の水分の増加を示す所見で，骨に加わる種々の刺激(外傷，物理的ストレス，炎症，循環障害など)で生じることが知られている。RAで認められる骨髄浮腫は滑膜炎に伴う反応性変化と考えられ，滑膜炎のある関節に特異的に認められる[9]。われわれの手関節MRIによる検討では滑膜炎のある関節の23%に骨髄浮腫が認められ，滑膜炎のない関節には認められなかった。骨髄浮腫の頻度はdynamic studyにおける造影効果の立ち上がり速度(E-rate)との相関があり，滑膜炎の活動性が高いほど骨髄浮腫の認められる頻度が高いことがわかった。骨髄浮腫はCRPやDASなどとも相関があり，臨床的にも炎症の活動性と関連があることがわかっている。また，骨侵食の前駆状態(pre-erosive lesion)であり，関節破壊あるいは関節機能の予後を予測する重要な因子であることもわかってきた[10),11)]。

● 関節軟骨

関節軟骨の障害は単純X線写真では関節裂隙の狭小化として認識され，進行したRAでのみ認められる変化である。これに対してMRIでは関節軟骨を直接描出することが可能で，関節軟骨病変の早期描出に有用であることが期待される[12)]。しかし，早期変化を捉えるにはMRIの解像度が不十分であり，とくに手関節などの小さな関節では評価が困難なことが多い。最近開発されたマイクロコイルを使用すると，手関節の軟骨でも高解像度の画像を得ることが可能であり，今後の臨床応用が期待される。

MRI画像の評価

MRI画像の評価にはスコア化，容積測定，dynamic studyが行われ，治療効果の判定に有用であることが報告されている。しかし評価の方法は報告者によってまちまちで，標準化されたものはまだ確立されていない。

● スコアによる評価

MRIにおける滑膜炎，骨変化，腱鞘炎，関節裂隙の狭小化の程度などをスコアによって総合的に評価し，半定量化する方法がある。単純写真におけるSharp scoreやLarsen scoreなどに相当する。最初に提唱されたものは1993年のRomingerらによる方法で，手関節における骨侵食，滑膜炎と関節液貯留，腱鞘炎の程度をスコア化するものである[13)]。このほかにもさまざまなスコア化の方法が提唱されているが，多くの要素を取り入れるほど煩雑になること，主観的要素が入るために再現性が問題になること，などが欠点としてあげられる。

現在，ヨーロッパを中心とした多施設共同プロジェクト(OMERACT；Outcome Measures in Rheumatoid Arthritis Clinical Trials)では，MRI所見のスコアの標準化の試みが行われている[14)]。

● 滑膜の容積測定

肥厚した滑膜の容積による滑膜炎の評価はいくつかの報告があり，臨床症状，治療効果あるいは予後との相関があることが報告されている[17)~21)]。この方法はスコア化に比べて客観性と再現性に優れるが，滑膜の範囲を抽出するための方法が煩雑という欠点がある。抽出の方法には手作業で造影された範囲をトレースする方法，造影された領域とそうでない領域を閾値を設定して分割する方法がある。後者では特別なプログラムが必要となる。また，造影効果の有無で画像を二値化するため，造影効果の強さの程度を評価できない点に問題が残る。

● dynamic studyによる評価

dynamic studyは造影剤を急速に静注したあとの滑膜の造影効果の経時的変化を捉える方法で，典型的にはS字型のdynamic curveが得られる。このカーブの立ち上がりの速さ(E-rate)は，滑膜炎の血流の程度と相関し，組織学的な滑膜炎の活動性を反映していることが報告されている[19)~21)]。

われわれは両手指関節のdynamic studyを行う

方法を考案し，RAの早期診断，予後および活動性評価における有用性を検討している。dynamic studyから得られたdynamic curveはワークステーションで解析され，各ピクセルのE-rateに基づいたカラー表示を行うことができる(図5)。このカラー表示では関節の各部位におけるE-rateの違いを視覚的に認識でき，臨床所見との比較や経時的変化の評価に有用である。

