WEGENER'S GRANULOMATOSIS

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Abstract

The immunopathologic disease, Wegener's granulomatosis, presents a challenge to the anesthesiologist due to multisystem involvement resulting in potential abnormalities of the airway, respiratory, circulatory, renal, and central/peripheral nervous systems. It is a systemic vasculitis of small, medium and occasional large arterial involvement. A familiarity with the proper approach to perioperative management is essential. Additional considerations must be made as problems arise from immunosuppressant and corticosteroid treatment.

Keywords: Wegener's, granulomatosis, vasculitis, immunosuppressant, airway lesion.

Introduction

Wegener's Granulomatosis (WG), is an uncommon immunopathologic disease characterized by necrotizing granulomatosis in the upper and lower respiratory tracts combined with glomerulonephritis. It was first described by Klinger in 1933 and by other investigators such as Rossle in 1933, Wegener in 1936 and 1939 and Ringertz in 1947[1]. It is a systemic vasculitis of small, medium and occasional large arterial involvement. Arterioles as well as venules have also been implicated in the pathogenesis[2-6]. This rare disease has an estimated prevalence of 3 per 100,000 persons affected. While much more common in whites when compared to blacks, the disease shows no gender affinity with 1:1 male to female ratio. Presentation before adolescence is uncommon, and although the mean age of onset is approximately 40 years, it can be found at any age[7].

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Case Report

A 51-year-old, black female, weighing 68 kg and measuring 170 cm, without any significant medical or surgical history was flown in by air ambulance from the British Virgin Islands and presented with a four week history of bilateral lower extremity edema accompanied by hematuria, fever, and rash. She received hemodialysis, vancomycin, prednisone, and furosemide for acute renal failure. She went into respiratory failure and required intubation and ventilator support shortly after, with settings of 50% fraction of inspired oxygen, a respiratory rate of 18 breaths per minute, and a tidal volume of 600 mL prior to air ambulance. She has no known allergies. She denied use of nicotine, alcohol, or drugs. Family history was positive for lymphoma, brain tumor, and gastric cancer.

Physical exam revealed a middle-aged female, awake and comfortable on ventilator support. She was afebrile with a blood pressure of 131/78 mmHg, a heart rate of 97 beats per minute, and an O_2 saturation of 100%. Pulmonary exam revealed mild bilateral rhonchi throughout all fields. The rest of the exam was unremarkable.

Laboratory data showed a white blood cell count of 10.8 x 1,00/mL, hemoglobin of 9.2 g/dL, hematocrit of 27%, and platelets of 99,000/mL. Metabolic panel revealed sodium of 138 mEq/L, potassium of 4 mEq/L, chloride of 104 mEq/L, Bicarbonate of 27 mEq/L, blood urea nitrogen of 42 mEq/L, and creatinine of 3.7 mg/dL. Albumin was 1.9 g/dL. Autoimmune serologies revealed positive ANA greater than 1:1280 and ANCA greater than 100 along with low levels of complement. Cardiolipin antibody was negative. Prothrombin time was 14.7 seconds, partial thromboplastin time was 34 seconds, and INR was 1.5.

Chest radiography revealed bilateral interstitial infiltrates. Echocardiogram revealed mildly elevated pulmonary pressure. A renal biopsy was performed and showed sclerosing crescentic glomerulonephritis.

After renal biopsy, the patient was taken for right lung biopsy by video assisted thoracoscopic surgery. Arterial blood gas showed pH of 7.45, pCO_2 44 torr, pO_2 79 torr, CO_2 of 30 mmol/L, and an O_2 saturation of 40%. Assist control ventilation settings included a respiratory rate of 18 breaths per minute, a tidal volume of 500 mL, FiO_2 of 100%, and a PEEP of 5.

After application of routine monitors, the patient was pre-oxygenated and administered 2 mg midazolam as well as cistracurium 20 mg IV. General anesthesia was induced with 100 mg fentanyl. The patient was intubated with a double lumen tube (DLT) to allow collapse of the left lung. After biopsy, the DLT was exchanged for an 8.0 cuffed ETT. The patient was escorted out of the operating room with packed red blood cells infusion, stable vital signs, and a triple lumen catheter placed in the left subclavian vein.

