Management of Wegener’s Granulomatosis and Microscopic Polyangiitis

Case Studies and Commentary, Jason M. Springer, MD, Carol A. Langford, MD, MHS, and Curry L. Koening, MD, MS

Abstract

- **Objectives**: To present key concepts in diagnosing and treating Wegener’s granulomatosis and microscopic polyangiitis.
- **Methods**: Review of the literature and case-based discussion.
- **Results**: Wegener’s granulomatosis and microscopic polyangiitis are rare systemic inflammatory diseases characterized by vasculitis of small and medium-sized blood vessels. Both diseases may affect any organ and can usually be differentiated by clinical history and physical exam. The kidneys and lungs are commonly affected in both diseases, and patients may present with symptoms of acute renal failure or hemoptysis secondary to pulmonary capillaritis. Recognizing the presenting signs and symptoms of these diseases may avoid delays in diagnosis and in initiating appropriate treatment, which can be organ- and life-saving. Prednisone used in combination with immunosuppressive medications such as cyclophosphamide has converted these conditions from universally fatal diseases into manageable chronic conditions.
- **Conclusion**: Familiarity with the presenting signs and symptoms together with knowledge of treatment strategies and potential drug toxicities are important in providing excellent care for patients with these rare conditions.

Wegener’s granulomatosis (WG) and microscopic polyangiitis (MPA) are chronic inflammatory diseases that are rapidly fatal if not recognized and treated promptly. Both cause vasculitis of small and medium-sized blood vessels and predominantly affect the kidneys and lungs (Figure). WG is differentiated from MPA as it also causes granulomatous inflammation that predominantly affects the nasal and paranasal sinuses [1]. The incidence of WG is estimated at 8 per million per year [2], while the incidence of MPA is estimated at 3 per million per year [2–4].

Therapeutic strategies that can induce and maintain a durable remission while sparing medication side effects have changed the approach to treating WG and MPA. Prior to the development of treatment, the mean survival time for WG was 5 months [5], with 90% of patients dying within 2 years of their diagnosis [6]. The advent of cyclophosphamide (CYC) used in combination with prednisone allowed for greater than 90% of patients to achieve some form of disease remission. CYC and prednisone changed the natural course of WG and MPA from being once rapidly fatal diseases to manageable chronic diseases [6].

Although the survival rates for WG and MPA have greatly improved, the morbidity rates caused by medications used to treat these diseases and the tissue damage caused by disease relapses have been less encouraging. The high rate of serious side effects associated with long-term CYC use led investigators to look for alternative therapeutic strategies that would allow for durable remission rates with less toxicity. These strategies have focused on either reducing the cumulative dose of CYC or avoiding the use of CYC altogether. Even though WG and MPA are clinically different diseases, most of the treatment strategies discussed in this article can be applied to both diseases.

The diagnosis of WG and MPA is suspected based upon a patient’s clinical history and physical examination. Approximately 20% of patients with WG will present with renal involvement on their initial visit, with frequencies of up to 77% being seen in some series. Up to 86% will develop glomerulonephritis at some point during their disease course [6,7]. Renal disease in both WG and MPA is usually asymptomatic and vigilance for detection is critical, as untreated renal vasculitis almost invariably leads to end-stage renal failure requiring renal replacement therapy. Active glomerulonephritis presents as microscopic hematuria, typically with proteinuria, and can be accompanied by a rapid rise in creatinine. Evaluation of a fresh urine sediment with light microscopy by an experienced observer in patients.

From the Department of Internal Medicine (Dr. Springer) and the Division of Rheumatology (Dr. Koening), University of Utah, Salt Lake City, UT; and the Center for Vasculitis Care and Research, Cleveland Clinic, Cleveland, OH (Dr. Langford).
with renal disease may show dysmorphic red blood cells (RBCs) or RBC casts. A definitive diagnosis can be made by renal biopsy, with the most common microscopic finding in WG and MPA being that of a focal, necrotizing, segmental crescentic glomerulonephritis with few to no immune complexes seen on immunofluorescence. If not treated promptly, end-stage renal disease invariably occurs and renal replacement therapy may be required.

