Main tract stenosis complicated by granulomatous with polyangiitis: A case report

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Abstract. Granulomatosis with polyangiitis (GPA) is a rheumatic auto-immune disease involved in vasculitis. It is rarely reported that anti-neutrophil cytoplasmic antibodies (ANCAs) associated with GPA would cause main tract stenosis. The current report documents a 54-year-old woman, with a history of severe cough, presented with wheezing and shortness of breath. Although she was treated with cephalosporin antibiotics for half a month, the symptoms were not alleviated. Accordingly, laboratory testing, radiology and pathology was performed at the Department of Respiratory and Critical Care Medicine, Huashan Hospital. Blood samples were tested negative for ANCAs. Chest CT revealed stenosis of the main trachea and uneven thickening of the tracheal wall. Nasal sinuses CT scanning indicated thickening of the nasal mucosa. Pathological analysis demonstrated chronic granulomatous inflammation with focal lesions. According to the classification criteria of ACR/EULAR provisional 2017, the patient was diagnosed with the ANCAs-negative GPA. Following treatment with oral prednisone only for 6 months, obstruction of main tract was significantly improved. This case study is of interest for the promotion a potentially novel therapeutic intervention for GPA associated with the absence ANCA of in clinic.

Introduction

Granulomatosis with polyangiitis (GPA) is a rare, autoimmune-mediated systemic disease that is characterized by necrotizing and granulomatous vasculitis of small blood vessels, including arterioles, venules and capillaries (1). The incidence of GPA is ~1/100,000 in the United Kingdom, Germany and Norway, where GPA usually occur in older people, but are relatively rare in children and young people (2). Although GPA mainly affects the upper and lower respiratory tract, kidneys and eyes, neurological manifestations and infectious diseases have been previously associated with GPA (3-5).

The pathogenesis of GPA is considered to involve a combination of environmental and infectious factors on the basis of genetic susceptibility (6,7). This condition is closely associated with the presence of anti-neutrophil cytoplasmic antibodies (ANCAs) in blood, including perinuclear-ANCA (pANCA) and cytoplasmic-ANCA (cANCA) (8). However, ≤10% patients with GPA can test negative for ANCA (9). If the histopathological results and highly suspected clinical features can be used to confirm the diagnosis of GPA, positive ANCA serology is not a key element for the diagnosis of GPA (10). GPA involves the production of ANCA against proteinase 3 (PR3) in ~80% of the GPA cases and against myeloperoxidase (MPO) in ~10% of the GPA cases (6). The presence of single nucleotide polymorphisms in the HLA-DPB1 locus, with variants rs141530233 and rs1042169 being previously reported examples, are at higher risk of vasculitis associated with ANCA against PR3 (11). Additionally, some drugs have been reported to serve as triggers for ANCA-associated GPA, including cepotaxime, anti-thyroid medication, anti-tumour necrosis factor α agents; however, cases of ANCA-associated vasculitis induced by pharmacological agent are normally resolved following discontinuation of the drug in question (12).

At present, the diagnostic criteria of GPA are based on the combination of clinical manifestation, ANCA serology, radiology and histopathology, according to the ACR/EULAR provisional 2017 (10). The severity of ANCA associated with GPA can be divided into mild, moderate and severe based on the involvement of other organs (13). Although cyclophosphamide and corticosteroid combination therapy have been applied for induction therapy in GPA, cyclophosphamide has a potential side effects such as fertility risks and teratogenicity, limiting
the duration of therapy (14). Although other agents, including rituximab, methotrexate, azathioprine and leflunomide, have demonstrated therapeutic effects of varying degrees in patients with GPA (7), no treatment option currently exists for patients with ANCA-negative GPA. The present report documents a rare case of ANCA-negative GPA involving main tract stenosis (MTS), where the patient with GPA improved following treatment with oral prednisone only. The present case study provides a prospective therapeutic option for ANCA-negative GPA.

