表 1　MCTD 診断の手引き（1996 年改訂）

MCTD の概念：SLE，SSc，PM/DM などにみられる症状や所見が混在し，血清中に抗 U1 RNP 抗体がみられる疾患である．

Ⅰ．共通所見	1．レイノー現象
	2．指ないし手背の腫脹
Ⅱ．免疫学的所見	抗 U1 RNP 抗体
Ⅲ．混合所見	
A．SLE 様所見	1．多関節炎
	2．リンパ節腫脹
	3．顔面紅斑
	4．心膜炎または胸膜炎
	5．白血球減少（4,000/μl 以下）または血小板減少（10 万/μl 以下）
B．SSc 様所見	1．手指に限局した皮膚硬化
	2．肺線維症，拘束性換気障害（%VC ＝ 80% 以下）または肺拡散能力低下（% DLco ＝ 70% 以下）
	3．食道蠕動低下または拡張
C．PM 様所見	1．筋力低下
	2．筋原性酵素（CK）上昇
	3．筋電図における筋原性異常所見

診断：1．Ⅰの 1 所見以上が陽性．
2．Ⅱの所見が陽性
3．ⅢのA，B，C 項のうち，2 項以上につき，それぞれ 1 所見以上が陽性．以上の 3 項を満たす場合を MCTD と診断する．

（厚生労働省 MCTD 班）

表 2　MCTD における肺高血圧症（PH）診断の手びき

Ⅰ．臨床および検査所見
1）労作時の息切れ
2）胸骨左縁収縮性拍動
3）第Ⅱ肺動脈音の亢進
4）胸部 X 線像で肺動脈本幹部の拡大あるいは左第 2 弓突出
5）心電図上右室拡大あるいは右室負荷
6）心エコー上右室拡大あるいは右室負荷
Ⅱ．肺動脈圧測定
1）右心カテーテルで肺動脈平均圧が 25 mmHg 以上
2）超音波ドプラ法による右心系の圧が右心カテーテルの肺動脈平均圧 25 mmHg 以上に相当

診断：MCTD の診断基準を満たし，Ⅰの 4 項目以上が陽性，あるいはⅡのいずれかの項目が陽性の場合，PH ありとする．Ⅰの 3 項目陽性の場合，PH 疑いとする．
除外項目：1）先天性心疾患，2）後天性心疾患，3）換気障害性肺性心

（西間木友衛：リウマチ 31：159－166，1991）

各疾患の組み合わせはさまざまであるが，SLE と SSc の組み合わせが最も多い．女性に多く 40 歳代に高頻度（MCTD とほぼ同じ年齢，性別分布）である．

② 診断のポイント

SLE，SSc，PM の分類（診断）基準に従う．

③ 治療のしかた

病型に応じて治療を選択する．MCTD に比して OL の予後は不良である．

【諏訪　昭】

疾患と治療 9

二次性アミロイドーシス

- AA蛋白の沈着により臓器障害をきたす予後不良な病態であり，関節リウマチ(RA)の合併症として重要である．
- 十二指腸粘膜生検でのAA蛋白検出の診断的意義が高い．
- RAの治療に加え，免疫抑制薬・調節剤，ステロイド薬投与や，対症療法として透析療法，中心静脈栄養，抗生物質投与を行う．

1 症　状

a. 疾患概念

AA蛋白が身体諸臓器の間質に沈着することにより機能障害を起こす．二次性アミロイドーシスの基礎疾患として，RAは重要である．アミロイドーシス発症例では，RA進行例が多い．

b. 臨床症状

初期症状は，消化器症状(下痢，腹痛，悪心，嘔吐，腹部膨満感)，腎症状(腎機能障害，蛋白尿，血尿)，心症状(心不全，高血圧，不整脈)，その他の症状(体重減少，発熱，貧血，甲状腺機能低下)である．経過中，心不全，腎障害は進行し，腎不全に至る．低蛋白血症，から敗血症や肺炎を併発する．主な死因は，腎不全，心不全と感染症である．

2 診断のポイント

消化管や腎生検によりAA蛋白を証明する．光学顕微鏡では，AA蛋白はコンゴレッド染色により，燈赤色に染まる．偏光顕微鏡では，AA蛋白は緑色複屈折性を示し，過マンガン酸処理によってその染色性と複屈折性が消失する．

1) 上部消化管内視鏡検査

十二指腸第2部でのAA蛋白の陽性率が高く，同粘膜生検が最も優れたスクリーニング法である．無症候でもアミロイド沈着が証明される例もある．

2) 尿検査

蛋白尿，血尿．

3) 心電図

肢誘導低電位差，$V_{1\text{-}3}$誘導のQSパターン，左軸偏位，心房細動，刺激伝導障害．

3 治療のしかた

a. RAの治療

NSAIDs，DMARDSによるRAの炎症のコントロールが重要である．

b. 二次性アミロイドーシスに対する治療

1) 免疫抑制薬・調節剤

リウマトレックス，ブレジニン，イムラン，エンドキサンなどを投与する．

[処方例]

- リウマトレックス　4～8mg/週

2) ステロイド薬

プレドニン5～10mg/日やステロイドパルス療法を行う．

[処方例]

- ソル・メドロール1g/日，静注，連続3日間
- その後プレドニゾロン60mg/日（約1mg/体重kg)(分3)，毎食後，

c. 対症療法

腎不全に対して血液透析を行う．絶食と中心静脈栄養により腸管の安静を図り，水分，カロリー補給，電解質補正を行う．低蛋白血症に対して蛋白製剤を投与する．下痢症状に止痢剤はしばしば無効で，サラゾピリンが有効なこともある．貧血に対して輸血を行う．感染症に対して抗生物質を投与する．

【諏訪　昭】

疾患と治療 10

成人 Still 病

○成人 Still 病(ASD)は，若年性関節リウマチの急性発症型(Still 型)が成人に発症したもの．
○発熱，関節痛，定型的皮疹を特徴とする．
○不明熱の鑑別として重要．

1 症　状

1) 発熱

弛張熱が突然出現し，数時間で消失する．

2) 関節痛，関節炎

近位指節間(PIP)関節，中手指節間(MP)関節，手，膝，股，肩関節にみられる．一過性のこともあるが，慢性関節炎もある．

3) 定型的皮疹

有熱時に体幹や四肢近位部にサーモンピンクの皮疹が出現し，解熱時には消失する．皮膚を線状に強くこすると，その線上に断続的な隆起疹がみられる(ケブネル現象)．

2 診断のポイント

膠原病，悪性腫瘍，感染症を除外する(表 1)．

3 治療のしかた

a. NSAIDs

NSAIDs を用いる．NSAIDs による肝不全や血管内凝固症候群に注意する．

[処方例]
○ロキソニン 180 mg/日(分 3，毎食後)

b. ステロイド薬

半数以上の例ではステロイド薬を要する．少数例では，プレドニゾロン少量でも有効であるが，無効例では大量投与を行う．

c. DMARDs

[処方例]
○プレジニン 150 mg/日(分 3，毎食後)
○リウマトレックス 4～8 mg/週

表 1　成人 Still 病の診断基準

【診断項目】		
1) 大基準	a)	39℃ 以上の発熱が 1 週間以上持続する
	b)	2 週間以上持続する関節痛
	c)	定型的皮疹
	d)	白血球増多：10,000/μl 以上，顆粒球 80％以上
2) 小基準	a)	咽頭痛
	b)	リンパ節腫脹
	c)	肝機能障害
	d)	RF や抗核抗体が陰性
3) 除外疾患	a)	感染症(特に敗血症，伝染性単核症)
	b)	悪性腫瘍(特に悪性リンパ腫)
	c)	リウマチ性疾患(特に結節性多発動脈炎，関節外症状を伴うリウマチ性血管炎)
4) 参考項目	フェリチンが高値(正常の 5 倍以上)を示す	

【判定】大基準 2 つ以上を含む 5 項目以上の大・小基準を満たし，除外項目を否定できる場合成人 Still 病と診断する．

(厚労省自己免疫疾患の病因・病態解析と新たな治療法の開発に関する調査研究班)

【諏訪　昭】

疾患と治療
15

リウマチ性多発筋痛症

- リウマチ性多発筋痛症(PMR)は，躯幹近位筋群の激しい痛みとこわばり，炎症反応亢進を主症状とする原因不明の炎症性疾患．
- 高齢者に好発する．
- 側頭動脈炎(TA)を合併しやすい．

1 症　状

発症年齢は60歳以上で，平均70歳である．女性に多い(男女比は1:2)．筋症状は，躯幹近位筋(項頸部，肩甲帯，上腕，腰背部，大腿)にみられる．筋痛(自発痛，運動痛，把握痛)とこわばりが主で，原則として筋力低下，筋萎縮はない．症状は急激に発症し，通常は対称性である．肩関節痛がしばしばみられ，まれに関節炎を伴う．発熱，体重減少，全身倦怠感を認める．

2 診断のポイント

a. 検　査

赤沈亢進(＞40mm/時)，CRP上昇(＞10mg/dl)を特徴とする．白血球増加，貧血，血小板増加もみられるが，筋原性酵素は正常である．リウマトイド因子や抗核抗体は陰性で，X線所見も正常である．

b. 診　断

診断は，診断基準(表1)によるが，血清反応陰性RA，PM/DM，SLE，PN，線維筋痛症候群などの膠原病，悪性腫瘍，感染症などを鑑別する．PMRの20～30%にTAを合併し，TAの50～70%にPMRを合併する．