Tracheostomy was performed 9 days later with a delay due to an elevated partial thromboplastin time of 53.1 seconds and platelets of 28/mL. After 4 units of platelets and 2 units of fresh frozen plasma, PTT shortened to 29.4 seconds and platelets increased to 44/mL. After routine monitors were applied, the patient was pre-oxygenated and administered 12 mg cistracurium in 3 equal doses over thirty minutes. Tracheostomy was performed without complication. Assist control ventilation was set to 18 breaths per minute with a tidal volume of 500 mL, a PEEP of 8, and an FiO_2 of 50%, and the patient was escorted to the ICU.

The rest of the hospital course was uneventful. The patient tolerated tracheostomy collar well, continued with hemodialysis three times per week, was administered IV methylprednisolone and monthly cyclophosphamide, and plans for psychiatric and rehabilitation therapy were coordinated.

Clinical Manifestations

Involvement of the upper airways occurs with a 95% prevalence in WG patients. They often present with severe upper respiratory tract findings. In addition to paranasal sinus pain and drainage, these finding can include purulent or bloody discharge not necessarily associated with nasal mucosal ulceration. In addition to an upper respiratory tract contribution to the disease, lower respiratory tract symptoms may be present and may include cough, dyspnea, and hemoptysis in 85-90% of patients. Chest x-ray findings are varied but can include alveolar opacities, diffuse hazy opacities, nodules (may cavitate) and pleural opacities[8]. The second most common clinical manifestation occurs in

the kidneys in 77% of patients. This common trait of WG can manifest as acute renal failure with microscopy revealing red cells, red cell casts, and proteinuria without evidence of immune complex deposition on biopsy[2].

While WG is known for upper and lower airway involvement with associated kidney manifestations, any area of the body may be affected. Among others, eye and skin involvement occur with a relatively high frequency. Eye involvement occurring in 52% of patients ranges from mild conjunctivitis to dacryocystitis, episcleritis, and other pathology. Consequently, these pathologies may lead to proptosis. Skin lesions can occur as papules, vesicles, palpable purpura, ulcers or subcutaneous nodules [Table 1].

Table 1
Systemic manifestations of Wegener's Granulomatosis

Organ System	Manifestations	Reference
Eyes	Conjunctivitis, episcleritis, nasolacrimal duct obstruction, proptosis, retinal vasculitis, corneal ulceration, optic neuropathy, diplopia, uveitis	9, 10
Nervous	Cranial nerve abnormalities, external ophthalmoplegia, mononeuritis multiplex, central nervous system mass lesion, hearing loss	9
Heart	Myocarditis, pericarditis, conduction system abnormalities	9
Skin	Palpable purpuric, hemorrhage, vesicular ulcerative lesions	11
Joints	Arthritis, myalgias, arthralgias	9
Others areas that may show involvement	GI and GU tracts, subglottis or trachea, thyroid, parotid glands, breast, liver	

WG is also known for having nonspecific symptoms such as night sweats, malaise, fatigue, arthralgias, anorexia, and weight loss. Fever can be present but often represents an underlying infection as opposed to the primary disease process[2]. WG may present, rarely, with tumor-like masses outside the lung instead of parenchymal lung nodules. If these cases are not recognized, unnecessary surgeries may ensue[12].

There can be misleading similar renal lesions without the necessary systemic problems of Wegener's. These patients are considered to have microscopic polyarteritis. Others with no systemic symptoms may be presumed to have idiopathic necrotizing glomerulonephritis; however, both of these disorders may develop the classic respiratory tract lesions[13] or possess antineutrophil cytoplasmic antibodies (ANCAs) resulting in a similar and possibly exact picture of WG[14-15].

Lab Findings

Aberrant hematologic lab values are most notable, evidenced by a markedly elevated erythrocyte sedimentation rate (ESR), normocytic normochromic anemia, leukocytosis, and thrombocytosis. Mild hypergammaglobulinemia (particularly of the IgA class) is also a characteristic lab finding[2].