図5　dynamic studyによる治療効果判定

69歳，女性。

ⓐ：初診時のdynamic study。

手指関節15カ所におけるdynamic curveを示す。

ⓑ：このdynamic curveの最大造影速度(E-rate)に基づくカラー表示画像。

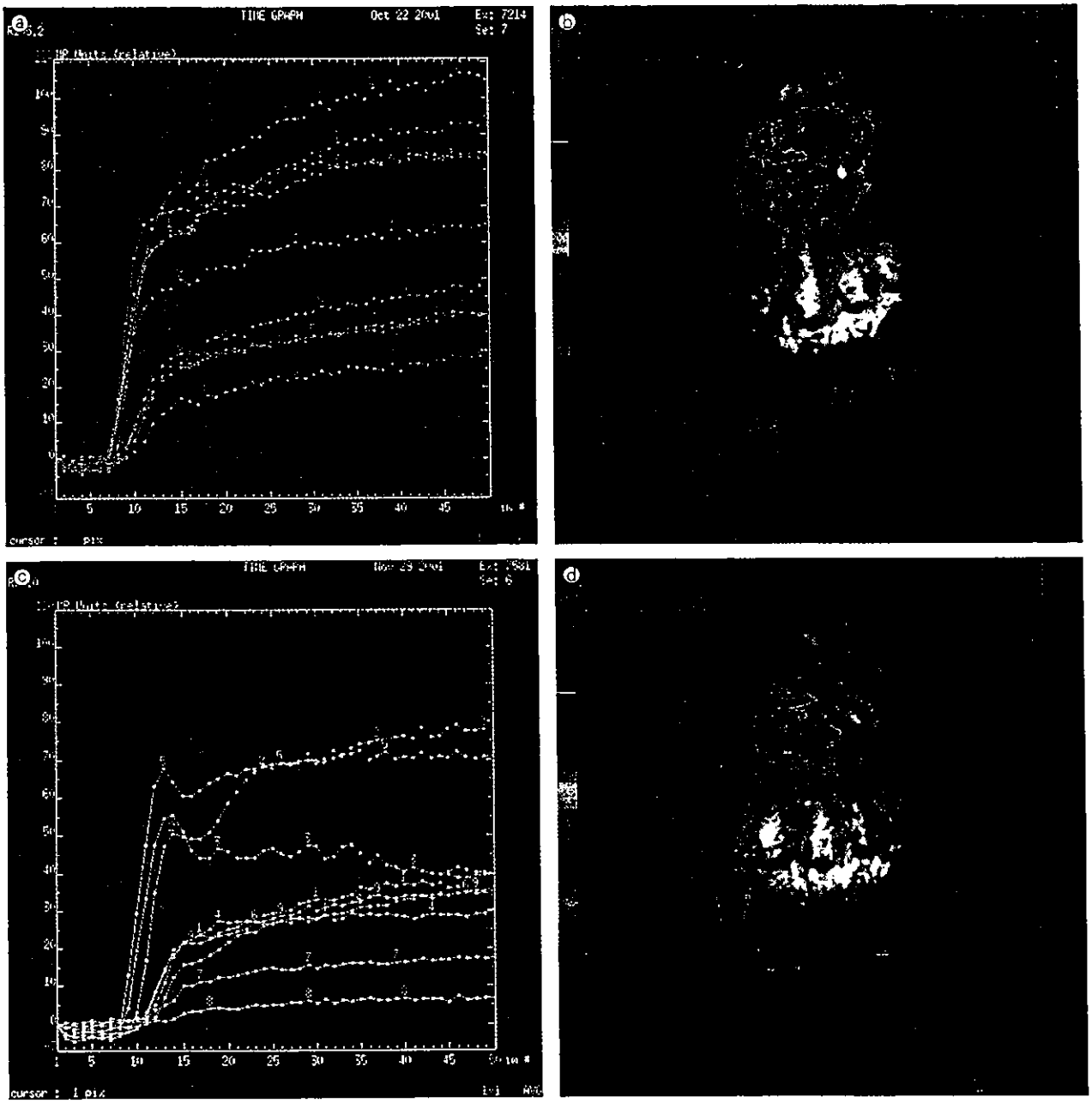
手根関節の滑膜炎の活動性が高いこと，第2，4，5指のPIP関節の活動性は比較的低いことがわかる。

ⓒ：治療後約1カ月のdynamic study。

dynamic curveの傾きおよびピークの低下がみられる。

ⓓ：治療後約1カ月のカラー表示画像。

滑膜炎の活動性が低下した部位がよくわかる。



MRIによるRAの早期診断

MRIは上述したように，滑膜炎や骨変化を理学所見やX線写真よりも敏感に把握することが可能であり，早期診断における有用性が期待される。しかし，これらの変化は非特異的であり，MRI所見だけではRAの診断をくだすことは困難である。

杉本らは，両手関節のMRIにおける対称性関節炎をARAの診断基準に加えることで，RAの診断の感度および特異度の向上が得られることを報告した[22), 23)]。

われわれは早期RAと診断された65例と非RA21例を対象にして，手関節MRIの所見と血清マーカーを組み合わせて多変量解析を行った。その結果，①抗CCP抗体陽性もしくはIgM-RF陽性(オッズ比10.4)，②MRIでの対称性手関節炎(オッズ比4.3)，③MRIでの骨侵食(オッズ比16.5)が早期診断に有意に寄与することが示された。これら3項目のうち2項目以上の陽性をRAと診断した場合の感度は83.1%，特異度は95.2%という成績が得られた。さらに症例数を増やしての検討が必要であるが，RAの早期診断においてMRI所見が理学所見やX線所見にとって代わるものになることが期待される。

おわりに

RAの診断におけるMRIの有用性について，最近の研究報告を含めて概説した。MRIによる滑膜や骨変化の描出は早期診断および予後の判定に有用である。しかし，現時点ではガイドラインといえるMRIの標準的な適応・評価基準はなく，今後さらに検討が必要である。

