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Anti-Glomerular Basement Membrane Disease

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1. Introduction

Anti–glomerular basement membrane (anti-GBM) disease is a rare autoimmune disorder characterized by rapidly progressive glomerulonephritis (RPGN) with diffuse crescentic formation on renal biopsy, and it is a well-characterized cause of glomerulonephritis.
In 1919, an autopsy of an 18-year-old male patient, who had developed hemoptysis and acute renal failure after experiencing flu-like symptoms, revealed massive alveolar hemorrhage, glomerulonephritis with fibrinous exudates in Bowman's capsule and necrotizing vasculitis in the spleen and gut (Goodpasture, 1919). Stanton and Tange reported 9 cases with alveolar hemorrhage and RPGN as Goodpasture's syndrome (Stanton & Tange, 1958). Anti-GBM disease was defined as the presence of serum autoantibodies to the noncollagenous domain of the alpha 3 chain of type IV collagen or a linear binding of IgG to glomerular capillary walls as detected by direct immunofluorescence in patients with RPGN. Anti-GBM disease was divided into two types: anti-GBM disease without alveolar hemorrhage was regarded as renal-limited anti-GBM disease, and that with alveolar hemorrhage was defined as Goodpasture's syndrome.
This review focuses on anti-GBM disease by comparing international differences in prevalence, clinical features, treatments and outcomes in order to improve the prognosis of anti-GBM disease.

2. Prevalence

Anti-GBM disease is relatively rare, with an estimated annual incidence of about 0.5-1.0/million population (Table 1). It has been estimated to cause 0.2-2.4% of biopsy-proven glomerulonephritis cases in Europe, but less than 0.2% in Asia. It causes about 10% of RPGN (or necrotizing and/or crescentic glomerulonephritis) in Europe, more than 10% of RPGN in the United States, and less than 10% in Asia. In Japan, to improve the prognosis of patients with RPGN, a nation-wide survey of patients with RPGN in 365 hospitals between 1989 and 2000 was conducted, and clinical characteristics including initial symptoms, laboratory findings and histological findings were investigated along with treatment methods and outcomes (Hirayama et al., 2008). Among patients with RPGN, 6.6% had anti-GBM disease. In comparison with foreign countries, this Japanese rate of anti-GBM disease in RPGN was lower.

Authors	Year	Nation	Incidence (/million/yr)	Frequency (%)		
				GN	2nd GN	RPGN
Rychlík et al.	2004	Czech	0.17	0.31 *	1.2 *	
Heaf et al.	1999	Denmark	0.6			12.8 +
Andrassy et al.	1991	Germany	0.55			7.9
Daly et al.	1996	Ireland		2.4 *		
Schena et al.	1997	Italy	0.1	0.20 *	1.5 *	
Grcevska et al.	1995	Macedonia				3.6 +
Naumovic et al.	2009	Serbia	0.02	0.18 *	0.74 *	
Rivera et al.	2002	Spain				14.6 +
Saxena et al.	1991	Sweden				13.4 +
Williams et al.	1988	United Kingdom	1.12(0.2 – 4.0)			
Angangco et al.	1994	United Kingdom		0.81 *		11.2 +
Parfrey et al.	1985	Canada				11.5 +
Wilson and Dixon	1973	United States		7.0 *		
Jennette	1993	United States				14.6 +
Briganti et al.	2001	Australia	0.99	0.8 *		
NZGS	1989	New Zealand		5.9 *		
Date et al.	1987	India		0.04 *		
Sumethkul et al.	1999	Thai		0.10 *		3.3 +
Tang et al.	2003	China		0.15 *		8.7 +
Li, FK. et al.	2004	China(HongKong)	0.6			
Li, LS. et al.	2004	China		0.21 *	0.86 *	
Hirayama et al.	2008	Japan				6.6

The incidence of patients with anti-GBM disease is expressed as the number per 1 million population per year. The frequencies of patients with anti–GBM disease in glomerulonephritis, secondary glomerulonephritis or rapidly progressive glomerulonephritis are expressed as percentages. *Biopsy-proven glomerulonephritis. Blanks are unavailable data. Abbreviations: yr, years; GN, glomerulonephritis; 2nd GN, secondary glomerulonephritis; RPGN, rapidly progressive glomerulonephritis (including +necrotizing and/or crescentic glomerulonephritis); NZGS, The New Zealand Glomerulonephritis Study.

Table 1. Prevalence of anti–GBM disease in various countries.

All age groups are affected, but the peak incidence of anti-GBM disease is in the third decade in young men, with a second peak in the sixth and seventh decades affecting men and women equally (Figure 1). Alveolar hemorrhage is more common in younger men, while isolated renal disease is more frequent in the elderly, with a near-equal gender distribution. In that survey (Hirayama et al., 2008), the mean age at onset of renal-limited anti-GBM disease was 52.6±17.0 years. There was only one peak incidence of anti-GBM disease, and this peak occurred in the fifth and sixth decades. The gender distribution was nearly equal in renal-limited anti-GBM disease (male: female = 1: 0.94).

