Case report

Disappearance of angina attacks after administration of mepolizumab

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SUMMARY

A 75-year-old woman with bronchial asthma and angina presented with dyspnea. She was using nifedipine, nitroglycerin, pranlukast and salmeterol plus fluticasone propionate inhalations. We diagnosed her with severe bronchial asthma. Oral steroids prescribed for the asthma symptoms had only temporary effects. Therefore, we additionally prescribed mepolizumab; the bronchial asthma improved and the angina attacks disappeared. However, after the patient discontinued treatment, the bronchial asthma and angina attacks recurred, which were treated with nitroglycerin. When she returned 12 weeks later, we resumed mepolizumab administration; the bronchial asthma improved and the angina attacks disappeared again. Hence, we concluded that her angina was due to eosinophilia since the angina attacks disappeared with the mepolizumab therapy. Despite limitations such as lack of arterial blood gas data, perfusion scan, gastrointestinal fiberoscopy and Aspergillus skin and precipitation tests, we believe that this is the first report to suggest mepolizumab treatment for angina attacks.

BACKGROUND

Mepolizumab is an anti-interleukin-5 (IL-5) recombinant humanised monoclonal antibody. IL-5 is essential for eosinophil growth, differentiation, migration and survival; consequently, mepolizumab reduces the peripheral blood eosinophil count. Currently, mepolizumab is administered for the treatment of bronchial asthma and eosinophilic granulomatosis with polyangiitis.¹² Bronchial asthma with eosinophilia can be associated with olfactory disorders, eosinophilic chronic rhinosinusitis and variant angina.^{3–5} Conversely, previous studies have reported that variant angina with aspirin-exacerbated respiratory disease (AERD) may resolve with prednisolone administration.^{6–8} Therefore, if mepolizumab is administered to patients having bronchial asthma with complications, it might improve both the asthma and the associated complications.

CASE PRESENTATION

A 75-year-old woman presented with resting dyspnea in mid-December 20XX. She was a non-smoker and non-drinker. She inhaled 500 µg fluticasone propionate plus 50 µg salmeterol two times per day for bronchial asthma. However, repeated asthma attacks persisted. Moreover, she could not

perform numerous activities of daily living owing to dyspnea.

Her medical history was remarkable for bronchial asthma and anaphylactic shock following administration of non-steroidal anti-inflammatory drugs (NSAIDs), anaphylactic shock following administration of a penicillin drug, uterine myomectomy and right inguinal hernia surgery at the ages of 30, 34, 36 and 37 years, respectively. She became aware of reduced olfactory sensation at the age of 40 years. She developed hyperlipidemia and angina at 73 years of age. Her angina symptoms comprised heaviness, tightness and/or pain in the chest, which disappeared on treatment with 0.3 mg nitroglycerin. She underwent a cardiac catheter examination; however, it did not show stenosis of the coronary artery. Moreover, she underwent an ergonovine provocation test, which did not show spasm of the coronary artery. However, she experienced mild chest pain after the injection of ergonovine. The patient did not undergo a perfusion scan or a stress echocardiographic study. Hence, we considered that the patient's presentation was compatible with, but not diagnostic of, microvascular angina and that variant angina could not be excluded. She was prescribed oral nifedipine (20 mg/day) and sublingual nitroglycerin (0.3 mg) for chest pain. Subsequently, she experienced angina symptoms, which were treated with nitroglycerin administration, approximately every 3 months. Notably, she did not have a family history of bronchial asthma, atopic dermatitis, sudden death or heart disease.

INVESTIGATIONS

On arrival, the patient's height, weight, blood pressure, pulse rate and respiratory rate were 159.6 cm, 48.0 kg, 137/73 mm Hg, 73 bpm and 24 breaths/min, respectively. We did not perform an arterial blood gas study. Room-air pulse oximetry was 97%. Pulse oximetry was not performed on presentation of angina symptoms because they occurred outside the hospital. Physical examination revealed wheezes in the bilateral lung fields, but her heart sounds were normal; overall, the physical examination was otherwise normal. Blood serologic examination revealed eosinophilia (peripheral blood leucocyte count: 4700/µL, eosinophil percentage: 16%), hypoproteinemia (total protein: 6.3 g/dL, albumin: 3.7 g/dL) and hyperlipidemia (total cholesterol: 203 mg/dL, triglycerides: 69 mg/dL, high-density lipoprotein cholesterol: 76 mg/dL, low-density lipoprotein cholesterol: 111 mg/dL, fasting plasma glucose: 77 mg/dL). Chest radiography revealed slight ground

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Figure 1 Chest CT shows ground glass opacities (red arrow) near the pleura of the middle and lower lobes of the right lung in mid-December 20XX.

