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Case Report

Mepolizumab in allergic bronchopulmonary aspergillosis complicated by infection

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ABSTRACT

Allergic bronchopulmonary aspergillosis (ABPA) is an allergic reaction caused by the fungus *Aspergillus*, and it is often treated with steroids or antifungal agents. However, long-term use of these medications can lead to infections and drug interactions. We present the case of a 71-year-old woman with ABPA who was diagnosed with hepatitis B and active hepatitis C, and sputum analysis revealed the presence of bacteria. Oral steroids were initially administered, but the patient was switched to mepolizumab because of numerous infectious complications. The early introduction of mepolizumab is effective in patients with ABPA complicated by infectious diseases.

1. Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity reaction to the fungus *Aspergillus*, characterized by the onset of bronchial asthma and increased levels of eosinophils in the blood [1]. The standard treatment for ABPA typically involves administering systemic steroids and antifungal agents, both of which can elicit many undesirable side effects. Steroids have been known to exacerbate pre-existing infections, whereas antifungal medications can interact with a wide range of other drugs [2–4]. As a result, many patients find it challenging to sustain treatment and often experience relapse. In recent years, the use of biologics to treat ABPA, without the need for systemic administration of steroids or antifungal agents, has been reported. Although there have been several recent reports on the use of mepolizumab in ABPA [4–20], it remains uncertain whether the early introduction of this medication in ABPA complicated by infection is effective in controlling the disease or exacerbating complications. We present a case study of the early introduction of mepolizumab in a patient with ABPA complicated by infection.

2. Case report

An elderly female patient, 71 years of age, presented to our institution with a persistent, wet cough and an overall feeling of malaise that had persisted for several weeks. Her medical history was notable for bronchial asthma, which had not been previously treated, as well as surgical intervention and chemotherapy for rectal cancer and liver metastases. The patient had no history of smoking or known allergies, and her occupation was food processing. She had no known contact with animals. A physical examination revealed wheezing, and there was a history of expectoration of mucus plugs. There was no numbness or weakness in the limbs. Laboratory analysis revealed elevated levels of blood eosinophils (3724/μL) and elevated levels of serum total IgE antibodies (10,528 IU/

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mL). *Aspergillus*-specific IgE antibodies were later found to be present at 44.2 IU/μL. *Aspergillus*-specific IgG antibodies and *Aspergillus* antigens were negative. Imaging studies, including chest radiography and computed tomography (CT) scans revealed infiltrating shadows and frosted shadows in the right upper and left lower lung fields, as well as mucus plugs and central bronchiectasis. The sputum culture was positive for *Aspergillus fumigatus*. Grocott's stain of the sputum mucus plug exhibited findings consistent with filamentous fungi. Bronchoscopy revealed the absence of mucus plugs in the bronchial lumen. Based on these findings, the patient was diagnosed with ABPA (Table 1) [21]. Respiratory function tests revealed mixed ventilatory impairment with vital capacity (VC) of 1.64 L (64.6%), forced expiratory volume in 1 second (FEV1) of 0.67 L (35.8%), forced vital capacity (FVC) of 1.4 L, and FEV1/FVC of 47.8%. The patient's exhaled NO concentration was 63 ppb. Blood tests were negative for hepatitis B surface antigen; positive for hepatitis B core and surface antibodies, with undetectable levels of hepatitis B virus DNA; and positive for hepatitis C virus (HCV) antibody; and showed elevated levels of HCV RNA. Sputum cultures revealed the presence of *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, *Candida albicans*, and *Mycobacterium intracellulare*. The patient was found to have pre-existing hepatitis B infection, complicated by active hepatitis C, and numerous infectious complications. The patient was admitted to the hospital on the second day after presentation, and a bronchoscopy was performed. The patient was started on procaterol inhalation to manage bronchial asthma attacks and regular inhalation of budesonide, glycopyrronium, and formoterol. The patient was given “wait-and-see” treatment for hepatitis B and hepatitis C due to the absence of fever and abnormal blood test results. The patient was started on prednisolone 20 mg (0.5 mg/kg) for ABPA and quickly experienced an improvement in wheezing and coughing. However, due to the potential for complications from infection and potential interactions with other drugs, mepolizumab was introduced. Mepolizumab 100 mg/4 weeks was introduced on day 21 of admission (Fig. 1). Prednisolone was gradually reduced and discontinued completely 4 months later. After discontinuation of prednisolone, the patient had no airway symptoms, re-elevation of eosinophil counts, or worsening of FEV1. Chest radiography and CT scans also showed no deterioration (Figs. 1 and 2, Fig. 3).