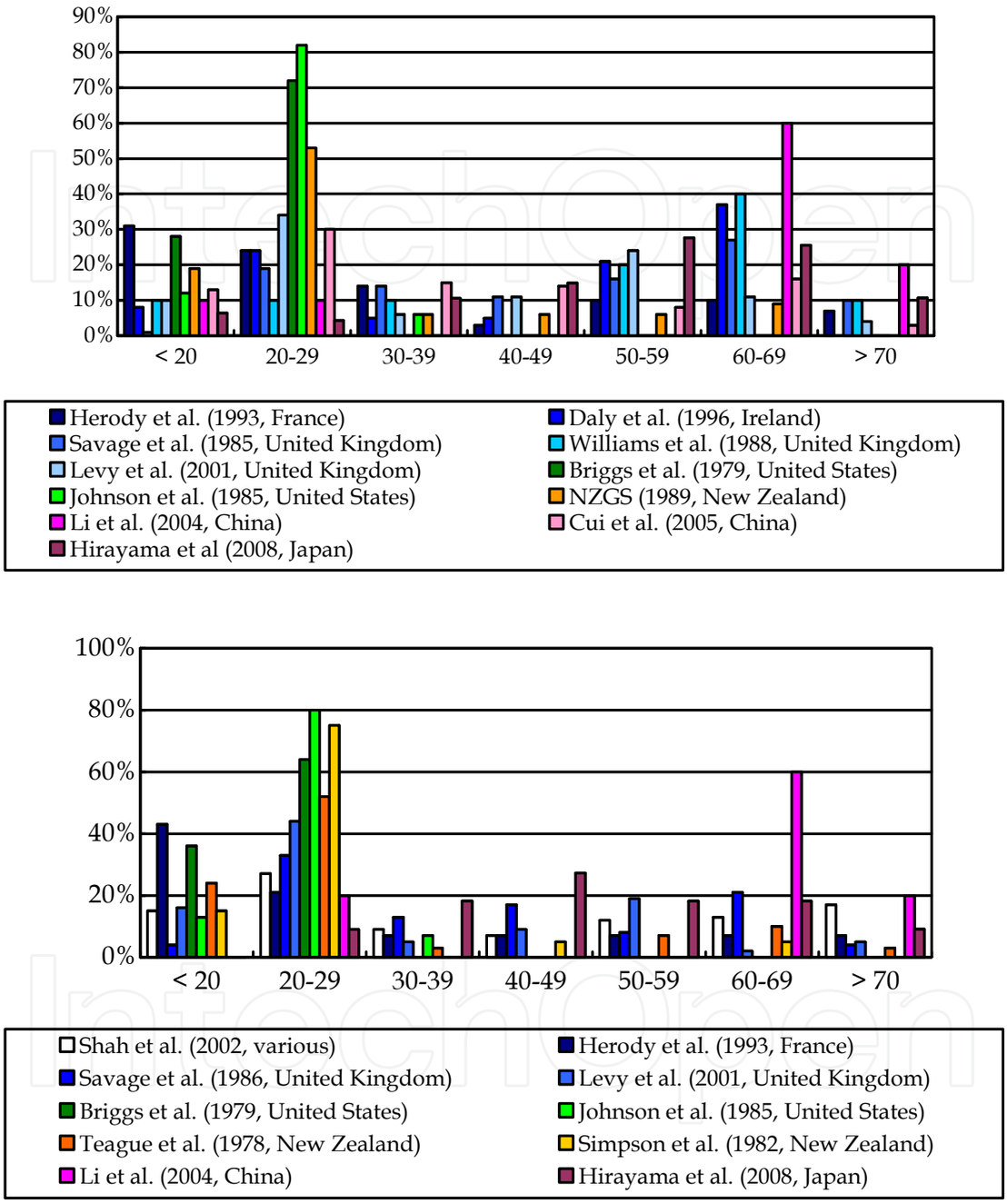

Fig. 1. Investigations of age distribution in anti-GBM disease (upper) and Goodpasture's syndrome (lower).

The histograms show the number of patients with anti-GBM disease classified by patient age at the onset of the disease. Abbreviations: GN, glomerulonephritis; Biopsy, biopsy-proven glomerulonephritis; RPGN, rapidly progressive glomerulonephritis; NZGS, The New Zealand Glomerulonephritis Study; N.A., not available.

Alveolar hemorrhage is observed in 35-62% of patients with anti-GBM disease in Europe, the United States, and China, and it is more common in younger patients and in men, whereas renal-limited anti-GBM disease is more common in older patients and in women. In Japan, alveolar hemorrhage of patients with anti-GBM disease was less frequent (23.4%) and the age at onset of Goodpasture's syndrome was lower (49.4±14.4 years), but it was more common in females (male: female = 1: 1.75).
This disease appears to be more common in Caucasians and very rare in those of African origin (Pusey, 2003; Ooi et al., 2008). There is apparently a higher incidence of onset of Goodpasture's disease in the spring and summer, as well as localized clustering of the disease, perhaps suggesting an infectious relationship (Pusey, 2003). Anecdotal associations with urinary tract infections and lithotripsy, which may subclinically affect the glomerular basement membrane, have also been reported (Pusey, 2003; Ooi et al., 2008).

3. Pathogenesis

In 1934, Masugi reported nephrotoxic glomerulonephritis induced by anti-kidney serum in an experimental model (Masugi, 1934), after which a linear binding of IgG to glomerular capillary walls was detected by direct immunofluorescence (Ortega & Mellors, 1956). In 1964, a linear immunostaining of IgG was observed in 2 patients with Goodpasture's syndrome (Scheer & Grossman, 1964), and in another study the kidney serum of patients with Goodpasture's syndrome and of patients with crescentic glomerulonephritis without alveolar hemorrhage contained antibodies that reacted with the GBM of humans and animals (Lerner et al., 1967). Those authors also demonstrated that those anti-GBM antibodies caused glomerulonephritis when injected into animals.

3.1 Structure of GBM

GBM, which exists between endothelial cells and podocytes, consists of type IV collagen, heparansulphate proteoglycan, laminine and fibronectin. Type IV collagen, which consists of 3 of 6 alpha-chains (α1 to α6) encoded by three pairs of genes on chromosomes 2, 13 and X, and its molecules were trimeric (α1α1α2, α3α4α5 and α5α5α6). This basement membrane, found in kidney, lung, cochlea and eye, comprises the surface on which epithelial cells rest. In kidneys, α3α4α5 molecules were found in the GBM, particularly the epithelial side; α1α1α2 molecules were in the mesangium, the endothelial side of the GBM, tubular basement membranes and Bowman's capsule; and α5α5α6 molecules were in tubular basement membranes and Bowman's capsule. Each alpha-chain was made by one long collagenous domain and two terminal noncollagenous globular domains: the C-terminal noncollagenous (NC1) domain and the N-terminal domain (the 7S domain). Mature GBM is a lattice-like structure comprised in part by heterotrimers of α3, 4 and 5 chains, which form a triple helix with short NC1 and 7S domains (Sado et al., 1998). The NC1 domain of the α3 chain of a tissue-specific type IV collagen [α3(IV)NC1] monomer is structured into the collagen IV network through the association of α3, α4 and α5 chains to form a triple helical protomer and through the oligomerization of these protomers via end-to-end associations and intertwining of triple helixes (Hudson et al., 2003).

3.2 Anti-GBM antibodies

The target of the anti-GBM antibodies was identified as α3(IV)NC1 (Saus et al., 1988). The two conformational epitopes of anti-GBM antibodies have been defined as E_A and E_B

(Kalluri et al., 1996; Borza et al., 2000). The E_A epitope is 17-31 amino acids on the N-terminal side, and the E_B epitope is 127-141 amino acids on the C-terminal side (Netzer et al., 1999). Alterations of the amino acid sequence translated by the COL4A3 gene, which encodes α3(IV)NC1, are not major factors, because no mutation of the COL4A3 gene was found (Persson et al., 2004). It was suggested that E_A and E_B, as cryptic B-cell epitopes, were enclosed in the quaternary structure of the hexamers created by sulfilimine crosslinks between the trimers of adjacent NC1 chains (Vanacore et al., 2008, 2009). Recently, in patients with Goodpasture's disease, elevated autoantibody titers to α3(IV)NC1 and α5(IV)NC1 monomers at diagnosis were associated with the eventual loss of renal function (Pedchenko et al., 2010). In that study, these anti-GBM antibodies bound to specific epitopes that encompassed region E_A in the α5(IV)NC1 monomer and regions E_A and E_B in the α3(IV)NC1 monomer, but did not bind to the native crosslinked α345(IV)NC1 hexamer. Thus, it is a dissociation of the NC1 hexamers that expose the pathogenic epitopes on the α3 and α5 chains, precipitating the production of anti-GBM antibodies (Pedchenko et al., 2010). It was suggested that the autoantibody itself may subsequently alter antigen conformation and expose further epitopes, causing an epitope-spreading phenomenon (Salant, 2010).