Diagnosis

Diagnosis is confirmed by biopsy demonstrating necrotizing granulomatous vasculitis. The biopsy of a nasopharyngeal lesion, if present, is preferred since this method is less invasive. However, If this lesion is not present or unable to be biopsied, an affected organ, such as the kidney or lung, may be biopsied. The renal biopsy is preferable because it is easier to perform and more often diagnostic than a lung biopsy. The results are distinct showing segmental necrotizing glomerulonephritis with little or no immunoglobin deposition (pauci-immune)[16]. The diagnosis is also suggested by the presence of circulating ANCAs that are usually directed against proteinase 3 (c-ANCA). A range of 65% to over 90% of patients with Wegener's granulomatosis are positive for ANCA[14-15,18].

Differential diagnoses include other vasculitides (e.g. microscopic polyarteritis), Goodpasture's syndrome, tumors of the upper airway of lung, and infectious processes. These host of infections include histoplasmosis, mucocutaneous leishmaniasis, rhinoscleroma, lymphomatoid granulomatosis and the spectrum of midline destructive diseases. Special attention must be paid to anti-glomerular basement membrane (GBM) antibody disease because this pathology may present similarly to Wegener's as it manifests with both renal and pulmonary components[17].

Pathogenesis

Histopathologic hallmarks of WG are necrotizing vasculitis of small arteries with granuloma formation that may be either intravascular or extravascular. The complex process begins with an inflammatory event. Later, a highly specific pathogenic immune response follows where previously unavailable epitopes of neutrophil granule proteins come into play. This mechanism is responsible for the generation of the high serum titer of autoantibodies (or ANCAs). These ANCAs are then directed against the primary granules of neutrophils and monocytes, with proteinase-3 (PR3) and Myeloperoxidase (MPO) being most commonly targeted antigens[19-22]. The lung involvement generally appears as multiple, bilateral, nodular cavitary infiltrates. On the other hand, upper airway lesions, usually in the sinuses and nasopharynx, often reveal inflammation, necrosis and granuloma formation, with or without vasculitis[2].

The pathogenesis of Wegener's may involve a lack of alpha-1 antitrypsin (AAT) which *in vivo* is the primary inhibitor of PR3. Patients that have an AAT deficiency are at an increased risk for WG suggesting a role for the increased presence of PR3 at inflammation sites. Future research may establish a more concrete relationship[23-24].

The coordination of ANCA production begins with an autoantibody response which subsequently produces ANCAs. Via the process of epitope spreading, the mechanism generalizes to the rest of a macromolecular protein complex. Since the process is antigen driven, the disease may be intricately linked to T cell activation. This observation is supported by the fact that patients with active WG have much higher levels of CD4+T cell and monocytic activation compared to normal individuals. Additionally, extremely high levels of the Th1 cytokines, TNF-alpha and interferon (INF)-gamma, are seen in patients with active Wegener's. Furthermore, monocytes from these patients produce a large amount of interleukin-12, a major inducer of cytokines. Altogether these data suggest that IL-10, a monocyte antagonist, may inhibit the Th1 pathway in the disease as shown *in vitro*[25].

"Primed" neutrophils are those with increased numbers of cell surface levels of membrane associated PR3. Once these neutrophils are primed, the ANCAs can bind causing abnormal constitutive activation through crosslinking of MPO and PR3 or by binding of Fc receptors. This pathway is supported by the observation that patients with ANCA-associated vasculitis demonstrate increased numbers of primed neutrophils in renal biopsy specimens with severity resembling the activity of the disease. Moreover, the interaction and upregulation of neutrophil activity by endothelial cells may play an important role in pathogenesis[26-30].

Finally, recent animal models have shown evidence for the pathogenic potential of ANCAs. Two types of mice are employed: MPO knockout mice and recombinase-activating gene 2 (RAG-2) deficient mice. The RAG-2 deficient mice lack both T and B cells. In one model, MPO knockout mice were immunized with mouse MPO creating anti-MPO splenocytes and anti-MPO antibodies. RAG-2 deficient mice were injected with either anti-MPO splenocytes or control splenocytes (those producing no anti-MPO antibodies). Mice that received anti-MPO splenocytes developed clinical features of ANCA associated vasculitides, whereas RAG-2 deficient mice that received the control splenocytes suffered only a "mild immune complex glomerulonephritis". From this we can conclude that ANCAs have pathogenic potential and require a functioning immune system to mediate this pathology[31].