3. Discussion

The present case demonstrates the utility of mepolizumab in the management of patients with ABPA who present with concomitant infections. In this case, the administration of mepolizumab significantly reduced the dosage of systemic steroids required, additionally preventing concurrent infections. Furthermore, mepolizumab effectively maintained optimal airway symptoms, blood eosinophil counts, serum anti-IgE antibody levels, CT imaging results, and FEV1 in this patient.

Table 1
The present case met the new diagnostic criteria for ABPA. The present case met the criteria for allergic pulmonary mycosis because 6 criteria were met. In addition, sputum culture was positive for *Aspergillus* and for *Aspergillus*-specific IgE antibodies, leading to the diagnosis of ABPA.

	Diagnostic criteria for ABPA	Present case
1	Current or previous history of asthma or asthmatic symptoms	○
2	Peripheral blood eosinophilia (≥500 cells/mm^3)	○
3	Elevated total serum IgE levels (≥417 IU/mL)	○
4	Immediate cutaneous hypersensitivity or specific IgE for filamentous fungi	○
5	Presence of precipitins or specific IgG for filamentous fungi	
6	Filamentous fungal growth in sputum cultures or bronchial lavage fluid	○
7	Presence of fungal hyphae in bronchial mucus plugs	
8	Central bronchiectasis on CT	
9	Presence of mucus plugs in central bronchi, based on CT/bronchoscopy or mucus plug expectoration history	○
10	High attenuation mucus in the bronchi on CT	

IgE, immunoglobulin E; IgG, immunoglobulin G; CT, computed tomography.

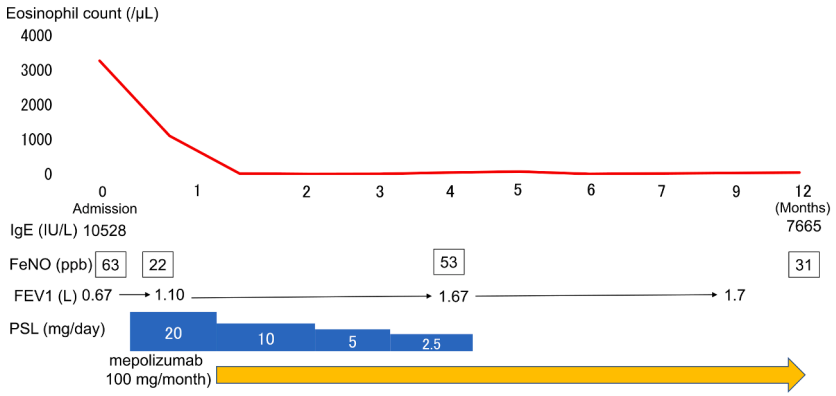

Fig. 1. The clinical course of the present case, including eosinophil count, blood total IgE antibody, FeNO, FEV1, PSL use, and mepolizumab use. After initiation of PSL, eosinophil count, and FeNO decreased and FEV1 increased. After starting the mepolizumab combination, PSL was gradually reduced, but eosinophils remained decreased and FEV1 remained increased. FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; PSL, prednisolone.

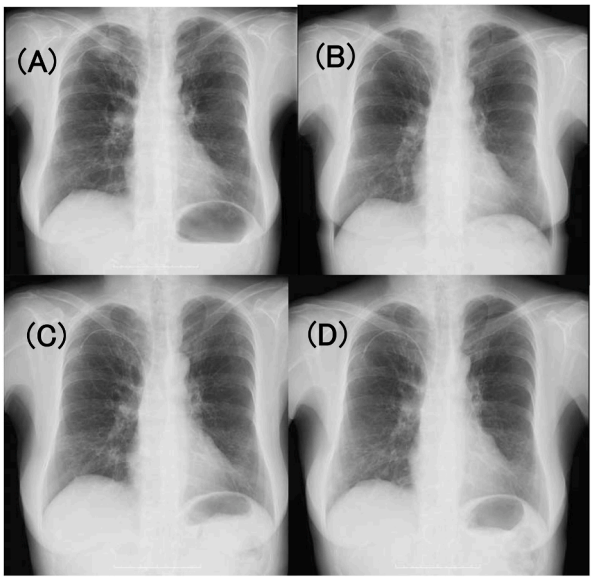

Fig. 2. Chest X-ray images of the patient. (A) At the time of the first presentation to our hospital; (B) 1 month after starting prednisolone; (C) 4 months after starting prednisolone (prednisolone was discontinued); (D) 7 months after starting prednisolone (3 months after stopping prednisolone).

