Granulomatosis with polyangiitis (GPA) is one of the antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides. Monoclonal gammopathy of undetermined significance (MGUS) is a condition that presents with a monoclonal protein without any clinical manifestations related to the monoclonal gammopathy. Here we report a case of a man who presented with cutaneous nodules, lung cavity, otitis media, and hematuria. He was diagnosed as having GPA based on the renal biopsy, myeloperoxidase-specific ANCA positivity and clinical manifestations. A diagnosis of MGUS was also made because immunolectrophoresis revealed monoclonal Bence-Jones protein-lambda; there were no symptoms related to the monoclonal protein. He was treated with a combination of glucocorticoid and rituximab. It has been recognized that autoimmune disorders are associated with MGUS which progress to multiple myeloma (MM) with an average 1% annual risk. Additionally, it has been reported that a history of autoimmune disease increases the risk of death in patients with MM or MGUS. We suggest importance of screening both for monoclonal protein in patients with autoimmune disorder and for autoimmune diseases in patients with MGUS or MM.

Keywords: Granulomatosis; Polyangiitis; Monoclonal gammopathy

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a necrotizing vasculitis with few or no immune deposits that predominantly affects small vessels. It is frequently associated with myeloperoxidase-specific ANCA (MPO-ANCA) or proteinase 3-specific ANCA (PR3-ANCA). The AAV involves microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA) [1]. GPA is a necrotizing granulomatous inflammatory condition usually involving the upper and lower respiratory tract, with necrotizing vasculitis affecting small to medium-sized vessels. GPA is usually accompanied by necrotizing glomerulonephritis [1]. Monoclonal gammopathy of undetermined significance (MGUS) is defined as the monoclonal protein in persons without any features of multiple myeloma (MM) or a related malignant disorder [2]. Patients with MGUS should have a serum monoclonal protein concentration < 3 g/dL, < 10% plasma cells in the bone marrow, and no clinical symptoms related to the monoclonal gammopathy [3]. As a rule, MGUS precedes MM and carries an average 1% annual risk of progression to MM or other lymphoproliferative disorder [4]. Although the pathogenesis of MGUS and MM is still not well understood, evidence suggests that immune dysregulation and/or sustained immune stimulation be related to the development of these two hematologic disorders [5]. A recent population-based study and a case series showed that several autoimmune conditions were associated with a significant risk of developing MGUS [6]. A recent prospective study reported that 15% of patients with MGUS had a preceding autoimmune disorder [7]. There is insufficient data about the relationship between AAV and MGUS. Here, we report a case of GPA with concurrent MGUS.

Case Presentation

A 76-year-old Japanese man presented to our hospital with persistent fever and skin rash on both forearms which emerged one week earlier. Two years prior to the current presentation, he developed intermittent microscopic hematuria and was examined by abdominal ultrasound and urinary cytology. No significant abnormalities were found, and no further investigations were performed at that time. Six months before admission, a chest radiograph revealed a nodule in the left middle lung field; there were no other symptoms. He was referred to a pulmonologist and chest computed tomography (CT) and cultures and cytology of sputum were performed. The chest CT showed a cavity in the left lingular segment with mild interstitial pneumonia (Figure 1). Sputum cultures were all negative for bacterial, fungal, and mycobacterial growth. No malignancy was detected. The patient was followed up at that hospital. A month prior to admission to our hospital, he presented with vertigo and hearing loss in the left ear. A diagnosis of left otitis media with effusion was made, and he was treated by tympanic drainage. He had also received treatment for dyslipidemia and benign prostatic hypertrophy for several years. He reported no history of recent travel and no history of contact with a sick person. He was admitted to our hospital for further evaluation and treatment. He had no complaints of arthralgia, weight loss, oral ulcer, visual disturbance, epistaxis, hoarseness, dyspnea, chest pain, hemorrhagic diarrhea, headache, and paralysis. On physical examination, he appeared mildly ill. His temperature was 37.9°C, blood pressure 117/73 mmHg, pulse rate 71 beats per minute.
Immunoelectrophoresis revealed monoclonal Bence-Jones protein-lambda in serum and urine. Bone marrow aspiration cytology showed normocellular marrow with no dysplasia or increase in plasma cells. Karyotyping showed no abnormal chromosomes. A diagnosis of MGUS was made based on the presence of monoclonal Bence-Jones protein-lambda in serum at a concentration < 3 g/dL, < 10% plasma cells on bone marrow cytology, and no clinical manifestations of monoclonal gammopathy. Although the subtype of ANCA in this patient was MPO-ANCA, he had otitis media with effusion and a pulmonary cavity present for over 6 months which were considered as surrogate makers for granulomatous disease. Based on a classification algorithm proposed by Watts et al [8], he was diagnosed as having GPA.

Treatment was commenced with intravenous (IV) methylprednisolone 1 mg/kg/day and subsequently rituximab 500 mg/week was added. The therapy resulted in rapid improvement of fever, skin rash, hematuria, and proteinuria. The patient was switched from IV methylprednisolone to oral prednisolone 1 mg/kg/day after 1 week of administration; the dose was then tapered gradually. Two weeks after initiation of the treatment, Birmingham...
vasculitis activity score version 3 (BVAS version 3) decreased from 20 points to 1 point [9]. After the second dose of rituximab infusion, MPO-ANCA titer decreased from 1007 to 725 IU/mL, and peripheral B cell became undetectable. Rituximab infusion as remission induction treatment was stopped after the second dose because of the rapid clinical response and to prevent excess immunosuppression, which could lead to serious infections. We planned maintenance remission treatment with rituximab infusion every six months. Subsequently, the clinical course has been stable without any signs of flare, and he was discharged on hospital day 30. After four months of treatment, he was still in remission (BVAS 0 point) and MPO-ANCA titer decreased to 28.2 IU/mL.

