

2. Armstrong RA, Kane AD, Cook TM. Outcomes from intensive care in patients with COVID-19: a systematic review and meta-analysis of observational studies. *Anaesthesia*. 2020;75:1340–9.
3. Bassetti M, Giacobbe DR, Vena A, Wolff M. Diagnosis and Treatment of Candidemia in the Intensive Care Unit. *Semin Respir Crit Care Med*. 2019;40:524–39.
4. Epelbaum O, Chasan R. Candidemia in the Intensive Care Unit. *Clin Chest Med*. 2017;38:493–509.
5. Mastrangelo A, Germinario BN, Ferrante M, Frangi C, Li Voti R, Muccini C, et al. Candidemia in COVID-19 patients: incidence and characteristics in a prospective cohort compared to historical non-COVID-19 controls. *Clin Infect Dis*. 2020. <http://dx.doi.org/10.1093/cid/ciaa1594>, ciaa1594.
6. Antinori S, Bonazzetti C, Gubertini G, Capetti A, Pagani C, Morena V, et al. Tocilizumab for cytokine storm syndrome in COVID-19 pneumonia: an increased risk for candidemia? *Autoimmun Rev*. 2020;19:102564. <http://dx.doi.org/10.1016/j.autrev.2020.102564>.
7. Schoot TS, Kerckhoffs APM, Hilbrands LB, van Marum RJ. Immunosuppressive Drugs and COVID-19: A Review. *Front Pharmacol*. 2020;11:1333. <http://dx.doi.org/10.3389/fphar.2020.01333>.
8. Arastehfar A, Carvalho A, Nguyen MH, Hedayat MT, Netea MG, Perlin DS, et al. COVID-19-Associated Candidiasis (CAC): An Underestimated Complication in the Absence of Immunological Predispositions? *J Fungi (Basel)*. 2020;6:211. <http://dx.doi.org/10.3390/jof6040211>.
9. Bishburg E, Okoh A, Nagarakanti SR, Lindner M, Migliore C, Patel P. Fungemia in COVID -19 ICU Patients, a Single Medical Center Experience. *J Med Virol*. 2020. <http://dx.doi.org/10.1002/jmv.26633>.
10. Nowicki JL, Dean NR, Watson DI. A Case Report of Candida albicans Costochondritis after a Complicated Esophagectomy. *Plast Reconstr Surg Glob Open*. 2016;4:e608. <http://dx.doi.org/10.1097/GOX.0000000000000599>.
11. Crawford SJ, Swan CD, Boutlis CS, Reid AB. Candida costochondritis associated with recent intravenous drug use. *IDCases*. 2016;4:59–61.
12. Zapatero J, López Longo J, Monteagudo I, Carreño L. Costal chondritis in heroin addicts: a comparative study with postsurgical chondritis. *Br J Dis Chest*. 1988;82:341–6.
13. Yang SC, Shao PL, Hsueh PR, Lin KH, Huang LM. Successful treatment of Candida tropicalis arthritis, osteomyelitis and costochondritis with caspofungin and fluconazole in a recipient of bone marrow transplantation. *Acta Paediatr*. 2006;95:629–30.

Luis Gorospe-Sarasúa^{a,*}, José Ignacio Gallego-Rivera^a, Gemma María Muñoz-Molina^b, Rosa Mariela Mirambeaux-Villalona^c, Odile Ajuria-Illarramendi^d, Andrés González-García^e e Ignacio Barbolla-Díaz^e

^a Servicio de Radiodiagnóstico, Hospital Universitario Ramón y Cajal, Madrid, España

^b Servicio de Cirugía Torácica, Hospital Universitario Ramón y Cajal, Madrid, España

^c Servicio de Neumología, Hospital Universitario Ramón y Cajal, Madrid, España

^d Servicio de Medicina Nuclear, Hospital Universitario Ramón y Cajal, Madrid, España

^e Servicio de Medicina Interna, Hospital Universitario Ramón y Cajal, Madrid, España

* Autor para correspondencia.

Correo electrónico: luisgorospe@yahoo.com (L. Gorospe-Sarasúa).

