Case Reports

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
50(1) 1–10

DOI: 10.1177/03000605211070492
journals.sagepub.com/home/imr
SAGE

Severe pediatric asthma with a poor response to omalizumab: a report of three cases and three-dimensional bronchial wall analysis

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Abstract

Omalizumab is used for the treatment of persistent severe allergic asthma in adults and children. However, some patients remain symptomatic even after omalizumab treatment. In bronchial asthma, chronic inflammation of the bronchial wall causes thickening of the airway wall, resulting from irreversible airway remodeling. Progression of airway remodeling causes airflow obstruction, leading to treatment resistance. We report three Japanese children with severe asthma who had a poor response to omalizumab treatment. They had a long period of inadequate management of asthma before initiating omalizumab. Even after omalizumab treatment, their symptoms persisted, and the parameters of spirometry tests did not improve. We hypothesized that omalizumab was less effective in these patients because airway wall remodeling had already progressed. We retrospectively evaluated the bronchial wall thickness using a three-dimensional bronchial wall analysis with chest computed tomography. The bronchial wall thickness was increased in these cases compared with six responders. Progressed airway wall thickness caused by airway remodeling may be associated with a poor response to omalizumab in children with severe asthma.

Keywords

Bronchial asthma, omalizumab, bronchial wall thickness, child, computed tomography, airway

Date received: 17 February 2021; accepted: 13 December 2021

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Introduction

Asthma is caused by chronic allergic inflammation of the airways, and is characterized by recurring respiratory symptoms and a variable expiratory flow limitation.[1] Chronic allergic inflammation of the bronchial wall causes thickening of the airway wall, resulting from irreversible airway remodeling.[2] The basis of treatment is the control of airway inflammation by appropriate anti-inflammatory therapy depending on the severity, which leads to the normalization of respiratory function and improvement of the quality of life. Although pediatric bronchial asthma is currently well controlled by inhaled corticosteroids (ICSs) and leukotriene receptor antagonists, severe asthma affects approximately 5% of all pediatric patients with asthma.[3]

Omalizumab is a recombinant humanized anti-immunoglobulin E (IgE) monoclonal antibody and was approved in 2013 in Japan as an add-on therapy for children with severe asthma. Omalizumab binds to free IgE and prevents it from attaching to the surface of mast cells and basophils.[4] A reduction in free serum IgE concentrations results in a decrease in the levels of IgE receptors in mast cells and basophils, preventing them from responding to allergens.[5] This has been reported to reduce the frequency of acute exacerbation, hospitalization, and emergency room visits in children with severe asthma.[6–8] A multicenter study of additional 24-week omalizumab treatment in Japanese children with severe asthma showed a significant improvement in asthma symptom scores, daily activity scores, and nighttime sleep scores.[9] Additionally, the rates of asthma exacerbation and hospitalization due to asthma were decreased after omalizumab treatment (69% and 78%, respectively).

There is, however, a subgroup of cases where adequate symptomatic control is not achieved even after starting omalizumab treatment.[10,11] Biomarkers, such as the blood eosinophil count, fractional exhaled nitric oxide (FeNO), and serum periostin, have been reported to predict omalizumab reactivity in adult asthma,[12–15] but studies in children are still lacking.

The progression of airway remodeling causes irreversible airflow obstruction, leading to treatment resistance. We hypothesize that a poor response to omalizumab is due to progressed airway remodeling. We report three pediatric patients with severe bronchial asthma with a poor response to omalizumab whose bronchial wall thickness was assessed retrospectively using a three-dimensional (3D) bronchial wall analysis with computed tomography (CT). These patients were compared with six responders.

Case report

Case 1 (non-responder #1)

An 11-year-old boy had repeated asthma exacerbations with frequent hospital admissions since he was 1 year old. Although his family physician diagnosed him with moderate-to-severe asthma, he was prescribed only montelukast without an ICS for 10 years. He had asthma attacks several times a month and was hospitalized several times a year. His family doctor referred him to our hospital because of the repeated asthma attacks.