表1　PMRの診断基準

1. 両側性肩の疼痛および(または)こわばり
2. 発症2週間以内
3. 赤沈40mm/時以上
4. 朝のこわばり1時間以上
5. 年齢65歳以上
6. うつ状態および(または)体重減少
7. 両側性上腕部圧痛

上記診断基準項目7項目中3項目を満足する場合，または少なくとも1項目と側頭動脈炎を示す臨床的あるいは病理組織学的異常が共存する場合にはprobable PMRとしてよい．

3 治療のしかた

ステロイド薬が奏功する．奏功しない場合は診断を疑う．初期量として少量(プレドニゾロン10～20mg/日)を2～4週間継続．臨床症状・検査所見を参考に，以後2～4週毎に10%ずつ減量する．維持量(5mg/日)を1～2年間継続する．ステロイド中止可能例と長期治療を要する例や再発例もある．TA合併例ではステロイド大量療法を行う．

[処方例]
- プレドニゾロン20mg/日(分3)
- タケプロン15mg/日(分1，朝食後)

▽トピックス▽

【線維筋痛症候群】
筋・骨格系など関節外組織の疼痛とこわばり，疲労感を主症状とする症候群である．基礎疾患のない場合，臨床検査で特徴的な異常はみられず，自覚症状と触診による特異的部位での圧痛点から診断される．抗炎症療法は無効で，抗うつ薬や睡眠薬が，顕著な症状である睡眠障害による疲労に有効である．

【諏訪　昭】

膠原病に伴う肺障害

pulmonary disorders in collagen vascular disease

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病態と診断

膠原病における肺障害は高頻度で，肺胞・間質性病変，気道病変，血管病変，胸膜病変など多彩である．各疾患における肺障害の頻度や臨床像は異なり，原因も原病，感染症，薬剤など多岐にわたる．肺障害の診断と活動性評価は，臨床所見，血液検査（SP-A，SP-D，KL-6），画像（胸部X線，CT，Gaシンチ），肺機能検査，気管支肺胞洗浄液検査，肺生検（経気管支/胸腔鏡下/開胸）による．

治療方針

A. 間質性肺炎

臨床像より慢性型，亜急性-急性型，急速進行型に分けられ，組織学的にはDAD（diffuse alveolar damage），COP（cryptogenic organizing pneumonia），UIP（usual interstitial pneumonia），LIP（lymphocytic interstitial pneumonia），NSIP（non-specific interstitial pneumonia）などに分類され，治療反応性や予後が異なる．特発性IPに比べ臨床像・病理組織像も多様である．活動性症例にステロイドを用い，重症例や治療抵抗例ではステロイドパルス療法や免疫抑制薬を併用する．

1. 軽症，慢性例　自然軽快例や，強皮症（SSc），多発性筋炎/皮膚筋炎（PM/DM），関節リウマチ（RA）には治療を要しない慢性例もある．

2. 亜急性-急性例　RA，全身性エリテマトーデス（SLE），PM/DM，重複症候群/MCTDなどの活動性症例でステロイド療法を行う．COPやNSIPの反応性は高い．

Rp 処方例

プレドニゾロン錠（5 mg）　6-12錠　分3　食後

3. 急速進行性間質性肺炎　筋症状の乏しいamyopathic DM，RA，SLEにみられる予後不良な病態であり，ステロイドパルス療法または免疫抑制薬併用を行う．

Rp 処方例　1）を用い，効果不十分の場合には下記2）または3）を併用する．

1）ソル・メドロール注　1回1,000 mg　1日1回を5%ブドウ糖注射液500 mLに混和し1時間以上かけて点滴静注　3日間　（保外）．後療法としてプレドニゾロン錠1 mg/kg/日を投与する．

2）エンドキサン注　1回0.5-1.0 g/m²　1日1回をソリタ-T3号注500 mLに混和し2時間以上かけて点滴静注（2-4週間ごと）　（保外）．十分な飲水または補液により出血性膀胱炎を予防する．

3）ネオーラルカプセル（25 mg）　2-6カプセル　分2-3　食後　（保外）．血中濃度トラフ値100-150 ng/mL程度とする．

B. 肺胞出血

SLEや血管炎（特にMPO-ANCA陽性例）にみられる予後不良な病態である．急性呼吸不全，進行性貧血，胸部X線上両側びまん性スリガラス様陰影を呈する．ステロイドパルス療法，シクロホスファミドパルス療法，血漿交換療法を行う．

C. 肺高血圧症

皿複症候群/MCTD，強皮症，SLEなどで認める難治性病態である．労作時呼吸困難，第II肺動脈音亢進，胸部X線/CT検査で肺動脈本幹部拡大，左第2弓突出，心電図検査で右室負荷・肥大，右房負荷所見を認め，肺機能検査，ドプラ心エコー検査，右心カテーテル検査，肺換気シンチにより診断する．PGI_2経口薬，Ca拮抗薬，抗凝固療法，抗血小板薬を用い，NYHA分類III度以上ではエンドセリン受容体拮抗薬やPGI_2（エポプロステノール）持続静注療法を考慮する．早期例には免疫抑制療法が有効な場合がある．

Rp 処方例　下記のいずれか，または適宜組み合わせて用いる．

1）ドルナー錠（20 μg）　6-9錠　分3　食後　（保外）

2）カルスロット錠（20 mg）　1錠　分1　食後　（保外）

3）ワーファリン錠　1-3 mg　分1-2　食後　（保外）

4）プレタール錠（100 mg）　2錠　分2　食後　（保外）

5）ドラクリア錠（62.5 mg）　2-4錠　分2　食後

D. 薬剤性肺障害

抗リウマチ薬〔メトトレキサート（MTX），レフルノミド，金製剤，ブシラミン，サラゾスルファピリジン〕は肺障害を惹起する．MTX肺炎は用量非依存的で，高齢，糖尿病，IP，薬剤過敏症はリスクとなる．MTX中止後ステロイド大量療法（パルス療法）を行う．レフルノミド肺炎ではクエストラン投与を行う．

E. 胸膜炎

中等量ステロイドを投与する．

■患者説明のポイント

- 原病・治療薬により免疫能が低下するため，感染に注意するよう指導する．
- 急激な咳嗽，呼吸困難を認めたら，直ちに受診させる．
- ステロイドや免疫抑制薬の効果，副作用〔感染症（日和見感染），肝脱障害，糖尿病，高血圧，高脂血症，骨粗鬆症，精神症状，眼症状，腎障害など〕についてよく説明する．
- 服薬方法を遵守し，自己判断で服薬を変更・中止しないよう指導する．

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Association between autoantibodies to the Ku protein and DPB1*

The Ku protein, a heterodimer consisting of 70-kd (p70) and 80-kd (p80) polypeptide subunits, binds free ends of double-stranded DNA (dsDNA). Once associated with DNA it creates a binding site for the catalytic subunit of the holoenzyme known as DNA-dependent protein kinase. This enzyme is essential for repairing dsDNA breaks that occur during radiation injury and V(D)J recombination (1).

Autoantibodies to the Ku protein were identified originally in 9 individuals among a randomly selected group of 330 Japanese patients (3%) with various connective tissue diseases studied with a classic immunodiffusion assay. Six of the patients who tested positive for autoantibodies came from a subgroup of 11 individuals (55%) with polymyositis–scleroderma (PM–scleroderma) overlap syndrome (2).

A somewhat different picture of anti-Ku autoantibodies emerged from studies of patients in the US. Reeves observed anti-Ku autoantibodies in the sera of 39% of patients with systemic lupus erythematosus (SLE), 55% of patients with mixed connective tissue disease, and 40% of patients with scleroderma, using an enzyme-linked immunosorbent assay (3). These antibodies also appear to be much more common among African American patients than white patients with SLE (4). Using immunoprecipitation assays, Francoeur et al observed anti-Ku antibodies in 10% of patients with SLE and in no samples obtained from patients with scleroderma (5). These observations suggest that anti-Ku antibodies have unique clinical associations in different racial groups, but further studies applying the same assay systems to different populations simultaneously will be required to confirm this speculation.

In the last several years, it has become clear that autoantibodies to nucleoproteins are antigen driven and require T helper cell support. Therefore, variations of autoantibody correlations in different patient groups seem likely to reflect racial differences in distribution of major histocompatability complex (MHC) phenotypes and the pattern of peptide antigens that are presented to T cells. We have now explored this idea through a genotypic analysis of all patients with anti-Ku autoantibodies at our institution in Japan.

A total of 750 Japanese patients were screened for autoantibodies in a radioimmunoprecipitation assay (6), and 21 were found to have anti-Ku autoantibodies. The presence of these antibodies was confirmed in an immunoblot assay using extracts of HeLa cells. The clinical diagnosis was established from a review of the medical record (Table 1). None of these patients had familial relationships. Clinically, 13 patients had PM or overlap syndromes with myositis (5 had PM–scleroderma, 4 had PM–scleroderma–SLE overlap, 2 had PM–SLE overlap, and 2 had PM), 5 had SLE, 2 had autoimmune hepatitis, and 1 had scleroderma according to established classification criteria (7–10). Forty-six healthy unrelated Japanese individuals served as control subjects. The HLA class II (DRB1, DQA1, DQB1, and DPB1) alleles were identified from restriction fragment length polymorphisms of polymerase chain reaction–amplified genomic DNA (11).

