Goodpasture syndrome

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Abbreviations

ANA- antinuclear antibodies

ANCA- antineutrophil cytoplasmic antibodies

CI- confidence interval

DIC- disseminated intravascular coagulation

ELISA- enzyme-linked immunosorbent assay

ESRD- end stage renal disease

FFP- fresh frozen plasma

GBM- glomerular basement membrane

GS- Goodpasture syndrome

IIF- indirect immunofluorescence

LM- light microscopy

PE- plasma exchange

Pmp- per million population

RBC- red blood cells

RIA- radioimmunoassay

RPGN- rapidly progressive glomerulonephritis

RRT- renal replacement therapy

WB- western blot

WBC- white blood cells

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Abstract

This graduation thesis is a narrative review for Goodpasture syndrome (GS), a rare autoimmune disease affecting the kidneys and lungs. This eponymous syndrome, first described by Goodpasture in 1919, refers to the renopulmonary vascular damage done by circulating antibodies and their subsequent post-deposition inflammatory damage. The complex pathogenesis of the disease includes genetic predisposition, central tolerance defect, glomerular basement membrane (GBM) exposure revealing a culprit epitope, subsequent antibodies production against GBM and finally, culmination with antibody deposition in the kidneys and lungs. The autoantibodies thereafter, trigger a fulminant inflammatory reaction carried by cell-mediated and complement-dependent immune processes. The symptoms that follow range in severity from dyspnea to pulmonary hemorrhage and respiratory failure in the lungs, and from oliguria and hematuria to rapidly progressive glomerulonephritis (RPGN) in the kidneys. Therefore, physicians should have a high clinical suspicion of GS with any respiratory symptoms presentation in RPGN patients. Early diagnosis is imperative for treatment and is performed through serological tests and kidney biopsy. Treatment revolves around antibodies removal through plasma exchange and immunosuppressive therapy to halt further antibodies production. Pulmonary symptoms usually resolve, while recovery of renal function is poor and patients often require renal replacement therapy. Fortunately, GS seldom recur and patients who survive the initial ailment have a favorable prognosis.

Sažetak

Ovaj diplomski rad narativni je prikaz Goodpastureovog sindroma (GS), rijetke autoimune bolesti koja zahvaća bubrege i pluća. Ovaj istoimeni sindrom, koji je prvi opisao Goodpasture 1919 godine, odnosi se na renopulmonalno vaskularno oštećenje uzrokovano cirkulirajućim protutijelima s posljedičnim upalnim oštećenjem nakon odlaganja istih. Složena patogeneza bolesti uključuje genetsku predispoziciju, poremećaj centralne tolerancije, izlaganje bazalne membrane (GBM) otkrivajući pri tome ključni epitop, potom proizvodnju protutijela protiv GBM-a i konačno, kulminaciju s taloženjem protutijela u bubrezima i plućima. Protutijela zatim pokreću fulminantnu upalnu reakciju posredovanu staničnim imunološkim procesima i komplementom. Simptomi koji slijede variraju u težini od dispneje do plućnog krvarenja i respiratornog zatajenja u plućima, te od oligurije i hematurije do brzo progredirajućeg glomerulonefritisa (RPGN) u bubrezima. Stoga bi liječnik trebao posumnjati na GS kod pojave bilo kakvih respiratornih simptoma u bolesnika s RPGN-om. Rana dijagnoza je imperativ za liječenje, a provodi se serološkim testovima i biopsijom bubrega. Liječenje je usmjereno na uklanjanje protutijela putem izmjene plazme i imunosupresivnom terapijom kako bi se zaustavila daljnja proizvodnja protutijela. Plućni simptomi obično nestaju, dok je oporavak bubrežne funkcije slab i pacijentima je često potrebno bubrežno nadomjesno liječenje. Srećom, GS se rijetko ponavlja i pacijenti koji prežive početnu epizodu bolesti imaju povoljnu prognozu.