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総　　説

早期関節リウマチの画像診断

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はじめに

DMARDsによる関節リウマチの早期治療は，関節破壊の防止と予後の改善に重要な役割を果たすと考えられている．しかし，早期RAの確実な診断は困難なことが多く，早期から強力な治療を行うべきかどうか判断することは容易でない．関節リウマチにおける早期の病理組織学的変化は滑膜炎であるが，単純X線写真では滑膜炎は軟部組織の腫脹として描出されずにすぎず，早期診断には限界がある．これに対して，MRIは滑膜炎の描出や血流評価，X線写真で認識できない骨変化の評価が可能であり，RAの早期診断，活動性判定，予後評価における有用性が明らかになってきた．さらに最近では超音波やPETの応用も注目されている．これらの画像診断を有効に利用するには，表1にまとめたような各画像診断の特徴を知っておく必要がある．本稿では早期RAの診断におけるMRIの臨床応用を中心に，画像診断の有用性と限界について述べる．

1．単純X線写真

1987年のARAの診断基準では関節周囲の骨量減少(periarticular osteopenia)および骨浸食像(bone erosion)がRAのX線所見として挙げられている．単純X線写真はRAの診断における基本的検査であり，どの施設でも標準化された方法で病変の進行度を判定できるという利点がある．また，変形関節症や乾癬性関節炎など他の関節疾患との鑑別にも有用である．特に骨浸食像は特異性が高いが，早期診断における臨床的価値は少ない．これは，単純X線写真が滑膜炎を描出することができないこと，骨の前後面や重なりがある部位での骨浸食像を描出しにくいことに起因している．MRIや超音波検査などの画像診断は，このような単純X線写真の欠点を補いうるものとして臨床応用が試みられてきた．

2．MRI

1）MRIで描出される関節病変

MRIは，単純X線写真で描出困難な滑膜炎，腱鞘炎，骨髄，関節軟骨などの病変を描出するのに優れており，RAの早期診断や活動性評価における有用性が報告されている．

滑膜炎

MRIは滑膜炎に伴う滑膜肥厚がT1強調像で低信号，T2強調像で低～高信号として描出される．T2強調像における信号の違いは線維化や滑膜の炎症の程度に左右され，線維化の強い慢性滑膜炎では比較的低信号に描出されることが多い．これに対して早期の滑膜炎で線維化の少ないものでは比較的高信号に描出され，通常のT1・T2強調像で関節液と区別がつかないことがあるが，造影MRIでは造影された滑膜と造影効果のない関節液を明瞭に区別することができる．特に脂

Key Words：rheumatoid arthritis, early diagnosis, MR imaging, ultrasonography, PET scan
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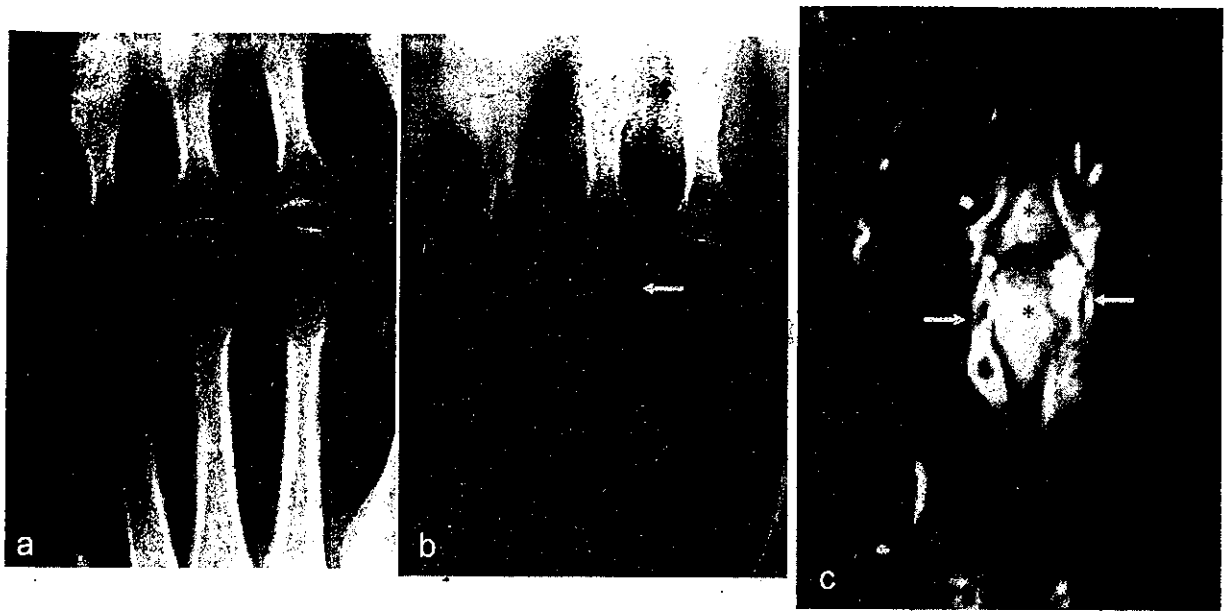

図1 42歳女性 関節リウマチにおけるMTP関節の変化
初診時の単純X線写真：関節周囲の骨減少以外に異常を認めない．
約10ヶ月後の単純X線写真：中足骨頭に骨浸食像が出現している（→）．
初診時の造影MRI：肥厚した滑膜に高度の造影効果がみられる（→）．また関節近傍の骨髄浮腫にも造影効果を認める（＊）