The HLA class II genotypes of all 21 patients are shown in Table 1. DRB1*0901 (62% of subjects versus 28% of controls; $P = 0.009$, odds ratio [OR] = 4.1), DQA1*0302 (62% versus 59%), and DQB1*0303 (62% versus 30%) were elevated in the study group, but none of these associations were statistically significant. However, DPB1*0501 was present in all patients with anti-Ku autoantibodies, compared with 59% of control subjects. This association was significant ($P = 0.0016$, OR 30) and remained significant ($P = 0.03$) when corrected for the number of alleles examined. Thirteen of the 21 patients (62%) with anti-Ku antibodies had myositis. Ten of these individuals (77%) had the class II haplotype of DRB1*0901-DQA1*0302-DQB1*0303, compared with 38% of anti-Ku–positive patients without myositis and 28% of controls ($P = 0.004$, OR 8.5). Four patients were homozygous for DRB1*0901, DQA1*0302, and DQB1*0303, but we found no indication of more severe disease in this group.

Studies of HLA associations with anti-Ku autoantibodies are limited. Yaneva and Arnett reported that the HLA class II antigen DQw1 was present in 17 of 19 anti-Ku positive patients (89%), compared with its frequency in local white (58%) and African American (61%) controls ($P = 0.01$, relative risk 5.8) (12). Although this allele occurs at increased frequency in patients with SLE, it is not associated with myositis and scleroderma. In the present study, the most striking finding is the universal occurrence of DPB1*0501 in 21 consecutive patients with anti-Ku autoantibodies. The DRB1*0901-DQA1*0302-DQB1*0303 haplotype also correlates with myositis in this patient cohort. Both DPB1*0501 and the DRB1*0901-DQA1*0302-DQB1*0303 haplotype are more common in the Japanese population than in the white population (13). It should be noted that DPB1*0501 is also a risk factor for Graves' disease in Japan (14). These findings suggest that there is a common immunogenetic background for Graves' disease and the anti-Ku autoimmune response. Therefore, these associations help to rationalize the earlier findings that anti-Ku autoantibodies are more clearly associated with myositis among the Japanese population.

Among the patients studied here, 9 had PM–scleroderma overlap syndrome with anti-Ku antibodies but none had the anti–PM-Scl, specificity. In the US population, ~10% of patients with this syndrome develop anti–PM-Scl. We have examined >100 patients with this overlap syndrome, but none have had anti–PM-Scl, nor have any of the >3,000 patients screened in our clinical diagnostic laboratory. Therefore we believe this autoantibody is rare among Japanese individuals. An explanation may be that anti–PM-Scl antibodies have been linked with DR3, a phenotype that is uncommon in the Japanese population (13). In any case, the MHC phenotype appears to exert a stronger influence over expression of specific autoantibodies than over the emergence of individual autoimmune syndromes. Further studies including analysis of MHC-restricted T cell responses could provide important clues for understanding mechanisms of onset of the PM–scleroderma overlap syndrome and the expression of anti-Ku antibodies.

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Table 1. HLA class II genes in Japanese patients with anti-Ku autoantibodies*

Patient no.	Diagnosis	DRB1*	DQA1*	DQB1*	DPB1*
1	PM/SSc	0405/1101	0303/0505	0401/0301	0501/0402
2	PM/SSc	0901/080302	0302/0103	0303/0601	0501/0202
3	PM/SSc	0901/080302	0302/0103	0303/0601	0501/0201
4	PM/SSc	0901/0405	0302/0303	0303/0401	0201/0501
5	PM/SSc	0901/0901	0302/0302	0303/0303	0501/0402
6	PM/SSc/SLE	0901/0901	0302/0302	0303/0303	0501/0402
7	PM/SSc/SLE	0901/1401	0302/0104	0303/0503	0501/0201
8	PM/SSc/SLE	0901/1502	0302/0103	0303/0601	0501/0901
9	PM/SSc/SLE	0901/0901	0302/0302	0303/0303	0501/0201
10	PM/SLE	0901/0901	0302/0302	0303/0303	0501/0201
11	PM/SLE	0405/0405	0303/0303	0401/0401	0501/0301
12	PM	0901/0802	0302/030101	0303/0302	0501/4101
13	PM	0405/1502	0303/0103	0401/0601	0501/0901
14	SLE	0901/1501	0302/0102	0303/0602	0501/0501
15	SLE	1501/0802	0401/0102	0302/0602	0201/0501
16	SLE	0405/080302	0303/0103	0401/0601	0501/0501
17	SLE	0901/080302	0302/0103	0303/0601	0501/0201
18	SLE	080302/1302	0103/0102	0601/0604	0501/0401
19	SSc	0405/0405	0303/0303	0401/0401	0501/0201
20	AIH	0802/0802	030101/030101	0302/0302	0201/0501
21	AIH	0901/0802	0302/030101	0303/0302	0501/0501

* PM = polymyositis; SSc = systemic sclerosis (scleroderma); SLE = systemic lupus erythematosus; AIH = autoimmune hepatitis.

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CASE REPORT

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Sensorimotor polyneuropathy as an initial clinical manifestation of sarcoidosis

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Abstract A 45 year-old Japanese woman developed numbness and tingling of both hands and feet. Electrophysiological examination revealed sensorimotor polyneuropathy. She was diagnosed as suffering from sarcoidosis on the basis of the pathological findings from dermal biopsy. Steroid therapy effectively improved the clinical symptoms. Although sarcoid neuropathy is rare, this case suggests sensorimotor polyneuropathy is an important symptom of sarcoidosis and can represent the initial clinical manifestation of the disease.

Key words Axonal degeneration · Electromyography (EMG) · Sarcoidosis · Sensorimotor polyneuropathy

Introduction

Sarcoidosis is a disorder of unknown cause, which affects multiple organs with formation of granulomatous lesions and causes many different clinical manifestations including neurological signs. Among its various manifestations, sarcoid neuropathy is a rare complication of sarcoidosis. Here, we report a Japanese patient with sarcoidosis who showed progressive gait disturbance due to sensorimotor polyneuropathy.

Case report

A 45-year-old Japanese woman developed numbness and tingling of both hands and feet in March 2000. Magnetic resonance imaging of the spine was performed at another hospital and no major abnormality was observed. In April, she began to have painful legs with difficulty in walking. She was referred to our outpatient clinic for further examination in June 2000. At the time of admission, she had fever at 37°C and had pain in her lower extremities. She was a housewife with no alcohol habit and had never been exposed to any toxic chemical materials. On physical examination, there was slight edematous erythema in her feet. However, there was no facial erythema, xerostomia, scleroderma, muscle atrophy, or subcutaneous nodules. Neurological examination revealed symmetric muscle weakness in the plantar extensors and flexors, iliopsoas, hamstrings, and gastrocnemius muscles graded as 3–4/5, as well as painful paresthesia. Cutaneous sensation was impaired in glove and stocking distribution to the ankles and wrists. Brachioradialis and Achilles tendon reflexes were absent. However, there were no cranial nerve abnormalities.

Laboratory findings (Table 1) showed an erythrocyte sedimentation rate (ESR) of 39 mm/h; there was a normal urinalysis and blood count with no eosinophilia. Liver and renal functions were normal. The serum creatine kinase, calcium, vitamin B_{12}, and folic acid values were within the normal range. Serum angiotensin-converting enzyme (ACE) was 23.6 IU/l (normal 7.7–29.4 IU/l), but lysozyme was elevated to 12.5 μg/ml (normal 4.2–11.5 μg/ml). Hypergammaglobulinemia was found and C-reactive protein was slightly elevated to 0.24 mg/dl. Cryoglobulin, antineutrophil cytoplasmic autoantibodies (PR-3 ANCA, MPO-ANCA), and immune complexes were within normal limits. Anti-dsDNA, anti-SS-A, anti-SS-B, anti-RNP, anti-Jo-1 antibodies, and the tuberculin skin test were all negative.

In nerve conduction studies in June 2000 (Table 2), distal motor latencies were prolonged in the median and ulnar nerves. Compound muscle action potentials (CMAPs) were very low in amplitude in the tibial and peroneal nerves, and temporal dispersion and conduction block were not detected. Sensory nerve action potentials (SNAPs) of the median nerve were also low in amplitude. However, motor and sensory conduction velocities were relatively preserved

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Table 1. Laboratory data on admission

ESR	39 mm/h	Blood chemistry		Immunological	
Urinalysis		TP	7.0 g/dl	IgG	1880 mg/dl
Protein	(–)	Alb	3.6 g/dl	IgA	501 mg/dl
Sugar	(–)	BUN	12.3 mg/dl	IgM	245 mg/dl
Cast	(–)	Cre	0.6 mg/dl	CRP	0.24 mg/dl
CBC		Ca	9.2 mg/dl	C3	65 mg/dl
WBC	4400/μl	IP	3.1 mg/dl	C4	17 mg/dl
	(Band+Seg 65, Lymph 20, Mono 9, Eosino 5, Baso 1)	LDH	218 IU/l	IC (Anti-C3d)	11.8 μg/ml
RBC	4.02×10^6/μl	ALT	36 IU/l	RF	<10 IU/ml
Hb	12.2 g/dl	AST	31 IU/l	ANA	(–)
Ht	37.2 %	CK	48 IU/l	Cryoglobulin	(–)
Plt	25.2×10^4/μl	FBS	91 mg/dl	PR3-ANCA	(–)
		ACE	23.6 IU/l	MPO-ANCA	(–)
		Lysozyme	12.5 μg/ml	Anti-dsDNA	(–)
		Vitamin B_{12}	1090 pg/dl (233–914)	Anti-U1RNP	(–)
				Anti-SSA	(–)
				Anti-SSB	(–)
				Anti-Jo-1	(–)

IC, immune complex

Table 2. Nerve conduction studies

	June 2000	January 2001	January 2003
Median nerve (rt)			
DLT (ms)	6.8	4.2	4.7
CMAP (mV)	4.0	9.9	13.4
MCV (m/s)	50.0	48.7	47.3
SNAP(μV)	12	18	49
SCV (m/s)	29.2	42.4	42.4
Ulnar nerve (rt)			
DLT (ms)	5.2	3.7	4.4
CMAP (mV)	7.0	17	18
MCV (m/s)	52.5	52.5	48.6
Tibial nerve (rt)			
DLT (ms)	N.E.	5.1	4.1
CMAP (mV)	N.E.	4.0	15.2
MCV (m/s)	N.E.	38.6	43.7
Peroneal nerve (rt)			
DLT (ms)	5.3	4.8	5.4
CMAP (mV)	0.2	–	64
MCV (m/s)	42.8	40.7	41.7

DLT, distal latency time; CMAP, compound muscle action potential; MCV, motor conduction velocity; SNAP, sensory nerve action potential; SCV, sensory conduction velocity; N.E., not evoked

in all nerves tested. In needle electromyography, denervation potentials were observed in the distal muscles. These findings were compatible with sensorimotor polyneuropathy due to axonal degeneration rather than segmental demyelination.

