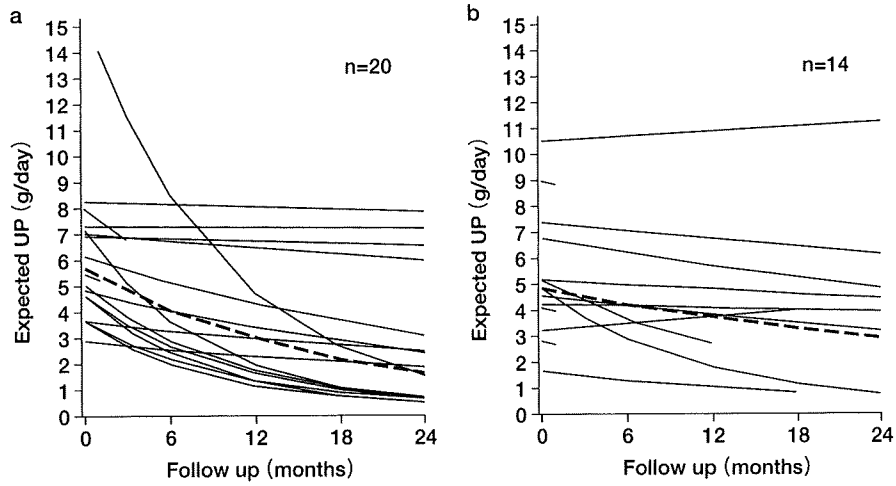

図5　低アルブミン血症（≦3 g/dL）を有する膜性腎症患者の尿蛋白量推移
ミゾリビン併用下（a）と非併用下（b）における尿蛋白量の推移。個々の患者を実線で，それぞれの平均を破線で示す。（文献6）より引用，改変）

Ⅲ．原発性糸球体腎炎に対する治療効果

小児においては，IgA患者をはじめ，治療効果について比較的多くの報告がなされているが，詳細は他稿「小児腎炎・ネフローゼ症候群の免疫抑制療法」に委ねる。一方，成人例でもIgA腎症や巣状糸球体硬化症[5]，膜性腎症，微小変化群など種々の疾患に対する効果が単発的に報告され，現在IgA腎症へのMZR適応拡大の治験が始まっている。しかしながら，原発性ネフローゼ症候群に対するわが国での市販後調査[6]では，MZR併用群での統計学的に有意な尿蛋白減少効果は認められなかった。ただし，サブ解析において，低アルブミン血症（≦3 g/dL）を有する膜性腎症患者ではMZR併用中に尿蛋白が減少する傾向（**図5**）を認め，これら患者群では長期的投与による効果が期待できることが述べられている。さらに，巣状糸球体硬化症によるネフローゼ再燃の報告[5]では，通常の投与方法（150 mg/日，分3）では改善が得られなかったが，250～500 mgを週2回のみパルス的に服用することによって寛解とステロイド減量が得られた。原発性糸球体腎炎・成人例に対する報告は，必ずしも満足できる結果とは言い難いが，投与用量設定も視野に入れ，対象症例の選択や投与方法の調整を行うことで有用性が認められると考える。筆者らは，特発性膜性腎症患者に対する経口パルス療法について，現在無作為化比較試験を進行中である。

Ⅳ．ANCA関連血管炎に対する治療効果

LNと同様，ステロイドとCPMの併用療法が中心であるが，先述のとおりCPMは種々の副作用から長期的併用が困難となる。また，高齢者に好発し，感染が危惧される場合も多く，ステロイドの用量に制限を受ける症例にもしばしば遭遇する。Hirayamaら[7]は，ステロイドとCPMの併用により寛解した後，血清ANCA値の上昇を認めた5名の患者（いずれも血清ANCA値上昇以外に再燃所見を認めない）に対してMZR投与（100～150 mg/日）を試みた。4名の患者では臨床的再燃を認めることなく血清ANCA値が正常範囲に低下しており（**図6**），先制的投与による再発予防の有効性を示唆している。さらに，副作用のためステロイド，CPMがそれぞれ減量・中止された70歳女性の血管炎再燃に対して，MZRの併用のみで寛解導入が得られた症例も報告されている[3]。なお，ANCA

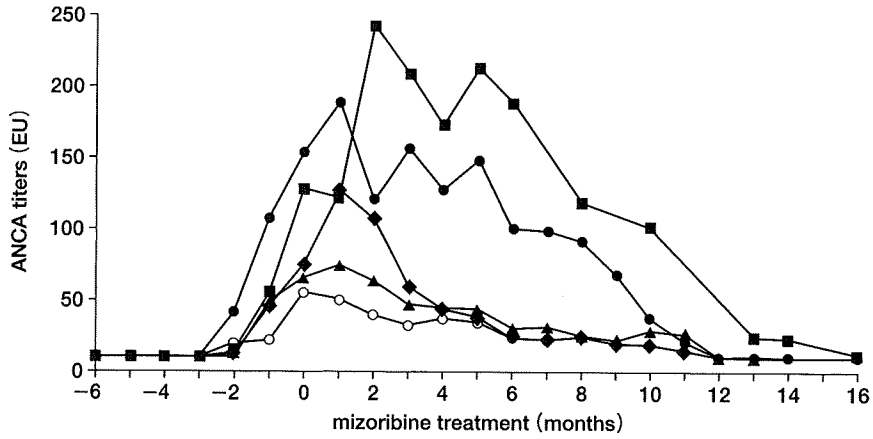

図6　ANCA関連腎炎患者におけるミゾリビン投与後の血清ANCA値の推移
経過中に血清ANCAの上昇のみられた患者（n=5）。1名の患者（○で表記）でのみ臨床的再燃を認めた。（文献7）より引用，改変）

関連血管炎では急速な腎機能障害を認めるため投与量に注意を要するが，血清クレアチニン1.8 mg/dL前後の本症例では，50 mg/日程度の投与で適切な血中濃度が得られている。

おわりに

昨今，腎炎・腎症の治療に種々の免疫抑制薬の併用が提唱され，その使い分けが議論となる。かつて，ラットの慢性拒絶モデルにおいてシクロスポリンによる血管内膜肥厚が抑制されることを報告した[8]ように，MZRは他剤との相補的な使用も展望される。血中濃度の調整や対象症例の選別など検討課題は山積しているが，長期間安全に使用できる薬剤として，今後の腎炎・腎症治療に対する貢献を期待する。

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新しい臨床検査

血液・膠原病

抗好中球細胞質抗体—ANCA

吉原　堅*　有村義宏*

Key Words

ANCA
全身性血管炎症候群
肺胞出血
間質性肺炎
急速進行性腎炎

* 杏林大学第一内科

はじめに

抗好中球細胞質抗体（antineutrophil cytoplasmic antibody；ANCA）は，好中球細胞質のアズール顆粒内に存在する蛋白分解酵素などに対する自己抗体である．ANCAは全身性血管炎症候群のうち，小型血管炎の発症に関与すると考えられており，これらはANCA関連血管炎と総称され，顕微鏡的多発血管炎（microscopic polyangiitis；MPA），Wegener肉芽腫症（Wegener granulomatosis；WG），Churg-Strauss症候群（Churg-Strauss syndrome；CSS．アレルギー性肉芽腫性血管炎ともいう）の3疾患が含まれる．ANCAの測定は，これら3疾患の診断，治療効果の判定および活動性の評価に有用であると考えられている．

ANCAの測定

現在，わが国では間接蛍光抗体法によるANCAの検出のほか，ELISAによるPR3-ANCA，MPO-ANCAの測定が行われている．

1．間接蛍光抗体（**Indirect immunofluorescence**；**IIF**）法

IIF法は，まずホルマリン固定した健常人の末梢血好中球を基質として用い，患者血清を加えた後，抗ヒトIgG FITC抗体を反応させて判定する．細胞質が均質に染色された場合にANCA陽性とする．次にエタノール固定した好中球を用いて同様に反応を行い，細胞質が均質に染色された場合に細胞質性ANCA（cytoplasmic pattern ANCA；C-ANCA）陽性，好中球の核の周囲に強い染色を認めた場合に核辺縁性ANCA（perinuclear pattern ANCA；P-ANCA）陽性と判別する．このC-ANCAとP-ANCAの染色性の相違は，抗原物質の電荷の違いにより生じるもので，対応抗原の違いを現している．対応抗原が陽性荷電を有する場合，陰性荷電の核に引き寄せられてP-ANCAパターンを示し，そうでない場合には細胞質内に均等に分布してC-ANCAパターンとなる．P-ANCAの代表はミエロペルオキシダーゼ（MPO）に対するMPO-ANCAで，C-ANCAの代表はプロテイナーゼ3（PR-3）に対するPR3-ANCAである．

IIF法でのANCA測定にはわが国ではおもにMBL社のANCAIIF kit（フルオロANCAテスト）が用いられており，20倍以上で陽性とする．

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表1 各種ELISAによるANCA基準値

ANCA種類	ELISA kit	基準値
PR3-ANCA	ネフロスカラー・PR3-ANC	＜10 EU
	Bindazyme PR3-ANCA	＜3.5 U/mL
MPO-ANCA	ネフロスカラー・MPO-ANC	＜20 EU
	Bindazyme MPO-ANCA	＜9.0 U/mL