**CASE 1**

**Initial Presentation**

A 37-year-old man presents to the emergency department with 3 days of hemoptysis and shortness of breath.

**History**

Over the past week, he has also noticed a red, raised rash on his feet and lower legs. He reports a 6-month history of nasal crusting and epistaxis and 6 sinus infections and 3 ear infections over the past 2 years. These infections originally responded to antibiotics, but these symptoms have become more resistant to treatment over the past year. He reports a 10-lb weight loss and severe fatigue that developed over the preceding 3 months.

**Physical Examination and Laboratory and Imaging Studies**

Physical examination reveals a thin-appearing male in moderate respiratory distress. His temperature is 101°F, blood
pressure is 90/60 mm Hg, and heart rate is 110 bpm. His right tympanic membrane is red with an air-fluid level. He has pain to palpation of his frontal and maxillary sinuses and bloody crusts noted on his anterior nasal septum. He has diffuse rales by lung auscultation and palpable purpura on his lower legs and feet. Initial blood work reveals a white blood cell (WBC) count of 12,000/mm³ with 76% neutrophils, 16% lymphocytes, and 2% eosinophils; hemoglobin of 10 g/dL; platelets of 495,000/mm³; sedimentation rate of 93 mm/hr; creatinine level of 3.5 mg/dL; and a urinalysis with 3+ hematuria and 1+ proteinuria. Urine microscopy reveals dysmorphic RBCs and RBC casts. Antinuclear antibody (ANA) testing is negative and serum antineutrophil cytoplasmic antibody (ANCA) testing is pending. A noncontrast computed tomography (CT) scan of the chest reveals bilateral pulmonary infiltrates and small, scattered nodules; the largest in diameter measures 2 cm and is located in the left upper lobe.

• What is the diagnosis?

The constellation of findings including upper and lower respiratory symptoms, renal dysfunction, and palpable purpura are most consistent with WG. The diagnosis of WG is suspected based upon a patient’s clinical history and physical examination. Head and neck manifestations occur in 99% of patients with WG [8]. Symptoms may include epistaxis, nasal crusting, sinus congestion, ear pain, hearing loss, eye pain, and redness. Less common ear, nose, and throat (ENT) manifestations include septal perforation, saddle-nose deformity, nasolacrimal duct obstruction, orbital inflammatory mass, and subglottic stenosis. Eighty-five percent of patients with WG will develop pulmonary involvement at some point in their disease course [6]. Pulmonary hemorrhage may be rapidly fatal if not diagnosed and treated early. It does not always present with hemoptyis and should be considered in any patient with dyspnea, a rapid drop in serum hemoglobin, or diffuse pulmonary infiltrates seen on chest imaging. Other lung manifestations of WG include lung nodules and/or cavities and bronchial stenosis secondary to inflammation.

Renal dysfunction is a common manifestation of WG and may present as rapidly progressive glomerulonephritis or as hematuria and/or proteinuria in the presence of a normal glomerular filtration rate. Palpable purpura commonly occurs in many patients with WG. Neurologic manifestations such as peripheral neuropathy, mononeuritis multiplex, or central nervous system involvement may also occur [9].

• What is the differential diagnosis?