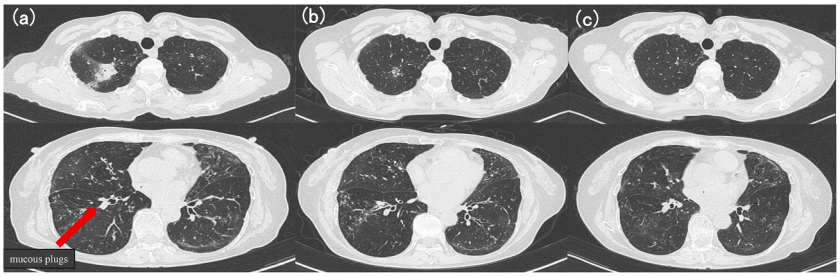

Fig. 3. Computed tomography images of the patient. (a) At the time of the first presentation to our hospital; (b) 3 days after starting prednisolone; (c) 10 months after starting prednisolone (6 months after stopping prednisolone).

ABPA is an allergic disease traditionally treated with systemic steroids. However, patients with ABPA often relapse and require prolonged steroid treatment [22]. In addition to steroids, antifungal agents may be used as a therapeutic option for recurrent cases of ABPA [2]. Systemic steroids elicit many side effects and have been reported to exacerbate coexisting infections with prolonged use [4]. Furthermore, interactions with antifungal agents may render some antimicrobial and antiviral agents ineffective.**3**

In the present case, the patient's disease was complicated by several other infections, including hepatitis B, hepatitis C, non-tuberculous *Mycobacterium* (NTM), and colonization of *Pseudomonas aeruginosa* and MRSA. There is a concern that prolonged steroid use could induce respiratory tract infection and increase the risk of hepatitis B reactivation. Furthermore, the concurrent use of antifungal agents could render other antibacterial and antiviral drugs ineffective because of drug interactions.

In the present case, the severity of bronchial asthma was defined as moderate based on the patient's almost daily nocturnal coughing and shortness of breath on exertion. In general, ABPA is difficult to control with standard therapy because of the long-term and sustained exposure to *Aspergillus*. In addition, leukotriene receptor antagonists cannot be used for the same reasons as antifungal agents. Concurrent use of leukotriene receptor antagonists may also render other antibacterial and antiviral drugs ineffective owing to drug interactions. In general, mepolizumab is used only to control severe asthma. To control our patient's symptoms, we decided to use a biologic; namely, mepolizumab, which is expected to be effective because the main etiology of ABPA involves elevated eosinophil levels.

In recent years, several studies have reported the use of biologics in ABPA, which do not require systemic steroids or antifungal agents [20,22–26]. However, omalizumab, a monoclonal anti-IgE antibody, is not suitable for patients with high serum anti-IgE antibody levels, as in the present case. Several reports have shown that mepolizumab (an anti-IL-5 monoclonal antibody), benralizumab (an anti-IL-5Rα monoclonal antibody), and dupilumab (an anti-IL-4,13 monoclonal antibody) are effective in reducing eosinophilic inflammation associated with ABPA [10,12,14,15]. Dupilumab was not used in our patient because the interval of injections was short, once every 2 weeks, and the pain associated with the injections was judged to be an obstacle to continued treatment. There is no clear distinction between mepolizumab and benralizumab; however, mepolizumab, which has been reported to be used more frequently from a safety perspective, was selected in this case. Mepolizumab is a potent suppressor of eosinophilic inflammation and has

Table 2
Reported cases of ABPA complicated by infection which were treated with mepolizumab.

