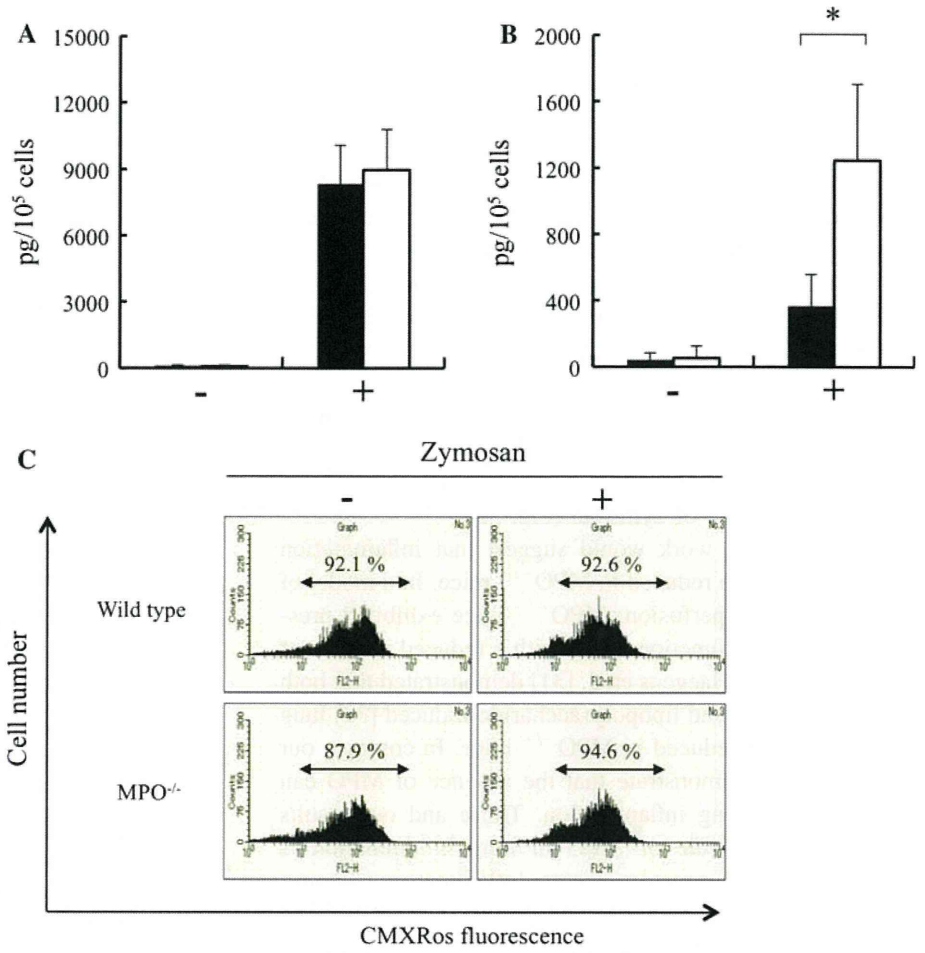

Fig. 5 Production of MIP-2 from macrophages and neutrophils in vitro and determination of mitochondrial membrane potential. Alveolar macrophages (**a**) and bone marrow neutrophils (**b**) were prepared from wild-type (*black bars*) and MPO$^{-/-}$ (*white bars*) mice. The cells were incubated with (+) or without (−) zymosan for 6 h. MIP-2 levels of four mice with each genotype were determined by ELISA. The data are means ± SD, $*P < 0.005$. After the incubation, the neutrophils were stained with CMXRos and $\Delta\Psi$ was measured by flow cytometry as described in "Materials and methods". The representative data of three independent experiments are presented in *panel* **c**

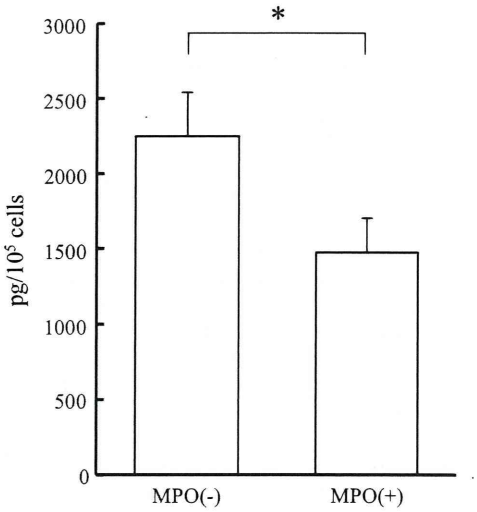

Fig. 6 Exogenously added MPO decreased the production of MIP-2 from MPO-deficient neutrophils. Bone marrow neutrophils prepared from MPO$^{-/-}$ mice were treated with zymosan for 6 h in the absence (−) and presence (+) of human MPO enzyme, and MIP-2 levels were determined by ELISA. Data from four different experiments are expressed as mean ± SD, $*P < 0.05$

by mutant neutrophils provides a possible explanation for the rapid accumulation of neutrophils in the lungs of mutant mice.

Zymosan has been widely used as a model of fungus-mediated inflammation, initiating phagocytosis and the production of inflammatory cytokines and chemokines [11, 12]. Our increased understanding of zymosan recognition by the immune system has come primarily from in-vitro studies. Early studies indicated that the inflammatory response to zymosan was dependent on the presence of Toll-like receptor-2 (TLR2) [23–25]. However, subsequent studies demonstrated a requirement for dectin-1 [11, 26, 27]. To further understand how neutrophil-derived HOCl regulates MIP-2 production, we measured surface expression of TLR2 and dectin-1 on isolated neutrophils. Flow cytometry revealed that there was no significant difference in the expression level between mice with different genotypes (data not shown). Therefore, it is unlikely that neutrophil-derived ROS regulate the number of these receptors. Further research is necessary to determine how MPO regulates MIP-2 production.

The zymosan-exposed $MPO^{-/-}$ mice showed a continuous increase in neutrophil recruitment at least up to day 6 (Fig. 1), suggesting that, in addition to the up-regulation of MIP-2 production at 6 h post-zymosan treatment, additional underlying mechanisms contribute to the enhanced lung inflammation in the mutant mice. We previously reported that apoptosis in MPO-deficient neutrophils stimulated by phorbol myristate acetate was significantly slower than in normal neutrophils [28, 29]. Therefore, as a possible mechanism, retardation of neutrophil apoptosis due to MPO deficiency causes an increase in neutrophil numbers in the zymosan-exposed lungs of $MPO^{-/-}$ mice. However, the present data do not favor this hypothesis because we found no obvious difference in cell death between wild-type and $MPO^{-/-}$ neutrophils cultured for 6 h in the presence of zymosan (Fig. 5c).

Most previous work would suggest that inflammation should actually be reduced in $MPO^{-/-}$ mice. In a model of renal ischemia reperfusion, $MPO^{-/-}$ mice exhibited preservation of renal function along with a reduced number of neutrophils [30]. Haegens et al. [31] demonstrated that both asbestos-induced and lipopolysaccharide-induced [32] lung inflammation is reduced in $MPO^{-/-}$ mice. In contrast, our present results demonstrate that the absence of MPO can lead to severe lung inflammation. Those and our results suggest that the role of MPO in lung inflammation is dependent on inflammatory agents. Inflammatory response to zymosan is dependent on the presence of TLR2 and dectin-1, whereas the inflammatory response to lipopolysaccharide is dependent on TLT4 [12, 33]. MPO may contribute in opposite ways to the signaling of different TLRs such as TLR2 and 4. Although further studies are needed to clarify the mechanism by which neutrophils deficient in MPO accumulate at zymosan-exposed sites, our new findings in this study could provide an alternative way of thinking about MPO-dependent inflammation.

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全身性疾患に伴う腎障害の診断と治療の実際

血管炎の腎病変

Renal injury in vasculitides

特集

武曾 惠理
MOSO Eri

全身性疾患と腎障害

Key words 血管炎 急速進行性糸球体腎炎 高安病 結節性多発動脈炎 ANCA関連血管炎

血管炎はさまざまなサイズの全身の血管壁の炎症を総称しているが，その病態も多彩である．一般的な症状として，発熱，食欲不振，筋力低下，筋肉痛，末梢神経障害，乏尿などの多彩な症状をきたすが，大血管から，中小血管，毛細血管，細静脈から大静脈まで，すべての血管に炎症は発症する．これらの代表的な疾患群の分類は1994年にChapell hill分類として用いられているが[1]，その流域に応じた臓器や組織障害をきたす．とくに動脈炎の場合，炎症を起こしている場所の病変とその血流の途絶による臓器，組織障害が問題となる．腎病変においても，腎動脈という大血管から，中血管である弓状動脈やさらに小葉間動脈などの小血管から糸球体に至る細小血管や毛細血管まで，動脈だけをとっても炎症が起こることにより引き起こされる病態はさまざまである．とくに，Anti-neutrophil cytoplasmic antibody(ANCA)が陽性となる細小血管炎(ANCA関連血管炎)については，その腎病変はしばしば急速進行性であり，腎，生命予後に深く関連する．これらを最近の診療ガイドラインによる診療指針の紹介も含めて，とくに腎を巻き込む血管炎について，その血管のサイズによって診断と治療の動向を解説する．

大型血管炎の腎病変

腎を栄養する大血管の炎症では，炎症症状だけではなく，腎の虚血による症状が起こる．とくに高安動脈炎で特徴的な所見があり，他の大型動脈炎である側頭動脈炎やバージャー病では腎病変をきたすことはまれである．