Acute renal failure and pulmonary hemorrhage in the setting of sinusitis, serous otitis, and palpable purpura strongly suggest a systemic vasculitis such as WG. The differential diagnosis of WG also includes other forms of systemic vasculitis and mimics of vasculitis that can present with similar symptoms. Patients with MPA may present with clinical features similar to WG. These include pulmonary hemorrhage and acute renal failure. Upper airway manifestations such as nasal disease and hearing loss have been reported in MPA [7], but the cause is not known and not thought to be secondary to granulomatous inflammation as in WG. Patients with Churg-Strauss syndrome may develop lung nodules, pulmonary hemorrhage, and less commonly renal involvement. Sinusitis in association with nasal polyposis and mononeuritis multiplex are common manifestations of Churg-Strauss syndrome. Churg-Strauss syndrome is typically associated with eosinophilia and asthma, which this patient did not have. Patients with antiglomerular basement membrane (anti-GBM) disease (also called Goodpasture’s syndrome) and systemic lupus erythematosus may also present with lung and kidney failure, but upper respiratory involvement is unusual. Skin rash and pleural involvement are common in patients with systemic lupus erythematosus, whereas pulmonary hemorrhage is less common. Sarcoidosis can frequently affect the lungs and sinuses but kidney involvement is less common. Chest imaging in patients with sarcoidosis usually shows hilar lymphadenopathy and interstitial lung disease.

Mimics of WG can include bacterial infections with organisms such as Streptococcus pneumonia and Staphylococcus aureus, viruses such as cytomegalovirus, and fungal organisms such as coccidiomycosis, histoplasmosis, and blastomycosis. In this patient who presents with kidney manifestations and purpura, endocarditis is of particular concern. Malignancies may also present with symptoms similar to WG (Table 1).

• What laboratory and radiographic evaluation should be recommended in this patient?

The initial laboratory evaluation of a patient with suspected vasculitis should include a complete blood count (CBC), basic metabolic profile, liver enzyme tests, blood and sputum cultures, and a urinalysis. Patients with systemic vasculitis may present with a leukocytosis or thrombocytosis. Leukopenia...
and thrombocytopenia are unusual, and other diagnoses should be sought if these are detected. Patients suspected of having WG, MPA, Churg-Strauss syndrome, or renal-limited vasculitis should have their urine analyzed for hematuria and/or proteinuria. Urine microscopy may reveal dysmorphic RBCs or RBC casts, both of which are highly suggestive of glomerulonephritis.

Serum ANCA testing can be helpful if the diagnosis of WG or MPA is being considered. In patients with WG or MPA, 2 immunofluorescent patterns of ANCA may be seen: a cytoplasmic ANCA (cANCA) that is targeted towards proteinase 3 (PR3), an enzyme found in the granules of neutrophils, and a perinuclear ANCA (pANCA) directed against myeloperoxidase (MPO). PR3-cANCA can be found in 75% to 90% of patients with active WG, with 5% to 20% having MPO-pANCA. In patients with MPA, MPO-pANCA is the predominant antibody, occurring in over 85% of patients; PR3-cANCA is seen in 5% to 15%. ANCA should not be considered mandatory for the diagnosis of WG or MPA as up to 20% of patients may be ANCA-negative. Although the sensitivity and specificity of ANCA are high [10,11], the diagnostic utility will be influenced by the clinical picture, as WG and MPA are rare diseases. In patients who have a high pretest probability for the disease (eg, sinus, lung, and renal involvement), a positive ANCA has a sufficiently high predictive value that a tissue biopsy may not be necessary. However, in patients who have clinical features that carry a low pretest probability of disease (eg, sinus and pulmonary disease), the predictive value of a positive ANCA will be far lower such that a biopsy should be performed to rule out an infection, neoplasm, or another disease process. Although the presence of ANCA may be helpful in diagnosing WG or MPA, ANCA is also detectable in patients with Churg-Strauss syndrome and renal-limited vasculitis. Furthermore, patients with bacterial endocarditis, inflammatory bowel disease, autoimmune liver diseases, malignancies, or diabetes may have detectable ANCA [12]. These ANCA are usually targeted to proteins other than PR3 or MPO.

Serum ANA and complement levels may be helpful if patients are suspected of having systemic lupus erythematosus. Rheumatoid factor and cyclic citrullinated protein antibodies should be considered in patients with clinical features of rheumatoid arthritis. Serum anti-GBM antibodies are helpful if a patient is suspected of having anti-GBM disease and should be performed at initial presentation.