<https://doi.org/10.1016/j.arbres.2020.12.002>

0300-2896/ © 2020 SEPAR. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

Acute Eosinophilic Pneumonia Associated With SARS-CoV-2 Infection



Neumonía eosinofílica aguda asociada con la infección por SARS-CoV-2

Dear Editor,

Acute eosinophilic pneumonia (AEP) is a rare condition characterized by an eosinophil infiltration of pulmonary parenchyma, which leads to an acute respiratory illness. It can be idiopathic or secondary to various agents, including infectious diseases.¹ We describe a case of AEP related to SARS-CoV-2 infection, expressed as a recurrence of respiratory symptoms after initial recovery from Covid-19 pneumonia.

A 61-year-old man without relevant medical history arrived at the emergency room with dyspnea, having started with fever and cough 2 weeks before. He did not smoke and denied other toxic use. A chest x-ray showed bilateral peripheral opacities and a nasal-oropharynx PCR for SARS-CoV-2 was positive. Mild elevation of ferritin, CRP and IL-6 was observed. The patient was admitted to the hospital with the diagnosis of Covid-19 pneumonia and treatment began with hydroxychloroquine, azithromycin and lopinavir/ritonavir (following the current hospital protocol at that moment), plus oxygen therapy at an initial FiO₂ of 28%. Patient's clinical and respiratory condition progressively improved and he was discharged after 5 days.

He came back to the hospital after one week because of recurrence of dyspnea and mild fever. New bilateral consolidations were observed in the chest X-ray, with no major changes in inflammatory parameters compared to previous admission. Slight elevation of neutrophils was observed, with normal eosinophil count (200 cells/ml). The PCR for SARS-CoV-2 at this time was negative. With the suspicion of infectious vs inflammatory complication, ceftriaxone and iv methylprednisolone 60 mg

per day were started, and the patient was readmitted to the hospital.

The CT scan showed bilateral subpleural ground glass opacities with areas of consolidation, with an air bronchogram sign and associated bronchiectasis (Fig. 1a). A bronchoscopy for bronchoalveolar lavage (BAL) and transbronchial biopsy was performed on the fifth day after admission. Bacterial cultures and bacilloscopy of BAL, bronchial aspirate and biopsy were negative. SARS-CoV-2 PCR was positive in bronchial aspirate but negative in BAL. The differential cell count in BAL fluid had 50% macrophages, 30% lymphocytes, and 20% polymorphonuclears (including 5% eosinophils). The biopsy showed a prominent mixed infiltrate in interstitium and alveoli with numerous eosinophils, compatible with partially treated AEP (Fig. 1b).

The patient completed one week of hospitalization, with both clinical and radiological improvement, and he was discharged continuing prednisone at a dose of 30 mg per day. During follow up in outpatient consultation the study was completed with HIV and *Strongyloides stercoralis* serology, as well as ANA and ANCA antibodies, which were all negative. A CT scan was repeated after one month, showing resolution of consolidation areas with persistence of minimum ground glass infiltrates. At this time, complete functional recovery was objectified with a forced vital capacity of 141% with no obstructive spirometric pattern, a carbon monoxide diffusion capacity of 84%, and absence of oxygen desaturation in the six minute walking test.

AEP presents as an acute respiratory illness, whose symptoms appear within days or weeks. Severity can go from mild disease to acute respiratory distress syndrome, with potential progression to death. It can be idiopathic or secondary to inhalational toxics, drugs or infections.¹

Diagnosis is challenging, especially during the current pandemic situation, since the clinical picture might resemble COVID-19 disease.² Diagnosis is based on clinical and laboratory criteria, with a leading role of cytological analysis of BAL fluid, where eosinop-

