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【 CASE REPORT 】

Colitis with Hypereosinophilia following the Second Dose of the BNT162b2 mRNA COVID-19 Vaccine: A Case Report with a Literature Review

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Abstract:
A 61-year-old man presented with a 7-day history of watery diarrhea and loss of appetite after receiving the second dose of the Pfizer-BioNTech COVID-19 vaccine. Laboratory studies showed significant eosinophilia and an elevated IgE level (white cell count, 18.4×10^9/L; eosinophil count, 9.5×10^9/L; and IgE level, 540 IU/L). Symptoms resolved 10 days after vaccination without any steroids or antiallergic medications, and the eosinophil count had also returned to within normal limits 2 months later. Several cases of eosinophilic disorders following receipt of any type of injectable COVID-19 vaccine have been reported, so the etiology should be examined.

Key words: COVID-19, mRNA, vaccine, diarrhea, hypereosinophilia

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Introduction

The Pfizer-BioNTech vaccine, a messenger ribonucleic acid (mRNA) vaccine modified form of the uridine nucleotide, is effective against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is being distributed worldwide. In the two and half years since the emergence of the SARS-CoV-2 virus, more than 11 billion vaccine doses have been administered (1). Although the vaccine is known to cause few serious adverse reactions, symptoms such as a fever, malaise, headache, and chills are known to occur frequently, generally immediately after vaccination. As vaccination progresses around the world, anaphylactic reactions have been reported in a small number of people who have received the mRNA vaccine, and safety studies are becoming more important (2, 3). While fatal anaphylactic reactions are rare, the mechanism underlying such allergic reactions is unclear and needs to be studied in detail.

We herein report a case of persistent watery diarrhea with hypereosinophilia after vaccination with the BNT162b2 mRNA coronavirus disease 2019 (COVID-19) vaccine of likely allergic etiology.

Case Report

A 61-year-old man presented with a 7-day history of watery diarrhea and loss of appetite after receiving the second dose of the Pfizer-BioNTech COVID-19 vaccine. The watery diarrhea, which had started 6 hours after vaccination, was severe, with more than 15 bowel movements in 24 hours but was not accompanied by skin rash, respiratory symptoms, or a fever. His medical history included diabetes mellites, hyperlipidemia, and hyperuricemia. He was taking the following oral medications regularly: mirabegron, sitagliptin, metformin, rosuvastatin, and febuxostat. He had not recently started taking any medications. He had smoked 15 cigarettes for 48 years and had drunk a glass of a Japanese spirit (Chu-Hai) every day. The patient had no history of food or drug allergies, and no recent history of suspicious food intake or exposure to relevant sick contacts. Family members living with the patient who had eaten meals together with

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him did not show any similar symptoms.

Upon an examination, he was tachycardic (pulse 100/min), but the rest of his vital signs were normal. The abdominal examination was unremarkable, and no skin lesions were observed. Laboratory studies showed significant eosinophilia and an elevated IgE level (white blood cell count, 18.4×10^9/L; eosinophil count, 9.5×10^9/L; neutrophil count, 6.0×10^9/L; lymphocytes, 2.0×10^9/L; monocytes, 0.8×10^9, and IgE level, 540 IU/L), even though the white blood cell count had been normal one and half years earlier at a routine checkup. Inflammatory markers and liver function tests were normal. Routine stool cultures were negative for specific bacteria or parasites.

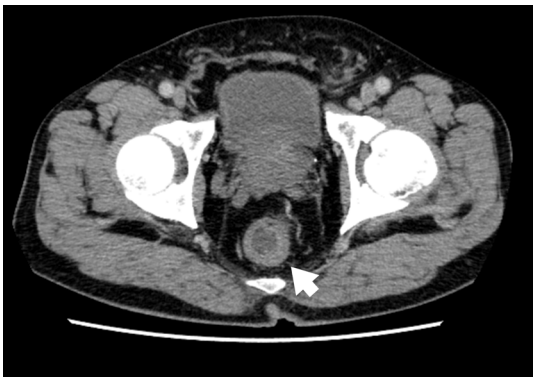

Figure 1. **Enhanced computed tomography revealing the thickened wall of the rectum.**

Enhanced computed tomography showed a mildly thickened wall of the colon, which was prominent in the rectum and sigmoid colon (Fig. 1, white arrow). There were no obvious inflammatory changes or ascites in the small intestine. Sigmoid colonoscopy revealed edematous mucosa throughout, obliterating the visualization of the normally evident submucosal vascular pattern, and scattered superficial longitudinal erosive alterations (Fig. 2a, white arrowheads). In the examined location, these inflammatory mucosal alterations were detected. A rectal biopsy showed lymphohistiocytic infiltrates with 15-20 eosinophils per high-power field (Fig. 2b).