Chest imaging is necessary in all patients where WG and MPA are suspected since lung disease may be asymptomatic. Patients presenting with pulmonary hemorrhage may have bilateral lung infiltrates seen on radiographic imaging. Chest imaging in WG patients may reveal bilateral or solitary lung nodules. These nodules may be cavitary or solid in appearance. Noncontrast CT imaging of the chest is more sensitive than chest radiograph at identifying lung involvement [13]. For patients with lung infiltrates or cavitary lung nodules, a bronchoalveolar lavage is important to rule out infection in which the diagnosis may be unclear.

### What initial treatment should be recommended for this patient?

Treatment decisions should be based upon the severity of a patient's disease. Severe disease is defined as inflammation severe enough to pose a threat to a patient's life or vital organ function. Manifestations of severe disease in WG would include rapidly progressive glomerulonephritis, pulmonary hemorrhage, coronary arteritis, central nervous system involvement, vasculitis of the gastrointestinal tract, mononeuritis multiplex, peripheral neuropathy, scleritis, or retinal vasculitis. Some of these features may also occur in MPA. Nonsevere disease is defined as manifestations that do not pose a threat to vital organs and may include...
Table 2. Medications Used in the Treatment of Wegener’s Granulomatosis and Microscopic Polyangiitis

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adverse Events</th>
<th>Laboratory Monitoring</th>
<th>Contraindications (Relative and Absolute)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>Pancytopenia, hepatotoxicity, leukemia, lymphoma, infection, malignancy (skin), nausea/vomiting, rash, hypersensitivity, elevated liver enzymes</td>
<td>Weekly CBC, Cr, AST, ALT for first month, every other week for the second month, monthly thereafter</td>
<td>Homozygous TPMT deficiency; use with caution in TPMT heterozygous patients starting at a lower dose with close monitoring of CBC. Hypersensitivity to AZA, pregnancy. Avoid live vaccines. Increased risk of myelosuppression when combined with ACEi, significant interaction with allopurinol requiring AZA dose reduction</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Pancytopenia, hypersensitivity pneumonitis, liver fibrosis, cirrhosis, teratogenicity, liver enzyme elevation, stomatitis, diarrhea, infection</td>
<td>Weekly CBC, Cr, AST, ALT for first month of starting drug, every other week for the second month, monthly thereafter</td>
<td>Pregnancy, breast-feeding, severe pulmonary impairment, chronic liver disease, alcoholism, blood dyscrasias. Avoid live vaccines. Interaction with trimethoprim-sulfamethoxazole double-strength twice a day can be safely combined with doses given for Pneumocystis prophylaxis</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Adrenal insufficiency, avascular necrosis, osteoporosis, psychosis, gastric ulcers, Cushing’s, infection, psychosis, mood disorders, growth retardation in children, poor wound healing, glaucoma, cataracts, hyperglicemia, hypertension, weight gain, striae</td>
<td>Serum glucose every 2–4 weeks, annual bone density</td>
<td>Severe active infection</td>
</tr>
</tbody>
</table>

ACEi = angiotensin-converting enzyme inhibitor; ALT = alanine aminotransferase; AST = aspartate transaminase; AZA = azathioprine; CBC = complete blood count; Cr = creatinine; TNF = tumor necrosis factor; TPMT = thiopurine methyltransferase; UA = urinalysis.

sinus, skin, joint, or pulmonary disease without respiratory compromise [14].

Several medications have been studied in the treatment of WG and MPA (Table 2). For patients with severe disease, combination CYC and prednisone may be life-saving and is the treatment of choice. However, CYC has been associated with a number of severe side effects, especially when a patient has taken it for a long period of time. Acute toxicities can include infection, pancytopenia, and hemorrhagic cystitis. Some of the most severe side effects of CYC may be permanent and may not occur until several years after discontinuation of the drug. These include transitional cell carcinoma of the bladder, infertility, leukemia, lymphoma, and sterility [5,6]. The toxicity associated with CYC has led investigators to look for ways to limit patients’ cumulative exposure to CYC or ways to avoid CYC altogether. Today’s treatment regimens utilize an induction-maintenance approach whereby CYC is used for 3 to 6 months for remission induction. After remission is achieved, patients are switched to a less toxic medication such as methotrexate (MTX) or azathioprine (AZA) to maintain remission. For patients with less severe disease, remission induction and maintenance may be achieved using less toxic medications such as methotrexate.