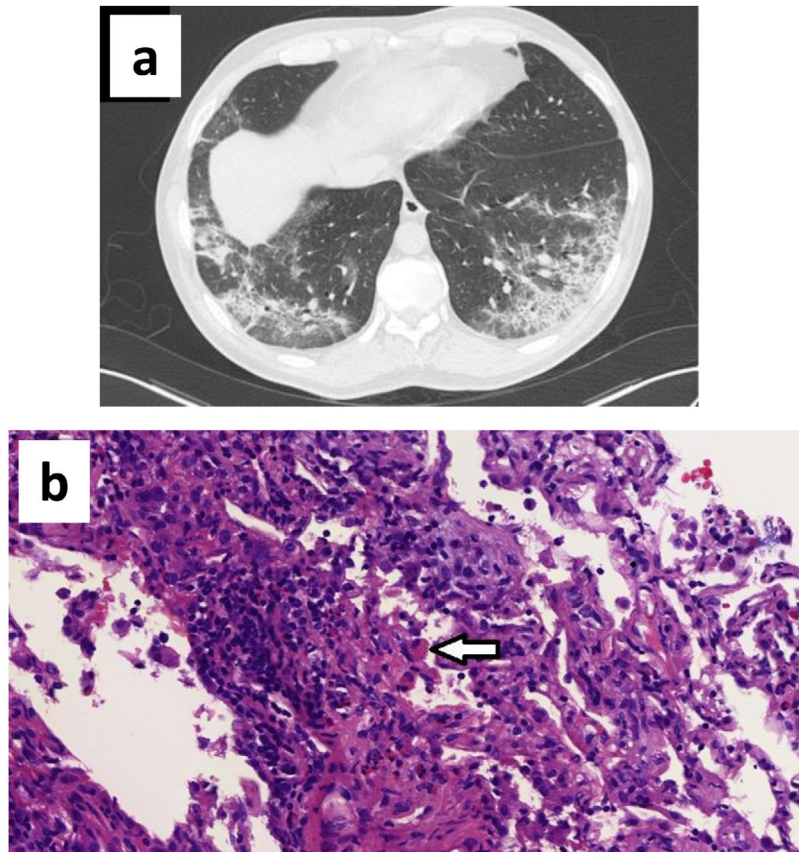


Fig. 1. (a) CT scan showing ground glass opacities with areas of consolidation, air bronchogram and bronchiectasis; (b) Hematoxylin eosin staining (40× magnification) showing prominent lymphoplasmacytic interstitial infiltrate with numerous eosinophils. Alveoli infiltrate with mixed cellularity (lymphocytes, plasma cells, eosinophils, foamy macrophages, fibroblasts). Note one macrophage with phagocytized eosinophil granules (arrow).

hils usually represent more than 25% of the cells. Lung biopsy is not usually required, unless an alternative diagnosis needs to be excluded. Management consists in cessation of exposure to underlying causes when identifiable, and treatment with systemic glucocorticoids in most cases. Clinical and radiological response is usually rapid and complete without any long term sequelae.¹

The diagnosis of AEP in our patient was established through biopsy which confirmed pulmonary eosinophilia. However, as a main limitation in this case report, the BAL fluid differential count only showed 5% of eosinophils. This low percentage could be related to the fact that bronchoscopy was performed 5 days after initiation of glucocorticoids. As seen in other AEP case reports, eosinophils in BAL fluid return to normal as the illness resolves, in some cases within a few days after initiation of treatment so steroids could have influenced this result.^{3,4} Another feature supporting AEP diagnosis in our patient is the rapid clinical and radiological response, considered an important diagnostic criterion.

Regarding possible etiologies of AEP in this case, SARS-CoV-2 would be suggested as a first option. The infection was confirmed by PCR technique and the initial clinical picture was typical. At readmission, recurrence of symptoms with worsening of pulmonary infiltrates would recall the inflammatory phase in Covid-19 disease, but the biopsy results were unusual. Previous histopathological reviews of Covid-19 pneumonia have not reported the presence of eosinophils as a common finding, and the role of pulmonary eosinophilia does not seem to be relevant in the physiopathology.^{5–7} Therefore, we could suggest our case as a rare eosinophilic complication differentiated from typical Covid-19 disease. Although parasites and fungus are the infectious agents most frequently associated with AEP, other viruses such as Influenza A H1N1 have been

reported, so an eventual association with SARS-CoV-2 could also be possible.^{8,9}

Other potential causes of AEP would be related to the treatment that our patient had received. A few cases of drug induced eosinophilic pneumonia have been reported associated to azithromycin and antimalarial drugs, including chloroquine, but none to lopinavir/ritonavir.^{10,11} Against this possibility, there is the fact that patient's clinical condition was improving while on these drugs, whereas symptoms reappeared once the treatment was over.

We finally want to highlight the importance of having a clinical suspicion of AEP when patients affected by Covid-19 pneumonia experience a recurrence or worsening of symptoms, since early glucocorticoid therapy would avoid further complications. In these cases, BAL should be ideally performed before instauration of treatment for proper diagnosis.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declare that they have no conflict of interest.