財団法人田附興風会医学研究所北野病院腎臓内科 部長

高安動脈炎

1)疾患の概要

大動脈および基幹動脈と，その分枝の狭窄をきたす血管炎である．若い女性に多く(男女比：1：9)，アジアや日本に発症者が多い．大血管外膜栄養血管の血管炎が病変発症部位とされている．発熱，倦怠感などの全身症状に加えて，侵される血管が栄養する臓器症状が多彩に表れる．46％に上下肢の血圧の差がみられ，時に脈拍が消失する「脈なし病」といわれるゆえんである．病理

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所見では大動脈の外膜，中膜，内膜の三層ともに炎症が及ぶ．外膜の線維性肥厚と炎症性細胞浸潤に始まり，中膜の平滑筋細胞消失，弾性線維の破壊と膠原線維増加，内膜肥厚と線維化をきたす．HLA-B52.39に有意な相関があり，侵される血管は人種によって異なっていることが知られている．わが国では，頸部から胸部の大動脈および頸動脈などの分枝が侵され，大動脈弁閉鎖不全をきたす例が多い．一方，アジア中部，インドなどでは，腹部大動脈を侵す例がほとんどである[2]．

2)腎　病　変

腹部大動脈を侵された場合，腎虚血がしばしば引き起こされ，腎血管性高血圧症をきたしたり，時には両側腎動脈が急速に閉塞して急性腎機能低下をきたす．慢性に経過する場合，炎症をきたしている側の血管流域では，慢性虚血により萎縮腎となることもしばしばある．

(1)診断

①症状と所見：発熱，食欲不振など全身炎症症状に加えて，腎血管性高血圧，時には急速腎機能低下による尿毒症症状をきたすこともある．理学的所見では腹部のbruitが聴取されることもある．検尿所見は血尿は陰性で，タンパク尿は時に陽性．Cr値，BUN上昇，K値は一般的に低い(高レニン，アルドステロンによる)，CRP，赤沈亢進等，全身炎症所見は陽性化するが，ANCAは陰性．

②画像所見：超音波で左右の腎サイズの不均一や，慢性に経過した場合閉塞側の腎萎縮をきたす．MRI，MRAによる活動期のT2強調画像による血管壁シグナルの増強など，3D再構成CT画像で腎血管の狭窄を立体的に診断することができる．

(2)治療

ステロイドの使用や適切な免疫抑制剤の併用で，最近の厚生労働省での報告では，1996年以後に発症した症例では，腎障害など大きな臓器障害をきたすことが少なくなってきている[3]．さらに新たな生物製剤による治療も効果をあげている[4]が，狭窄が腎機能低下を進行させる場合，血管への直接の拡張手段(外科的血管再建術，ステント留置，PTAなど)で腎血管性高血圧の是正や，腎機能改善も得られている．

中型血管炎

全身の中，小筋型動脈に起こる血管炎では，やはり全身の炎症性病変に加えて，臓器内での主要動脈の炎症により，臓器機能の障害が起こる．代表的なこのサイズの血管炎は，川崎病と結節性多発動脈炎であるが，前者では冠状動脈瘤をきたす心筋虚血が問題となるのに対し，後者では多臓器での主要動脈炎による機能障害が起こり，腎障害も主要な臓器障害である．

結節性多発動脈炎

1)疾患の概要

50～60歳の比較的高年齢に発症し，男女比もほぼ均等である．人口10万人に0.2～0.7人程度の発症で，近年減少傾向である．全身炎症症状は必発で，関節炎症状，筋症状も頻度が高い，多臓器の障害を呈し，リベドや結節の触知，虚血性心血管症状，腸間膜動脈炎による虚血性腸炎や消化管出血，脳出血や多発性単神経炎などの神経症状など，多彩である．

2)腎　病　変

腎臓は約50％の症例で侵される．

(1)診断

①症状と検査所見：高血圧の発症は頻度が高い．血尿は時に出現するが，虚血性病変をきたしている場合は尿所見に乏しいこともある．一方，腎機能低下はしばしば発生するが，急速進行性腎炎としての腎機能低下はわが国の1,772例の急速進行性糸球体腎炎のうちでも15例(0.9％)程度である[5]．細小血管炎に頻度の高いマーカーであるANCA，とくにmyeloperoxidase(MPO)への抗体は通常陰性であるが約10％程度陽性症例がある．

②画像：腎内の血栓や梗塞により，腎エコー検

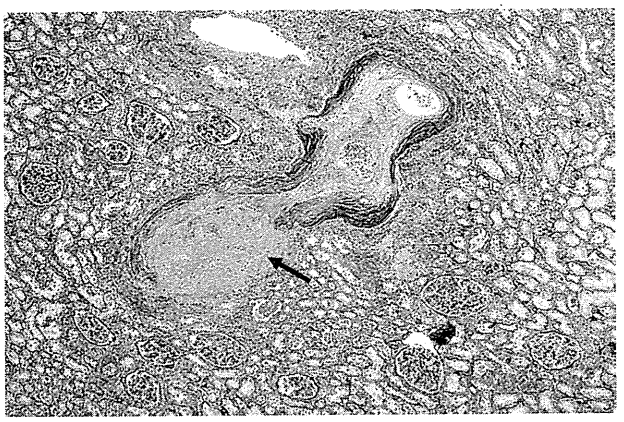


図1 結節性多発動脈炎の腎生検における弓状動脈の壊死性病変像(PAS染色×50)(文献8より)

査で,表面の不整や皮質の部分的皮薄化を認める.また多発性の1cm前後の結節性動脈瘤が腎臓内に発生し,CTや血管造影で確認できることもある.

③病理所見(図1):腎動脈や弓状動脈ではⅠ期;急性期,Ⅱ期:急性炎症期,Ⅲ期:肉芽期,Ⅳ期:瘢痕期 に分けられ,急性期は筋線維の腫脹,内膜浮腫,血管腔狭小化があり,次にフィブリノイド変性,好中球や好酸球,単球などの細胞浸潤が認められるが巨細胞はまれで,内・外弾性板の断裂を認め,瘢痕化した血管は最終的に動脈瘤や狭窄を呈する.その血流域の広範な虚血病変として,糸球体の完全硬化や虚血性萎縮,間質の線維化をきたす.一方,基本的には細動脈を侵すことは少ないが,時に糸球体を含む毛細血管炎をきたすこともあり,以下に述べるANCA関連血管炎と同様の壊死性半月体形成性糸球体腎炎をきたすこともある.

(2)治療

急性期治療では,ステロイドパルスを含む十分量のステロイド治療(1mg/kg/日)を8週間持続させ,その後漸減し10mg/日を維持量とする.難治例にはシクロフォスファミド,アザチオプリンを1～2g/日を1ヵ月以上投与する[6].

細小型血管炎

小葉間動脈から糸球体輸出入細動脈,糸球体毛細血管,傍尿細管毛細血管,静脈までを含む血管に起こる炎症で,全身の同サイズの血管を巻き込むが,腎糸球体に炎症が及ぶことが多く腎障害発症頻度は高い.とくにそのなかでもANCA陽性の血管炎(ANCA関連血管炎)については,急速進行性糸球体腎炎の原因疾患としてわが国の統計では70%近くを占めており,腎病変への対処が必須である.このタイプの血管炎を起こす疾患群ではWegener肉芽腫症(Wegeners granulomatosis:WG),顕微鏡的多発血管炎(microscopic polyangiitis:MPA),アレルギー性肉芽腫性血管炎(Churg-Strauss症候群:CSS)が代表的である.最近これらの血管炎に対する診療ガイドラインが,厚生労働省難治性疾患克服研究事業の成果としてまとめられた.

1. ANCA関連血管炎の概要

1)顕微鏡的多発血管炎(MPA)

発症頻度は最近の宮崎,沖縄の疫学調査では100万人に15人だが,65歳以上では45～50と高齢者に圧倒的に多い[7].MPO-ANCAの陽性頻度が非常に高い.ANCA関連血管炎のなかでも最もわが国に頻度が高い.肺や消化管の血管炎症状も多い.

2)ウェジナー肉芽腫症(WS)

鼻出血,中耳炎,咽頭痛,血痰などを呈し,上気道を主とする肉芽腫性血管炎を呈する.とくにproteinase(PR)3に対するANCAの発現が特徴的で,欧米では上述のMPAに比し,有意に発症頻度が高いが,わが国では極端に低い.

3)アレルギー性肉芽腫性血管炎,チャーグ・ストラウス症候群(CSS)

気管支喘息が先行し好酸球増多を特徴とする.中年に発症し,わが国では約500名弱が登録されている.先行する難治性の喘息症状で時に好酸球性肺炎をきたすが,さらに消化器症状,皮膚症状,急性心外膜炎をきたすこともある.MPAと同様にMPO-ANCAが陽性であることが多い.