Age (yr)	Sex	Infectious diseases	Other treatments	Steroid dose	FEV1 (L)	Image change	Time from initial visit to start of administration	Authors (report year) [Ref]
43	F	Cystic fibrosis, NTM	ICS/LABA, OCS, ITCZ, omalizumab	PSL 50mg⇨off	Stable	Stable	11 years	Boyle et al. (2021) [6]
60	F	NTM	LTRA, OCS, ITCZ	PSL 10mg⇨5mg	1.43⇨1.49	Improved	5 years	Tsubouchi et al. (2019) [4]
50	M	MRSA arthritis, CKD	OCS, ITCZ	PSL 30mg⇨off	NA	Improved	40 days	Yanagihara et al. (2020) [17]
63	F	Cystic fibrosis, *Pseudomonas aeruginosa*, and MRSA carriage	ICS/LABA, LTRA, OCS	PSL 7.5mg⇨ 5mg	Stable	NA	>5 years	Zhang et al. (2020) [19]
34	F	Cystic fibrosis, *Pseudomonas aeruginosa*, and MRSA carriage	ICS/LABA, LTRA, OCS	PSL⇨off	1.2⇨2	NA	>5 years	Zhang et al. (2020) [19]
24	F	Cystic fibrosis, *Pseudomonas aeruginosa*, and MRSA carriage	ICS/LABA, LTRA, OCS	PSL 20mg⇨5mg	1.5⇨2	NA	1 year	Zhang et al. (2020) [19]
71	F	NTM, hepatitis B, *Pseudomonas aeruginosa*, and MRSA carriage	ICS/LABA/LAMA, OCS	PSL 20mg⇨off	0.67⇨1.7	Improved	21 days	Present case

NTM, non-tuberculous mycobacterial disease; CKD, chronic kidney disease; FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β-agonists; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; MRSA, methicillin-resistant *Staphylococcus aureus*; OCS, oral corticosteroids; PSL, prednisolone.

been shown to decrease steroid use and enhance FEV1 in patients with severe asthma and an eosinophil phenotype [7,8,10,14,15,19,20,27,28]. There have been numerous reports on using mepolizumab in ABPA after discontinuing systemic steroids or antifungal medications for various reasons. Several cases of mepolizumab use for ABPA have been reported in PubMed and the *Journal of Central Medicine*. In the literature, we found 55 cases of mepolizumab being used to treat ABPA [4–20]. In all 55 cases, mepolizumab decreased steroid use and eosinophil count [7,8,10,19,20,27]. Overall, 6 patients had concomitant infectious diseases; these 6 cases and the present case are described in Table 2 [4,6,17,19]. These patients had a mean age of 49.2 (25–71) years, 6 patients (86.7%) were female, and all had infectious complications. All patients received prior treatment with oral steroids and were able to reduce or discontinue steroids after introducing mepolizumab. FEV1 improved in 4 patients (57.1%), and imaging findings improved in 3 patients (42.9%). The time from ABPA diagnosis to the introduction of mepolizumab was the shortest in our case, whereas several years elapsed before the introduction of mepolizumab in most cases. In all cases, airway symptoms, blood eosinophil counts, and serum IgE antibody levels tended to decrease. In the present case, airway symptoms, blood eosinophil counts, serum IgE antibody levels, CT findings, and FEV1 improved rapidly after steroid induction and were well maintained after switching to mepolizumab.

The present case highlights the efficacy of early intervention with mepolizumab in patients with complicated ABPA accompanied by concurrent infections. As documented in the literature, mepolizumab has been shown to improve airway symptoms, blood eosinophil counts, imaging findings, and FEV1 in such cases. Furthermore, it significantly reduces the need for systemic steroid therapy, thereby curtailing the risk of exacerbating concurrent infections. There is often a significant delay between the diagnosis of ABPA and the initiation of mepolizumab therapy [4,6,17,19]. However, the present case exemplifies the benefits of early intervention, with mepolizumab being introduced 21 days post-diagnosis. This early introduction of mepolizumab may be a viable strategy to optimize airway symptoms, blood eosinophil counts, IgE levels, CT imaging results, and FEV1 while simultaneously reducing the need for systemic steroids and preventing the exacerbation of concurrent infections. In the present case, the benefits of mepolizumab were observed for 12 months. Previous studies have reported favorable safety and efficacy profiles for long-term use of mepolizumab. However, further studies on the long-term use of mepolizumab are required [29].

4. Conclusion

This case study illustrates the efficacy of initiating mepolizumab therapy for the treatment of ABPA in patients with numerous infectious complications. Prompt initiation of mepolizumab in a patient with ABPA and concomitant infections was deemed to yield a positive outcome.

Patient consent for publication

Informed consent was obtained from the patient.

Declaration of competing interest

All authors of the manuscript declare that there are no conflicts of interest.