His physique was normal, and his body mass index was 22.9 kg/m^2. He had allergic rhinitis as a comorbidity, but no chronic sinusitis or gastroesophageal reflux disease. His father and three older sisters also had bronchial asthma. His asthma control test (ACT) score was 13 points at referral. Blood tests showed eosinophilia (758/μL), a high serum non-specific IgE concentration (876 IU/L), and inhaled allergen sensitization with house dust mites. The serum

periostin concentration was 53.1 ng/mL, and the FeNO concentration was 39 ppb. Spirometry showed a decrease in the predicted forced expiratory flow in 1 second (57.0%), predicted peak expiratory flow (%PEF) (49.8%), and predicted maximal mid-expiratory flow (63.8%). After the hospital visit, a medium dose of salmeterol/fluticasone inhalation was added, but his asthmatic symptoms persisted. A change to inhalation of high-dose salmeterol/fluticasone and the combined use of oral sustained-release theophylline and oral prednisolone was started. Despite good inhalation procedures and medication adherence, monthly hospital consultations still occurred owing to asthma exacerbation. We explained the need for additional administration of omalizumab. Consent was then obtained from the patient and parents, and omalizumab was started. Chest computed tomography (CT) was performed to distinguish other respiratory illnesses, and it showed marked thickening of the bronchial wall. Unfortunately, during 1 year of omalizumab treatment, he showed no reduction in the number of unscheduled consultations due to asthma exacerbations or the need for systemic steroids, and no improvement in his ACT score. The parameters in the spirometry test and FeNO concentrations remained unchanged without any obvious improvement. After he had continued omalizumab treatment for 1 year and 3 months, we abandoned this treatment with the consent of the patient and his family.

Case 2 (non-responder #2)

A 14-year-old boy had a repeated cough and wheezing with frequent unscheduled hospital consultations since he was 1 year old. Although he was diagnosed with moderate asthma at the age of 5 years, his family doctor had not prescribed any long-term medications, and he was being treated with inhaled β_2-agonists only during asthma attacks.

The boy had suffered from asthma attacks several times a month and had been hospitalized several times a year since the age of 12 years. Therefore, his family doctor prescribed montelukast and a moderate dose of fluticasone inhalation. Because he had suffered repeated asthma attacks thereafter, he switched to medium-dose salmeterol/fluticasone inhalation, and an oral theophylline sustained-release preparation was added. His family doctor referred him to our hospital because his asthma symptoms were not able to be controlled.

The boy's physique was normal, and his body mass index was 22.1 kg/m^2. He had allergic rhinitis as a comorbidity, but no chronic sinusitis or gastroesophageal reflux disease. His mother had allergic rhinitis, but his family had no history of asthma. His ACT score was 12 points at referral. Blood tests showed no eosinophilia (150/μL), a high serum non-specific IgE concentration (319 IU/L), and inhaled allergen sensitization with house dust mites and cat dander. His serum periostin concentration was 39.9 ng/mL, and his FeNO concentration was 6 ppb. Spirometry showed a decrease in the %PEF (71.2%). After the hospital visit, high-dose salmeterol/fluticasone inhalation was started, but he still made unscheduled visits several times a month because of asthma attacks. His inhaler technique and adherence to treatment were good. Therefore, we explained the need for additional administration of omalizumab, and obtained consent from the patient and parents. Subcutaneous omalizumab was then started. Chest CT showed marked thickening of the bronchial wall. Despite 1 year of treatment, he showed no reduction in the number of asthmatic attacks and no improvement in his ACT score (from 12 to 13 points). The parameters in the spirometry test and

FeNO concentrations remained unchanged without any obvious improvement. We abandoned omalizumab treatment with the consent of the patient and his family.