Slit-lamp biomicroscopy revealed that the patient had uveitis. Swelling of bilateral hilar lymph nodes was observed by chest computed tomography (Fig. 1), and gallium scintigraphy disclosed abnormal uptake of bilateral hilar lymph nodes that was consistent with the finding of active sarcoidosis. The dermal biopsy of leg erythema showed non-caseating granuloma with infiltration of lymphocytes and a few giant cells, but no eosinophils (Fig. 2). Diseases possibly causing peripheral neuropathy due to axonal

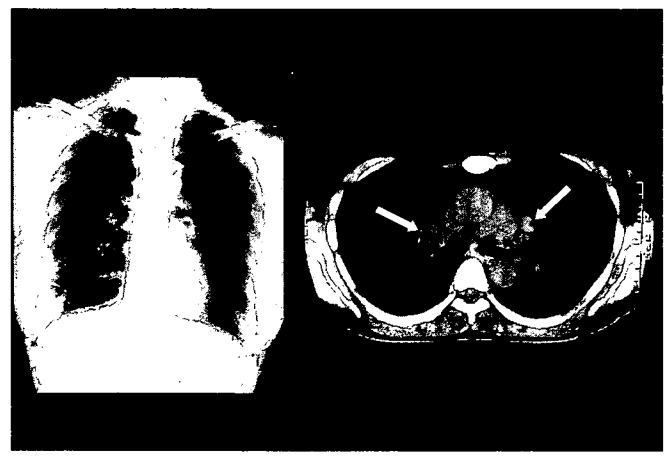

Fig. 1. Chest computed tomography findings on admission. Bilateral hilar lymphadenopathy was present (*arrows*)

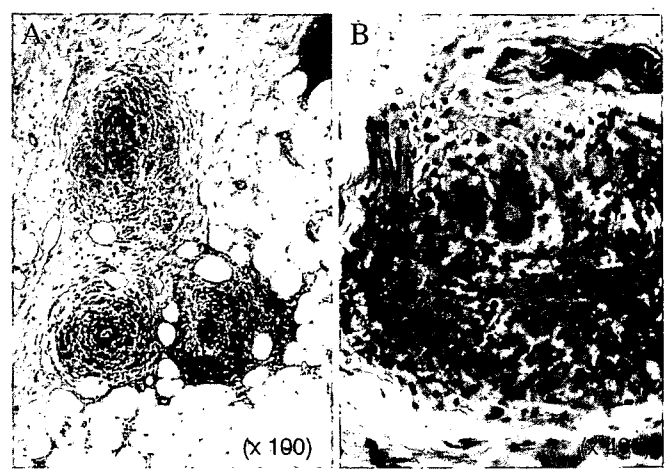

Fig. 2A,B. Histological sections of the erythematous dermal biopsy specimen (H&E staining; **A** ×100, **B** ×400). In higher magnification, non-caseating granuloma with infiltrating lymphocytes and a few giant cells are noted

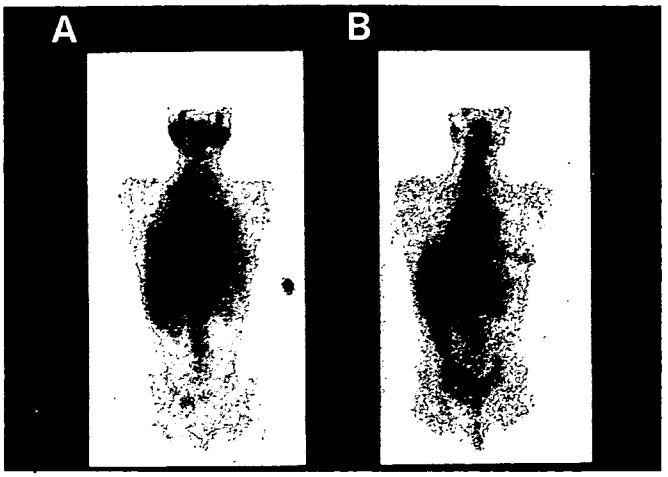

Fig. 3. Gallium scintigraphy of the whole body before (**A**) and after (**B**) steroid treatment. Abnormal uptake in the bilateral hilum improved markedly after treatment

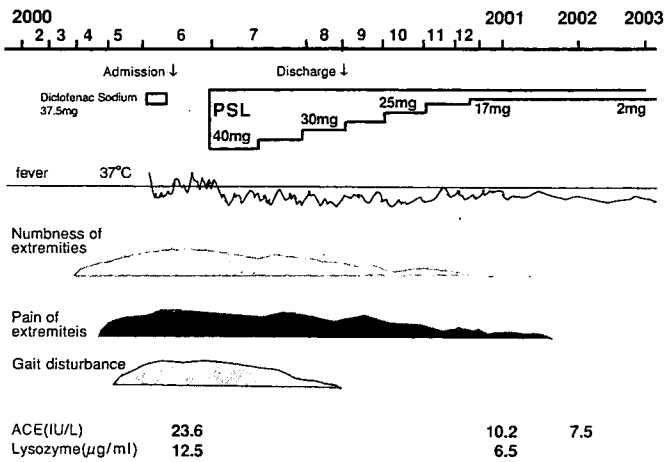

Fig. 4. Clinical course of this case. After prednisolone (*PSL*) treatment, numbness and pain of the extremities and gait disturbance were improved. Serum levels of angiotensin-converting enzyme (*ACE*) and lysozyme were also decreased

degeneration, such as metabolic diseases, toxic diseases, chronic inflammatory demyelinating polyneuropathy, infectious diseases, Vitamin B_{12} deficiency, and other collagen diseases, were all absent.

In July 2000, the diagnosis of sarcoidosis was made and the patient was started on 40mg daily of prednisolone (PSL), resulting in partial improvement of numbness and painful difficulty in walking. The following nerve conduction studies in January 2001 and January 2003 showed a marked improvement in CMAPs in the median, ulnar, tibial, and peroneal nerves, and SNAPs in the median nerve (Table 2). Abnormal uptake in the bilateral hilum also improved greatly after treatment (Fig. 3). Although the PSL dose was tapered gradually, her symptoms of peripheral neuropathies have been well controlled for 3 years. She continued to take the low dose of PSL (2mg daily) with no severe adverse events (Fig. 4).

Discussion

This is a case of sarcoidosis that showed sensorimotor polyneuropathy as an initial clinical manifestation. Neurological involvement in sarcoidosis has been reported to occur in 5%–15% of cases.[1,2] Moreover, in the context of neurological involvement, the prevalence of peripheral neuropathy including cranial nerve abnormality is estimated to occur in 4%–14% of cases,[3] although a recent study reported a higher incidence of peripheral nerve involvement.[4]

Previous studies have reported similar cases of sarcoidosis indicating spinal peripheral neuropathy (Table 3).[5–13] Of these, clinical features of 16 cases, including ours, are available for comparison. Ten of these 16 patients (63%) presented with peripheral neuropathy associated with sarcoidosis as an initial manifestation.[5–10,13] Thirteen (81%) cases had pulmonary symptoms during their course.[5,7–9,11–13] All patients were given corticosteroid therapy with improvement of their symptoms with only one exception. The patterns of neuropathy were variable, as seen in the previous studies.[4,6] Eight of 16 (50%) had sensorimotor polyneuropathy, four (25%) multifocal sensorimotor neuropathy, three (19%) multifocal sensory neuropathy, and one (6%) multifocal motor neuropathy.

The previous reports[1,6,7,11,12] indicated that sarcoidosis could elicit both compressive neuropathy due to perineural granuloma formation and ischemic neuropathy due to periangitis. Typically, complete compression causes Wallerian degeneration followed by demyelination, while vasculitis induces segmental demyelination first because Schwann cells are more vulnerable to ischemia. Although we did not perform sural nerve biopsy, the electrophysiological findings suggested that the main mechanism involved in this case was axonal degeneration. It is likely that sarcoid nodules observed in the specimen of skin biopsy compress the myelinated and unmyelinated neural fibers. Moreover, granulomatous vasculitis or vessel occlusion due to granulomas might also be involved in the neurological manifestations. In general, neuropathies due to vasculitis indicate mononeuritis multiplex. However, symmetrical polyneuropathy was also seen in previous reports.[5–7,14] Our case suggested symmetrical sensorimotor polyneuropathy. This might have been due to the severity and duration of the disease or the effects of systemic inflammation causing vasculitis.

