PERIOPERATIVE MANAGEMENT OF THE PATIENT WITH GOODPASTURE'S SYNDROME

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Introduction

Goodpasture's Syndrome (GS) is characterized by the classic triad of diffuse pulmonary hemorrhage, glomerulonephritis, and circulating anti-basement membrane antibodies[1]. It is an uncommon disorder, with an incidence estimated to be 0.3 cases per 100,000 people per year[2]. There is a male predominance, with a male to female ratio between 2:1 and 9:1[3]. The disease may present at any age, although it most commonly manifests between the ages of 20 and 30 years[1]. Goodpasture first described the pulmonary renal syndrome in 1919 during the influenza epidemic. However, it was not until 1958 that Stanton and Tange referenced Goodpasture's original description in their report of young men with pulmonary hemorrhage and glomerulonephritis[1]. The role of anti-GBM antibodies in the pathogenesis of GS was discovered in 1967[1]. Reported risk factors for the development of GS include exposure to hydrocarbons, cigarette smoking, and a preceding viral illness, especially influenza[2].

Clinical Manifestations

While there is considerable variation in the clinical presentation of GS, the initial symptoms most cases include progressive dyspnea and hemoptysis (seen in 80% to 95%), which may range in severity from blood-tinged sputum to massive hemorrhage[4]. Additionally, some patients have alveolar hemorrhage, evident only on biopsy or bronchoalveolar lavage[1]. Between 20% and 40% of patients have only renal disease, and less than 10% have only pulmonary disease[1]. Patients may present initially with hemoptysis only, then develop glomerulonephritis months or years later. Alternatively, some patients may present with glomerulonephritis and either later develop pulmonary hemorrhage or never develop pulmonary hemorrhage[2]. Unlike systemic inflammatory disorders, GS typically does not cause clinical signs of inflammation, although some patients may have prodromal symptoms such as nausea, vomiting, fatigue, and weight loss.

Continuous pulmonary hemorrhaging can result in hypoxemia and significant iron deficiency, with decreased levels of serum iron and ferritin[1]. If massive hemoptysis occurs, the alveolar spaces are rapidly flooded with blood, resulting in respiratory failure. Acute pulmonary hemorrhage is seen as bilateral patchy areas of dense alveolar infiltrates on chest radiographs, and air bronchograms are also often present[2]. The apices and costophrenic angles are generally not involved[3]. Some patients may have a normal chest radiograph; however, CT scan may reveal parenchymal abnormalities[3]. After a patient has an acute episode of pulmonary hemorrhage, serial chest radiographs demonstrate a predictable change in pattern. Within 2 to 3 days, the initial patchy areas of consolidation disappear and a reticulonodular pattern becomes evident[3]. The pattern becomes distinctly reticular within 1 week, and the chest radiograph usually returns to normal in 10 to 12 days[3].

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GS patients with renal disease usually have rapidly progressive glomerulonephritis (RPGN). Renal dysfunction causes azotemia, as well as proteinuria, hematuria, and red blood cell casts are seen on urinalysis. [1] Without treatment, end-stage renal failure may occur within days to weeks after the onset of symptoms[2].

Pathogenesis

Genetics are likely involved in the pathogenesis of GS, given that there is a strong association between the disease and HLA-DR2. There is an increased incidence of HLA-DR2 in patients with GS when compared to the general population[5]. However, additional factors must also be involved, as most cases are sporadic. GS is defined by the presence of antibodies that target the carboxyl-terminal region of the alpha-3 chain of type IV collagen[1]. Only the lungs and kidneys, are involved despite the presence of type IV collagen throughout the body. This effect may be explained because the antigen is more accessible to the antibody in the alveoli and glomeruli or because of the predominance of the alpha-3 chain in the alveoli and glomeruli rather than in other tissues[1]. Structural differences between the alveoli and glomeruli may explain why some patients develop only alveolar hemorrhage or only glomerulonephritis, as opposed to the combination of the two pathologies. One such difference is the presence of fenestrae in the glomerular endothelium, which grant greater accessibility of the antibodies to the basement membrane[1]. These fenestrae are absent in the alveolar endothelium[3].

