INTRODUCTION

Chest tightness, cough, and fever are common symptoms of many diseases. Many patients with these chief complaints are examined in medical facilities. Although bronchitis, bronchial asthma, cough-variant asthma, or reflux esophagitis is often diagnosed, a lack of diagnosis is common. We suggest that these patients often have inflammation of the trachea and main bronchi.

Chest computed tomography (CT) is very useful in detecting chest diseases in patients presenting with chest symptoms or fever. Central airway abnormalities such as wall thickening are also easy to detect by chest CT. Characteristic central airway wall thickening is typically observed in central airway amyloidosis, relapsing polychondritis, granulomatosis with polyangiitis, and adenoid cystic carcinoma, among other diseases.

Here, we present three patients with cough, chest tightness or fever exhibiting inflammation of the trachea, and main bronchi with diffuse wall thickening and without abnormalities in other organs. The patients were diagnosed with the aid of chest CT and bronchoscopy.

CASE PRESENTATIONS

2.1 Case 1

A 58-year-old Japanese man with a previous history of hypopharyngeal cancer visited Toyama Prefectural Central Hospital due to dry cough and chest tightness aggravated over 4 months. The patient was a current smoker and worked as a cook. No problems were noted upon auscultation. Blood test results showed an eosinophil...
count of 53 cells/μl, a C-reactive protein level of 10.09 mg/dl (normal range: 0–0.14), and an immunoglobulin G4 (IgG4) concentration of 131 mg/dl (normal range: 5–117) (Table 1). Chest CT revealed moderate diffuse wall thickening of the trachea and main bronchi (Figure 1A). Flexible bronchoscopy detected an imbricate, edematous tracheal, and bronchial wall (Figure 1B). Bronchial biopsy specimens indicated airway inflammation with moderate eosinophilic and mild plasmacytic infiltration (Figure 1C, Appendix S1). His other organs were systematically examined for abnormalities, including CT of the head and trunk and blood and urine tests, but no abnormal findings were found.

Prednisolone 0.5 mg/kg/day was administered; the patient’s symptoms improved promptly, and the airway wall thickness exhibited a gradual reduction on chest CT after 4 months of treatment. The prednisolone dose was gradually reduced and stopped after 1 year of treatment.

### 2.2 Case 2

A 46-year-old Japanese man visited Toyama Prefectural Central Hospital due to dry cough that had persisted for 1 month. He was a current smoker. No problems were noted upon auscultation. Blood test results showed a

| TABLE 1  | Clinical data of Case 1 |
|-----------|-------------------------|
| **Sex**   | Male                    |
| **Age**   | 58                      |
| **Smoking** | Smoking 20 cigarettes a day from 20 years of age to the first visit |
| **Profession** | Cook                   |
| **Allergy history** | None                  |
| **Previous history** | hypopharyngeal cancer |

| **Blood test** | **Normal range** |
|----------------|------------------|
| **Hematology** |
| White blood cells | 8.8×10³/μl |
| Neutrophils      | 82.6%          |
| Eosinophils      | 0.6%           |
| Basophils        | 0.1%           |
| Lymphocytes      | 10.4%          |
| Monocytes        | 6.3%           |
| Red blood cells  | 3.88×10⁶/μl    |
| Hemoglobin       | 11.6 g/dl      |
| Platelets        | 476×10³/μl     |
| **Biochemistry** |
| Total protein    | 7.6 g/dl       |
| Lactate dehydrogenase | 152 U/L   |
| Aspartate aminotransferase | 14 U/L |
| Alanine aminotransferase | 10 U/L  |
| Creatin phosphokinase | 60 U/L |
| Blood urea nitrogen | 10 mg/dl |
| Creatinine       | 0.65 mg/dl    |
| **Serology**     |
| C-reactive protein | 10.09 mg/dl   |
| Myeloperoxidase-antineutrophil cytoplasmic autoantibodies | <0.5 U/ml |
| Proteinase3-antineutrophil cytoplasmic autoantibodies | 0.6 U/ml |
| Antinuclear antibodies | 40 |
| Immunoglobulin G4 | 131 mg/dl |
| Immunoglobulin E  | 20 IU/ml      |
C-reactive protein level of 6.58 mg/dl and an IgG4 concentration of 191 mg/dl (Table 2). Diffuse wall thickening of the trachea and main bronchi was observed on chest CT (Figure 2A), and flexible bronchoscopy showed an edematous tracheal and bronchial wall (Figure 2B). Airway inflammation with mild plasmacytic infiltration was detected based on bronchial biopsy specimens (Figure 2C, Appendix S2). Most immunoglobulin G-positive plasma-cytes were positive for IgG4, and the IgG4/CD138 ratio was 0.56. His other organs were systematically examined for abnormalities, including CT of the head and trunk and blood and urine tests, but no abnormal findings were found.

