제22차 대한류마티스학회 연수강좌

- 개원의를 위한 증례 중심의 류마티스 질환 치료지침 -

일시: 2016년 4월 10일(일) 08:30∼13:35
장소: 건국대학교병원 대강당(지하3층)
# 제22차 대한류마티스학회 연수강좌

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## PROGRAM

<table>
<thead>
<tr>
<th>시간</th>
<th>프로그램</th>
<th>강사</th>
</tr>
</thead>
<tbody>
<tr>
<td>08:30</td>
<td>접수 및 등록</td>
<td></td>
</tr>
<tr>
<td>08:55</td>
<td>개회사</td>
<td>고은미 이사장</td>
</tr>
<tr>
<td>09:00</td>
<td>제 1 세션 좌장 : 고은미(성균관의대)</td>
<td></td>
</tr>
<tr>
<td>09:00</td>
<td>초음파를 이용한 관절통 감별진단</td>
<td>김현숙(순천향의대)</td>
</tr>
<tr>
<td>09:30</td>
<td>류마티스질환에 흔히 시행하는 검사</td>
<td>신기철(서울의대)</td>
</tr>
<tr>
<td>10:00</td>
<td>류마티스관절염의 진단과 치료</td>
<td>주지현(가톨릭의대)</td>
</tr>
<tr>
<td>10:30</td>
<td>척추관절염의 진단과 치료</td>
<td>이상훈(경희의대)</td>
</tr>
<tr>
<td>11:00</td>
<td>Coffee Break</td>
<td></td>
</tr>
<tr>
<td>11:30</td>
<td>제 2 세션 좌장 : 유빈(울산의대)</td>
<td></td>
</tr>
<tr>
<td>11:30</td>
<td>루푸스의 진단과 치료</td>
<td>김해림(건국의대)</td>
</tr>
<tr>
<td>12:00</td>
<td>혈관염의 진단과 치료</td>
<td>김용길(울산의대)</td>
</tr>
<tr>
<td>12:30</td>
<td>통풍의 진단과 치료</td>
<td>이창훈(원광의대)</td>
</tr>
<tr>
<td>13:00</td>
<td>골관절염의 진단과 치료</td>
<td>윤횘현(가톨릭의대)</td>
</tr>
<tr>
<td>13:30</td>
<td>맺음말</td>
<td></td>
</tr>
</tbody>
</table>

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제 1 세션

좌장 : 고은미 (성균관의대)
초음파를 이용한 관절통 감별진단

순천향대학교 의과대학 류마티스내과

김 현 숙

관절통 진단에 필요한 것?

+ Visualization is more important!!
외래에서 관절초음파를 하는 이유?

- 정확한 진단
- 관절염의 진단에 도움(류마티스 관절염, 골관절염, 통증)
- 경과의 추적관찰
- 안전하고 정확한 관절강내 주사
- 환자에게 질병의 이해도를 높힘

류마티스관절염의 조기진단

plain X-ray: normal
MRI: bone marrow edema, erosion
US: erosion
관절초음파 잡기

- Proximal: Left, Medial: Left
- 표면에 수직으로 움직이다
- 너무 세게 누르지 않는다

초음파 탐측자 종류

- 7.5 – 20 MHz linear transducer
  - Linear, 12-5 MHz
  - Curvilinear, 9-4MHz
  - Compact linear, 15-7 MHz
관절초음파 어떤 순서로 사용?

- 이학적 검사로 추정 진단이 있어야 vs. 그냥 막 댄다
- 운동제한이나 열감이 있는 관절 vs. 아프다는 관절
- 관절염인지 vs. 관절 주위의 문제인지
- (진단을 위한) 추가 검사를 결정
- (필요시) 관절강/관절 주위에 약물 투여

관절초음파의 흔한 오류

- Anisotropy
- Control of depth/focus
RA의 조기진단

- 35세 여자 PIP, MCP 관절통, 압통과 증상은 미미

Erosion 크기가 너무 작거나 위치가 좋지 않아 엑스선으로 확실하지 않은 경우

(Adopted from prof. HR Kim)

• Irregular bony erosion in MCP joint: (not definite on plain radiographs in early RA)

슬관절 초음파: 될 볼 수 있다?

• Intra-articular finding
  – Effusion
  – Synovium – proliferation, blood flow
  – Erosion
  – Cartilage
  – Bony spur

• Extra-articular finding
  – Tendon – tendinitis, tear
  – Bursitis
  – Enthesitis
김현숙: 초음파를 이용한 관절통 감별진단

RA와 OA의 감별

- 63세 여자 무릎 관절통, RF+(34 IU/mL)

슬관절: suprapatellar long. view
슬관절: Effusion

슬관절: Synovitis in RA
슬관절: Synovitis with effusion

슬관절: medial long. view
슬관절: osteophyte in OA

통풍의 진단에 도움

• 43세 남자 발목과 팔꿈치의 압통성 부종: RF-
통풍의 진단에 도움

통풍의 감별진단: 가성통풍

Chondrocalcinosis + acute synovitis = pseudogout

(Adopted from prof. HR Kim)
결정유발 관절염의 초음파적 감별

(Adopted from prof. HR Kim)
손관절 주위의 문제

- 53세 여자 아침에 일어 나면 손이 뻐ǘ해함
- ESR/CRP-정상, RF⁺(20 IU/mL), CCP Ab (-)
- Rt 3rd MCP 압통, rocking

손관절 주위의 문제

- 63세 남자 무증상 Lt 4th DIP 부종
- ESR/CRP-정상
주관절 주위의 문제

- 53세 여자 2주전부터 팔꿈치를 펼 수가 없이 아프다
- Epicondyle tenderness

주관절의 문제

- 53세 여자 2주전부터 팔꿈치를 펼 수가 없다.
- RA로 MTX, PDL, NSAIDs 2년간 복용 중
- RA flare-up??
슬관절 통증의 감별

- 53세 남자 2일전부터 왼무릎 통증과 열감
- 손에 닿기만 해도 통증

슬관절: Prepatellar view

: Patella, Prepatellar bursa
슬관절: Prepatellar/Infrapatellar bursitis

슬관절: Infrapatellar long. view
슬관절: Patellar tendinitis (Jumper’s knee)

45세 여자 무릎 통증. 최근 에어로빅 시작.

슬관절 통증의 감별진단

- 63세 여자 걷음때마다 심해지는 통증
- 슬관절의 부종 (-)

Bursa lies below pes anserine
슬관절: Anserine bursitis

슬관절 통증의 감별진단

- 63세 여자 다리가 당기고 겉을 때마다 불편
- OA로 치료 중.슬관절 부종 (-)
슬관절: Baker’s cyst

어깨통증시 고려할 주요 구조물

<table>
<thead>
<tr>
<th>List</th>
<th>Structures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal anatomy of shoulder joint</td>
</tr>
<tr>
<td>2</td>
<td>Biceps tendon</td>
</tr>
<tr>
<td>3</td>
<td>Subscapularis tendon</td>
</tr>
<tr>
<td>4</td>
<td>Supraspinatus tendon</td>
</tr>
<tr>
<td>5</td>
<td>Infra spinatus tendon</td>
</tr>
<tr>
<td>6</td>
<td>A-C joint, SASD bursitis, calcific tendinitis</td>
</tr>
</tbody>
</table>
견관절: Biceps tendon

1. Transverse bicipital groove view
2. Longitudinal bicipital view

견관절: NORMAL biceps tendon

Transverse view  Longitudinal view
건관절: Biceps tenosynovitis

Transverse view

정상 소견

건관절: Biceps tenosynovitis

Lt shoulder anterior transverse
건관절: Biceps tenosynovitis

장상 소견

건관절: Biceps subluxation

장상 소견
건관절: Supraspinatus tendon

장관절: NORMAL SSP tendon

- Deltoid m.
  - hypoechoic to the supraspinatus tendon in young pt.
  - isoechoic with increasing age (â†’ atrophies, fat infiltration)
- Peribursal fat pad line: thin, hyperechoic line
- Articular cartilage of humeral head: thin hypoechoic line
견관절: supraspinatus tendon tear

Thickness
1. Intrasubstance tear
2. Partial thickness Articular surface tear
3. Partial thickness Bursal surface tear
4. Full thickness tear

견관절: SSP tendon tear: articular type
견관절: SSP tendon tear: bursal type

견관절: SSP tendon: intrasubstance type
견관절: full thickness SSP tendon tear

Full thickness tear
견관절: NORMAL infraspinatus tendon

deltoid m.
Infraspinatus
GL

견관절: Glenohumeral joint effusion

deltoid m.
IS
GL
Rt. glenohumeral joint
Acromioclavicular joint

Normal View

Subacromial-subdeltoid bursa

Thin (< 2 mm), hypoechoic sac between two layers of hyperechoic fibroadipose tissue

Subacromial-subdeltoid bursitis

Subacromial-subdeltoid bursitis
Take home message

• 정확한 진단을 위해서는 무엇보다도 자세한 병력 청취와 진찰이 선행되어야 하며 증상을 바탕으로하여 standard scan 과 순서, 반드시 체크 해야 하는 구조물은 숙지합니다.

• 류마티스내과에서 시행하는 초음파는 어렵지 않습니다!!!

• 정상 scan 을 바탕으로, pathologic finding 을 인지할수 있도록 합니다.

• 보고자 하는 면에 수직으로, 최대한 표면에 밀착 시켜, 영상을 토착이 잘도록 합니다.
류마티스 질환의 진단을 위해 흔히 시행하는 검사

서울대학교 의과대학 류마티스내과
신기철

Don’t order a laboratory test unless you know why you’re ordering it and what you will do if it comes back abnormal.

*Rheumatology’s Ten Golden Rules* by Sterling G. West, M.D.
레이마티스 임상검사

- 혈액검사
- 활막액 검사
- 편평혈미경 검사
- 손톱주름모세혈관 혈미경검사

금일 다룰 검사

- 적혈구 침강속도
- C-반응 단백
- 레마티스 인자
- 항CCP항체
- 항핵항체
- 보체
- 항홍성구세포질항체
- HLA-B27
- 요산
- 활막액 검사
• ESR may take a few days to a week to elevate and a similar amount of time to regress once the inflammatory stimulus is gone.

• ESR is helpful to confirm a clinical impression regarding the presence or absence of inflammatory disease, although occasionally patients with inflammatory diseases present with a normal ESR.

• Age and obesity elevate the ESR.

• Resolution of the ESR is a useful marker of treatment success in illnesses such as rheumatoid arthritis, septic arthritis, and osteomyelitis.

*J Am Acad Orthop Surg 2003*

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![Graph showing comparison of time course of ESR and CRP level after a single inflammatory stimulus.](image-url)

*Am J Med 1996*
리우마티스 인자

- Rheumatoid factor (RF)
- Antibodies directly against Fc portion of IgG
- IgM RF
- RF could be present prior to RA diagnosis (Arthritis Rheum 2004)
  - 30% of RA patients had positive RF (median 4.5 years)
- Higher RF titer suggests greater likelihood of rheumatic disease

리우마티스 인자 양성

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>75-80 %</td>
</tr>
<tr>
<td>Elderly people</td>
<td>5 %</td>
</tr>
<tr>
<td>Rheumatic diseases</td>
<td></td>
</tr>
<tr>
<td>Primary Sjögren’s syndrome</td>
<td>75-90 %</td>
</tr>
<tr>
<td>Mixed cryoglobulinemia</td>
<td>90-100 %</td>
</tr>
<tr>
<td>SLE</td>
<td>20-30 %</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>20-30 %</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>50-60 %</td>
</tr>
<tr>
<td>Chronic bacterial infection</td>
<td></td>
</tr>
<tr>
<td>Subacute bacterial infection</td>
<td>25-50 %</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>5-33 %</td>
</tr>
<tr>
<td>Interstitial pulmonary fibrosis</td>
<td>10-50 %</td>
</tr>
<tr>
<td>Chronic active hepatitis</td>
<td>25-40 %</td>
</tr>
</tbody>
</table>
항CCP 항체

- Anti-cyclic citrullinated peptide (anti-CCP)
- Anti-citrullinated protein antibody (ACPA)
- Higher specificity for RA than RF
- Highly related with smoking as Risk factor for RA
- ACPA-positive RA patients are at risk of progressive joint damage (Arthritis Rheum 2008)
## CCP2 검사