Introduction

Goodpasture syndrome (GS) is an uncommon, but life-threatening and organ-specific autoimmune disease that involves both the lungs and kidneys. GS is a rare subtype of autoimmune glomerular diseases with an estimated incidence of 1-2 per million in Europe and the USA (1). The pathogenesis of the disease is due to auto-antibodies against alpha 3 chain of collagen type IV, which is prevalent in capillaries' basement membrane in the kidneys and lungs. GS is a subset of anti-glomerular basement membrane (GBM) disease and occurs in 40-60% of these patients (2). The combination of pulmonary-renal involvement separates GS from isolated kidney or lung anti-GBM disease. GS typically presents as rapidly progressive glomerulonephritis (RPGN) and pulmonary hemorrhage. The disease is associated with high morbidity and mortality (3). Historically, the mortality rates have improved since the introduction of immunosuppression therapy from 96% to 47% (4). Despite its overall rarity, GS accounts for 10-20% of cases of RPGN (5). As a subtype of RPGN, GS histological findings include glomerular fibrinoid necrosis and crescent formation with characteristic linear deposits of immunoglobulin along the basement membranes on immunofluorescence (6). The rapid progression of GS requires a prompt diagnosis and high clinical suspicion in patients with RPGN. The current guidelines suggest a serological testing in all RPGN patients that present with alveolar hemorrhages confirmed by high-resolution CT scan (7). Immunoassays for anti-GBM are considered diagnostic but up to 10% of patients may present as false-negative (8). In these patients the diagnosis is made by renal biopsy demonstrating linear deposition of antibodies on the basement membrane. The mainstay of treatment is through rapid removal of the antibodies by plasma exchange and immunosuppression in order to halt further production of antibodies. Even though early and effective treatment managed to increase overall 5 years survival to over 90%, renal survival remains poor and patients often need renal replacement therapy (RRT), dialysis and/or kidney transplantation (9).

Epidemiology

GS is considered a rare disease with reports varying between countries, however, the incidence is estimated to be around 1-2 per year per million population (pmp) around the world. In Ireland, a comprehensive evaluation of GS was performed in 2016, and found the incidence to be 1.64 per year pmp (10). Similarly, a 2012 New Zealand study estimated the incidence to be 1.79 per year pmp (11). However, in China the estimated incidence is 0.6 per year pmp (12) and close to the Netherlands incidence of 0.7 per year pmp (13). A recent nationwide USA study demonstrated a 10.3 GS per 1 million admissions (14). The reports vary due to the rarity of the disease and therefore the infrequency in which single centers treat and report it. As discussed later, there is an apparent environmental connection to GS and single center studies might not truly represent the population at risk. Similarly, certain genetic components linked to GS pathogenesis and genetic diversity around the world could contribute to varying incidence rates. Moreover, there is variation in studies' methods and some do not define the population at risk at all, which makes incidence calculation impossible and introduces biases to the studies. Due to these inconsistencies, there is an issue relating GS to environmental exposure, as has been postulated and shown evidence by some of the studies, and more comprehensive country-based epidemiological research (such as the Irish study) is needed to ascertain a relationship.

Age distribution of GS seems to be bimodal with peak incidences in the third and seventh decades (15). Younger patients tend to be males but in the older patients there is neutrality in gender distribution. However, older patients are predisposed of having ANCA (antineutrophil cytoplasmic antibodies) as well, which was suggested to be significant for the pathogenesis of GS (16). The environment plays an important role in the pathogenesis of GS as will be discussed later, and temporal as well as spatial relationships are thought to contribute to GS incidence. Thus, winter months and influenza season are thought to predispose the population for GS (17–19). Recently, GS incidence increased in the COVID pandemic, although a causal relationship is still speculative (20–22).

The recent comprehensive Irish study managed to observe a temporal significance of young males with pulmonary involvement to certain times of the year (10). Likewise, they managed to associate GS to certain regions and counties in Ireland, further strengthening the apparent environmental correlation to GS. Moreover and in support of that notion, pulmonary hemorrhage was found to be significantly more prevalent in smokers compared to non-smokers (23).