肪抑制法を併用することが望ましい[1]（図1）．滑膜炎の評価にはスコア化[2]，容積測定[3]，dynamic study[4]などが行われ，治療効果の判定に有用であることが報告されている．しかし標準化された評価法はまだ確立されていない．

腱鞘炎，滑液包炎

腱鞘炎（腱鞘滑膜炎）は腱鞘内の液体貯留あるいは腱鞘滑膜の肥厚として描出される．肥厚した腱鞘滑膜の描出には造影MRIが有用である（図2）．我々の造影MRIによる検討では早期RAにおける腱鞘炎の頻度はきわめて高く，RA患者27例53手関節のうち，初診時の検査で49関節（92%）に腱鞘炎を認めた．また，関節周囲の滑液包にもしばしば滑液包炎をきたし，滑膜肥厚や液体貯留を認める．

骨浸食像および骨髄浮腫

MRIにおける骨浸食像は骨皮質欠損およびその近傍の骨髄における限局性の異常信号（T1強調像で低信号，T2強調像で等～高信号，STIRで高信号）で，造影MRIで造影効果がみられる．MRIは単純X線写真よりも早期から骨浸食像を描出できることが報告されている[5][6]．

骨髄浮腫は単純X線では認識できず，MRIではじめて認められる変化である．MRIではT1強調像で低信号，T2強調像で等～高信号を示し，STIR法で高信号を示す境界不明瞭な異常信号として認められ，造影効果を示す（図1）．RAで認められる骨髄浮腫は滑膜炎に伴う反応性変化と考えられ，滑膜炎の認められる関節に特異的に認められる[7]．我々の手関節MRIによる検討では滑膜炎のある関節の23%に骨髄浮腫が認められ，滑膜炎のない関節に骨髄浮腫は認められないこと，滑膜炎の活動性が高いほど骨髄浮腫の認められる頻度が高いことがわかった．また，骨髄浮腫は骨浸食の前駆状態（pre-erosive lesion）であり，関節破壊あるいは関節機能の予後を予測する重要な因子であることがわかってきた[8]．

関節軟骨

関節軟骨の障害は単純X線写真では関節裂隙の狭小化として認識され，進行したRAでのみ認められる変化である．これに対してMRIでは関節軟骨を直接描出することが可能で，関節軟骨病変の早期描出に有用であることが期待される．しかし，早期変化を捉えるにはMRIの解像度が不十分であり，特に手関節などの小さな関節では評価が困難なことが多い．最近開発されたマイクロコイルを使用すると手関節の軟骨

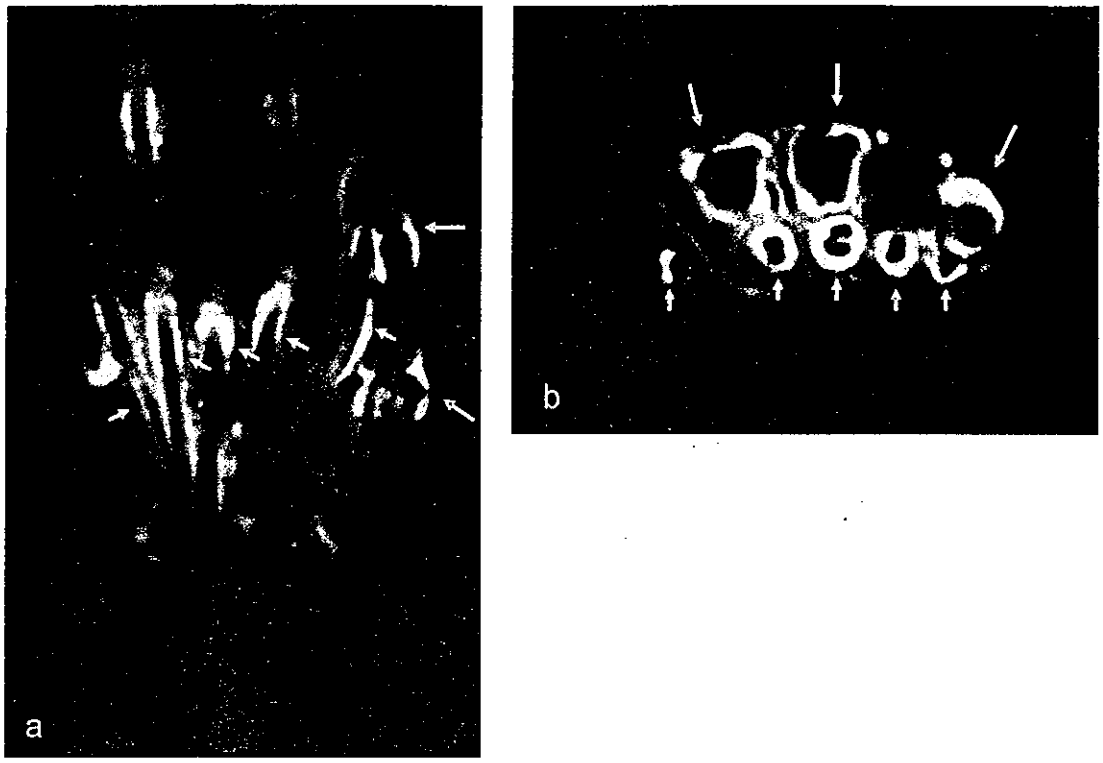

図2　54歳女性　関節リウマチにおける滑膜炎と腱鞘炎
a，b 手関節造影 MRI（脂肪抑制併用）冠状断像および横断像で，関節の滑膜炎（→）とともに，腱鞘炎を示す腱周囲の造影効果が認められる（矢頭）．