3.3 Crescent formations

The anti-GBM antibody bound to GBM ligates Fc receptors, leading to the activation of monocytes, neutrophils, eosinophils, basophils and macrophages. These release chemokines that attract a further influx of neutrophils into glomeruli, causing severe tissue injury, including the disruption of the GBM. Renal injury in anti-GBM disease is amplified by the activation of complements and protease after the binding (Sheerin et al., 1997; Baricos et al., 1991). The release of reactive oxygen species by neutrophils is also probably an important pathogenic mechanism of tissue injury.

The histogenesis and origin of cellular crescents, which are cap-like multilayered accumulations of proliferating cells, have remained controversial. Although early ultrastructural studies suggested that crescents are formed by proliferating epithelial cells (Morita et al., 1973; Min et al., 1974), subsequent histochemical studies with antibodies against leukocytes identified the presence of monocytes-macrophages in cellular crescents (Atkins et al., 1976; Thomson et al., 1979). It was demonstrated that epithelial cells predominated in crescents of patients during the early phases of disease; later phases were characterized by rupture of the basement membrane of Bowman's capsule and subsequent infiltration of cellular crescents, predominantly by macrophages (Boucher et al., 1987). The composition of cellular crescents may change during the progression of disease after the inciting glomerular injury (Ophascharoensuk et al., 1998).

The main stimulus to the migration of macrophages and neutrophils is probably the exudation of fibrin in Bowman's space caused by the disruption of the GBM and Bowman's capsule (Tipping et al., 1988). Several possible causes of acute renal injury in anti-GBM disease were identified, including the functional roles of a number of macrophage proinflammatory mediators, such as IL-1 (Lan et al., 1993), TNF-alpha (Lan et al., 1997; Le Hir et al., 1998) and matrix metalloproteinase (Kaneko et al., 2003). In epithelial crescent formation in the glomerulus, thrombin generated by coagulation (He et al., 1991) and growth-factor cytokines (IL-1 and IL-2) released by monocytes and platelets (Adler et al., 1990) stimulate the migration of epithelial cells. Moreover, interleukin-12 (Kitching et al., 1999) and interferon-γ (Timoshanko et al., 2002) are also involved.

3.4 Environmental and genetic factors

Environmental factors are thought to play a role in triggering the disease. In the first case of Goodpasture's syndrome, intercurrent infection amplifies the intensity of inflammatory responses and can aggravate disease and so make it clinically apparent. There are a number of case reports of clusters of patients with anti-GBM disease (Perez et al., 1974), which may implicate an infective agent; however, no clear viral association has been identified. Group A type 12 streptococcal cell membrane shares some cross-reactivity with the human glomerular basement membrane, generating another hypothesis: that infection may initiate anti-GBM antibody production (Blue & Lange, 1975).

Goodpasture's syndrome has been noted to occur more frequently in smokers (Salama et al., 2001). Lazor et al. (2007) reported that 89% of their patients with Goodpasture's syndrome were active smokers. In another study, alveolar hemorrhage was present in 100% of patients who smoked and in only 20% of nonsmokers with Goodpasture's disease (Donaghy & Rees, 1983). No significant difference in circulating anti-GBM antibody titers was found between smokers and nonsmokers, suggesting that cigarette smoking may increase the permeability of lung capillaries and thus expose alveolar basement membranes to circulating anti-GBM antibodies (Donaghy & Rees, 1983; Klasa et al., 1988). Other inhaled substances may also be associated with anti-GBM disease, including cocaine (García-Rostan y Pérez et al., 1997; Lazor et al., 2007), hard metals such as inert tungsten carbide and cobalt (Lechleitner et al., 1993), smoke inhalation (Klasa et al., 1988) and possibly volatile hydrocarbon solvents (Beirne & Brennan, 1972; Bombassei & Kaplan, 1992). In particular, hydrocarbon exposure may influence the development of alveolar hemorrhage (Churchill et al., 1983; Bonzel et al., 1987). Another environmental factor, alemtuzumab, which is a humanized anti-CD52 monoclonal antibody, recently was identified as a cause of anti-GBM disease (Clatworthy et al., 2008).

Genetic factors appear to play a role in susceptibility to anti-GBM disease. As a genetic factor of anti-GBM disease, the human leukocyte antigen (HLA) complexes are known to influence susceptibility to anti-GBM disease. A strong association with HLA-DR2 specificity has been confirmed (Rees et al., 1978). In HLA genotyping, DRB1*1501 (the serologically defined HLA-DR2 gene) and DRB1*1502 (HLA-DR15 gene) allele at the DRB1 locus is associated with anti-GBM disease in Caucasians (Fisher et al., 1997), Chinese (Yang et al., 2009) and Japanese (Kitagawa et al., 2008). The strongest association was with HLA DRB1*1501 but, when the effect of this gene was excluded, subsequent analysis revealed an increased frequency of DRB1*04 and DRB1*03 and a decreased frequency of DRB1*07 and DRB1*01 (Phelps & Rees, 1999). Other genetic influences of anti-GBM disease have been identified, including the immunoglobulin heavy chain Gm locus that encodes the constant region of the IgG heavy chain (Rees et al., 1984), polymorphisms of FCGR genes that encode the Fc receptor for IgG (FcγR) (Zhou et al., 2010a, 2010b) and kallikrein genes (Liu et al., 2009).

4. Clinical symptoms

General malaise (fatigue), weight loss, fever, arthralgia or myalgia may be the initial features of anti-GBM disease in a pattern similar to but much less prominent than that in systemic vasculitis. Symptoms relating to anemia may also occur even in the absence of significant hemoptysis.

Authors	Year	Nation	symptoms					
			fatigue	fever	dys-pnea	hemo-ptysis	macro hemat uria	oligo-anuria
Shah et al. *	2002	Various	15% (8/54)	28% (15/54)	26% (14/54)	65% (35/54)	7% (4/54)	17% (9/54)
Lazor et al.	2007	France & Switzerland	64% (18/28)	43% (12/28)	79% (22/28)	75% (21/28)	36% (10/28)	18% (5/28)
Merkel et al.	1994	Germany	40% (14/35)	28% (10/35)	14% (5/35)	51% (18/35)	20% (7/35)	N.A.
Daly et al.	1996	Ireland	N.A.	N.A.	N.A.	25% (10/40)	35% (14/40)	50% (20/40)
Williams et al.	1988	United Kingdom	N.A.	N.A.	10% (1/10)	10% (1/10)	10% (1/10)	60% (6/10)
Proskey et al. *	1970	United States	51% (29/56)	22% (12/56)	57% (32/56)	82% (46/56)	12% (7/56)	N.A.
Wilson et al.	1973	United States	34% (17/50)	14% (7/50)	32% (16/50)	46% (23/50)	42% (21/50)	10% (5/50)
Briggs et al.	1979	United States	22% (4/18)	11% (2/18)	44% (8/18)	50% (9/18)	56% (10/18)	N.A.
Walker et al.	1985	Australia	N.A.	N.A.	N.A.	62% (13/21)	N.A.	62% (13/21)
Teague et al. *	1978	New Zealand	68% (19/28)	26% (7/27)	78% (21/27)	86% (25/29)	43% (12/28)	N.A.
Li et al.	2004	China (Hong Kong)	N.A.	N.A.	N.A.	40% (4/10)	N.A.	40% (4/10)
Cui et al.	2005	China	N.A.	N.A.	N.A.	59% (57/97)	27% (26/97)	52% (50/97)
Hirayama et al.	2008	Japan	53% (25/47)	57% (27/47)	6% (3/47)	15% (7/47)	19% (9/47)	28% (13/47)

The frequencies of patients with each symptom are expressed as percentages. *All investigated patients had Goodpasture's syndrome. Abbreviations: N.A., not available.

