

## CASE REPORT

### A case of granulomatosis with polyangiitis preceded by subacute thyroiditis

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#### Introduction

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, is a systemic inflammation disease caused by necrotizing granulomatous vasculitis of medium and small vessels. The vasculitis predominantly affects the upper and lower respiratory tracts and the kidneys [1], but also the skin, mucous membranes, eyes, joints, and the nervous system [2]. Antineutrophil cytoplasmic antibodies (ANCA) are highly positive in 80–90% of patients with active generalized GPA [3]. The annual incidence of GPA is 4.9 to 10.5 patients per million in Europe, and it is more common in Scandinavians than other ethnic groups [4]. The Japan Intractable Diseases Information Center reported that the annual prevalence of GPA in Japan was only 2.3 patients per million in 1997 [5].

Subacute thyroiditis is a hyperthyroidism presenting self-limited thyrotoxicosis with neck pain and tenderness of the thyroid region. It is presumed to be caused by viral infection or a postviral inflammatory process. Thyroid autoimmunity does not appear to play a primary role in the disorder, but it is strongly associated with HLA-B35 in many ethnic groups [6]. Hyperthyroidism is typically seen at presentation, followed by euthyroidism,

#### Key Clinical Message

Granulomatosis with polyangiitis can be a complication of thyroid disease, not only autoimmune disease but also subacute thyroiditis.

#### Keywords

Granulomatosis with polyangiitis, hyperthyroidism, subacute thyroiditis, Wegener's granulomatosis.

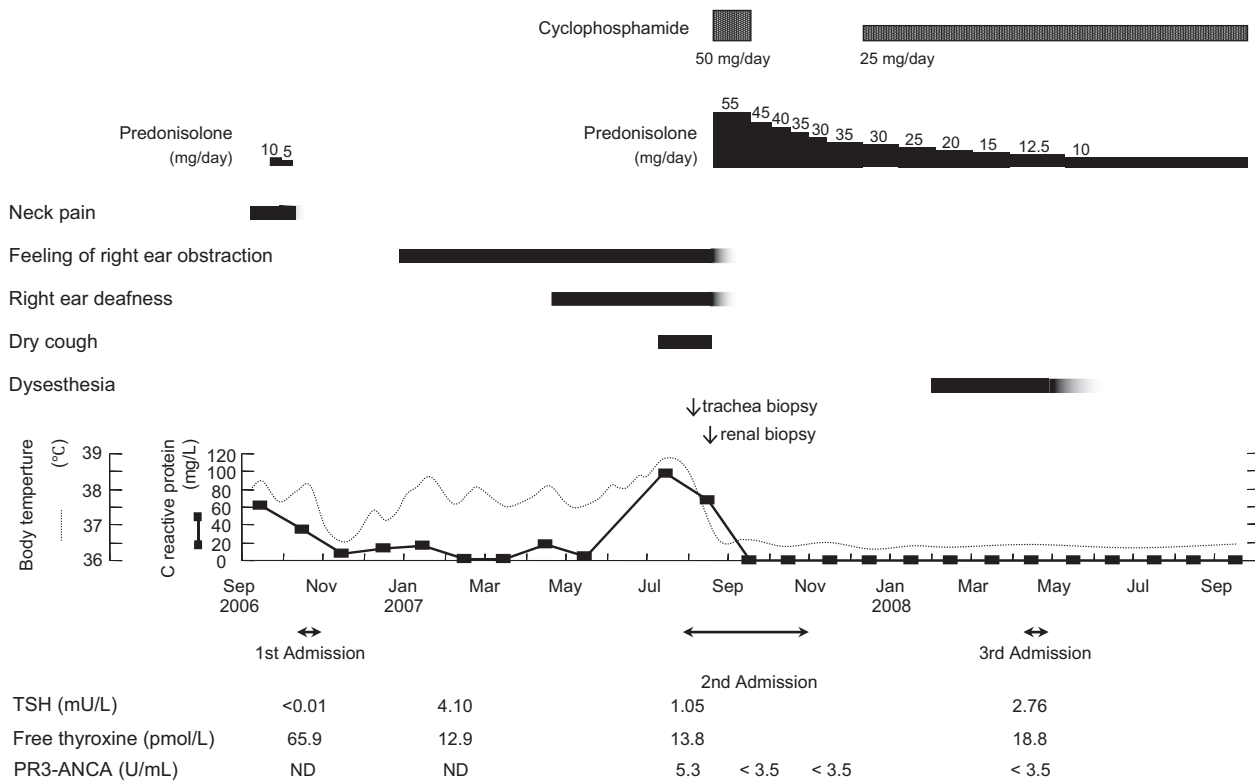
hypothyroidism, and ultimately restoration of normal thyroid function.