We were able to perform nerve conduction tests before and after treatment. The electrophysiological parameters showed improvement after treatment. This suggests that nerve conduction studies are useful for evaluating the efficacy of treatment even when marked improvement of physiological symptoms is not seen.

Corticosteroid therapy is recommended for the peripheral neuropathy of sarcoidosis and is effective in most patients, although a placebo-controlled double-blind trial has not been performed. The improvement of electrophysiological parameters might be a consequence of the decreased ischemia due to vasculitis as well as reduction of

Table 3. Clinical manifestation of published neurosarcoidosis only manifesting the spinal peripheral neuropathy

First author/year[Ref.]	Age (years)/ sex	Initial manifestation	Pattern of neuropathy	Other symptoms	Therapy	Efficacy of PSL
Oh/1979[5]	58/F	Peripheral nerve	Sensorimotor polyneuropathy	Lung	100 mg	(+)
Nemni/1981[6]	29/F	Peripheral nerve	Sensorimotor polyneuropathy	(–)	150 mg every 2 days	(+)
Galassi/1984[7]	70/M	Peripheral nerve	Sensorimotor polyneuropathy	Lung	100 mg every 2 days	(+)
	54/M	Peripheral nerve	Sensorimotor polyneuropathy	Lung	High dose	(+)
Okada/1986[8]	25/M	Peripheral nerve Skin	Multifocal sensory neuropathy	Lung/skin/eye	60 mg every 2 days	(+)
Yamane/1986[9]	53/F	Peripheral nerve Skin	Sensorimotor polyneuropathy	Lung	40 mg	(–)
Krendel/1992[10]	39/F	Peripheral nerve Skin	Sensorimotor polyneuropathy	Skin	40 mg	(+)
Iwata/1993[11]	58/F	Lung	Multifocal sensory neuropathy	Lung/skin/eye	30 mg	(+)
Sharma/1996[12]	40/M	N.A.	Sensorimotor polyneuropathy	Lung/skin/heart	(+)	(+)
	33/M	N.A.	Multifocal motor neuropathy	Lung/skin/eye	(+)	(+)
	48/M	N.A.	Multifocal sensory neuropathy	Lung/lymph node	(+)	(+)
	50/M	N.A.	Multifocal sensory neuropathy	Lung	(+)	(+)
	46/F	N.A.	Multifocal sensory neuropathy	Lung/skin	(+)	(+)
Said/2002[13]	63/M	Peripheral nerve	Multifocal sensorimotor neuropathy	Lung	1 mg/kg	(+)
	69/M	Peripheral nerve	Multifocal sensorimotor neuropathy	(–)	(+)	(+)
Present study	45/F	Peripheral nerve Skin	Sensorimotor polyneuropathy	Lung/skin/eye	40 mg	(+)

N.A., not available

compression injury due to resolution of granulomatous lesions.

Sarcoidosis shows a wide variety of clinical features and its diagnosis is difficult in the absence of clinical manifestations such as cutaneous or pulmonary involvement. Any of the preceding neurologic manifestations can occur without any evidence of systemic features of sarcoidosis.[5–7,9,10] It is therefore important to consider the possibility of systemic disease including sarcoidosis even when only peripheral neuropathy is found.

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Vertebral Fracture and Bone Mineral Density in Women Receiving High Dose Glucocorticoids for Treatment of Autoimmune Diseases

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ABSTRACT. ***Objective.*** To evaluate the factors influencing the occurrence of vertebral fracture in patients receiving high dose glucocorticoids (GC).

Methods. A cross-sectional study was performed on women who had received at least 0.5 mg/kg of oral glucocorticoid for the treatment of autoimmune diseases for more than 1 month between 1998 and 2003. Logistic regression analysis and chi-square test were used to examine the effects of glucocorticoid dose and other factors on vertebral fractures. Receiver-operating characteristics curve (ROC) analysis was used to determine the bone mineral density (BMD) cutoff value for the risk of vertebral fracture.

Results. The study population comprised 160 women, including 35 with vertebral fractures. In ROC analysis, the BMD threshold of the risk of fracture for postmenopausal women (0.787 g/cm^2, T score −2.1) was lower than that for premenopausal women (0.843 g/cm^2, T score −1.7). Among patients with fractures, 7 of 16 premenopausal patients had normal BMD values (T score > −1), whereas only one of 19 postmenopausal patients showed a comparable level of BMD. Additionally, vertebral fracture was more frequent for patients with high total cholesterol values (> 280 mg/dl) than for those with normal total cholesterol values (< 220 mg/dl). Moreover, patients with high total cholesterol values had lower BMD values than those with normal total cholesterol values.

Conclusion. The fact that vertebral fracture frequently occurred in premenopausal patients with normal BMD and evidence that hyperlipidemia correlated with fracture suggest the pathology of vertebral fracture secondary to high dose glucocorticoid therapy is multifactorial and possibly involves lipid metabolism. (J Rheumatol 2005;32:863–9)

Key Indexing Terms:

OSTEOPOROSIS	VERTEBRAL FRACTURE	GLUCOCORTICOID
MENOPAUSE	BONE MINERAL DENSITY	HYPERLIPIDEMIA

Glucocorticoids are widely used for the treatment of a variety of autoimmune diseases. Even now, when various novel drugs for the treatment of these diseases are being introduced, glucocorticoids remain the main drugs of choice. However, it has been well established that the use of glucocorticoids can lead to rapid loss of bone mineral density

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(BMD) and to an increased risk of fracture[1]. Several epidemiologic studies have reported a doubling of the risk of hip fracture for users of glucocorticoids[2-4], while large-scale studies have demonstrated a rapid increase in fracture risk following the start of glucocorticoid therapy and a strong correlation of risk with daily glucocorticoid dose[4,5]. Other smaller studies have shown that the cumulative dose, rather than the daily dose, was the more reliable and accurate predictor of fracture[6,7]. When high dose glucocorticoids are used, the loss of bone such as vertebrae can be rapid and lead to vertebral compression fractures within a few months.

Glucocorticoids are also known to affect bone through various pathways, affecting mainly bone formation and, to a lesser extent, bone resorption[8,9]. Findings have been accumulating about the possible role of micro-architectural changes in glucocorticoid induced fracture, although fracture in glucocorticoid users may also occur simply as a result of bone loss. A recent hypothesis is that osteocyte apoptosis is an important factor in deterioration of bone quality and the concomitant rapid increase in the risk of fracture[10]. In addition, there is a report that glucocorticoid users with fracture had considerably higher BMD than patients with fracture due to primary osteoporosis[11]. These reports support the notion that a non-BMD-related mechanism may also be responsible for inducing fracture in users of glucocorticoids[12].

We conducted a multicenter, cross-sectional analysis, specifically investigating high dose glucocorticoid users treated for autoimmune diseases, to determine the BMD cutoff value for the risk of vertebral fracture, and to examine the correlation between glucocorticoid induced vertebral fracture or loss of BMD and multiple factors including menopause, glucocorticoid dose, and other glucocorticoid induced secondary complications.

MATERIALS AND METHODS

Study population of glucocorticoid users. Data on 160 Japanese women, aged 16–85 years and treated with glucocorticoids for autoimmune diseases, were collected from the rheumatology departments of 11 institutions that joined the Research Committee for Glucocorticoid-Induced Osteoporosis organized by the Japanese Ministry of Health, Labor and Welfare. This study was limited to patients who had been receiving oral glucocorticoid therapy (mean daily dose 0.5 mg/kg prednisone or equivalent) for at least 1 month between April 1998 and March 2003. The basic clinical data including risk factors and dose and duration of glucocorticoid therapy were collected retrospectively by treating physicians in reference to medical records from each institution, and the collected data were reviewed by the central committee for selecting eligible patients. As for treatment or prevention of osteoporosis, there were no restrictions for enrollment of patients based on protocols for the use of bisphosphonates, calcium, vitamin D, or other antiresorptive drugs. Diseases they were treated for included systemic lupus erythematosus (SLE; 79 cases), Sjögren's syndrome (15 cases), polymyositis (13 cases), mixed connective tissue disease (12 cases), adult onset Still's disease (8 cases), polymyalgia rheumatica (7 cases), dermatomyositis (6 cases), systemic sclerosis (5 cases), and others (15 cases). Patients with rheumatoid arthritis were excluded from this study.

BMD of the patients was assessed for the lumbar spine (L2–L4), femoral neck, and radial head by means of dual-energy x-ray absorptiometry (DEXA). Since the DEXA machines used for the measurement of BMD differed from hospital to hospital, the raw BMD values were converted to comparable values for the QDR-2000 (Hologic Inc., Waltham, MA, USA) as described[13]. High dose glucocorticoid therapy was defined as a mean daily dose > 0.5 mg/kg of prednisone or equivalent dose of other glucocorticoids for at least 1 month.

Vertebral fracture was confirmed radiologically by lateral radiographs of the thoracolumbar spine with the method established by Orimo, *et al*[14]; the presence of vertebral fracture was semiquantitatively confirmed if either the ratio of middle/anterior or middle/posterior height of a vertebral body was < 0.8, or the ratio of anterior/posterior height of a vertebral body was < 0.75. The judgment of fracture was double-checked by 2 examiners in each institution. If BMD was measured more than once in the same patient, the last BMD value was adopted for patients without vertebral fracture, and for patients with fracture, the BMD measured at the timepoint nearest the radiological confirmation of initial vertebral fracture was used.