2. ELISA（Enzyme linked immunosorbent assay）

抗原特異的ANCAを測定するもので，現時点でその臨床的有用性が明らかになっているのは，PR3-ANCAとMPO-ANCAの2種類のANCAである．その測定にはELISA kitが発売されており，わが国ではニプロ社製ネフロスカラー・PR3-ANC/MPO-ANC，Binding Site社（Birmingham, England）製Bindazyme kitの2種類がおもに用いられている．各検査法の基準値は表1に示す．

どのようなときに測定するか

ANCAが陽性を示すのは，ANCA関連血管炎においてである．わが国ではELISAによるMPO-ANCA，PR3-ANCAの測定が一般に行われている．

1. MPO-ANCA

MPO-ANCAはMPA（腎症候のみでほかの全身的な血管炎症候を伴わない腎限局型，いわゆる特発性半月体形成性腎炎を含む）のほぼ全例，CSSの40～50%で陽性を示す．

a）顕微鏡的多発血管炎

MPAは，わが国のANCA関連血管炎のなかでは最も頻度が高い疾患で，そのほとんどの症例でMPO-ANCAが陽性を示す．したがってMPAにおけるMPO-ANCAは，実質的には疾患標識マーカーとして利用可能なほど有用性が高い．しかし，まれにMPO-ANCA陽性のWegener肉芽腫症もあるので，診断には注意を要する．MPAの典型例では，いわゆる肺腎症候群として，肺胞出血あるいは間質性肺炎（肺線維症）と急速進行性腎炎を呈する．発症平均年齢は70.4歳と高齢者に好発する[1]．

従来，典型的な肺腎症候群を呈して診断に至る症例も多かったが，近年は高齢者の不明熱や，検診での検尿異常を契機にMPO-ANCA陽性から診断される症例も認められる．高齢者に咳嗽，呼吸困難や血痰あるいは腎機能障害や検尿異常，その他上強膜炎などの眼症状，筋痛，関節痛，紫斑などの皮膚症状，多発単神経炎に代表される末梢神経障害など，血管炎を疑う症候を認めた場合にはMPO-ANCAを測定する．また，わが国のMPAでは間質性肺炎の合併が多く，特発性間質性肺炎と考えられる症例でも，検尿異常や腎機能障害を伴う例ではMPO-ANCA測定を考慮する．

b）Churg-Strauss症候群

Churg-Strauss症候群は，喘息，好酸球増多，血管炎症状を3主徴とする疾患である．CSSにおいては，その約半数の症例でMPO-ANCAが陽性を示す．

MPO-ANCA陽性CSSは，高齢者に多く，肺胞出血や急速進行性腎炎などの重篤な血管炎症状を伴う例が多い[2]．一方，ANCA陰性例では肺浸潤や心筋障害など好酸球の組織浸潤に伴う症状が前面に認められる[3]．

したがって，CSSでのMPO-ANCA測定は診断の補助と，臓器障害やその予後の判定に有用と考えられる．

2. PR3-ANCA

PR3-ANCAはWGの90%以上で陽性を示し，疾患標識抗体として位置づけられている．

Wegener肉芽腫症は，上気道症状（E:Ear, nose and throat），肺症状（L:Lung），腎症状（K:Kidney）および全身の血管炎症状を示す疾患で，典型的には上記のE，L，Kの順に病期が進行し，すべての症候を認めた場合には全身型，K以外の症状を認める場合には限局型と称する．全身型ではPR3-ANCAが高率に陽性を示すが，限局型，特にEのみに病変が留まり，血管炎症状が乏しく肉芽腫病変が主体の場合には，PR3-ANCA陰性の場合もあり[4]，組織学的診断が鍵となる．

いずれのANCAも上記の全身性血管炎症候群が疑われるときに測定する．ANCAが陽性を示す場合には，血管炎の存在が示唆されるが，低力価陽性を示した場合には，慎重な判断が必要な場合もある．血管炎以外では，ヒドララジン，プロピルチオウラシル，ミノサイクリンなどの薬剤誘発性，非Hodgkinリンパ腫などの悪性疾患，HCVやHIVなどのウイルス感染に関連したANCA陽性例が知られている．近年，感染性心内膜炎に合併したPR3-ANCA陽性例の報告が散見され，紫斑などの皮疹や腎症候を伴う場合が多く，鑑別として重要である．

関連したその他の検査

ANCA関連血管炎では，肺病変，腎病変の合併が多い．ANCA陽性例では血管炎の評価，鑑別のための検査を行う必要がある．

1．血液検査

貧血，血小板増多，白血球増多，赤沈の亢進，CRP強陽性を認める．CSSでは著明な好酸球増多をきたす．腎機能や肝機能の評価，抗核抗体やリウマトイド因子などの自己抗体も確認しておく．肺出血と急速進行性腎炎を伴う例では，抗GBM抗体も測定する．肺病変の評価にLDHやKL-6，SPDなども参考になる．

治療に際してはIgGやリンパ球数をモニターし，真菌やニューモシスチス肺炎，サイトメガロウイルス感染症などの日和見感染に注意しながら，適宜β-D-グルカンやサイトメガロウイルス抗原なども調べる．血糖値やコレステロール値などにも注意が必要となる．

2．尿検査

検尿では軽度の蛋白尿と顕微鏡的血尿を認めることが多く，赤血球円柱や顆粒球円柱などの腎炎性の沈渣を伴う．ネフローゼ症候群や肉眼的血尿はまれである．

3．画像検査

胸部X線写真，胸腹部CT検査，心臓超音波検査などで病変の広がりを調べる．副鼻腔，耳，眼窩，頭蓋内病変などの評価には頭部CTやMRIも有用である．

4．その他

感染症の除外のため，血液培養を含めた各種培養を行う．症例により腎生検や皮膚生検などの組織検査，気管支鏡検査，呼吸機能検査，消化管内視鏡検査，末梢神経伝導速度検査のほか，眼科的検索，耳鼻科的検索も必要となる．

臨床的に血管炎が強く疑われるにも関わらずANCA陰性の場合や，ANCA陽性で臨床的に非典型的な症候を示す場合には，IIFおよびELISAによるANCAの検出を組み合わせて，総合的に判断することが必要である[5]．

ANCA関連血管炎では病状が急速に進行し，重篤化する場合も多いので，ANCA陽性を認めた場合には専門医へ紹介するのがよい．

ANCA値と疾患活動性

ANCA関連血管炎は適切な治療がなされないと致死的な経過をとりうる疾患であり，また再燃率も高い．治療には副腎皮質ステロイド薬および免疫抑制薬による免疫抑制療法が行われるが，過剰な免疫抑制は治療に伴う副作用の発現率を高め，かたや治療強度が不十分な場合には病状の進行や再燃の危険性が高

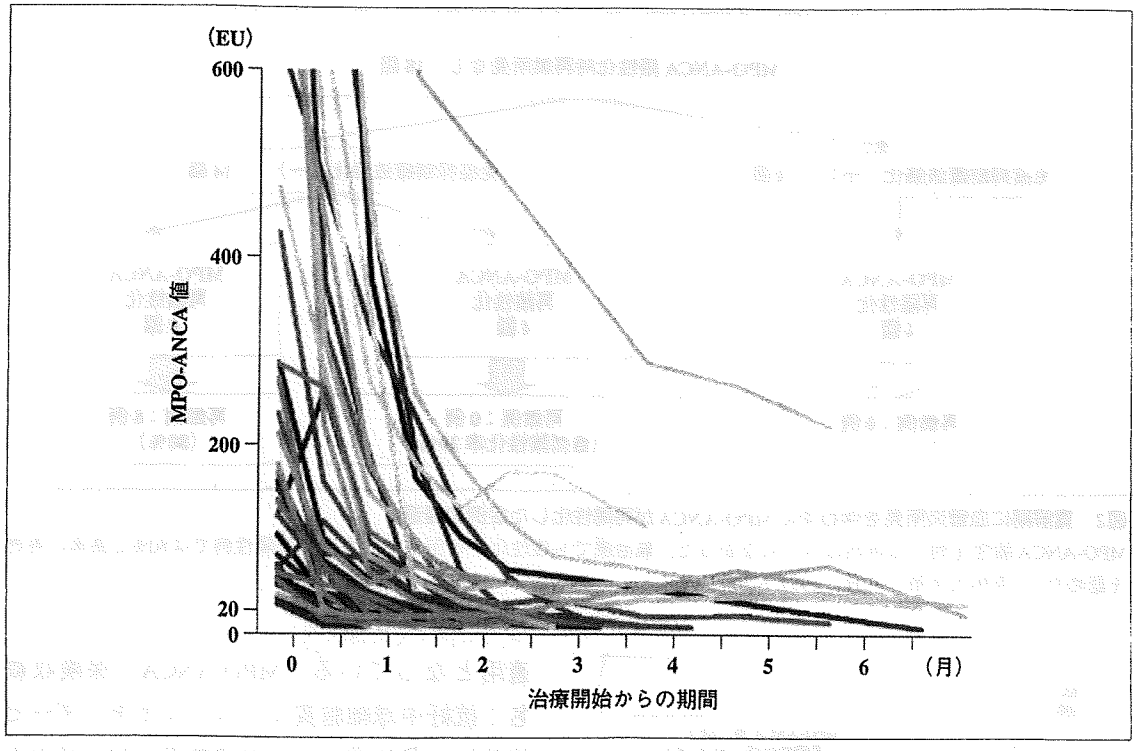

図1　寛解導入治療後のMPO-ANCA値の推移（ニプロ社製　MPO-ANCA測定試薬による）

まる．そのため，疾患活動性の評価が重要である．

ANCA抗体価は疾患活動性と平行して変動することが多く，疾患活動性の指標として有用と考えられている．筆者らが経験したMPO-ANCA関連血管炎のうち，寛解導入期から継時的に抗体価を観察しえた46症例中33例，71.7%では，寛解導入療法後にMPO-ANCA値は陰性化した．陰性化までに要した期間は2週間以内～7か月まで認められ，多くは3か月以内に陰性化し，陰性化までの平均期間は2.2か月であった．陰性化に至らない症例でも，抗体価は低下傾向を示した（図1）．