After 5 days, the patient developed severe cryptogenic hemoptysis. We treated him with methylprednisolone 1 g for 3 days, after which prednisolone 0.5 mg/kg/day was administered. The patient’s symptoms disappeared promptly, and the airway wall thickness exhibited a gradual reduction on chest CT. The prednisolone dose was gradually reduced to 10 mg/day and was continued as a maintenance therapy to control his symptoms and inflammation.

He was challenging to diagnose as having IgG4-related disease, even under the 2019 ACR / EULAR IgG4-RD Classification Criteria. After 5 days, the patient developed severe cryptogenic hemoptysis. We treated him with methylprednisolone 1 g for 3 days, after which prednisolone 0.5 mg/kg/day was administered. The patient’s symptoms disappeared promptly, and the airway wall thickness exhibited a gradual reduction on chest CT. The prednisolone dose was gradually reduced to 10 mg/day and was continued as a maintenance therapy to control his symptoms and inflammation.

2.3 | Case 3

A 76-year-old Japanese man with a history of bronchial asthma and chronic obstructive pulmonary disease for 2 years visited Toyama Prefectural Central Hospital due to a dry cough and approximately 38°C fever that lasted 2 weeks. No problems were noted upon auscultation. Blood test results showed an eosinophil count of 518 cells/μl, a C-reactive protein level of 4.75 mg/dl, an IgG4 concentration of 51 mg/dl, and normal levels of myeloperoxidase and proteinase 3-anti-neutrophil cytoplasmic antibodies (Table 3). Chest CT showed diffuse wall thickening of the trachea and main bronchi (Figure 3A), and flexible bronchoscopy revealed an edematous tracheal and bronchial wall (Figure 3B). The bronchial biopsy specimens indicated tracheitis with palisading granuloma and multinucleated giant cells in the subepithelial area of the tracheal mucosa (Figure 3C, Appendix S3). His other organs were systematically examined for abnormalities, including CT of the head and trunk and blood and urine tests, but no abnormal findings were found.

We treated the patient with prednisolone 0.5 mg/kg/day. His symptoms disappeared promptly, and the airway wall thickness exhibited a gradual reduction on chest CT. The prednisolone dose was gradually reduced for 6 months and then stopped.

3 | DISCUSSION

These case reports demonstrate that patients with cough, chest tightness, and fever may have inflammation of the trachea and main bronchi without abnormalities in other organs, which can constitute the
pathogenesis of various clinical conditions. Previous reports have presented some cases of inflammation of the trachea and main bronchi with abnormalities in the lung and/or other organs, such as a case of IgG4-related disease$^{4-6}$ and a case of granulomatosis with polyangiitis.$^{7,8}$ However, there is no past report on inflammation localized to the trachea and main bronchi. We referred to this presentation as tracheobronchitis in the title because these three cases presented with lesions confined to the trachea and main bronchi.

In this series, CASE 1 showed eosinophilic and plasmacytic infiltration based on bronchial biopsy specimens, suggesting an allergic mechanism. He had a mild increase in plasma IgG4 and few IgG4-positive cells in the airways. He was challenging to diagnose as having IgG4-related disease, even under the 2019 ACR / EULAR IgG4-RD Classification Criteria.$^3$ For CASE 2, mild IgG4-positive plasmacytic infiltration based on bronchial biopsy specimens was observed, indicating localized IgG4-related disease under the 2019 ACR / EULAR IgG4-RD Classification Criteria. CASE 3 exhibited palisading granuloma and multinucleated giant cells in the bronchial biopsy specimens, which led us to suspect a subtype of localized granulomatosis with polyangiitis. Although inflammation of the central airway was observed in all three cases, there is a distinct possibility that these three diagnoses had different underlying mechanisms.

### TABLE 2 Clinical data of CASE 2

| Sex               | Male                   |
|-------------------|------------------------|
| Age               | 46                     |
| Smoking           | Smoking 20 cigarettes a day from 20 years of age to the first visit |
| Profession        | Sheet-metal shop owner |
| Allergy history   | None                   |
| Previous history  | None                   |

| Blood Test         | Normal range          |
|--------------------|-----------------------|
| Hematology         |                        |
| White blood cells  | $6.8 \times 10^3/\mu l$|
| Neutrophils        | 68.8%                 |
| Eosinophils        | 3.8%                  |
| Basophils          | 0.4%                  |
| Lymphocytes        | 21.6%                 |
| Monocytes          | 5.4%                  |
| Red blood cells    | $4.5 \times 10^6/\mu l$|
| Hemoglobin         | 12.7 g/dl             |
| Platelets          | $407 \times 10^3/\mu l$|
| Biochemistry       |                        |
| Total protein      | 7.3 g/dl              |
| Lactate dehydrogenase | 126 U/L          |
| Aspartate aminotransferase | 26 U/L         |
| Alanine aminotransferase | 35 U/L         |
| Creatin phosphokinase | 57 U/L             |
| Blood urea nitrogen | 10 mg/dl           |
| Creatinine         | 0.9 mg/dl             |