In the absence of other obvious triggers, we diagnosed the patient with enteritis involving eosinophils associated with the COVID-19 vaccine. The symptoms resolved 10 days after vaccination without any steroids or antiallergic medica-

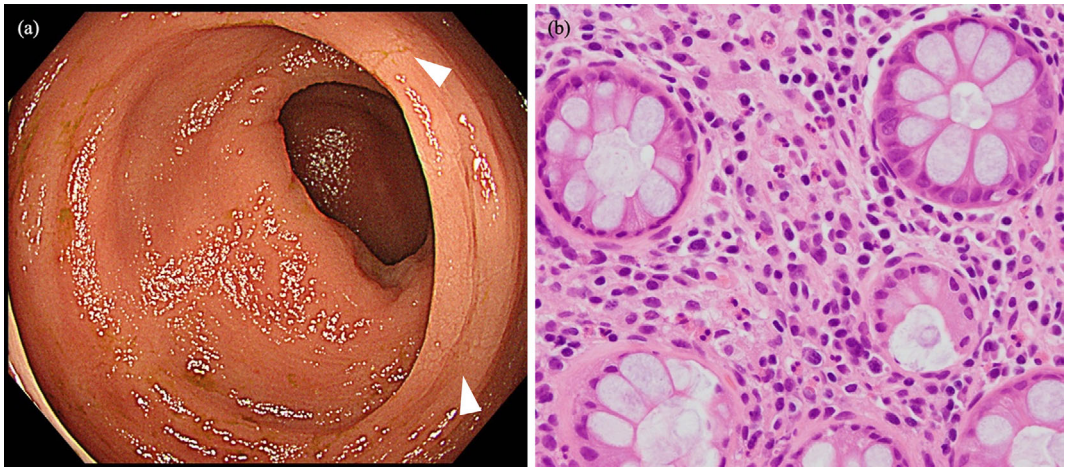

Figure 2. **(a) Endoscopic image of the rectum showing the edematous mucosa, obliterating the visualization of the normally evident submucosal vascular pattern, and scattered superficial longitudinal erosive alterations (white arrowheads). (b) Eosinophilic infiltration of the lamina propria of the colon (Hematoxylin and Eosin staining ×40).**

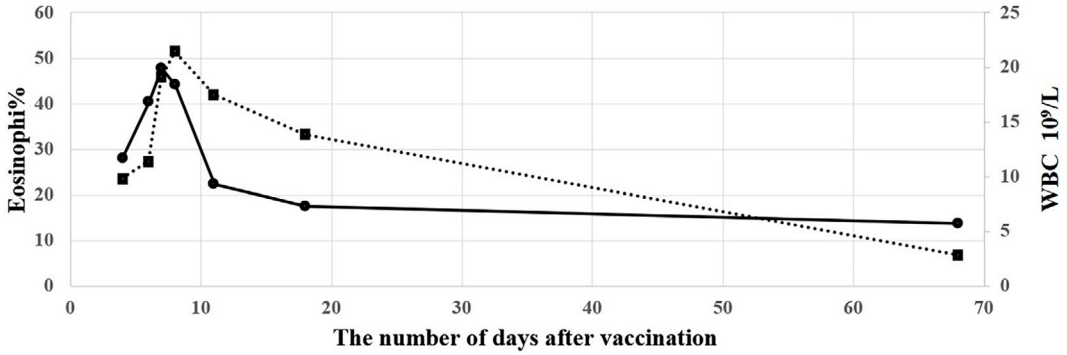

Figure 3. **The patient's clinical course with the WBC count (■) and the rate of eosinophils (%, ●).**

Table. Types of Eosinophilic Disorders following COVID-19 Vaccination in Previous Studies.