治療により陰性化したANCAは，そのまま陰性で経過する場合もあるが，治療の緩和あるいは中止により再び陽性化する場合もある．寛解期にMPO-ANCA値を定期的に測定し，抗体価の再陽性化を認めた自験16例の検討では，25回のMPO-ANCA値再上昇を認め，そのうち15回，60%に病状の再燃を認めた[5]．このうち7回では血管炎症状を認めた時点で測定したANCA値が陽性化していた．

25回のうち18回では，MPO-ANCA値の再上昇を認めた時点で再燃所見は認めなかった．18回のうち4例では，再陽性化の時点で免疫抑制療法の強化が行われMPO-ANCAは陰性化し，その後再燃を認めなかった．このときの治療強化の内容はミゾリビンの開始や増量およびプレドニゾロン投与量で平均5.3±3.8 mg/日から8.6±5.4 mg/日と軽度のステロイド増量であった．また，免疫抑制療法の強化を行わなかった14例中，4例ではMPO-ANCAが自然に再陰性化した．これらのANCA値が上昇した後，再び陰性化した例では血管炎の再燃はみられなかった（図2）．

一方，ANCA陽性が持続する例では80%と高率に再燃を認め，これらでは連続的にANCA値が上昇したのち，平均3.9か月で血管炎症候の再燃を認めた（図3）．

ANCA関連血管炎の寛解期に，ANCA値の

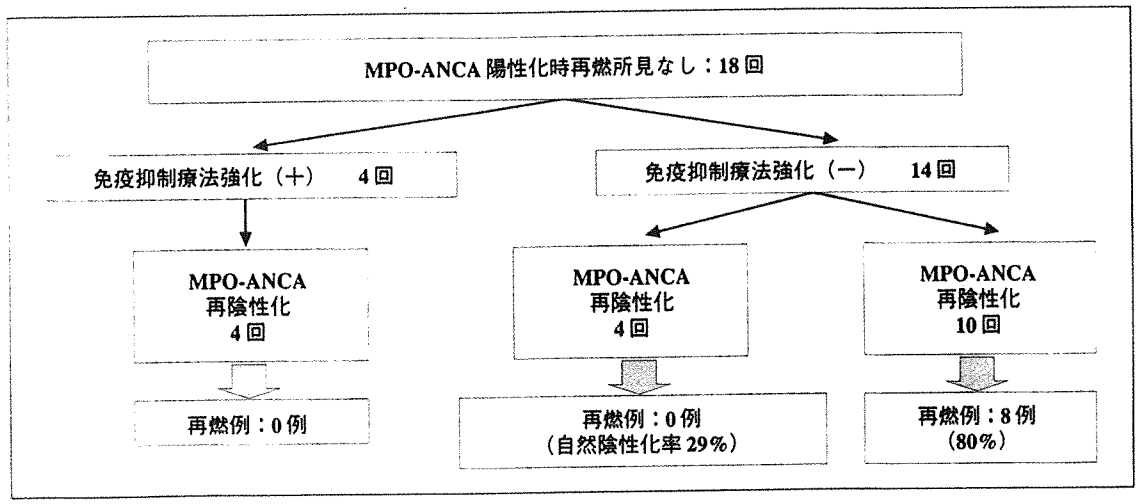

図2　寛解期に血管炎所見を伴わずにMPO-ANCAが再陽性化した症例の経過
MPO-ANCA陰性化例には再燃はみられなかった．無治療でも陰性化する例があった．持続陽性例では80%と高率に再燃を認めた．（杏林大学第一内科，1991～2006年）

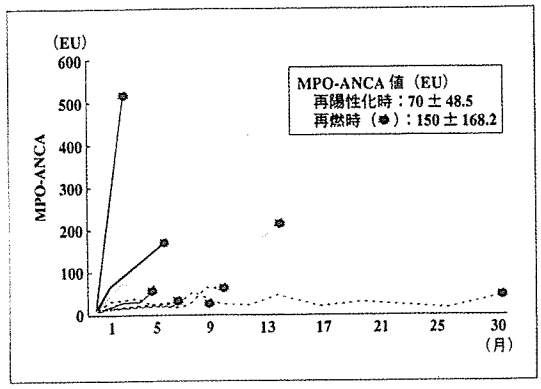

図3　MPO-ANCA再上昇から再燃までの抗体価の推移（n＝8）

再上昇のみで治療の強化に踏み切るべきかについては議論の余地の残るところであるが，軽度の免疫抑制療法の強化を行いANCAを陰性化させることで，再燃を予防できる可能性もあり，特に複数回にわたりANCA値が上昇傾向を続ける場合には，再燃の危険が高く治療強化を検討するべきと思われる．

健康保険上の取り扱い

IIF法によるC-ANCA（保険収載名：細胞質性抗好中球細胞質抗体）およびELISAによるPR3-ANCAはWegener肉芽腫症の診断で保険適用となっている．MPO-ANCA（保険収載名：抗好中球細胞質ミエロペルオキシダーゼ抗体）は急速進行性糸球体腎炎に対してのみ保険適用となっており，その診断および経過観察のために測定した場合に算定できる．

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ORIGINAL ARTICLE

A nationwide survey of rapidly progressive glomerulonephritis in Japan: etiology, prognosis and treatment diversity

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Abstract
Background The etiology, prevalence, and prognosis of rapidly progressive glomerulonephritis (RPGN) including renal vasculitis vary among races and periods.
Method To improve the prognosis of Japanese RPGN patients, we conducted a nationwide survey of RPGN in the nephrology departments of 351 tertiary hospitals, and found 1772 patients with RPGN (Group A: diagnosed between 1989 and 1998, 884 cases; Group B: diagnosed between 1999 and 2001, 321 cases; and Group C: diagnosed between 2002 and 2007, 567 cases). ANCA subclasses, renal biopsy findings, treatment, outcome and cause of death were recorded.
Result The most frequent primary disease was renal-limited vasculitis (RLV) (42.1%); the second was microscopic polyangiitis (MPA) (19.4%); the third was anti-GBM-associated RPGN (6.1%). MPO-ANCA was positive in 88.1% of RLV patients and 91.8% of MPA patients. The proportion of primary renal diseases of RPGN was constant during those periods. The most frequent cause of death was infectious complications. The serum creatinine at presentation and the initial dose of oral

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prednisolone decreased significantly in Groups B and C compared to Group A. However, both patient and renal survival rates improved significantly in Groups B and C (survival rate after six months in Group A: 79.2%, Group B: 80.1%, and Group C: 86.1%. Six-month renal survival in Group A: 73.3%, Group B: 81.3%, and Group C: 81.8%).

Conclusion Early diagnosis was the most important factor for improving the prognosis of RPGN patients. To avoid early death due to opportunistic infection in older patients, a milder immunosuppressive treatment such as an initial oral prednisolone dose reduction with or without immunosuppressant is recommended.

Keywords Anti-neutrophil cytoplasmic antibody (ANCA) · Myeloperoxidase (MPO) · Microscopic polyangiitis (MPA) · Renal vasculitis · Rapidly progressive glomerulonephritis (RPGN) · RPGN clinical grading system

Introduction

Rapidly progressive glomerulonephritis (RPGN) is defined as a clinical syndrome involving abrupt or insidious onset of hematuria, proteinuria, anemia, and rapidly progressive renal failure. The number of RPGN patients has increased recently [1], which may be a consequence of the wider availability of anti-neutrophil cytoplasmic autoantibody (ANCA) assays, improved recognition of the disease, increased referral rates to tertiary centers, and more efficient approaches to renal biopsy in recent years [2]. Furthermore, the prognosis for patients with RPGN is regarded as having improved over the last 20 years [2], especially the short-term prognosis of renal-limited vasculitis [3]. In contrast, the prognosis for older patients with RPGN and the long-term renal survival of patients with RPGN are still a concern [4–6]. RPGN is a condition that is not commonly encountered in individual nephrology departments, and the etiology of RPGN is diverse. Consequently, we started this observational study in 1998 to clarify the actual status of Japanese patients with RPGN, treatment attitudes regarding RPGN, the prognosis for these patients, and to formulate clinical guidelines for Japanese patients with RPGN. To do this, we conducted a nationwide survey of RPGN patients between 1989 and 2007. In 2002, we published our Japanese clinical guidelines for RPGN based on the survey results for 715 cases of RPGN in Japan [7]. From our observational study, we showed yearly changes in both primary renal diseases for RPGN, and the effect of the clinical guidelines on both the physician's treatment attitude toward RPGN patients and the outcome before and after the clinical guidelines had been published. Furthermore, we evaluated the effect of the Japanese clinical guidelines for RPGN on the outcome by analyzing our prospective cohort of RPGN patients in Japan.