Discussion

GPA is a necrotizing granulomatous inflammation that presents as varying clinical manifestations. GPA is one type of AAV. GPA and MPA are more common than EGPA, which accounts for only 10–20% of patients diagnosed with an AAV [10]. Distinct antigen-specific immunoassays revealed PR3-ANCA in 75–80% of patients with GPA and MPO-ANCA in 8–12% of these patients. In total, 11–15% of patients with GPA tested negative for both PR3-ANCA and MPO-ANCA [11]. The incidence of MPO-AAV and PR3-AAV varies worldwide. In Japan, it has been reported that 84% of AAV patients were MPO-ANCA positive [12]. In the RAVE trial, which compared rituximab with cyclophosphamide for induction treatment of AAV, ANCA specificity was not useful predictor of complete remission at six months both in the entire cohort and in the two treatment groups [13]. A post hoc analysis showed that complete remission at 6 months was achieved with comparable frequency in both treatment groups in the subgroup of 66 patients with MPO-ANCA (61% versus 64%; p = 0.80), whereas rituximab was significantly more effective than cyclophosphamide in the subgroup of 131 patients with PR3-ANCA (65% versus 48%; p = 0.04) [14]. Among patients with a clinical diagnosis of GPA, those positive for MPO-ANCA more frequently had limited disease without severe organ involvement, a higher prevalence of subglottic stenosis, a less frequent need for cyclophosphamide or rituximab therapy, and fewer relapses than those positive for PR3-ANCA [15]. Although a diagnosis of GPA was made in our case, we shortened the course of rituximab from 4 weeks to 2 weeks because of the rapid clinical response and to prevent excessive immunosuppression, which could lead to serious infections. As mentioned above, the subtype of ANCA (MPO-ANCA) in this patient, which is associated with fewer relapses also supported this shortening of the duration of remission induction therapy with rituximab [15]. In this patient, we found that MGUS was superimposed on GPA concurrently. The prevalence of MGUS increases with age. A recent population-based study reported that the prevalence of MGUS was 3.2% in persons ≥ 50 years of age and 5.3% in those ≥ 70 years [16]. Recently, it has been recognized that monoclonal proteins can cause kidney disease directly even if they do not meet the criteria for MM. These hematologic conditions that result in kidney disease are now defined as monoclonal gammapathy of renal significance (MGRS) [17]. The spectrum of renal diseases in MGRS is broad, including AL amyloidosis and proliferative glomerulonephritis with monoclonal immunoglobulin deposits and C3 glomerulopathy with monoclonal gammapathy and others [17]. A kidney biopsy is crucial to make the diagnosis. Renal biopsy is essential to ensure that the monoclonal gammapathy is pathogenic, and could provide information on whether the histopathology is prognostically significant [18]. A diagnosis of MGRS is made by demonstration of monoclonal deposits in the kidney. Monoclonal deposits can be comprised of monoclonal light chains, heavy chains, or intact immunoglobulins, but restriction to a single class of light chain and/or heavy chain is essential [17]. We diagnosed MGUS rather than MGRS in this case because immunohistochemical analysis of renal biopsy specimens showed non-specific deposits of IgG, and kappa and lambda light chains. Renal biopsy showed necrotizing glomerulonephritis and crescent formation accompanied by fibrinoid necrosis suggestive of small vessel vasculitis. Nasr et al. [19] reported that crescents were present in 32.4% of proliferative glomerulonephritis with monoclonal IgG deposits, but glomerular necrosis was observed in only 8.1%. It is possible that the monoclonal immunoglobulin produced by the B-cell clone in MGUS can interact with self-antigens and stimulate an autoimmune antibody. These processes may be related to the development of autoimmune diseases [20]. On the other hand, there is evidence that immune dysregulation and/or sustained immune stimulation might have an effect on the development of MM and MGUS [5]. Thus, MM/MGUS could develop owing to chronic inflammation of autoimmune disorder.
A recent meta-analysis demonstrated that autoimmune disorders were associated with a nearly 42% increase in risk of MGUS [21]. However, it was difficult to provide a pathological correlation between GPA and MGUS in this case. Case report of AAV concurrent with MGUS is scarce. Esnault et al. [22] reported that ANCA were detected in 8–10% of patients with monoclonal gammopathies, but none of them had AAV. Recently, genomewide association study (GWAS) on MGUS patients showed common genetic SNP between MGUS and GPA [23]. This finding supports causal relationship between GPA and MGUS in our case. Further studies are needed to find out a causal relationship for monoclonal immunoglobulin in autoimmune disorders and to determine whether treatment of the underlying monoclonal proteins can result in clinical improvement [24]. It has been reported that a history of autoimmune disease increases the risk of death in patients with MM or MGUS [25]. Therefore, we should carefully follow patients who have MM or MGUS with autoimmune diseases. MGUS is known to progress to MM with an average 1% annual risk. More recently, it has been recognized that MGUS precedes appearance of MM by several years in nearly all cases [26]. Patients with MGUS should be regularly examined to avoid overlooking progression to a more severe condition such as MM or MGGRS. In conclusion, it has been recognized that autoimmune disorders are associated with MGUS or MM. We suggest importance of screening both for monoclonal protein in patients with autoimmune disorder and for autoimmune diseases in patients with MGUS or MM. In our case, screening for monoclonal protein in patients with autoimmune disorder could select for patients with MGUS or MM.

Consent

Written informed consent was obtained from the patient who participated in this study.

Conflict of Interest

None of the authors received any financial support and they declare no conflicts of interest.

References


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