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References

[1] R. Agarwal, Allergic bronchopulmonary aspergillosis, Chest 135 (3) (2009) 805–826, https://doi.org/10.1378/chest.08-2586.
[2] D.A. Stevens, H.J. Schwartz, J.Y. Lee, et al., A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis, N. Engl. J. Med. 342 (11) (2000) 756–762, https://doi.org/10.1056/NEJM200003163421102.
[3] R.B. Moss, Treatment options in severe fungal asthma and allergic bronchopulmonary aspergillosis, Eur. Respir. J. 43 (5) (2014) 1487–1500, https://doi.org/10.1183/09031936.00139513.
[4] H. Tsubouchi, S. Tsuchida, S. Yanagi, et al., Successful treatment with mepolizumab in a case of allergic bronchopulmonary aspergillosis complicated with nontuberculous mycobacterial infection, Respir. Med. Case Rep. 28 (2019) 100875, https://doi.org/10.1016/j.rmcr.2019.100875.
[5] S.A.M. Eldaabossi, A. Awad, N. Anshasi, Mepolizumab and dupilumab as a replacement to systemic glucocorticoids for the treatment of chronic eosinophilic pneumonia and allergic bronchopulmonary aspergillosis - case series, Almoosa specialist hospital, Respir. Med. Case Rep. 34 (2021) 101520, https://doi.org/10.1016/j.rmcr.2021.101520.
[6] M. Boyle, S. Mulrennan, S. Morey, S. Vekaria, N. Popowicz, A. Tai, Mepolizumab use in cystic fibrosis-associated allergic bronchopulmonary aspergillosis, Respirol. Case Rep. 9 (1) (2020) e00696, https://doi.org/10.1016/j.rmcr.2021.101520.
[7] I.C. Eraso, S. Sangiovanni, E.I. Morales, L. Fernández-Trujillo, Use of monoclonal antibodies for allergic bronchopulmonary aspergillosis in patients with asthma and cystic fibrosis: literature review, Ther. Adv. Respir. Dis. 14 (2020) 1753466620961648, https://doi.org/10.1177/1753466620961648.
[8] S. Soeda, M. To, Y. Kono, et al., Case series of allergic bronchopulmonary aspergillosis treated successfully and safely with long-term mepolizumab, Allergol. Int. 68 (3) (2019) 377–379, https://doi.org/10.1016/j.alit.2018.12.008.
[9] S. Hirota, Y. Kobayashi, T. Ishiguro, et al., Allergic bronchopulmonary aspergillosis successfully treated with mepolizumab: case report and review of the literature, Respir. Med. Case Rep. 26 (2019) 59–62, https://doi.org/10.1016/j.rmcr.2018.11.013.
[10] T. Terashima, T. Shinozaki, E. Iwami, T. Nakajima, T. Matsuzaki, A case of allergic bronchopulmonary aspergillosis successfully treated with mepolizumab, BMC Pulm. Med. 18 (1) (2018) 53, https://doi.org/10.1186/s12890-018-0617-5.
[11] N. Oda, N. Miyahara, S. Senoo, et al., Severe asthma concomitant with allergic bronchopulmonary aspergillosis successfully treated with mepolizumab, Allergol. Int. 67 (4) (2018) 521–523, https://doi.org/10.1016/j.alit.2018.03.004.
[12] M.C. Altman, J. Lenington, S. Bronson, A.G. Ayars, Combination omalizumab and mepolizumab therapy for refractory allergic bronchopulmonary aspergillosis, J. Allergy Clin. Immunol. Pract. 5 (4) (2017) 1137–1139, https://doi.org/10.1016/j.jaip.2017.01.013.
[13] N. Matsumoto, T. Shigekusa, A. Matsuo, H. Tsubouchi, S. Yanagi, M. Nakazato, Allergic bronchopulmonary aspergillosis complicated by eosinophilic chronic rhinosinusitis successfully treated with mepolizumab, Respirol. Case Rep. 7 (7) (2019) e00465, https://doi.org/10.1002/rcr2.465.
[14] F. Schleich, E.S. Vaia, C. Pilette, et al., Mepolizumab for allergic bronchopulmonary aspergillosis: report of 20 cases from the Belgian Severe Asthma Registry and review of the literature, J. Allergy Clin. Immunol. Pract. 8 (7) (2020) 2412–2413.e2, https://doi.org/10.1016/j.jaip.2020.03.023.