Subjects and methods

Subjects

We retrospectively collected records of patients with RPGN from 1989 to 1998 and prospectively collected the clinical records of RPGN patients from 1999 to 2007 by mailing a questionnaire form annually to 351 nephrology departments of tertiary hospitals in Japan. This study was approved by the medical ethics committee at the Graduate School of Comprehensive Human Sciences, University of Tsukuba in accordance with the guidelines on epidemiological research from the Ministry of Health, Labor and Welfare of Japan. The definition of RPGN was based on clinical findings as follows: rapidly progressing renal failure from several weeks to a few months accompanied by the following nephritic urinary abnormalities: hematuria (mostly microscopic hematuria, but occasionally gross hematuria), proteinuria, and red blood cell casts or granular casts in the urine sediment. One hundred seventy-one nephrology departments responded and presented 1772 RPGN cases for this study.

We evaluated the RPGN cases by stratifying patients into three periods depending on the year of diagnosis of RPGN. The RPGN patients who were diagnosed between 1989 and 1998 were classified into the first period (Group A: 884 cases), and these subjects were retrospective cases. The RPGN patients who were diagnosed between 1999 and 2001 were classified into the second period (Group B: 321 cases); this was the period when we started the analysis of Japanese cases of RPGN and when some of the results were announced in Japan. The RPGN patients who were diagnosed between 2002 and 2007 were classified into the third period (Group C: 567 cases); this was the period after we had published the Japanese guidelines for RPGN in 2002 [7].

Clinical evaluation and treatment methods

Baseline characteristics including age, sex, comorbid conditions, features of prodromal illness, and clinical, biochemical, serological, and urinary features at patient presentation were obtained from clinical records. Follow-up clinical data including serum creatinine, ANCA titer, anti-GBM anitibody titer, C-reactive protein, recurrence and outcome concerning survival, dialysis dependence after 1, 2, 3, 6, 12, and 24 months, start of dialysis therapy, the final follow-up date, and cause of death were also documented. Relapse was defined as a rise in the creatinine

concentration with nephritic sediment and other signs or symptoms of vasculitis. The initial dose of oral prednisolone, its duration of initial dose, and immunosuppressive treatment were also recorded.

The classification of RPGN was based on Glassock's classification [8]. The diagnosis of primary renal disease for RPGN was made by each institution.

Statistical analysis

Regarding differences in the continuous variables between the groups, the unpaired Student's t test was applied after a symmetrical distribution was confirmed. Otherwise, the Mann–Whitney U test was applied. We used the chi-square test to analyze the frequencies of categorical variables. Both renal and patient survival rates were estimated by the Kaplan–Meier method. A prognostic factor was determined by the chi-square test, and then hazard ratios for patient outcome were estimated using a Cox regression model after confirming the proportionality in each model. To evaluate prognostic factors among our subjects at the start of treatment, we selected age, renal function (serum creatinine, urinary volume), glomerular damage (hematuria, proteinuria, cast formation), general status (serum albumin, serum total protein, hemoglobin), systemic inflammation (C-reactive protein, erythrocyte sedimentation rate, WBC count), and extrarenal complications (blood pressure, presence of lung involvement). Lung involvement indicates existence of chest X-ray abnormality, interstitial pneumonitis or lung bleeding. A p value of less than 0.05 was considered significant. The statistical analyses were performed in part using SPSS software v.15.0.

Results

Classification, causes, and yearly changes of RPGN in Japan

Table 1 shows the number of patients with RPGN and yearly changes in frequencies. Among the total RPGN patients, 42.0% showed pauci-immune-type crescentic GN (renal-limited vasculitis: RLV), 19.4% MPA, and 2.6% Wegener's granulomatosis; thus, 64.0% exhibited pauci-immune-type RPGN. Anti-GBM-type RPGN and Goodpasture's syndrome were exhibited by 6.1% of RPGN patients. Among cases of primary crescentic GN, only 2.0% were immune-complex-type RPGN. Most of the cases of immune-complex-type RPGN were secondary RPGN due to other primary glomerulonephritis or secondary RPGN due to lupus or cryoglobulinemia.

Among patients with pauci-immune-type RPGN, the proportion of RLV was slightly decreased, whereas the proportion of MPA was increased during the observation period. The rate of patients with anti-GBM antibody was constant, and one quarter of these had been complicated with lung disease during the last 20 years (namely Goodpasture's Syndrome). The number and proportion of primary immune-complex-type RPGN cases among the total decreased recently.

Among all RPGN patients, female subjects were predominant. This difference was mainly due to patients with systemic lupus erythomatosus (SLE) and MPA. On the other hand, a slight male predominance was observed in patients with Wegener's granulomatosis. Among all RPGN subjects, the mean age significantly increased during the observation period. The main reason for this change was a significant increase in the mean age of subjects with RLV, MPA, and anti-GBM antibody-mediated RPGN in recent years (Table 2).

Yearly changes in renal function and other values at presentation during the observation period

The mean serum creatinine level at presentation among all RPGN patients was significantly reduced in Groups B and C compared to Group A. However, serum creatinine at presentation was not reduced in anti-GBM antibody-associated crescentic GN, Goodpasture's syndrome, SLE, and Wegener's granulomatosis. Urinary protein at presentation was significantly reduced in anti-GBM antibody-associated crescentic GN between Groups B and C, and in SLE between Groups A and C. However, urinary protein was significantly increased in immune-complex-associated GN between Groups A and C, and in RLV between Groups A and B. CRP was significantly increased in Goodpasture's syndrome between Groups A and B, and Groups A and C, and significantly decreased in MPA between Groups A and C. There was no significant difference in hemoglobin at presentation during the observation period (Table 3). Among all RPGN patients, 18.8% of the subjects had interstitial pneumonitis, and 10.5% of the subjects had lung bleeding.

The prevalence of ANCA subgroups was analyzed in the subjects with RLV, MPA, and Wegener's granulomatosis (Table 4). The positive rate of MPO-ANCA among patients with RLV was 88.1%, that of MPA was 91.8%, and that of Wegener's granulomatosis was 22.7%. The positive rate of PR3-ANCA among patients with RLV was 7.4%, that of MPA was 6.1%, and that of Wegener's granulomatosis was 71.1%. Furthermore, 38 patients with RLV, 13 patients with MPA and 3 patients with Wegener's granulomatosis were both MPO-ANCA and PR3-ANCA positive, and 71 patients with RLV, 21 patients with MPA and 6 patients with Wegener's granulomatosis were both MPO-ANCA and PR3-ANCA negative.

Table 1 Number of patients with RPGN and yearly changes in frequencies

Diagnosis	Classification	Group A		Group B		Group C	Total RPGN cases		
		n	%	*n*	%	*n*	%	*n*	%
Primary									
Crescentic GN	Anti-GBM antibody-associated crescentic GN	39	4.4	20	6.2	22	3.9	81	4.6
	Immune-complex-associated crescentic GN	26	2.9	3	0.9	6	1.1	35	2.0
	Renal-limited vasculitis	345	39.0	151	47.0	249	43.9	745	42.0
	Overlapped crescentic GN	19	2.1	5	1.6	7	1.2	31	1.7
	Undifferentiated primary crescentic GN	14	1.6	2	0.6	12	2.1	28	1.6
Primary GN with crescents	Mesangioproliferative glomerulonephritis	9	1.0	2	0.6	4	0.7	15	0.8
	Membranous nephropathy	2	0.2	2	0.6	1	0.2	5	0.3
	IgA nephropathy	25	2.8	9	2.8	9	1.6	43	2.4
	Non-IgA mesangial proliferative GN	4	0.5	2	0.6	2	0.4	8	0.5
	Other primary GN	2	0.2	0	0.0	1	0.2	3	0.2
Systemic disease-associated									
	Goodpasture's syndrome	14	1.6	5	1.6	8	1.4	27	1.5
	Systemic lupus erythematosus	50	5.7	5	1.6	11	1.9	66	3.7
	Wegener's granulomatosis	23	2.6	9	2.8	14	2.5	46	2.6
	Microscopic polyangiitis	157	17.8	58	18.1	129	22.8	344	19.4
	Other necrotizing vasculitis	6	0.7	5	1.6	4	0.7	15	0.8
	Purpura nephritis	18	2.0	5	1.6	13	2.3	36	2.0
	Cryoglobulinemia	5	0.6	3	0.9	4	0.7	12	0.7
	Rheumatoid arthritis	18	2.0	2	0.6	4	0.7	24	1.4
	Malignant neoplasm	2	0.2	1	0.3	0	0.0	3	0.2
	Other systemic diseases	22	2.5	9	2.8	9	1.6	40	2.3
Infection-associated									
	Poststreptococcal acute glomerulonephritis	8	0.9	2	0.6	0	0.0	10	0.6
	Abscess	1	0.1	2	0.6	3	0.5	6	0.3
	Hepatitis C virus	1	0.1	1	0.3	0	0.0	2	0.1
	Other infectious diseases	13	1.5	2	0.6	5	0.9	20	1.1
Drug-associated		7	0.8	1	0.3	2	0.4	10	0.6
Others		7	0.8	1	0.3	9	1.6	17	1.0
Unknown		47	5.3	14	4.4	39	6.9	100	5.6
Total		884	100.0	321	100.0	567	100.0	1772	100.0

Prognosis and cause of death

During the entire observation period, 351 patients (39.7%) died in Group A, 110 patients (34.3%) died in Group B, and 102 patients (18.0%) died in Group C. Table 5 shows the causes of death in those subjects. The most frequent cause of death was infectious complications. The second was respiratory failure. The rate of infection was the highest in Group C, because infection as a cause of death was frequent in the early phase of treatment. Figure 1A shows the results of a Kaplan–Meier analysis of patient survival. Patient survival was significantly improved in Group C compared to that in Group A ($p < 0.05$). The six-month survival rate was 79.2%, that for 12 months was 75.5%, and that for 24 months was 72.0% in Group A. The corresponding values for Group B were 80.1, 78.3, and 72.8%, respectively. In Group C, they were 86.1, 82.8, and 77.7%, respectively.

