Reumatologia 2015; 53, 6: 345–351
DOI: 10.5114/reum.2015.57642

Granulomatosis with polyangiitis – therapeutic challenge

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Abstract

The antineutrophil cytoplasmic antibody (ANCA) associated vasculitides (AAV) are a group of primary vasculitides that affect predominantly small- to medium-sized blood vessels. The pathology of granulomatosis with polyangiitis (GPA) typically features a granulomatous and sometimes necrotizing vasculitis targeting predominantly the respiratory tract and kidneys, including necrotizing granulomatous inflammation. The diagnosis can be delayed due to the nonspecific nature of the symptoms. Cyclophosphamide and glucocorticoids have been the cornerstone of remission-induction therapy for severe antineutrophil cytoplasmic antibody-associated vasculitis for years. Recently, the monoclonal antibody rituximab was approved for the treatment of GPA, providing an alternative to cyclophosphamide for induction therapy of AAV. In the present case study we used azathioprine as the maintenance drug. However, because of relapse we tried mycophenolate mofetil (MMF) as a second-line drug successfully. This case confirms that MMF is not only well tolerated but also effective in GPA to maintain remission.

Key words: mycophenolate mofetil, azathioprine, polyangiitis.

Introduction

The antineutrophil cytoplasmic antibody (ANCA) associated vasculitides (AAV) are a group of primary vasculitides that affect predominantly small- to medium-sized blood vessels. Granulomatosis with polyangiitis (GPA), formerly Wegener granulomatosis, typically features a granulomatous and sometimes necrotizing vasculitis targeting predominantly the respiratory tract and kidneys including necrotizing granulomatous inflammation [1, 2]. Granulomatosis with polyangiitis is a rare multisystem autoimmune disease of unknown etiology [3]. Granulomatosis with polyangiitis has a spectrum of clinical presentations that includes recurrent respiratory infection, renal and/or ocular manifestations, and nonspecific systemic symptoms. The clinical picture of this disease is not always typical, and due to various symptomatology its diagnosis may be a serious problem, and therefore a wide differential diagnosis is necessary. It should always be remembered that many diseases may imitate GPA. Therefore diagnosis, especially in cases with an atypical clinical course (negative serology, atypical location of organ lesions), has to be carefully evaluated and verified if possible [4]. The diagnostic criteria for granulomatosis with polyangiitis were established by the American College of Rheumatology [5].

Symptoms are often non-specific and diagnosis can be delayed. Limited disease refers to patients with AAV and one or more involved organ systems, but no renal disease or immediately life-threatening complications (Table I). Cyclophosphamide (CYC) and glucocorticoids (GC) have been the cornerstone of remission-induction therapy for antineutrophil cytoplasmic antibody-associated vasculitis for years. Recently, the monoclonal antibody rituximab (RTX) was approved for the treatment of GPA, providing an alternative to CYC for induction therapy of AAV.

Case report

A 59-year-old woman with a history of hiatal hernia was referred to a general practitioner's office because of

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Submitted: 13.11.2015; **Accepted:** 19.01.2016

Table I. EUVAS disease categorization of ANCA-associated vasculitis [4]

Category	Definition
Localized	Upper and/or lower respiratory tract disease without any other systemic involvement or constitutional symptoms
Early systemic	Any, without organ-threatening or life-threatening disease
Generalized	Renal or other organ threatening disease, serum creatinine < 500 µmol/l (5.6 mg/dl)
Severe	Renal or other vital organ failure, serum creatinine > 500 µmol/l (5.6 mg/dl)
Refractory	Progressive disease unresponsive to glucocorticoids and cyclophosphamide

cough, joint and muscle pain for about 8 weeks accompanied by elevated body temperature up to 38°C lasting for two weeks. Physical examination showed no abnormalities. Blood tests revealed mildly elevated leucocyte count with neutrophilia and elevated inflammatory markers, while urinalysis showed hematuria. Hepatitis and HIV infection were excluded. The concentration of rheumatoid factor and activity of creatine kinase were within references ranges. Chest X-ray and ECG were normal. Ultrasound scan of the abdominal cavity was performed but no pathology was found. Empirical antibiotic therapy was administered, but no improvement was observed after 7-day treatment as upper respiratory tract infection was suspected. Several courses of antibiotic therapy (e.g. azithromycin, ciprofloxacin) were administered on an out-patient basis to treat the upper respiratory tract inflammatory disease, but no clinical improvement was obtained. Rheumatological and hematological consultations were planned. However, after 3 months of the lack of effects of antibiotic therapies and persistent elevated body temperature the patient was referred to the Internal Medicine and Rheumatology Department (2010).