As with other autoimmune diseases, GS is considered to be associated with HLA gene predisposition (24). This genetic susceptibility is considered as the first part of the “two hits hypothesis” with the other being a chemical or biological insult (25). The strongest relation of GS to a genetic factor is the association to HLA-DRB1*1501 (26) with odds ratios ranging from 4.5 (27) to 8.5 (28), depending on the study and the population in question. Yet, a recent meta-analysis study demonstrated positive relations to DRB1*03 and DRB1*04 and a protective association with DRB1*07 (26). Furthermore, the study also reported an enhanced susceptibility for DRB1*1501 coinherited with DRB1*07 suggesting an interaction between the two alleles with a possibly therapeutic target. The critical T-cell epitope was found to be $a3_{136\text{-}146}$ of the peptide chain and is the core immunogenic region for the autoimmune reaction (28). This was proven by comparing between MHC II knockout mice with either HLA-DRB1*1501 or HLA-DRB*01 and their reaction to the immunogenic peptide of $a3_{136\text{-}146}$, demonstrating a strong anti-GBM production in the former but not the latter (28).

Pathogenesis

GS is an autoimmune disorder and a subtype of anti-GBM (glomerular basement membrane) disease. GS is distinguished from renal anti-GBM disease (i.e. isolated anti-GBM nephritis) due to involvement of both renal and pulmonary small blood vessels. This syndrome occurs when auto-antibodies are produced against the noncollagenous domain of alpha 3 chain of collagen type IV (α3(IV)NCI), a common macromolecule found in the basement membrane (1). The collagen IV family is composed of 6 genetically distinct combinations of alpha chains (α1-α6) with α3α4α5 protomer being expressed in renal and

pulmonary basement membranes only. The α3, α4, α5 chains trimerize to form trimetric protomers which coalesce to form hexamers through disulfide bonds, which conceal the Ea and Eb (29) epitopes of α3 (also known as the Goodpasture antigen) in the process. Once the disulfide bonds, and subsequently the hexamer, are disrupted by either a chemical or inflammatory insult, the epitopes are revealed and inducing an immune reaction in genetically susceptible individuals. Antibodies against α5 epitope have also been serologically evident in GS patients and are considered a contributing factor for disease progression. The anti-GBM antibodies are subsequently deposited in the renal and pulmonary capillaries causing local inflammation through an activation of both the complement system and the cellular immunity via Fc receptors.

The disruptive event causing the hexamer dissociation is vital for the pathogenesis of the disease as it forms a neoepitope for which antibody production and binding occur (30). That critical insult was postulated to be responsible for the connection between smoking and GS as smoking inhibits the anabolic enzyme that forms disulfide bonds, rendering the epitope more susceptible for exposure. Similarly, ANCA are thought to damage the underlying glomerular basement membrane and to expose the epitope for anti-GBM generation in ANCA-positive patients. Yet, double positive patients are also postulated to occur due to T-cell mimicry of similar molecular epitopes and thus, not necessarily linked to GS pathogenesis (31).

The autoantibodies generation was found to be related to low thymus autoantigen presentation (32). The Goodpasture antigen (noncollagenous domain of the alpha 3 chain of type IV collagen in the basement membrane- α3(IV)NCI) is presented normally during development in thymic epithelial cells which are predominantly involved with negative selection. Therefore, high-avidity autoreactive T-cells should undergo apoptosis during development (33), which does not happen in GS patients due to inefficient antigen presentation. Moreover, the Goodpasture antigen is also presented during the disease itself but may fail to produce a regulatory response to halt the disease. Both etiologies are believed to be related for the strong HLA association GS patients possess.

Clinical presentation

GS usually presents as pulmonary hemorrhage and rapidly progressive glomerulonephritis (RPGN); a clinical syndrome used to describe a rapid loss of renal function (days to weeks) with nephritic syndrome urinalysis characteristics and crescentic cellular formation in the Bowman's capsule (34). RPGN is further subclassified by the immunopathological categories to anti-GBM, immune-complex and pauci-immune glomerulonephritis. Anti-GBM is considered the most aggressive type of RPGN with the highest frequency of renal insufficiency and crescent formation at the time of diagnosis (5).

GS patients would often present, like other RPGN patients, with acute renal failure; hematuria and flank pain with urinalysis often discovering nephritic characteristics. As such, hematuria, subnephrotic proteinuria and white blood cells (WBC) would present in the urinalysis with further microscopic evaluation unveiling red blood cells (RBC) casts with/without WBC casts. Thus, patients present with renal failure and volume overload symptoms and over half of patients need RRT at the time of diagnosis.