<table>
<thead>
<tr>
<th>Group</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA total</td>
<td>71.7</td>
<td>-</td>
</tr>
<tr>
<td>Early RA</td>
<td>61.6</td>
<td>-</td>
</tr>
<tr>
<td>Established RA</td>
<td>75.2</td>
<td>-</td>
</tr>
<tr>
<td>Controls</td>
<td>-</td>
<td>95.2</td>
</tr>
<tr>
<td>Non-RA</td>
<td>-</td>
<td>94</td>
</tr>
<tr>
<td>Healthy</td>
<td>-</td>
<td>99</td>
</tr>
</tbody>
</table>

Nat Rev Rheumatol 2011

## 항CCP 항체가 양성일 수 있는 기타 질환

- 전신홍반루푸스
- 쇼그렌 증후군
- 건선관절염
- Tuberculosis (Arthritis Rheum 2008): up to 30%
- others: COPD
항핵항체

- Antinuclear antibody
- 검사에 사용하는 세포: HEp-2 cells vs. Mouse liver
- 검사목적
  - 자가면역질환 혹은 결제조직질환의 임상상을 보이는 환자의 진단에 도움
  - 역가(titer): 높은 역가는 진단을 더 시사할 수
  - 위양성: 정상인에서도 나타날 수
  - 위음성: low anti-Ro/La Antigen in HEp-2 cells, high titers of ANA
All patients with a positive rheumatoid factor do not have rheumatoid arthritis, and all patients with a positive antinuclear antibody do not have systemic lupus erythematosus

*Rheumatology’s Ten Golden Rules by Sterling G. West, M.D.*

### 항핵항체 양성 질환

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE</td>
<td>93%</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>85%</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>93%</td>
</tr>
<tr>
<td>Inflammatory myositis</td>
<td>61%</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>41%</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>48%</td>
</tr>
<tr>
<td>Drug-induced lupus</td>
<td>100%</td>
</tr>
<tr>
<td>Discoid lupus</td>
<td>15%</td>
</tr>
<tr>
<td>Other autoimmune diseases</td>
<td></td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis</td>
<td>46%</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>63-91%</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>10-40%</td>
</tr>
<tr>
<td>Primary autoimmune cholangitis</td>
<td>10-40%</td>
</tr>
<tr>
<td>Idiopathic pulmonary arterial hypertension</td>
<td></td>
</tr>
<tr>
<td>Antigen</td>
<td>Nature</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>Hep-2 cell nuclei</td>
<td>ANA</td>
</tr>
<tr>
<td>dsDNA</td>
<td>Native, double-stranded DNA</td>
</tr>
<tr>
<td>Histones</td>
<td></td>
</tr>
<tr>
<td>Sm</td>
<td>Small nuclear RNAs complexed with protein</td>
</tr>
<tr>
<td>Nuclear RNP (U1RNP)</td>
<td>Small nuclear RNAs complexed with protein</td>
</tr>
<tr>
<td>SSB/SSA (RNP)</td>
<td>Protein associated with RNA</td>
</tr>
<tr>
<td>SS-B/La</td>
<td>Protein bound to small RNA</td>
</tr>
<tr>
<td>Ku</td>
<td>DNA binding proteins</td>
</tr>
<tr>
<td>Kc</td>
<td>Nuclear protein</td>
</tr>
<tr>
<td>PCNA/cyclin</td>
<td>Cell cycle protein</td>
</tr>
<tr>
<td>HSP90</td>
<td>Heat shock protein</td>
</tr>
<tr>
<td>P ribosomal protein, RNP</td>
<td>Filibosomal phosphoprotein</td>
</tr>
<tr>
<td>ssDNA</td>
<td>Single-stranded DNA</td>
</tr>
<tr>
<td>IgG, glycoprotein</td>
<td>Antigenic proteins, cardiolipin</td>
</tr>
</tbody>
</table>

_Clin Chest Med 2010_

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**Patient Presentation**

**History, P/E, Investigation**

**Diagnosis**

Possible SLE, SJS, MCTD, overlap with RA, GPA

ANA + Screening test -

Identify Ab

IF pattern, ELISA

Further testing if clinically indicated

anti-La SJS

anti-Ro SLE

anti-dsDNA SLE

anti-Sm SLE

anti-RNP SLE MCTD

RF, anti-CCP RA

cANCA anti-PR3 GPA

_Autoimmunity Rev 2007_
보체

- Complement
- 보체의 항염증(pro-inflammatory) 작용
  - Chemotaxis of cells to inflammatory site
  - Release of mediators
  - Activation of cells; endothelial and epithelial cells etc
  - Dilation of blood vessels
- 보체상승 : 급성반응단백
- 보체감소
  - Formation of Immune complexes
  - Autoimmune hemolytic anemia
  - Recurrent infection
보체 검사

- CH50
  - Ability of serum to lyse sheep RBC sensitized with rabbit IgM antibody
  - Screening tool detecting of deficiency of the classical pathway
- Plasma C3, C4
  - Nephelometric immunoassay etc.

항중성구세포질항체

- Anti-neutrophil cytoplasmic antibody (ANCA)
- 양성으로 나올 수 있는 질환
  - Granulomatosis with polyangiitis (Wegener's granulomatosis)
  - Microscopic polyangiitis
  - Renal-limited vasculitis
  - Eosinophilic granulomatosis and polyangiitis (Churg-Strauss sd)
  - Anti-GBM antibody disease
  - Drug-induced ANCA-associated vasculitis
  - Nonvasculitic rheumatic disorders
  - Ulcerative colitis, primary sclerosing cholangitis
ANCA 양성 혈관염

- 간접면역형광검사
- C-, P- pattern
- ELISA
  - anti-proteinase3 (PR3)
  - anti-myeloperoxidase (MPO)

<table>
<thead>
<tr>
<th></th>
<th>C-ANCA/anti-Pr3</th>
<th>P-ANCA/anti-MPO</th>
<th>C-ANCA/Pr3 or P-ANCA/MPO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wegener granulomatosis</td>
<td>56%–95%</td>
<td>5%–23%</td>
<td>85%–95%</td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
<td>8%–26%</td>
<td>49%–85%</td>
<td>67%–96%</td>
</tr>
<tr>
<td>Churg-Strauss syndrome</td>
<td>33%</td>
<td>33%</td>
<td>56%</td>
</tr>
</tbody>
</table>

WG: Granulomatosis with polyangiitis
CSS: Eosinophilic Granulomatosis with polyangiitis

HLA-B27

- 90% 이상의 강직성 척추염에서 양성으로 발견
- 척추관절염의 2010 ASAS 분류기준에 포함
- 우리나라 강직성 척추염에 가장 흔한 유전자 아형
  - B*2705 (Kor J Lab Med 2008)
- 정상인의 2.7%에서도 HLA-B27 양성
- HLA-B27 검사 양성 소견으로만 척추관절염을 확진할 수는 없음
- 하지만, HLA-B27 및 척추관절염 양성이 모두 음성인 환자는 척추관절염의 진단을 재고하는 것이 필요함
혈청 요산과 급성통풍

- 고요산혈증을 보인 건강검진 내원자의 통풍 유병률 (대한류마티스학회지 2004)
- 남성 16.6 %, 여성 6.7 %
- 고요산혈증은 급성 통풍 발작 때의 진단에 필수적이지 않다.
- 통풍 발작시 정상 혈청 요산 농도 보인 환자: 26 %

(대한내과학회지 1997)

스트레스 호르몬, 급식 등 요인 때문에 평소보다 낮게 측정될 수
정상 활막액

- Viscous
- Contains hyaluronic acid, lubricin, proteinases, collagenases
- Function
  - Reduction of friction
  - Shock absorption
  - Nutrient and waste transporation

Patients with an acute inflammatory monoarticular arthritis need a joint aspiration to rule out septic arthritis and crystalline arthropathy.

*Rheumatology’s Ten Golden Rules*  
by Sterling G. West, M.D.
활막액 검사

- Color
- Clarity
- Viscosity
- Lab
  - Complete WBC count, differential count
  - Gram stain
  - Proper cultures
  - Crystal exam

---

### Synovial Effusions: Classification

<table>
<thead>
<tr>
<th>Type of Fluid</th>
<th>Special Features</th>
<th>Leukocytes/µl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Clear, Colorless, Viscous</td>
<td>&lt;200 (&lt;25% PMNs)</td>
</tr>
<tr>
<td>Noninflammatory</td>
<td>Clear, Yellow, Viscous</td>
<td>200-2,000 (&lt;25% PMNs)</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Cloudy, Yellow, Watery, Glucose May be Low</td>
<td>2,000-100,000 (&gt;50% PMNs)</td>
</tr>
<tr>
<td>Septic</td>
<td>Purulent, Glucose Very Low</td>
<td>&gt;80,000 (&gt;75% PMNs)</td>
</tr>
</tbody>
</table>
### Synovial Effusions: Classification

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</tr>
<tr>
<td></td>
<td>Glucose Very Low</td>
<td></td>
</tr>
</tbody>
</table>

**Analyzer**

**Compensator**

**Polarizer**

© ACR
신기철: 류마티스 질환의 진단을 위해 폭이 시명하는 검사
손톱주름 모세혈관 현미경검사

요 약

- 류마티스 임상검사는 진단 및 감별진단을 위한 유용한 정보를 제공할 수 있다.
- 임상상이 뒷받침되지 않은 선별검사의 시행은 오히려 진단에 결리돌이 된다.
- 건강검진에서 류마티스 인자, 항핵항체 검사의 유용성에 대해서는 재고가 필요하다.
- 감염성 관절염의 진단외에도 염증성 관절염의 진단이 불분명한 경우 활막액 검사가 도움이 될 수 있다.
A good history and physical examination, coupled with knowledge of musculoskeletal anatomy, is most important when evaluating a patient with a rheumatic disorder. You have to examine the patient!

Rheumatology’s Ten Golden Rules
by Sterling G. West, M.D.
Evaluation of Pts with Musculoskeletal Complaints

Goals
Accurate diagnosis
Timely provision of therapy
Avoidance of unnecessary diagnostic testing
Identification of acute, focal/monarticular "red flag" conditions

Approach
Determination of chronology (acute vs chronic)
Determination of the nature of the pathologic process (inflammatory vs noninflammatory)
Determination of the extent of involvement (monarticular, polyarticular, focal, widespread)
Anatomic localization of complaint (articular vs nonarticular)
Consider the most common disorders first
Formulate a differential diagnosis
주지현: 류마티스관절염의 진단과 치료

정말 관절의 문제인가?

만성 vs 급성?

염증성 vs 비염증성?

관절의 갯수는?

이환부위별 관절 질환의 분류

Nonarticular condition
Consider
- Trauma/fracture
- Fibromyalgia
- Polymyalgia rheumatica
- Bursect
- Tendinitis

Not

Is it articular?

Yes

Consider
- SLAP
- Olecranon
- Hypopitot
관절외 부위별 질환의 분류

BURSITIS - BURSAE INFLAMMATION

Polymyagia rheumatica
Bursitis
Trauma/Fracture
Tendinitis

부위별 관절 질환의 분류

Spondyloarthropathy
Osteoarthritis
Rheumatoid arthritis
Articular vs Non articular 의 특징

- Articular disorders
  - deep or diffuse pain,
  - pain or limited range of motion on active and passive movement,
  - swelling (caused by synovial proliferation, effusion, or bony enlargement), crepitation, instability, “locking,” or deformity.
- Nonarticular disorders
  - painful on active, but not passive (or assisted), range of motion,
  - point or focal tenderness in periarticular structures
  - elicited with a specific movement or position
  - physical findings remote from the joint capsule
  - seldom demonstrate swelling, crepitus, instability, or deformity of the joint itself.