Bibliografía

- De Giacomi F, Vassallo R, Yi ES, Ryu JH. Acute eosinophilic pneumonia. Causes diagnosis, and management. *Am. J. Respir. Crit. Care Med.* 2018;197:728–36. <http://dx.doi.org/10.1164/rccm.201710-1967CI>.

- Hu QD, Mao N, Huang XC, Chen DG, Zhang Q. Pneumonia combined with acute eosinophilic pneumonia in patients with maintenance hemodialysis. *Blood Purif.* 2020;28:1–5. <http://dx.doi.org/10.1159/000509789>.
- Philit F, Etienne-Mastroianni B, Parrot A, Guérin C, Robert D, Cordier JF. Idiopathic acute eosinophilic pneumonia: a study of 22 patients. *Am. J. Respir. Crit. Care Med.* 2002;166:1235–9. <http://dx.doi.org/10.1164/rccm.2112056>.
- Pope-Harman AL, Davis WB, Allen ED, Christoforidis AJ, Allen JN. Acute eosinophilic pneumonia. A summary of 15 cases and review of the literature. *Medicine (Baltimore).* 1996;75:334–42. <http://dx.doi.org/10.1097/00005792-199611000-00004>.
- Tian S, Hu W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. *J Thorac Oncol.* 2020;15:700–4. <http://dx.doi.org/10.1016/j.jtho.2020.02.010>.
- Barton LM, Duval EJ, Stroberg E, Ghosh S, Mukhopadhyay S. COVID-19 autopsies, Oklahoma, USA. *Am. J. Clin. Pathol.* 2020;153:725–33. <http://dx.doi.org/10.1093/ajcp/aqaa062>.
- Lindsley AW, Schwartz JT, Rothenberg ME. Eosinophil responses during COVID-19 infections and coronavirus vaccination [published online ahead of print, 2020 Apr 25]. *J. Allergy Clin. Immunol.* 2020. <http://dx.doi.org/10.1016/j.jaci.2020.04.021>. S0091-6749(20)30569-8.
- Larrañaga JM, Marcos PJ, Pombo F, Otero-González I. Acute eosinophilic pneumonia as a complication of influenza A (H1N1) pulmonary infection. *Sarcoidosis Vasc. Diffuse Lung Dis.* 2016;33:95–7. Published 2016 Mar 29.
- Jeon EJ, Kim KH, Min KH. Acute eosinophilic pneumonia associated with 2009 influenza A (H1N1). *Thorax.* 2010;65:268–70. <http://dx.doi.org/10.1136/thx.2009.133025>.
- Bartal C, Sagy I, Barski L. Drug-induced eosinophilic pneumonia: a review of 196 case reports. *Medicine (Baltimore).* 2018;97:e9688. <http://dx.doi.org/10.1097/MD.0000000000009688>.

- Coëtmeur D, Guivarch G, Briens E, Lopes C. Pneumopathie éosinophilique aiguë: rôle possible de la chloroquine [Acute eosinophilic pneumonia Possible role of chloroquine]. *Rev. Mal. Respir.* 1998;15:657–60.

Vicente Descalzo^a, Fernando Salvador^{a,*}, Irene Sansano^b, Óscar Persiva^c, Andrés Antón^d, David Clófent^e, Manuel López^e, Benito Almirante^a

^a Department of Infectious Diseases, Vall d'Hebron University Hospital, Barcelona, Spain

^b Department of Pathology, Vall d'Hebron University Hospital, Barcelona, Spain

^c Department of Radiology, Vall d'Hebron University Hospital, Barcelona, Spain

^d Department of Microbiology, Vall d'Hebron University Hospital, Barcelona, Spain

^e Department of Pulmonology, Vall d'Hebron University Hospital, Barcelona, Spain

* Corresponding author.

E-mail address: fmsalvad@vhebron.net (F. Salvador).

<https://doi.org/10.1016/j.arbres.2020.12.009>

0300-2896/© 2020 SEPAR. Published by Elsevier España, S.L.U. All rights reserved.