Case report

In January 2019, a 54-year-old woman presented with a history of severe cough, wheezing, shortness of breath but no fever. Immediately, she was admitted to the Jiangyou People’s hospital (Mianyang, Sichuan), where primary CT scans indicated asymmetrical thickening of the tracheal wall and small calcified nodules in the right upper and middle lobes. The patient was diagnosed with an acute respiratory disease, who subsequently confirmed by oral communication that cephalosporin antibiotics was applied for ~half a month; however, the symptoms were not relieved. On April 15, 2019, she was admitted to the Department of Respiratory and Critical Care Medicine, Huashan Hospital (Shanghai, China). A general physical examination suggested that the inhalation and expiratory breathing were restricted. Neurological manifestations, skin lesions and superficial lymphadenopathy were not visible or accessible.

One week prior to admission to The Huashan hospital, namely April 7, 2019, she was examined for pulmonary volume capacity (PVC) and ventilation function (PVF) using the MasterScreen™ PFT System (Vyaire Medical, Inc.) at the outpatient department (Shanghai, China). PVC examination revealed the following information: i) forced expiratory volume in 1 sec (FEV1), 1.16 l; ii) FEV1/pre-predicted value, 62.9%); iii) FEV1/forced vital capacity (FVC), 60.02%; iv) peak expiratory flow, 1.60 l/sec; and v) 75% of maximal expiratory flow, 1.14 l/sec (predicted value, 5.02 l/sec). PVF test showed that the top of the ascending line was seriously low whereas the descending line plateaued above the horizontal axis, indicating that the flow-volume loop was insufficient. It suggested that the inhalation and exhalation of the patient was obstructed (Fig. 1A).

On April 16, 2019, the results of blood tests were as follows: i) Eosinophil count, 616x10^6 cells/l; ii) Erythrocyte sedimentation rate (ESR), 29 mm/h (normal range: ≤20 mm/h); iii) anti-nuclear antibodies, 1:1,000-fold (ANAs; normal range: ≤1:100-fold); iv) anti-cytoplasmic reticular/mitochondrial antibodies-21, positive (AC-21; normal range, negative); v) MPO-ANCA, 4.9 RU/ml (normal range: 0~20 RU/ml); and vi) PR3-ANCA, 5.8 RU/ml (normal range, 0~20 RU/ml). In addition to laboratory results, the MasterScreen™ PFT System (Vyaire Medical, Inc.) at 37˚C for 30 min; vi) enhancing the signal using a DAB kit (cat. no. dab-2032; Fuzhou Maixin Biotech Co., Ltd.); vii) counterstaining with hematoxylin for 2 min at room temperature; viii) photographing under a light microscope (magnification, x200; SS/F1-1; Nikon Corporation). Sources and instructions of antibodies above were listed in Table SI.

In addition, on April 17, 2019, the biopsy performed using transbronchial needle aspiration (NA-201SX-4021-21 G; Olympus Corporation) demonstrated chronic necrotizing granulomatous inflammation (Fig. 4D). The results of the IHC analysis were as follows: i) LCA, -; ii) VIM, +; iii) CK, -; iv) CgA, -; v) Syn, -; vi) TTF-1, -; vii) WT-1, -; viii) P63, -; ix) NapsinA, -; x) P40, -; xi) Ziehl-Neelsen staining, -; and xii) periodic acid–Shiff staining, - (Fig. S1). According to the classification criteria of ACR/EULAR provisional 2017 (10), the patient scored 5 points, including cartilaginous involvement (2 scores) and granuloma on biopsy (3 scores). The diagnosis of MTS caused by GPA was established. Finally, the patient was treated with prednisone (5 mg/tablet). The starting dose was 25 mg per day (0.5 mg/kg, orally), which was then reduced to 20 mg per day after 2 months, followed by a reduction by one tablet every two months.

After six months, the pulmonary function indicated improved conditions: FEV1, 2.19 l; FEV1/pre, 170.0%; and FEV1/FVC, 81.86% (Fig. 1B). The chest CT scan indicated that the narrow tract was relieved (Fig. 2B, D and F). The obstruction of main trachea was significantly improved (Fig. 4C). The laboratory results were as follows: ESR, 13 mm/h (normal range: NSE ≤20 mm/h); ANAs, 1:320-fold (normal range, 1:100-fold).