Figure 2 Chest CT shows ground glass opacities (red arrow) near the pleura of the lingular segment of the left lung in mid-December 20XX.

glass opacities (GGOs) in the bilateral middle lung fields, and chest CT revealed GGOs near the pleura of the middle lobe of the right lung and lingular segment of the left lung (figures 1 and 2). Paranasal sinus CT scanning revealed mucosal hyperplasia and retention of liquid in the bilateral ethmoid sinuses (figure 3). The Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) score⁹ was 15 points (disease side, both sides: score 3; CT shadow, ethmoid $\geq$ maxillary: score 2; eosinophil count in the peripheral blood $>10\%$; score 10).

DIFFERENTIAL DIAGNOSIS

The major causes of bronchial asthma include allergic bronchopulmonary aspergillosis (ABPA) and eosinophilic granulomatosis with polyangiitis.

The patient's serum IgE level was evaluated and was found to be high (470 IU/mL); however, there were no signs of proximal bronchiectasis on chest CT. We could not perform Aspergillus skin and precipitation tests. Thus, there was a possibility of ABPA based on the Rosenberg clinical and immunologic criteria.

The patient tested negative for myeloperoxidase-antineutrophil cytoplasmic antibodies and did not have neuropathy. Moreover, we did not perform a biopsy. However, eosinophilic granulomatosis with polyangiitis was considered because the patient's signs and symptoms met the 1990 criteria of the American College of Rheumatology.

The major causes of abnormal shadows in the lungs on chest CT and eosinophilia include chronic eosinophilic pneumonia and hypereosinophilic syndrome. We did not perform bronchoalveolar lavage. Therefore, there was a possibility of chronic eosinophilic pneumonia.

Since it was not possible to perform all the necessary diagnostic tests to rule out the conditions discussed above, careful observation of the patient was needed. We also needed to consider Löffler endocarditis as a differential diagnosis because the patient had chest pain with eosinophilia. Löffler endocarditis involves acute necrotic, thrombotic and fibrotic stages. We excluded hypereosinophilic syndrome based on the criteria of Chusid *et al*¹⁰ because her peripheral blood eosinophil count was lower than $1500/\mu\text{L}$ on arrival. Moreover, echocardiography performed in early March, 12 weeks after discontinuation of the initial therapy, revealed normal results with no evidence of wall abnormality. However, we did not perform cardiac MRI or a stress echo test to evaluate myocardial malfunction, fibrosis and ischaemic heart disease. Moreover, mepolizumab decreased her peripheral blood eosinophil count. Hence, we considered that Löffler endocarditis could not be excluded.

There could have been a perfusion defect that was not detectable (no perfusion scan) and, as a result, a decrease in blood oxygen because of the asthma attack could have produced angina symptoms due to hypoxaemia in addition to the perfusion defect (microvascular stenosis in the coronary arteries).

We suspected that her bronchial asthma was an AERD because she had a medical history of anaphylactic shock to NSAIDs, olfactory disorder and eosinophilia. However, this diagnosis could not be confirmed by a positive aspirin provocation test.

The patient did not complain of heartburn, difficulty swallowing, sensation of a lump in her throat or laryngitis. However, she did have chest pain. Hence, gastro-oesophageal reflux disease and oesophageal spasms were considered to be among the causes of the chest pain. Furthermore, hypereosinophilic oesophagitis never developed in this patient. All of the above conditions could mimic an angina attack. Notably, oesophageal

Figure 3 CT of the paranasal sinuses shows mucosal hyperplasia and retention of liquid in the bilateral ethmoid sinuses in mid-November 20XX+1.

spasms respond well to nitrates and hypereosinophilic esophagitis could respond to mepolizumab therapy.