Daily, oral CYC dosed at 2 mg/kg/day in combination with prednisone 1 mg/kg/day are effective at achieving a complete remission in 75% of patients with WG [1]. Because CYC is renally eliminated, dose adjustments are usually necessary in patients with renal insufficiency. Elderly patients are also at greater risk of CYC toxicity and represent another population where dose reduction should be considered. Intravenous (IV) CYC 15 mg/kg, 3 infusions given every 2 weeks then every 3 weeks thereafter, was compared with CYC 2 mg/kg/day given for 3 months followed by 1.5 mg/kg/day in a recent randomized trial [15]. Although IV CYC was found to be equally effective for inducing remission and was associated with a lower cumulative CYC dose and occurrence of leukopenia, the use of a consolidation phase and the frequency of blood count monitoring may have negatively influenced the daily CYC results. In addition, relapse occurred in 19% of those...
who received IV CYC as compared with 9% who received daily administration, although this study was not powered to detect a difference between relapse rates. If IV CYC is to be given, it should be used according to this schedule as this remains the only regimen for which there has been proven efficacy. These data support that daily CYC remains an effective option and provides support for limiting use to 3 to 4 months, thereby reducing the cumulative exposure, together with blood count monitoring every 1 to 2 weeks to prevent leukopenia.

For patients with life-threatening manifestations of WG or MPA, IV methylprednisolone at doses of 1 g/day for 3 consecutive days has been used by some investigators as initial therapy to prevent organ damage [14]. Plasma exchange has been used with some success as an adjunctive therapy in patients with rapidly progressive renal failure. Patients with renal dysfunction (serum creatinine > 5.8 mg/dL) due to WG or MPA who received plasma exchange as adjuvant therapy to CYC and prednisone had faster renal recovery than those who received CYC and prednisone in combination with IV methylprednisolone. However, 12-month mortality rates were no different between the 2 groups [16]. Although consideration of plasma exchange for pulmonary hemorrhage has been favored by some physicians, the published evidence supporting its efficacy is limited [17]. The role of plasma exchange for patients with renal or pulmonary failure due to MPA or WG is currently being tested in a multicenter randomized trial.

Rituximab, a monoclonal antibody directed towards the CD20 antigen found on the plasma membrane of B-lymphocytes, has been reported in some small case series to produce remission in patients who have failed or could not tolerate CYC [18–20]. Rituximab is currently being studied in 2 large controlled trials, both with encouraging preliminary results [21,22].

The optimal duration and initial dosing of corticosteroid therapy is still unknown. One approach is to initiate prednisone at 1 mg/kg/day (usually around 60 mg/day) for the first month. After 1 month, the prednisone can be tapered at a rate of 5 mg every 1 to 2 weeks until at 20 mg/day. The dose of 20 mg/day may be continued for 2 weeks then reduced by 2.5 mg every 1 to 2 weeks until a dose of 10 mg/day is reached. Then the prednisone may be reduced by 1 mg/week until discontinued unless the patient has a recurrence of symptoms.

**Patient Follow-up**

The patient returns to clinic for a follow-up visit 4 months after starting CYC and prednisone. His hemoptysis and rash have resolved but he continues to have some nasal crusting. His sinus congestion has improved, but he continues to have decreased hearing in his left ear. The hematuria has resolved and his creatinine is now 1.1 mg/dL. A noncontrast CT scan of the lungs shows complete resolution of the lung nodules with some scarring in the apices of both lungs.