Diagnosis

Microscopic abnormalities associated with GS include intra-alveolar blood, hemosiderin-laden macrophages in the alveoli and interstitium, interstitial fibrosis, and type II cell hyperplasia[1]. Occasionally, there may be a lymphocytic interstitial infiltrate. Results of electron microscopy have been inconsistent, with findings ranging from no abnormalities to thickening, splitting, discontinuity, or smudging of the basement membrane[1]. However, none of these findings is diagnostic of GS. Confirmation of the diagnosis is accomplished by performing a renal biopsy and proving the presence of tissue-bound anti-basement membrane antibodies by enzyme-linked immunosorbent assay (ELISA)[3]. If a biopsy is contraindicated, the diagnosis can be made by serologic testing and demonstration of the presence of anti-basement membrane antibodies in the serum with either indirect immunofluorescence or ELISA. Focal or diffuse crescentic and necrotizing glomerulonephritis is seen on light microscopic examination of kidney tissue, and immunofluorescence shows linear staining of IgG along the glomerular basement membrane[3]. Immunofluorescence of lung tissue demonstrates diffuse linear staining along the alveolar wall, usually attributable to IgG.

Pulmonary function testing is not useful in diagnosing GS, but may help in monitoring the course of the disease[4]. Patients generally demonstrate a restrictive pattern, along with a decreased diffusing capacity and a decrease in resting Pa_{O2}, which may exist even during remission of the disease[3]. The diffusing capacity of the lung for carbon monoxide (DL_{CO}) may be increased due to intraalveolar blood binding to carbon monoxide[4]. When measured throughout the disease, the Diffusing Capacity of the Lung for Carbon Monoxide (DL_{CO}) may help to identify an acute pulmonary hemorrhage versus other causes of radiographic opacities[4].

Prognosis and Treatment

Prior to the development of immunosuppressive therapy and plasmapheresis, GS was usually fatal, secondary to either lung hemorrhage or renal failure. However, corticosteroids, immunosuppressants, and plasmapheresis have greatly improved outcome, although some patients remain dependent on dialysis[1]. Three to six months of treatment are usually required, though symptoms begin to resolve within two months[5]. Plasmapheresis rapidly decreases the level of circulating anti-basement membrane antibody, while corticosteroids and immunosuppressants (namely, prednisone and cyclophosphamide) decrease the production of antibody[6]. If irreversible kidney damage has taken place at the time of diagnosis, the patient may receive a kidney transplant only after the anti-basement membrane antibodies have been cleared from the serum[3]. Otherwise, if irreversible kidney damage has not occurred when the diagnosis is made, chronic immunosuppression can prevent progression

of renal damage and a kidney transplant often is not necessary[3].

Anesthetic Considerations

Preoperative Assessment

Elective surgery should be delayed until the disease is in an inactive state[5]. Chest radiographs, pulmonary function studies, and arterial blood gases can be used to evaluate the patient's pulmonary status, while renal function studies, urinalysis, and blood chemistries indicate renal function[5]. Causes of renal insufficiency, other than glomerulonephritis, should also be sought. Prerenal factors such as hypovolemia and decreased cardiac output can compound the GS-induced renal dysfunction, and should be corrected to avoid further kidney damage. Dialysis-dependent patients should be dialyzed shortly before surgery to correct volume overload, hyperkalemia, and acidosis[5]. Renal failure often demands that drug selection and dosing be modified. In general, the technique of choice when applicable would be the use of local anesthetics for local or regional blockade whenever possible with careful sedation. However, there are significant considerations in the delivery of anesthetics to GS patients.

Pulmonary

Due to the alveolar hemorrhage that occurs in GS, oxygenation of the patient during surgery is the principal challenge of the anesthesiologist[5]. Blood in the alveoli makes gas exchange difficult. Furthermore, continuous alveolar hemorrhaging results in anemia, which plays an additional role in diminished tissue oxygen delivery[5]. A larger than normal sized endotracheal tube should be used to intubate to allow for better pulmonary suction. Care should be taken to avoid high airway pressure, increased oxygen tension, and other stresses on the lungs, as this may worsen antibody-mediated lung injury[5].

Renal

Renal failure in GS, as in all cases of renal failure, can affect the volume of distribution, metabolism, and excretion of certain anesthetic drugs. Water-soluble metabolites that are minimally active may accumulate and prolong the effects of the parent drug[7]. The elimination half-life of drugs that are excreted unchanged by the kidneys can be prolonged in renal failure. The protein loss and uremia that occur in renal failure may potentiate the effects of drugs that are typically protein-bound[7].

