Review on Good Pasture Syndrome: An Uncommon Disease

***P Roshan Ali[1], Divyam Kumar Singh[2], L Manasa Goud[3]**

1.Department of pharmacology , CMR college of pharmacy ,Telangana,India
2.Department of pharmacology , CMR college of pharmacy , Telangana,India
3.Department of pharmacology , CMR college of pharmacy , Telangana,India

*[*1]p.roshan.ali@gmail.com,[2]nikunj2303raj@gmail.com ,[3]manasagoudladdipeerla@gmail.com*

Abstract

Good pasture disease is an uncommon disease. It is an autoimmune disorder that is frequently characterized by rapid progressive glomerular nephritis, and occasionally pulmonary haemorrhage. Good pasture syndrome is also called as Anti-Glomerular Basement Membrane (GBM) disease, due to the deposition of the autoantibodies in the glomerular and alveolar basement membrane. Good pasture is an autoimmune disease of the kidney and lungs which are mediated by the antibodies and T-cells that are directed to cryptic epitopes hidden in the basement membrane. The particular cause of Good pasture is unknown, but environmental factors and specific behaviours of people are at higher risk. Its frequency of occurrence in the general population is confined to 1(or)2 cases in a million population every year. Good pasture syndrome can equally affect both men and women. Most of the patients were found to be chronic smokers, nearly half of the patients. The alpha-3 chains of type (IV) collagen are present in only a few specialized membranes such as those found in kidneys and lungs. Kidney biopsy is the standard test for Good pasture syndrome. Plasmapheresis is the therapy used to eliminate auto-antibodies. Other treatments include hemodialysis, Intravenous steroid pulses etc.

Keywords: *Aberrant, pasture disease, autoimmune-glomerulonephritis, plasmapheresis, hemodialysis*

Introduction

Good Pasture Syndrome is also commonly known as Anti-glomerular basement membrane disease [GBM], due to the deposition of the autoantibodies in the glomerular alveolar basement membrane.

It is one of the rarest autoimmune disorders[1]. Good pasture syndrome is mainly found to be in association with both kidneys and the lungs. As it exerts its effect on glomerular and pulmonary membranes respectively.

Good pasture syndrome is completely curable if diagnosed early. If left untreated good pasture syndrome can lead to end-stage renal failure, which ultimately under severe conditions can also lead to death.

The glomerular basement membrane consists of type iv collagen**.** alpha 3 chain, which gets attached with autoantibodies which causes glomerulonephritis[2,3].
Good pasture syndrome is an autoimmune disease of the kidneys and lungs which are mediated by antibodies and T cells that are directed to cryptic epitopes hidden in the basement membrane[4].
The basement membrane is the thin sheet which surrounds the cell, which forms an anatomical barrier which makes cells meet connective tissue[5,6].
Good Pasture Syndrome was named after the pathologist Ernes Good Pasture who described this disorder for the first time in 1919[27,15].
Glomerular nephritis and lung haemorrhage are caused at the time of the influenza infection epidemic[12]. Good Pasture Syndrome is a monophasic illness.[17]
At last we can define Good Pasture Syndrome as a rare, organ-specific and fatal autoimmune disease[28,29].

Epidemiology

The epidemiological factors associated with [GBM] are:
1. Age
2. Sex
3. Place of residence
4.Work of the patient
5.Exposure to chemicals[13]

This condition is observed in 1 to 2 individuals within a population of 1 million every year. Good pasture syndrome had been seen to equally affect both men and women.
But more frequently good pasture is often seen in men of young age; probably under 30 years old. Extensive research suggests that the probability of this condition developing in white people was more than in black people
It has two types of age phases; they are 1)20 to 30 years old and 2)60 to 70 years old, In the first phase, the pulmonary basement membrane is mostly involved.
In the second phase, rare chance of pulmonary involvement in the good pasture syndrome[5,10]**.**
Women of older age groups and Men who belong to young age groups tend to be frequently associated with this disease[5].
About 60%-80% of the patients are seen to be manifested with both renal and pulmonary disease. Other 20%-40% of patients only have renal disease.
Approximately 10%-20% of patients are associated with crescentic glomerulonephritis. Less than 10% of patients are only with pulmonary disease[21,23].