でも高解像度の画像を得ることが可能であり，今後の臨床応用が期待される．

3）MRI による RA の早期診断

MRI は上述したように，滑膜炎や骨変化を理学所見や X 線写真よりも敏感に把握することが可能であり，早期診断における有用性が期待される．しかし，これらの変化は非特異的であり，MRI 所見だけでは RA の診断を下すことは困難である．

杉本らは 両手関節の MRI における対称性関節炎を ARA の診断基準に加えることで，RA の診断の感度および特異度の向上が得られることを報告した[9]．我々は早期 RA 65 例と診断された 65 例と非 RA 21 例を対象にして，手関節 MRI の所見と血清マーカーを組み合わせて多変量解析を行った．その結果，1）抗 CCP 抗体または RA 因子陽性（オッズ比 10.4），2）MRI での対称性手関節炎（オッズ比 4.3），3）MRI での骨浸食（オッズ比 16.5）が早期診断に有意に寄与することが示された．これら 3 項目のうち 2 項目以上陽性を RA と診断した場合の感度は 83.1%，特異度は 95.2% という成績が得られた．さらに症例数を増やして検討が必要であるが，RA の早期診断において MRI 所見が理学所見や X 線所見にとってかわるものになることが期待される．

3．超音波検査（ultrasonography，US）

近年の US 装置の改良により，高解像度の画像が得られるようになり，手指関節の検査にも応用が可能となってきた．US の利点は外来でも手軽に検査が可能で，繰り返しの経過観察が容易であること，X 線被爆がないことなどが挙げられる．特に手足の MP 関節，肩関節，膝関節などの表在に近い部位では滑膜肥厚や骨浸食像の評価が可能である．さらに，Doppler や超音波専用造影剤を用いることで滑膜炎の活動性評価も可能である[10]．

US は，手の MCP 関節，足の MTP 関節などで単純写真よりも高率に骨浸食像が描出可能である．しかし，骨の重なりがある部分の評価は難しく，例えば手根骨や第 2 ～ 4 MP 関節では単純写真よりも骨浸食像

表1 関節病変評価における画像診断の有用性

所 見	単純X線写真	US, Doppler	MRI	核医学検査, PET
滑膜炎	+	++	+++	++
関節液	+	++	+++	−
骨減少	++	−	−	−
骨髄浮腫	−	−	+++	−
骨浸食	++	++	+++	+
関節軟骨	+	−	++	−
病変の分布	++	+	+	+++

の描出能が劣る．USの欠点としては，検査部位が限定されること，検査を行う人の技術に診断能が影響されること，多数の関節を検査する場合は検査時間がかかりすぎること，などが挙げられる．このような特徴から，USは早期診断のためのスクリーニング検査よりも，限定した関節における治療効果判定に適していると思われる．

4．核医学検査

核医学検査は全身の関節の検査が同時に可能であり，代謝異常を反映した結果が得られる点で，他の画像診断にない情報を得ることができる．骨シンチグラムでは関節炎近傍の骨に集積がみられ，関節炎の活動性および多発性関節炎の分布を調べるのに適している．最近の研究ではRAの早期診断，活動性評価における18F-FDG PETの有用性が注目されている[11]．

おわりに

早期RAの診断における画像診断の応用について，MRIを中心に概説した．画像診断の標準的な適応・評価基準はまだ確立されておらず，今後さらに検討が必要である．

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〈*Abstract*〉

Diagnostic Imaging of Early Rheumatoid Arthritis

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Early diagnosis of RA is a high priority because the therapies with DMARDs show the most promise when treated early. Conventional radiography remains the standard in the evaluation of RA, but it is insensitive for showing early bone damage or synovitis. MR imaging is suitable in detecting early bone damage and synovitis. It is, therefore, helpful in diagnosis of early RA and evaluation of treatment effect at its early stage. Recently, other imaging modalities, such as ultrasound or PET scan, have also been used in the evaluation of early RA.

Autoimmunity Reviews

Mannose Binding Lectin: Genetics and Autoimmune Disease

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Key Words
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Abstract:
Mannose binding lectin (MBL) is a serum protein with structure and functions similar to those of complement factor C1q, and is a key molecule in innate immunity. Interestingly, absence or extremely low concentration of serum MBL (MBL deficiency) seems to be a risk factor for occurrence of autoimmune diseases, in particular systemic lupus erythematosus. In addition, individuals with MBL deficiency are at risk of infection when in immunocompromised conditions. The concentration of serum MBL is greatly influenced by relatively common single nucleotide polymorphisms of the MBL gene. Therefore, typing of the MBL gene, or measurement of serum MBL may be valuable for determining the risk of infections in patients with systemic autoimmune diseases, who frequently undergo immunosuppressive therapies. MBL deficiency may also be a risk factor for atherosclerosis and arterial thrombosis, both being common complications of autoimmune diseases. On the other hand, MBL may be pathological in tissue injuries, and the precise roles of MBL in autoimmune diseases, and the value of MBL gene typing or serum MBL measurement in a clinical setting are yet to be clarified. Recently, presence of anti-MBL autoantibodies in sera of SLE patients has been reported. The significance of this autoantibody remains to be elucidated.