Table 6 shows the survival rates in patients with each type of RPGN. Patients with RLV and MPA showed a significant improvement in survival in Group C, whereas patients with other types of RPGN did not.

Figure 1B shows the results of a Kaplan–Meier analysis of renal survival. Renal survival was significantly improved in Groups B and C compared to Group A ($p < 0.05$). The six-month survival rate was 73.2%, that at 12 months was 71.9%, and that at 24 months was 68.7% in Group A. The corresponding values in Group B were 81.3,

Table 2 Sex and age distribution of RPGN cases at presentation

	Group A				Group B				Group C			
	Male (%)	Mean age	SD	Age range	Male (%)	Mean age	SD	Age range	Male (%)	Mean age	SD	Age range
Primary												
Crescentic GN												
Anti-GBM antibody-associated crescentic GN	48.8	52.05	16.51	10–79	45.0	54.83	18.82	19–83	40.9	61.59	18.34	11–77[b,c]
Immune-complex-associated crescentic GN	53.9	54.27	18.66	14–77	66.7	70.00	9.09	60–82	50.0	51.50	24.82	11–75
Renal-limited vasculitis	44.6	61.85	14.95	6–88	54.3	64.98	14.13	13–91	50.0	67.28	13.12	1–92[a,b,c]
Overlapped crescentic GN	44.4	60.84	15.61	6–82	20.0	64.80	9.20	50–73	42.9	51.29	26.24	8–72
Undifferentiated primary crescentic GN	69.3	56.62	23.92	8–84	0.0	73.00	14.00	59–87	50.0	63.36	15.29	29–81
Primary GN with crescents												
Mesangioproliferative glomerulonephritis	77.8	50.56	26.50	6–75	100.0	71.50	6.50	65–78	100.0	74.75	1.30	73–76
Membranous nephropathy	50.0	59.00	3.00	56–62	50.0	41.00	27.00	14–68	100.0	21.00	0.00	21–21
IgA nephropathy	70.8	40.32	19.38	8–75	77.8	56.11	14.39	31–77	75.0	42.78	26.03	8–78[a]
Non-IgA mesangial proliferative GN	33.3	53.75	14.15	30–65	50.0	40.00	30.00	10–70	100.0	64.00	1.00	63–65
Other primary GN	100.0	60.50	3.50	57–64					0.0	3.00	0.00	3–3
Systemic disease-associated												
Goodpasture's syndrome	42.9	54.36	15.46	23–76	60.0	62.20	9.43	45–72	75.0	70.88	10.64	57–93[b,c]
Systemic lupus erythematosus	34.0	35.84	14.55	13–72	0.0	55.80	11.03	44–75	36.4	46.73	19.04	15–75[a,b,c]
Wegener's granulomatosis	59.1	46.68	17.36	16–85	66.7	57.11	12.15	77–32	57.1	55.71	18.21	14–80
Microscopic polyangiitis	47.1	64.60	11.98	7–87	39.7	65.14	16.08	5–91	49.5	68.77	12.00	7–88[b,c]
Other necrotizing vasculitis	50.0	60.67	9.83	75–47	20.0	52.00	21.42	14–79	75.2	69.25	14.55	46–83
Purpura nephritis	55.6	45.83	19.98	11–75	20.0	39.40	24.30	11–77	61.5	52.33	28.35	5–82
Cryoglobulinemia	20.0	60.00	9.06	51–77	33.3	58.00	12.19	47–75	50.0	56.75	23.25	17–74
Rheumatoid arthritis	33.3	58.33	13.25	22–77	0.0	68.50	10.50	58–79	0.0	64.50	7.40	52–70
Malignant neoplasm	100.0	62.50	3.50	59–66	0.0	59.00	0.00	59–59				
Other systemic diseases	27.3	41.00	21.80	3–72	11.1	54.22	13.02	20–67	22.2	62.22	9.35	47–75[b,c]
Infection-associated												
Poststreptococcal acute glomerulonephritis	75.0	42.38	23.53	7–84	0.0	76.50	4.50	72–81				
Abscess	100.0	73.00	0.00	73–73	50.0	32.50	16.50	16–49	33.3	47.33	17.75	31–72
Hepatitis C virus	100.0	68.00	0.00	68–68	100.0	71.00	0.00	71–71				
Other infectious diseases	92.3	54.92	15.95	25–78	100.0	60.50	9.50	51–70	80.0	63.60	8.14	54–72
Drug-associated	28.6	54.29	13.20	36–77	0.0	64.00	0.00	64–64	100.0	80.00	1.00	79–81[b,c]
Others	28.6	43.29	21.36	2–78	0.0	64.00	0.00	64–64	55.6	51.78	28.01	2–78
Unknown	39.3	59.89	20.82	5–83	50.0	66.64	10.41	56–91	29.7	64.03	16.20	4–80[c]
Total	48.5	57.47	17.96	2–88	47.4	62.80	15.93	5–91	48.5	64.72	16.56	1–93[a,b,c]

[a] $p < 0.05$ between Groups A and B

[b] $p < 0.05$ between Groups A and C

[c] $p < 0.05$ between Groups B and C

78.6, and 75.4%, respectively. In Group C, they were 81.8, 80.5, and 76.7%, respectively.

Table 7 shows the renal survival rate for each type of RPGN. Patients with RLV and MPA showed a significant improvement in survival in Groups B and C compared to Group A. However, renal survival in patients with Goodpasture's syndrome showed a significant exacerbation in Groups B and C in comparison with Group A.

For immunosuppressive treatment as an initial treatment, rates of cyclophosphamide administration (Group A: 22.5%, Group B: 26.6%, and Group C: 21.5%) or methyl prednisolone administration (Group A: 69.5%, Group B: 68.5%, and Group C: 70.4%) were not different during our observation period. However, the initial dose of oral predonisolone showed a significant reduction in Groups B and C compared to Group A in RLV (Group A: 0.81 ± 0.26 mg/kg/day, Group B: 0.73 ± 0.22 mg/kg/day, and Group C: 0.71 ± 0.24 mg/kg/day) and in MPA (Group A: 0.91 ± 0.29 mg/kg/day, Group B: 0.81 ± 0.28 mg/kg/day, and Group C: 0.75 ± 0.24 mg/kg/day, respectively).

Table 3 Clinical characteristics at presentation

	Serum creatinine (mg/dl)		Urinary protein (g/day)		CRP (mg/dl)		Hemoglobin (g/dl)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Primary								
Anti-GBM antibody-associated crescentic GN								
Group A	6.7	4.2	2.3	2.8	8.6	8.8	9.5	1.9
Group B	7.6	7.6	3.5	2.8	9.6	9.3	9.2	1.9
Group C	4.8	3.4	1.3[c]	0.7	10.3	8.3	9.6	2.1
Immune-complex-associated crescentic GN								
Group A	4.8	3.4	1.5	1.1	3.8	3.7	9.4	2.2
Group B	3.1	0.3	3.4	2.8	1.6	1.5	9.6	1.8
Group C	1.9	1.2	4.0[b]	3.2	3.8	4.6	11.3	2.2
Pauci-immune crescentic GN								
Group A	4.7	3.5	1.9	1.9	5.1	5.6	9.2	2.2
Group B	3.6	2.7	2.4	2.8	5.1	5.0	9.4	2.2
Group C	3.7[a,b]	2.8	2.0[a]	1.7	5.3	5.2	9.5	2.0
Primary GN with crescents								
Group A	6.3	3.0	4.7	1.3	2.4	2.1	9.8	0.8
Group B	4.8	4.6	3.9	3.7	3.6	5.2	10.4	2.7
Group C	4.1	3.4	3.7	3.1	4.3	7.3	9.9	2.7
Systemic disease associated								
Goodpasture's syndrome								
Group A	7.0	4.6	3.7	2.6	8.6	8.1	8.8	2.0
Group B	9.5	4.1	1.0	0.0	25.1	11.4	9.4	1.9
Group C	6.4	2.9	2.4	1.6	16.8[a,b]	7.2	10.3	1.3
Systemic lupus erythematosus								
Group A	2.4	1.8	5.3	3.9	2.5	5.9	9.0	2.0
Group B	3.1	1.6	4.8	3.0	1.2	0.8	9.6	0.9
Group C	1.9	1.5	1.6[b]	1.4	1.9	2.2	9.5	2.3
Wegener's granulomatosis								
Group A	4.5	5.3	0.9	0.4	10.3	9.7	9.8	1.6
Group B	4.1	4.2	0.8	0.8	10.6	4.9	9.3	2.6
Group C	3.0	2.6	1.2	0.8	7.4	6.2	10.1	2.0
Microscopic polyangiitis								
Group A	4.5	3.2	1.6	2.8	9.5	7.8	9.0	1.9
Group B	3.4	2.7	1.6	4.0	9.2	6.1	8.9	1.9
Group C	3.3[a,b]	2.4	1.4	1.4	7.5[b]	6.7	9.2	1.9
Total								
Group A	4.4	3.5	2.2	2.7	6.3	7.0	9.4	2.1
Group B	3.9	3.6	2.5	3.2	6.2	6.5	9.3	2.3
Group C	3.6[a,b]	2.8	2.0	2.0	6.2	6.4	9.6	2.1