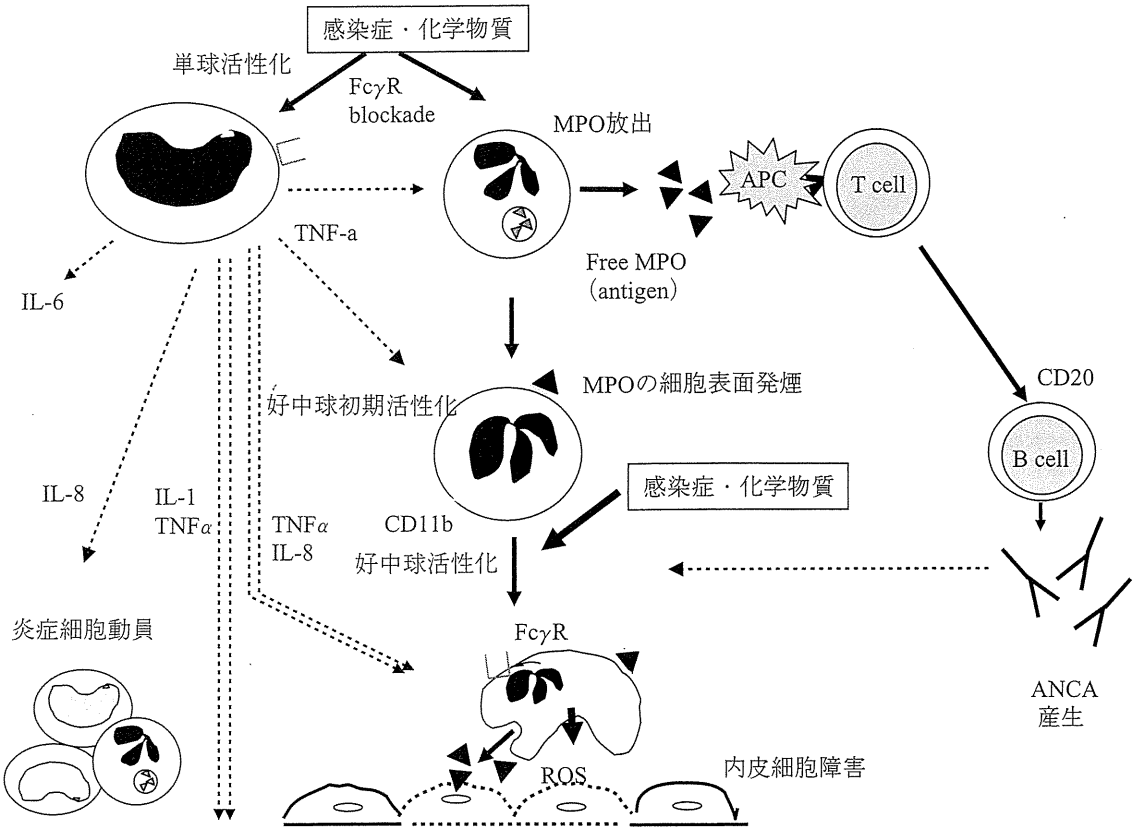


図2 ANCA関連血管炎の発症と病変進行機序の仮説

2. 腎 病 変

(1)病態

図2のようなANCA発現とそれによる血管炎発症の機序が考えられているが，とくに腎病変では糸球体毛細管係締にこの病変が及ぶ．

(2)診断

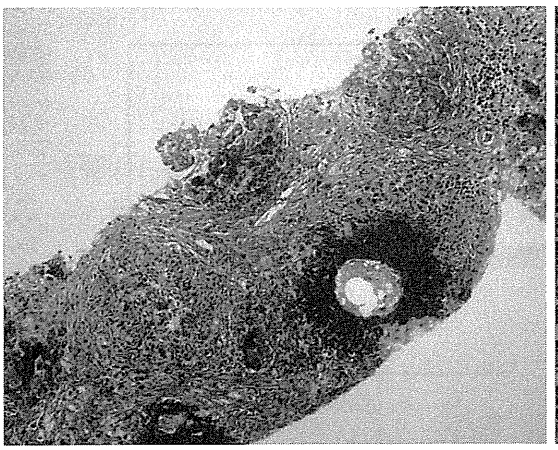
①尿所見：まず顕微鏡的血尿(潜血陽性)，赤血球円柱，タンパク尿として現れ，時に肉眼的血尿となることもある．

②血液・生化学所見：白血球数の増加と，好中球分画の上昇．CSSではとくに好酸球分画の増多を伴う．また長期化すると血小板の増多も認め，貧血も顕在化する．しばしば腎機能低下をきたし，時にCr値の上昇が急激である．

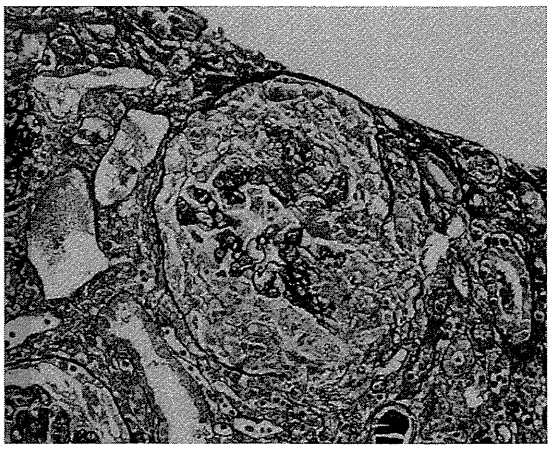
③画像所見：超音波所見では，急性期の腎の腫大がしばしば見られる．

④病理所見：腎生検が診断や病勢の決め手になる．小動脈の壊死を伴う血管構築の破壊が起こり，これが腎糸球体の毛細血管に及ぶと壊死性半月体形成性糸球体腎炎の形態を取り，基底膜やBowmann嚢の破壊や好中球の浸潤，核崩壊などが認められる(図3)．間質には好中球を伴う炎症性細胞浸潤や，PTCおよび尿細管炎も急性期にはしばしば認める．WGでは，肉芽腫をきたすこともあり，またCSSでは，好酸球の浸潤が特徴的である．蛍光抗体法では各種免疫グロブリンや補体の沈着はまれで(pauci-immune)ある．慢性期には，血管の硬化性病変と糸球体硬化，間質の線維化が顕著となる．

わが国ではこれらの病変の活動性および慢性病変のパラメーターを，糸球体，尿細管間質，血管にまとめた[8]が，最近，糸球体病変のみを評価して，全硬化糸球体が50％以上を占めるものを硬化型，正常糸球体が50％以上を占めるものを巣状障害型，細胞性半月体形成糸球体が50％以上を占めるものを半月体形成型，以上のどれでもないものを混合型として分類し，100症例のANCA関連血管炎(WG 39例，MPA 61例)で予後を評価したところ，5年間の観察では巣状，半月体形成，混合，硬化型の順に腎機能低下速度が速かった[9]．この



小動脈のフィブリノイド壊死を伴う血管炎マッソン・トリクローム染色(×100)



基底膜の破壊や炎症性細胞浸潤，細胞性半月体形成をきたし，ボウマン氏嚢の破たんをきたした糸球体(PAM 染色×400)

図3 ANCA 関連血管炎(MPA)の腎病理所見

結果は，本血管炎の腎病変の予後を組織所見，とくに糸球体病変がよく反映することを示しているが，欧米の限られた症例数のみの評価であり，わが国のようにMPAが中心の症例に限られる場合の予後については，さらなる評価が行われることが期待されている．

(3)治療

①急性期血管炎の寛解導入治療

(ア)ステロイドおよび免疫抑制療法：大量のステロイド(プレドニゾロン1～2mg/kg/日または，メチルプレドニゾロン0.5～1gのパルス治療を3日間，その後経口ステロイドに移行)治療を初期の3～6ヵ月間に行い，肺出血や腎機能低下などの臓器障害を阻止する．WGにはシクロフォスファミドパルス療法(月に1度を6回)も，施行される．

わが国では急速進行性糸球体腎炎をきたす場合，その重症度をスコア化し，その合計点で重症度をⅠ－Ⅳ期に分けてそれによる治療アルゴリズムを作成しており，これらによる後ろ向きの予後評価では，前述の1,772症例でほぼ重症度に沿った予後を呈していた(**図4**)．今回の診療ガイドラインにおいても，この方法による治療選択が勧められている[5]．

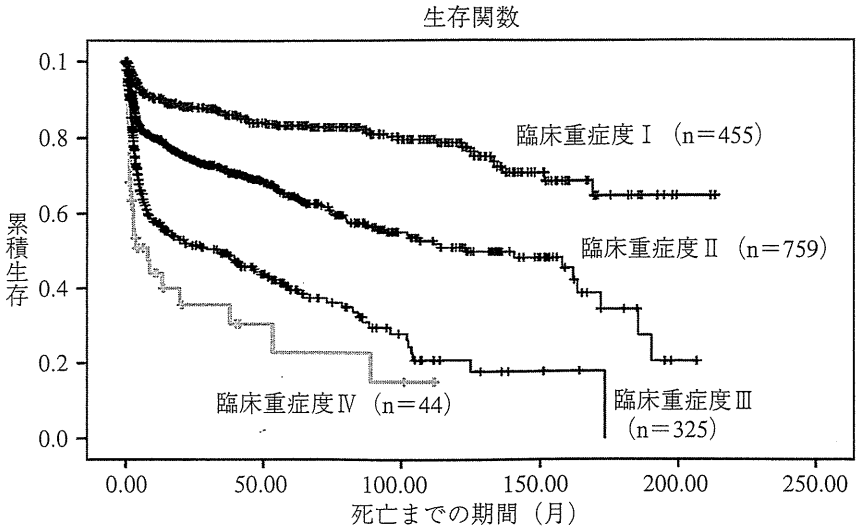
(イ)抗凝固療法：壊死性血管炎が明らかな場合，ヘパリンやワーファリンなどの抗凝固剤を用いることにより，組織の硬化を抑制するが，出血性病変がある場合は不可．

