Silva LF, Pierre de Oliveira E, Nascimento Saldiva PH, et al. Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19. J Thromb Haemost. 2020, http://dx.doi.org/10.1111/jth.14844.
12. Kligerman SJ, Franks TJ, Galvin JR. Organization and fibrosis as a response to lung injury in diffuse alveolar damage, organizing pneumonia, and acute fibrinous and organizing pneumonia. Radiographics. 2013;33:1951–75, http://dx.doi.org/10.1148/rg.337130057.
13. Zhang H, Zhou P, Wei Y, Yue H, Wang Y, Hu M, et al. Histopathologic changes and SARS-CoV-2 immunostaining in the lung of a patient with COVID-19. Ann Intern Med. 2020, http://dx.doi.org/10.7326/M20-0533.
14. Buja LM, Wolf DA, Zhao B, Akkanti B, McDonald M, Lelenwa L, et al. The emerging spectrum of cardiopulmonary pathology of the coronavirus disease 2019 (COVID-19): report of 3 autopsies from Houston Texas, and review of autopsy findings from other united states cities. Cardiovasc Pathol. 2020;48:107233, http://dx.doi.org/10.1016/j.carpath.2020.107233.
15. Yao XH, Li TY, He ZC, Ping YF, Liu HW, Yu SC, et al. A pathological report of three COVID-19 cases by minimal invasive autopsies. Case Reports. Zhonghua Bing Li Xue Za Zhi. 2020;49:411–7, http://dx.doi.org/10.3760/cma.j.cn112151-20200312-00193.

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https://doi.org/10.1016/j.arbres.2020.06.029

Alteración funcional pulmonar en el seguimiento precoz de pacientes con neumonía por COVID-19

Pulmonary Function in Early Follow-up of patients with COVID-19 Pneumonia

Estimado editor:

La enfermedad causada por la nueva cepa de coronavirus (SARS-CoV-2), COVID-19, provoca un cuadro clínico diferente a lo conocido hasta ahora, con un espectro de enfermedad muy amplio que incluye desde casos con enfermedad leve, neumonía, hasta casos graves con fallo multiorgánico. Más de 2.900.000 pacientes se han recuperado en el mundo hasta ahora, existen muchas dudas sobre si esta recuperación es completa o quedan secuelas, y se ha sugerido la aparición de fibrosis pulmonar. Datos iniciales de estudios radiológicos con TACAR sugieren que pueden tardar meses en resolverse[1]. Apenas existen datos hasta el momento de su repercusión futura en la fisiopatología respiratoria y del papel de las pruebas funcionales en el seguimiento del enfermo.

En nuestro hospital de 850 pacientes ingresados hasta ahora con COVID-19 el 85% ha presentado neumonía sin necesidad de ingreso en UCI, una proporción similar a la publicada en estudios a gran escala en China con un 80%[2], y también fuera de China, con un porcentaje de pacientes que ingresan en el hospital pero no precisan UCI que oscila entre el 76% en Nueva York[3] y el 84% Italia[4]. El seguimiento de estos enfermos con neumonía que no precisa ventilación mecánica invasiva supone una incógnita y un gran volumen de trabajo por su elevado número. Dado que los recursos son limitados es importante una planificación adecuada.

Por ello, con el objetivo de conocer la repercusión funcional de la neumonía por COVID-19 en pacientes que no precisaron ventilación mecánica invasiva ni UCI, organizamos un seguimiento a las 4-6 semanas tras el alta hospitalaria de todos pacientes con SARS-CoV-2 diagnosticado por reacción en cadena de la polimerasa (PCR) ingresados en nuestro servicio con neumonía confirmada en radiología simple. El estudio fue aprobado por el CEIC de Euskadi.

Material y método

Estudio prospectivo. Se incluyeron los primeros 104 pacientes consecutivos con neumonía por COVID-19 que no habían precisado ingreso en UCI, tras negativización de PCR y previo consentimiento. Se excluyeron de este estudio a las gestantes y a los pacientes con enfermedad pulmonar previa y alteración funcional confirmada. Se realizó exploración funcional y se analizaron datos demográficos, resultados clínicos y radiográficos al mes.

La exploración funcional se realizó siguiendo la normativa SEPAR por personal con experiencia con los equipos Masterlab, Jaeger, Würzburg, Alemania. La espirometría forzada se realizó en situación basal. La técnica de medición de la difusión de monóxido de carbono (DLCO) se realizó mediante el método de respiración única. Se utilizaron valores de referencia para población mediterránea y criterios de aceptabilidad en todas las variables funcionales según la normativa española y europea[5,6].

Resultados

De los 104 pacientes estudiados 82 de ellos, el 78,8%, presentaron una DLCO normal > 80% sobre el valor teórico. Solo 7 pacientes presentaron una DLCO < 70%, y solo un paciente presentó afectación moderada con DLCO < 60%. La FVC fue normal en 100 pacientes (96%) y la FEV1 en el 93% de los pacientes. Un 11% presentó FEV1/FVC < 70%.

Al analizar los factores asociados a deterioro de la función pulmonar solo hubo diferencias significativas en la necesidad de oxígeno de alto flujo en gafas nasales, que podría reflejar la gravedad de la neumonía, aunque este dato debe ser interpretado con