Treatment

Aggressive immunotherapy is warranted in the case of WG since studies show that up to 90% of patients would die within two years without this treatment modality[2]. The mainstay of treatment that has reversed the drastic fatality numbers is cyclophosphamide combined with oral glucocorticoid. The current recommended dosage is 1.5 to 2 mg/kg per day of cyclophosphamide. Higher doses of 3-4 mg/kg per day may be given for several days to those that are acutely ill with severe disease. The dosage of cyclophosphamide should be adjusted to maintain the leukocyte count above 3000/μL while keeping an absolute neutrophil count above 1500/μL. The dose of corticosteroid for the first month is usually 1 mg/kg per day of oral prednisone. After clinical signs of disease remission throughout the first month, this dose

may be tapered down to 5-10 mg/week. Furthermore, this regimen should be followed for one year after complete remission and then gradually tapered down and stopped. Complete remission may take months to 1-2 years to achieve, with a median time of 12 months[2]; however, a 2003 study involving 155 patients with ANCA-associated vasculitis may have a better estimate of 77% remission within 3 months and 93% remission within 6 months[32]. The former study more likely shows a population of patients with more severe disease, i.e. greater than the median. The dosage of glucocorticoids should be administered at the beginning of the cyclophosphamide treatment usually in the form of prednisone 1 mg/kg per day for the first month. Afterwards, one may use an alternate day schedule. Finally, the course of therapy is tapered and discontinued after approximately six months of treatment[2].

Using the cyclophosphamide-corticosteroid regimen outline from above, greater than 90% of patients have significant improvement while 75% of all patients will achieve remission. Unfortunately, up to 50% of those who achieve remission will have a relapse[2]. Most relapses are once again inducted into remission, however, at some point many patients will experience some degree of morbidity from the disease such as renal insufficiency, hearing loss, tracheal stenosis, and saddle nose deformity. Therefore, it is important to note that having elevated ANCA titers is not necessarily indicative of active disease as titers may remain elevated for years after remission[32-36].

Monthly intravenous cyclophosphamide must be considered as an alternate regimen due to the toxic side effects of a daily cyclophosphamide dose. At present, studies have shown an equal or lesser effect of using monthly dosing[37]. Another treatment option involves the use of a methotrexate-prednisone course of therapy. This modality has been shown to be efficacious in patients other regimens have been unsuccessful. The methotrexate was well tolerated with reversible GI disturbances, pneumonitis and oral ulcers reportred in some cases[38]. If using methotrexate, one must incorporate folic acid at 1-2 mg/day or folinic acid 2.5-5 mg/week (24 hours after taking methotrexate). Plasmapheresis, another alternative, may help those with severe pulmonary hemorrhage, anti-GBM antibody disease, or dialysis dependent renal failure[39]. Cyclophosphamide resistance is rare with some experts citing that they never have seen a patient with a true form. Treatment is unclear, and simple adjustment of dose or monitoring of compliance oftentimes may ameliorate the "resistance".

Drug side effects can be numerous from the above medications. The glucocorticoid side effects may include diabetes mellitus (8%), cataracts (21%), osteoporosis, and cushingoid features. Cyclophosphamide related side effects are more severe with at least 30% of patients developing cystitis. Bladder cancer will manifest in 6%, myelodysplasia in 2% and a high risk of permanent infertility in both women and men[2]. Although the risk is low, a fatal complication of immunosuppressive therapy in WG is neumocystis carinii pneumonia (PCP), which occurs in as many as 6% of patients. Prophylaxis with trimethoprim-sulfamethoxazole at 160/800 mg three times weekly, may not only be cost saving but also life prolonging[40-41].