(ウ)血漿交換療法：初期に重篤で急性に進行する場合，ANCAなどの自己抗体や炎症性サイトカインの血中からの除去を目的として，施行される．

(エ)生物学的製剤

i)大量免疫グロブリン(IVIg)は免疫力を落とすことなく，むしろ補助して免疫修飾作用，抗感染症が期待できる．大量γグロブリン(IVIg：400mg/kg/日，5日間)をMPAの急性期に免疫抑制療法前に単独で施行し，急性炎症と腎機能低下阻止が可能となり，さらに後療法を行うことで，6ヵ月の生命，腎の予後を有意に改善することが報告され[10]，老齢者が多く，感染症の危険が高い本疾患の補助療法として期待される．

ii)炎症性サイトカインであるTNFαや，自己抗体産生細胞で細胞性免疫にもかかわるとされるB細胞表面マーカーであるCD20などに対するモノクロナル抗体(それぞれインフリキシマブ，リツキシマブ)を経静脈的に注入して寛解導入をはかる試みが欧米を中心に行われ，とくにリツキシマブでは，シクロフォスファミドパルス療法との前向きランダム化比較試験で米国(RAVE)[11]，欧



臨床所見スコア

スコア	Cre(mg/dl)	年齢	肺病変の有無	CRP 値(mg/dL)
0	Cre＜3.0	Age＜60	無	CRP＜2.6
1	3.0≦Cre＜6.0	60≦Age＜70	−	2.6≦CRP＜10.0
2	6.0≦Cre	70≦Age	有	10.0≦CRP
3	透析	−	−	−

臨床学的重症度

臨床学的重症度(Grade)	合計スコア
Ⅰ	0～2
Ⅱ	3～5
Ⅲ	6～7
Ⅳ	8～9

図4 急速進行性腎炎症候群全症例における臨床学的重症度別の生存曲線(1,772例)

表1 炎症血管サイズによる代表的疾患の病変の特徴

代表的疾患	高安病	結節性多発動脈炎（古典的 PN）	顕微鏡的多発血管炎（顕微鏡的 PN）
病理所見			
侵襲血管のタイプ	全層性動脈炎	壊死性動脈炎	壊死性血管炎
血管炎のタイプ	胸腹部大動脈	中・小筋型動脈	小血管（毛細血管，細動静脈）
臨床所見			
急速腎機能低下（原因）	あり（腹部大動脈狭窄）	まれ（急速進行性腎炎）	多い（急速進行性腎炎）
高血圧	多い	多い	まれ
肺出血	まれ	まれ	多い
間質性肺炎	まれ	まれ	あり
再発	あり	まれ	あり
MPO-ANCA	陰性	陰性	陽性
動脈造影所見	あり（大動脈狭窄）	あり（小動脈瘤，狭窄）	なし
確定診断	MRI MRA CT アンギオ 腎エコー	CT アンギオ，時に腎生検	腎生検

州(RITUXIVAS)[12]で施行されたが，12ヵ月の時点で，ほぼ同等の効果が得られ，副作用についても同等という結果であった．長期予後は不明である．わが国では10症例以下に使用されているが，がんの発生率が高く，積極的な評価を行う段階に入っていない．

②寛解維持療法

近年，急性期治療がある程度効を奏し，長期に寛解を維持する治療の必要性が高まった．ステロイド少量(5～10mg/日)を続ける．小量のアルキル化製剤の使用も考慮され，現在，ミコフェノレートモフェチル(MMF)やブレディニンの長期寛解維持の治験が進んでいる．

以上の治療に際し，とくに免疫抑制剤は腎機能障害時の使用においては，腎機能に応じた投与量の調整が必要であることを銘記すべきである．

終わりに

以上，大血管から細小血管までさまざまな血管炎があり，その腎病変を代表的疾患について比較した(表1)．その発症機序については不明な点が多いが，腎障害が発症すると重篤であり，とくに細小血管炎では老齢者に発症するため，治療そのものがその副作用や腎毒性のため，十分になされない場合も多く難渋するところである．

近年，老齢者の透析患者では，腎硬化症に次いで，本疾患が原因となっていることもあり，まず，微熱や食欲不振など，全身炎症性症状，さらに上気道や肺症状を呈し，血尿，CRP 上昇，腎機能低下をきたす場合，本疾患を疑い，腎組織診断を含めた適切な診断で治療を推進して進行を防ぎ，副作用を最少にする治療を選択して寛解導入を早期に行うことが求められている．

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免疫グロブリン大量療法*

武曾恵理**

はじめに

献血など多くのヒトの血液（血漿）から精製した免疫グロブリンには種々の抗体が含まれることから，これらを生成して経静脈的に大量に投与する高用量ヒト免疫グロブリン静注療法（IVIg：intravenous immunoglobulin）は大きく分けて2つの意味で，免疫に関する病態で使用されている。すなわち，① 免疫グロブリンが低下する病態での補充による免疫能の補強，② 炎症反応，自己免疫反応の抑制，である。健康なヒトの血漿中には免疫グロブリンとして（年齢によって正常値は異なるが）IgG 500～1,000 mg/dL，IgA 50～170 mg/dL，IgM 50～150 mg/dL くらいの量がある。この免疫グロブリンの量が不足する（IgG 量として 500 mg/dL 以下）と感染に対して弱くなる。すなわち免疫不全状態となる。このようなときに IVIg を行うことで，感染症に対する防御力が高まる。さらに IVIg には種々のウイルス感染に対する抗体が含まれているため，これらに対して，非特異的に感染防御作用が高まる。一方，今回の特集にあるようなさまざまな自己免疫疾患に対しては，② の炎症反応，自己免疫反応の抑制効果が期待されており，これらの作業機序，および特殊な疾患への効果の話題について述べる。

表1　IVIg の免疫制御作用

- Fc レセプターへの作用
  - マクロファージとエフェクター細胞における Fc レセプターの阻害
  - 抗体依存性 cytotoxicity の誘導
  - 抑制性 Fcγ レセプター IIB の誘導
- 抗炎症作用
  - 補体を介する組織障害の軽減
  - 免疫複合体を介する炎症の軽減
  - 抗炎症性サイトカインの誘導
  - 内皮細胞活性化の抑制
  - 微生物毒素の中和
  - ステロイド使用量の減少作用
- B cell および抗体への作用
  - 急性骨髄 B cell repertoires の制御
  - Fcγ レセプターを介する抑制シグナル伝達
  - 抗体産生の選択的抑制および亢進
  - 抗イディオタイプ抗体による血中自己抗体の中和
- T cell に対する作用
  - ヘルパー T cell からのサイトカイン産生の制御
  - T cell スーパー抗原の中和
- 細胞増殖への作用
  - リンパ球増殖抑制作用
  - アポトーシスの制御

I　IVIg の免疫修飾作用機序

一般に IVIg 療法の免疫修飾作用の発現には表1のような機序が考えられている[1]。

* Intravenous immunoglobulin

key words：IVIg，Fc レセプター，FcR，抗イディオタイプ抗体

** 財団法人田附興風会医学研究所北野病院腎臓内科　Muso Eri
〔〒530-0025　大阪市北区扇町 2-4-20〕

表 2　効果が比較試験で証明されている IVIg の自己免疫疾患および炎症性疾患の一覧

- 特発性血小板減少性紫斑病
- ギランバレー症候群
- 慢性炎症性脱髄性多発神経根症（CIDP）
- 重症筋無力症
- 多発性運動神経疾患
- ステロイド抵抗性皮膚筋炎
- 川崎病
- GVHD 予防
- ANCA 関連血管炎☆（Churg-Strauss 症候群の末梢神経炎）
- 自己免疫性ぶどう膜炎☆
- 多発性硬化症
- 紅斑性天疱瘡☆

☆予備的試験で効果が報告されており比較試験が現在進行中。

1．Fc レセプター（FcR）を介する機序

近年，FcR を介したマクロファージの貪食能の調整が考えられている。血小板減少性紫斑病などでは，マクロファージへの血小板と自己抗体との免疫複合体の貪食がマクロファージ表面の FcR を介して行われ，血小板が取り込まれて減少するが，この FcR を IgG の Fc 部分が接着することでブロックし，血小板減少を抑制する。一方，neonatal（n）FcR は血管の endosome に発現して，血中から IgG を取り込み保護して分化（異化）を抑制し，再度血管内に供給しているが，これは自己免疫病の状態では，自己抗体が再度血中に放出されることになる。この系で，IVIg を先に投与すると血管内皮細胞に無制限に IgG が取り込まれて FcRn をブロックし，血中の自己抗体の endosome での取り込みによる異化防御を妨げ自己抗体は分解，異化が進むと考えられる。一方，Ravetch らは ITP の系で抑制性の FcγRIIB を刺激して，本来の刺激系の FcR の作用を抑制。自己抗体によって刺激されるマクロファージのサイトカイン産生などを防ぐことも証明した[2]。

2．抗炎症作用

IVIg は補体膜攻撃成分（membrane attack complex）である C5～C9 の減少をもたらすが，これは Ig が直接，活性化補体成分である C3c や C4b 成分に結合してその作用を止めることによる[3]。各種の *in vitro* の系では活性化された末梢血単核球，マクロファージからの TNFα や IL-1 の分泌の抑制作用が知られており，IL-1 阻害作用のある IL-1ra や sIL-1rII および IL8 の翻訳や分泌を刺激することも報告されている[4]。