The daily, cumulative, and maximum glucocorticoid doses, and the total duration (in days) of prior glucocorticoid therapy were also entered into the analysis. Clinical factors that may affect the occurrence of vertebral fracture, comprising age, body mass index (BMI), menopause, BMD (T scores), hypertension, total cholesterol, and HbA1c were evaluated. Diagnoses for hypertension and diabetes mellitus were determined according to American Heart Association[15] and American Diabetes Association[16] guidelines, respectively. Hyperlipidemia was diagnosed according to the criteria of the Japanese Atherosclerosis Society[17], in which total cholesterol level > 220 mg/dl is regarded as hyperlipidemia.

Statistical analysis. Logistic regression analysis was used to calculate the influence of various variables on vertebral fracture including age, BMI, menopause, BMD, and glucocorticoid related parameters. For determination of BMD cutoff values to identify women with vertebral fracture, sensitivity, specificity, and BMD cutoff values were calculated using receiver-operating characteristics curve (ROC) analysis. As for patients with vertebral fracture, the chi-square test was used to determine the difference in BMD between premenopausal and postmenopausal glucocorticoid users. P values < 0.05 were deemed to be statistically significant. The MedCalc statistical analysis software package (MedCalc Software, Mariakerke, Belgium) was used for statistical analyses.

RESULTS

Variables affecting vertebral fracture in high dose glucocorticoid users. For this study, 160 patients were assessed. The baseline information of enrolled patients is shown in Table 1. BMD values of this group negatively correlated with patients' age ($p < 0.001$, $r = -0.366$). A logistic regression analysis of patients with vertebral fracture (fracture group) and those without vertebral fracture (non-fracture group) is presented in Table 2. The respective mean BMD values of the fracture group (35 cases; 19 postmenopausal, 16 premenopausal) and the non-fracture group (125 cases) were 0.781 and 0.871 g/cm^2 ($p = 0.004$). There was a significant difference between the 2 groups in BMI and BMD, but no difference in age, ratio of menopause, and total glucocorticoid dose, as shown in Table 2. The logistic regression analyses including the other glucocorticoid related variables such as cumulative days of glucocorticoid use, mean glucocorticoid dose (daily), cumulative glucocorticoid dose, and maximal glucocorticoid dose showed no significant difference between the 2 groups (data not shown). The mean daily glucocorticoid dose for premenopausal women (age 34.9 ± 9.4 yrs) was 16.4 ± 16.5 mg/day and for postmenopausal

Table 1. Baseline characteristics of 160 patients in the study.

	Premenopausal	Postmenopausal	Total	p
Age, yrs, mean ± SD	34.9 ± 9.4	62.6 ± 9.9	47.9 ± 16.9	< 0.05
BMI, kg/m^2	21.7 ± 14.1	22.0 ± 3.5	21.9 ± 3.6	NS
BMD, g/cm^2	0.926 ± 0.149	0.767 ± 0.149	0.852 ± 0.168	< 0.05
Daily prednisolone dose*, mg/day	16.4 ± 16.5	10.7 ± 9.9	13.7 ± 14.1	< 0.05
Cumulative dose of prednisolone*, g	17.1 ± 31.3	8.2 ± 10.4	12.8 ± 24.0	NS
Duration of glucocorticoid treatment, days	1993.1 ± 2091.9	2069.9 ± 2317.4	2027.8 ± 2189.4	NS

* Adjusted to the dose equivalent to prednisolone. NS: not significant.

Table 2. Logistic regression analysis of treatment related variables and vertebral fracture in high dose user of glucocorticoid.

	Vertebral Fracture			
	Yes	No	Z	p
Age, yrs, mean ± SD	50.7 ± 3.2*	47.1 ± 1.4	0.5925	0.554
Menopause (%)	19/35 (54.3)	56/125 (44.8)	0.270	0.787
BMI	22.4 ± 0.8	21.8 ± 0.3	1.961	< 0.05
BMD, L2–4, g/cm^2	0.781 ± 0.033	0.871 ± 0.014	2.218	< 0.03
Total glucocorticoid dose*, g	24.3 ± 6.6	22.2 ± 4.4	0.789	0.430

* Adjusted to the dose equivalent to prednisolone.

women (age 62.6 ± 9.9 yrs) 10.7 ± 9.9 mg/day ($p < 0.05$). Compared to postmenopausal glucocorticoid users, premenopausal glucocorticoid users had significantly higher average BMD (L2–L4) in the lumbar spine, femoral neck, and radial head (data not shown).

For postmenopausal women, the mean BMD value of the fracture group was significantly lower than that of the non-fracture group ($p < 0.01$), as shown in Figure 1. In contrast, there was no significant difference in BMD values between the fracture group and non-fracture group among premenopausal women. Of special interest is that 7 of the 16 premenopausal patients (43.7%) in the fracture group showed normal values (T score > –1), whereas only one of the 19 postmenopausal patients (5.3%) did ($p < 0.01$). There was no statistically significant difference between the fracture group and non-fracture group for maximum glucocorti-

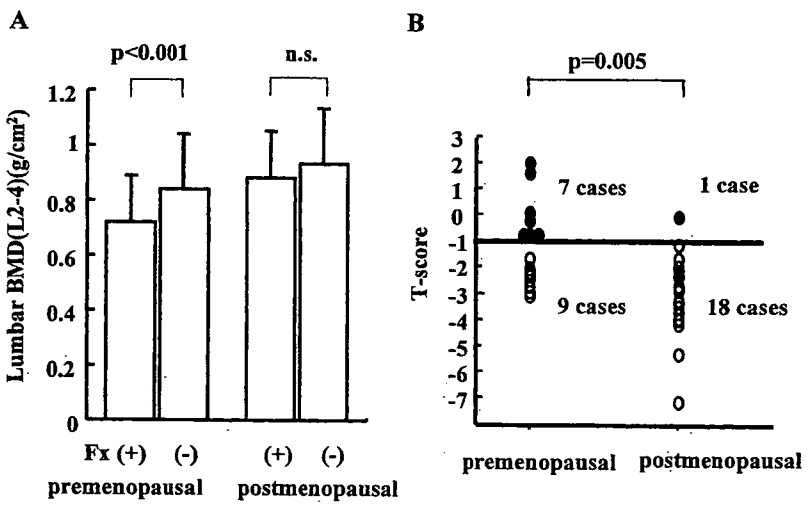

Figure 1. (A) Lumbar BMD from fracture (Fx) and non-fracture patient groups taking high dose glucocorticoids. There were significant differences in lumbar BMD between fracture and non-fracture groups in premenopausal women ($p < 0.001$), whereas no difference was detected between the 2 groups in postmenopausal women. ns: not significant. (B) T scores from premenopausal or postmenopausal women with vertebral fracture. Premenopausal glucocorticoid users frequently incurred vertebral fracture even when BMD was not reduced (T > –1) compared with postmenopausal women ($p = 0.005$). ●: fracture patients whose T scores were not reduced.

coid dose, mean daily glucocorticoid dose, disease background, and history of methylprednisolone pulse therapy in premenopausal women (data not shown).

BMD cutoff values for vertebral fracture in glucocorticoid users assessed by ROC analysis. ROC analysis was used to determine the BMD cutoff level for vertebral fracture in high dose glucocorticoid users. The cutoff values were defined as the values that proved to be effective for the sensitive and specific differentiation of subjects with and without vertebral fracture. As shown in Figure 2, the cutoff values for the risk of vertebral fracture for premenopausal, postmenopausal, and total patients were 0.843, 0.787, and 0.787 g/cm^2, respectively.

Hyperlipidemia correlates with BMD value and vertebral fracture. The influence of common glucocorticoid induced complications such as hyperlipidemia, diabetes mellitus, and hypertension on vertebral fracture were not entered into the logistic regression analysis, since those variables are not recognized as independent to glucocorticoid dose-related variables. Table 3 shows that hyperlipidemia has negative correlation with BMD, while HbA1c level did not correlate with BMD values. Nor did hypertension correlate with the level of BMD (data not shown). Then we compared patients with normal total cholesterol (< 220 mg/dl) value to those with above-normal values for further analysis. The peak value of total cholesterol after initiation of glucocorticoid therapy was used for the analysis in each patient. When we raised the comparative total cholesterol level to > 280 mg/dl, patients with high total cholesterol (> 280 mg/dl) value had lower BMD ($p = 0.016$) and higher risk of vertebral fracture (relative risk 3.1, $p = 0.032$) than those with normal total cholesterol level (Figure 3). These results suggest that hyperlipidemia following high dose glucocorticoid therapy may contribute to the risk for BMD reduction and vertebral fracture.

DISCUSSION

High dose glucocorticoid therapy is often the first choice for patients with autoimmune diseases, such as SLE, that frequently affect premenopausal women. Although the efficacy of bisphosphonate has recently been reported in high dose glucocorticoid users[18], there is only limited knowledge of the clinical risk factors for secondary osteoporosis occurring in high dose glucocorticoid users. This is the first extensive study focusing on the relationship of vertebral fracture and BMD in patients with high dose glucocorticoid therapy. We observed unique effects of high dose glucocorticoid therapy: First, the BMD cutoff value for the risk of vertebral fracture applicable to premenopausal glucocorticoid users was higher than that applicable to postmenopausal glucocorticoid users. Second, premenopausal glucocorticoid users, even with normal BMD values, were found to frequently incur vertebral fracture. Third, hyperlipidemia significantly correlated with vertebral fracture and low BMD.