Additionally, GS patients present with pulmonary hemorrhage of varying degrees, ranging from life-threatening hemoptysis to milder forms of alveolar hemorrhage (35). Therefore, a careful physical examination is needed with RPGN patients that might reveal subtle lung crackles. Other respiratory symptoms include: dyspnea, tachypnea, cough, cyanosis, and even overt respiratory failure.

Other than renal and pulmonary symptoms presentation suggests a different diagnosis and further investigation. The differential diagnosis list for renopulmonary involvement is extensive and includes, but not limited to: ANCA-associated vasculitis, ANCA-negative vasculitis, drug induced vasculitis, autoimmune connective tissue disease, antiphospholipid syndrome, infectious diseases, primary lung disease leading to renal damage and vice versa (**Table 1**).

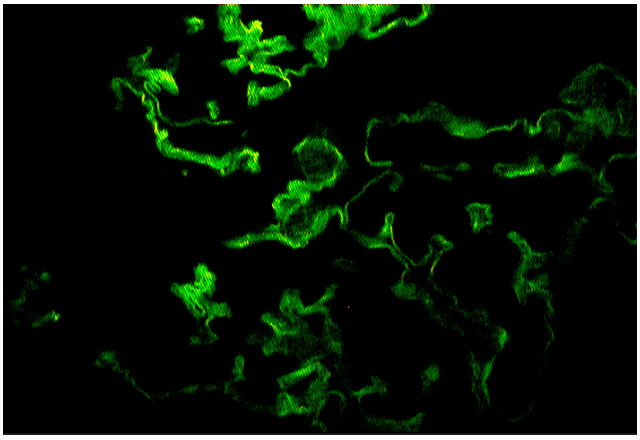
Table 1. Differential diagnosis for renopulmonary syndrome	
ANCA-associated vasculitis	Granulomatosis with polyangiitis
	Microscopic polyangiitis
	Eosinophilic granulomatosis with polyangiitis
ANCA-negative vasculitis	Henoch Schonlein purpura
	IgA vasculitis
	Mixed cryoglobulinemia
	Behcet's disease
Drug induced vasculitis	Hydralazine
	Propylthiouracil
	D-penicillamine
Autoimmune connective tissue disease	Systemic lupus erythematosus
	Polymyositis
	Systemic sclerosis
Antiphospholipid syndrome	With vasculitis or pulmonary embolism
Infectious disease	Infections that target both the lung and kidneys, for instance: legionella, tuberculosis, leptospirosis, hantavirus, cytomegalovirus, etc.
Primary lung disease leading to renal involvement	Lung malignancy with immune-complex nephritis or respiratory tract infection causing pre-renal failure, etc.
Primary kidney disease leading to pulmonary involvement	Nephrotic syndrome causing pulmonary embolism or acute renal failure leading to pulmonary edema, etc.