3．T cell への作用

T cell の Th1/Th2 の平衡の偏りが膠原病の活動期にはしばしば観察されるが，IVIg にはこれらの偏りを是正する作用が認められる。また細菌性の superantigen による T-cell への刺激が血管炎などの活動期に確認されている。これに対しては，IVIg に含まれる細菌性 superantigen の中和抗体による抑制作用や，T cell レセプターへの結合阻止作用がその効果を発揮する。

4．B cell および自己抗体 idiotype ネットワークへの作用

各種自己免疫疾患においては，特殊自己抗体の B cell による産生が病態発現，活動性にかかわっており，これを IVIg が制御することで，疾患活動性が抑制されている可能性がある。一方，この分野でより重要視されているのはその variable region である F(ab')2 に依存している系で，これらの自己抗体には多くの正常人の Ig が認識する共通の idiotype が存在することが示唆される。

II　IVIg 療法適応疾患

最初に IVIg 療法の有効性が確立された疾患は突発性血小板減少性紫斑病でそれ以来現在までいくつかの自己免疫疾患や炎症性疾患に対して本法の比較試験が試みられ，優位性が確認されて実際に保険治療で認められているものが増えてきている（表 2）。

ANCA 関連血管炎に対しては，現在まで有効症例報告や，比較試験が欧米やわが国からも発信されている。筆者らは急速進行性糸球体腎炎を呈す

る急性期に，IVIg のみで治療した 12 例で有意な活動性の抑制と腎機能低下の進行阻止が可能となったことを報告した[5]。寛解維持に関しては，定期的に IVIg 投与を行うことで，有意な寛解維持期間の延長が報告されており，高齢者で感染症を合併することの多い微小血管炎には，感染予防，阻止効果も期待して免疫修飾療法としての IVIg が有効であり，さらなるエビデンスにより保険収載が望ましい。一方，ANCA 陽性微小血管炎の 1 つである Churg-Strauss 症候群の末梢神経炎に対しては，最近前向き比較試験で効果が証明され，保険治療が可能となった。

Ⅲ 免疫グロブリン製剤の組成および安全性

献血グロブリンは数万のヒトの血液のプール血清成分から分離されている。分離の方法や，自然凝固を防ぐための処理については，各社独自の工夫で製造されておりそれぞれに違いがあるが，すべての製品は世界保健機構（WHO）が定めた基準（免疫グロブリンサブクラスをすべて一定の割合で含有することや，ある種の抗原に対する一定の抗体価をもっていることなど）を満たしていることが確認されている。

多くの献血者からの血液成分を用いた製剤である以上，既知あるいは未知のウイルスの混入に関してはその可能性を絶対的に否定することは困難である。しかし，例えば C 型肝炎ウイルスに関していえば，まず献血者の検査を徹底的に行い，完全に陰性のものを選ぶこと，さらに慎重な超遠心，ペプシンによる消化，活性化剤の追加により活性のあるウイルスの混入を限りなくゼロに近づける努力がなされている。IVIg 治療の副作用として腎障害の報告があり，この原因は IVIg 製剤を安定化させるために含有される二糖類の sucrose が高浸透圧血症を引き起こすためとされている。この問題は腎機能低下が問題となる血管炎などでは注意を要し，sucrose を含まない乾燥スルホ化ヒト免疫グロブリン製剤の使用が勧められる。

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Guideline for Management of Vasculitis Syndrome (JCS 2008)

– Digest Version –

JCS Joint Working Group

Table of Contents

(*Circ J* 2011; **75:** 474–503)

I Introduction

1. Background of the Guideline

1 Classification of Vasculitis Syndromes

Vasculitis syndromes are classified, according to the size of the affected vessels, into large-vessel, medium-vessel, and small-vessel vasculitis (**Table 1**). Large-sized vessel vasculitis, ie, vasculitis occurring in the aorta and its major branches to the extremities, the head and the neck, includes Takayasu arteritis and temporal arteritis. Medium-sized vessel vasculitis, ie, vasculitis occurring in the major arteries and their branches to the visceral organs, includes polyarteritis nodosa (PAN), Kawasaki disease, and Buerger disease. Small-sized vessel vasculitis occurs in the arterioles, capillaries, and venules. In some cases, small arteries are also affected. Small-sized vessel vasculitis is classified according to the involvement of immune complexes. Vasculitis involving immune complexes include Henoch-Schönlein purpura, essential cryoglobulinemia, and malignant rheumatoid arthritis (MRA) (rheumatoid vasculitis). Small-sized vessel vasculitis not involving immune complexes include microscopic polyangiitis (MPA), Wegener's granulomatosis, and allergic granulomatous angiitis. Since these three conditions are associated with the presence of marker antibodies, ie,

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Mailing address: Scientific Committee of the Japanese Circulation Society, 8th Floor CUBE OIKE Bldg., 599 Bano-cho, Karasuma Aneyakoji, Nakagyo-ku, Kyoto 604-8172, Japan. E-mail: meeting@j-circ.or.jp

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Table 1. Classification of Vasculitis Syndromes by Size of Affected Vessels

Classification	Affected vessels	Types of vasculitis
Large-sized vessel vasculitis	Aorta and its major branches	Takayasu arteritis* Temporal arteritis*
Medium-sized vessel vasculitis	Major arteries to visceral organs and their branches	Buerger disease* Polyarteritis nodosa* Kawasaki disease
Small-sized vessel vasculitis	Arterioles, capillaries, and venules Sometimes small arteries are affected as well.	ANCA-associated vasculitis Microscopic polyangiitis* Wegener's granulomatosis* Allergic granulomatous angiitis* Immune complex vasculitis Henoch-Schönlein purpura* Essential cryoglobulinemia* Malignant rheumatoid arthritis*

*Described in the present guidelines.
The six underlined diseases are investigated by the Specific Disease Study Group of the MHLW. Polyarteritis nodosa and microscopic polyangiitis were categorized collectively as "periarteritis nodosa" until 2005. From 2006 on, these diseases have been clearly distinguished.
ANCA, antineutrophil cytoplasmic antibodies; MHLW, Ministry of Health, Labour and Welfare.

antineutrophil cytoplasmic antibodies (ANCA), they are collectively referred to as ANCA-associated vasculitis.

2 Epidemiology of Vasculitis Syndromes

Many types of vasculitis syndromes are rare and intractable diseases with unknown etiology, and are designated by the Ministry of Health, Labour and Welfare (MHLW) of Japan as Specific Diseases, which have been investigated by the Intractable Vasculitis Study Group. Among such diseases, Takayasu arteritis, Buerger disease, PAN, MPA, Wegener's granulomatosis, and MRA, which are relatively prevalent and difficult to treat, are included in the Disease List for the Specific Disease Treatment Research Program which provides Medical Care Certificates to patients and reimburses a portion of healthcare expenses (**Table 1**). Since the certification of patients with these six diseases is renewed annually to provide Medical Care Certificates, the numbers of patients with these diseases can be estimated on the basis of the number of certified patients. **Figure 1** shows change over times in number of annual certificates during the last 12 years.

As shown in **Figure 1**, the most prevalent types of vasculitis are Buerger disease, Takayasu arteritis, and MRA, and the numbers of patients with these conditions have been remained unchanged or tended to decrease over time during the last 12 years. On the other hand, the numbers of patients with PAN and Wegener's granulomatosis have increased steadily, and have doubled or tripled in the last 12 years. In the patient application system for Specific Diseases, PAN and MPA were categorized collectively as "periarteritis nodosa" until 2005. From 2006 on, these diseases have been clearly distinguished. The exact number of patients with these two conditions was thus uncertain, with patients with MPA accounting for an overwhelming percentage of those with "periarteritis nodosa" in a survey in the 1990s. Therefore, it is estimated that the number of patients with ANCA-associated vasculitis including MPA and Wegener's granulomatosis has been increasing in Japan. There are differences between Japan and Western countries in the composition of patients with ANCA-associated vasculitis. In Japan, but not Western countries, MPA is more common than Wegener's granulomatosis. There are also differences in the epidemiology of large-sized vessel vasculitis between Japan and Western countries. In Japan, Takayasu arteritis is prevalent and temporal arteritis is rare, whereas in Europe and the United States temporal arteritis is more prevalent than Takayasu arteritis. Guidelines for the treatment of vasculitis syndromes in Japan have long been awaited because of these substantial differences in the epidemiology and pathology of vasculitis syndromes between Japan and Western countries.

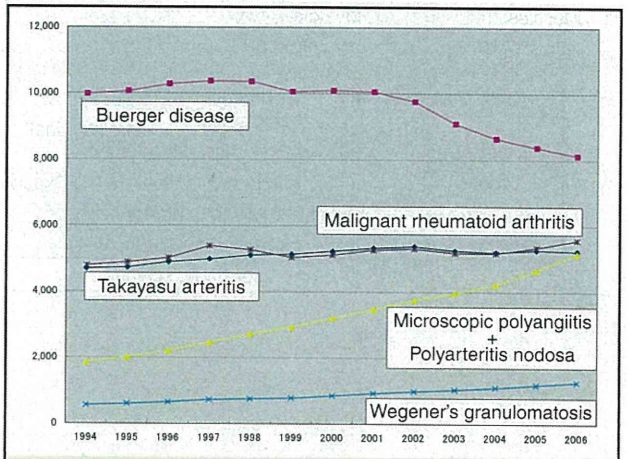

Figure 1. Changes over time in numbers of patients with vasculitis (Numbers of patients who receive Medical Care Certificates for Specific Diseases).