GN glomerulonephritis

[a] $p < 0.05$ between Groups A and B

[b] $p < 0.05$ between Groups A and C

[c] $p < 0.05$ between Groups B and C

Prognostic factors and clinical grading

Age (<59, 60–69, >70), serum creatinine (<3.0, 3.0–6.0, ≥6.0 mg/dl), proteinuria (>1.5 g/day), serum albumin (≥3.0 g/dl), C-reactive protein (<2.6, 2.6–10, ≥10 mg/dl), presence of lung involvement and systolic blood pressure (>140 mmHg) are a significant prognostic factors for predicting patient survival in Group A according to the chi-square test ($p < 0.05$). We selected age, serum creatinine, C-reactive protein, and presence of lung involvement as strong independent prognostic factors ($p < 0.01$) by using a Cox regression model in Group A. We created an RPGN grading system based on these four values. Every subject was categorized into four clinical grades by summing the four prognostic factor scores (Table 8). Figure 2A shows the results of a Kaplan–Meier analysis of

Table 4 Positive rate of MPO-ANCA and PR3-ANCA

	RLV		MPA		Wegener's granulomatosis	
	n (tested)	Positive rate (%)	*n* (tested)	Positive rate (%)	*n* (tested)	Positive rate (%)
MPO-ANCA						
Group A	326	86.8	143	94.4	21	28.6
Group B	149	83.2	58	86.2	9	0.0
Group C	248	92.7	129	91.5	14	28.6
Total	723	88.1	330	91.8	44	22.7
PR3-ANCA						
Group A	321	10.6	135	5.2	22	68.2
Group B	143	6.3	55	7.3	9	88.9
Group C	240	3.8	121	6.6	14	64.3
Total	704	7.4	311	6.1	45	71.1

Table 5 Cause of death

	Group A		Group B		Group C	
n	884		321		568	
Deceased patients, *n*, %	351	39.71%	110	34.27%	102	17.96%
Mean observation period, month (range)	59.4	(0.0–13.6)	36.8	(0.0–98.8)	17.5	(0–59.2)
Infection	169	48.1%	42	38.2%	57	55.9%
Respiratory failure	102	29.1%	27	24.5%	25	24.5%
Interstitial pneumonitis	37	10.5%	16	14.5%	20	19.6%
Pulmonary bleeding	48	13.7%	8	7.3%	12	11.8%
Cerebral hemorrhage	22	6.3%	6	5.5%	6	5.9%
Congestive heart failure	35	10.0%	14	12.7%	6	5.9%
Myocardial infarction	3	0.9%	6	5.5%	1	1.0%
Gastrointestinal bleeding	33	9.4%	15	13.6%	7	6.9%

patient survival in Group A patients by clinical grading category. Six-month survival of Group A patients with grade I was 89.3%, grade II was 77.3%, grade III was 62.1%, and grade IV was 52.4%. Using this grading system, we can predict not only short-term prognosis but also long-term prognosis. In the Group B and Group C patients, this clinical grading system can predict both short and long-term patient prognosis very well (Fig. 2B, C).

Discussion

In 1998, we started this survey of RPGN cases because we had no epidemiological data on RPGN in Japan, and even though the number of RPGN patients is increasing, the number of cases of RPGN that are found in a single nephrology department annually are limited. During the early years of this study, we felt that the prognosis of RPGN patients in Japan was very poor compared to other races and countries. We started to analyze the etiology of this.

Couser [9] proposed a classification of RPGN based on immunofluorescence microscopy findings, and reported the proportions of patients with RPGN to be 20% for linear (anti-GBM antibody), 40% for granular (immune complex) and 40% for pauci-immune (idiopathic) types in 1988. Since the discovery of ANCA as a marker of idiopathic pauci-immune crescentic GN (namely RLV) as well as MPA [10–12], the proportion of pauci-immune-type RPGN patients has increased. This increment was also observed when the age of subjects increased [13]. The immunofluorescence microscopy findings in our subjects consisted of 64.0% with pauci-immune, approximately 20.0% with granular, and 6.1% with linear patterns. Those proportions were almost constant during our observation period. Considering the age of our subjects, the rate of immunofluorescence microscopy findings was almost the same as those in previous reports [13]. However, the prevalences of both

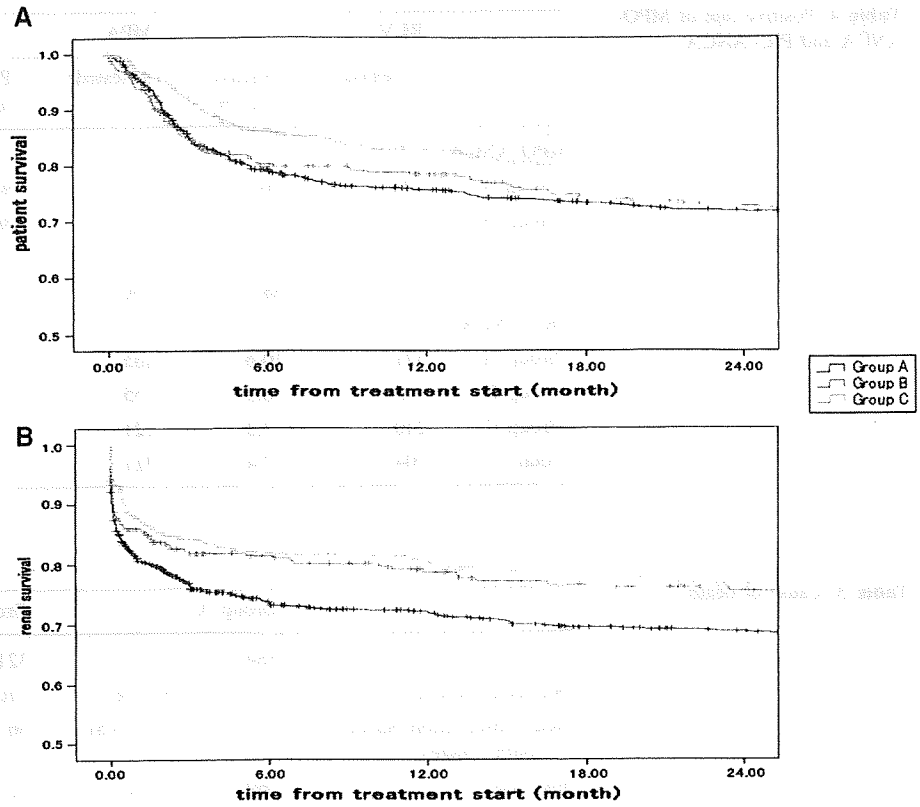

Fig. 1 Patient survival and renal survival of RPGN patients in Japan. **a** Patient survival was significantly improved in Group C compared to Groups A and B. **b** Renal survival was significantly improved in Groups B and C compared to Group A

MPO-ANCA and PR3-ANCA were quite different. Others reported that the proportion of PR3-ANCA-positive patients in pauci-immune crescentic GN or MPA was 28–50% [5, 14]. MPO-ANCA-positive patients showed a slower deterioration of renal function, were predominantly female, and were older than PR3-ANCA-positive patients [14]. From previous reports, the mean age ranged from 45 to 56 years in PR3-ANCA-positive patients and from 57 to 63 years in MPO-ANCA-positive patients [14]. The reason for the predominance of MPO-ANCA may be related to the older age at presentation of our RPGN patients. Although a recent increase in the average age was observed in patients with MPA, the prevalence of MPO-ANCA-positive patients decreased slightly. Furthermore, several reports have suggested that susceptibility to MPO-ANCA-associated vasculitis is related to environmental factors such as air pollution [15] and exposure to silica [16], latitude [17], or genetic factors such as polymorphism of the *CD18* gene [18] and HLA-DRB1*0901 [19]. Further investigations are needed to clarify racial and demographic differences associated with the prevalence of MPO-ANCA-associated vasculitis.

The RPGN patients included in our study often died due to infectious complications. Gayraud et al. [20] reported that patients older than 65 years treated for MPA with corticosteroid and cyclophosphamide often died due to infectious complications compared with those receiving corticosteroid alone. Booth et al. [21] also reported that treatment with cyclophosphamide often induced leukopenia and was strongly associated with sepsis, and sepsis was a determinant of survival.