ROC analysis showed that the BMD cutoff value for the risk of vertebral fracture for premenopausal women was 0.843 (T score = −1.7) and for postmenopausal women 0.787 (T score = −2.1). These cutoff values lie between 70% (T score = −2.6) and 80% (T score = −1.7) of the young adult

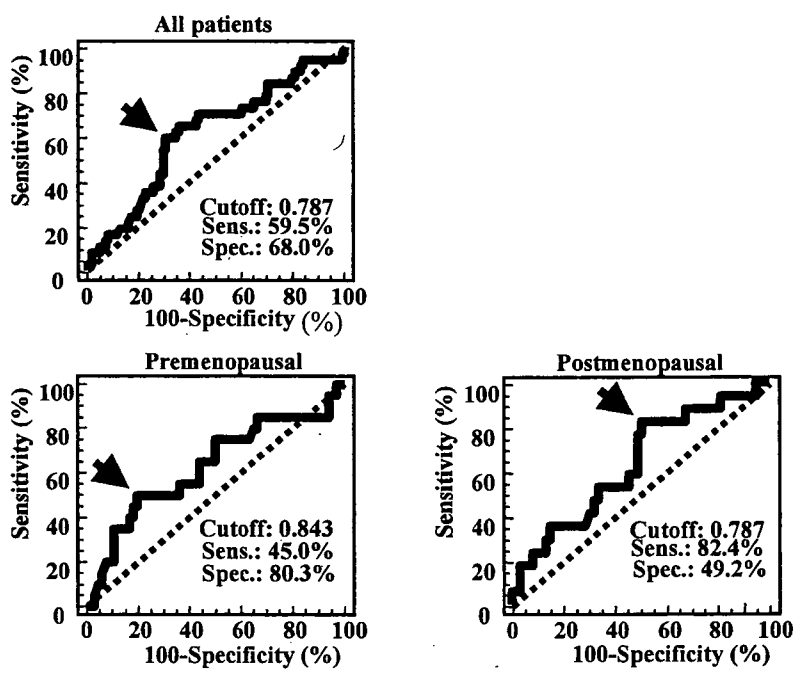

Figure 2. ROC analysis of lumbar BMD values for all patients, premenopausal and postmenopausal patients with vertebral fracture treated with high dose glucocorticoid. Arrows indicate cutoff points. Sens: sensitivity; Spec: specificity.

Table 3. The relationship between other glucocorticoid related complications and BMD or vertebral fracture in high dose glucocorticoid users (chi-square test).

Vertebral Fracture	Yes	No	p
Diabetes mellitus	26	134	
HbA1c, mg/dl*	7.68 ± 1.93	5.15 ± 0.66	< 0.01
BMD, g/cm^2	0.858 ± 0.149	0.850 ± 0.17	NS
Vertebral fracture, yes/no (%)	5/21 (19.2)	29/105 (21.6)	NS
Hyperlipidemia (cases)	95	65	
Total cholesterol, mg/dl*	283.2 ± 54.8	207.8 ± 23.0	< 0.01
BMD, g/cm^2	0.834 ± 0.176	0.876 ± 0.173	0.03
Vertebral fracture, yes/no (%)	23/72 (24.2)	11/54 (16.9)	NS

* Peak values after glucocorticoid therapy are shown. Patients whose value was > 220 mg/dl was defined to have hyperlipidemia. NS: not significant.

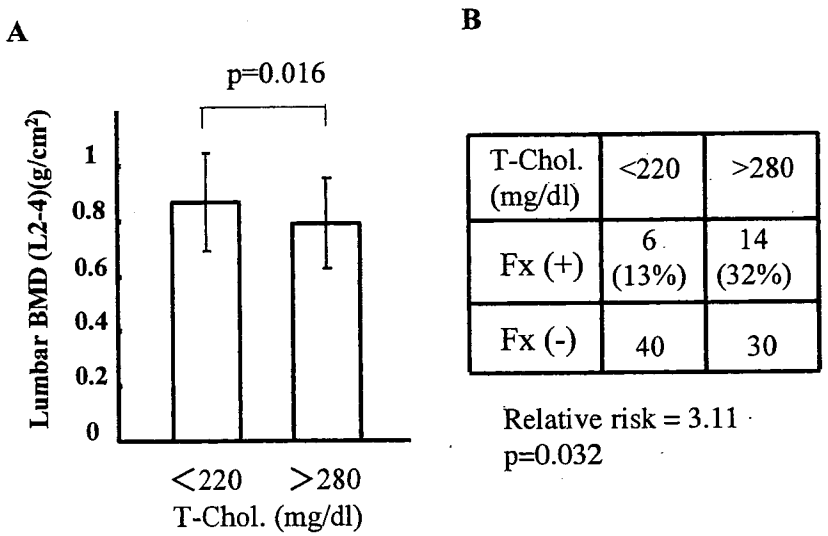

Figure 3. Influence of hyperlipidemia on lumbar BMD and vertebral fracture (Fx) in high dose glucocorticoid users. (A) Comparison of lumbar BMD between patients with high (> 280 mg/dl) and with normal (< 220 mg/dl) total cholesterol (T-Chol) values. (B) Comparison of the ratio of vertebral fracture between patients with high (> 280 mg/dl) and with normal (< 220 mg/dl) total cholesterol values. Chi-square analysis revealed that vertebral fracture was more frequent in patients with high total cholesterol level than in those with normal level (relative risk = 3.11, p = 0.032).

mean value of a large-scale Japanese study of primary osteoporosis by Orimo, *et al*, in which the cutoff value for osteoporosis was determined to be 70% of young adult mean[14]. There have been arguments about the difference of BMD threshold for fractures between postmenopausal users of glucocorticoids and nonusers. There are reports showing the BMD distribution of patients with vertebral fractures was similar for glucocorticoid users and nonusers[19,20]. On the other hand, other studies found that postmenopausal women taking glucocorticoids had a higher risk of fracture compared with nonusers, even at comparable levels of BMD[11,21]. Although our study was not designed to address this controversy, the relatively high BMD cutoff value, 80% of the young adult mean, for premenopausal women established in our study suggests that BMD alone may not be sufficient for predicting the risk of vertebral fracture for premenopausal users of glucocorticoids.

This notion is supported by our finding that premenopausal glucocorticoid users frequently experienced complications of vertebral fracture even when they registered normal BMD values. Vertebral fracture was seen in as many as 43% of premenopausal glucocorticoid users even when their BMD values were not particularly low (T score > −1). Recent guidelines from Europe and North America have been developed to establish intervention thresholds for glucocorticoid induced osteoporosis in patients with high BMD levels[22,23] or regardless of BMD level[24]. The recent guidelines of the American College of Rheumatology advocate intervention for all patients whose therapy calls for use of > 5 mg/day glucocorticoid for at least 3 months, and for

patients on a longterm glucocorticoid regimen with a BMD below a T score of –1.0[22]. Guidelines from the UK advocate an intervention threshold at a T score of –1.5 for patients who are scheduled to be given > 7.5 mg/day glucocorticoid for at least 6 months[23]. Our results suggest the need for developing a new therapeutic approach to prevent glucocorticoid induced osteoporosis in addition to starting antiresorptive therapy at high BMD thresholds.

Accumulating findings indicate that BMD is not the only factor that affects the risk of vertebral fracture[1,12,25]. One mechanism for the rapid onset of fracture risk could be osteocyte apoptosis, which leads to a deterioration of bone quality and a rapid increase in fracture risk[10]. Osteocyte apoptosis is prevalent in glucocorticoid induced osteoporosis[26]. The network of osteocytes is thought to detect microdamage to bone and be involved in bone repair remodeling. Therefore, osteocyte apoptosis together with glucocorticoid induced suppression of osteoblast generation could lead to growing micro-damage and a resultant increase in bone fragility. Thus, it is important to develop a new method to estimate bone fragility besides BMD measurement.

Another candidate factor that may contribute to the risk of osteoporosis from our study is hyperlipidemia. Our results showed that high total cholesterol (> 280 mg/dl) may be a risk factor for low BMD and vertebral fracture. There are reports of *in vitro* studies suggesting that low density lipoprotein oxidation products could promote osteoporosis by inhibiting osteoblast differentiation and by directing progenitor marrow stroma cells to undergo adipogenic instead of osteogenic differentiation[27,28]. Although these *in vitro* studies imply the possible involvement of lipid metabolism in the process of osteoporosis, there has been no report confirming the relationship of hyperlipidemia and glucocorticoid induced osteoporosis, and many clinical trials examining the efficacy of HMG-CoA reductase in preventing osteoporosis have had negative results. Therefore, further investigation is needed to establish a therapeutic strategy for preventing glucocorticoid induced osteoporosis in patients with hyperlipidemia.

Some reports stress the importance of daily glucocorticoid dose (mean) over cumulative glucocorticoid dose as an effective predictor of fracture[4,5,11], while others stress cumulative rather than daily glucocorticoid dose[6,7]. We detected no statistically significant difference between the occurrence of fracture and the mean daily glucocorticoid dose ($p = 0.483$) or cumulative glucocorticoid dose ($p = 0.794$), probably because of the limitation of our cross-sectional study and the limited numbers of patients with fracture. An important factor affecting our results may be differences in the use of antiresorptive drugs, especially bisphosphonates. This may be due partly to the Japanese legislative environment, since prophylactic use of drugs has not been allowed yet in the Japanese health insurance system. As this is a cross-sectional study, there are some limitations to interpreting our results. The onset of vertebral fracture is not predictable in prevalent fracture cases, and in these cases the influence of BMD may be different from that in incident fracture cases. To address these questions, we are now conducting a randomized cohort trial on patients who start glucocorticoid administration at a high dose, > 0.5 mg/kg.