Laboratory tests demonstrated elevated inflammatory markers, i.e. erythrocyte sedimentation rate (ESR 88 mm/h), C-reactive protein level (127 mg/l), and white blood cell count (27.3 k/µl), as well as anemia (Hgb 11.7 g/dl). The creatinine level was 1.3 mg/dl, while glomerular filtration rate (GFR) was 50.8 ml/min/1.73 m^2. cANCA antibody level tested with ELISA significantly exceeded the reference values, while pANCA antibodies, antinuclear antibodies and rheumatoid factor were not found. The activity of creatine kinase was in the reference range. The urinalysis showed hematuria and proteinuria, but there were no clinical data on urinary tract infection. A urine culture was sterile. Additional signs and symptoms were manifested during hospital stay: cough, purulent and bloody discharge from the nose, nocturnal joint and muscle pain, arthritis of the small joints in the hands with several hours of morning stiffness. Chest X-ray showed multiple nodules in both lungs, some with cavitation. The patient was consulted by a laryngologist and a nephrologist. The laryngologist performed a biopsy which revealed a multisystemic necrotizing, granulomatous inflammatory process affecting small vessels. The urinalysis showed microscopic hematuria associated with proteinuria. The serum creatinine concentration was elevated (creatinine 1.6 mg/dl, GFR 41.3 ml/min/1.73 m^2). Therefore the renal biopsy was performed and histopathological examination revealed focal segmental glomerulosclerosis (FSGS).

Table II shows the results of imaging and laboratory tests at different stages of treatment. A diagnosis of granulomatosis with vasculitis was made on the basis of clinical, radiological and histopathological findings. The treatment was started with GC and pulses of CYC 15 mg/kg per dose every 2 weeks at the beginning (3 pulses) and next every 3 weeks for a total dose of 16 g. After treatment with CYC the maintenance therapy with azathioprine (AZA) was started. For a period of 5 years remission had been achieved.

The follow-up visits and examinations were continued at the Rheumatology Department Ambulatory Office. The patient was in good condition, laboratory tests were in the reference ranges, and there were no deviations in imaging studies. In April 2015, the patient showed no dyspnea, no fever, no respiratory tract or ENT disorders, and no skin lesions. The patient was in a good general condition, with vesicular breath sounds on auscultation, soreness and discrete edema of ankles, and degenerative changes.

Laboratory tests showed ESR of 17 mm/h and a C-reactive protein level of 13.7 mg/l. However, progression of the pulmonary lesion was observed in CT scans of the chest (large lumps in the superior lobe of the left lung that were not seen previously; Fig. 1).

The treatment was continued with mycophenolate mofetil (MMF) at the dose of 2 × 500 mg/day for 2 weeks, then 2 × 1 g/day, prednisone 7.5 mg/day and trimethoprim/sulfamethoxazole (960 mg/day) as infection prophylaxis was administered.

Table II. The results of imaging and laboratory tests at different stages of treatment

	Diagnosis	Remission after CYC treatment	Relapse	Remission after MMF treatment
Creatine (mg/dl)	1.6	1.1	1.7	1.0
GFR (ml/min/1.73 m^2)	41.3	60.1	38.8	66.1
cANCA	+++	+	+++	+
ESR mm/h	88	14	11	7
CRP mg/l	127	6.2	13.7	2.6
WBC (k/µl)	27.3	11.4	24.5	10.5
Hb (g/dl)	11.7	12.8	11.3	13.1
Hematuria	+	negative	negative	negative
Proteinuria	++	negative	negative	negative
CT scans	positive	negative	positive	negative

After four months, the patient reported good general condition, and denied shortness of breath, joint pain, and fever. The treatment was tolerated well. On physical examination, normal breath sounds were present, joint mobility was preserved, and joint swelling was absent. Laboratory tests showed low ESR 7 mm/hour, CRP 2.6 mg/l; blood cell counts and renal and liver tests were normal. The chest CT demonstrated regression of lung lesions (Fig. 2). The treatment has been continued. After four months of treatment the patient did not suffer from side effects of MMF.