Take-home messages

Bullet point: Mannose binding lectin (MBL) is a serum protein important in innate immunity and is protective against various infective organisms.

Bullet point: MBL binds carbohydrates on various infectious agents, and has an opsonin effect. In addition, it activates the lectin pathway of the complement cascade.

Bullet point: There is a large inter-individual difference in the serum concentration of MBL, caused mainly by MBL gene polymorphisms (SNP). Individuals with the minority alleles have lower serum MBL concentration.

Bullet point: Individuals homozygous for the minority allele of the MBL gene have higher risk of infection during infancy and when under immunosuppressive therapies.

Bullet point: Individuals homozygous for the minority allele of the MBL gene seem to be at a higher risk of acquiring autoimmune diseases, systemic lupus erythematosus (SLE) in particular.

Bullet point: Autoantibodies against MBL are present in some SLE patients, but their significance remains unclear.

Introduction

Mannose binding lectin (MBL) is a serum protein produced in the liver, and is a key molecule in innate immunity. MBL, along with other molecules such as surfactant protein A (SP-A) and surfactant protein D (SP-D), is a member of the collectin family, the characteristic of which being possession of a carbohydrate recognition domain (CRD) and a collagenous domain [1].

MBL is a trimer protein composed of 3 identical polypeptides with a molecular weight of around 32Kd (228 amino acids), and 3 to 6 trimers further combine to make a huge bouquet-like structure similar to that of complement C1q [2] (Figure 1-A). Each polypeptide consists of a CRD, a neck domain, a collagen domain and a cystein rich region. MBL binds to various organisms by its CRD, and excises an opsonin effect. The multimeric structure of MBL allows it to bind to various microorganisms including gram positive and negative bacteria, mycobacterium, viruses and fungi. The binding of MBL leads to agglutination of these microorganisms and will help their clearance by phagocytes. In addition, MBL activates the complement pathway (the lectin pathway) through mannose binding lectin associated serine proteases (MASPs). Therefore, MBL is important in host defense, especially in infancy, when the acquired immunity has not fully developed. Individuals lacking this protein could develop severe episodes of bacterial infections from early life [3,4]. MBL is also important when the immune system of an individual is compromised, such as when a patient is under immunosuppressive therapy, or receiving chemotherapies or bone marrow transplant [5].

While MBL is an acute phase protein and its production is enhanced by inflammatory stimuli, polymorphisms of the MBL gene is known to greatly influence serum MBL concentration. The MBL gene, located on the long arm of chromosome 10 at 10q11.2-q21, contains 4 exons [2]. There are 5 known single nucleotide polymorphisms (SNPs) that affect serum MBL concentration [6-9] (figure 1-B). Codon 52 (+223), 54(+230) and 57(+239) polymorphisms are all on exon 1, and the minority alleles are designated allele D, B, C, respectively, while the majority allele is designated allele A. Presence of any of the minority alleles (collectively designated allele O) results in an amino acid substitution and significant reduction of serum MBL concentration. Furthermore, homozygosity

for the minority alleles (genotype OO) results in almost complete deficiency of serum MBL [6,7]. This has been attributed to increased degradation of the mutated protein [7]. Frequencies of the minority alleles differ significantly among ethnicities, varying from around 1% to up to around 30 %. In the promoter region of the MBL gene, polymorphisms are reported at positions -550, -221 and +4, and these polymorphisms also influence the levels of serum MBL [9,10] (Table 1). Thus, some individuals with MBL genotype AO or even AA may have extremely low serum MBL concentration. In this review, however, we will focus on the SNPs in the coding region of the MBL gene.

Mannose binding lectin and autoimmune diseases

A number of studies have suggested that MBL deficiency, or low serum MBL levels caused by the SNPs described above may be associated with occurrence of SLE [11]. By a meta analysis of 8 previous studies, it has been shown that presence of the minority alleles (B, C or D alleles) confer a 1.6 times overall increased risk of acquiring SLE [11]. In the same study, by observing their own patients, Garred et al reported that the lag time from the appearance of the first lupus attributable symptom to the diagnosis of definite SLE was shorter in patients carrying at least one minority allele than in patients homozygous for the majority allele [11]. Two possible explanations for the associations between MBL deficiency and the occurrence of SLE are suggested (Figure 1-C). Firstly, MBL can bind to and initiate uptake of apoptotic cells by macrophages [12], and an abnormal accumulation of cell debris would occur in MBL deficient individuals, and would serve as a source of autoantigens. In accord with this hypothesis, Seelen et al [13] recently reported that anticardiolipin and anti-C1q antibodies were observed significantly more frequently in SLE patients with MBL minority alleles than those without those alleles, and that presence of those antibodies were associated with decreased serum MBL concentration and function. It is also reported that MBL can bind DNA, and MBL may have a role in clearance of DNA [14]. Secondary, since MBL has a major role in innate immunity, individuals with MBL deficiency might have higher possibilities of being infected with pathogens that have some roles in the pathogenesis of SLE. However, these hypotheses are yet to be proved. The recent production of MBL deficient mice

[16] may shed a light on the relationship between MBL deficiency and autoimmune diseases.