- **How should this patient's medications be managed?**

This patient’s disease appears to be in remission. Remission is clinically defined as the absence of active inflammatory disease causing organ damage. In clinical trials, a variety of scoring instruments have been used to standardize assessment across investigators and to quantify active disease and disease-related damage [23,24]. While these scoring instruments are not routinely used in clinical practice, some clinicians find them useful in reflecting on the pattern of disease involvement and the spectrum of permanent injury that can occur. The persistent nasal crusting and hearing loss occurring in this patient may be due to damage of the nasal mucosa and middle ear structures caused by WG.

Jayne and colleagues [25] reported that patients who achieved remission initially with CYC and prednisone and switched to AZA 2 mg/kg/day between 3 and 6 months after induction therapy maintained remission rates similar to patients who continued CYC for 1 year. Other investigators have shown similar results with MTX [26,27]. This patient may be switched from CYC to either MTX or AZA as maintenance therapy as his serum creatinine is now normal and he does not have any other contraindications to MTX (Table 2). The decision to treat with MTX versus AZA should be based on individual factors, as Pagnoux and colleagues [26] demonstrated no appreciable difference in toxicities between the 2 drugs. MTX should be started at doses of 15 mg/week (0.3 mg/kg/week) and increased to doses of 20 to 25 mg/wk over 4 weeks. The recommended maintenance dose of AZA is 2 mg/kg/day. Not all patients will tolerate the recommended doses because of side effects. For these patients, the highest tolerable dose should be used [25–27].

Mycophenolate mofetil, an inhibitor of purine synthesis, dosed at 1000 mg twice a day, has been studied as a maintenance agent in WG, but there remain fewer published data with this agent than with MTX or AZA [28,29]. Leflunomide at doses of 20 to 40 mg/day has been effective in some studies at maintaining remission; however, toxicities such as an increased rate of infection, hypertension, peripheral neuropathy, and leukopenia raise concern with its use in patients with WG and MPA [30,31]. Etanercept, a tumor necrosis factor modulatory drug, added to standard maintenance therapy in patients with WG was not effective at maintaining remission when compared with placebo. Furthermore,
malignant tumors developed in 6 patients who had received both etanercept and CYC [14].

- How should this patient be monitored?

Despite the success of standard induction agents in achieving remission, 50% to 70% of remissions will be followed by 1 or more relapses [6,14]. Detecting relapses early and reinstituting therapy quickly is key in preventing further damage from WG or MPA. Clinical examination at a physician visit at least every 3 months may help detect signs of disease relapse. Patients should be asked about symptoms that may be suggestive of active disease such as joint pain, epistaxis, weight loss, fevers, cough, and progressive neuropathy. Patients should be examined for bloody nasal crusts, otitis media, sinus pain, eye inflammation, and rash. Patients should be taught to perform dipstick urinalysis at home on a weekly basis to detect asymptomatic renal disease that may present as new hematuria with or without proteinuria.

Patients should be monitored for toxicities related to their medications (Table 2). Patients receiving corticosteroids should periodically be evaluated for diabetes, hypertension, cataracts, glaucoma, and osteoporosis. CBC, serum creatinine, and liver enzymes performed on a regular basis are necessary to monitor for toxicities related to medications. Blood count monitoring should be performed every 1 to 2 weeks in patients receiving daily CYC and is essential in preventing leukopenia. The dosage of CYC should be lowered or temporarily held to maintain a WBC greater than 4000/mm³ (absolute neutrophil count > 1500/mm³). Patients starting MTX or AZA should have similar weekly blood tests drawn for the first month while the dosages are being adjusted. The frequency of these tests may be decreased to once per month once a stable dose has been reached and laboratories are stable. Monthly sedimentation rate, C-reactive protein, and urinalysis may be helpful in monitoring for disease relapse. Current data supports that a rising ANCA is not reliable in predicting relapse at the level of the individual patient and treatment decisions should not be made based on changes in ANCA titers alone [32].

- Should any medications be prescribed to prevent side effects caused by immunosuppressive medications?