3 Common Clinical Features and Approaches to Diagnosis of Vasculitis Syndromes

(1) Common Clinical Features

Since vasculitis syndromes are caused by "inflammation" of "blood vessels", patients exhibit signs and symptoms of ischemia and hemorrhage of multiple organs as well as inflammation. Clinical features are classified largely into systemic signs/symptoms of inflammation and localized visceral signs/symptoms specific to affected organs.

1) Systemic Manifestations

I. Fever of unknown origin (FUO): A high, often spiking, fever of 38 to 39°C often develops.

Table 2. Visceral Manifestations of Large/Medium-Sized Vessel Vasculitis and Small-Sized Vessel Vasculitis

I. Visceral manifestations of large/medium-sized vessel vasculitis	
Common carotid artery:	Dizziness, headache, syncope
Maxillary artery:	Jaw claudication
Ophthalmic artery:	Loss of vision
Subclavian artery:	Numbness of upper limbs, cold sensation, easy fatigability, difference in blood pressure between the right and left arms, lack of pulse
Renal artery:	Hypertension, renal insufficiency
Mesenteric artery:	Ischemic enterocolitis
Coronary artery:	Angina pectoris, myocardial infarction
Pulmonary artery:	Cough, bloody sputum, dyspnea, pulmonary infarction
II. Visceral manifestations of small-sized vessel vasculitis	
Skin:	Livedo reticularis, subcutaneous nodules, purpura, skin ulcer, finger/toe-tip necrosis
Peripheral nerve:	Mononeuritis multiplex
Muscles:	Myalgia
Joints:	Arthralgia
Kidneys:	Necrotizing (crescentic) glomerulonephritis
Gastrointestinal tract:	Gastrointestinal ulcer, gastrointestinal hemorrhage
Heart:	Myocarditis, arrhythmia
Lungs:	Pulmonary alveolar hemorrhage
Serous membranes:	Pericarditis, pleuritis
Eyes:	Retinal hemorrhage, scleritis

II. Systemic signs/symptoms: Body weight often de-creases due to persistent high fever. Patients complain of vague symptoms such as weakness and generalized malaise.

2) Localized Visceral Signs/Symptoms

The visceral signs/symptoms of vasculitis syndromes arise simultaneously (or sequentially) as signs/symptoms associated with multiple organs. Visceral signs/symptoms are caused by ischemia or hemorrhage due to injury of affected blood vessels, and differ in nature by size of the affected blood vessels (Table 2).

i) Visceral Signs/Symptoms of Large- and Medium-Sized Vessel Vasculitis (Table 2-I):

Since large- and medium-sized vessels run from the aorta to visceral organs, the signs/symptoms of vasculitis result from injury to organs supplied by the affected blood vessels, and include pulse deficit, jaw claudication, loss of vision, and acute abdomen. Injury of large- or medium-sized vessels in the kidneys causes rapidly progressive hypertension and renal insufficiency.

ii) Visceral Signs/Symptoms of Small-Sized Vessel Vasculitis (Table 2-II):

The characteristic skin finding of small-sized vessel vasculitis is palpable purpura that often develops in the lower limbs. Mononeuritis multiplex is a clinical manifestation of vasculitis of medium- or small-sized vessel arteries feeding the affected nerves. It may manifest as sensory disturbance such as hyperesthesia or hypoesthesia, and, when progressive, leads to motor disturbance that may cause a drop hand or foot. The clinical features of vasculitis in small-sized vessels of the kidneys include those of nephritis, such as hematuria, proteinuria, and cylindruria. When pulmonary alveolar hemorrhage due to arteriolitis or venulitis develops, patients may expectorate bloody, foamy sputum.

(2) Approaches to Diagnosis

It is important that physicians suspect the possibility of vas-

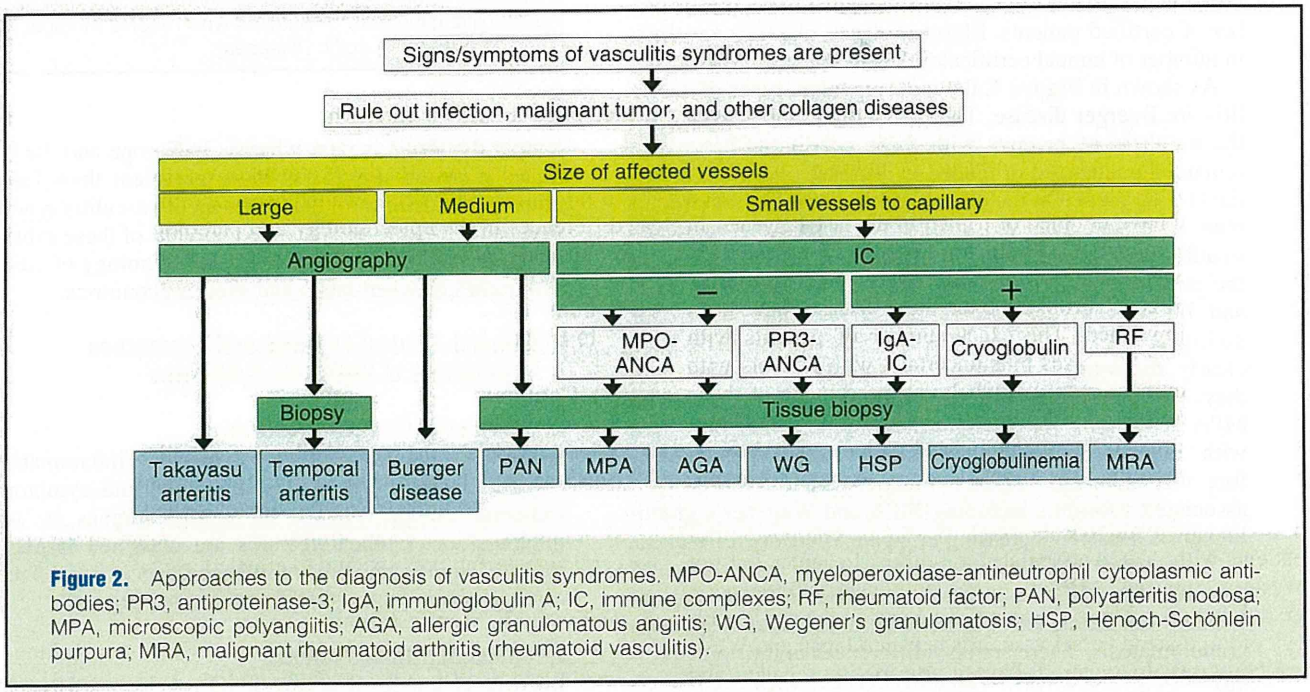

Figure 2. Approaches to the diagnosis of vasculitis syndromes. MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibodies; PR3, antiproteinase-3; IgA, immunoglobulin A; IC, immune complexes; RF, rheumatoid factor; PAN, polyarteritis nodosa; MPA, microscopic polyangiitis; AGA, allergic granulomatous angiitis; WG, Wegener's granulomatosis; HSP, Henoch-Schönlein purpura; MRA, malignant rheumatoid arthritis (rheumatoid vasculitis).

culitis in patients who present with "fever and various systemic manifestations that appear unrelated". The differential diagnosis of vasculitis syndromes should include infections, malignant tumors, and collagen disease and other similar diseases. Approaches to diagnosis differ depending on the size of the affected blood vessels (**Figure 2**). Angiography is useful in the diagnosis of large- and medium-sized vessel vasculitis. Small-sized vessel vasculitis is classified by the presence/absence of immune complexes. In patients with positive immune complexes, attention should be carefully evaluated for the presence/absence of immunoglobulin (Ig) A immune complexes and cryoglobulins. Patients with MRA may show positive immune complex and very high levels of rheumatoid factor.

The vasculitis not involving immune complexes includes ANCA-associated vasculitis. Patients should be carefully examined for myeloperoxidase (MPO)-ANCA and proteinase-3 (PR3)-ANCA. In patients with vasculitis other than Takayasu arteritis, which injures the aorta and its major branches, biopsy of affected vessels is a useful method for diagnosis.

4 Drugs for Vasculitis Syndromes and Treatment-Related Complications

(1) Glucocorticoid

Glucocorticoid are the drug of first choice in the treatment of many types of vasculitis. Adverse drug reactions (ADRs) to glucocorticoid include diabetes, infections, peptic ulcer, psychiatric symptoms, osteoporosis/spinal compression fracture, hypertension, glaucoma/cataract, and hyperlipidemia. Since these ADRs may develop at different points of time during glucocorticoid therapy, physicians should monitor patients carefully and provide appropriate measures when ADRs develop. Most ADRs can be controlled with treatment with additional drugs such as antiulcer drugs for digestive ulcer. However, prophylactic medication with bisphosphonates is necessary for elderly patients to prevent spinal compression fracture, which will cause pain, decrease in activities of daily livings (ADL) and quality of life (QOL), and additional complications due to being bedridden.[1,2] Occasionally, it may be difficult to distinguish the emergence of infection from the recurrence of vasculitis. Since opportunistic pulmonary infections are commonly associated with the use of glucocorticoid, physicians should observe patients carefully for tuberculosis, pneumocystis pneumonia, cytomegalovirus (CMV) pneumonia, and other pulmonary infections.[3] It is recommended that immunosuppressive drugs may be used with glucocorticoid concomitantly to spare doses of glucocorticoid.