Pathogenesis

The particular cause of good pasture syndrome is still unknown, however recent studies and thorough experimental data suggest that environmental factors and specific behaviours of the people are at a higher risk.
This is usually seen with Environmental factors like (Exposure to hydrocarbon fumes, Tobacco smoke, Cocaine inhalation, Metallic Dust exposure, etc).

Scientists Krakower and Greenspon first identified that an antigen caused the glomerular basement membrane in the late 1950s.

According to some groups of scientists LERNER, GLASSROCK and DIXON, suggest that if antibodies are removed from the diseased kidney and injected into experimental animals such as sheep, rabbits, mice, goats and rats these lead to nephritis followed by renal failure[5,7].

Anti Glomerular membrane disease (or) good pasture syndrome produces autoantibodies. These autoantibodies bind to the epitope of the glomerular and pulmonary membranes and cause tissue damage[5].

According to recent studies, the circulating antibodies in the good pasture syndrome are targeted to the type IV collagen of chained alpha domain. While another study by NEILSON and CO, suggests that the first five non-collagenous1 [NC1] domains of type IV collagen.

Which is the only alpha-3 that has the capability of binding with good pasture syndrome sera during expressing the recombinant proteins[7].

To study this effect. Good pasture antigens were isolated from the human glomerular basement membrane. But it was found that the glomerular basement membrane is mostly insoluble. To solubilise them, the collagenase enzyme was used.

This technique of isolation is done by chromatography[8]. Most of the patients were current or former smokers, nearly half of the patients.

Antigens of the Good Pasture gets inclined in the case of severe smoking[17]. Followed by increased proteinuria levels leading to anti-glomerular basement membrane or good pasture syndrome[9].

The location of the Good Pasture epitope is at the carboxyl-terminal of the alpha-3NC-1domain which binds to the antibodies developed by the molecular cloning technology[18].

The alpha 3 chains of type IV collagen is present in only a few specialised membranes such as lungs and kidneys.2/3 rd of the patients with anti-glomerular basement membrane antibodies may lead to good pasture syndrome.

1/3 rd with anti-glomerular basement membrane nephritis without the pulmonary disease could lead to good pasture syndrome[14].

Some other causes of Goodpasture Syndrome are due to the infection of Aspergillus fumigatus by inhalation of toxins, chemicals which cause inflammation in the alveolar basement membrane and get disrupted leading to the formation of anti -GBM autoantibodies[20].

Symptoms

Symptoms in GBM can vary from person to person based on the degree of disease manifestation. Mostly the symptoms developed are associated either with pulmonary or renal manifestations.

Symptoms of renal failure tend to occur first than pulmonary disease-associated symptoms.

The symptoms associated with pulmonary manifestations are:

1. Hemoptysis
2. Shortness of breath
3. Cough
4. Dyspnea
5. Respiratory failure (if severe)

The symptoms associated with renal manifestation are :

1. Anaemia
2. Hematuria
3. High blood pressure
4. Oedema

Renal functions get declined within days to weeks in Goodpasture Syndrome. Some symptoms associated with this are proteinuria, oliguria, and glomerular hematuria[16,19,25].

Diagnosis

1. **Kidney biopsy:** is the standard test for Good pasture syndrome[15,18].

2. **Urinalysis:** It involves observation of proteinuria, hematuria.
3. **RBC Counts**: Complete blood count to identify the levels of haemorrhage.
4. **Pulmonary function test:** is done to identify carbon monoxide binding.
5. **Chest radiography :** for pulmonary parenchymal damage.
6. **Detection of levels of anti-glomerular basement membrane (ANTI GBM) antibodies:**

Mostly a few years ago, the diagnosis of anti-GBM (Anti glomerular basement membrane disease was based on the linear accumulation of the immunoglobulins on the glomerular basement membrane.

The subsequent methods to detect the anti-GBM antibodies (Anti glomerular basement membrane)are indirect immunofluorescence on normal human[3].

In 5% of patients with Good Pasture Syndrome, the circulating antibodies remain undetected[15,17].