Discussion

The current case presents a patient of local GPA-induced MTS with negative-ANCAs. The patient improved significantly after the initial treatment of oral prednisone. It has been reported that GPA involves the nasal, ears, oropharynx, trachea and bronchi (15), where the ANCA serology in patients with GPA are mostly positive (15,16). However, if ANCAs is tested negative, the upper and lower respiratory disease may be misdiagnosed due to the atypical manifestation in GPA, (17). Histopathological analysis serves an imperative role in the diagnosis of GPA (8). The involvement of the main airway could cause inspiratory and expiratory changes. The flow-volume tracings from the current patient indicated a fixed main airway obstruction. In addition, the FEV1/FVC
was decreased markedly. Positive correlation was observed between the degree of airway obstruction and the platform change of the respiratory phase (18). Furthermore, since bronchoscopy visualized the main tract to be compressed externally, the possibility of bronchogenic tumor could not be ruled out (4). This was initially suspected to be a neoplasm, but the appearance of the lesion by endoscopic examination and biomarkers were contrary to the expected diagnosis. A panel of tumor-related immunohistochemical markers were also demonstrated to be negative. The pathological results revealed chronic necrotizing granulomatous inflammation (16).

GPA is an agnogenic, autoimmune-mediated systemic condition, where airway ailments as a result of GPA is a benign disease that is more prevalent in older adults (8). Currently, the standard treatment is a combination of corticosteroids with cyclophosphamide in the induction period, followed by lower

**Figure 1.** Improvements in PVC and PVF after treatment with prednisone. (A) Data before prednisone therapy. (B) The improvement after prednisone therapy. PVC, pulmonary volume capacity; PVF, pulmonary ventilation function; FEV1, forced expiratory volume in 1 second; pre, predicted value; FVC, forced expiratory volume.

**Figure 2.** Thoracic CT images. (A) Severely MTS before treatment and (B) substantial alleviation of MTS after treatment in view of lung window; yellow arrow. (C and D) Corresponding images in the mediastinal window to (A) and (B) respectively. (C) Obstruction before therapy and (D) changes after therapy in mediastinal window. (E) Chest CT by three-dimensional reconstructing revealed changes of MTS before therapy and (F) after therapy from the coronal plane, red arrow. MTS, main tract stenosis.

**Figure 3.** Sinus CT images. Sinus CT scans showed signs of local mucosal thickening of the bilateral maxillary sinus (black arrow).
doses of corticosteroids in combination with azathioprine or methotrexate in the maintenance period (14). However, a population-based cohort study of 195 patients observed a persistent increased risk for overall malignancies after the usage of cyclophosphamide (19). Clinical trials and observational studies have reached an agreement that glucocorticoids are a fundamental drug for the standard induction therapies in patients with GPA (20). A patient diagnosed with GPA manifesting as bronchial stenosis with MPO-ANCA (+) demonstrated a distinct reduction in a rash and improvement in arthralgia and systemic malaise following treatment with prednisolone (21). Immunosuppressive therapies have prolonged 5-year survival to 70-80%, but recurrence occur in ~50% patients within 1.5 to 15 years (18,20).

Persistent positive-ANCAs (22), CD27-CD38hi B-cell frequency (23) and non-standardized glucocorticoid therapy are key risk factors for a poor prognosis. Although endobronchial involvement may improve symptoms, further studies are required to investigate whether the incomplete excision of the lesion can cause a relapse of the existing granulomata development (24). Currently, targeting molecules, including B-cell activating factor (25), C5a receptor (26) and interleukin-6 (27), have been identified as potential candidates for therapies in treating GPA and to reduce the glucocorticoid-related drug reaction. However, further study is required to optimize the treatment individually. In the present case, although ANCAs serology was tested to be negative, GPA should also be considered as a differential diagnosis.

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Availability of data and materials

The data collected and analyzed during this study are included in this published article.

Authors' contributions

DBZ conceived and led the preparation of the manuscript. PZ conceived and collected the data. YZZ drafted the manuscript. YZZ completed the bronchoscopy and collected biopsies, as well as making the pathological sections. YYY issued the lung function report and drafted the manuscript. XIZ organized and analyzed the figures and pathological sections. JL performed the pathological photography, the literature search and discussed the manuscript. ZWZ prepared the immunohistochemical analysis and revised the manuscript. NZ designed the study, edited and revised the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Informed consent for all data and clinical history was obtained from the patient. Informed consent for all data and clinical history was obtained for all patients included in the study. All authors read and approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

References