Case 3 (non-responder #3)

A 13-year-old boy had suffered recurrent asthma exacerbations with frequent hospital admissions since he was 3 years old. His family physician diagnosed him with asthma and prescribed him daily montelukast. However, he took montelukast only when his asthma symptoms were exacerbated and did not visit the hospital regularly. Since then, he had suffered asthma attacks several times a month and been hospitalized two to three times a year, where he was treated with inhaled β_2-agonists only during asthma attacks. His family doctor prescribed moderate-dose fluticasone inhalation in addition to montelukast. His family doctor referred him to our hospital because of the repeated asthma attacks.

The boy's physique was normal, and his body mass index was 17.9 kg/m^2. He had allergic rhinitis as a comorbidity, but no chronic sinusitis or gastroesophageal reflux disease, and his father had a history of asthma in childhood. His ACT score was 6 points at referral. Blood tests showed no eosinophilia and a high serum non-specific IgE concentration (1420 IU/L). He was sensitized to multiple perennial inhalants (house dust mites, dog dander, cat dander, *Alternaria*, penicillium, *Cladosporium*, and *Aspergillus*). His serum periostin concentration was 49.6 ng/mL, and his FeNO concentration was 9 ppb. Spirometry showed decreased values of the predicted forced expiratory flow in 1 second (42.5%), % PEF (50.9%), and predicted maximal mid-expiratory flow (54.6%).

After the boy's hospital visit, his prescription was switched to high-dose fluticasone inhalation with oral montelukast and low-dose oral prednisolone. He was unable to use salmeterol inhalation because of palpitation, and he was also unable to use the oral theophylline sustained-release formulation owing to headaches. We re-educated him and his parents about the importance of regular medication and checked their medication status with a pharmacist. We also provided him with guidance on proper inhalation procedures. Despite good inhalation procedures and medication adherence, there was no improvement in his asthma symptoms. Therefore, we explained the need for additional administration of omalizumab, and obtained consent from the patient and parents. Subcutaneous omalizumab was then started. Chest CT showed thickening of the bronchial wall. Unfortunately, over 10 months of treatment, he showed no reduction in the number of unscheduled consultations and hospitalizations for asthma exacerbations or the need for systemic steroids, and there was no improvement in his ACT score (from 6 to 7 points). The parameters in the spirometry test and FeNO concentrations remained unchanged without any obvious improvement. After 12 months of treatment, he refused to continue omalizumab.

The reporting of this study conforms to the CARE guidelines.[16]

Three-dimensional-CT bronchial wall analysis

We retrospectively collected data on nine pediatric patients with asthma who had undergone chest CT before omalizumab treatment in the Department of Pediatrics at the Matsuyama Red Cross Hospital between April 2015 and March 2019. These patients consisted of six responders in addition to the three non-responders described above. Asthma symptoms were assessed using the childhood ACT (C-ACT) for patients aged 4 to 11 years or the ACT for patients aged 12 to 15 years.

Table 1. Clinical characteristics and blood test results in severe asthmatic patients before the initiation of omalizumab treatment.

Patient	Age (years)	Sex	BMI (kg/m^2)	Allergic comorbidity	Age at asthma onset (years)	ACT/ C-ACT	Blood eosinophil count (cells/μL)	Serum total IgE (IU/L)	Allergen sensitization	Serum periostin (ng/mL)
Non-responder #1	11	M	22.9	AR	1	13	758	876	HDM	53.1
Non-responder #2	14	M	22.1	AR	4	12	150	319	HDM, cat dander	39.9
Non-responder #3	13	M	17.9	AR	3	3	39	1420	HDM, dog dander, cat dander, *Alternaria*, penicillium, *Cladosporium*, *Aspergillus*	49.6
Responder #1	10	M	15.2	AR	5	15	400	257	HDM	51.2
Responder #2	12	F	17.1	AR	6	15	199	239	HDM, dog dander	81.7
Responder #3	8	F	16.2	AR	2	8	298	879	HDM, cat dander	104.2
Responder #4	8	F	15.1	AR, FA	4	17	665	1198	HDM, dog dander, cat dander, *Alternaria*, penicillium, *Aspergillus*	88.2
Responder #5	7	F	15.7	AR	2	8	317	330	HDM	82.8
Responder #6	9	M	18.8	AR	6	12	312	413	HDM	82.0

BMI, body mass index; ACT, asthma control test; C-ACT, childhood asthma control test; IgE, immunoglobulin E; M, male; AR, allergic rhinitis; HDM, house dust mites; F, female; FA, food allergy.