7. **ELISA(Enzyme-linked immunosorbent assay):** is the common diagnostic method of anti-glomerular basement membrane or good pasture(GPS).

It detects the anti-glomerular basement membrane antibodies. Good pasture syndrome(GPS) Also have high serum creatinine (over 5.7mg/dl) and many glomerular crescents(>50%).

Severity of the diseases is directly proportional to the level of circulating anti-glomerular basement membrane antibodies.

The Autoantibody present in the good pasture syndrome is majorly IgG(in a few cases IgA or IgM) are detected in serum and kidney[10].

This disease was associated with the IgG1 subclass but not with subclass IgG4 anti-glomerular basement membrane antibodies.IgG2 &IgG4 subclass do not cause any interactions[11].

In crescentic glomerulonephritis, the glomerular capillary walls are damaged due to the deposition of IgG antibodies[24].

Treatment

1. **Plasma exchanges (plasmapheresis):** It is the combination of exchange of plasma with immunosuppression to eliminate pathogenic autoantibodies so, this will lead to the removal of non-selective plasma proteins and the most probable adverse side effects.

So, alternative targeted therapies are safer and do not cause any side effects. The studies say that plasmapheresis treatment shows improved renal and patient survival compared with the immunosuppressive treatment.

A rapid fall in circulating anti-glomerular basement membrane antibodies results in improved kidney function on treatment with plasmapheresis [12,29].

Standard therapy includes 14 exchanges of 4 litres each over two weeks, the treatment is along with prednisone and immunosuppressive drugs such as cyclophosphamide[7].

Generally, with the treatment of plasma exchange, the patient may recover from complete lung damage but the kidneys get healed a little slowly[22].

2. Hemodialysis : Hemodialysis is used as a treatment for purifying the blood of a person whose kidneys are dysfunctional due to glomerular basement membrane autoantibodies(glomerular nephritis).

Mostly half of the patients require organ support; requires hemodialysis at initial treatment[12].

The serum creatinine level should be less than 500 micro mol/L in case of the renal form of Good Pasture Syndrome for increased survival to another 1 year[26].

3. **Renal Transplantation:** Renal transplantation is widely used for end-stage renal disease. After renal transplantation, anti-glomerular basement membrane disease can occur.

Mostly 3 to 5% male patients suffering from hereditary nephritis who have gone renal transplantation also known as de novo anti-glomerular basement membrane disease(anti-GBM).

If the anti-glomerular basement membrane antibodies (anti-GBM antibodies) are present in the serum for more than 12 months renal transplantation is done[5].

4. **Intravenous steroid pulses:** Only low doses are required. In high doses, intravenous glucocorticoids are not used to treat anti-glomerular basement membrane disease(AntiGBM)

5. **Oral steroid therapy:** It is the first-line approach to this disease. It has low risk compared to other therapies

6.**Intravenous cyclophosphamide infusions**[10,11] : Along with plasmapheresis the cyclophosphamide when co-administered, shows a better outcome to inhibit the production of the autoantibody and minimizes the risk of inflammation and infection.

7. **Immuno adsorption :** It is the technique used to eradicate the selective pathogenic autoantibodies, but it does not remove the other plasma components present and it prevents the severity of hypersensitive reactions i.e; allergic reactions and also avoids the risk of infections. The removal of IgG Antibodies by immunoadsorption had shown a normal function of kidneys in infants with good pasture syndrome.

The recombinant form of good pasture antigen will immensely develop immunoadsorption therapy in future.

It is the alternate form of extracorporeal therapy. It is more effective than plasmapheresis[12]. Plasmapheresis and immunosuppressive drugs can predict one-year survival in 87% of the patients[26].

8.Corticosteroids[12] **:** These are the drugs that lower inflammation. This therapy includes the modification of functions of epidermal and dermal cells of leukocytes participating in proliferative inflammation and allergies as well as allergic asthma in pulmonary manifestations.

Acknowledgments

The authors are thankful to chairman, Mr.Ch.Gopal Reddy ,CMR college of pharmacy, kandlakoya(v) medchal , Hyderabad , India

References

[1] Kalluri R. Goodpasture syndrome. Kidney international. 1999 Mar 1;55(3):1120-2.