Thiopental requires a decreased induction dose because its free fraction is nearly doubled in renal failure[8]. The dosing of ketamine, on the other hand, does not need to be altered because it is not highly protein-bound and its free fraction is minimally affected by renal failure[9]. Etomidate exhibits less protein binding in renal failure patients than it does in normal patients, but the larger free fraction does not appear to alter its clinical effects[10]. Propofol is quickly metabolized by the liver into inactive metabolites that are then excreted by the kidney; thus renal failure does not result in extension of its clinical effects[11]. The plasma free fraction of benzodiazepines is increased by renal failure because these drugs are normally highly protein-bound. Additionally, benzodiazepines have active metabolites that can accumulate after repeated doses in renal failure and lead to prolonged sedation[7]. Midazolam is metabolized to an active alpha-hydroxy compound, and 60-80% of the drug is excreted in this form[12]. The metabolite accumulates after long-term infusions in renal failure, therefore causing a longer time of sedation[13]. Renal failure patients are more sensitive to the sedative effects of alprazolam because it has less protein binding and an increased free fraction when compared to individuals with normal renal function[14]. Dexmedetomidine is hepatically metabolized. When given to patients with impaired renal function, sedation was longer when compared to patients with normal renal function, likely due to less protein binding in the presence of renal dysfunction[15].

While the pharmacokinetics of a single dose of morphine are unaffected in a chronic renal failure patient, long-term administration causes its active metabolite morphine-6-glucuronide to accumulate and exert potent analgesic and sedative effects[16]. Thus, the dose of morphine should be decreased in the presence of renal dysfunction. Meperidine is metabolized to the neurotoxic compound normeperidine, which must be excreted by the kidneys and therefore should not be administered to patients with renal failure[7].

Hydromorphone's active metabolite hydromorphone-3-glucuronide also accumulates in renal failure patients and can cause cognitive dysfunction and myoclonus[17]. Renal failure patients have a longer elimination time for oxycodone, thus repeated doses cause prolonged effects[18]. Codeine is not recommended for long-term use in patients with renal dysfunction because it can also cause prolonged narcosis[16]. Because fentanyl does not have active metabolites, has an unchanged free fraction, and has a short redistribution phase, it is well-tolerated and is a good choice[19]. Alfentanil has decreased protein binding in the presence of renal disease, but because its elimination half-life and clearance are unaffected, the total dose should be similar to that for patients without renal disease[20].

With the exception of succinylcholine, atracurium, cis-atracurium, and mivacurium, muscle relaxants rely heavily on renal excretion and therefore result in prolonged effects in patients with chronic renal failure[7]. In renal failure, most nondepolarizing muscle relaxants must be either excreted by the liver or metabolized to inactive forms[7]. Some muscle relaxants, such as vecuronium, are metabolized to active compounds that must be excreted by the kidneys, resulting in prolonged effects in GS patients[7]. Because succinylcholine does not result in a major prolongation of clinical effects, it may be used for rapid-sequence intubation.

Due to the shorter duration of action, the intermediate-acting atracurium, cis-atracurium, and rocuronium are preferred over the long-acting muscle relaxants for patients with renal failure[5]. Atracurium and cis-atracurium are recommended because their metabolites do not depend on renal clearance and the elimination half-life, clearance, and duration of action are not affected by renal failure[21]. Vecuronium exhibits prolonged effects in patients with renal dysfunction due to decreased plasma clearance and increased elimination half-life[22]. An additional cause for lengthening of the clinical duration of vecuronium is that it is metabolized to 3-desmethylvecuronium, an active compound that accumulates in renal failure[23]. Mivacurium is a short-acting muscle relaxant that, like succinylcholine, is eliminated by pseudocholinesterase. In renal failure patients with a lower level of plasma pseudocholinesterase, recovery from a dose of mivacurium is slower[24].

Conclusion

Although it is uncommon, Goodpasture's Syndrome is a disease that anesthesiologists may encounter and which poses many challenges. The extensive renal involvement dictates which drugs should be administered and which avoided. Complex pulmonary manifestations require that special care be taken in management of the airway. Patients should be treated with corticosteroids, immunosuppressants, and plasmapheresis to render the disease dormant before elective surgery is performed.

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