(2) Cyclophosphamide (Endoxan®)

Cyclophosphamide (CY), an essential component of the treatment of intractable vasculitis, inhibits DNA replication by alkylating DNA and leads to cell death. During CY therapy, physicians should carefully observe patients for cytopenia, hepatic dysfunction, and infections, among other known ADRs to this drug. Since metabolites of CY may induce hemorrhagic cystitis by stimulating the mucous membrane of the urinary bladder, patients should take enough of water to promote frequent urination during treatment, and should receive mesna to prevent cystitis when they receive intermittent intravenous CY. The incidence of malignant tumor increases when the cumulative dose exceeds 5 to 10 g. Physicians should also be aware of the risk of impairment of fertility. Since the use of CY for the treatment of vasculitis is not covered by the National Health Insurance (NHI) of Japan, physicians should obtain adequate informed consent from patients when this drug is used for vasculitis syndromes.

(3) Azathioprine (Imuran®, Azanin®)

Azathioprine inhibits purine metabolism. During the initial phase of treatment, patients should be carefully observed for ADRs to azathioprine such as cytopenia and hepatic dysfunction.

Since bone marrow suppression may develop when azathioprine is used with allopurinol (Zyloric®), azathioprine should be administered at 25 to 50% of the recommended dose during treatment with both drugs. Azathioprine is indicated for (1) recipients of kidney transplantation, and (2) prevention of rejection after organ transplantation under the NHI of Japan.

(4) Methotrexate (Methotrexate®, Rheumatrex®, Metolate®)

Methotrexate (MTX) is a folic acid antagonist. Rheumatrex® and Metolate® are indicated for the treatment of rheumatoid arthritis (RA), but are not covered by the NHI of Japan for the treatment of vasculitis syndromes. Physicians should obtain adequate informed consent from patients when these drugs are used to treat vasculitis syndromes.

It should be noted that MTX is typically administered orally bid 1 or 2 days a week. Since MTX is teratogenic, women who wish to become pregnant must discontinue treatment with it more than 6 months before pregnancy. Hepatic dysfunction tends to develop at higher doses but often improves after dose reduction. Cytopenia often develops in association with renal dysfunction and in elderly patients with dehydration, since MTX is excreted through the kidneys and these conditions may increase MTX concentration in the blood. MTX is therefore contraindicated for patients with renal failure. Although the incidence of interstitial pneumonia as an ADR to MTX is low, patients with interstitial pneumonia should be carefully observed during treatment. Since Pneumocystis pneumonia may develop in elderly patients and patients with respiratory disease, serum β-D-glucan should be measured periodically during treatment. When necessary, patients should receive prophylactic treatment with sulfamethoxazole-trimethoprim (SMX/TMP) (Baktar® 2 tablets/day, 3 days a week). Since MTX and TMP potentiate each other's effects, the dose of MTX should be reduced.

(5) Aspirin (Bayaspirin®, Bufferin 81®)

Aspirin inhibits platelet aggregation by blocking the synthesis of thromboxane A_2 through inhibition of cyclooxygenase 1 (Cox-1). It also inhibits the expression of interferon (INF)-γ, which plays a role in intimal hyperplasia in patients with temporal arteritis.[4] It is known that inflammation and glucocorticoid may promote arteriosclerosis. Patients with vasculitis syndromes should be considered for treatment with statins and angiotensin II receptor antagonists in combination with aspirin.

5 Prophylaxis and Management of Treatment-Related Complications

The following guidelines have been proposed by the Study Group on Complications of Immune Disease and Treatment (Chairman: Hirofumi Hashimoto) of the Immune/Allergic Disease Prevention/Treatment Study Project supported by the MHLW of Japan.[3]

Table 3. Classification of Recommendations and Level of Evidence

(1) Classifications of recommendations on treatment	
1) Class I:	Treatment SHOULD be administered.
2) Class IIa:	IT IS REASONABLE to administer treatment.
3) Class IIb:	Treatment MAY BE CONSIDERED.
4) Class III:	Treatment should NOT be administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL.
(2) Levels of evidence	
1) Level A:	Data derived from multiple randomized clinical trials or meta-analyses
2) Level B:	Data derived from a single randomized trial or nonrandomized studies
3) Level C:	Only consensus opinion of experts

(1) Pneumocystis Pneumonia

1) Criteria for Prophylaxis Against Pneumocystis Pneumonia in Patients With Autoimmune Disease

Patients requiring primary prophylaxis

- Patients aged ≥50 years
- Patients receiving glucocorticoid
  Patients receiving prednisolone (PSL) at ≥1.2 mg/kg/day or receiving ≥0.8 mg/kg/day PSL in combination with immunosuppressive drugs.
  Criteria for discontinuation of prophylaxis: Patients whose dose of PSL is ≤0.4 mg/kg/day.
- Patients receiving immunosuppressive drugs
  Patients receiving ≥0.8 mg/kg/day PSL or with a peripheral lymphocyte count of ≤500/μL.
  Criteria for discontinuation of prophylaxis: Patients whose dose of PSL is ≤0.4 mg/kg/day or with a peripheral lymphocyte count of ≥500/μL over time.

Patients requiring secondary prophylaxis (prophylaxis for recurrent Pneumocystis pneumonia after improvement following treatment)

- All patients who have experienced Pneumocystis pneumonia
  Criteria for discontinuation of prophylaxis: Same as for primary prophylaxis.

2) Regimens for Prophylaxis Against Pneumocystis Pneumonia

I. SMX/TMP compound (Baktar®, 1 tablet contains 1 g) 1 g/day to 4 g/week (2 g per administration) to 8 g/week (4 g per administration)

II. Inhaled pentamidine isethionate (Benambax®: Each ampule contains 300 mg of pentamidine isethionate) 300 mg/month to 300 mg/2 weeks

3) Precautions Regarding Laboratory Findings

Peripheral lymphocyte count should be measured, and patients with a count of ≤1,000/μL should be observed carefully and considered for prophylactic treatment, although the threshold for this treatment may differ by age. Prophylactic treatment is recommended for patients with a count of ≤500/μL.

(2) Prevention and Treatment of Bone Fractures in Female Patients Receiving Glucocorticoid at High Doses

Patients with a bone mineral density of <80% of the young adult mean (YAM) are at high risk of bone fracture, and are absolutely indicated for treatment and prevention. Since bone fractures may occur even in patients with a stable bone mineral density (T score > -1 SD), careful management is required. During long-term treatment with high-dose glucocorticoid, active vitamin D[3] and bisphosphonates should be considered regardless of the level of T score. Hyperlipidemia is considered as a risk factor for bone fracture (risk ratio [RR] = 3.11). Although bisphosponates are considered effective in the treatment of osteoporosis, it is unclear whether they are effective in preventing bone fracture in the early phase of treatment.

2. Basic Principles for Preparation of the Guidelines

1 Selection of Diseases

We selected types of vasculitis syndromes covered in the present guidelines for Management of Vasculitis Syndromes according to the epidemiology and size of affected vessels, among other factors, to ensure contribution to practice by cardiologists and general practitioners. We prepared the guidelines for the following five disease groups. Among the five groups, Takayasu arteritis and Buerger disease, which are prevalent in Japan and often treated by cardiologists, are described in detail. The diagnosis and treatment of the remaining three diseases, which are not prevalent and often treated by rheumatologists, are briefly summarized.

(1) Takayasu arteritis
(2) Buerger disease
(3) Temporal arteritis
(4) Polyarteritis nodosa (PAN)
(5) Small-sized vessel vasculitis (microscopic polyangiitis [MPA], Wegener's granulomatosis, allergic granulomatous angiitis, Henoch-Schönlein purpura, essential cryoglobulinemia, and malignant rheumatoid arthritis [MRA])

2 Classification of Recommendations

The present guidelines were prepared on the basis of the results of studies in Japan and foreign countries to provide up-to-date, standard treatment guidelines for patients with vasculitis syndromes. Since both the numbers of participants in clinical studies and the number of randomized clinical studies are small, study results with a low level of evidence were also referenced. The levels of recommendation and evidence are rated according to the classification listed in **Table 3** as used in other Guidelines for the Diagnosis and Treatment of Cardiovascular Diseases.

3. Structure of the Guidelines

The present guidelines include a general description of vasculitis in the Introduction as well as descriptions of individual diseases. The Introduction describes the classification of vasculitis to ensure understanding of vasculitis syndromes, as well as ADRs to glucocorticoids and immunosuppressive drugs, which are used as the main component of drug treatment for patients with vasculitis syndromes and require careful management during treatment.

In the sections on individual diseases, the five types of vasculitis listed above are described on the basis of the following characteristics.

(1) Definition and epidemiology
(2) Pathogenesis
(3) Pathological findings
(4) Clinical features and laboratory findings
(5) Diagnostic methods and criteria
(6) Policies and guidelines of treatment
(7) Prognosis

Pathological findings are critical for the proper understanding and correct diagnosis of vasculitis syndromes. The original version of the guidelines include descriptions and typical photos of pathological findings to ensure correct diagnosis of vasculitis syndromes.