Discussion

Granulomatosis with polyangiitis and microscopic polyangiitis are systemic vasculitides with small to medium vessel involvement. Together with idiopathic pauci-immune necrotizing glomerulonephritis, which is considered a renal limited variant of MPA, they are the most common cause of rapidly progressive glomerulonephritis. These entities are frequently associated with ANCA, and are therefore categorized together as AASV [6]. The pathogenesis of granulomatosis with polyangiitis has

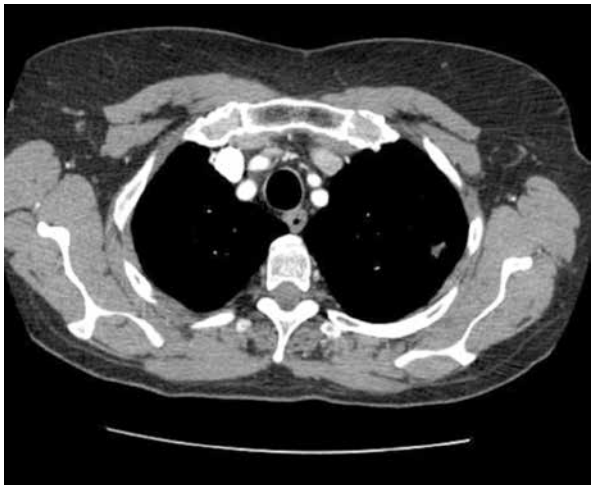

Fig. 1. Areas of consolidation with retraction and band-like extensions towards the pleura are visible in segments 1/2 and 3 of the left lung. These lesions are up to 1.5 and 2 cm diameter. Multiple minor ill-defined masses are localized in lower lobes of both lungs. Progression is seen in comparison to previous scan.

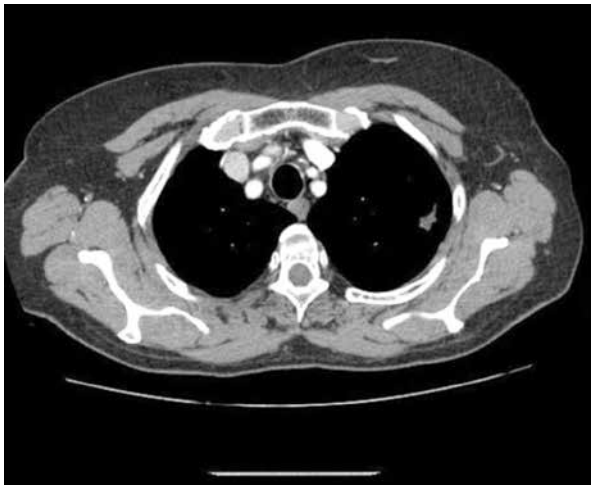

Fig. 2. Regression of nodular masses in segments 1/2 and 3 of the left lung to the size 10 and 12 mm in diameter. Regression of multiple nodules of both lungs (diameter up to 1 mm). Conclusion: partial regression of nodular masses in superior lobe of the left lung, otherwise CT image is comparable to previous examination.

not been explained completely, but both cellular and humoral components are involved. Circulating ANCA play a key role in the pathogenesis of the disease and may correlate with its activity. GPA is a systemic, necrotizing and granulomatous vasculitis that affects predominantly the upper and lower respiratory tract and the kidney. It is the most common ANCA vasculitis. Fever is a common clinical phenomenon. In most cases, the cause of fever can be determined quickly.

The clinical problem starts when the patient has fever for a long period without any easily detectable cause. The cause of fever can be classified as follows: infectious agent, neoplasm, immune or metabolic disorder, genetic abnormality of inflammasome functioning. The clinical course of fever may vary (continuous, remittent, intermittent, hectic). Detection of the cause of chronic fever is not always possible. Infections, pharyngitis, pneumonia, sarcoidosis, bacterial and infective endocarditis, meningoencephalitis, aseptic meningitis, hepatitis, atypical pneumonia caused by viruses, *Chlamydia* species, or *Mycoplasma tuberculosis*, human immunodeficiency virus, abscess, appendicitis, cholecystitis, and carcinoma should be considered in the differential diagnoses. Due to the prevalence of different symptoms, diagnosis is often established quite late. Symptoms of the disease tend to be in varying degrees of severity. At the beginning they may be slight, making the diagnosis of GPA challenges for clinicians.