After the disease enters remission, maintenance doses utilizing different medications are employed in order to lessen the aforementioned toxicities. Methotrexate at 0.3 mg/kg per week may be administered orally in place of cyclophosphamide. If this drug is tolerated, and increased regimen can be administered and maintained for two years, then tapered down, and ultimately discontinued. Furthermore, azathioprine at 2 mg/kg per day can be given as an alternative to methotrexate. Additionally, since there are no head to head comparison studies of these two drugs, debate still exists as to which regimen is superior[42-43].

If apparent manifestations of kidney failure are present, renal transplantation may be performed, although there is limited data as to long term outcomes. Case reports show that both renal and extrarenal manifestations may still occur. Even the ureter can become involved, possibly leading complications of stenosis and obstructive uropathy. In addition, relapse rates may be lower due to continued immunosuppression, but long term results in the "cyclosporine" era are unavailable[44-48].

Several alternative therapies and maintenance medications such as trimethoprim-sulfamethoxazole, mycophenolate mofetil, and cyclosporine have been

employed with varying success. Currently, no consensus has been reached on their benefit owing to the paucity of data. Future therapies utilizing anticytokines, anti-T/B cell antibodies, IV immunoglobulin, etoposide (chemotherapeutic agent), and 15-deoxyspergualin (immunosuppressant) are being studied with hopes of limiting remission and decreasing morbidity and mortality not only from the primary disease but also from the treatments themselves[49-57].

Perioperative Anesthetic Considerations

Pre-operative assessment

The approach to the patient with WG begins with a careful preoperative assessment which includes upper airway evaluation, chest x-ray, and if warranted pulmonary function tests (PFTs). Evaluation of the upper airway is used to recognize any ulcerating or obstructing lesions, as they are present in 95% of cases. Symptoms and complications secondary to these lesions include cough, dyspnea, hemoptysis, pleuritic chest pain, pneumothorax, and pulmonary hemorrhage. Chest x-ray may reveal nodules, cavitations, consolidation, effusions, pleural thickening, or hilar lymphadenopathy. PFTs may show reduced lung volumes complicated by obstructive airway disease patterns[58].

Respiratory

Patients with WG commonly have destructive lesions of the epiglottis. A thickened or fibrotic laryngeal wall may be present, which may result in a narrow lumen, with or without evidence of vasculitis. The laryngeal mucosal lining may be lost or even replaced by granulation tissue. Additionally, ulcerative or proliferative types of lesions commonly present with subglottic involvement.

Laryngoscopy should be used by the anesthesiologist to identify ulcers on the palate, pharynx, or epiglottis. Palatal or pharyngeal perforations may be observed, as well. Afterwards, careful planning and gentleness should be advised during the intubation to avoid bleeding from granulomas or displacement of brittle, ulcerated tissue down into the trachea or larynx. In fact, preoperative tracheostomy may be necessary if ulcers and lesions are extensive. Following extubation, edematous granulation tissue may obstruct the airway, therefore close observation postoperatively is compulsory. Finally, a regional anesthetic approach may be preferable to avoid airway instrumentation and its inherent complications in this population[59].

If vasculitis is present in the lungs, progression may lead to total occlusion of veins and arteries. Usually thin-walled cavities develop in the lower lobes, but thick-walled versions may grow secondary to central necrosis. These pulmonary changes may lead to increased dead space and mismatch of ventilation-perfusion. Furthermore, bronchial obstruction and/or destruction can lead to increased pulmonary shunting as well as arterial desaturation. For this reason, frequent suctioning of necrotic debris may be needed to keep the airway clear. Monitoring of arterial blood gases help assure that adequate oxygenation and ventilation occur. Even if a regional technique is employed, supplemental O_2 may be required[59].

Cardiovascular

Vasculitis of veins, peripheral arteries coronary arteries, granulomas, and necrotizing changes are included in the cardiovascular effects of WG. If coronary involvement is present, anesthetic management requires avoidance of intraoperative myocardial ischemia secondary to increased preload, afterload, heart rate, or coronary artery spasm. In cases with valvular heart defects or cardiomyopathy, hemodynamic status will determine the need for extensive monitoring and the use of adjuncts such as pacemakers and vasodilators. Digital arteritis and infarcts occurring at the tips of the digits may complicate the scenario. In these cases, the anesthesiologist use indwelling arterial lines with caution and limit the use of arterial punctures[59]. Lastly patients on corticosteroid therapy are typically given a standard dose of 100 mg of hydrocortisone immediately prior to surgery to prevent an Addisonian hypotensive crisis as long term therapy will reduce the capacity of the body to respond to the stress of surgery.