Reference	Eosinophilic disorder	Age (years)	Sex	Eosinophilia	Type of vaccine	Treatment	Outcome
(16)	Myocarditis	57	F	Absent	BNT162b2	-‡	Died
(19)	Myocarditis	-	M	Present	BBV152	Steroid	Recovered
(27)	Myocarditis	69	M	Present	BNT162b2	Pulsed steroid	Recovered
(18)	EGPA†	63	M	Present	mRNA-1273	Pulsed steroid, cyclophosphamide	Recovered
(9)	EGPA (relapse)	71	F	Present	BNT162b2	Pulsed steroid	Recovered
(11)	EGPA	79	F	Present	mRNA-1273	Steroid	Recovered
(28)	EGPA (relapse)	Middle age	M	Present	BNT162b2	Pulsed steroid	Recovered
(12)	Panniculitis	35	F	Not described	BBIBP-CorV	Preserved	Recovered
(10)	Cellulitis	71	F	Present	BNT162b2	Oral steroid	Recovered
(20)	Cellulitis	12	M	Absent	BNT162b2	Cetirizine, triamcinolone	Recovered
(14)	Pneumonia	66	M	Present	ChAdOx1 nCoV-19	Intravenous steroid	Recovered
(39)	Pneumonia	38	F	Present	Not described	Steroid	Recovered
		47	F	Present	Not described	Steroid	Recovered
(22)	Pneumonia	37	M	Present	BNT162b2	Not described	Recovered
(15)	Pneumonia	73	F	Present	BNT162b2	Oral steroid	Recovered
(29)	Pneumonia	55	F	Present	ChAdOx1 nCoV-19	Pulsed steroid	Recovered
(24)	Pneumonia (relapse)	88	F	Present	BNT162b2	Pulsed steroid	Recovered
(25)	Asthma	55	F	Present	BNT162b2	Intravenous steroid	Recovered
(8)	Dermatosis	70	M	Present	ChAdOx1 nCoV-19	Not described	Not described
(26)	Pustular folliculitis	38	F	Not described	BNT162b2	Topical steroid	Recovered
(21)	DRESS	45	F	Present	ChAdOx1 nCoV-19	Intravenous steroid	Recovered
(13)	DRESS	68	M	Present	BNT162b2	Oral steroid	Recovered
		31	M	Present	mRNA-1273	Oral steroid	Recovered
		72	M	Present	BNT162b2	Oral steroid	Recovered
(17)	DRESS	47	M	Present	BNT162b2	Intravenous steroid	Recovered
(23)	Subserosal gastroenteritis	34	F	Present	BNT162b2	Steroid	Recovered
Present case	Colitis	61	M	Present	BNT162b2	Preserved	Recovered

F: female, M: male, EGPA: eosinophilic granulomatosis with polyangiitis, DRESS: drug reaction with eosinophilia and systemic symptoms accompanied by organ failure

‡Died before treatment was administered.

tions, and the eosinophil count also returned to the normal range two months later (Fig. 3).

Discussion

Although the causes of eosinophilia are diverse and generally not easy to pinpoint, allergic reactions to drugs and foods are reported causes (4, 5). Most cases are mild and do not require any intensive treatment, but a drug reaction with eosinophilia and systemic symptoms accompanied by organ failure (DRESS) can be fatal (6). In the present case, no other abnormalities, such as a skin rash or fever, were observed, but the course of symptoms and elevated eosinophil levels resembled those of allergic hypereosinophilia (7). A rectal biopsy showed an eosinophilic infiltrate, and the pathological picture resembled that of eosinophilic colitis; however, endoscopic findings with typical of eosinophilic enteritis, such as ulcers and nodular changes, were not observed. Therefore, hypersensitivity to COVID-19 vaccine was considered more likely.