Patients who achieved a well-controlled state (C-ACT or ACT scores $\geq$20) were categorized as responders, and those whose asthma control failed to improve (C-ACT or ACT scores $<$19) were categorized as non-responders. The clinical features of the patients are shown in Table 1.

A 3D-CT bronchial wall analysis using CT images was performed using the AZE VirtualPlace Workstation (AZE, Ltd., Kanagawa, Japan). The 3D bronchial skeleton was automatically reconstructed using a certain threshold level, which was determined on an individual basis to obtain airway images as distal as possible. The obtained airway segmentations were then manually corrected for identifying any bifurcation by careful inspection using longitudinal and short-axis images. Bilateral third-generation segmental bronchi were selected for further assessment. Bronchial wall cross-sectional images were taken at several points of each third-generation bronchial path between the bifurcations (Figure 1). The bronchial wall thickness, inner diameter, inner luminal area, and total bronchial area in third-generation bronchi were measured. For the comparison of bronchial wall thickness, the percentage of bronchial wall thickness (%WT) and the percentage of the bronchial wall area were used to eliminate the potential effect of varying body sizes of patients of different ages. The %WT was calculated as $2 \times$ bronchial wall thickness/(inner diameter $+ 2 \times$ bronchial wall thickness) $\times 100$. The percentage of the bronchial wall area was calculated as (bronchial area $-$ inner luminal area)/bronchial area $\times 100$. For the assessment of bronchial inner luminal

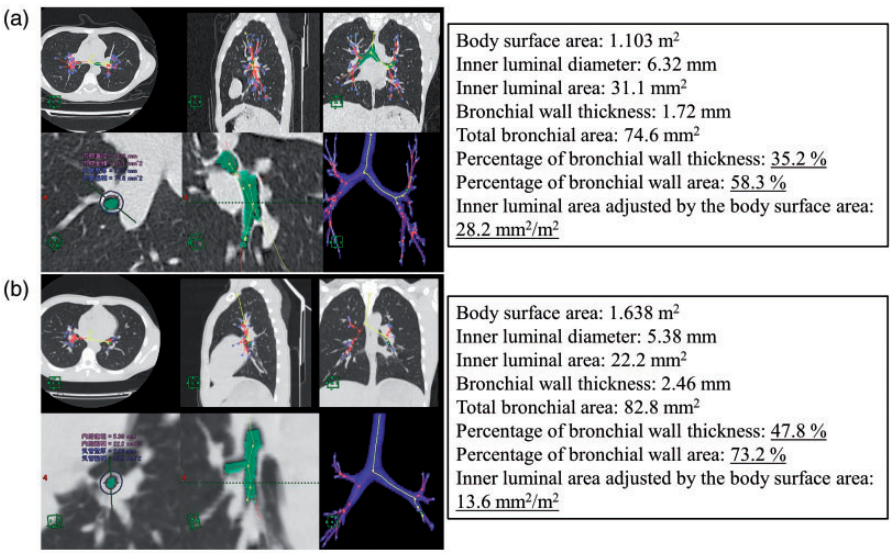

Figure 1. Representative images from three-dimensional bronchial wall analysis in (a) a responder case and (b) a non-responder case. Short-axis images in third-generation segmental bronchi were obtained. The inner diameter, inner luminal area, bronchial wall thickness, and total bronchial area were measured using the AZE VirtualPlace Workstation. The percentage of bronchial wall thickness, percentage of bronchial wall area, and bronchial inner luminal area adjusted by the body surface area were calculated.

Table 2. Changes in parameters of the spirometry test and FeNO concentrations at baseline and after 1 year of omalizumab treatment.