Table 2. Investigations of clinical symptoms in anti-GBM disease at the initial presentation.

The principal clinical features relate to the development of renal failure due to RPGN or alveolar hemorrhage (Table 2). Hemoptysis is the predominant symptom of alveolar hemorrhage. Alveolar hemorrhage may cause severe impairment of oxygenation, so intensive care and artificial ventilation are sometimes needed. The mild lung symptoms are only dry cough and shortness of breath. Although one-third to two-thirds of patients with anti-GBM disease demonstrate alveolar hemorrhage in general, in our survey, 23.4% (11/47) of patients with anti-GBM disease suffered from alveolar hemorrhage (Hirayama et al., 2008). A minority of patients exhibited macrohematuria. Anirua or oliguria was seen in 17-62% of patients at presentation, and these findings suggested a poorer prognosis (Levy et al., 2001; Hudson et al., 2003).

5. Laboratory examinations

In general, all patients with anti-GBM disease had microscopic hematuria on urinalysis. Proteinuria is modest, but can be heavier when the disease has a more subacute course. In our survey (Hirayama et al., 2008), the mean 24-hour excretion of urinary protein in renal-limited anti-GBM disease was 2.1±3.0 g and that of Goodpasture's syndrome was 3.7±3.2 g.

Authors	Year	Nation	Urinary protein (g/day)	Serum creatinine (mg/dL)	ESRD (%)
Shah et al.	2002	Various	N.A.	6.62 (N.A.)	35% (27/78)
Herody et al.	1993	France	N.A.	N.A.	55% (16/29)
Lazor et al.	2007	France & Switzerland	1.2 (0 – 35.0)	1.27 (0.61 – 21.47)	41% (11/28)
Andrassy et al.	1991	Germany	6.4 (0 – 15.3)	12.8 (6.1 – 16.5)	67% (2/3)
Merkel et al.	1994	Germany	N.A. (0.2 – 3.5)	11.41 ± 5.64 (0.19 – 22.96)	71% (20/28)
Daly et al.	1996	Ireland	N.A.	5.1 ± 6.8 (N.A.)	50% (20/40)
Segelmark et al.	2003	Sweden	N.A.	8.94 (5.44 – 12.34)	46% (36/79)
Savage et al.	1986	United Kingdom	N.A.	N.A.	64% (69/108)
Williams et al.	1988	United Kingdom	N.A.	11.80 ± 4.67 (1.60 – 18.37)	70% (7/10)
Levy et al.	2001	United Kingdom	N.A.	3.59 (0.6 – 10.9)	55% (39/71)
Briggs et al.	1979	United States	2.6 ± 0.5 (1.9 – 3.5)	5.94 ± 7.11 (0.8 – 30.0)	33% (6/18)
Johnson et al.	1985	United States	4.3 ± 5.2 (0 – 22.0)	4.87 ± 6.93 (0.9 - 25.0)	12% (2/17)
Jennette	2003	United States	1.67 ± 3.35 (0.20- 16.20)	9.7 ± 7.2 (0.8 - 50)	N.A.
Walker et al.	1985	Australia	1.4 (0.4 – 5.4)	6.56 (1.24 – 32.35)	45% (10/22)
Simpson et al.	1982	New Zealand	N.A.	5.37 ± 5.22 (0.68 – 19.80)	10% (2/20)
Teague et al.	1978	New Zealand	N.A.	N.A.	14% (4/29)
Li et al.	2004	China (Hong Kong)	N.A.	6.96 ± 6.41 (1.19 – 22.09)	50% (5/10)
Cui et al.	2005	China	N.A.	N.A.	71% (69/97)
Hirayama et al	2008	Japan	2.4 ± 3.0 (0.1 – 12.2)	7.29 ± 4.19 (1.00 – 16.80)	60% (28/47)

Amounts of urinary protein and serum creatinine levels are expressed as means ± standard deviation or medians with ranges. Frequency of end-stage renal failure at presentation is expressed as a percentage. To convert serum creatinine in mg/dL to μmol/L, multiply by 88.4. Abbreviations: ESRD, end-stage renal disease; N.A., not available.

Table 3. Investigations of renal findings in anti-GBM disease at the initial presentation.

Unfortunately, most patients with anti-GBM disease had renal failure at the time of diagnosis, and the number of patients needing dialysis was not a few (Table 3). In our survey (Hirayama et al., 2008), the mean serum creatinine (s-Cr) level in renal-limited anti-GBM disease was 7.07±4.21 mg/dl, while that in Goodpasture's syndrome was 7.99±4.31 mg/dl. Hemodialysis therapy had already been initiated in 59.6% (28/47) of the anti-GBM disease patients before the start of immunosuppressive treatments.

Anemia was observed in most patients with anti-GBM disease, and the mean hemoglobin concentration in renal-limited anti-GBM disease was 8.8±1.7 g/dl, while that in Goodpasture's syndrome was 7.5±1.1 g/dl. The mean erythrocyte sedimentation rate (ESR) in renal-limited anti-GBM disease was 105±44 mm/h, and that in Goodpasture's syndrome

was 82±45 mm/h. The mean serum C-reactive protein (CRP) level in renal-limited anti-GBM disease was 8.5±7.2 mg/dl, and that in Goodpasture's syndrome was 8.2±8.1 mg/dl. In comparison with other forms of RPGN, such as micropolyangiitis (MPA) and Wegener's granulomatosis (WG), there was no difference in inflammation markers such as leukocyte count, ESR and serum CRP. However, in patients with anti-GBM disease, the mean level of s-Cr at the time of diagnosis was higher than that in patients with MPA (4.54±3.13 mg/dl) or WG (3.84±3.24 mg/dl). Therefore, early diagnosis of anti-GBM disease is very important.

Although obvert hemoptysis may not be immediately present in patients with Goodpasture's syndrome and alveolar hemorrhage may not be immediately obvious in radiological examinations, an elevated alveolo-arterial oxygen difference ($AaPO_2$) can be a sensitive indicator of alveolar hemorrhage. An elevated red blood cell count in bronchoalveolar lavages, as detected by bronchoscopy, is useful information for the diagnosis of alveolar hemorrhage, but lung biopsy does not contribute to this diagnosis (Lazor et al., 2007).