There are many reports of GPA accompanied by autoimmune thyroid diseases, but there is only one case report of GPA that accompanied by subacute thyroiditis during immunosuppressive therapy [7]. Herein, we report a rare case of GPA which is preceded by subacute thyroiditis that, as far as we know, is the first published report.

#### Case Report

A 53-year old Japanese woman was referred to our department in September 2006 because of fever and right thyroid tenderness lasting for 3 weeks. She was diagnosed as having subacute thyroiditis at another clinic and had already had taken 10 mg per day of oral prednisolone (PSL) for 1 week, followed by 5 mg per day for another week. Her neck pain faded after 2 weeks; however, fever and fatigue persisted and appetite began to decrease. She was admitted to our hospital for further workup in October 2006 (Fig. 1).

She had undergone appendectomy at age 20 and laparoscopic cholecystectomy for cholelithiasis at age 38. She was on no regular medication or dietary supplement.



**Figure 1.** Clinical course. TSH, thyroid stimulating hormone; PR3-ANCA, proteinase 3- antineutrophil cytoplasmic antibody; ND, no data.

Neither prior upper respiratory infection nor measles-mumps-rubella vaccine was mentioned. Physical examination showed low grade fever of 37.3°C, blood pressure 96/63 mmHg, and pulse rate 96 per minute at rest. She had anxiety but no tremor and difficulty of swallowing was seen. Initial laboratory testing showed a normal white blood cell count (6410/ $\mu$ L) with normal fraction and elevated C-reactive protein (CRP 35 mg/L). The erythrocyte sedimentation rate (ESR) was not tested at this admission. Thyroid stimulating hormone (TSH) was decreased to less than 0.01 mU/L (normal range, 0.27–4.20) and free thyroxine (FT4: 65.9 pmol/L [normal range, 11.6–21.9]) was elevated in serum. Tests for antithyroglobulin antibody, antithyroid peroxidase antibody, and thyroid stimulating antibody were negative. Ultrasound showed no enlargement of the thyroid but diffuse heterogeneous internal-echo. Iodine uptake of thyroid scintigraphy was diffusely suppressed. All data were compatible with the diagnostic criteria of subacute thyroiditis [8]. Fever resolved by itself in a week of admission, we treated her with only oral administration of a nonselective beta blocker, propranolol 10 mg three times a day for the thyrotoxic symptoms.

In November 2006, after a 2-week symptom free period, an intermitted fever around 38.0 degrees Celsius developed that persisted for 8 months. Upper and lower

respiratory tract symptoms were as follows, sense of right ear obstruction from January 2007, right deafness from May, and dry cough and numbness of the right pharynx from July. Headache and fatigue were reported. In August 2007, she was again admitted to our hospital (Fig. 1).

Physical examination was unremarkable except for erosion of the pharynx and subungual purpura in the left middle finger. The laboratory testing of the second admission (Table 1) showed a normal white blood cell count (7370/microL) with normal fraction, elevated serum CRP (87 mg/L), ESR (133 mm/h), and proteinase-3 antineutrophil cytoplasmic autoantibody (PR3-ANCA 5.3 U/mL [normal, less than 3.5]). Serum creatinine was normal, but it was noted that she had microhematuria without proteinuria for 10 years. However, granular cast was positive on this admission. Because of the absence of proteinuria, renal disease, heart failure, liver dysfunction, and diarrhea, we assumed a decreased albumin level due to chronic inflammation.

Audiogram revealed right mild sensorineural deafness. Her chest X-ray was normal but chest enhanced computed tomography (CT) revealed thickness of the trachea wall (Fig. 2) and mild stenosis of the left main bronchial tube. Enhanced magnetic resonance imaging of the nasal sinuses and brain showed no abnormalities.