Pneumonia caused by Pneumocystis jiroveci has been reported to occur in 6% of WG patients who did not receive prophylaxis against the organism. The risk is highest during the initial treatment period or during treatment for disease relapse. All patients treated for WG as well as MPA should receive chemoprophylaxis against Pneumocystis jiroveci [33]. One tablet of trimethoprim-sulfamethoxazole 160/800 mg given 3 times a week or 1 tablet of trimethoprim-sulfamethoxazole 80/400 mg prescribed daily will prevent most cases of Pneumocystis jiroveci. Patients with allergies or contraindications to taking sulfa medications may be prescribed either dapsone 100 mg daily or atovaquone 1500 mg daily. Monthly inhaled pentamidine 300 mg can also be used but may not offer the same degree of protection as the other agents [34].

Daily calcium and vitamin D is advised for prophylaxis against osteoporosis caused by chronic corticosteroid use. Bisphosphonates should also be considered in appropriate patients taking corticosteroids [35]. Oral proton pump inhibitors or histamine-2 receptor blockers may be considered by some providers for prophylaxis against gastric and duodenal ulcerations associated with corticosteroids. Care should be taken to avoid live, attenuated vaccines in patients receiving immunosuppressive drugs. In addition, live, attenuated vaccines should be avoided in household contacts [36]. Daily folic acid or weekly folinic acid replacement have been shown to reduce the hepatic side effects of methotrexate and may decrease the mucocutaneous and gastrointestinal side effects seen with methotrexate [37]. Oral cyclophosphamide should be taken once daily in the morning followed by at least two 8-oz glasses of fluid to reduce the risk of bladder toxicity. In some cases, mesna may be given in combination with IV CYC to reduce bladder toxicity [38]. Contraception should be emphasized for both male and female patients while being treated with potentially teratogenic medications. Depot leuprolide acetate 3.75 mg, a synthetic gonadotropin-releasing hormone analog, given before IV CYC was found to significantly reduce the rate of premature ovarian failure in female patients with systemic lupus erythematosus [39].

Further Follow-up

The patient presents to his primary care physician 3 years after discontinuing therapy for WG. He had been healthy until 3 months prior to his visit when he developed symptoms of sinus congestion, nasal crusting, epistaxis, and nonproductive cough. Physical examination reveals a new septal perforation with bloody crusts noted on the posterior edge of the perforation. He also has pain to sinus palpation. His skin exam is notable for palpable purpura. Laboratories including a CBC, complete metabolic profile, and urinalysis are normal. A noncontrast CT of the chest shows the development of 3 new lung nodules. One is noted in the left upper lobe and the other 2 are in the right lower lobe.
**WEGENER’S GRANULOMATOSIS**

- **How should this patient be managed?**

  The patient’s symptoms and physical examination findings are suggestive of a recurrence of WG. This is further supported by a CT of the chest revealing new lung nodules. His prior use of immunosuppressive medications places him at high risk of infection, which would need to be ruled out prior to restarting immunosuppression. For patients without critical organ dysfunction, weekly MTX at dosages of 20 to 25 mg/wk in combination with prednisone may be a reasonable induction agent [40,41]. De Groot and colleagues [41] showed weekly MTX in combination with prednisone was as effective as CYC in achieving remission in patients without severe organ dysfunction.

- **Are there disease manifestations of WG that may not be amenable to standard systemic therapeutics alone?**

  Nasal and paranasal sinus disease are the most common ENT manifestations in WG [42]. Inflammation of the nasal and paranasal mucosa may lead to sinus damage and poor mucosal drainage, which may lead to persistent sinonasal symptoms despite good control of the underlying disease. Daily nasal irrigation with saline can help to remove nasal crusts and prevent infections [43]. Subglottic stenosis occurs between 7% and 23% of patients with WG [6,44–47] and is often due to cicatricial scar formation from old active disease. Increased immunosuppression may not be beneficial in these patients, but many will respond to interventional therapies such as intraleisional corticosteroid injection in combination with subglottic dilation [46,48,49].