The diagnosis of anti-GBM disease is dependent on the detection of anti-GBM antibodies in either the circulation or the kidney tissue. These serum antibodies are usually detected using an enzyme-linked immunosorbent assay or radioimmunoassay method. The antibodies have not been reported to occur in the absence of disease, and false negatives are rare when appropriate checks are performed. In our survey (Hirayama et al., 2008), 91.5% (43/47) of patients with anti-GBM disease were diagnosed via the detection of serum anti-GBM antibodies.

In serological examinations, other autoantibodies were not usually detected. However, in our survey (Hirayama et al., 2008), anti-nuclear antibodies were detected in 11.8% of renal-limited anti-GBM disease and in 27.3% of patients with Goodpasture's syndrome. Anti-DNA antibody was not detected in renal-limited anti-GBM disease, but it was detected in 22.2% of patients with Goodpasture's syndrome. Moreover, anti-neutrophil cytoplasmic antibodies (ANCA) were detected in 12.8% (5/39) of patients with anti-GBM disease; a perinuclear pattern was detected in all five anti-GBM disease patients with ANCA, and a cytoplasmic pattern was detected in one. Anti-GBM antibody and ANCA coexisted in 15 - 50% of cases of anti-GBM disease described in the previous literature (Jayne et al., 1990; Bosch et al., 1991; Yang et al., 2005; Rutgers et al., 2005; Levy et al., 2004). Other studies revealed that patients with double-positive antibodies were predominantly MPO-ANCA, older and male (Jayne et al., 1990; Bosch et al., 1991; Yang et al., 2005; Rutgers et al., 2005). In our survey (Hirayama et al., 2008), the age at onset of patients with double-positive antibodies was higher (mean age, 52.6 years), but female-dominant (male : female = 1 : 4). The prognosis of patients with double-positive antibodies varied; the renal and patient survival rates of patients with double-positive antibodies were reported to be either better (Jayne et al., 1990; Bosch et al., 1991), not significantly different (Yang et al., 2005), or worse (Rutgers et al., 2005; Levy et al., 2004) than those of patients with anti-GBM antibody alone. In our survey (Hirayama et al., 2008), the prognosis of patients with double-positive antibodies was poor; two died and the remaining three required maintenance hemodialysis. Alveolar hemorrhage was observed in two of five patients with double-positive antibodies, and three of them had interstitial pneumonitis.

6. Imaging examinations

Kidneys were usually normal-sized or enlarged due to inflammation. In our survey (Hirayama et al., 2008), ultrasonography showed that 61.0% of patients with anti-GBM

disease had kidneys of normal size, while atrophic kidneys were observed in 12.2% of patients and enlarged kidneys were observed in 26.8%. There were no specific morphological abnormalities on any type of renal imaging examinations.
In cases with Goodpasture's syndrome, shadows usually involve the central lung fields with peripheral and upper-lobe sparing on chest radiography or computed tomography (Figure 2). Although the shadows are generally symmetrical, they can be markedly asymmetrical.

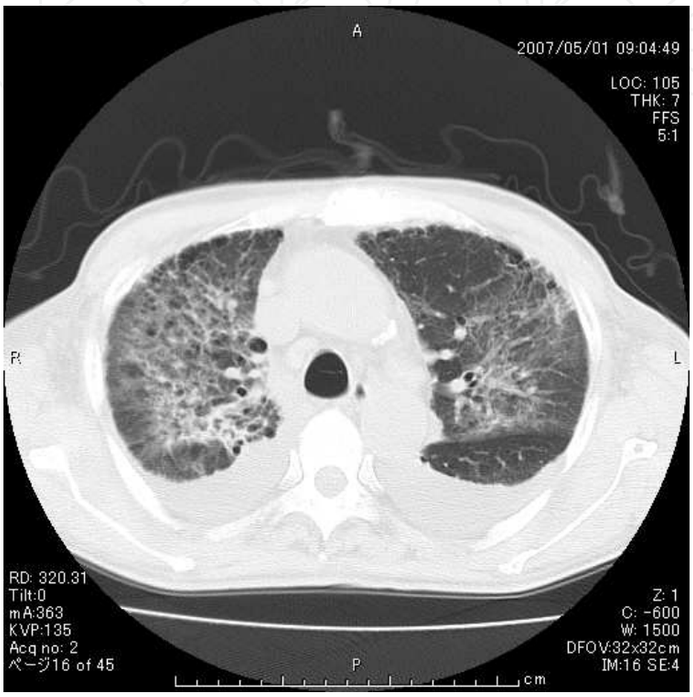

Fig. 2. Chest computed tomography in a patient with Goodpasture's syndrome.

Symmetrical shadows involved the central lung fields with peripheral sparing. Bilateral pleural effusions due to hypervolemia in acute kidney injury were also observed.

7. Pathological findings

A renal biopsy is essential in suspected anti-GBM disease both to confirm the diagnosis and to assess the renal prognosis. Glomerular fibrinoid necrosis and crescent formation with linear staining of the glomerular capillary walls for IgG are the histological hallmarks of anti-GBM disease.

7.1 Light microscopic findings

The histological pattern of disease starts with mesangial expansion and hypercellularity. It progresses to focal and segmental glomerulonephritis with infiltration by inflammatory cells, accompanied by segmental necrosis with prominent breaks in the GBM. Later, glomeruli develop an extensive crescent formation composed of parietal epithelial cells and macrophages in association with the destruction of the GBM (Figure 3). The crescents are usually at the same stage of evolution.