Regardless of the mechanisms involved, MBL deficiency by itself is not sufficient to cause SLE. Unlike C1q deficiency, which is very strongly associated with lupus or lupus like syndromes [16-21], the majority of individuals with MBL genotype OO do not acquire SLE or any other autoimmune diseases, and are not significantly vulnerable to infectious agents when they are healthy and mature. Some other factors must be necessary for individuals with MBL genotype OO individuals to acquire SLE. What those factors are is still unknown.

While the association between MBL deficiency and SLE suggests that MBL has protective functions against occurrence of autoimmune diseases, deposition of MBL in kidneys of SLE patients [22] and glands of Sjogren's syndrome patients [23] have been reported. MBL may bind to carbohydrates of various proteins and may activate the lectin pathway of the complement pathway. From this point of view, MBL may have a role in the development of tissue damage in these diseases. Thus, MBL may be a double-edged blade in autoimmune diseases. This is also true for the role of MBL in infections. MBL is reported to enhance the progression of some infectious diseases [24], and in this situation, MBL deficiency can be beneficial. The relatively large prevalence of MBL deficiency in the general population also suggests that MBL deficiency may be advantageous for survival in certain conditions.

How MBL and the lectin pathway of the complement activation cascade affect the clinical course of SLE is not well known. It has been shown than a weak but significant positive relationship exist between serum MBL concentration and CH50, suggesting that the serum levels of MBL are associated with the disease activity of SLE in some way [25]. In this study, Takahashi et al also studied the time course of serum MBL concentration in newly diagnosed patients. In SLE patients with MBL genotype AA, serum MBL concentrations did fluctuate during the course of the disease, but there was no clear trend common to all patients. In some patients, serum MBL concentration decreased after initiation of immunosuppressive therapy, while in others serum MBL concentration increased in parallel with CH50 values. Serum MBL levels

are determined by a balance of production and consumption. Since MBL is an acute phase protein, MBL production may be increased in SLE patients with severe inflammation, while deposition of MBL to various tissues may lower its serum concentration. The levels of increase or deposition to tissues would differ among individual patients. Thus, most probably, concentration of serum MBL cannot be simply interpreted to SLE disease activity or an involvement of a particular organ.

Association between MBL and rheumatoid arthritis (RA) has also been suggested. It has been suggested that MBL may bind IgG with altered glycosylation and thus may be pathogenic in patients with RA [26]. However, from the results of clinical studies, it seems that RA patients with MBL genotypes OO show more rapid progression of joint destruction than those without this genotype [27]. If this finding could be confirmed by additional studies, typing of the MBL genotypes may become of value to identify RA patients with a higher risk of rapid joint destruction, and will aid in the selection of therapies for individual RA patients.

Few reports on the relationships between MBL gene polymorphisms and other autoimmune diseases exist. Mullighan et al [28] reported that there is no association between occurrence of Sjogren's syndrome and MBL genotypes. Tsutsumi et al reported that MBL deficiency may be a minor risk factor for the occurrence of type I diabetes [29]. Recently, we examined the MBL genotypes in 53 patients with mixed connective tissue disease (MCTD). Among these patients, only 1 patient had genotype BB (Tsutsumi et al, unpublished observations). Thus, unlike SLE, MBL genotype OO do not seem to be a risk factor for having MCTD.

MBL and vascular disorders

MBL also may be implicated in vascular diseases in both the general population and in autoimmune disease patients. It is reported that MBL enhances tissue injury caused by reperfusion, and administration of anti-MBL antibodies ameliorates myocardial ischemia-reperfusion injury in rat models [30]. In addition, MBL mediated complement activation has been reported to be important in mice renal ischemia-reperfusion injury model [31]. On the other

hand, MBL deficiency is reported to be associated with enhanced atherosclerosis [32] and coronary artery disease [33] in humans. In addition, a recent report indicated a strong association between the OO genotype of the MBL gene and occurrence of arterial thromboses in patients with SLE [34]. In this study, genotypes of the MBL gene were investigated in 91 patients with SLE. Among their 7 patients with MBL genotype OO, 6 had history of arterial thromboses, while 18 of SLE patients with MBL genotypes AA or AO had such history. They concluded that having an OO genotype of the MBL gene may be a major risk factor of having arterial thrombosis in patients with SLE. Several explanations for this association are possible. Possession of genotype OO may be associated with higher disease of SLE, which may enhance vascular injuries, and may necessitate larger amount of steroid for therapy. Alternatively, possession of genotype OO, and hence being deficient of functional MBL may render those SLE patients more susceptible to microorganisms associated with atherosclerosis. It has been suggested that *Chlamydia Pneumoniae* infection is related with occurrence of coronary heart diseases. Furthermore, it has been shown that individuals with MBL gene O alleles, and are positive for serum anti *Chlamydia Pneumoniae* antibodies may be more likely to have coronary artery disease [35]. *Chlamydia Pneumoniae* infection may enhance the development of coronary heart disease in SLE patients lacking serum MBL. To date, there is no direct evidence that this is indeed the case. If future studies confirm the association between MBL gene O alleles and arterial thromboses, it may become possible to identify SLE patients at a higher risk of having arterial thrombosis at the time of diagnosis. Taking appropriate protective measures would aid in the improvement of the prognosis of SLE patients. As the number of SLE patients with MBL genotype OO was not very large in this study, this observation need to be confirmed by future studies with a larger study population.