Tendinitis
이환부위 및 증상 지속의 기간별 관절 질환의 분류

1. Nonarticular condition
   - Consider
     - Trauma/fracture
     - Fibromyalgia
     - Polymyalgia rheumatica
     - Bursitis
     - Tendinitis

2. Articular
   - Is it articular?
     - Yes
     - Is complaint > 6 wk?
       - No
       - Acute
       - Chronic
     - No

3. Gout
   - Pseudogout
   - Reactive arthritis

4. Rheumatoid Arthritis
   - Spondyloarthritides
   - Ankylosing spondylitis
   - Psoriatic arthritis
   - Reactive arthritis
   - Osteoarthritis

Gout

- Joint – 1st MTP : almost always involved first
  then tarsal area, ankle, finger, elbow, knee...
- History of spontaneous resolution and relapse
- Lab – hyperuricemia,
- frequently accompanied by metabolic syndrome
Pseudogout

- Joint – Wrist, Knee (especially OA joint)
- X-ray – chondrocalcinosis (fibrous cartilage calcification)
증례 1

- 54 세 남자
- 회식한 다음날 새벽부터

Lt great toe pain and swelling

- Past Hx. 고혈압
- P/Ex 혈압 145/95
Lab

- CBC 12,700 (seg 85%)/ 12.7/ 355,000
- ESR 67 mm/hr, CRP 6.1 mg/dL
- BC; Glu 183 mg/dL, Cr 1.15 mg/dL, uric 8.1 mg/dL, AST 57 IU/L, ALT 75 IU/L, T-Bil 0.9 mg/dL, rGTP 321, Tchol 278 mg/dL, TG 421 mg/dL, HDL 35 mg/dL, LDL 159 mg/dL
- X-ray: soft tissue swelling around Lt 1st MTP joint but no joint damage

• What would you like to do next?
증례 2

- 69 세 여자
- 하루 전부터

Rt knee pain, swelling, and redness

- Past history – Osteoarthritis of knee joints
- Lab CBC 15,700 (seg 89%)/ 10.6/ 421,000
  ESR 101 mm/hr , CRP 7.2 mg/dL
Synovial fluid

- WBC 45,700/mm³ (seg 95%)
- Gram stain – many wbc, no microorganism
- Culture – no bacterial growth
- What more?
CPPD crystals

염증성 vs 비염증성 관절 질환의 분류

Consider
- Acute arthritis
- Infectious arthritis
- Gout
- Pseudogout
- Reactive arthritis
- Initial presentation of chronic arthritis

Acute

Is inflammation present?
1. Is there prolonged morning stiffness?
2. Is there soft tissue swelling?
3. Are there systemic symptoms?
4. Is the ESR or CRP elevated?

Chronic

Chronic noninflammatory arthritis
Chronic inflammatory arthritis

Osteoarthritis
Osteonecrosis
Charcot arthritis
**Inflammatory**의 특징

- Joint - swelling, redness, heat
- Prolonged morning stiffness
- Systemic symptoms
- Synovial fluid WBC count
- Acute phase reactant
  - ESR (erythrocyte sedimentation rate)
  - CRP (C-reactive protein)
  - Others - anemia, hypoalbuminemia

**Osteoarthritis**

- Joints - Hand - DIP, PIP, 1st carpometacarpal, Knee, Hip
- Stiffness - 30 분이하
- Lab - ESR : normal or a little bit elevated
  - CRP : normal
  - Anti-CCP : neg,
  - RF : usually neg, occasionally pos
- X-ray; sclerosis, osteophytes, asymmetric joint narrowing
OA hand

OA hand X-ray
증례 3

• 67 세 여자
• 3 년 전부터

Stiffness of both hands, pain of DIP and PIP joint
- 자고 난 뒤 손이 뻗랫해서 주먹을 쥐기 힘들고, 손가락이 둘어지고 손가락 끝마디가 아픈데, 특히 어디 막으면 통증이 심하다.
• P/Ex – DIP, PIP – 굽어지고 딱딱함 (Heberden, Bouchard node)

flexor tendon – not tender
Tinel/ Phalen sign - neg
Lab

- CBC 6,700/ 11.8/ 201,000
- BC Cr 1.0 mg/dL, Alb 3.9 g/dL, others - WNL
- ESR 67 mm/hr, CRP 0.35 mg/dL (<0.47)
- RF 37.1 IU/mL (<20.0)
- Anti-CCP antibody 2.3 U/mL (<7.0)
주제: 류마티스관절염의 진단과 치료

이환관절의 개수 및 분포에 따른 질환의 분류

- Chronic inflammatory arthritis
- How many joints involved?
  - 1-3
  - >3
- Chronic inflammatory mono/oligoarthritis
  - Consider
  - Indolent infection
  - Psoriatic arthritis
  - Reactive arthritis
  - Pauciarticular JIA
- Chronic inflammatory polyarthritis
- Is involvement symmetric?
  - No
  - Yes
- Consider
  - Psoriatic arthritis
  - Reactive arthritis
Ankylosing spondylitis

- Joint – Sacroiliac, C-/D-/L- spine, shoulder, hip
  Enthesis
- Body stiffness – limited in forward bending

Diagnostic Standard for AS:
Modified NY Classification Criteria (1984)¹

<table>
<thead>
<tr>
<th>Clinical components:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low back pain and stiffness for &gt; 3 months in duration</td>
</tr>
<tr>
<td>Improves with exercise, but is not relieved with rest</td>
</tr>
<tr>
<td>Limitation of motion of the lumbar and frontal planes</td>
</tr>
<tr>
<td>Limitation of chest expansion relative to normal values correlated for age and sex</td>
</tr>
<tr>
<td>Radiological component:</td>
</tr>
<tr>
<td>Sacroiliitis Grade ≥2 bilaterally or Grade 3-4 unilaterally</td>
</tr>
</tbody>
</table>

Old criteria
- Defined before TNF blockers
- Sacroiliitis detectable by X-ray occurs lately
- No magnetic resonance imaging (MRI)
- Used for clinical trial

Definite AS if the radiological criterion is associated with at least one clinical criterion²

Probable AS if three clinical criteria present or radiologic criteria present without clinical criteria²

Diagnostic Standard for AS: Modified NY Classification Criteria (1984) (Cont’d)

Radiographic stage
(Ankylosing Spondylitis)

Back Pain Radiographic sacroiliitis

Back Pain Syndesmophytes

Modified NY criteria (1984)

The greatest problem in the management of AS was the lack of effective treatments. In recent years, NSAIDs and TNF-blockers have been shown to have good efficacy in the treatment of AS.

Adapted from Rudwaleit M et al. Arthritis Rheum 2005;52:1000-1008

Diagnostic Standard for AS: Modified NY Classification Criteria (1984) (Cont’d)

Pre-radiographic stage
(Axial undifferentiated SpA)

Radiographic stage
(Ankylosing Spondylitis)

Back Pain IBP
MRI active sacroiliitis

Back Pain Radiographic sacroiliitis

Back Pain Syndesmophytes

Modified NY criteria (1984)

- Recent application of MRI techniques has demonstrated (and confirmed) that ongoing active (“acute”) inflammation in fact does occur in the sacroiliac joints and/or spine prior to the appearance of changes detectable radiographically
- The presence and absence of radiographic sacroiliitis in patients with SpA represent different stages of a single disease continuum

Adapted from Rudwaleit M et al. Arthritis Rheum 2005;52:1000-1008
ASAS Classification Criteria for Axial SpA

In patients with back pain \( \geq 3 \) months and age at onset \(<45\) years

- Sacroiliitis* on imaging
  - plus
  - \( \geq 1 \) SpA feature**

OR

- HLA-B27
  - plus
  - \( \geq 2 \) other SpA features**

* Sacroiliitis on imaging:
  - Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA
  - or
  - Definite radiographic sacroiliitis according to modified New York criteria

**SpA features:
  - Inflammatory back pain
  - Arthritis
  - Enthesitis (heel)
  - Uveitis
  - Dactylitis
  - Psoriasis
  - Crohn’s disease/ulcerative colitis
  - Good response to NSAIDs
  - Family history for SpA
  - HLA B27
  - Elevated CRP


---

Psoriatic Arthritis

- Joint – Hand, Feet – DIP, PIP
  - hip, knee, ankle
  - Sacroiliac and Spine
  - Enthesis
- Skin and nail lesions
증례 4

* 27 세 남자
* 8 주 전부터

아침에 잠자리에서 일어면 심해지는 허리 및 둔부의 통증
1-2 시간 지나야 호전되고, 소염진통제 복용시 호전됨

* P/Ex.

허리를 앞으로 굽힐 때 - 손이 무릎 밑으로 안 내려온다.
두운 상태에서 고피절을 외전시킬 때 - 둔부 통증생긴다.
- CBC 9.750 (seg 76%)/ 11.9/ 411,000
ESR 72 mm/hr, CRP 2.9 mg/dL
RF <2.0 IU/mL, anti-CCP 1.2 U/mL
Short tau inversion recovery (STIR) or Contrast-enhanced T1-weighted (fat-saturated) image
증례 5

• 27 세 남자
• 8주 전부터

Lt knee swelling, Pain, tenderness of Lt heel

• Past history – ant. uveitis of Rt eye
Lab

- CBC 10,700 (seg 73%) / 12.8/ 359,000
- BC Cr 0.7 mg/dL, Alb 3.2 g/dL, others - WNL
- ESR 87 mm/hr, CRP 2.35 mg/dL (<0.47)
- RF 17.1 IU/mL (<20.0)
- Anti-CCP antibody 0.3 U/mL (<7.0)
- Lt knee synovial fluid – WBC 16,700/mm3 (seg 76 %)
주지현: 류마티스관절염의 진단과 치료
이환관절의 개수 및 분포에 따른 질환의 분류

1. Chronic inflammatory arthritis
2. How many joints involved?
   - $1 \sim 3$
   - $>3$
3. Chronic inflammatory polyarthritis
4. Is involvement symmetric?
   - Yes
5. Are PIP, MCP, or MTP joints involved?
   - No
   - Unlikely to be rheumatoid arthritis
     - Consider
       - GLE
       - Scleroderma
       - Polymyositis
   - Yes
     - Rheumatoid arthritis
Rheumatoid Arthritis

• Joints: Hand – PIP, MCP, thumb IP, Wrist,
  Feet – 2nd to 5th MTP
  Large joints – shoulder, elbow, hip, knee, ankle
• Stiffness – 1 시간 이상
• Lab; ESR, CRP 상승, RF/anti-CCP Ab 양성
• X-ray; erosions, symmetric joint narrowing

Epidemiology

• 0.5~1 % prevalence
• Overall incidence of RA has been decreasing in recent decades,
  whereas the prevalence has remained the same because
  individuals with RA are living longer.
• Incidence and prevalence of RA varies according to geographical
  distribution and races
• F>M 2~3:1
  - estrogen may affect the development of RA
Etiology

- The cause of RA remains unknown.

![Diagram showing genetic predisposition, environmental factors, and infectious agents in the etiology of RA.]

Pathogenesis

![Diagram illustrating the pathogenesis of rheumatoid arthritis, with labels for various cellular and molecular components.]

82
Clinical features of RA

- RA incidence increased b/w 25-55, plateaus 55-75, decreased after 75
- Presenting symptom <- inflammation of the joints, tendons, bursa

1) Morning joint stiffness > 1hr, eases with physical activity
2) Earliest involved joints: small joints of hand and feet
3) Initial pattern may be monoarticular, oligoarticular (<4 joints)
   or polyarticular (>5 joints)
4) Symmetrical distribution
Arthritis of hand: cardinal feature of RA

- Metacarpophalangeal (MCP), proximal phalangeal (PIP): most commonly involved
- Distal phalangeal (DIP) joints, usually a manifestation of coexisting osteoarthritis
- Flexor tendon tenosynovitis: frequent hallmark of RA -> decreased range of motion, reduced grip strength, and trigger finger
- Progressive destruction of joint and soft tissues -> chronic, irreversible deformities

Hand & Foot deformity

- Swan neck deformity
- Boutonniere deformity
- Z-line deformity
- Distal ulnar subluxation: piano-key movement
- Pes planovalgus (flat feet)
Other joints involvement of RA

- Large joints (knee, shoulder): often affected in established disease, although these joints may remain asymptomatic for many years after onset
- Atlantoaxial joint: clinically noteworthy < potential to cause compressive myelopathy and neurologic dysfunction
  - neurological manifestation rare
  - occurs less than 10 % of patients
- Temporomandibular joints:
  - occurs commonly
  - generally not associated with significant symptoms or functional impairment

RA hand-early
Laboratory findings

Rheumatoid factor

- Autoantibody reactive with the Fc portion of IgG
- Found in >2/3 of RA patients
- Found in 5% of healthy persons
- Not useful as a screening test
- Prognostic significance (+)
  + high titer of RF = more severe and progressive disease
    with extra-articular manifestations

Laboratory findings

Anti-CCP antibody

- Measured using ELISA
- 40% of seronegative RA patients → anti-CCP Ab (+)
- RF was false-positive in 44% of the patients with HCV-associated arthritis while none were anti-CCP positive
- CCP detectable > 14 years before clinical manifestations
- 90% of early arthritis patients that were anti-CCP(+) at baseline were classified as RA at the end of 1 yr follow-up
Classification Criteria for Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Joint involvement</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 large joint (shoulder, elbow, hip, knee, ankle)</td>
<td>0</td>
</tr>
<tr>
<td>2-10 large joints</td>
<td>1</td>
</tr>
<tr>
<td>1-3 small joints (MCP, PIP, thumb IP, MTP, wrists)</td>
<td>2</td>
</tr>
<tr>
<td>4-10 small joints</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 joints (at least 1 small joint)</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serology</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative RF and negative ACPA</td>
<td>0</td>
</tr>
<tr>
<td>Low + RF or low + anti-CCP Ab(≤3 times ULN)</td>
<td>2</td>
</tr>
<tr>
<td>High + RF or high + anti-CCP -Ab(&gt;3 times ULN)</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acute-phase reactants</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal CRP and normal ESR</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal CRP or abnormal ESR</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of symptoms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>≥6 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>

These criteria are aimed at classification of newly presenting patients who have at least one joint with definite clinical synovitis that is not better explained by another disease. A score of ≥6 fulfills requirements for definite RA.