**CASE 2**

**Initial Presentation**

A 57-year-old woman presents to her primary care physician with symptoms of lethargy, confusion, and decreased urination.

**History**

The patient was hospitalized 3 years ago with pulmonary hemorrhage and acute renal failure. A renal biopsy at that time revealed focal, segmental necrotizing glomerulonephritis with few immune complexes. She was diagnosed with MPA and treated with 6 months of daily oral CYC in combination with prednisone. She was later switched to AZA 2 mg/kg/day and treated for 2 years followed by taper and discontinuation of the medication. She has had no recurrent symptoms of her original disease and has not returned to see a physician since discontinuing AZA. At her last physician visit, her serum creatinine was 3.2 mg/dL, which was similar to her baseline creatinine at the time she completed remission/induction therapy. Her urinalysis at that time showed no blood and only trace protein.

**Physical Examination**

Her physical examination is remarkable only for lethargy during the exam. Her serum creatinine is 9.2 mg/dL, blood urea nitrogen is 88 mg/dL, and potassium is 5.4 mmol/L. Her urinalysis reveals trace protein. Liver enzymes and a CBC are unremarkable.

**Disposition**

She is admitted to the hospital for hemodialysis. A kidney biopsy while in the hospital reveals sclerosis in 11 of 12 glomeruli but no active glomerulonephritis.

- **What clinical features are commonly seen in patients with MPA?**

  Alveolar hemorrhage, pulmonary infiltrates, and pulmonary fibrosis may occur in patients with MPA. Rapidly progressive GN is also a common feature of MPA. Similar to WG, mononeuritis multiplex, central nervous system vasculitis, and purpura may be seen. Myalgias, arthralgias, and weight loss are frequently reported. ENT disease has been reported with varying frequency in different series [7], which may be related in part to differing interpretations of nomenclature definitions [1]. Systemic treatment for MPA is similar to that of WG [50].

- **What options are available to this patient to manage her renal failure?**

  This patient does not have active glomerulonephritis or any other features of active MPA and thus does not require institution of immunosuppressive therapy. As supported by the renal biopsy, her current renal failure is due to chronic progression to end-stage renal disease in a patient who sustained a prior renal insult. Twenty percent of patients with kidney disease secondary to WG or MPA will develop end-stage renal disease and will require some form of renal replacement therapy for their survival [51,52]. Furthermore, patients with severe glomerulosclerosis on kidney biopsy were less likely to develop renal recovery [52]. Renal transplantation is a reasonable option for patients who require renal replacement therapy. Gera and colleagues followed 35 patients who
received a renal transplantation either for MPA (n = 20) or WG (n = 15) at a single institution. The 5-year graft survival rate for patients transplanted due to MPA or WG was 94% and 100%, respectively [53]. These graft survival rates are comparable to graft survival rates for patients transplanted for causes other than diabetes [54]. These authors noted 3 disease relapses after transplantation, of which none affected the allograft [53]. Renal transplantation appears to be a viable option for patients with WG and MPA.

CONCLUSION

WG and MPA are rare systemic vasculitides that can be life-threatening if not diagnosed and treated promptly. The diagnosis of these diseases is usually based upon clinical features together with confirmation by biopsy of an affected organ. A positive ANCA is valuable in suggesting WG and MPA but should only be used in place of a tissue biopsy for diagnosis in clinical settings where there is a high probability of disease. Combination therapy with CYC and glucocorticoids has improved the survival rates in both of these diseases but are associated with numerous side effects. Therapeutic strategies that decrease the exposure to CYC through the use of induction-maintenance regimens and alternative agents for nonsevere disease have enabled physicians to most effectively utilize the efficacy of CYC for severe disease while minimizing its potential for toxicity.

Corresponding author: Curry L. Koening, MD, MS, Div. of Rheumatology, Univ. of Utah, 4200 SOM, 30 N 1900 E, Salt Lake City, UT 84132 Curry.Koening@hsc.utah.edu.

References