	Non-responder #1		Non-responder #2		Non-responder #3		Responder #1		Responder #2		Responder #3		Responder #4		Responder #5		Responder #6	
Parameters	Baseline	Post-1 year	Baseline	Post-1 year	Baseline	Post-1 year	Baseline	Post-1 year	Baseline	Post-1 year	Baseline	Post-1 year	Baseline	Post-1 year	Baseline	Post-1 year	Baseline	Post-1 year
ACT/C-ACT	13	13	12	13	6	7	15	25	15	25	8	20	17	23	8	23	12	23
FVC	111.8	108.8	110.0	109.5	77.2	96.1	96.8	114.7	110.0	116.7	103.2	107.6	106.8	102.8	107.2	107.2	93.6	123.2
(% pred)																		
FEV1	57.0	58.0	93.3	85.5	42.5	55.9	53.3	74.8	77.8	79.4	65.6	67.9	50.8	51.8	59.1	65.4	42.6	68.7
(% pred)																		
FEV1/ FVC (%)	79.3	81.3	90.2	80.8	80.6	85.5	82.0	95.8	90.9	91.4	92.8	89.6	78.3	83.6	86.0	86.4	73.8	84.4
PEF	49.8	49.0	71.2	68.7	50.9	45.2	60.2	83.2	74.4	109.2	72.7	87.4	66.5	74.5	48.7	65.5	51.0	67.5
(% pred)																		
MMF	63.8	61.2	117.7	89.9	54.6	79.8	60.8	125.2	119.0	122.8	117.8	130.0	63.3	89.1	86.1	88.2	37.0	111.7
(% pred)																		
FeNO (ppb)	48	39	6	7	9	7	40	31	51	64	9	11	41	60	7	5	9	7

ACT, asthma control test; C-ACT, childhood asthma control test; FVC, forced vital capacity; pred, predicted; FEV1, forced expiratory volume in 1 second; PEF, peak expiratory flow; MMF, maximal mid-expiratory flow; FeNO, fractional exhaled nitric oxide.

stenosis, the bronchial inner luminal area adjusted by the body surface area was calculated as previously reported.[15]

The parameters of spirometry tests, such as the predicted forced expiratory flow in 1 second, %PEF, and predicted maximal mid-expiratory flow, were increased in the responders after omalizumab treatment compared with those at baseline (Table 2). However, no improvement in spirometry test findings was observed in the non-responders. A 3D-CT bronchial wall analysis showed that the %WT and the percentage of the bronchial wall area in non-responders were higher than those in responders (Figure 2). Values of the bronchial inner luminal area adjusted by the body surface area in the non-responders were lower than those in the responders.

Discussion

We report three children with severe asthma who initiated omalizumab, but did not observe any improvement in their asthma symptoms. All three cases were older children who developed asthma in infancy and had many years of inadequate management that did not match their severity before starting omalizumab. Their spirometry test findings showed no improvement, even after omalizumab treatment, and chest CT performed before the administration of omalizumab also showed marked bronchial wall thickening in all three cases. Therefore, we hypothesized that the lack of improvement in the spirometry parameters in these non-responders was caused by progressed bronchial wall thickness as a result of airway tissue remodeling.

Chest 3D-CT of the airways is useful for objectively quantifying the degree of bronchial structural changes.[17–19] This method in adults with asthma shows that wall changes in the airways are correlated with airflow limitations, pathological abnormalities, and physiological impairment.[20–22]