Treatment 원칙

- 류마티스관절염에 대한 정확하고 빠른 조기 진단이 필수
- 일단 류마티스관절염이 진단되면 DMARD, 저용량 스테로이드, 생물학적 제제의 병합 치료를 지체 없이 시작한다 (Early combination therapy)
- 모든 환자들에게 근처라는 결과를 위해 적극적이고 공격적으로 치료한다 (Tight control for remission)
- 이환 기간, 절병성도, 및 나쁜 예후인자의 유무에 따른 약제 선택 한다.
- 치료 약제 부작용에 대한 주기적인 모니터링이 반드시 필요하다.
- 동반 질환에 대한 고려가 필요하다 (특히 심혈관 질환, 감염, 골다공증에 유의)
Treatment: DMARDs

- 류마티스관절염의 방사선적 진행(관절 파괴)의 속도를 늦추는 약제의 총칭
- 대부분의 류마티스관절염 환자에서 관절 파괴를 감소 또는 예방, 관절 기능 유지를 위해 반드시 사용한다.
- 작용 발현 시간이 늦다 (1~6개월, 대개 6주 이상)
- ESR이나 CRP 등 급성 염증 반응 물질의 수치에도 효과를 보인다.
- 약 2/3의 환자에서 효과를 보인다.

  Synthetic (Non-biologic) DMARDs: MTX, HCQ, SSZ, Au(gold), LEF, etc
  Biologic DMARDs: anti-TNF, anti-IL-1, anti-IL-6, anti-CD20, CTLA4 Ig, etc

Treatment: Biological DMARDs

- 류마티스관절염의 염증 유발 병인에서 관찰되는 여러 생물학적 반응을 조절하는 치료
- 화학적 공정이 아닌 동물이나 미생물에 의한 생물학적 공정에 의해서 생성된 종류의 약물

  항-cytokine 제제: TNF, IL-1, IL-6, RANKL 차단제
  항-면역세포 제제: B cell, T cell co-stimulation 차단제
  항-신호전달 제제: SyK, p38 MAP kinase, JAK3 차단제
Treatment: Steroids

- 조기 류마티스관절염에서 저용량의 스테로이드 (≤7.5mg/day)를 DMARD와 병합 투여 하는 것이 방사선적 진행을 억제한다.
- 진행된 류마티스관절염에서도 스테로이드 (<15mg/day)가 질병 활성도를 항상시킨다.

류마티스관절염에서 스테로이드 투여의 원칙

- DMARD 없이 스테로이드 단독 투여는 피하라.
- 관절 증세를 조절하는데 10mg/day 이상이 필요한 경우는 거의 없다.
- 최대의 효과를 보이는 최소한의 용량으로 줄이라.
- DMARDs가 효과를 보일 때까지 bridge therapy로 사용할 수 있다.
- 스테로이드 부작용을 놓 염두 해 두라.

Synthetic DMARDs for Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Serious Toxicities</th>
<th>Other Common Side Effects</th>
<th>Initial Evaluation</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxychloroquine</td>
<td>200-400 mg/d oral (≤6.5 mg/kg)</td>
<td>Irreversible retinal - damage Cardiotoxicity Blood dyscrasia</td>
<td>Nausea Diarrhea Headache Rash</td>
<td>Eye examination (&gt;40 years old or prior ocular disease)</td>
<td>Funduscopie &amp; visual field test every 12 month</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Initial: 500 mg oral twice daily Maintenance: 1000-1500 mg twice daily</td>
<td>Granulocytopenia Hemolytic anemia (with G6PD deficiency)</td>
<td>Nausea Diarrhea Headache</td>
<td>CBC, LFTs G6PD level</td>
<td>CBC every 2-4 weeks for first 3 months, then every 3 months</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>10-25 mg/week Orally or SQ Folic acid 1 mg/d to reduce Toxicities</td>
<td>Hepatotoxicity Myelosuppression Infection Interstitial pneumonia Pregnancy category X</td>
<td>Nausea Diarrhea Stomatitis/ mouth ulcers Alopecia Fatigue</td>
<td>CBC, LFTs Viral hepatitispenta Chest x-ray</td>
<td>CBC, creatinine, LFTs every 2-3 months</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>10-20 mg/d</td>
<td>Hepatotoxicity Myelosuppression Infection Pregnancy category X</td>
<td>Alopecia Diarrhea</td>
<td>CBC, LFTs Viral hepatitispenta</td>
<td>CBC, creatinine, LFTs every 2-3 months</td>
</tr>
</tbody>
</table>
## Biological DMARDs for Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Serious Toxicities</th>
<th>Other Common Side Effects</th>
<th>Initial Evaluation</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>3 mg/kg IV at weeks 0, 2, 6, then every 8 wks. May increase dose up to 10 mg/kg every 4 wks</td>
<td>1 Risk bacterial, fungal infections, Reactivation of latent TB, Lymphoma risk (controversial), Drug-induced lupus, Neurologic deficits</td>
<td>Infusion reaction, LFTs</td>
<td>PPD skin test</td>
<td>LFTs periodically</td>
</tr>
<tr>
<td>Etanercept</td>
<td>50 mg SQ weekly, or 25 mg SQ biweekly</td>
<td>As above</td>
<td>Injection site reaction</td>
<td>PPD skin test</td>
<td>Monitor for injection site reactions</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>40 mg SQ every other week</td>
<td>As above</td>
<td>Injection site reaction</td>
<td>PPD skin test</td>
<td>Monitor for injection site reactions</td>
</tr>
<tr>
<td>Golimumab</td>
<td>50 mg SQ monthly</td>
<td>As above</td>
<td>Injection site reaction</td>
<td>PPD skin test</td>
<td>Monitor for injection site reactions</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>400 mg SQ weeks 0, 2, 4, then 200 mg every other week</td>
<td>As above</td>
<td>Injection site reaction</td>
<td>PPD skin test</td>
<td>Monitor for injection site reactions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Serious Toxicities</th>
<th>Other Common Side Effects</th>
<th>Initial Evaluation</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept</td>
<td>Weight based: &lt;60 kg: 500 mg, 60-100 kg: 750 mg, &gt;100 kg: 1000 mg IV dose at weeks 0, 2, 6, and then every 4 weeks OR 125 mg SQ weekly</td>
<td>1 Risk bacterial, viral infections, Headache, Nausea</td>
<td>Injection site reaction, Headache</td>
<td>PPD skin test</td>
<td>Monitor for infusion reactions</td>
</tr>
<tr>
<td>Anakinra</td>
<td>100 mg SQ daily</td>
<td>1 Risk bacterial, viral infections, Reactivation of latent TB, Neutopenia</td>
<td>Injection site reaction, Headache</td>
<td>PPD skin test</td>
<td>CBC every month for 3 months, then every 4 months for 1 year Monitor for injection site reactions</td>
</tr>
<tr>
<td>Rituximab</td>
<td>1000 mg IV x 2, days 0 and 14. May repeat course every 24 weeks or more Premedicate with methylprednisolone 100 mg to decrease infusion reaction</td>
<td>1 Risk bacterial, viral infections, Infusion reaction, Cytopenia, Hepatitis B reactivation, Rash, Fever</td>
<td>CBC, Viral hepatitis panela</td>
<td>CBC at regular intervals</td>
<td>CBC at regular intervals</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>4-8 mg/kg IV monthly OR 162 mg SQ every other week (≤100 kg weight) 162 mg SQ every week (≥100 kg weight)</td>
<td>Risk of infection, Infusion reaction, LFT elevation, Dyslipidemia, Cytopenias</td>
<td></td>
<td>PPD skin test</td>
<td>CBC and LFTs at regular intervals</td>
</tr>
</tbody>
</table>
ACR/EULAR Provisional Definition of Remission in RA

At any time point, patient must satisfy all of the following:
Tender joint count ≤1
Swollen joint count ≤1
C-reactive protein ≤1 mg/dL
Patient global assessment ≤1 (on a 0–10 scale)

OR

At any time point, patient must have a Simplified Disease Activity Index score of ≤3.3

중례 6

• 42 세 여자
• 3 개월 전부터
Swelling, tenderness of both wrists and several hand PIP joints
Lab

- CBC 8,800/ 10.1/ 389,000
- BC Alb 3.2 g/dL, otherwise WNL
- ESR 67 mm/hr, CRP 2.5 mg/dL (<0.47)
- RF 67.1 IU/mL (<20.0)
- Anti-CCP antibody 99.3 U/mL (<7.0)

---

**Table 3. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis**

<table>
<thead>
<tr>
<th>Target population (Who should be tested?): Patients who</th>
<th>Score</th>
</tr>
</thead>
</table>
| 1) Have at least 1 joint with definite clinical synovitis (swelling)*  
2) With the synovitis not better explained by another disease |          |
| Classification criteria for RA (score-based algorithm): add score of categories A-D;  
a score of ≥6/10 is needed for classification of a patient as having definite RA:** |          |

**A. Joint involvement**

- Large joints‡
  - ≥2 large joints
- 3 small joints (with or without involvement of large joints)‡
- 4–10 small joints (with or without involvement of large joints)
- >10 joints (at least 1 small joint)*

**B. Serology** (at least 1 test result is needed for classification)††

- Negative RF and negative ACPA
- Low-positive RF or low-positive ACPA
- High-positive RF or high-positive ACPA

**C. Acute-phase reactants (at least 1 test result is needed for classification)‡‡

- Normal CRP and normal ESR
- Abnormal CRP or abnormal ESR

**D. Duration of symptoms¶¶

- <6 weeks
- ≥6 weeks

* "Large joints" refers to shoulders, elbows, hips, knees, and ankles.

† "Small joints" refers to the MCP, PIP, 2nd-5th MTP, thumb IP, and wrists.

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Imaging:

How? to early detect erosion and synovitis?

Why?
Early diagnosis

- Early starting DMARD therapy

Image – additional (1)
주지현: 류마티스관절염의 진단과 치료

Image – additional (2)

Image – additional (3)

Coronal T1 (A) and inversion recovery (a T2-weighted sequence) (B) images
강직성 척추염의 진단과 치료

경희대학교 의과대학 류마티스내과

이상훈

강직성 척추염
(ankylosing spondylitis)

1984년 미국 뉴욕 기준
- X선에서 반드시 천장관절 변화
- 척추 증상
  1. 3개월 이상의 만성 요통
  2. 요추의 운동범위 장애
  3. 흉추의 운동범위 장애(가슴둘레)

척추관절염
(spondyloarthritis)

1961년 로마 기준~현재 ASAS 기준
“류마티스 관절염과 구분하기 위해”
- RF (-)
- asymmetric, oligoarthritis
- lower limb
- HLA B27
- psoriasis
- 척추 휘부
- 포도막염
강직성 척추염의 진단과 치료

Axial SpA

- nonradiographic axial SpA
- Ankylosing spondylitis
- SI joint sparing axial SpA

PPh. SpA

Axial Spondyloarthritis

Non-radiographic stage
- Back pain
- Sacroiliitis on MRI

Radiographic stage
- Back pain
- Radiographic sacroiliitis
- Back pain
- Syndesmophytes

Modified New York Criteria 1984

Time (years)

1. 먼저 강직성 척추염을 먼저 진단한다.
   1) pelvis X-ray
   2) pelvis CT

2. Axial spondyloarthritis (척추 척추관절염)을 진단한다.
   1) SI joint MRI
   2) acute phase reactant (ESR, CRP)
   3) HLA B27
   4) peripheral arthritis, psoriasis, uveitis, IBD, enthesitis Hx

3. peripheral spondyloarthritis 진단

CASE

19세 남자가 양측 변갑아 가며 생기는 염덩이 통증으로 왔다.