The diagnosis of GPA is made on clinical manifestations, histological findings and the presence of ANCA in serum. The American College of Rheumatology criteria include: oral and nasal inflammation, abnormal chest radiography (nodules, fixed infiltrates, or cavities), urinary sediment (hematuria), and granulomatous inflammation on biopsy [5]. Treatment of GPA is divided into 2 phases: induction of remission (IR), followed by a maintenance phase (MP). In the IR it is necessary to use intensive immunosuppressive therapy (for example CYC and steroids). The MP is a less intensive therapy in which immunosuppressors (IS) such as AZA, methotrexate (MTX), and MMF, among others, may be employed. Their purpose is to maintain remission and lower the adverse effects associated with IS.

Maintenance therapy is mandatory to reduce the relapse rate. Nowadays, in the majority of patients disease can be brought into remission with CYC and GC. However, depending on disease characteristics patients with AAV have a 29–60% risk of experiencing relapses of disease within 5 years despite maintenance therapy after induction of remission with less toxic agents, such as AZA, MTX or MMF [7]. More recently, RTX has been found effective in both induction and maintenance of remission in AAV [8]. Azathioprine is the main maintenance drug, although MTX, MMF or leflunomide (LEF) may be used as a second-line drug [9]. Hiemstra et al. [10] showed that relapses were more common in the MMF group (42/76 patients) compared with the AZA group (30/80 patients). In the present case study we tried AZA as the maintenance drug. However, because of relapse we used MMF as a second-line drug successfully.

Cyclophosphamide at the induction phase followed by AZA is a frequently used therapeutic regimen and is associated with a high remission rate. This regimen is widely used in many centers [11, 12]. Intravenous intermittent administration of CYC is equally effective in inducing remission as daily oral administration and is associated with fewer adverse effects, but the relapse rate is slightly higher (CYCLOPS study) [13]. Cyclophosphamide and GC have been the standard therapy for remission induction for decades [14]. However, not all patients have a remission with this combination of drugs, and those who do often have disease flares requiring repeated treatment. Moreover, patients also suffer from side effects of CYC, including infertility, cytopenia, infections, bladder injury, and cancer, as well as the multiple adverse effects of lengthy courses of glucocorticoid treatment. For remission maintenance the choice may be AZA or MMF.

Azathioprine is an immunosuppressive drug used in organ transplantation and autoimmune disease and belongs to the chemical class of purine analogues [15]. The main adverse effect of AZA is bone marrow suppression, which can be life-threatening. Azathioprine is also listed by the International Agency for Research on Cancer as a group 1 carcinogen (carcinogenic to humans). Methotrexate is equivalent to AZA for maintenance therapy, but adverse effects are not lower [16]. Its prescription should be restricted to patients with a localized form of GPA and during the maintenance period [12, 17].

In generalized, non-organ-threatening disease, remission can be induced with methotrexate and steroids, where the steroid dose is reduced after a remission has been achieved and MTX used as maintenance. In the case of organ-threatening disease, intravenous CYC with GC is recommended. Once remission has been achieved, AZA and GC can be used to maintain remission. In severe kidney vasculitis, the same regimen is used but also plasma exchange may be needed. In pulmonary hemorrhage, high doses of CYC with intravenous methylprednisolone may be used, or alternatively CYC, steroids, and plasma exchange. Randomized controlled trials have shown that RTX is non-inferior to CYC followed by AZA (CYC/AZA) for remission induction in severe GPA and MPA [17]. Current approaches to treatment in induction and maintenance of AAV are well established (Table III) [18].