Ultimately, we diagnosed the patient with angina, bronchial asthma, sinobronchial syndrome, chronic rhinosinusitis and hyperlipidemia.

TREATMENT

We prescribed two inhalations of 160 µg budesonide plus 4.5 µg formoterol three times per day, in addition to the following daily oral medications: 112.5 mg pranlukast, 200 µg mometasone furancarboxylic acid, 20 mg nifedipine and sublingual 0.3 mg nitroglycerin on angina attack. We also prescribed diet and exercise therapy. However, we observed repeated exacerbation and remission of asthma symptoms, so we prescribed oral prednisolone (25 mg) for 5 days. Oral prednisolone administration temporarily improved the bronchial asthma symptoms. Next, we subcutaneously administered 100 mg mepolizumab every 4 weeks, beginning in mid-November 20XX+1. The patient reported that the dyspnea disappeared in early December. When she presented in mid-December, we recognised that the wheezes in her bilateral lung fields and angina attacks had disappeared. We continued administration of mepolizumab in mid-December. However, she voluntarily ceased to attend our hospital and discontinued the mepolizumab therapy because she reported feeling comfortable and that the asthma symptoms had disappeared.

OUTCOME AND FOLLOW-UP

Beginning in mid-February 20XX+2, the patient experienced daily asthma symptoms and angina attacks, which were treated with nitroglycerin, administered four times in February. She returned in early March, 12 weeks after discontinuation of the

initial therapy. At that time, we were unaware of the angina attacks and were only able to confirm exacerbation of bronchial asthma. We resumed administration of mepolizumab, and the angina and asthma symptoms disappeared. In early June, we became aware of the angina attacks that occurred in February; we then performed electrocardiography, echocardiography and serum cardiogenic enzyme examinations, which showed normal results. The peripheral blood leucocyte count and eosinophil percentage were 5300/µL and 0.6 %, respectively.

DISCUSSION

We diagnosed the patient with, among other conditions, bronchial asthma and angina. Moreover, we suspected AERD, which is not an allergic reaction to aspirin, but intolerance to NSAIDs that inhibit cyclooxygenase 1.¹¹ It is typically confirmed by a provocation test, but diagnosis based on typical patient history has also been reported.^{12–15} Pooling patient-history data from 10 European countries, Szczeklik *et al*¹³ reported that AERD appears at a mean age of 29.7 ± 12.5 years. In addition, 51% of the patients in that study required chronic systemic corticosteroid therapy, with rates of rhinitis and nasal polyps among them at 82.4% and 60.4%, respectively. Furthermore, Taniguchi *et al*⁴ reported that most patients with AERD exhibited complications of eosinophilic chronic rhinosinusitis, along with symptoms of an olfactory disorder, eosinophilic otitis media, eosinophilic enterocolitis and variant angina at rates of 80%, higher than 50%, 30% and 10%–20%, respectively. Additionally, Taniguchi⁵ reported that a patient with AERD showed higher counts of peripheral blood eosinophils than did patients with other types of bronchial asthma.

It has been hypothesised that an attack of AERD accompanies the overproduction of cysteinyl leukotrienes (Cys-LTs) and underproduction of prostaglandin E₂.¹⁴ Higashi *et al*¹⁵ demonstrated that the basal excretion level of urinary leukotriene E₄ (U-LTE₄), identified as a major metabolite of Cys-LTs, is significantly higher in patients with AERD than in patients without the disease. In this case, we did not perform the provocation test because we were not able to secure a safe environment to avoid anaphylaxis. If we could have examined U-LTE₄ before and after mepolizumab therapy, we suspect that U-LTE₄ might have been included in our diagnosis of AERD.

Chusid *et al*¹⁰ and the WHO published diagnostic criteria for hypereosinophilic syndrome,¹⁶ including three items: (1) persistent eosinophilia of 1500/µL for longer than 6 months; (2) lack of evidence for parasitic, allergic or other known causes of eosinophilia and (3) presumptive signs and symptoms of organ involvement. Additionally, Watanabe¹⁷ reported that organ damage often developed when the peripheral blood eosinophil count exceeded 2000/µL. In this case, the patient's pathology did not match the diagnostic criteria for hypereosinophilic syndrome. Moreover, her peripheral blood eosinophil count was lower than 2000/µL. However, we suspected that the eosinophil count infiltrating the coronary artery, rather than the peripheral blood eosinophil count, might be more closely related to angina. van der Bel-Kahn *et al*⁶ reported that eosinophils infiltrated the coronary artery of a patient with AERD who died of multiple myocardial infarcts. Naito⁷ reported that a patient with variant angina and AERD exhibited angina symptoms for several days, even when the peripheral eosinophil count decreased to 0/µL with systemic steroid therapy. Moreover, the present patient's angina attacks stopped with mepolizumab administration.