1) inflammatory back pain vs mechanical back pain

Inflammatory Back Pain (IBP)
According to Various Criteria

<table>
<thead>
<tr>
<th>Cailin et al.</th>
<th>Rudwaleit et al.</th>
<th>IBP experts (ASAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- age at onset &lt; 45 yrs</td>
<td>- morning stiffness &gt; 30 min</td>
<td>- age at onset &lt; 45 yrs</td>
</tr>
<tr>
<td>- duration of back pain &gt; 3 months</td>
<td>- improvement with exercise, not with rest</td>
<td>- insidious onset</td>
</tr>
<tr>
<td>- insidious onset</td>
<td>- inactivity</td>
<td>- improvement with exercise</td>
</tr>
<tr>
<td>- morning stiffness</td>
<td>- awakening at 2/3 of the night</td>
<td>- no improvement with rest</td>
</tr>
<tr>
<td>- improvement with exercise</td>
<td></td>
<td>- pain at night</td>
</tr>
</tbody>
</table>

IBP if 4 / 5 are present.  
IBP if 2 / 4 are present.  
IBP if 4 / 5 are present.
CASE

19세 남자가 1년전부터 시작된 양측 변갈아 가며 생기는 엉덩이 통증으로 왔다.

1) inflammatory back pain vs mechanical back pain
2) Pelvis x-ray
3) pelvis CT
Diagnosis

Modified New York Criteria for ankylosing spondylitis

1. chronic inflammatory back pain
2. limitation of motion in ant. flexion, lat. flexion and extension
3. limitation of chest expansion to 2.5cm or less at the 4th ICS

bilateral sacroiliitis (grade > II/II)
unilateral sacroiliitis (grade >III)
이상훈: 강직성 척추염의 진단과 치료

CASE

24세 남자가 1년 전부터 시작된 요통으로 병원에 왔다.

통증의 양상

자는 동안 허리가 아파서 깨고, 주로 오전에 아프고 오래 앉아 있으면 아프다.
간혹 엉치 부위가 아프기도 하다.

1) inflammatory back pain vs mechanical back pain.
2) 강직성 척추염을 배제하기 위해 pelvis X-ray, CT 시행.
3) nonradiographic Axial Spondyloarthritis 를 진단.
CASE

24세 남자가 1년 전부터 시작된 요통으로 병원에 왔다.

1) inflammatory back pain vs mechanical back pain.

통증양상
머리를 감으려고 허리를 굽힐 때 아프다.
오래 앉아 있으면 허리가 아프고, 엉치와 허벅지 뒤편이 당간다.

NASAIIDs 먹어도 효과가 전혀 없다.

신체검진
no tenderness in SI jt, L spine

Mechanical back pain >> inflammatory back pain
CT, MRI, ESR, CRP, HLA B27 : all negative

Diagnostic Pyramide for Axial Spondyloarthritis

Chronic low back pain
Inflammatory back pain + LR 3.1
Heel pain (enthesitis) + LR 3.4
Peripheral arthritis LR 4.0
Dactylitis LR 4.5
Acute anterior uveitis LR 7.3
Pos. Family history LR 6.4
Good response to NSAIDs LR 5.1
Elevated acute phase reactants LR 2.5
HLA-B27 + LR 9.0
MRI LR 9.0

Axial SpA LR likelihood ratio

Rudwaleit M et al. Arthritis Rheum 2005;52:1000-6 (with permission)
16세 남자가 양측 변갈이 가며 생기는 엉덩이 통증으로 왔다.

1) inflammatory back pain vs mechanical back pain

2) Pelvis x-ray

3) pelvis CT

CASE

STIR oblique coronal image
CASE

16세 남자가 양측 변갑에 가며 생기는 염증이 통증으로 왔다.

4) SpA features
   - ESR 40mm/hr, CRP : 1.3 mg/dL
   - HLA B27 +
   - NSAIDs response +
### ASAS Classification Criteria for Axial Spondyloarthritis (SpA)

In patients with $\geq 3$ months back pain and age at onset $< 45$ years

<table>
<thead>
<tr>
<th>Sacroiliitis on imaging*</th>
<th>OR</th>
<th>HLA-B27</th>
</tr>
</thead>
<tbody>
<tr>
<td>plus</td>
<td></td>
<td>plus</td>
</tr>
<tr>
<td>$\geq 1$ SpA feature*</td>
<td></td>
<td>$\geq 2$ other SpA features*</td>
</tr>
</tbody>
</table>

*SpA features
- inflammatory back pain
- arthritis
- enthesitis (heel)
- uveitis
- dactylitis
- psoriasis
- Crohn's\'s disease
- good response to NSAIDs
- family history for SpA
  - HLA-B27
  - elevated CRP

*Sacroiliitis on imaging
- active (acute) inflammation on MRI
  - highly suggestive of sacroiliitis associated with SpA
- definite radiographic sacroiliitis according to mod NY criteria

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### Imaging Comparison

#### 2005, 9

![Image 1](image1.png)

#### 2006, 5

![Image 2](image2.png)

#### 2007, 5

![Image 3](image3.png)
Axial Spondyloarthritis

Non-radiographic stage
- Back pain
- Sacroilitis on MRI

Radiographic stage
- Modified New York Criteria 1984
  - Back pain
  - Radiographic sacroilitis
  - Back pain
  - Syndesmophytes

Time (years)

Proposed Sequence of Structural Damage in Ankylosing Spondylitis

- Inflammation
- Erosive damage
- Repair
- New bone formation


이상훈: 강직성 척추염의 진단과 치료

**MRI 급여 인정 기준**

1. 척추질환
   1. 염증성 척추병증
   2. 척추 골절
   3. 강직성 척추염

2. 진단
   1. 진료소 추가촬영의 필요성이 있는 경우 별도 인정함.

3. 신경학적
   1. 예: 2의 a~b에 해당하는 질환은 진단시 1회 인정하되, 새로운 병변이 발생되어 추가촬영한 경우에 인정함.
제22차 대한류마티스학회 연수강좌 - 개원의를 위한 증례 중심의 류마티스 질환 치료지침

치료의 목표 = 진행을 억제

1. NSAIDs: maximum dosage 48시간 후: 거의 효과가 없어짐.
2. TNF-alpha blocker: NSAIDs 각 2주씩 2개 이상 FAIL (보험기준 12주)
3. DMARDs (+-): pph arthritis: sulfasalazine
4. local steroid injection (enthesitis)
5. physical therapy

Modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS)

- Lateral view lumbar and cervical spine
- Anterior sites of the vertebrae are scored for
  - Squaring
  - Erosions
  - Sclerosis
  - Syndesmophytes
- Score range 0-72

mSASSS recommended by ASAS

Ankylosing Spondylitis Disease Activity Score (ASDAS) 2

Calculation of the ASDAS

\[ \text{ASDAS}_{\text{CRP}} = 0.12 \times \text{Total Back Pain} + 0.08 \times \text{Duration of Morning Stiffness} + 0.11 \times \text{Patient Global} + 0.07 \times \text{Peripheral pain/Swelling} + 0.58 \times \ln(\text{CRP}+1) \]

\[ \text{ASDAS}_{\text{ESR}} = 0.08 \times \text{Total Back Pain} + 0.07 \times \text{Duration of Morning Stiffness} + 0.11 \times \text{Patient Global} + 0.09 \times \text{Peripheral pain/Swelling} + 0.29 \times \text{Y-ESR} \]

**ASDAS \text{CRP} is the preferred ASDAS but the ASDAS \text{ESR} can be used in case CRP is not available.**

CRP in mg/l; all patient assessments on a 10 cm scale.


ASDAS Cut-Offs for Status Scores

- Inactive disease
- Moderate disease activity
- High disease activity
- Very high disease activity

Figure 2
Histologic evidence of defective fracture healing in COX-2−/− mice. Histologic sections were obtained from tibial fractures of adult wild-type (a, c, and e) and COX-2−/− mice (b, d, and f) at 7 (a and b), 14 (c and d), and 21 days (e and f) after fracture, and stained with Alcian blue; hematoxylin as described in Methods. Fractures in wild-type mice undergo extensive calcification resulting in little residual cartilage (arrow) and extensive woven bone formation (asterisk) by day 14 (c). This progresses to a remodeling bony union (#) by day 21. In the COX-2−/− mice there is little evidence of endochondral bone formation in the medullary canal, which is filled with undifferentiated mesenchymal tissue (asterisk) on day 14 (d). Concurrently, significant amounts of unmineralized cartilage persists (arrow) (d). By 21 days there are large amounts of fibrotic tissue (#) between the fractured bones, evidence of a fracture nonunion (f).

NSAID Therapy in Ankylosing Spondylitis: Radiographic Progression

Less Radiographic Progression (mSASSS*) after 2 Years of Continuous vs. On Demand Use of NSAIDs (n = 150)

<table>
<thead>
<tr>
<th>Continuous NSAIDs</th>
<th>On demand NSAIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>mod. SASSS (mean change)</td>
<td></td>
</tr>
<tr>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

*adjusted with limited time sequence


Patients with Risk Factors for Radiographic Spinal Progression ( Syndesmophytes, Elevated CRP) Benefit most from NSAID Therapy

AS patients with syndesmophytes at baseline and elevated time-averaged CRP

Low NSAID intake (n=11) NSAID Intake Score <50
High NSAID intake (n=7) NSAID Intake Score 250

AS patients without syndesmophytes and with normal time-averaged CRP

Low NSAID intake (n=26) NSAID Intake Score <50
High NSAID intake (n=7) NSAID Intake Score 250

TNF alpha blocker

1. infliximab (chimeric human/mouse anti-TNF-α monoclonal antibody),
2. etanercept (soluble p75 TNF-α receptor-IgG fusion protein),
3. adalimumab or 4. golimumab (human anti-TNF-α monoclonal antibodies)

3개월간 2가지 이상의 NSAIDs 혹은 DMARDs를 투여 후에도 BASDAI가 4이상일 때 투여 가능
(전신 피로감, 근육통증, 부역부통증, 밑저관절 통증, 조조강직)

TNF alpha blocker 금여 기준

두 가지 중류 이상의 비스테로이드항염제(NSAIDs) 혹은 DMARDs로 3개월 이상 치료를 하였으나 치료효과가 미흡하거나, 상기 약제들의 부작용 등으로 치료를 중단한, 증증의 활동성 감소

1) Modified New York criteria 1984(이래 창조)를 근거로 하여, 방사선학적 기준(Radiologic criteria)과 2개 이상의(1)항은 반드시 포함)의 임상적 기준(Clinical criteria)이 동시에 만족하는

2. 평가방법
가) 투여 3개월째 평가를 통하여 Bath 감각성척추염 활성도(BASDAI)가 50% 또는 2(scale 0~10)이상 감소한 경우 추가 6개월의 투여를 인정함
나) 이후에는 6개월마다 평가를 하여 첫 3개월째의 평가결과가 유지되며 추가투여를 인정함.
Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) on an NRS

1. How would you describe the overall level of fatigue today? (1-10 scale)
   - 1: Virtually no fatigue
   - 10: Very severe fatigue

2. How would you describe the overall level of back pain today? (1-10 scale)
   - 1: Virtually no pain
   - 10: Very severe pain

3. How would you describe the overall level of pain in joints other than neck, back, hips, or knees today? (1-10 scale)
   - 1: Virtually no pain
   - 10: Very severe pain

4. How would you describe the overall level of discomfort you have today as compared to your usual level of discomfort? (1-10 scale)
   - 1: Virtually no discomfort
   - 10: Very severe discomfort

5. How would you describe the overall level of morning stiffness you have today? (1-10 scale)
   - 1: Virtually no stiffness
   - 10: Very severe stiffness

6. How long does your morning stiffness last from the time you wake up? (1-10 scale)
   - 0: Less than 1 hour
   - 10: More than 2 hours

Calculation of BASDAI:
- Compute the mean of questions 5 and 6.
- Calculate the sum of the values of questions 1-4 and add the result to the mean of questions 5 and 6.
- Divide the result by 5.