To our knowledge, there have been several reports of eosinophilic disorders associated with COVID-19 vaccines, and these reports has been increasing in frequency because of worldwide immunization efforts (Table) (8-29). According to these reports, a variety of different organs are injured, often with mild symptoms; however, cases have been reported in which COVID-19 vaccination triggered a drug reaction (DRESS) with increased eosinophils and systemic symptoms (13, 17, 21), eosinophilic myocarditis requiring extracorporeal circulatory support (27), or death due to eosinophilic cardiomyopathy after vaccination with BNT162 b2 (16). Eosinophil-related syndrome has been reported with various COVID-19 vaccines, although those cases were most commonly reported after BNT162b2 vaccination. This may be related to immune mechanisms against COVID-19 rather than an immediate response to the vaccine solution or other factors. In a previous study (8-29), symptoms developed several days after vaccination (1-12 days) in all but 2 of the

cases. May et al. reported that eosinophilic pneumonia developed symptomatically seven weeks after the first dose of the ChAdOx1 nCov-19 vaccine (29). In contrast, Miqdadi et al. reported acute respiratory distress appearing five hours after vaccination (14), and this short duration between vaccination and the disease onset was very similar to the present case. Unlike ordinary allergic reactions, and similar to the other reported cases, the symptoms persisted for more than a week in the present case.

There have been several reports of hypereosinophilia with vaccines other than the COVID-19 vaccine, such as eosinophilic pneumonia (30, 31), Wells syndrome (32), and DRESS (33). However, whether or not this has a common etiology with the hypereosinophilia that develops after the COVID-19 vaccine has remained unclear. Aluminum adjuvant in vaccines for pertussis, tetanus, human papillomavirus, pneumococcus, and hepatitis B has also been associated with post-vaccine eosinophilia (34). Immunization with aluminum adjuvant induces Th2-type cell-mediated immune responses, including hypereosinophilia. No aluminum adjuvant is used in mRNA-1273, BNT162b2, or ChAdOx1 nCoV-19 vaccines, but instead it has been noted that the polyethylene glycol (PEG) in these vaccines may cause allergic symptoms (35). However, allergic reactions to PEG are reportedly very rare, and whether or not PEG is associated with the development of hypereosinophilia is unclear.

Although the etiology of mRNA vaccine-induced eosinophilic disorders remains unknown, these cases may have relevance to drug-specific T cells (13), type IV hypersensitivity, or autoimmune conditions (17). Furthermore, the development of eosinophilic disease after vaccination may be similar to the pathogenesis of hypereosinophilia that may accompany the onset of COVID-19. A few studies have reported that symptomatic COVID-19-positive patients sometimes have mild eosinophilia. In one report, laboratory tests revealed that 28.7% of COVID-19-infected patients had mild eosinophilia (eosinophil count 500-1,500/μL) (36). Eosinophilia was associated with lower inflammatory response and better outcomes in these patients than those without eosinophilia. Furthermore, in a case of post-vaccine eosinophilic dermatitis, the rash that developed was reported to be very similar to COVID-19-related papulovesicular varicella-like exanthema (8). Although the detailed role of eosinophils in COVID-19 infections remains unclear (37), a further analysis of eosinophilic disorders after COVID-19 vaccination may help elucidate the mechanism underlying the immune response to COVID-19 involving eosinophils.

Diarrhea symptoms have been reported in 4.61% of cases following COVID-19 vaccination, and in most cases, they do not require special treatment (38). Our case report demonstrated that a previously unrecognized kind of eosinophilia-associated diarrhea may exist among cases of post COVID-19 vaccination diarrhea. Although eosinophilic gastrointestinal disorders often do not require specific treatment if symptoms are not severe, for the reported eosinophil-related disease as summarized in this study, steroids are required in many cases to improve symptoms, and medium-term treatment may be required. Therefore, it is essential to make an early diagnosis of colitis with hypereosinophilia and choose an appropriate treatment.

To our knowledge, this is the first case report of colitis with persistent diarrhea with hypereosinophilia following COVID-19 vaccination, reminding us of that careful medical attention is necessary in the setting of post-COVID-19 vaccine diarrhea symptoms.

The authors state that they have no Conflict of Interest (COI).