In 2002, we published a Japanese version of the RPGN clinical guidelines based on data for 715 RPGN patents collected until 2001, who formed part of the Group A patients in this study [7, 22]. Based on a prognostic analysis of these patients, age, serum creatinine level and CRP level at the start of immunosuppressive treatment, and involvement of lung disease were significant prognostic markers in RPGN patients. In detailed prognostic analysis, we found that treatment with corticosteroids and immunosuppressants had a favorable effect on survival in patients in the ≤60 year-old group; however, no additional benefit of immunosuppressants on long-term renal survival in patients in older groups was observed. Further, an initial dose of oral prednisolone of >0.8 mg/kg/day was a significant risk factor for early death [7]. Hauer et al. [24] and Vizjak et al. [23] reported that the renal histology of MPO-ANCA-positive patients showed that diffuse, chronic sclerotic lesions predominated on histologic analysis. Thus, to relieve the inflammatory reaction of patients with MPO-ANCA, a lower dose of oral prednisolone is sufficient. Consequently, we recommended in the clinical guidelines (i) that early diagnosis and referral to nephrologists are important and (ii) mild treatment with a lower dose of oral

Table 6 Suvival rates at 6, 12, and 24 months

	6 months		12 months		24 months	
	Number of follow-ups	%	Number of follow-ups	%	Number of follow-ups	%
Primary						
Anti-GBM antibody-associated crescentic GN						
Group A	39	83.5	29	80.5	28	80.5
Group B	18	88.9	15	88.9	15	82.5
Group C	22	81.1	14	81.1	14	81.1
RLV[a]						
Group A	342	81.1	254	76.2	230	72.4
Group B	147	84.5	113	81.5	103	75.6
Group C	240	89.7	165	87.4	134	82.1
Systemic disease-associated						
Goodpasture's syndrome						
Group A	14	71.4	9	63.5	6	54.4
Group B	5	60.0	3	60.0	3	60.0
Group C	8	62.5	5	37.5	1	37.5
Systemic lupus erythematosus						
Group A	50	85.9	42	85.9	42	83.8
Group B	5	60.0	3	60.0	3	60.0
Group C	10	90.0	9	90.0	8	78.8
Wegener's granulomatosis						
Group A	23	78.3	18	78.3	18	78.3
Group B	9	66.7	6	66.7	5	53.3
Group C	13	67.7	8	67.7	6	67.7
MPA[a]						
Group A	157	68.4	102	65.7	90	61.2
Group B	57	77.9	39	77.9	37	73.6
Group C	126	82.6	81	79.3	57	73.3
Total[a,b]						
Group A	883	79.2	643	75.5	586	72.0
Group B	321	80.1	228	78.3	211	72.8
Group C	556	86.1	365	82.8	281	77.7

GN glomerulonephritis

[a] $p < 0.05$ between Groups A and C

[b] $p < 0.05$ between Groups B and C

prednisolone (0.6–0.8 mg/kg/day) for the initial treatment of MPO-ANCA-positive MPA or RLV with or without intravenous pulse methyl prednisolone treatment [7]. A significant reduction of the mean serum creatinine level at presentation among RPGN patients and a significant reduction of oral prednisolone dose were observed in patients with RLV and MPA in Groups B and C. Finally, the survival rates of RLV and MPA patients have recently shown a significant improvement. Furthermore, even with mild immunosuppressive treatment in recent years, the renal survival of these patients has also significantly improved. The main reasons for such an improvement in renal survival are early referral to nephrologists and early treatment initiation in those patients. After announcing the results of our survey, we believe that recognition of RPGN in general practice has improved.

Based on the prognostic analysis of these patients, we created an RPGN patient clinical grading system (Table 8) based on scoring the age, renal function, CRP level, and involvement of lung disease at the start of immunosuppressive treatment using data on Group A patients. This clinical grade category also predicts patient prognoses for Groups B and C quite well. The Birmingham Vasculitis Activity Score (BVAS) is useful tool for evaluating disease activity and predicting the survival of patients with systemic vasculitis [25]. However, when BVAS is used for RPGN patients, the BVAS renal score is always maximized, since RPGN involves proteinuria, hematuria and renal dysfunction by definition. Consequently, it is difficult to predict a prognosis for renal vasculitis patients or RPGN patients with BVAS.

Table 7 Renal survival rates at 6, 12, and 24 months

	6 months		12 months		24 months	
	Number of follow-ups	%	Number of follow-ups	%	Number of follow-ups	%
Primary						
Anti-GBM antibody-associated crescentic GN						
Group A	31	44.7	12	44.7	11	44.7
Group B	17	58.8	8	58.8	8	51.5
Group C	18	48.5	8	48.8	8	41.6
RLV[b]						
Group A	320	72.4	189	70.9	175	66.7
Group B	137	87.9	99	85.2	87	79.8
Group C	233	83.1	136	81.0	134	75.2
Systemic disease-associated						
Goodpasture's syndrome						
Group A	8	60.0	3	40.0	2	40.0
Group B	2	0.0	0	0.0	0	0.0
Group C	5	20.0	1	0.0	0	0.0
Systemic lupus erythematosus						
Group A	47	89.1	39	86.8	38	84.4
Group B	3	66.7	2	66.7	1	66.7
Group C	11	80.8	8	80.8	8	80.8
Wegener's granulomatosis						
Group A	20	85.0	15	85.0	15	85.0
Group B	7	85.7	5	85.7	4	85.7
Group C	12	83.3	7	83.3	5	83.3
MPA[a,b]						
Group A	144	74.0	81	72.1	72	69.9
Group B	53	88.0	32	85.1	29	85.1
Group C	118	89.0	71	89.0	50	87.0
Total[a,b]						
Group A	812	73.3	483	71.9	442	68.7
Group B	288	81.3	183	78.6	163	75.4
Group C	521	81.8	296	80.5	226	76.7

GN glomerulonephritis

[a] $p < 0.05$ between Groups A and B

[b] $p < 0.05$ between Groups A and C

Although the benefits of an early start to treatment and a reduced dose of oral prednisolone were recognized, the most frequent cause of death was infectious complications in Group C. The main reason for this high frequency of infectious complications in Group C was the shorter duration of observations in Group C. During the late follow-up period, the dose of immunosuppressant was further reduced, and the possibility of opportunistic infection was reduced. Several previous studies have suggested that prophylactic treatment with trimethoprim/sulfamethoxazole significantly reduces the occurrence of opportunistic infections [26]. Recent improvements in prognosis during initial treatment may relate to prophylactic treatment with trimethoprim/sulfamethoxazole in our subjects. Further studies are needed to clarify this point.

For the treatment of active renal vasculitis, to avoid relapses, and to improve long-term renal outcomes, treatment with cyclophosphamide is one choice; however, prolonged immunosuppression with a safer immunosuppressive agent, such as azathioprine [27], mycophenolate mofetil [28], or mizoribine [29], should also be considered.

Furthermore, the prognoses for anti-GBM antibody-associated RPGN, Goodpasture's syndrome and Wegener's granulomatosis are still poor in Japan. An early diagnosis system and effective treatment methods should be established as soon as possible for Japanese patients with these diseases. However, the average age at presentation of the patients with those diseases increased by ten years during our study. The higher age at

Table 8 Clinical grading for predicting RPGN patient prognosis

Clinical score	Serum creatinine (mg/dl)	Age (years old)	Lung involvement	Serum CRP (mg/dl)
0	<3	≤59	Negative	<2.6
1	3–6	60–69		2.6–10.0
2	≥6	≥70	Positive	>10
3	Dialysis			