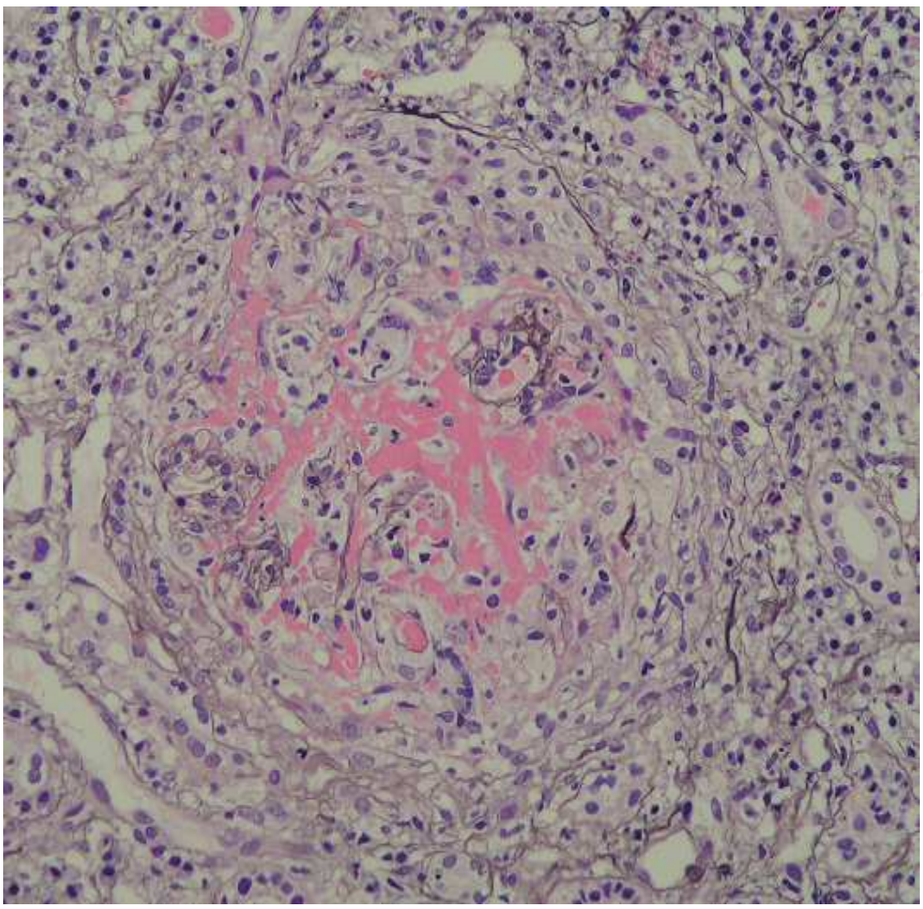

Fig. 3. Periodic acid-Schiff methenamine silver (PAM)−stained glomerulus in a patient with anti-GBM disease.

The disruption of the capillary walls, segmental necrosis and cellular crescent formation are observed. Rupture of the basement membrane of Bowman's capsule and periglomerular infiltration of inflammatory cells are also observed. Interstitial edema with infiltration of inflammatory cells is revealed.

Various degrees of crescent formation are observed in more than 90% of patients with anti-GBM disease. In Europe, the United States and Asian-Pacific, including Japan, the mean percentage of glomeruli showing crescent formation ranged from 40% to 100%, and about 70% to 100% of patients with anti-GBM disease had more than 50% crescentic glomeruli (Figure 4). Anti-GBM disease is pathologically the most severe form of glomerulonephritis (Holdsworth et al., 1985; Jennette, 2003, Hirayama et al., 2008).

Although tubules are usually normal, epithelial flattening is revealed in the severe acute phase. In the chronic phase, tubules in the area of severe injury undergo atrophy and some disappear. Acute tubulitis sometimes occurs if there is a linear staining of tubular basement membranes for IgG. Interstitial edema with infiltration of inflammatory cells is predominant in the acute phase, whereas interstitial fibrosis is revealed in the chronic phase. Interstitial infiltrates are composed of neutrophils, eosinophils, lymphocytes, monocytes and macrophages. If Bowman's capsules are disrupted, inflammatory cells infiltrate around glomeruli and have a granulomatous appearance. Acute inflammation of renal vessels,

except for glomerular capillaries, is not typical for anti-GBM disease, unless the case has concurrent ANCA (Bosch et al., 1991).

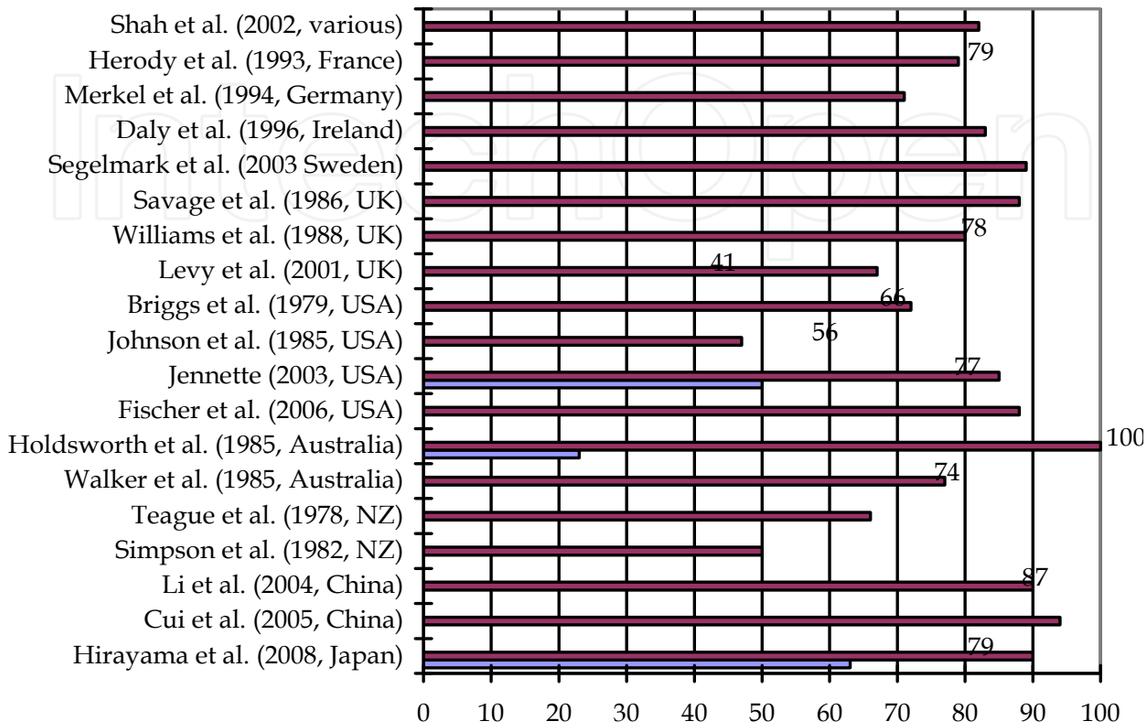

Fig. 4. Previous investigations of crescent formation in anti-GBM disease and ANCA-associated vasculitis.

Each bar shows the frequency of patients with 50% or more crescents in anti-GBM disease (purple) and ANCA-associated vasculitis (blue). The numbers show the mean percentage of glomeruli showing crescent formation in anti-GBM disease. Abbreviations: UK, United Kingdom; USA, United States; NZ, New Zealand.

7.2 Immunofluorescence findings

The immunohistologic feature of anti-GBM disease is linear staining of the glomerular capillary walls for IgG (Figure 5). IgG1 is the predominant IgG subclass in staining of the glomerular capillary walls (Bowman et al., 1987; Segelmark et al., 1990). Linear staining for IgM and IgA is less common, but rare cases with anti-GBM disease have linear staining only for IgA and circulating IgA-class anti-GBM antibodies in the absence of IgG-class anti-GBM antibodies in the serum or staining in glomeruli (Border et al., 1979; Gris et al., 1991; Borza et al., 2005). Granular or discontinuous linear staining for C3 is observed in most cases with anti-GBM disease, but glomerular staining for C3 is negative for some cases (Wilson and Dixon, 1973). Irregular staining for fibrin is observed in portions of glomerular necrosis and cellular crescents.