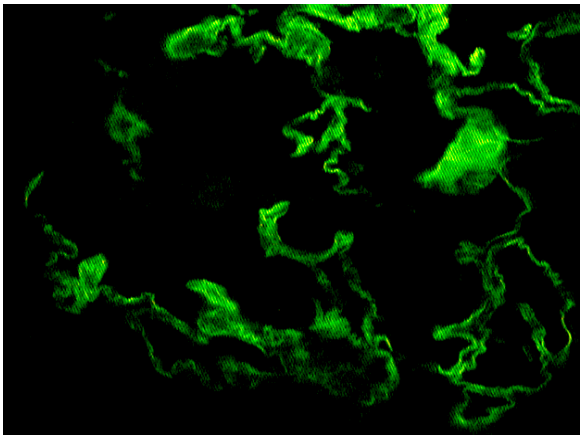
Diagnosis

The diagnosis of GS is based on clinical findings, positive serological testing and renal biopsy. The current guidelines emphasize early detection and treatment for GS and thus, recommend testing in each RPGN patient with concurrent pulmonary involvement (2). The initial set of testing is serological and should include anti-GBM, ANCA and ANA (antinuclear antibodies). There are several serological detection techniques including indirect immunofluorescence (IIF), radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA) and western blot (WB). Generally, each assay varies but has a considerably high sensitivity (95-100%) and specificity (94-100%) (36). However, false-negative and false-positive still do occur, with the former being potentially catastrophic. For instance, confirmed cases of GS (by renal biopsy) were found to be negative with ELISA testing but positive with IIF (37). There are several postulated hypotheses regarding this known false-negative phenomena, including; a different autoantibody such as IgA targeting GBM (38), a relatively low affinity of standardized ELISA to antibodies (39), late serological testing after antibodies disappearance from the blood while clinical symptoms are still present, delayed kidney damage by complement system and T-cells leading to late serological testing as well, and sequestration of high affinity antibodies in kidneys leaving the low-affinity to be scrutinized in the blood. Regardless of the reason, false-negative can occur in up to 10% GS patients tested by standardized ELISA (8,40). Insofar, the current guidelines recommend early kidney biopsy in RPGN patients with pulmonary symptoms, even if the initial serological findings are negative (2). Thus, renal biopsy is the most reliable method for excluding GS in clinically susceptious patients.

When appropriated, renal biopsy shows in light microscopy (LM) a typical RPGN pattern of diffuse crescentic and necrotizing glomerulonephritis (41). Widespread crescent formation is due to GBM disruption and fibrinoid necrosis, typically of the same age, indicating the acute nature of the disease (1). The definitive feature of GS is, however, the linear deposition of IgG (predominantly subclass IgG-1) and complement (C3) along the GBM in immunofluorescence (IF) (**Figure 1,2**). IF findings are gold-standard for GS diagnosis and patients are considered positive and treated with that finding alone.

Readily accessible imaging modalities like chest x-ray and CT can provide useful information for GS diagnosis. Chest x-ray initially can present with nonspecific bilateral hazy opacities and with disease progression eventually demonstrate diffuse infiltrative opacification corresponding to the diffuse alveolar hemorrhage (**Figure 3**). CT can display parenchymal consolidation, ground glass appearance and in later stages of the disorder, reticular pattern and interlobular septal thickening (**Figure 4**).





Figures 1,2. Immunofluorescence staining demonstrating a linear deposition of IgG on GBM consistent with GS. *(Courtesy of Prof. Marijana Ćorić, Department of Pathology and Cytology, University Hospital Centre Zagreb; School of medicine University of Zagreb)*

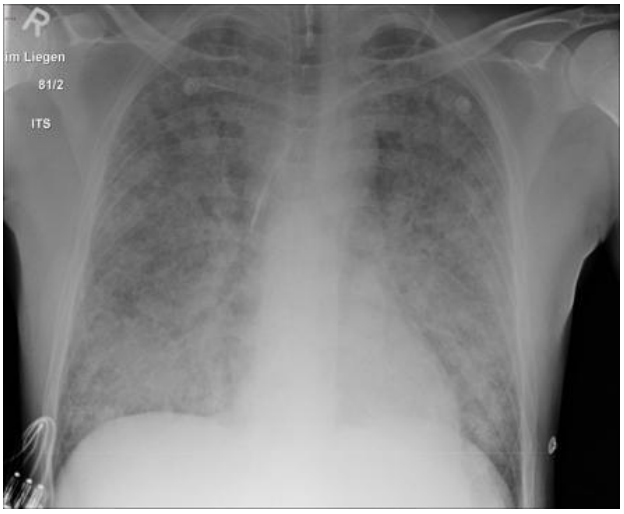


Figure 3. Chest X-ray in GS patient demonstrating diffuse infiltrative opacification consistent with diffuse alveolar hemorrhage. *(Case courtesy of Sajoscha A. Sorrentino, Radiopaedia.org, rID: 14859)*