Alternatively, a VAS between 0 and 10 cm or 0 and 100 mm can be used. ASAS prefers to use a NRS.
강직성 척추염의 치료

TNF-alpha blocker

X. Baraliakos, J. Davis, W. Tsuji, and J. Braun

Arthritis & Rheumatism Vol 52, April 2005

강직성 척추염의 치료

Rate of mSASSS Progression

▶ TNF-inhibitor Early
▶ TNF-inhibitor Late

Cumulative Probability

Summary

(1) 전장관절 MRI 검사가 중요하며 원인을 확인하여 적절한 치료를 진행할 수 있다.
(2) 스펙트럼의 류마티스 합병증에 대해 조기에 치료를 시작해야 한다.
(3) NSAIDs로 70%의 환자에서 치료 반응을 보였다고 2년간 귀중한 치료 시 75%에서 치료 반응이 보였다.
(4) NSAIDs에 반응하지 않는 환자에서 TNF alpha blocker의 투여로 치료를 시작해야 한다.
제 2 세션

좌장 : 유 빔(울산의대)
Diagnosis and Treatment of Systemic Lupus Erythematosus

2012 Clinical and Immunologic Criteria used in the SLICC Classification System

Clinical criteria
- Acute cutaneous lupus
- Subacute cutaneous lupus
- Chronic cutaneous lupus
- Oral ulcers or nasal ulcers
- Nonscarring alopecia
- Synovitis
- Serositis
- Renal
- Neurologic
- Hemolytic anemia
- Leukopenia or lymphopenia
- Thrombocytopenia

Immunologic criteria
- ANA
- Anti-dsDNA antibody
- Anti-Sm antibody
- Antiphospholipid antibody
- Low serum complement
- Direct Coombs’ test

✓ Criteria are cumulative and need not be present concurrently.
✓ Requirements: ≥4 criteria (including at least 1 clinical and 1 immunologic criterion) or biopsy-proven nephritis compatible with SLE in the presence of ANAs or anti-dsDNA antibodies.
Clinical criteria
1. Acute or subacute cutaneous lupus

Acute cutaneous lupus
- Lupus malar rash (do not count if malar discoid)
- Bullous lupus
- Toxic epidermal necrolysis variant of SLE
- Maculopapular lupus rash
- Photosensitive lupus rash
  *in the absence of dermatomyositis*

Subacute cutaneous lupus
- Nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with post-inflammatory dyspigmentation or telangiectasias

Clinical criteria
1-1. Acute cutaneous lupus

Lupus malar rash
- Erythematous, elevated, pruritic or painful, in a malar distribution, commonly precipitated by exposure to sunlight
Clinical criteria

1-1. Acute cutaneous lupus

Bullous lupus
- an autoantibody-mediated subepidermal blistering disease

Maculopapular lupus rash
- appearance of small and red spots on the skin.
- combination of macules and papules, which cause inflammation and hyperpigmentation on the skin.
Clinical criteria

1-2. Subacute cutaneous lupus

- Nonindurated psoriaform
- Annular polycyclic lesions

- Subacute cutaneous lupus typically manifests in 1 of 2 forms
- Strongly associated with anti-Ro and anti-La antibodies and articular manifestations
- Photosensitive distribution

Clinical criteria

2. Chronic cutaneous lupus

- Classic discoid rash
  - Localized (above the neck)
  - Generalized (above and below the neck)
- Hypertrophic ( verrucous ) lupus
- Lupus panniculitis ( profundus )
- Mucosal lupus
- Lupus erythematosus tumidus
- Chillblains lupus
- Discoid lupus/lichen planus overlap
Clinical criteria

2. Chronic cutaneous lupus

Discoid rash
- the most common chronic dermatitis in lupus
- Lesions are roughly circular with slightly raised, scaly hyperpigmented erythematous rims and depigmented, atrophic centers in which all dermal appendages are permanently destroyed.

Clinical criteria

2. Chronic cutaneous lupus

Hypertrophic (verrucous) lupus
- Hypertrophic verrucous or vegetative plaques with indurated borders and minimal scaling frequently reported on extensors of forearms, face, and upper part of trunk
Clinical criteria

2. Chronic cutaneous lupus

Lupus panniculitis (profundus)
- Persistent, firm, well defined nodules and plaques on face, scalp, breast, arms, thighs, and buttocks characterize it generally, which may ulcerate and heal with scarring.

Lupus erythematosus tumidus
- Erythematous papules, plaques, or annular lesions with a succulent appearance
- On sun-exposed areas such as the neck, shoulders, face, and arms.
- The absence of desquamation, follicular plugs, or atrophy
- Heal without leaving a scar or hypopigmentation.
Clinical criteria

2. Chronic cutaneous lupus

Chilblains lupus
- Painful erythematous nodules on fingers and toes during cooler months.

Clinical criteria

2. Chronic cutaneous lupus

Discoid lupus/lichen planus overlap
- a flat-topped, polygonal, violaceous papule 2–6 mm in diameter
- characteristic shiny appearance of the individual papules
Clinical criteria

3. Oral or nasal ulcers

**Oral ulcers**
- Palate
- Buccal
- Tongue

**Nasal ulcers**
in the absence of other causes, such as vasculitis, Behchet’s disease, infection (herpesvirus), inflammatory bowel disease, reactive arthritis, and acidic foods

Clinical criteria

4. Nonscarring alopecia

- Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs)
in the absence of other causes such as alopecia areata, drugs, iron deficiency, and androgenic alopecia

* Scarring alopecia in DLE
Clinical criteria
5. Synovitis

- Synovitis involving 2 or more joints, characterized by swelling or effusion
  OR
- Tenderness in 2 or more joints and at least 30 minutes of morning stiffness

Clinical criteria
6. Serositis

- Typical pleurisy for more than 1 day
- OR pleural effusions
- OR pleural rub

- Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day
- OR pericardial effusion
- OR pericardial rub
- OR pericarditis by electrocardiography
  \( \text{in the absence of other causes, such as infection, uremia, and Dressler's pericarditis} \)
Clinical criteria

7. Renal

- Urine protein-to-creatine ratio (or 24-hour urine protein) representing 500 mg protein/24 hours
  OR
- Red blood cell casts

Clinical criteria

8. Neurologic

- Seizures
- Psychosis
- Mononeuritis multiplex
  \[\text{in the absence of other known causes such as primary vasculitis}\]
- Myelitis
- Peripheral or cranial neuropathy
  \[\text{in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus}\]
- Acute confusional state
  \[\text{in the absence of other causes, including toxic/metabolic, uremia, drugs}\]
Clinical criteria

9-11. Hemolytic anemia, leukopenia, thrombocytopenia

- Hemolytic anemia
- Leukopenia (4,000/mm³ at least once) 
  *in the absence of other known causes such as Felty’s syndrome, drugs, and portal hypertension*
  OR
- Lymphopenia (1,000/mm³ at least once) 
  *in the absence of other known causes such as corticosteroids, drugs, and infection*
- Thrombocytopenia (100,000/mm³ at least once) 
  *in the absence of other known causes such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura*

Immunologic criteria

1. ANA level above laboratory reference range
2. Anti-dsDNA antibody level above laboratory reference range
   (or 2-fold the reference range if tested by ELISA)
3. Anti-Sm: presence of antibody to Sm nuclear antigen
4. Antiphospholipid antibody positivity as determined by any of the following:
   - Positive test result for lupus anticoagulant
   - False-positive test result for rapid plasma reagin
   - Medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM)
   - Positive test result for anti-ß2-glycoprotein I (IgA, IgG, or IgM)
5. Low complement: Low C3, C4, or CH50
6. Direct Coombs’ test *in the absence of hemolytic anemia*
Frequency of various manifestations of SLE

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>Onset</th>
<th>Anytime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>77%</td>
<td>85%</td>
</tr>
<tr>
<td>Constitutional</td>
<td>53%</td>
<td>77%</td>
</tr>
<tr>
<td>Skin</td>
<td>53%</td>
<td>78%</td>
</tr>
<tr>
<td>Arthritis</td>
<td>44%</td>
<td>63%</td>
</tr>
<tr>
<td>Renal</td>
<td>38%</td>
<td>74%</td>
</tr>
<tr>
<td>Raynaud's</td>
<td>33%</td>
<td>60%</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>24%</td>
<td>54%</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>23%</td>
<td>50%</td>
</tr>
<tr>
<td>Mucous membranes</td>
<td>21%</td>
<td>52%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>18%</td>
<td>45%</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>16%</td>
<td>32%</td>
</tr>
<tr>
<td>Pleurisy</td>
<td>16%</td>
<td>30%</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>13%</td>
<td>23%</td>
</tr>
<tr>
<td>Lung</td>
<td>7%</td>
<td>14%</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>5%</td>
<td>11%</td>
</tr>
<tr>
<td>Azotemia</td>
<td>3%</td>
<td>8%</td>
</tr>
<tr>
<td>Myositis</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>2%</td>
<td>6%</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Diagnosis of SLE

- **Laboratory test**
  - CBC, PT, aPTT
  - BC
  - UA with microscopy
  - ANA, ENA
  - Antiphospholipid.ab
  - Complements
  - Chest X-ray
  - ECG

- **History**
  - Skin rash
  - Photosensitivity
  - Raynaud phenomenon
  - Arthralgia
  - Alopecia
  - Mucosal ulcer
  - Weight gain
  - General symptoms

- **Physical examination**
  - Skin rash
  - Arthritis
  - Alopecia
  - Mucosal ulcer
  - Digital pitting scar
  - Pitting edema
  - Lymphadenopathy
  - Splenomegaly
  - Serositis
**Diagnosis of SLE**

Symptom complex suggested of SLE

Lab test: ANA, CBC, U/A

- All tests normal
  - Symptoms subside: **Not SLE**
  - Symptoms persist: ANA positive

- All tests normal
  - ANA positive: Definite SLE (≥4 criteria) or Possible SLE (<4 criteria)
    - Definite SLE (≥4 criteria)
    - Possible SLE (<4 criteria)

- All negative: Repeat ANA, add anti-dsDNA, anti-Ro
- Some positive: Treatment

**Prevalence of serological features in SLE**

<table>
<thead>
<tr>
<th>Serological features</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinuclear antibodies</td>
<td>96</td>
</tr>
<tr>
<td>Anti-DNA antibodies</td>
<td>78</td>
</tr>
<tr>
<td>Anti-Ro (SSA) antibodies</td>
<td>25</td>
</tr>
<tr>
<td>Anti-LA (SSB) antibodies</td>
<td>19</td>
</tr>
<tr>
<td>Anti-RNP antibodies</td>
<td>13</td>
</tr>
<tr>
<td>Anti-Sm antibodies</td>
<td>10</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>18</td>
</tr>
<tr>
<td>IgG anticardiolipin antibodies</td>
<td>24</td>
</tr>
<tr>
<td>IgM anticardiolipin antibodies</td>
<td>13</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>15</td>
</tr>
</tbody>
</table>
Monitoring of SLE disease activity

<table>
<thead>
<tr>
<th>Domain/outcome</th>
<th>Measure(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease activity</td>
<td>SLEDAI and its versions and modifications (SLEDAI, SLEDAI-2K, Mex-SLEDAI, SELENA-SLEDAI)</td>
</tr>
<tr>
<td></td>
<td>SRI-50</td>
</tr>
<tr>
<td></td>
<td>BILAG index</td>
</tr>
<tr>
<td></td>
<td>SLAM and its versions (SLAM, SLAM-R, SLAQ)</td>
</tr>
<tr>
<td></td>
<td>Flare indices: SELENA-SLEDAI Flare Index, BILAG (development of new A or B scores)</td>
</tr>
<tr>
<td></td>
<td>Others: ECLAM, LAI, SIS, RIFLE</td>
</tr>
<tr>
<td>Damage</td>
<td>SLICC-ACR damage index</td>
</tr>
<tr>
<td></td>
<td>LDIIQ</td>
</tr>
<tr>
<td></td>
<td>Renal biopsy, end stage renal disease</td>
</tr>
</tbody>
</table>

*Nat. Rev. Rheumatol. 11, 613–620 (2015)*

Non-pharmacological management

- **Sunscreens** that block both ultraviolet-A and ultraviolet-B radiation, with a sun protection factor $\geq 55$

- **Smoking cessation**

- Modifiable risk factors for **coronary heart disease**

- **Avoid** specific medications can cause exacerbations of SLE high-dose estrogen and sulphonamide antimicrobial agents
Non-pharmacological management

- **Oral contraceptives** containing low-dose estrogen or progesterone-containing compounds are probably safe in mild, well-controlled SLE

- **Hormone replacement therapy** in postmenopausal women might be associated with increased flares of SLE

- **Pregnancy** should be avoided during active disease owing to the high risk of miscarriage and exacerbation of SLE