Linear staining of tubular basement membranes for IgG sometimes occurs (Lehman et al., 1975; Andres et al., 1978).

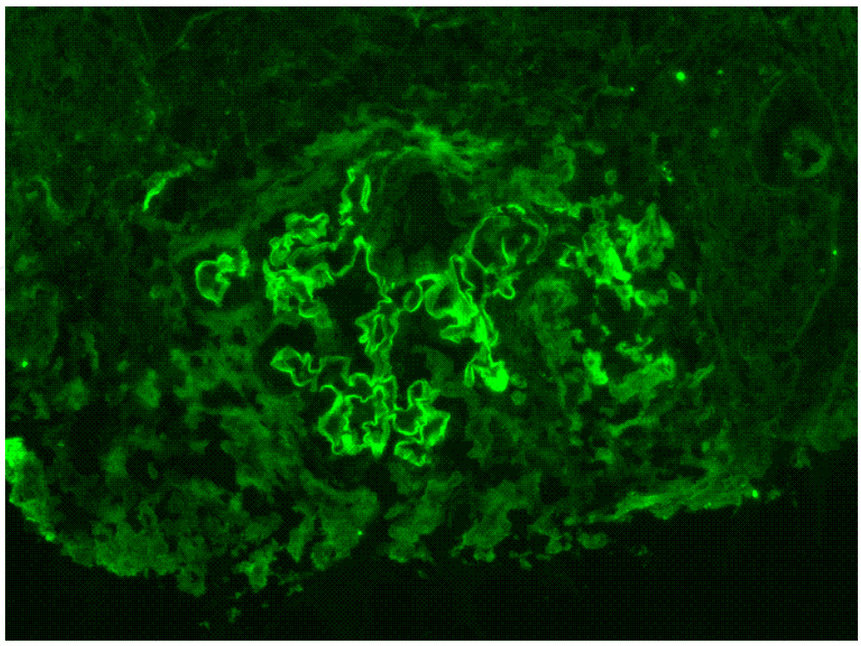

Fig. 5. Direct immunofluorescence for IgG in a patient with anti-GBM disease.

Linear staining for IgG along glomerular capillary walls is observed, but staining for IgG at the part of the cellular crescent is not.

7.3 Electroscopic findings

The rupture of GBM with variable degrees of endothelial swelling and lucent expansion of the subendothelial zone is common urtrasturactural findings in the acute phase of anti-GBM disease. Rupture of Bowman's capsule, focal effacement of epithelial foot processes and accumulation of epithelial cells and macrophages in Bowman's spaces are also observed. Occasionally, neutrophils are identified in capillaries, especially at sites where GBM is disrupted. Those findings are also observed in pauci-immune crescentic glomerulonephritis, but electron-dense deposits are absent, unlike the case with immune complex-type crescentic glomerulonephritis.

8. Treatments

As the pathogenesis of anti-GBM disease became clear, treatment regimens were designed to remove the circulating pathogenic anti-GBM antibodies by therapeutic plasma exchange, attenuate the pathogenic antibody-mediated glomerular inflammatory responses by administration of corticosteroids and suppress further production of these pathogenic antibodies by the use of immunosuppressive agents.

8.1 Therapeutic plasmapheresis

To remove the circulating pathogenic anti-GBM antibodies, therapeutic plasma exchange is recommended as the initial treatment. The effectiveness of therapeutic plasmapheresis for improving renal function has been reported. In the most commonly used regimens, plasma exchange of 4 L of plasma for 5% human albumin was performed daily for 14 days or until

the circulating anti-GBM antibodies were no longer detected (Lockwood et al., 1976). In the presence of alveolar hemorrhage, 300-400 ml of fresh-frozen plasma was given at the end of each treatment.

To reduce the replacement of plasma, anti-GBM antibody removal has been modified. Immunoadsorption to remove circulating IgG immunoglobulins without the need for protein substitution during daily treatments may also be beneficial in Goodpasture's disease. Anecdotal case reports suggest that it may be an alternative to plasmapheresis in patients with severe renal failure (Laczika et al., 2000). There was a case report of Goodpasture's syndrome that we treated with double filtration plasmapheresis combined with immunosuppression therapy (Nagasu et al., 2009). In that therapy, the removal efficiency for the anti-GBM antibody was 24 to 60% for each procedure.

8.2 Corticosteroids

To attenuate the pathogenic antibody-mediated glomerular inflammatory responses, corticosteroid is also a key element of this treatment. According to the most commonly used regimens, oral dosing of prednisolone at 1 mg/kg/day ideal body weight (maximum 80 mg daily) continues for at least 2 weeks, after which the dose is reduced every second week to 30 mg by 8 weeks. After that, the dosages of prednisolone are tapered to 2.5-5.0 mg/week and maintained at 7.5-10 mg/kg/day. Oral corticosteroids have generally been continued for at least 6 months. Intravenous administration of methylprednisolone 10 mg/kg (500-1000 mg) once daily for 1-3 days has been advocated for patients with severe alveolar hemorrhage or very rapid deterioration of renal function (Johnson et al., 1985).

8.3 Immunosuppressive agents

To further suppress the production of pathogenic anti-GBM antibodies, a combination of immunosuppressive agents is usually given. Among these immunosuppressive agents, cyclophosphamide is usually administered. According to the most commonly used regimens, the oral dose is 2-3 mg/kg/day (this is rounded down to the nearest 50 mg; reduced to 2 mg/kg/day in patients over 55 years) for 3 months. This administration is stopped if white blood cell counts fall below 4,000/μL. In such cases the agent is restarted at a lower dose once the white blood cell counts return above 4,000/μL. Intravenous cyclophosphamide (IVCY) is not usually administered, but it may be useful for a refractory case of the standard therapy (Baumgartner et al., 1995).

Although azathioprine is sometimes used as maintenance therapy, it alone does not provide adequate immunosuppression to modify the disease.

8.4 Therapeutic options for refractory diseases

There is very little study on the treatment of refractory anti-GBM disease. Cyclosporine is controversial; at 6 mg/kg/day it was effective for an anti-GBM disease patient treated with corticosteroid, cyclophosphamide and plasma exchange (Querin et al., 1992), whereas it was not useful (Pepys et al., 1982). Small numbers of case reports of successful outcomes with mycophenolic acid or mycophenolate mofetil in patients unresponsive to or intolerant of standard therapy have been published (Garcia-Canton et al., 2000; Kiykim et al., 2010; Malho et al., 2010). Rituximab, a chimeric monoclonal anti-CD20 antibody, was effective for a case of relapsed anti-GBM disease that was resistant to standard treatment (Arzoo et al., 2002). In that case, rituximab (375 mg/m^2) was administered once a week for 6 consecutive weeks; the symptoms completely resolved and anti-GBM antibody titers were decreased from 51 U/mL

to the undetectable range. However, these treatments cannot yet be recommended as a first-line therapy because no randomized controlled trials have been carried out.