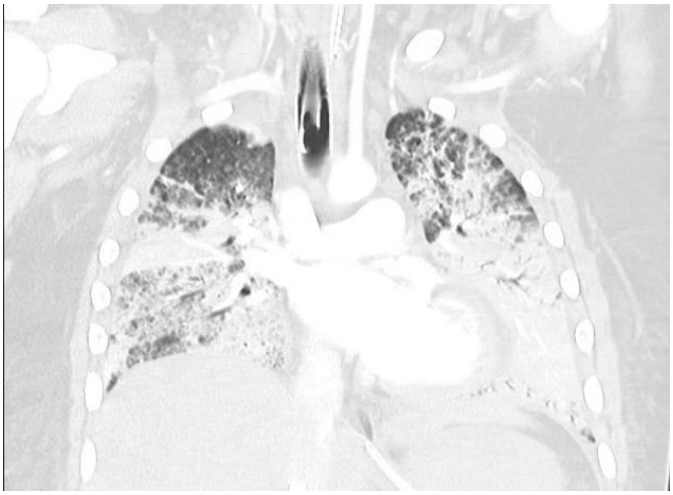


Figure 4. Coronal CT in GS patient showing widespread lung consolidation and ground glass pattern with the rest of the lungs, a finding indicating alveolar obliteration. *(Case courtesy of Bruno Di Muzio, Radiopaedia.org, rID: 61650)*

Treatment

Due to the severity and acute nature of GS, prompt diagnosis and aggressive treatment is required in this emergent state. The aim of the current treatment for GS is to remove circulating anti-GBM antibodies through plasma exchange (PE) while administering immunosuppressive therapy to both suppress further antibodies production and to limit reno-pulmonary damage (2). As the main pathological culprit for GS, anti-GBM should be removed by PE as soon as GS is confirmed and in cases with high clinical suspicion, even before GS confirmation through kidney biopsy. Rapid removal of antibodies is associated with improved kidney function survival and accelerated alveolar recovery. PE with immunosuppressive therapy hasten antibodies clearance from 14 months in untreated patients to within 8 weeks in treated patients in 1980's (42). However, nowadays with improved technique and technology, antibodies clearance occurs mostly within 14 days (2). Regardless of the timeline, PE should continue until anti-GBM antibodies are no longer detectable (43). Based on large cohort study results, intensive PE and immunosuppressive therapy showed better long term outcomes of both patients'

mortality and morbidity (44). PE is to be performed against 5% albumin with fresh frozen plasma (FFP) given to GS patients at the end of PE. As such, patients should be closely monitored afterwards for development of thrombocytopenia, coagulopathy and disseminated intravascular coagulation (DIC). The pulmonary symptoms respond well to treatment and patients usually have good kidney function due to early clinical presentation and treatment (44).

As mentioned, daily immunosuppressive therapy is adjuvant to PE and mainly consist of cyclophosphamide and glucocorticoids. Cyclophosphamide is given 2-3 mg/kg orally for 2-3 months with close monitoring for leukopenia, in which case it should be reduced or stopped depending on leukopenia severity (45). In case of leukopenia occurrence or if anti-GBM antibodies are still present serologically after three months on cyclophosphamide, treatment can be continued with azathioprine or mycophenolate instead in combination with the standard daily glucocorticoids (2). Glucocorticoids are given for 6 months with pulsation initially of methylprednisolone up to 1000 mg/day in 3 consecutive days. Thereafter, prednisone is given 1 mg/kg orally daily with subsequent reduction to 20 mg/day by 6 weeks. Refractory anti-GBM is rare but can be treated with second line therapy of rituximab (46). Due to the rarity of GS recurrence, maintenance therapy is not required and patients can be tapered off completely by 6 months (8,44). However, patients that had relapses, had them years later and with close association to smoking (47–49). Therefore, patients should be advised of the importance of smoking cessation and be offered appropriate supportive therapy, if needed (50).

Depending on remaining renal function, patients may require immediate RRT at time of diagnosis and unsurprisingly are associated with poorer outcomes, which will be further elaborated later (44). RRT is an umbrella term which consists of various techniques of compensating for renal function loss (e.g. hemodialysis, peritoneal dialysis, etc.) and definitive replacement treatment in the form of transplantation (51). Nowadays, with current recommended therapy and after the initial insult to the kidneys, kidney damage progresses slowly yet kidney survival seems to depend on kidney function at time of presentation, as discussed later (44). However, most surviving patients eventually need kidney support in the form of dialysis or definitive transplantation. Candidates for transplantation should have seronegative evidence for anti-GBM for at least six months

before undergoing transplantation (2). Generally, renal transplantation outcomes are favorable and comparable to other ESRD diseases transplantations (52).
Respiratory support may also be required depending on pulmonary involvement and severity. Patients may be intubated and mechanically ventilated, yet, pulmonary hemorrhage abates with antibodies removal and immunosuppression.