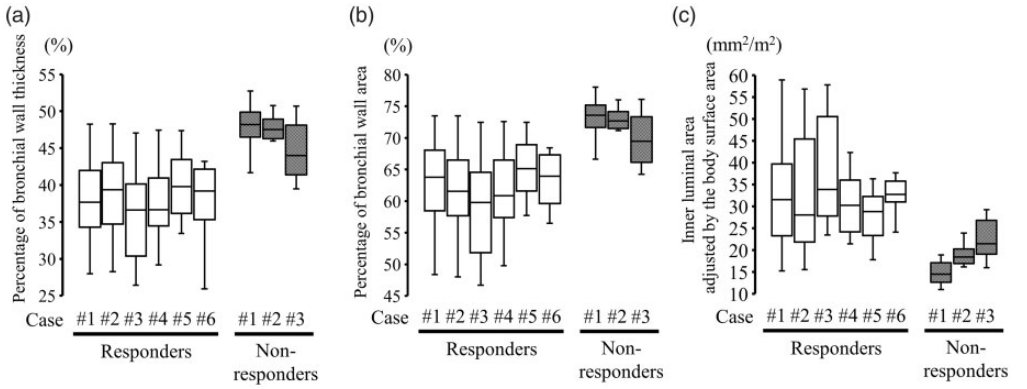

Figure 2. Box-and-whisker plots of the (a) percentage of bronchial wall thickness, (b) percentage of bronchial wall area, and (c) bronchial inner luminal area adjusted by the body surface area at several points of third-generation segmental bronchi obtained by a three dimensional-bronchial wall analysis with chest computed tomography in each patient. In the box-and-whisker plots, the line indicates the median value, the box indicates the interquartile range, and the whiskers indicate the 95% confidence interval.

Previous studies have shown that the extent of bronchial wall thickness assessed with 3D-CT analysis is greater in asthmatic cases with a longer disease duration;[23] however, few such studies have been performed in children. Recent advances in CT equipment have enabled images with a high spatial resolution to be obtained. Additionally, the remarkable development of image analysis software has allowed 3D analyses of relatively fine structures to be performed. In this study, we found that the airway structure could be measured by 3D-CT bronchial wall analyses, even in children. Additionally, bronchial wall thickness and bronchial inner luminal stenosis were more evident in non-responders to omalizumab treatment than in responders. This finding suggested that the thickening of the bronchial wall as a result of irreversible airway tissue remodeling may have already been remarkably progressed in the non-responders, causing the response to omalizumab to be diminished in these patients.

Several studies have reported that bronchial wall thickness was improved by ICSs or omalizumab treatment in adult patients with severe asthma.[23–25] Airway wall thickness on CT images includes not only irreversible tissue structural changes, but also reversible airway mucosal changes caused by swelling or the infiltration of inflammatory cells.[26] This reversible mucous membrane thickness in the airways can be reduced by the initiation of an ICS or omalizumab to suppress airway inflammation, resulting in improved airway wall thickness in CT images. We consider that earlier treatment with omalizumab in children with severe asthma before progression of airway wall remodeling may prevent subsequent deterioration of respiratory function and quality of life. Although examining whether omalizumab improves airway wall thickening is important, CT was not performed after the administration of omalizumab in our study for ethical reasons because CT examinations involve radiation exposure.

The main limitation to this study was the small sample size, and that only children with severe asthma who had undergone CT were retrospectively examined. We believe that further prospective studies in a sufficiently large cohort of severe asthmatic children will help confirm our results.

However, an appropriate clinical study considering the risk of radiation exposure and benefit will need to be designed.

Conclusion

We report three asthmatic children who initiated omalizumab, but had no improvement in their asthma symptoms. Additionally, bronchial wall thickness was greater in these non-responders compared with responders. This difference may have been caused by the progression of airway tissue remodeling, which can lead to a poor response to omalizumab treatment in children with severe asthma. However, future studies are required in a sufficiently large number of cases to confirm the reliability of this finding.

Acknowledgement

The authors would like to thank AZE, Ltd., for their assistance with the 3D bronchial analysis.

Availability of data and materials

All data are available by request from the authors.

Author contributions

MT, MI, and HT designed this case report and performed bronchial wall analysis. MT wrote the manuscript. MT and MI contributed to the analysis of the data. YK and MT performed data collection. All authors have read and approved the final manuscript.

Ethics statement

Ethics committee approval was not required in our institution because this study was a case report. Written consent for publication was obtained from all of the patients and their parents.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

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

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