9. Prognosis

Most patients without treatment died shortly after diagnosis of anti-GBM disease; the survival rate at 12 months was 4%, and the renal survival rate was 2% (Benoit et al., 1963). Although mortality has improved by the introduction of intense immunosuppression, renal survival remains very poor because of the delayed diagnosis of anti-GBM disease or delayed initiation of induction therapies.

9.1 Outcomes

The prognosis for patients with anti-GBM disease is poor; the survival rate at 6-12 months was 67-94%, but the renal survival rate was 15-58% in Europe, the United States, China and Japan (Table 4).

Authors	Year	Nation	Treatment	N	AH (%)	1-year survival (%)	
						Patient	Renal
Herody et al.	1993	France	OCS+CYC+AZA	29	50	93	41
Lazor et al.	2007	France & Switzerland	OCS+CYC+PE	24	100	100	58
Merkel et al.	1994	Germany	OCS+CYC+PE	35	57	89	29
Daly et al.	1996	Ireland	IS+PE	40	67	98	20
Segelmark et al.	2003	Sweden	OCS+CYC+PE	79	24	66	25
Peters et al.	1982	United Kingdom	IS+PE	41	56	76	39
Savage et al.	1986	United Kingdom	IS+PE	108	52	78	20
Levy et al.	2001	United Kingdom	OCS+CYC+PE	71	62	77	53
Proskey et al.	1970	United States	IS	56	100	77	23
Wilson et al.	1973	United States	IS	53	60	53	13
Beirne et al.	1977	United States	IS	29	54	42	17
Briggs et al.	1979	United States	IS(+PE)	18	61	84	22
Johnson et al	1985	United States	OCS+CYC	9	78	89	22
			OCS+CYC+PE	8	100	100	75
Walker et al.	1985	Australia	IS+PE	22	62	59	45
Teague et al.	1978	New Zealand	IS+PE	29	100	64	31
Simpson et al.	1982	New Zealand	no treatment	8	100	63	25
			OCS+AZA	4	100	100	50
			OCS+CYC+PE	8	100	100	63
Li et al.	2004	China (Hong Kong)	IS+PE	10	40	70	15
Cui et al.	2005	China	IS+PE	97	58	92	22
Hirayama et al	2008	Japan	OCS+CYC	21	14	86	24
			OCS+CYC+PE	22	36	68	14

Abbreviations: N, number of patients; AH, alveolar hemorrhage; IS, immunosuppressants (including methylprednisolone pulse therapy, oral corticosteroids, cyclophosphamide or azathioprine); PE, plasma exchange; OCS, oral corticosteroids; CYC, cyclophosphamide; AZA, azathioprine.

Table 4. Investigations of treatments for anti–GBM antibody disease.

Renal function improves in 15-75% of patients with anti-GBM disease through the combination of plasma exchange with corticosteroids and immunosuppressive agents, whereas the renal survival rates of anti-GBM disease patients treated with immunosuppressive agents alone ranged from 2-22%. Improvement of renal function is usually evident within days of the start of plasma exchange. However, it should be emphasized that this regimen has never been properly assessed by a prospective randomized controlled trial because of the rarity and acuteness of the condition. The only reported randomized controlled trial was very small and used lower doses of both plasma exchange and cyclophosphamide than those that are generally used in practice.
Although the effectiveness of treatment using therapeutic plasma exchange combined with immunosuppressive agents to improve renal function has been reported, only half of patients with anti-GBM disease had been treated with plasma exchange in our survey (Hirayama et al., 2008). Therefore, there was no significant difference in the renal survival rates between anti-GBM antibody disease patients treated with and without plasma exchange (P = 0.683 by the Log-rank Mantel-Cox test). Moreover, there was no significant difference in mortality between anti-GBM antibody disease patients treated with and without plasma exchange (P = 0.109).

9.2 Predictors of survival

The best predictors of renal survival are s-Cr at the initiation of treatment and the mean percentage of crescent formations. Renal function improves coincidentally with the introduction of plasma exchange in about 80-95% of patients with s-Cr levels less than or equal to 5.7-6.8 mg/dL (500-600 μmol/L), but in far fewer of those with higher s-Cr levels or those who require dialysis. Unfortunately, most patients with anti-GBM disease had renal failure at the time of diagnosis, and the mean percentage of crescent formation was high in anti-GBM disease patients. Therefore, in most patients with anti-GBM disease, the diagnosis may have been made too late to improve renal function by combination therapy.

9.3 Relapse/recurrence

Relapses of anti-GBM disease are rarely observed, in contrast to most other autoimmune kidney diseases. The anti-GBM antibodies seem to disappear spontaneously after 12-18 months (Levy et al., 1996). However, several reports demonstrated recurring cases with anti-GBM disease (Adler et al., 1981; Hind et al., 1984; Klasa et al., 1988; Levy et al., 1996). In our survey (Hirayama et al., 2008), relapse or recurrence was also rare in patients with anti-GBM disease (13.9%) in comparison with patients with ANCA-associated vasculitis, such as WG (29.4%) and MPA (29.3%). Therefore, remission induction therapy is more important in anti-GBM disease. The mean time to recurrence is estimated to be 4.3 years (range, 1-10 years), and that late recurrence may occur with a frequency of 2-14%. During relapses, circulating anti-GBM antibodies often reappear. The combination of plasmapheresis and immunosuppressive agents as re-remission induction therapy is also successful in relapsing cases (Levy et al., 1996).

10. Conclusion

Anti-GBM disease is a rare but well-characterized glomerulonephritis. It occurs across all racial groups but is most common in Caucasians. Although the effectiveness of treatment using therapeutic plasma exchange combined with immunosuppressive agents to improve

renal function has been reported, the prognosis for patients with this disease is poor. To improve the prognosis, it may be necessary to detect this disease in earlier stages and to treat it without delay.

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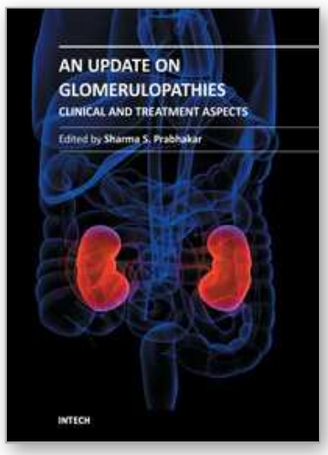

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An Update on Glomerulopathies - Clinical and Treatment Aspects is a systemic overview of recent advances in clinical aspects and therapeutic options in major syndromes of glomerular pathology. The book contains twenty four chapters divided conveniently into five sections. The first section deals with primary glomerulopathies, and the second section is devoted to glomerulopathies complicating infectious conditions. The third section deals with systemic autoimmune disorders and vasculitides which constitute major causes of glomerular disease and often renal failure. The fourth section includes chapters discussing the glomerular involvement in some major metabolic and systemic conditions. The final section has chapters which relate to some general aspects of glomerular diseases. This book will form an excellent reference tool for practicing and academic nephrology community.

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