References

1. WHO coronavirus (COVID-19) dashboard [Internet]. [cited 2022 Jun 1]. Available from: https://covid19.who.int/.
2. Remmel A. COVID vaccines and safety: what the research says. Nature **590**: 538-540, 2021.
3. Shimabukuro T. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine - United States, December 14-23, 2020. Am J Transplant **21**: 1332-1337, 2021.
4. McCarthy AJ, Sheahan K. Classification of eosinophilic disorders of the small and large intestine. Virchows Arch **472**: 15-28, 2018.
5. Walker MM, Potter M, Talley NJ. Eosinophilic gastroenteritis and other eosinophilic gut diseases distal to the oesophagus. Lancet Gastroenterol Hepatol **3**: 271-280, 2018.
6. Abdelnabi M, Elmssary M, Sekhon J, Benjanuwattra J. Acute onset of fever, eosinophilia, rash, acute kidney injury, and a positive monospot test in a patient on lamotrigine: DRESS syndrome. Lancet **399**: 1902, 2022.
7. Bridges AJ, Marshall JB, Diaz-Arias AA. Acute eosinophilic colitis and hypersensitivity reaction associated with naproxen therapy. Am J Med **89**: 526-527, 1990.
8. Cinotti E, Perrot JL, Bruzziches F, et al. Eosinophilic dermatosis after AstraZeneca COVID-19 vaccination. J Eur Acad Dermatol Venereol **36**: e171-e172, 2022.
9. Costanzo G, Ledda AG, Ghisu A, Vacca M, Firinu D, Del Giacco S. Eosinophilic granulomatosis with polyangiitis relapse after COVID-19 vaccination: a case report. Vaccines **10**: 13, 2021.
10. de Montjoye L, Marot L, Baeck M. Eosinophilic cellulitis after BNT162b2 mRNA COVID-19 vaccine. J Eur Acad Dermatol Venereol **36**: e26-e28, 2022.
11. Ibrahim H, Alkhatib A, Meysami A. Eosinophilic granulomatosis with polyangiitis diagnosed in an elderly female after the second dose of mRNA vaccine against COVID-19. Cureus **14**: e21176, 2022.
12. Kaikati J, Ghanem A, El Bahtimi R, Helou J, Tomb R. Eosinophilic panniculitis: a new side effect of Sinopharm COVID-19 vaccine. J Eur Acad Dermatol Venereol **36**: e337-e339, 2022.
13. Korekawa A, Nakajima K, Fukushi K, Nakano H, Sawamura D. Three cases of drug-induced hypersensitivity syndrome associated with mRNA-based coronavirus disease 2019 vaccines. J Dermatol **49**: 652-655, 2022.
14. Miqdadi A, Herrag M. Acute eosinophilic pneumonia associated with the anti-COVID-19 vaccine AZD1222. Cureus **13**: e18959, 2021.
15. Ozturk AB, Çağlayan B, Kapmaz M, et al. Hypersentivity reactions to COVID-19 vaccines: a case of eosinophilic pneumonia following Sinovac/CoronaVac vaccination. Euro Ann Allergy Clin Immunol. Forthcoming.
16. Ameratunga R, Woon ST, Sheppard MN, et al. First identified case of fatal fulminant necrotizing eosinophilic myocarditis following the initial dose of the Pfizer-BioNTech mRNA COVID-19