Renal

Glomerular destruction along with extensive tubular atrophy occurs in patients with WG. Caution should be used when administering anesthetics and drugs that require renal excretion. The following drugs

have active or toxic metabolites that are dependent on renal excretion: opioids including morphine, meperidine, diazepam, and midazolam; muscle relaxants including: vecuronium and pancuronium; and the anti-hypertensive sodium nitroprusside. Rapid accumulation of these metabolites may place the patient in significant danger. Moreover, one can anticipate a decrease in renal clearance of highly ionized, lipid-insoluble agents. It follows that maintenance doses of highly protein bound anesthetic agents will be 30-50% lower. Loading doses, which often are more dependent on redistribution than elimination, oftentimes remain the same[60]. Anesthetic agents that predominately depend on renal elimination are included in Table 2.

Table 2
Anesthetics predominately dependent upon renal excretion

Muscle Relaxants	Anticholinergic	Cholinergic	Cardiovascular
gallamine	atropine	neostigmine	digoxin
pancuronium	glycopyrrolate	pyridostigmine	milrinone
pipecuronium		edrophonium	amrinone
d-tubocurarine			amphetamines
vecuronium			
doxacurium			

Consideration must also be given to the possible depression of pseudocholinesterase activity following dialysis, the presence of hyperkalemia with resultant arrhythmias, hypertension, anemia, and coagulation defects, as in any patient with renal failure[59].

Use of Succinylcholine

The depolarizing neuromuscular blocking agent, succinylcholine, is hydrolyzed by the plasma pseudocholinesterase enzyme (PSC). Conditions that reduce the activity of this enzyme may lead to prolonged action of succinylcholine and extended apnea. The cyclophosphamide used to treat WG patients inhibits PSC, possibly in a dose-dependant manner[61]. There are other case reports of succinylcholine and even mivacurium causing prolonged apnea[62,63], but older case reports have described uncomplicated and successful use of succinylcholine in patients treated with cyclophosphamide, as well[64].

Regional Anesthesia

WG patients may be candidates for regional anesthesia, for example, when procedures concerning the urogenital tract may be needed. Cases have been described where spinal anesthesia in WG patients were used with success.

Some concerns for general anesthesia may also be concerning for a regional approach. A WG patient with cardiac disease may also have peripheral neuropathy as part of their clinical picture[65]. The neuropathy may be a sequela from underlying vasculitis of the vasa vasorum of peripheral nerves or in association with a necrotizing myopathy. A neurological assessment should be perfomed prior to anesthesia in these cases[66].

Complications from bleeding may be of concern for a regional technique, as well. This tendency to bleed may arise due to 1) cytotoxic therapy (cycophosphamide or methotrexate) leading to thrombocytopenia, 2) circulating immune complexes leading to a low grade disseminated intravascular coagulation, or 3) complications from general vasculitis and granulomatous inflammation with cutaneous, meningeal, or spinal hemorrhages[66]. Literature reports have also noted spontaneous subdural hemorrhage and spinal vasculature abnormalities as complications[67-69].

The anesthesiologist must weigh the risks and benefits of regional and general anesthesia when these cases arise. Platelet levels and clotting studies should be performed. If these return as normal and the patient has no neurological signs, it is likely that a regional approach will be without complications. Neurological deficits, if present, may suggest underlying vascular abnormalities or granulomatous infiltration of the cord. In these situations, computed tomography or magnetic resonance imaging is warranted before attempting spinal or epidural anesthesia[66].

Conclusion

Wegener's granulomatosis is a complex systemic autoimmune disease that presents many challenges to treatment. Although much success has come from current cyclophosphamide-corticosteroid treatments, vigorous relapse rates and high morbidity illustrate the need for continued study and treatment alternatives.

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