While the criteria for diagnosis of vasculitis syndromes proposed by the American College of Rheumatology (ACR) are commonly used in many countries, in Japan the criteria for diagnosis proposed by the Intractable Vasculitis Study Group of the MHLW of Japan are mainly used. No studies have compared the sensitivity and specificity of these criteria in patients in Japan. The present guidelines thus describe the criteria commonly used in the clinical setting and include important aspects of the ACR's guidelines and WHLW's guidelines.

Standard pharmacological and non-pharmacological treatments currently used for each type of vasculitis are described in the guidelines. In the sections on Takayasu arteritis and Buerger disease, the types of patients indicated for surgery, surgical procedures used, and the results of surgery that have been obtained from research in vascular surgery in Japan are described in detail.

Recently, treatment with biological agents, gene therapy, and revascularization therapy have been attempted in treating patients not responding to conventional treatment. The present guidelines describe the current status of these new therapies and future trends.

II Takayasu Arteritis

1. Definition and Epidemiology

1 Definition

Takayasu arteritis is a type of aortitis that affects the aorta and its primary branches, the coronary arteries, and pulmonary arteries. In Japan, it is often referred to as aortitis syndrome, while it is called Takayasu arteritis in Europe and the United States. Its incidence differs by race/ethnicity and geographical area. In Japan, young female patients are predominant. Pathological changes develop around the tunica adventitia and then spread to the tunica intima. The main clinical features are systemic inflammation, pain due to vasculitis, and signs/symptoms of stenosis, occlusion or dilatation of blood vessels. Injury to organs due to blood flow disorder and aneurysms are also problematic.

In 1908, Professor Mikito Takayasu of the Department of Ophthalmology of Kanazawa University reported "a case of bizarre change of central vessels of the retina" in a female patient 22 years of age in whom funduscopy revealed flowering-like vascular anastomoses at an annual meeting of the Japanese Ophthalmological Society.[5] The name "Takayasu disease" was first used by Yasuzo Niimi in 1942.[6] In 1951, Shimizu et al reported cases of similar findings with the term "pulseless disease".[7] Ueda et al conducted an extended study on histopathological and clinical findings, and established the term "aortitis syndrome".[8]

2 Epidemiology

(1) Incidence by Age and Sex

Takayasu arteritis is a Spec..ic Disease defined by the MHLW, and approximately 5,000 patients with this disease are registered in Japan. The number of newly diagnosed patients per 3-year period has ranged between 200 and 400, and has tended to decrease over time. At present, patients in their 50s account for the largest number of patients.[9] The male-to-female ratio is about 1:9, and age at onset peaks at around 20 years in female patients. In male patients, however, no distinct peak of age at onset is observed.

(2) Geographical Differences

Takayasu arteritis is prevalent in Asia and the Middle East, while reports of it in parts of North America other than Mexico are rare. Although female patients tend to be predominant in all geographical areas, the percentage of female patients is highest in Japan.[10]

2. Pathogenesis

The etiology of Takayasu arteritis is still unknown, although the possibility of involvement of genetic factors has been suggested.[11] Researchers have reported that cellular immunity plays a role in the development of vascular injury in patients with Takayasu arteritis. It has been assumed that stressors such as viral infection trigger immune system disorders, and that, as inflammation progresses, T cells play a central role in the destruction of vascular tissues.[12,13]

3. Pathological Findings

Takayasu arteritis is classified into four types on the basis of anatomy of the affected arteries.

(I) Arteritis affecting the aortic arch and its major branches
(II) Arteritis affecting the thoracic/abdominal aorta
(III) Arteritis affecting the entire aorta
(IV) Arteritis affecting the pulmonary artery

Although stenotic lesions in the above major arteries are typical findings, approximately 15 to 30% of patients with Takayasu arteritis have aortic aneurysms or aortic valve insufficiency.[14] In 1997, Numano et al[15] proposed a new method of classification based on angiographic findings into Types I to V, with subcategorization by the presence/absence of lesions in the coronary and pulmonary arteries (**Figure 3**).

Histological findings in the early stage consist of adventitial mononuclear infiltrates with perivascular cuffing of the vasa vasorum. Granulomatous panarteritis is a typical finding. In some patients, infarction and infiltration of Langhans

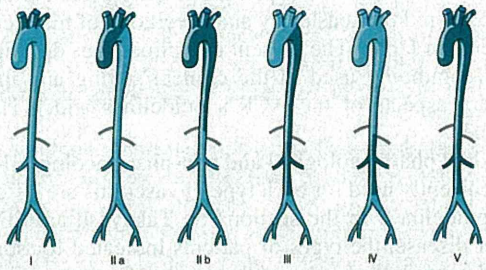

Figure 3. Classification of angiographic findings of Takayasu arteritis.
Takayasu arteritis is classified as follows on the basis of the distribution of lesions detected by angiography.
Type I: Branches of the aortic arch
Type IIa: Ascending aorta, aortic arch and its branches
Type IIb: IIa lesions + thoracic descending aorta
Type III: Thoracic descending aorta, abdominal aorta, and renal arteries
Type IV: Abdominal aorta and/or renal arteries
Type V: Type IIb + IV (ascending aorta, aortic arch and its branches, and thoracic descending aorta as well as abdominal aorta and/or renal arteries)
In addition to the above six types, the involvement of coronary lesions is indicated by C (+), and that of pulmonary arterial lesions by P (+).
Adapted from Toyoshima S, Tasaka K, Ozaki S. Immunology for Medicine and Pharmacology, Second Edition. p163. Tokyo Kagaku Dojin, Tokyo, 2008.

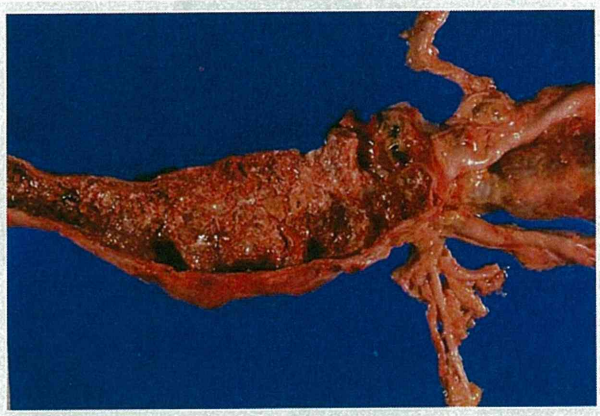

Figure 4. Macroscopic findings for the aorta in a patient with Takayasu arteritis. Due to significant calcification and atherosclerosis, the wall of the affected aorta has lost almost all elasticity, and exhibits a lead-pipe-like appearance.

giant cells containing fragmented elastic fibers are observed in the tunica media. Later, diffuse fibrosis of the tunica media and marked acellular fibrous thickening of the tunica intima are observed. Lymphocytic-plasmacytic infiltration with or without giant cells is also observed. Morphologically, it is difficult to differentiate Takayasu arteritis from extracranial giant cell arteritis.

In the scar stage, progressive intimal thickening and adventitial thickening with marked fibrosis are observed. In the outer layer of the tunica media, moth-eaten lesions with characteristic destruction of the elastic fibers are observed. Thickened vasa vasorum is observed in the thickened adventitia. Although, these findings are difficult to differentiate from end-stage arteriosclerosis, fibrosis of the intima is often accompanied by plate-like calcification. Atheroma is rarely observed. Lesions and luminal stenosis are observed in the proximal portions of bifurcated vessels as well. Affected portions of the aorta thus have a lead-pipe-like appearance, which is characteristic of Takayasu arteritis in the scar stage (**Figure 4**). Giant cells and tissue necrosis may be observed when histopathological samples in the scar stage are carefully observed.[16]

Table 4. Clinical Features of Takayasu Arteritis (Report of the Intractable Vasculitis Study Group of the MHLW in 1998)

Cerebral ischemic signs/syndrome	
Dizziness	33.0%
Headache	20.4%
Syncope	2.9%
Hemiplegia	2.1%
Masticatory fatigue	0.4%
Visual signs/symptoms	
Loss of vision	1.7%
Transient visual impairment	4.8%
Persistent visual impairment	5.0%
Aphose	5.9%
Upper limb signs/symptoms	
Lack of pulse	31.2%
Difference in blood pressure between arms	46.4%
Easy fatigability	24.9%
Cold sensation	11.3%
Numbness	12.3%
Cardiac signs/symptoms	
Shortness of breath	19.3%
Palpitations	20.0%
Chest pressure	14.8%
Respiratory signs/symptoms	
Bloody sputum	1.6%
Shortness of breath	7.4%
Hypertension	41.1%
Systemic signs/symptoms	
Fever	7.9%
Generalized malaise	16.5%
Easy fatigability	22.9%

MHLW, Ministry of Health, Labour and Welfare (formerly Ministry of Health and Welfare).

4. Clinical Features and Laboratory Findings

1 Clinical Features (Table 4)

Initial signs and symptoms of Takayasu arteritis include FUO, neck pain, and generalized malaise, which are similar to those of upper airway infection. Subsequently, signs/symptoms due to vascular lesions develop. Stenotic lesions may often cause signs/symptoms of cerebral ischemia and visual impairment due to stenosis of branches of the aortic arch; difference in blood pressure between the right and left arms and lack of a pulse due to ischemia in the upper limbs; hypertension due to renal artery stenosis and aortic coarctation; pulmonary infarction due to pulmonary artery stenosis; and in some cases angina due to coronary ostial stenosis.

Dilatated lesions may often cause aortic aneurysms/dissec-