Toxicidad pulmonar por carmustina: un diagnóstico a considerar a pesar de la época de COVID



Carmustine Pulmonary Toxicity: A Diagnosis to Bear in Mind Even in Times of COVID

Estimado director:

Las complicaciones pulmonares tras un trasplante de progenitores hematopoyéticos (TPH) ocurren hasta en el 37% de pacientes y ensombrecen su pronóstico¹. La mayoría de los estudios se han centrado en los TPH alogénicos, aunque los datos observados sobre las complicaciones pulmonares tras un TPH autólogo reportan una incidencia de más del 25% durante el primer año². Su importancia radica en las altas tasas de mortalidad que conlleva la aparición de afectación pulmonar. Presentamos el caso clínico de un varón de 51 años con clínica respiratoria en el primer año postrasplante.

Se trata de un varón de 51 años diagnosticado de linfoma T periférico estadio IVB, tratado con quimioterapia (CHOEP –ciclofosfamida, doxorubicina, vincristina, etopósido, prednisona– y triple terapia intratecal –metotrexate, citarabina, hidrocortisona–) seguido de TPH autólogo en febrero de 2020, previo acondicionamiento con régimen BEAM (carmustina, etopósido, citarabina, melfalán). En controles posteriores había alcanzado remisión completa. No presentaba antecedentes personales notables salvo haber sido exfumador con un índice paquete-año de 5 y moderada disminución en la capacidad de difusión tras la quimioterapia (DLCO 57). Ingresa en septiembre de 2020 por fiebre (38 °C) y disnea. A la exploración destacaban crepitantes bibasales, con una saturación de oxígeno del 91% a aire ambiente. La radiografía de tórax mostraba infiltrados pulmonares periféricos. Analíticamente presentaba ligera elevación de reactantes de fase aguda (PCR 43 mg/L, LDH 412 U/L) y pancitopenia estable postrasplante. La primera sospecha fue neumonía COVID-19, siendo la PCR nasofaríngea negativa en 2 ocasiones. Asimismo los hemocul-

tivos y los antígenos en orina de *S. pneumoniae* y *L. pneumophila* fueron negativos. A pesar de las pruebas mencionadas, y dado el contexto epidemiológico actual, ingresa en planta de Neumología con sospecha de neumonía COVID-19 como primera posibilidad diagnóstica.

Tras 48 h de ingreso presenta empeoramiento progresivo, con taquipnea y datos de insuficiencia respiratoria grave, con un cociente PaO₂/FiO₂ de 122. La radiografía de tórax de control mostraba una progresión de los infiltrados intersticiales bibasales (fig. 1A). Se solicita TAC torácica que muestra afectación en vidrio deslustrado (fig. 1B) indicativo de neumonía COVID-19. Se decide realizar broncoscopia con lavado broncoalveolar, obteniendo resultados microbiológicos (incluyendo gérmenes oportunistas y SARS-CoV2) negativos con citología normal. Asimismo, se solicita analítica completa incluyendo estudio de autoinmunidad, serología de neumonías atípicas, VIH, carga viral de CMV y subpoblaciones linfocitarias, sin encontrar datos reseñables. El ecocardiograma mostraba buena contractilidad biventricular sin otros hallazgos de interés. En espera de completar estudio, el paciente fue tratado con antibioterapia de amplio espectro así como corticoterapia a dosis de 0,5 mg/kg/24 h. Con el tratamiento administrado, el paciente presentó mejoría clínico-radiológica progresiva.

En el contexto epidemiológico actual, ante cualquier paciente admitido en el hospital con infiltrados pulmonares bilaterales y fiebre la primera sospecha diagnóstica es la neumonía COVID-19. Sin embargo, el diagnóstico diferencial es amplio y complejo. En el caso de nuestro paciente, en el que se descartan razonablemente las causas infecciosas, ampliamos el diferencial a causas no infecciosas en el primer año postrasplante.

La mayor parte de la literatura publicada hasta el momento se ha centrado en el TPH alogénico, sin embargo, hay reportes de incidencias de complicaciones pulmonares no infecciosas de hasta el 10% en pacientes sometidos a TPH autólogo³. Las más frecuentes son edema pulmonar, sea de causa cardiogénica o no cardiogénica, hemorragia alveolar difusa, síndrome de injerto y síndrome de neumonía idiopática. A excepción del síndrome de neumonía idiopática, cuyo diagnóstico es de exclusión, las prue-