In the treatment of variant angina with eosinophilia, Wong *et al*⁸ reported that most such patients improved with the administration of corticosteroids, but recurrent symptoms and myocardial

infarction often occurred after steroid treatment was reduced or withdrawn. In this case, we observed that angina attacks disappeared after the use of mepolizumab without systemic steroid therapy. In cases of eosinophilic variant angina that can be treated with mepolizumab, the side effects of systemic steroid therapy can be avoided. However, the risk of myocardial infarction after reduction or withdrawal of mepolizumab should be considered. In addition, it is important to consider whether the patient can continue using mepolizumab because of its high cost.

The JESREC study led to the creation of the JESREC score criteria for the diagnosis of eosinophilic chronic rhinosinusitis. The cut-off value of the JESREC score is 11 points; its sensitivity and specificity are 83% and 66%, respectively. Moreover, the study reported that only systemic steroid therapy is effective for the treatment of moderate to severe eosinophilic chronic rhinosinusitis.⁹ In this case, the JESREC score was 15 points, so the patient's presentation was consistent with eosinophilic chronic rhinosinusitis and olfactory disorder. Her olfaction only improved with mepolizumab administration. Furthermore, we recognised on paranasal sinus CT that the mucosal hyperplasia and retention of fluid in the bilateral ethmoid sinuses tended to improve after administration of mepolizumab. We suspect that the eosinophilic chronic rhinosinusitis was improved by mepolizumab, which does not occur with systemic steroid therapy.

In this case, the abnormal shadows in the lungs on chest CT decreased after the administration of mepolizumab. In addition, this patient did not meet the diagnostic criteria of hypereosinophilic syndrome. Therefore, we considered that this may be a case of chronic eosinophilic pneumonia. However, a clear aetiology for the abnormal shadows remains unknown, so the patient's follow-up

will be continued. We arranged for the patient to undergo further examinations as needed if her condition worsened.

In this report, we showed that mepolizumab may have the potential to treat eosinophilic variant angina. However, we have only encountered one case, so additional patients with eosinophilia with bronchial asthma and angina should be evaluated and reported. We believe that our case report provides preliminary evidence regarding the treatment of eosinophilic variant angina, without the side effects associated with systemic steroid therapy.

Limitations

- ▶ We could not obtain arterial blood gas study results.
- ▶ The patient did not undergo a perfusion scan.
- ▶ We did not evaluate for symptoms related to the gastrointestinal system, including gastro-oesophageal reflux disease symptoms and esophageal spasms, or hypereosinophilic esophagitis, as it never developed in this patient.
- ▶ We could not perform Aspergillus skin and precipitation tests.

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Patient's perspective

I had dyspnea due to asthma for 30 years, which impeded my usual daily activities, such as shopping. Moreover, I had experienced a serious condition after administration of non-steroidal anti-inflammatory drugs and antibiotics. The possibility of aspirin-exacerbated respiratory disease was indicated, and after mepolizumab administration, my asthma and angina attacks disappeared. In addition, I am glad that my sense of smell, which was weakened due to chronic sinusitis, has also improved. However, mepolizumab is very expensive. So, I hope to be able to reduce or discontinue the mepolizumab administration if my condition remains stable.

Learning points

- ▶ Mepolizumab may have the potential to treat variant angina with eosinophilia, without the side effects associated with systemic steroid therapy.
- ▶ The risk of acute coronary syndrome, after reduction or withdrawal of mepolizumab, should be considered in patients who exhibit bronchial asthma with angina.
- ▶ It is important to consider whether the patient can continue using mepolizumab because of its high cost.
- ▶ Mepolizumab may improve eosinophilic chronic rhinosinusitis, which does not occur with systemic steroid therapy.

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