[2] Borza D-B, Neilson EG, Hudson BG. Pathogenesis of Goodpasture syndrome: a molecular perspective. Semin Nephrol [Internet]. 2003;23(6):522–31. Available from: http://dx.doi.org/10.1053/s0270-9295(03)00131-1.

[3] Sinico RA, Radice A, Corace C, Sabadini E, Bollini B. Anti-glomerular basement membrane antibodies in the diagnosis of Goodpasture syndrome: a comparison of different assays. Nephrol Dial Transplant [Internet]. 2006;21(2):397–401. Available from: http://dx.doi.org/10.1093/ndt/gfi230.

[4] Kalluri R, Cantley LG, Kerjaschki D, Neilson EG. Reactive oxygen species expose cryptic epitopes associated with autoimmune goodpasture syndrome. J Biol Chem [Internet]. 2000;275(26):20027–32. Available from: http://dx.doi.org/10.1074/jbc.M904549199.

[5] Greco A, Rizzo MI, De Virgilio A, Gallo A, Fusconi M, Pagliuca G, et al. Goodpasture's syndrome: a clinical update. Autoimmun Rev [Internet]. 2015;14(3):246–53. Available from: http://dx.doi.org/10.1016/j.autrev.2014.11.006.

[6] Hellmark T, Segelmark M, Wieslander J. Anti-GBM antibodies in Goodpasture syndrome; anatomy of an epitope. Nephrol Dial Transplant [Internet]. 1997;12(4):646–8. Available from: http://dx.doi.org/10.1093/ndt/12.4.646.

[7] Bolton WK. Goodpasture's syndrome. Kidney international. 1996 Nov 1;50(5):1753-66.

[8]Wieslander J, Kataja M, Hudson BG. Characterization of the human Goodpasture antigen. Clin Exp Immunol. 1987;69(2):332–40.

[9] Shen C, Jia X, Cui Z, Yu X, Zhao M. Clinical-Pathological Features and Outcome of Atypical Anti-glomerular Basement Membrane Disease in a Large Single Cohort [Internet]. Vol. 11, Frontiers in Immunology. Frontiers Media SA; 2020. Available from: http://dx.doi.org/10.3389/fimmu.2020.02035.

[10] Pedchenko V, Kitching AR, Hudson BG. Goodpasture's autoimmune disease — A collagen IV disorder [Internet]. Vols. 71–72, Matrix Biology. Elsevier BV; 2018. p. 240–9. Available from:http://dx.doi.org/10.1016/j.matbio.2018.05.004.

[11] Ossman R, Buob D, Hellmark T, Brocheriou I, Peltier J, Tamouza R, et al. Factors Associated With Pathogenicity of Anti-Glomerular Basal Membrane Antibodies [Internet]. Vol. 95, Medicine. Ovid Technologies (Wolters Kluwer Health); 2016. p. e3654. Available from: http://dx.doi.org/10.1097/MD.0000000000003654.

[12] McAdoo SP, Pusey CD. Anti-Glomerular Basement Membrane Disease [Internet]. Vol. 12, Clinical Journal of the American Society of Nephrology. American Society of Nephrology (ASN); 2017. p. 1162–72. Available from: http://dx.doi.org/10.2215/CJN.01380217.

[13] Molinier S, Bonnet D, Moulin B, Mianne D, Martet G, Touze J, et al. Le syndrome de Goodpasture: rôle d'un facteur épidémiologique?? À propos de deux observations [Internet]. Vol. 16, La Revue de Médecine Interne. Elsevier BV; 1995. p. 589–94. Available from: http://dx.doi.org/10.1016/0248-8663(96)80757-0.

[14] Zhong Z, Tan J, Tang Y, Li Z, Qin W. Goodpasture syndrome manifesting as nephrotic-range proteinuria with anti-glomerular basement membrane antibody seronegativity: A case report: A case report. Medicine (Baltimore) [Internet]. 2020;99(39):e22341. Available from: http://dx.doi.org/10.1097/MD.0000000000022341.

[15] DeVrieze BW, Hurley JA. Goodpasture Syndrome. StatPearls [Internet]. 2020 Mar 25.