Clinical grade	Total score
I	0–2
II	3–5
III	6–7
IV	8–9

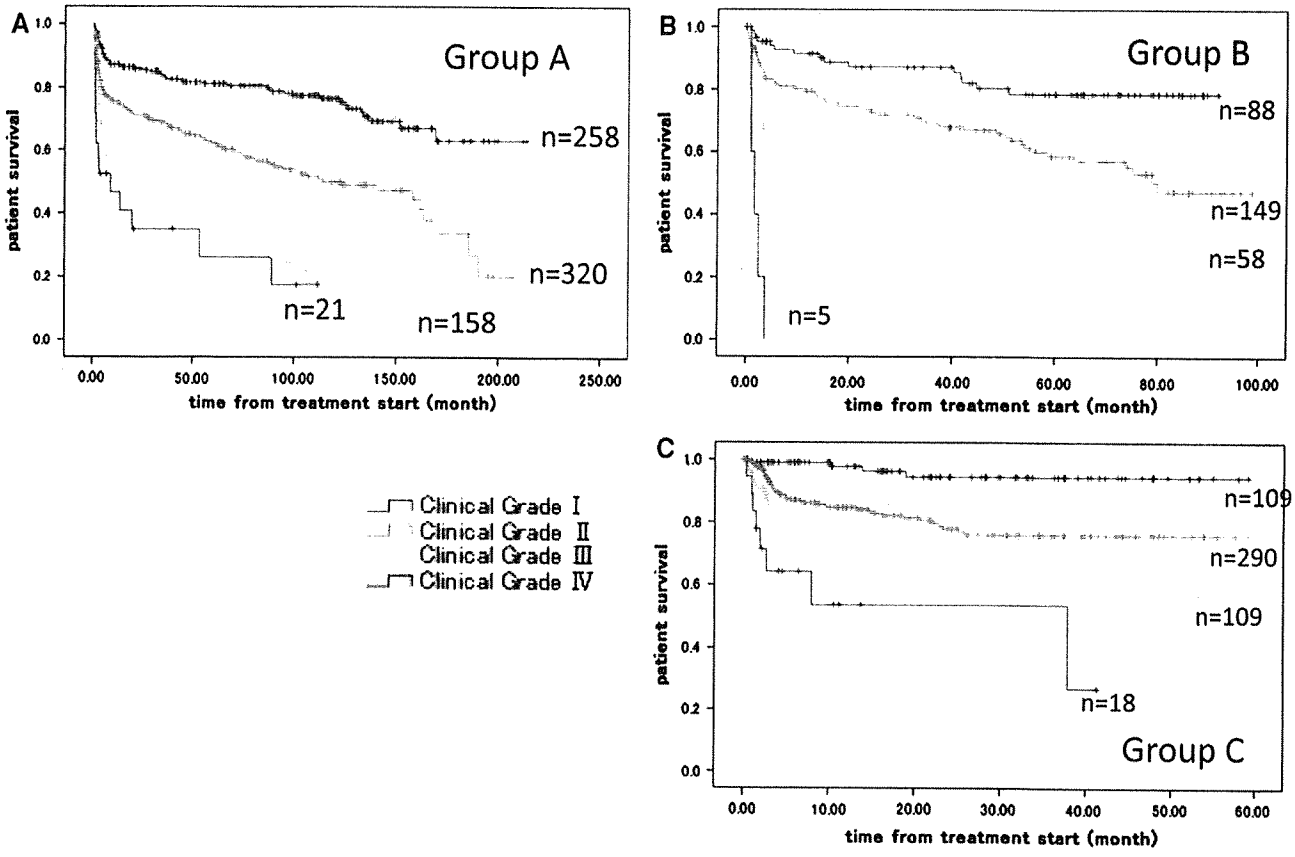

Fig. 2 Clinical grading system for predicting patient prognosis. The RPGN patient clinical grading system for predicting RPGN patient prognosis was produced based on Group A patients (**a**). However, this clinical grading system also fitted recent RPGN cases very well (**b**, **c**)

presentation may relate to the poor prognosis of those patients.

In summary, the prevalence of RPGN patients and primary renal disease were surveyed and compared among Group A (retrospective data), Group B (prospective data during the preparation of the clinical guidelines), and Group C (prospective data after the Japanese RPGN clinical guidelines were published). Following the recommendations of the clinical guidelines, both early referrals to nephrologists and mild immunosuppressive treatments were observed. These changes resulted in a significant improvement in the outcomes of Japanese patients with RPGN.

Table 9 Institutions that provided data for this survey

Department of Nephrology, Tsukuba Central Hospital	Department of Nephrology, National Tochigi Hospital	Internal Medicine I, Chiba University Hospital	Internal Medicine I, Hamamatsu Medical University Hospital	Department of Pediatrics, Shinshu University Hospital	Internal Medicine II, School of Medicine, Toho University
Department of Nephrology, Tsuruoka Kyoritsu Hospital	Department of Pediatric, Shimoshizu National Hospital	Department of Pediatrics, Chiba University Hospital	Department of Pediatrics, Hamamatsu Medical University Hospital	Department of Pediatrics, Niigata Prefectural Yoshida Hospital	Department of Pediatrics, School of Medicine, Toho University
Department of Nephrology and Rheumatology, Toyota Memorial Hospital	Kagawa Children's Hospital	Department of Nephrology, Kawasaki Medical University	Department of Pediatrics, Hamamatsu Red Cross Hospital	Department of Internal Medicine, Niigata Prefectural Central Hospital	Department of Nephrology, Toho University Omori Hospital
Nephrology and Dialysis Unit, MisatoKenwa Hospital and Clinic	Department of Pediatric, National Mie Hospital	Department of Pediatrics, Kawasaki Medical University	Department of Nephrology, Hamamatsu Rosai Hospital	Department of Pediatrics, Niigata City Hospital	Blood Purification Center, Tohoku University Hospital
Internal Medicine I, Aichi Medical University Hospital	Department of Pediatric, National Niigata Hospital	Department of Pediatrics, Kawasaki Kyodo Hospital	Internal Medicine II, Toyama Medical University Hospital	Blood Purification Center, Niigata University Medical and Dental Hospital	Department of Internal Medicine, Fujita Health University
Department of Pediatrics, Aichi Medical University Hospital	Department of Pediatric, National Nishisapporo Hospital	Department of Pediatrics, Kawasaki City Hospital	Department of Pediatrics, Toyama Medical University Hospital	Department of Nephrology, Niigata University Hospital	Department of Pediatrics, Department of Pediatrics, Fujita Health University
Pediatric Department, Ehime University Medical School Hospital	Department of Pediatric, National Nishitaga Hospital	Department of Pediatrics, Kurashiki Central Hospital	Department of Internal Medicine, Toyama Prefectural Central Hospital	Department of Invernal Medicine, Niigata Minami Hospital	Department of Invernal Medicine, Tokushima Prefectural Central University
Internal Medicine I, Asahikawa Medical College Hospital	Department of Pediatric, National Chiba-Higashi Hospital	Department of Internal Medicine, Sagamihara Kyodo Hospital	Internal Medicine, Toyama Red Cross Hospital	Department of Pediatric Nephrology, Nippon Steel Yawata Memorial Hospital	Department of Pediatrics, Tokushima University Hospital
Department of Pediatric, Asahikawa Medical College Hospital	Department of Pediatric, National Chubu Hospital	Department of Nephrology, Inoue Hospital	Department of Internal Medicine, Toyama Prefectural Central Hospital	Department of Invernal Medicine, Shinnittetsu Hachiman Memorial Hospital	Department of Internal Medicine, Tochigi Saiseikai Utsunomiya Hospital
Department of Nephrology, Anjo Kose Hospital	Department of Nephrology, Kurobe City Hospital	Internal Medicine I, Osaka Medical University Hospital	Department of Pediatrics, Fukui Medical University Hospital	Kobe University School of Medicine Faculty of Health Sciences	Internal Medicine II, Nara Medical University Hospital

Table 9 continued

Department of Urology, Kyorin University School of Medicine	Department of Internal Medicine, Saga University	Department of Pediatrics, Osaka Medical University Hospital	Department of Internal Medicine, Fukui Red Cross Hospital	Department of Nephrology, Kanagawa Prefectural Children's Medical Center	Department of Pediatrics, Nara Medical University Hospital
Internal Medicine I, Kyorin University School of Medicine	Department of Pediatric, Saga University	Internal Medicine I, Osaka City University Hospital	Department of Nephrology, Fukui Red Cross Hospital	Department of Nephrology, Kandatsu Hospital	Department of Nephrology, Minami Ichijo Hospital
Department of Pediatric, Kyorin University School of Medicine	Department of Internal Medicine, Kosei-kan, Saga Prefectural Hospital	Internal Medicine II, Osaka City University Hospital	Internal Medicine IV, Fukuoka University Hospital	Department of Nephrology, Mito Saiseikai General Hospital	Department of Nephrology, Nikko Memorial Hospital
Department of Clinical Genetics, Faculty of Health Sciences, School of Medicine, Kyorin University	Department of Internal Medicine, Saku Sogo Hospital	Department of Pediatrics, Osaka City University Hospital	Internal Medicine I, Fukuoka University Hospital	Department of Internal Medicine, Mito Central Hospital	Department of Nephrology, Hidaka Hospital
Department of Pediatric, Isezaki Municipal Hospital	Department of Internal Medicine, Sano Kosei Sogo Hospital	Osaka Red Cross Hospital	Department of Nephrology, Fukuoka University Hospital	Department of Nephrology, Mizushima Kyodo Hospital	Department of Pediatrics, Red Cross Medical Center
Department of Pediatric, Ibaraki Children's Hospital	Department of Internal Medicine, Saiseikai Yokohama-shi Nambu Hospital	Internal Medicine I, Osaka University Hospital	Department of Pediatrics, Fukuoka University Tsukushi Hospital	Internal Medicine I, St. Marianna School of Medicine Hospital	Internal Medicine I, Nippon Medical School Hospital
Department of Nephrology, Ibraki Prefectural Central Hospital	Department of Nephrology, Saiseikai Shimonoseki Sogo Hospital	Department of Pediatrics, Osaka University Hospital	Internal Medicine IV, Fukushima Prefectural Medical University Hospital	Yokohama Seibu Hospital, St. Marianna School of Medicine	Internal Medicine II, Nippon Medical School Hospital
Department of Nephrology, Ibaraki Seinan Medical Center Hospital	Department of Pediatrics, Saiseikai Kurihashi Hospital	NTT West Osaka Hospital	Department of Pediatrics, Fukushima Prefectural Medical University Hospital	Department of Pediatrics, St. Marianna School of Medicine Hospital	Department of Pediatrics, Nippon Medical School Hospital
Department of Nephrology, Utsunomiya Socialinsurance Hospital	Department of Nephrology, Saiseikai Nakatsu Hospital	Department of Nephrology, Osaka Prefectural Hospital	Internal Medicine V, The Hospital of Hyogo College of Medicine	Department of Pediatrics, Seirei Hamamatsu Hospital	Internal Medicine II, Nippon Medical School Hospital
Department of Internal Medicine, Urasoe Sogo Hospital	Department of Nephrology, Saitama Medical University Hospital	Department of Nephrology, Kumamoto Chuo Hospital	Department of Pediatrics, The Hospital of Hyogo College of Medicine	Department of Pediatrics, St. Lukes International Hospital	Department of Pediatrics, Nippon Medical School Chiba Hokusoh Hospital
Department of Internal Medicine, Yokosuka Kyosai Hospital	Department of Pediatric, Saitama Medical University	Department of Internal Medicine, Oita Medical University Hospital	Department of Pediatric Nephrology, The Hospital of Hyogo College of Medicine	Department of Pediatrics, Seirei Sakura Citizen Hospital	Department of Nephrology, Nihon Red Cross Medical Center