Prognosis

Due to the rarity of GS, there is difficulty extrapolating clinical significance from small sample studies about mortality and morbidity rates as these are reported with wide confidence intervals and fluctuating statistical power. Nonetheless, 1-year patient survival rates ranging from 65-93% were reported with the modern aforementioned therapy (12,44,53,54). Unsurprisingly, patients' characteristics at the time of presentation were closely associated with their prognosis. For instance, a large retrospective review study (n=71) found creatinine concentration to be a prognostic feature for patient survival, as patients with creatinine at the time of presentation under 500 µmol/L had 100% 1-year survival rate which dropped to 83% 1-year survival rate in patient above 500 µmol/L (44). This finding was later supported by a smaller British study (n=43) that concluded oliguria at time of presentation to be the strongest predicting factor for patient and kidney survival (55). Severe loss of renal function at the time of presentation renders therapy somewhat ineffective as patients' survival is not significantly altered whilst patients are exposed to aggressive and taxing therapy. Therefore, it is currently controversial whether treatment should be given to patients presenting with serum creatinine ≥600 µmol/L or with ≥80% crescent formation as the risks and therapeutic burden may outweigh the therapy benefits (44,56–58). Additionally, age was also found to be associated with a poorer prognosis in a very large New Zealand study (n=449), despite previous smaller studies reports (52). This finding was recently supported by another large French study (n=119) that collaborated age with poor patient and renal survival (9).

Renal survival reports with GS suffer from the same inconsistencies as mortality rate and 1-year renal survival rates vary from 15% to 40%. Notably, 1-year renal survival rate were reported to be 16% (CI 5-27%) by a British study (n=43) (55), 15% (CI 0-40%) by a small Chinese study (n=10) (12), 25% by a larger Chinese study (n=221) (53), and 40% by a large American study (n=71) (44). Somewhat paradoxically, patients presenting with pulmonary hemorrhage are more likely to recover renal function in the long term possibly due to early detection and treatment (9,44). However, they are at increased risk of short term mortality due to pulmonary complications.

As mentioned, often GS patients would undergo transplantation, with higher rates of retransplantation compared to other ESRD recipients (52). Graft survival is favorable with 63% 10-years graft survival and 21.2 years (95% CI 14.4-28.0 years) of first graft survival in a very large New Zealand study (n=449) (52). Similarly, GS recurrence in graft is rare (<3%) and graft failure due to GS recurrence is seldom seen (2,52). Graft failure mainly occurs due to chronic (54%) or acute (15%) rejection and is not related to GS itself (52).

Overall patients' mortality in GS is twofold; due to the disease progression and due to treatment complications. In the short term, patients can suffer from acute renal failure, respiratory failure, catheter sepsis, pneumonia and multi-organ failure. In the long term, patients can suffer from complications related to the aggressive immunosuppressive therapy such as infections, bone marrow suppression and cancer, which are in fact the leading causes of mortality (9,55). Likewise, dialysis and cardiovascular disease are major contributors for patients' mortality (52).

Conclusions

GS is a challenging disorder which requires high clinical suspicion and vigilance from practicing physicians. Due to the rapid nature of GS, there is an overall consensus about the importance of early diagnosis and treatment. Therefore, physicians should be aware of that importance and apply a low threshold of testing for GS in RPGN presenting patients. Treatment for GS had progressed greatly and despite the severity of the

disease, cautious optimism may be appropriate with early detection. Due to GS rarity, there is an issue of conflicting studies with low quality data analysis cited repeatedly without merit. A more comprehensive meta-analysis and high quality studies may illuminate future clinical GS connections and provide valuable therapeutic information.

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Biography

Guy Alush was born in Dimona, Israel in 1993. He graduated from Appleman high school in 2010 and served three years in combat in the IDF. He later came to Zagreb University in 2017 to study medicine and is planned to graduate in July 2023.

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