**Table 1.** Laboratory findings on the second admission (2007).

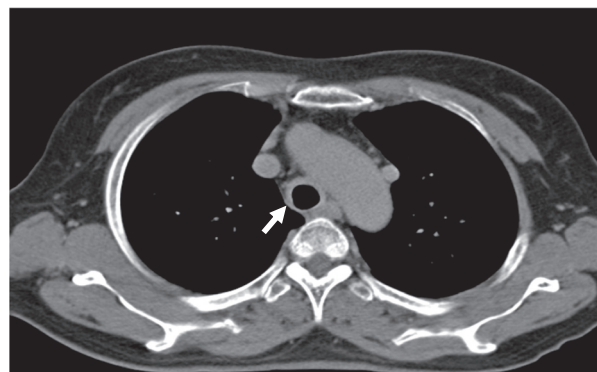
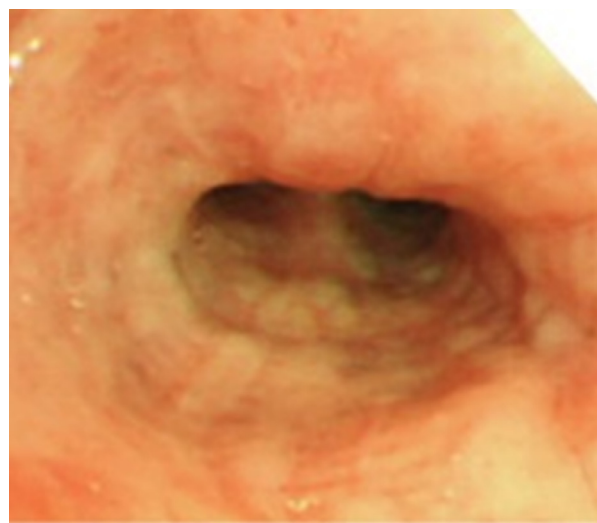
Urinalysis	
Occult blood	3+
Protein	Negative
Glucose	Negative
Urinary sediment	
Red blood cell	10–19/high power field
Granular cast	Positive
Creatinine clearance	131 mL/min
Hematology (normal range)	
White blood cell (3500–9000)	7370/ $\mu$ L
Neutrophil cell (40.0–70.0)	76.6%
Red blood cell (385–465)	$357 \times 10^4$ $\mu$ L
Hemoglobin (12.0–16.0)	87 g/L
Hematocrit (34.0–45.0)	27.9%
MCV (82.0–95.0)	78.2 fL
Platelet count (14.0–44.0)	$35.7 \times 10^4$ / $\mu$ L
ESR	131 mm/h
Biochemistry	
Total protein (67–83)	71 g/L
Albumin (40–50)	31 g/L
Total bilirubin (3–12)	10 mg/L
Aspartate aminotransferase (13–33)	23 U/L
Alanine aminotransferase (6–30)	32 U/L
Lactate dehydrogenase (119–229)	135 U/L
Urea nitrogen (2.9–7.9)	2.9 mmol/L
Creatinin (35–62)	60 $\mu$ mol/L
Calcium (2.2–2.6)	2.3 mmol/L
Ferritin (0.062–1.38)	2.3 $\mu$ g/L
ACE (8.3–21.4)	5.3 U/L
Serology	
C-reactive protein (<1.0)	87 mg/L
Rheumatoid factor (<20)	<5 U/mL
Antinuclear antibody	Negative
PR3-ANCA (<3.5)	5.3 U/mL
MPO-ANCA (<9.0)	<1.3 U/mL
QFTb-2G	Negative

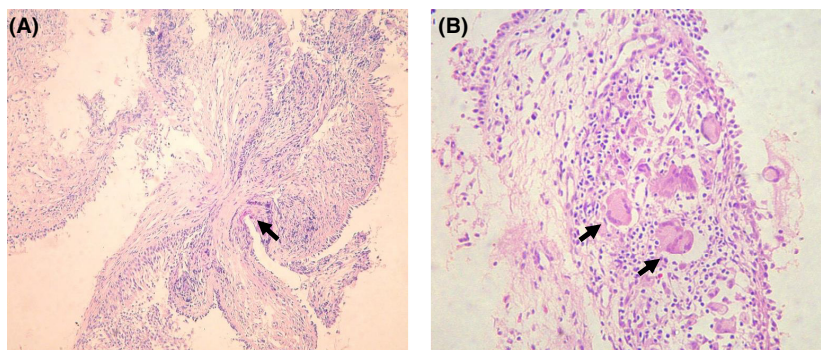
MCV, mean corpuscular volume; ESR, erythrocyte sedimentation rate; ACE, angiotensin conversion enzyme; PR3-ANCA, proteinase 3-antineutrophil cytoplasmic antibody; MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibody; QFTb-2G, QuantiFERON<sup>®</sup>-TB2G.