Our findings support the hypothesis that treatment with glucocorticoids influences the occurrence of vertebral fracture by means of a mechanism independent of BMD. Moreover, it will be necessary to develop a new approach to assess and reduce the risk of vertebral fracture in premenopausal users of glucocorticoids.

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Autoantibodies to a 140-kd Polypeptide, CADM-140, in Japanese Patients With Clinically Amyopathic Dermatomyositis

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Objective. **To identify novel autoantibodies specific for dermatomyositis (DM), especially those specific for clinically amyopathic DM (C-ADM).**

Methods. **Autoantibodies were analyzed by immunoprecipitation in 298 serum samples from patients with various connective tissue diseases (CTDs) or idiopathic pulmonary fibrosis (IPF). Antigen specificity of the sera was further examined by immunoblotting and indirect immunofluorescence (IF). The disease specificity and clinical features associated with the antibody of interest were determined.**

Results. **Eight sera recognized a polypeptide of ~140 kd (CADM-140 autoantigen) by immunoprecipitation and immunoblotting. Immunoreactivity was detected in the cytoplasm, and indirect IF revealed a granular or reticular pattern. Anti–CADM-140 antibodies were detected in 8 of 42 patients with DM, but not in patients with other CTDs or IPF. Interestingly, all 8 patients with anti–CADM-140 antibodies had C-ADM. Among 42 patients with DM, those with anti–CADM-140 autoantibodies had significantly more rapidly progressive interstitial lung disease (ILD) when compared with patients without anti–CADM-140 autoantibodies (50% versus 6%; $P = 0.008$).**

Conclusion. **These results indicate that the presence of anti–CADM-140 autoantibodies may be a novel marker for C-ADM. Further attention should be directed to the detection of rapidly progressive ILD in those patients with anti–CADM-140 autoantibodies.**

Polymyositis (PM)/dermatomyositis (DM) is a chronic inflammatory disorder that culminates in injury to the skin and muscle and, sometimes, is associated with interstitial lung disease (ILD) and/or neoplasia (1,2). A number of autoantibodies are associated with myositis, including those specific for aminoacyl–transfer RNA synthetase (anti-ARS) (3), signal recognition particle (anti-SRP) (4), and Mi-2 (5). These autoantibodies have proven to be clinically useful in the diagnosis and classification of these diseases and are predictive of responses to treatment.

It has been known for some time that certain patients may have the typical skin manifestations of DM but no evidence of myositis, a condition known as amyopathic DM. Recently, Sontheimer proposed the existence of a unique subgroup of patients with DM who have the clinical cutaneous features of DM but no evidence of clinical myositis symptoms for at least 2 years after the onset of skin manifestations (referred to as clinically amyopathic DM [C-ADM]) (6). In other words, C-ADM includes patients with amyopathic DM and patients with hypomyopathic DM (patients with subclinical signs of myositis and DM skin manifestations). Some patients with C-ADM, especially those in Japan (7), have been noted to develop rapidly progressive ILD. This condition in many of these patients is resistant to treatment, and fatal outcomes have been observed.

Because of the severity of ILD accompanying C-ADM, a marker autoantibody would be useful for early diagnosis and treatment monitoring. Potential marker autoantibodies have been described by Targoff et al, who, in a preliminary study, described specificity for a 95-kd Se protein, as well as an unidentified 155-kd protein (8). However, a full survey of the autoantibodies

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associated with C-ADM has not been performed. In the present study, we examined the sera from 15 Japanese patients with C-ADM to identify additional autoantibodies associated with this disease.

PATIENTS AND METHODS

Patients and sera. Serum samples were obtained from 255 randomly selected Japanese adult patients with connective tissue diseases (CTDs) who were being followed up in clinics at Keio University in Tokyo and collaborating medical centers. These sera were obtained, prior to therapy, from a cohort of 61 patients with PM, 42 with DM (including 15 with C-ADM), 50 with rheumatoid arthritis, 46 with systemic lupus erythematosus, 27 with mixed CTD/overlap syndrome, 22 with systemic sclerosis, and 7 with Sjögren's syndrome. Sera from 43 patients with idiopathic pulmonary fibrosis (IPF) and 16 normal human sera were used as control sera. The diagnosis of C-ADM was based on diagnostic criteria proposed by Sontheimer (6), i.e., DM patients with no clinical muscle symptoms for more than 2 years after the onset of skin manifestations.

The patients were diagnosed as having ILD according to the results of chest radiography, chest computed tomography (CT), and pulmonary function testing, which included the percent predicted values for forced vital capacity and diffusing capacity for carbon monoxide. A subset of patients with rapidly progressive ILD was defined as those presenting with progressive dyspnea and progressive hypoxemia, and a worsening of interstitial change on the chest radiograph within 1 month from the onset of respiratory symptoms.

Immunoprecipitation. The immunoprecipitation assay was performed using extracts of the leukemia cell line, K562, as previously described (9). A total of 10 μl of patient serum was mixed with 2 mg of polypeptide A–Sepharose CL-4B (Pharmacia Biotech AB, Uppsala, Sweden) in 500 μl of immunoprecipitation buffer (10 m*M* Tris HCl, pH 8.0, 500 m*M* NaCl, 0.1% Nonidet P40) and incubated for 2 hours at 4°C, and then washed 3 times with immunoprecipitation buffer.

For polypeptide studies, antibody-coated Sepharose beads were mixed with 100 μl of ^{35}S-methionine–labeled K562 cell extracts derived from 2×10^5 cells, and rotated at 4°C for 2 hours. After 6 washes, the Sepharose beads were resuspended in sodium dodecyl sulfate (SDS) sample buffer and the polypeptides were fractionated by 6% SDS–polyacrylamide electrophoresis gels. Radiolabeled polypeptide components were analyzed by autoradiography.

For analysis of RNA, the antigen-bound Sepharose beads were incubated with 100 μl of K562 cell extracts (6×10^6 cell equivalents per sample) for 2 hours at 4°C. To extract bound RNA, 30 μl of 3.0*M* sodium acetate, 30 μl of 10% SDS, 2 μl of carrier yeast transfer RNA (10 mg/ml; Sigma, St. Louis, MO), and 300 μl of phenol:chloroform:isoamyl alcohol (50:50:1, containing 0.1% 8-hydroxyquinoline) were added. After ethanol precipitation, the RNA was resolved using a 7*M* urea–10% polyacrylamide gel, which was subsequently silver-stained (Bio-Rad, Hercules, CA).

Immunoblotting. Immunoblotting analysis was performed using K562 cell extracts in a modification of the procedure described by Towbin et al (10).

Immunodepletion. A 10-μl aliquot of the prototype serum of autoantibodies to the 140-kd polypeptide was mixed with 2 mg of Sepharose beads and incubated for 2 hours at 4°C, followed by 3 washes with immunoprecipitation buffer. Another serum that recognized the 140-kd polypeptide was added in a dose-dependent manner (0 μl, 10 μl, 25 μl, and 50 μl) and then incubated. After 3 washes, immunoprecipitation for polypeptide analysis was performed as described above.

Indirect immunofluorescence (IF). Indirect IF was performed using HEp-2 cells and fluorescein-labeled anti-human immunoglobulin (Inova Diagnostics, San Diego, CA).

Clinical studies. The patients whose sera immunoprecipitated a 140-kd polypeptide were examined for their clinical symptoms, clinical course, muscle enzyme levels (creatine kinase [CK] and aldolase), results on chest radiographic and CT scans, and findings of skin pathology. An assessment of muscle weakness was performed using a manual muscle test (11). Some patients were also examined by electromyogram and muscle magnetic resonance imaging (MRI), and by pathologic analysis of the muscle.

Statistical analysis. The 2 groups of DM patients with or without autoantibodies to the 140-kd polypeptide were compared. The results of comparisons between groups were analyzed using the chi-square test, with Yates' correction where appropriate.

RESULTS

Detection of anti–140-kd polypeptide antibodies in patients with C-ADM. We screened 298 patient sera and 16 normal human sera by immunoprecipitation. Sera from 8 (19%) of 42 patients with DM immunoprecipitated a polypeptide of ~140 kd from ^{35}S-methionine–labeled K562 cell extracts (Figure 1A, lanes 1–8). All 8 patients were diagnosed as having C-ADM, a subtype of DM. In the analysis of RNA specificity, these sera did not immunoprecipitate any nucleic acid band, except for 1 patient's serum, which precipitated hYRNA of SSA/Ro components.

The C-ADM sera that immunoprecipitated the 140-kd polypeptide were also used to immunoblot K562 cell extracts. These sera from C-ADM patients displayed a similar reaction on immunoblot, with a polypeptide band of similar molecular weight (results not shown).

For identification of novel autoantibodies recognizing the 140-kd molecule, the polypeptide immunoprecipitated by the prototype serum was compared with antigens of similar molecular weight recognized by other known autoantibodies (Figure 1B). The protein recognized by the prototype serum migrated slightly faster than the 140-kd protein recognized by anti-MJ antibody (Figure 1B, lane 2) and faster than that recognized by anti–RNA helicase A antibody (Figure 1B, lane 3), but more slowly than the 120-kd protein precipitated by