[16] Stojkovic J, Zejnel S, Gerasimovska B, Gerasimovska V, Stojkovic D, Trajkovski M, et al. Goodpasture Syndrome Diagnosed One Year And A Half after the Appearance of the First Symptoms (Case Report). Open Access Maced. J Med Sci.

[17] Thibaud V, Rioux-Leclercq N, Vigneau C, Morice S. Recurrence of Goodpasture syndrome without circulating anti-glomerular basement membrane antibodies after kidney transplant, a case report. BMC Nephrol [Internet]. 2019;20(1):6. Available from: http://dx.doi.org/10.1186/s12882-018-1197-6.

[18] Kalluri R, Gunwar S, Reeders ST, Morrison KC, Maruyama M, Ebner KE, et al. Goodpasture syndrome. Localization of the epitope for the autoantibodies to the carboxyl-terminal region of the alpha 3 (IV) chain of basement membrane collagen. Journal of Biological Chemistry. 1991;266(35):24018–24.

[19] Zahir Z, Wani AS, Prasad N, Jain M. Clinicopathological characteristics and predictors of poor outcome in anti-glomerular basement membrane disease–a fifteen-year single centre experience. Renal Failure. 2021 Jan 1;43(1):79-89.

[20] Willauer AN, Prakash B, Saluja P, Schuller D. Anti-glomerular basement membrane (Goodpasture) disease exacerbated by invasive pulmonary aspergillosis. Proc (Bayl Univ Med Cent) [Internet]. 2020;33(4):616–8. Available from: http://dx.doi.org/10.1080/08998280.2020.1775480.

[21] Shiferaw B, Miro V, Smith C, Akella J, Chua W, Kim Z. Goodpasture's disease: An uncommon disease with an atypical clinical course. J Clin Med Res [Internet]. 2016;8(1):52–5. Available from: http://dx.doi.org/10.14740/jocmr2379w.

[22] Sinha VK, Hibbert C. Near-lethal acute kidney injury due to Goodpasture's syndrome: A case report. J Intensive Care Soc [Internet]. 2015;16(4):350–4. Available from: http://dx.doi.org/10.1177/1751143715593560.

[23] Tang W, McDonald SP, Hawley CM, Badve SV, Boudville NC, Brown FG, et al. Anti-glomerular basement membrane antibody disease is an uncommon cause of end-stage renal disease. Kidney Int [Internet]. 2013;83(3):503–10. Available from: http://dx.doi.org/10.1038/ki.2012.375.

[24] Qu Z, Cui Z, Liu G, Zhao M-H. The distribution of IgG subclass deposition on renal tissues from patients with anti-glomerular basement membrane disease. BMC Immunol [Internet]. 2013;14:19. Available from: http://dx.doi.org/10.1186/1471-2172-14-19.

[25] Kelly PT, Haponik EF. Goodpasture syndrome: molecular and clinical advances. Medicine (Baltimore) [Internet]. 1994;73(4):171–85. Available from: http://dx.doi.org/10.1097/00005792-199407000-00001.

[26] Huart A, Josse A-G, Chauveau D, Korach J-M, Heshmati F, Baudin E, et al. Outcomes of patients with Goodpasture syndrome: A nationwide cohort-based study from the French Society of Hemapheresis. J Autoimmun [Internet]. 2016;73:24–9. Available from: http://dx.doi.org/10.1016/j.jaut.2016.05.015.

[27] Bergs L. Goodpasture syndrome. Crit Care Nurse. 2005;25:57–8.

[28] Kalluri R, Melendez E, Rumpf KW, Sattler K, Müller GA, Strutz F, et al. Specificity of circulating and tissue-bound autoantibodies in Goodpasture syndrome. Proc Assoc Am Physicians. 1996;108(2):134–9.

[29] Suh K-S, Choi S-Y, Bae GE, Choi DE, Yeo M-K. Concurrent anti-glomerular basement membrane nephritis and IgA nephropathy. J Pathol Transl Med [Internet]. 2019;53(6):399–402. Available from: http://dx.doi.org/10.4132/jptm.2019.08.05.