Bronchoscopy revealed pale mucosa with diffuse granulation of trachea and bronchus (Fig. 3). Biopsy of the trachea showed that the bronchial wall was irregularly fibrotic with mild to moderate chronic inflammatory infiltrate. Some scattered noncaseating epithelioid cell clusters with multinucleated giant cells were found, but angiitis was not revealed (Fig. 4). Tuberculin skin test was not done, but we excluded *Mycobacterium tuberculosis* infection serial performed sputum cultures and negative interferon-gamma release assay (QuantiFERON-TB2G<sup>®</sup> Japan BCG Laboratory, Tokyo, Japan). We excluded sarcoidosis by low serum angiotensin converting enzyme (5.3 U/L, normal range 8.3–21.4) and normal calcium (2.3 mmol/L, normal range 2.2–2.6) levels, no hilar or mediastinal lymphadenopathy, and no lung parenchymal

changes on CT scan, no significant accumulation of gallium scintigraphy in the bilateral hilar area, no increase of lymphocytes in the bronchial lavage fluid and no other findings of sarcoidosis in the skin, eyes, and heart. We diagnosed the patient as having GPA based on the American College of Rheumatology proposed clinical criteria of 1990 [9].

Renal involvement is common in GPA. The presence of rapidly progressive glomerulonephritis is related to poor disease prognosis. However, a diagnosis of ANCA positive glomerulonephritis tend to be delayed for patients with asymptomatic hematuria in association with normal renal function. To clarify whether or not microhematuria and the newly detected granular cast were induced by GPA, renal biopsy was performed. Specimens showed no signs

**Figure 2.** Nonenhanced computed tomography of the chest. White arrow shows trachea wall thickness.**Figure 3.** Bronchoscopy photograph of the trachea above the bifurcation before treatment shows pale mucosa with diffuse granulation. The top of the picture is the anterior chest and the bottom is the posterior.



**Figure 4.** Pathology of tracheal mucosa biopsy. (A) Black arrow shows fibrosis area (Hematoxylin eosin (HE) stain  $\times 40$ ). (B) Black arrows show noncaseating epithelioid cell clusters with multinucleated giant cells (HE stain  $\times 400$ ).

of vasculitis or pauciimmune segmental necrotizing glomerulonephritis. The cause of the microhematuria was not identified; however, thin basement membrane nephropathy is relatively common. We did not do urinalysis for her family or do electron microscopy in our diagnosis. The possibility of IgA nephropathy was excluded by no episode of proteinuria and no mesangial hypercellularity in renal biopsy. Thus, we diagnosed her as GPA without renal disease.

The patient was treated with PSL 55 mg per day (1 mg/kg body weight) and cyclophosphamide 50 mg per day (0.9 mg/kg) (day 0) which led to impressive improvement of her symptoms and laboratory data. Her audiogram recovered to normal within a month and bronchoscopy findings also recovered in 2 months. Cyclophosphamide was interrupted on day 20 because of liver enzyme elevation (alanine aminotransferase 270 U/L). CRP and PR3-ANCA were not elevated. Pneumocystis pneumonia prophylaxis was done with trimethoprim 80 mg and sulfamethoxazole 400 mg per day. Due to drug-induced eruptions, we stopped them on day 22, and monthly inhalation of pentamidine 300 mg was started in their place. The initial dose of PSL was continued for 1 month then tapered (Fig. 1), and she was discharged with 30 mg per day of PSL in October 2007.

From February 2008, she felt dysesthesia of the right fingers and bilateral distal legs without fever or serological elevation of inflammatory markers. A neurologist of our hospital diagnosed these symptoms as mononeuritis multiplex due to GPA. In October 2014, she took 10 mg per day of PSL in the clinic, without recurrence. Microhematuria has continued, but serum creatinin has remained within normal limits.