vaccine (BNT162b2, Comirnaty): an extremely rare idiosyncratic hypersensitivity reaction. J Clin Immunol **42**: 441-447, 2022.
17. Schroeder JW, Gamba C, Toniato A, et al. A definite case of drug reaction with eosinophilia and systemic symptoms (DRESS) induced by administration of the Pfizer/BioNTech BNT162b2 vaccine for SARS-CoV2. Clin Dermatol **40**: 591-594, 2022.
18. Nappi E, De Santis M, Paoletti G, et al. New onset of eosinophilic granulomatosis with polyangiitis following mRNA-based COVID-19 vaccine. Vaccines **10**: 716, 2022.
19. Tiwari A, Karna G, Chakrabarti SS, Panda PK, Kaur U. Hypereosinophilic syndrome with myocarditis after inactivated SARS-CoV-2 vaccination - a case study. Curr Drug Saf. Forthcoming.
20. Ikediobi O, Eichenfield DZ, Barrio VR. Eosinophilic cellulitis in response to BNT162b2 COVID-19 vaccination. Pediatr Dermatol **39**: 823-824, 2022.
21. O'Connor T, O'Callaghan-Maher M, Ryan P, Gibson G. Drug reaction with eosinophilia and systemic symptoms syndrome following vaccination with the AstraZeneca COVID-19 vaccine. JAAD Case Rep **20**: 14-16, 2022.
22. Barrio Piqueras M, Ezponda A, Felgueroso C, et al. Acute eosinophilic pneumonia following mRNA COVID-19 vaccination: a case report. Arch Bronconeumol **58**: 53-54, 2022.
23. Lee JY, Lee JH. mRNA COVID-19 vaccine-associated subserosal eosinophilic gastroenteritis: a case report. J Korean Med Sci **37**: e 233, 2022.
24. Morikawa MM, Harada M, Kishimoto E, et al. BNT162b2 coronavirus disease-2019 vaccination accelerated rheumatoid arthritis disease activity in chronic eosinophilic pneumonia: a case report. Medicine **101**: e30806, 2022.
25. Ando M, Satonaga Y, Takaki R, et al. Acute asthma exacerbation due to the SARS-CoV-2 vaccine (Pfizer-BioNTech BNT162b2 messenger RNA COVID-19 vaccine [Comirnaty®]). Int J Infect Dis **124**: 187-189, 2022.
26. Rikitake S, Kokubu H, Yamamoto B, Manabe T, Fujimoto N. Eosinophilic pustular folliculitis developing at the site of COVID-19 vaccination. Clin Exp Dermatol **47**: 2022-2024, 2022.
27. Kimura M, Hashimoto T, Noda E, et al. Fulminant necrotizing eosinophilic myocarditis after COVID-19 vaccination survived with mechanical circulatory support. ESC Heart Fail **9**: 2732-2737, 2022.
28. Gill R, Rizvi M, Sadiq MS, Feldman M. Recrudescence of severe polyneuropathy after receiving Pfizer-BioNTech COVID-19 vaccine in a patient with a history of eosinophilic granulomatosis with polyangiitis. BMJ Case Rep **15**: e245749, 2022.
29. May J, Draper A, Aul R. Eosinophilic pneumonia and COVID-19 vaccination. QJM **115**: 251-252, 2022.
30. Pornsuriyasak P, Suwatanapongched T, Klaewsongkram J, Buranapraditkun S, Rotjanapan P. Acute respiratory failure secondary to eosinophilic pneumonia following influenza vaccination in an elderly man with chronic obstructive pulmonary disease. Int J Infect Dis **26**: 14-16, 2014.
31. Kikuchi R, Iwai Y, Watanabe Y, Nakamura H, Aoshiba K. Acute respiratory failure due to eosinophilic pneumonia following pneumococcal vaccination. Hum Vaccin Immunother **15**: 2914-2916, 2019.
32. Safran T, Masckauchan M, Maj J, Green L. Wells syndrome secondary to influenza vaccination: a case report and review of the literature. Hum Vaccin Immunother **14**: 958-960, 2018.
33. Solak B, Dikicier BS, Kara RO, Erdem T. DRESS syndrome potentially induced by allopurinol and triggered by influenza vaccine. BMJ Case Rep **2016**: bcr2016214563, 2016.
34. Terhune TD, Deth RC. Aluminum adjuvant-containing vaccines in the context of the hygiene hypothesis: a risk factor for eosinophilia and allergy in a genetically susceptible subpopulation? Int J Environ Res Public Health **15**: 901, 2018.
35. Barbaud A, Garvey LH, Arcolaci A, et al. Allergies and COVID-19 vaccines: an ENDA/EAACI position paper. Allergy **77**: 2292-2312, 2022.
36. Nair AP, Soliman A, Al Masalamani MA, et al. Clinical outcome of eosinophilia in patients with COVID-19: a controlled study. Acta Biomed **91**: e2020165, 2020.
37. Rodrigo-Muñoz JM, Sastre B, Cañas JA, Gil-Martínez M, Redondo N, Del Pozo V. Eosinophil response against classical and emerging respiratory viruses: COVID-19. J Investig Allergol Clin Immunol **31**: 94-107, 2021.
38. Kadali RAK, Janagama R, Peruru S, Malayala SV. Side effects of BNT162b2 mRNA COVID-19 vaccine: a randomized, cross-sectional study with detailed self-reported symptoms from healthcare workers. Int J Infect Dis **106**: 376-381, 2021.
39. Costa e Silva M, Sá Marques M, João D, Campainha S. Eosinophilic pneumonia associated to SARS-CoV-2 vaccine. Arch Bronconeumol **58**: 51-52, 2022.