The association between MBL genotypes of SLE patients and infection has been suggested [11,25,36]. Since the mainstream of therapy for SLE is immunosuppression, typing the MBL gene or measuring serum MBL before immunosuppressive therapies may aid in assessing the risk of infection during such therapies.

Autoantibodies against mannose binding lectin

It is well established that autoantibodies against complement C1q is found in 30-45% of SLE patients, and the presence of anti-C1q antibodies is associated with glomerulonephritis and hypocomplementemia. The relationship between C1q deficiency and SLE like symptoms is also well known. The structural and functional similarity between C1q and MBL, and the large differences of serum MBL concentration among individuals with the same MBL genotype prompted some investigators to search for the presence of anti-MBL autoantibodies (anti-MBL). Anti-MBL, if present, may bind to MBL and decrease its serum concentration. Alternatively, anti-MBL may bind to MBL already deposited in various tissues and enhance tissue injury.

Seelen et al reported that anti-MBL were indeed present in sera of some patients with SLE [37]. In addition, they found that anti-MBL is present as a complex with circulating MBL, and that an inverse relationship exists between titer of anti-MBL and the functional activity of MBL.

Takahashi et al found elevated anti-MBL levels in sera 9 of 111 SLE patients, compared to 2 of 113 healthy controls [38]. There was no significant relationship between the levels of anti-MBL and serum MBL concentration. Interestingly, not only subjects with MBL genotype AA, but also some subjects with genotype AB had elevated anti-MBL activity. They were not able to link the presence of anti-MBL to clinical parameters or features of SLE, including malar rash, photosensitivity, arthritis, serositis, renal disorders, neurological disorders, hematologic disorders or titers of other commonly measured autoantibodies such as anti-nuclear antibody, anti-DNA antibody, anti-Sm antibody and antiphospholipid antibody. In addition, no apparent relationship between positivity of anti-MBL and episode of infection was noticed. However, as only 9 patients were positive for anti-MBL in this study, it is too early to conclude that anti-MBL do not have any clinical significance.

A recent study by Mok et al also searched for anti-MBL in sera of SLE patients. In their cohort of 135 SLE patients, 32(23.7%) were positive for IgG anti-MBL [39]. They also reported the presence of IgM class anti-MBL in a small fraction of SLE patients. Differing from the study by Takahashi et al, they

noticed a significant positive relationship between the levels of serum MBL and titers of IgG anti-MBL, in patients positive for anti-MBL. However, similar to the study by Takahashi et al, they were also unable to find any relationships between serum anti-MBL levels and various parameters including overall disease activity, alopecia, cerebral involvement, autoimmune hemolytic anemia, oral ulceration, photosensitivity, polyarthralgia, renal involvement, serositis, skin rash, thrombocytopenia, and autoantibodies such as antinuclear antibody, anti-Sm, anti-RNP, anti-SS-A, anti-SS-B and anti-DNA antibodies.

The differences in the prevalence of anti-MBL in the studies by Takahashi et al [38] and Mok et al [39] may partly explained by the cut off levels used by these studies. While the study by Takahashi et al used mean + 2SD of values from healthy individuals, the study by Mok et al used 90 percentile of values from healthy subjects. If the cut off level for anti-MBL positivity was set at 90 percentile of values from healthy subjects in the study by Takahashi et al, the prevalence of anti-MBL in SLE patients would have been similar to that obtained in the study by Mok et al. At this stage, the prevalence and significance of anti-MBL autoantibody in patients with SLE still remains obscure.

Future prospective

A number of studies have established the relationship between the OO genotypes of the MBL gene and SLE. However, the mechanism by which this association occur is not clearly elucidated. In addition, The relationship between serum MBL levels and occurrence, progression and complications of SLE, and the value of serum MBL measurement in a clinical setting has not been clearly established. A cohort study in a larger scale is necessary to determine the clinical value of MBL gene typing or serum MBL measurement in a clinical setting. Mbl typing seems to be more promising at this time, but measurement of serum MBL by enzyme immunoassays would be more convenient. The significance of fluctuation in the levels of serum MBL in individual SLE patients is also still unclear. Whether MBL deficiency or presence of anti-MBL is associated with various complication of SLE, or with particular vascular involvements should also be addressed in a large cohort of patients. A clear knowledge of these issues may aid in improving the prognosis of SLE patients.

Furthermore, solid understanding of the role of MBL in various conditions will aid to assess whether some patients will benefit from MBL replacement, or measures to inhibit the action of MBL.

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