Table III. Suggested schema for the management of ANCA-associated vasculitis, adapted and updated from Pallan et al. [22]

Disease severity	EUVAS definition	Induction therapy	Maintenance therapy
Localized	Upper and/or lower respiratory tract disease without any other systemic involvement or constitutional symptoms	MTX and GKS	Low-dose steroids plus AZA or LEF or MTX (+ trimethoprim-sulphamethoxazole also added)
Early systemic	Any, without organ-threatening or life-threatening disease	MTX or CYC and GKS	Low-dose steroids plus AZA or MTX
Generalized	Renal or other organ threatening disease, serum creatinine < 500 µmol/l (5.6 mg/dl)	CYC (or RTX) and GKS	Low-dose steroids plus AZA MMF as second-line agent
Severe	Renal or other vital organ failure, serum creatinine > 500 µmol/l (5.6 mg/dl)	CYC and steroids plus plasma exchange (RTX instead of CYC)	Low-dose steroids plus AZA MMF as second-line agent
Refractory	Progressive disease unresponsive to GC and cyclophosphamide	Deoxyspergualin, antithymocyte globulin, or RTX	No consensus

MTX – methotrexate; GC – glucocorticoids; AZA – azathioprine; LEF – leflunomide; RTX – rituximab; MMF – mycophenolate mofetil; CYC – cyclophosphamide

Mycophenolate mofetil, an immune suppressive initially introduced for the prevention of solid organ allograft rejection, is increasingly used in autoimmune conditions, including vasculitis. Varying efficacy of MMF in ANCA-associated systemic vasculitides was observed, with over 50% of patients with relapsing disease achieving remission and marked falls in concomitant steroid doses. However, longer follow-up indicated a subsequent relapse rate of over 50% that may be associated with low MMF dosing [19]. In patients with ANCA-associated systemic vasculitides and renal involvement, MMF seems to be an effective and well-tolerated option in sustaining short- and medium-term remission [20]. The use of MMF in autoimmune disease is often limited by adverse effects. However, all patients should know that the side effects of MMF may be constipation, nausea, headache, diarrhea, vomiting, stomach upset, loss of appetite, bloating or trouble sleeping. Mycophenolate mofetil weakens the immune system and may make patients more likely to develop infections. Mycophenolate mofetil is a strong immunosuppressive drug with rather low toxicity due to its lymphocyte-selective mode of action [21].

Rituximab constitutes promising therapy for refractory GPA [22]. Rituximab associated with glucocorticoid treatment adapted for disease severity appeared to induce remission effectively in GPA patients. Maintenance treatment with low doses of RTX in a routine time-based protocol is safe and associated with low rates of relapse on treatment [23]. Rituximab is an effective remission-inducing agent in GPA. The addition of a conventional maintenance agent to RTX and GCs decreased the incidence of relapse and did not result in a higher incidence of adverse events [24]. Rituximab is generally well tolerated, but side effects include leucopenia and infection.

The European League against Rheumatism (EULAR) guidelines for the management of small and medium vessel vasculitis have been published [25]. The success and safety profile of RTX in refractory disease has led to trials in maintenance and induction therapy which may see it recommended as standard practice, although high cost may limit its use. The wide range of newer biologic agents now available brings huge possibilities for immunotherapy in relapsing or refractory disease. The RITUXVAS trial reported similar remission induction rates and safety between RTX- and CYC-based regimens for ANCA-associated vasculitis at 12 months [26]. Duration of response to RTX can be variable but is frequently prolonged, with a median time of 12–16 months [27].

The Rituximab in ANCA-Associated Vasculitis (RAVE) trial was a multicenter, randomized, placebo-controlled trial that compared RTX for remission induction and maintenance with standard therapy consisting of CYC followed by AZA in patients with severe AAV [28]. Treatment with RTX plus GCs would not be inferior to daily CYC plus GCs for remission induction and would permit discontinuation of prednisone within 6 months [28]. The RAVE trial showed that RTX matched the efficacy of CYC (standard therapy) in inducing remission in patients with severe AAV. The results held true for subsets of patients with major renal disease and those with alveolar hemorrhage. There were no significant differences in flare rates at 6 months and no difference in the rate of severe adverse events. However, participants receiving CYC experienced more selected adverse events, particularly leukopenia. Due to the high mortality rate in GPA (28.5% in our patients), aggressive treatment is needed sometimes [29]. Previous randomized trials and clinical observations show some possible limitations of treatment with CYC and GCs, so RTX seems to be a good

alternative in those patients in induction therapy as well as in maintenance therapy [30, 31].

Summary

In conclusion, this case confirms that MMF is not only well tolerated but is also effective in GPA to maintain remission. Therapy should be chosen individually, depending not only on the stage and severity of the disease, but also on genetic and some prognostic factors.

The authors declare no conflict of interest.

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