| Serology           |                        |
|--------------------|-----------------------|
| C-reactive protein | 6.58 mg/dl            |
| Myeloperoxidase-antineutrophil cytoplasmic autoantibodies | <0.5 U/ml |
| Proteinase3-antineutrophil cytoplasmic autoantibodies | 0.6 U/ml |
| Antinuclear antibodies | Negative         |
| Immunoglobulin G4  | 191 mg/dl             |
| Immunoglobulin E   | 7 IU/ml               |
FIGURE 2  CASE 2: (A) Chest plain computed tomography revealed thickening of the tracheal wall (A1) and the main bronchi (A2) (arrow). (B) Flexible bronchoscopy showed an edematous tracheal wall. (C) Bronchial biopsy specimens indicated bronchitis with mild plasmacytic infiltration (arrow) (hematoxylin and eosin stain)

TABLE 3  Clinical data of CASE 3

| Sex     | Male                     |
|---------|--------------------------|
| Age     | 77                       |
| Smoking | Smoking 60 cigarettes a day from 20 to 36 years of age |
| Profession | Former office worker |
| Allergy history | Bronchial asthma |
| Previous history | Bronchial asthma and chronic obstructive pulmonary disease (75 years old) |

| Blood Test                       | Normal range |
|----------------------------------|--------------|
| Hematology                       |              |
| White blood cells                | 7.2×10^3/μl  |
| Neutrophils                      | 70.2%        |
| Eosinophils                      | 7.2%         |
| Basophils                        | 0.3%         |
| Lymphocytes                      | 15.9%        |
| Monocytes                        | 6.4%         |
| Red blood cells                  | 4.46×10^6/μl |
| Hemoglobin                       | 13.4 g/dl    |
| Platelets                        | 334×10^3/μl  |
| Biochemistry                      |              |
| Total protein                     | 6.8 g/dl     |
| Lactate dehydrogenase            | 416 U/L      |
| Aspartate aminotransferase       | 18 U/L       |
| Alanine aminotransferase         | 18 U/L       |

(Continues)
Previously, it was not commonly considered that inflammation of the large airways would produce such diffuse wall thickening. However, in this report, we show that tracheobronchitis can cause various types of inflammation with wall thickening. It is suspected that tracheobronchitis is not a rare condition; however, it is likely less noticeable. It is challenging to diagnose because it is difficult to identify whether there is an abnormality only in that location. More attention should be paid to the wall of the trachea and main bronchi during the interpretation of chest CT findings in patients with chest symptoms or fever to fully understand their clinical condition. If the thickening of the airway wall is detected, we should investigate the cause of thickening with bronchial or tracheal biopsy using flexible bronchoscopy. The pathological findings in the biopsy tissue can reveal extensive airway conditions in these patients and guide appropriate treatment strategies.

It is also interesting why inflammation occurs locally in this area. The investigation of the causes of these pathologies is also interesting, smoking or inhalation of some substance may be involved. We hope that additional cases with similar findings are reported in the future to further our understanding of this clinical condition.

\[FIGURE 3\] CASE 3: (A) Chest plain computed tomography revealed thickening of the tracheal wall (A1) and the main bronchi (A2) (arrow). (B) Flexible bronchoscopy showed an edematous tracheal wall. (C) Bronchial biopsy specimens indicated a palisading granuloma (hematoxylin and eosin stain)

| Blood Test                                | Normal range |
|-------------------------------------------|--------------|
| Creatin phosphokinase                     | 40 U/L       |
| Blood urea nitrogen                       | 17 mg/dl     |
| Creatinine                                | 1.15 mg/dl   |

Serology

|                         | Normal range |
|-------------------------|--------------|
| C-reactive protein      | 4.75 mg/dl   |
| Myeloperoxidase-antineutrophil cytoplasmic autoantibodies | <0.5 U/ml |
| Proteinase3-antineutrophil cytoplasmic autoantibodies     | 0.6 U/ml     |
| Antinuclear antibodies | 40           |
| Immunoglobulin G4      | 51 mg/dl     |
| Immunoglobulin E       | 13 IU/ml     |
| Ferritin               | 187.2 ng/ml  |

\[TABLE 1\] (Continued)
AUTHOR CONTRIBUTIONS
HT drafted the manuscript and provided patient care. AU, AA, and SI performed pathological investigations. YM, TT, AM, MS, and NT performed bronchoscopy. HA created the computed tomography images.

CONFLICT OF INTEREST
None declared.

DATA AVAILABILITY STATEMENT
Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ETHICAL APPROVAL
This report was approved by the ethics committee at the Toyama Prefectural Central Hospital, and informed consent was obtained.

CONSENT
Written informed consent was obtained from the patient to publish this report in accordance with the journal’s patient consent policy.

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SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

How to cite this article: Taniguchi H, Masaki Y, Tsuda T, et al.. Tracheobronchitis in patients with diffuse wall thickening: Three case reports. Clin Case Rep. 2022;10:e05963. doi: 10.1002/ccr3.5963