## Discussion

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis include GPA, microscopic polyangiitis (MPA),

Churg-Strauss syndrome, and renal-limited vasculitis. All are associated with ANCA and have similar features on renal histology. Patients with GPA are more frequent in Europe but compared to MPA, GPA consists of only 10 percent of ANCA-associated vasculitis in Japan [10]. The difference in incidence of GPA between ethnic groups indicates the influence of genetic factors on the onset of the disease. Most men develop the disease from their thirties to sixties and women from their fifties to sixties, with neither sex showing a predominance. The pathogenesis of GPA is unknown, but it is presumed that cytokines produced during upper respiratory infection or inflammation itself activate PR3-ANCA and neutrophils, which sets-up vasculitis and tissue damage.

Subacute thyroiditis is a self-limited thyrotoxicosis with neck pain, commonly with fever, fatigue, malaise and anorexia, as was seen with this patient. Most patients develop subacute thyroiditis from their thirties to fifties. Different from GPA, women are three times more susceptible than men. Pathologically, subacute thyroiditis is caused by activated cytotoxic T lymphocytes sensitized by antigen from viral organs, such as mumps virus, coxsackie virus, influenza virus, or virus-induced host tissue damage.

There are some reports that subacute thyroiditis accompanied by other vasculitis is a possible initiator of the disease. Ohta *et al.* [11] reported that 11 of their 36 patients suffering from Takayasu's arteritis had at least one other chronic or subacute inflammatory disease and 2 of 11 patients had subacute thyroiditis. Oner *et al.* [12] reported Henoch-Schonlein nephritis associated with subacute thyroiditis, and they concluded that mumps virus infection is a triggering factor in the development of both Henoch-Schonlein purpura and subacute thyroiditis. Only 1 case of GPA accompanied by subacute thyroiditis has been previously reported [7]. We assume that the inflammation from the subacute thyroiditis played some role in the onset of GPA, but we cannot exclude the pos-

sibility of the coincidental incidence of these diseases because we did not check the PR3-ANCA titer during the first admission.

It is known that patients with severe GPA have a higher likelihood of previous thyroid disease, particularly Graves' disease or Hashimoto's thyroiditis, but not subacute thyroiditis [2]. One possible association of GPA and thyroid diseases is due to the patient's susceptibility to autoimmune diseases. Another reason is the fact that over 25% of patients with Graves' disease who are treated with propylthiouracil produce ANCA [13] and that some of them develop ANCA-associated vasculitis, including GPA [14].

The 1 year mortality of untreated GPA is 82%, and the main causes of death are renal and respiratory failure [15]. In 1973, Fauci et al. [1] discovered that a combination therapy of daily prednisone and cyclophosphamide induced complete remission in 75% of their patients. Administration of prednisone and cyclophosphamide for 6 months leads to remission by approximately 90% of patients. However, this treatment is difficult because it can cause serious side effects [16].

Currently, the disease activity is assessed based on the Birmingham Vasculitis Activity Score 2008 version 3 [17], and the treatment chosen depends on the severity categorization of the 2009 European Vasculitis Study [18]. Our case is categorized as early systemic vasculitis defined as any disease with constitutional symptoms that is not organ-threatening or life-threatening. For these patients, a regimen of glucocorticoids in combination with methotrexate for the initial therapy is recommended. For more severe patients, a regimen consisting of glucocorticoids in combination with either cyclophosphamide or rituximab is recommended. Rituximab is as effective as cyclophosphamide in inducing remission among patients with newly diagnosed or relapsing GPA [19, 20]. The rates of serious adverse events were similar with both drugs. The conclusion of preferred initial immunosuppressive regimen has not been reached. For patients who have contraindication to cyclophosphamide or refuse therapy because of concerns about fertility, hair loss, or the high risk of malignancy, rituximab is the preferred initial therapy.

Our case involved only the upper and lower respiratory system with no renal involvement. However generalized symptoms such as persistent fever and fatigue were seen. The case is simple, but we think that is the consequence of early diagnosis and treatment before the disease could become more complex.

In conclusion, we report a rare case of GPA that was preceded by subacute thyroiditis. GPA can be a complication of thyroid disease, not only autoimmune disease but also subacute thyroiditis.

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## Conflicts of Interest

N. F. has received research support from Daiichi Sankyo Healthcare Co., Ltd., Tokyo, Japan, Chugai Pharmaceutical Co., Ltd., Tokyo, Japan, MSD Ltd., Tokyo, Japan and Mitsubishi Tanabe Pharma, Osaka, Japan. The remaining authors disclose no conflicts.

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