- **Prevention for osteoporosis** in patients on glucocorticoids
  - Any dose, ≥ 3 months: calcium 1200mg/d and vitamin D 800 IU/d through either diet and/or supplements.
  - PD ≥ 7.5mg/d (or equivalent) for ≥ 3 months: bisphosphonates

---

Corticosteroids in SLE

- **Low dose** (PD 0.1-0.2mg/kg/d)
  - Arthritis
  - Skin

- **Medium dose** (PD 0.3-0.5mg/kg/d)
  - Serositis
  - Hematological
  - Vasculitis
  - Renal

- **High dose/pulses** (PD 0.6-2mg/kg/d)
  - Neuropsychiatric
Therapy for cutaneous lupus

• Photo-protection
• Topical corticosteroids, topical tacrolimus
• Low-dose oral corticosteroids + antimalarial
• MTX: 75-80% efficacy in patients with malar rash, bullous lupus, chilblain LE, subacute cutaneous lupus, discoid lupus, oral mucosal manifestations
• MMF (2g/d): dermatomyositis, subacute cutaneous lupus, discoid lupus
• Dapsone (25-100mg/d): bullous LE, subacute cutaneous lupus, mucosal ulcers
• Thalidomide (lowest dose as possible, 300-400 → 50-200mg/d): severe and refractory cutaneous lupus

Therapy for articular manifestations

Three kinds of articular manifestations in SLE
• Non-erosive arthritis affecting finger, wrist, and knee joints: mc
• Non-erosive deforming arthropathy (Jaccoud’s arthritis)
• Erosive arthritis (rhupus)

Non-erosive arthritis
• Low-dose glucocorticoids and/or antimalarials
• NSAIDs

For severe cases
• MTX (15-20mg/w), leflunomide, azathioprine, cyclosporin
Therapy for serositis

- Medium-dose glucocorticoids and/or antimalarials
- MTX, azathioprine, cyclosporin
- No controlled data

25/F. Aseptic meningitis, fever
Pericardial and pleural effusion
Leukopenia, ANA, anti-Sm, LA, Direct Coombs'

Classification of lupus nephritis

<table>
<thead>
<tr>
<th>ISN/RPS (2003) classification of lupus nephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
</tr>
<tr>
<td>Class II</td>
</tr>
<tr>
<td>Class III</td>
</tr>
<tr>
<td></td>
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<tr>
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<tr>
<td>Class IV</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>Class V</td>
</tr>
<tr>
<td>Class VI</td>
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<td></td>
</tr>
</tbody>
</table>
Therapy for lupus nephritis

**Class I LN**
- Podocytopathy on EM (minimal change disease)
- Interstitial nephritis

PD 0.25-0.5mg/kg/d ± AZA 1-2mg/kg/d

**Class II LN**
- Nephrotic syndrome

ACE inhibitor or ARB
- Proteinuria>1g/d
- Hematuria

PD 0.25-0.5mg/kg/d ± AZA 1-2mg/kg/d

Management should be based on concomitant extra-renal lupus manifestations

---

Therapy for lupus nephritis

- Class III\(\_A\) or III\(\_A/C\) (±V) LN
- Class IV\(\_A\) or IV\(\_A/C\) (±V) LN
- Class V LN if proteinuria>1g/24h despite the use of RAAS blockers

6 months
- **Induction**
  - CYC or MMF

At least 3 years
- **Maintenance**
  - MMF or AZA

**Pulsed methyl-PD**
- 3 days
  - Mod-to-high dose PD
- 1 month
  - Low-dose PD
Therapy for lupus nephritis

Pure class V
if proteinuria > 1 g/day
despite use of RAAS blockers

Induction
MMF 2-3g/day
+ PD 0.5mg/kg/day

6 months

Maintenance
MMF 1-2g/day
OR
AZA 2mg/kg/day

Re-induction
Cyclophosphamide (CYC) 500-1000 mg/m²/monthly x 6
+ Pulse GC followed by
PD 0.5-1.0mg/kg/day

Improved

Not improved

* AZA (2 mg/kg/day) may be considered as an alternative to MMF or CYC in selected patients without adverse prognostic factors, or when these drugs are contraindicated, not tolerated or unavailable. AZA use is associated with a higher flare risk.
Therapy for neuropsychiatric lupus

**Box 1 | Estimated cumulative incidences of NPSLE syndromes**

**Common (>5%)**
- Headache (20–40% in whites, 3–5% in Asians)
- Cognitive dysfunction (10–20% in whites, 1–2% in Asians; severe forms uncommon (3–5%)
- Mood disorders (10–20% in Caucasians, 1–2% in Asians)
- Seizure disorders (7–10%; recurrent i.e. >2 episodes (epilepsy) in 12–22%)
- Cerebrovascular disease (7–10% in whites/African Americans, 4–8% in Hispanics; >5% in Asians; ischemic stroke/TIA is the most common manifestation >80%)
- Anxiety disorder (4–8% in whites, 0.5–1% in Asians)

**Uncommon (1–5%)**
- Acute confusional state (3.0–4.5%)
- Psychosis (2.5–3.5%)
- Polyneuropathy (2.0–3.0%)
- Myelopathy (1.0–1.5%)

**Rare (<1%)**
- Cranial neuropathy (0.5–1.0%)
- Mononeuropathy (e.g., mononeuropathy 0.5–1.0%)
- Aseptic meningitis (0.5–1.0%)
- Movement disorders (0.0%)
- Deep vein thrombosis (0.2%)
- Acute inflammatory demyelinating polyradiculoneuropathy (AIDP; formerly known as Guillain–Barré syndrome) (0.1%)
- Autonomic disorder (0.1%)
- Myasthenia gravis (0.1%)
- Plexopathy (<0.1%)

---

Therapy for neuropsychiatric lupus

**Neurologic symptoms and signs**

- SLE disease activity
- Autoantibodies (especially aPL)
- Brain imaging
- CSF study
- EEG/EMG
- Additional studies

**Assessment for neurologic severity**

- Is it associated with SLE
  - Severe
  - Mild

- Active SLE
  - Non-active SLE
  - Not related to SLE

**Pathogenic therapy**
- Anticonvulsant, antipsychotic, antidepressant

**Symptomatic therapy**
- Inflammation, thrombosis, autoantibodies

---

Targeted immunotherapies for lupus

Inhibitors for interferon-α, BAFF, BAFF/APRIL, CD20, CD22, T cell co-stimulation, TWEAK (for LN)

Thank You!
전신 혈관염의 진단과 치료

울산대학교 의과대학 류마티스내과

김 용 길

Systemic Vasculitis

혈관벽의 지속적인 염증

혈관 폐쇄, 동맥류, 출혈, 조직 염증 침윤

장기 흐혈 및 기능 부전, 전신 염증
### Primary vs. Secondary vasculitis?

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulomatosis with Polyangiitis</td>
<td>Drug-induced vasculitis</td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
<td>Infection</td>
</tr>
<tr>
<td>Eosinophilic GPA</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>Rheumatic diseases</td>
</tr>
<tr>
<td>Giant cell arteritis</td>
<td>(RA, SLE, Sjogren's syndrome, Scleroderma)</td>
</tr>
<tr>
<td>Takayasu's arteritis</td>
<td></td>
</tr>
<tr>
<td>IgA vasculitis</td>
<td></td>
</tr>
<tr>
<td>Essential mixed cryoglobulinemia</td>
<td></td>
</tr>
<tr>
<td>Behçet's syndrome</td>
<td></td>
</tr>
<tr>
<td>Isolated vasculitis of the CNS</td>
<td></td>
</tr>
<tr>
<td>Cogan's syndrome</td>
<td></td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td></td>
</tr>
</tbody>
</table>

### Type of vessels

- **Aorta**
  - 1st branches

- **Main visceral arteries**
  - & initial branches

- **Intraparenchymal arteries, Arterioles, Capillaries**
Immune Complex Vasculitis
Cryoglobulinemic vasculitis
IgA vasculitis (Henoch-Schönlein)
Hypocomplementemic urticarial vasculitis
(Anti-C1q Vasculitis)

Medium Vessel Vasculitis
Polyarteritis Nodosa
Kawasaki Disease

Anti-GBM disease

ANCA-associated Vasculitis
Microscopic polyangitis
Granulomatosis with Polyangiitis (Wegener's)
Eosinophilic Granulomatosis with Polyangiitis
(Churg-Strauss)

Large Vessel Vasculitis
Takayasu's arteritis
Giant cell arteritis

Large vessel

Medium vessel

Small vessel
Takayasu’s arteritis (Aortic arch syndrome, pulseless disease)

- Mikito Takayasu (1859-1938)
  - Ophthalmologist
  - Noted the ocular manifestations in 1908.

- Most commonly in young women (≤40 yrs)

- Common presenting symptoms
  - Affected limb claudication, dizziness, syncope
  - Decreased brachial artery pulse
  - Asystolic BP between arms >10 mmHg
  - Stroke, renovascular hypertension

---

**Case 1**

32/F

C/C: Rt. arm and leg weakness, aphasia

- 내원 1년전부터 간헐적인 어지러움증 발생.
- 내원 4일전 오른쪽 상하지의 위치감발생.
- 내원 3일전 aphasia 소견 보여 ER 내원.

<table>
<thead>
<tr>
<th>내원 시 BP</th>
<th>Rt</th>
<th>Lt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm</td>
<td>Pulse 측지 안됨</td>
<td>110/60</td>
</tr>
</tbody>
</table>

CBC: 11000-11.0-350k, **ESR 39, CRP 3.02**, Cr 0.7
1. Takayasu’s arteritis
2. Microscopic polyangiitis
3. Eosinophilic granulomatosis with polyangiitis
4. Granulomatosis with polyangiitis
5. IgA vasculitis
Outcome

Outcome of Takayasu Arteritis with Inactive Disease at Diagnosis: The Extent of Vascular Involvement As a Predictor of Activation

Seokchan Hong, Seung-Hyeon Bae, Seo Min Ahn, Deo-Ho Lim, Yong-Gil Kim, Chung-Keun Lee, and Bin Yoo


Renovascular hypertension

Giant cell arteritis (Temporal arteritis, Cranial arteritis, Granulomatous arteritis)

- Old age (≥50 yrs)
- Headache of new-onset or new type
- Jaw claudication
- Decreased temporal artery pulse
- Visual loss
- Fever, malaise, anorexia, weight loss
- ESR ≥50 mm/hr, Anemia

Necrotizing arteritis, with granulomatous inflammation with multinucleated giant cells
Polyarteritis nodosa

- Necrotizing vasculitis of medium-sized arteries
  *without* glomerulonephritis or granuloma formation
- Livedo reticularis
- Testicular pain or tenderness
- Mesenteric angina, digital ischemia
- Mononeuritis multiplex
- Renovascular hypertension, Azotemia
- HBV (HBsAg or Ab)

Case 2

20/M

- 4개월 전 scrotum의 painful swelling 발생
- 군병원에서 2주간 항생제 치료하였으나 호전없이 결핵성 부고환염 의심 하에 3주간 결핵약 복용.
  - US: r/o chronic epididymitis or tuberculous epididymitis
  - Urine AFB (-)
- 3개월 전부터 lower abdominal pain, Rt.flank pain 발생
- 2주전부터 악화되어 ER 방문.
  - Fever (-), Weight loss 14kg/6mon
  - Diffuse tenderness on lower abdomen.
  - Rt. CVA tenderness
  - Palpable nodular mass in scrotum
- CBC: 9800-14.3-374k, CRP: 6.73mg/dL
- BUN/Cr: 9/1.0, AST/ALT: 39/47, U/A (-)
1. Rt hydronephroureterosis

2. Ascites c mesenteric & omental infiltration
R/O Peritoneal inflammation
(TB peritonitis?)
1. Polyarteritis nodosa
2. Microscopic polyangiitis
3. Eosinophilic granulomatosis with polyangiitis
4. Granulomatosis with polyangiitis
5. IgA vasculitis
Outcome

- 5 factors score
  - Cr levels > 1.58 mg/dL
  - Proteinuria > 1 g/day
  - Severe GI involvement
  - Cardiomyopathy
  - CNS involvement

<table>
<thead>
<tr>
<th>FFS at onset</th>
<th>5-yr mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>11.9%</td>
</tr>
<tr>
<td>1</td>
<td>25.9%</td>
</tr>
<tr>
<td>≥ 2</td>
<td>46%</td>
</tr>
</tbody>
</table>