[15] A. Tolebeyan, O. Mohammadi, Z. Vaezi, A. Amini, Mepolizumab as possible treatment for allergic bronchopulmonary aspergillosis: a review of eight cases, Cureus 12 (8) (2020) e9684, https://doi.org/10.7759/cureus.9684.
[16] C. Onitsuka, T. Homma, T. Kawahara, T. Kimura, Y. Miyata, H. Sagara, Mepolizumab improved airway hyperresponsiveness in a patient with allergic bronchopulmonary aspergillosis, Asian Pac. J. Allergy Immunol. (2021), https://doi.org/10.12932/AP-030521-1125.
[17] T. Yanagihara, M. Hirota, A. Egashira, et al., Successful treatment with mepolizumab for allergic bronchopulmonary mycosis complicated with bilateral septic arthritis of the knee joints caused by methicillin-resistant *Staphylococcus aureus*, Respir Med Case Rep 31 (2020) 101316, https://doi.org/10.1016/j.rmcr.2020.101316.
[18] M. Caminati, V. Batani, L. Guidolin, G. Festi, G. Senna, One-year mepolizumab for Allergic bronchopulmonary aspergillosis: focus on steroid sparing effect and markers of response, Eur. J. Intern. Med. 99 (2022) 112–115, https://doi.org/10.1016/j.ejim.2021.12.026.
[19] L. Zhang, L. Borish, A. Smith, L. Somerville, D. Albon, Use of mepolizumab in adult patients with cystic fibrosis and an eosinophilic phenotype: case series, Allergy Asthma Clin. Immunol. 16 (1) (2020) 3, https://doi.org/10.1186/s13223-019-0397-3.
[20] J. Dhariwal, A.P. Hearn, J.E. Kavanagh, et al., Real-world effectiveness of anti-IL-5/5R therapy in severe atopic eosinophilic asthma with fungal sensitization, J. Allergy Clin. Immunol. Pract. 9 (6) (2021) 2315–2320 https://doi.org/10.1016/j.jaip.2021.02.048, e1.
[21] K. Asano, A. Hebisawa, T. Ishiguro, et al., New clinical diagnostic criteria for allergic bronchopulmonary aspergillosis/mycosis and its validation, J. Allergy Clin. Immunol. 147 (4) (2021) 1261–1268.e5, https://doi.org/10.1016/j.jaci.2020.08.029.
[22] D. Huscher, K. Thiele, E. Gromnica-Ihle, et al., Dose-related patterns of glucocorticoid-induced side effects, Ann. Rheum. Dis. 68 (7) (2009) 1119–1124, https://doi.org/10.1136/ard.2008.092163.
[23] J.X. Li, L.C. Fan, M.H. Li, W.J. Cao, J.F. Xu, Beneficial effects of omalizumab therapy in allergic bronchopulmonary aspergillosis: a synthesis review of published literature, Respir. Med. 122 (2017) 33–42, https://doi.org/10.1016/j.rmed.2016.11.019.
[24] M. Jin, J.A. Douglass, J.S. Elborn, et al., Omalizumab in allergic bronchopulmonary aspergillosis: a systematic review and meta-analysis, J. Allergy Clin. Immunol. Pract. (2022), https://doi.org/10.1016/j.jaip.2022.12.012.
[25] M. Ali, O. Green, Dupilumab: a new contestant to corticosteroid in allergic bronchopulmonary aspergillosis, Oxf. Med. Case Rep. 2021 (4) (2021) omaa029, https://doi.org/10.1093/omcr/omaa029.
[26] S. Mikura, T. Saraya, Y. Yoshida, et al., Successful treatment of mepolizumab- and prednisolone-resistant allergic bronchopulmonary aspergillosis with dupilumab, Intern. Med. 60 (17) (2021) 2839–2842, https://doi.org/10.2169/internalmedicine.6679-20.
[27] B. Olivieri, E. Tinazzi, M. Caminati, C. Lunardi, Biologics for the treatment of allergic conditions: eosinophil disorders, Immunol. Allergy Clin. 40 (4) (2020) 649–665, https://doi.org/10.1016/j.iac.2020.07.001.
[28] R. Agarwal, I.S. Sehgal, S. Dhooria, A.N. Aggarwal, Challenging cases in fungal asthma, Med. Mycol. 57 (Suppl_2) (2019) S110–S117 https://doi.org/10.1093/mmy/myy063, https://doi.org/10.1093/mmy/myy063.
[29] S. Khatri, W. Moore, P.G. Gibson, et al., Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma, J. Allergy Clin. Immunol. 143 (5) (2019), 17421751 https://doi.org/10.1016/j.jaci.2018.09.033, e7.