Immune Complex Vasculitis
- Cryoglobulinemic vasculitis
- IgA vasculitis (Henoch-Schönlein)
- Hypocomplementemic urticarial vasculitis (Anti-C1q Vasculitis)

Medium Vessel Vasculitis
- Polyarteritis Nodosa
- Kawasaki Disease
  - Anti-GBM disease

Large Vessel Vasculitis
- Takayasu’s arteritis
- Giant cell arteritis

ANCA-associated Vasculitis
- Microscopic polyangiitis
- Granulomatosis with Polyangiitis (Wegener’s)
- Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)
Anti-Neutrophil Cytoplasmic Antibody (ANCA)

Cytoplasmic pattern (PR3)  Perinuclear pattern (MPO)

<table>
<thead>
<tr>
<th></th>
<th>ANCA (%)</th>
<th>PR3 (%)</th>
<th>MPO (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPA</td>
<td>90%</td>
<td>66%</td>
<td>24%</td>
</tr>
<tr>
<td>MPA</td>
<td>75%</td>
<td>26%</td>
<td>58%</td>
</tr>
<tr>
<td>EGPA</td>
<td>50%</td>
<td>&lt;5%</td>
<td>50%</td>
</tr>
</tbody>
</table>

- Not all patients with WG/MPA/CSS have ANCA
- Positive serologies alone are not diagnostic

PR3: Proteinase-3
MPO: Myeloperoxidase

Microscopic Polyangiitis (MPA)

- Necrotizing arteritis involving small-sized arteries
- Necrotizing *glomerulonephritis* is very common.
- *Pulmonary capillaritis* or *interstitial lung disease* often occurs.
Granulomatosis with Polyangiitis (GPA)

- Necrotizing glomerulonephritis is common

- Classic triad
  - Upper respiratory tract (sinusitis)
  - Lower respiratory tract (cavitary lung nodules, pneumonitis)
  - Kidney (RPGN)

Eosinophilic Granulomatosis with Polyangiitis

- ACR criteria (≥ 4/6)
  1) Asthma
  2) Eosinophilia >10%
  3) Mono- or polyneuropathy
  4) Non-fixed pulmonary infiltrates
  5) Paranasal sinus abnormality
  6) Histological evidence of a blood vessel with extravascular eosinophils

- 3 phases
  - Initial prodrome (~a few yrs)
    : Asthma or allergic rhinitis
  - Eosinophilia, eosinophilic infiltration.
  - Necrotizing arteritis
    : Lung, kidney, peripheral nerves.
### ANCA-associated vasculitis (AAV)

<table>
<thead>
<tr>
<th></th>
<th>Microscopic Polyangiitis (MPA)</th>
<th>Granulomatosis with Polyangiitis (GPA) (Wegener's granulomatosis)</th>
<th>Eosinophilic Granulomatosis with Polyangiitis (EGPA) (Churg-Strauss syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANCA</strong></td>
<td>75%</td>
<td>90%</td>
<td>50%</td>
</tr>
<tr>
<td>Typical results</td>
<td>P-ANCA (MPO)</td>
<td>C-ANCA (PR3)</td>
<td>P-ANCA (MPO)</td>
</tr>
<tr>
<td>Upper respiratory tract</td>
<td>Usually absent or mild Nasal septal perforation Saddle-nose deformity Allergic rhinitis Subglottic stenosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>Interstitial lung disease</td>
<td>Nodules, infiltrates or cavitory lesions Asthma Infiltrates (non-fixed lesion) Alveolar hemorrhage</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>Necrotizing crescentic glomerulonephritis (pauci-immune)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distinguishing features</td>
<td>No granulomatous inflammation</td>
<td>Upper airway disease, Granulomatous inflammation Asthma, allergic rhinitis, hypereosinophilia, Granulomatous inflammation</td>
<td></td>
</tr>
</tbody>
</table>

### Case 3

**31/M**  
**C/C: Cough**

- 내원 2개월전부터 cough, sputum 발생하여 개인병원에서 URI로 치료하였으나 호전 없고 fever 동반하여 내원.

- Skin lesion (+) 하지의 erythematous plaque.
- Neuropathy (-)

- CBC: 6700-13.6-220k, CRP: 9.35 mg/dL
- U/A: albumin ±, OB-
- FANA (-), PR3-ANCA (+)
1. Giant cell arteritis
2. Microscopic polyangiitis
3. Eosinophilic granulomatosis with polyangiitis
4. Granulomatosis with polyangiitis
5. IgA vasculitis

<table>
<thead>
<tr>
<th></th>
<th>Remission rate</th>
<th>5-yr survival</th>
<th>Relapse (common in the first 2 yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPA</td>
<td>90%</td>
<td>70%</td>
<td>10%</td>
</tr>
<tr>
<td>GPA</td>
<td>80%</td>
<td>90%</td>
<td>50%</td>
</tr>
<tr>
<td>EGPA</td>
<td>90%</td>
<td>90%</td>
<td>35%</td>
</tr>
</tbody>
</table>


- Immunosuppressive therapy is indicated in all patients with active GPA or MPA. Even patients with advanced renal disease at presentation are highly likely to benefit.

<table>
<thead>
<tr>
<th>eGFR (mL/min)</th>
<th>Remission rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤30</td>
<td>72%</td>
</tr>
<tr>
<td>≤20</td>
<td>68%</td>
</tr>
<tr>
<td>≤10</td>
<td>57%</td>
</tr>
</tbody>
</table>

Immune Complex Vasculitis
- Cryoglobulinemic vasculitis
- IgA vasculitis (Henoch-Schönlein)
- Hypocomplementemic urticarial vasculitis (Anti-C1q Vasculitis)

Medium Vessel Vasculitis
- Polyarteritis Nodosa
- Kawasaki Disease
- Anti-GBM disease

Large Vessel Vasculitis
- Takayasu’s arteritis
- Giant cell arteritis

ANCA-associated Vasculitis
- Microscopic polyangiitis
- Granulomatosis with Polyangiitis (Wegener’s)
- Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

Immune complex-mediated vasculitis
- Pathogenic immune complex formed between Ag & Ab
- Immune complexes precipitate into the tissues
  → complement activation
- Immune complex deposits in the vascular endothelium or capillary bed (skin, kidney, lung)
IgA vasculitis (Henoch-Schonlein purpura)

- The most common vasculitis of childhood.
- URI precedes skin manifestations (2/3).
- Palpable purpura, Bowel angina, Arthralgia, IgA nephropathy
- Serum IgA elevation (1/2).
- Usually self-limited, resolve within 2 month.
- Severity, recurrence: adults > children.

![IgA staining](image)

1990 ACR classification criteria

<table>
<thead>
<tr>
<th>Palpable purpura</th>
<th>혈소판 감소와 무관한 중상/이완성 출혈피부병변</th>
</tr>
</thead>
<tbody>
<tr>
<td>발병연령</td>
<td>첫 증상이 20세 이전</td>
</tr>
<tr>
<td>복통 (Bowel angina)</td>
<td>혈변을 포함한 하혈장염 or 식후 악화되는 전반적 복통</td>
</tr>
<tr>
<td>조직소견</td>
<td>Granulocytes in the walls of small arterioles and/or venules</td>
</tr>
<tr>
<td>2개 이상 (민감도 87%, 특이도 88%)</td>
<td></td>
</tr>
</tbody>
</table>

2008 EULAR classification criteria

<table>
<thead>
<tr>
<th>Palpable purpura (혈소판 감소와 무관한 중상/이완성 출혈피부병변)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 복통</td>
</tr>
<tr>
<td>2. 조직소견</td>
</tr>
<tr>
<td>3. 관절염/관절통</td>
</tr>
<tr>
<td>4. 신장침범</td>
</tr>
<tr>
<td>Palpable purpura + 1개 이상 (민감도 100%, 특이도 87%)</td>
</tr>
</tbody>
</table>
Case 4

20/M
C/C: Abdominal pain with hematochezia
- 원 1 년 전 both lower leg에 palpable purpura 발생
- 원 1 개월 전 다시 purpura 발생
- 원 10 일 전 elbow painful swelling 발생
- 원 당일 severe abdominal pain, hematochezia 발생

- CBC: 12700-12 3-394k, ESR 18, CRP 0.43
- U/A: Albumin ++, OB+
- Duodenofibroscopy: mild duodenitis
- Colonoscopy: incomplete study due to blood clot.
  r/o small bowel bleeding.

Skin biopsy:
leukocytoclastic vasculitis.
1. Polyarteritis nodosa
2. Microscopic polyangiitis
3. Eosinophilic granulomatosis with polyangiitis
4. Granulomatosis with polyangiitis
5. IgA vasculitis
Outcome

Late-onset IgA vasculitis in adult patients exhibits distinct clinical characteristics and outcomes.

Authors' information

Abstract

OBJECTIVES: The aim of this study was to determine whether adult IgA vasculitic patients who developed the disease at an older age differ from early-onset patients in terms of clinical features and outcomes.

METHODS: A total of 21 adult patients who were diagnosed with IgA vasculitis between January 1997 and December 2014 were reviewed retrospectively. Patients who developed the disease at an older age (≥30 years) were compared with those with an earlier onset of disease (<30 years, early-onset). Renal insufficiency was defined as an estimated glomerular filtration rate ≤60 millimetre.

RESULTS: In total, 100 adult patients were diagnosed with IgA vasculitis (mean age, 45.61 ± 11.24 years), of whom 31 (31%) had late-onset disease. Compared with early-onset patients, late-onset patients were more likely to have a history of upper respiratory tract infection (31%) versus 14% (p = 0.04), and more likely to have renal involvement at presentation (27%) versus 21% (p = 0.017). At the last follow-up visit, late-onset patients were more likely to have chronic renal insufficiency, including end-stage renal disease (15%) versus 9% (p = 0.007). Multivariate Cox analysis revealed that late-onset was a significant risk factor for renal insufficiency at follow-up (hazard ratio, 9.95; 95% confidence interval, 4.30–22.0; p < 0.001).

CONCLUSIONS: Patients with late-onset IgA vasculitis in adults exhibit distinct clinical features characterized by greater renal involvement and worse renal outcomes. Thus, watchful follow-up might be needed for adult IgA vasculitis patients, in particular those with late-onset disease.

Prognostic factors for renal failure

<table>
<thead>
<tr>
<th>Variable at Entry</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine &gt; 1.20 mg/dL</td>
<td>4.27</td>
<td>0.983 to 18.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proteinuria &gt; 1 g/24 h</td>
<td>7.56</td>
<td>3.72 to 15.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glomerular sclerosis &gt; 10%</td>
<td>1.63</td>
<td>1.53 to 2.54</td>
<td>0.02</td>
</tr>
<tr>
<td>Intestinal fibrosis &gt; 10%</td>
<td>3.13</td>
<td>3.16 to 1.78</td>
<td>0.0008</td>
</tr>
</tbody>
</table>


Cryoglobulinemic vasculitis

Cryoglobulin?

- Immune complexes with tendency to precipitate under cold.
- Detectable in various inflammatory conditions.
- Cryoglobulin deposit in vessels & complement activation → cryoglobulinemic vasculitis.

<table>
<thead>
<tr>
<th>Type</th>
<th>Monoclonal IgG, IgM, IgA</th>
<th>Waldenström's macroglobulinemia, Multiple myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>Monoclonal IgM, polyclonal IgG</td>
<td>Hepatitis C infection</td>
</tr>
<tr>
<td>Type</td>
<td>Polyclonal IgG, IgM</td>
<td>Rheumatoid arthritis, SLE</td>
</tr>
</tbody>
</table>
- Skin and glomeruli, peripheral nerves are often involved

  PAS-positive microthrombi (precipitated cryoglobulins) that are occluding some of the capillary loops.

- Low C4 and high RF titer

---

**Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)**

- Vasculitis accompanied by urticaria and hypocomplementemia affecting small vessels
  - presence of anti-C1q Abs
  - Glomerulonephritis
  - Arthritis
  - Asthma or obstructive pulmonary disease
  - Ocular inflammation

<table>
<thead>
<tr>
<th></th>
<th>Urticaria</th>
<th>HUV</th>
</tr>
</thead>
<tbody>
<tr>
<td>혈종</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>자주간</td>
<td>3시간 이내</td>
<td>24시간 이후</td>
</tr>
<tr>
<td>피부 후 부중간</td>
<td>병변 완전 소멸</td>
<td>백소 혼합</td>
</tr>
<tr>
<td>패혈 부종</td>
<td>-</td>
<td>통반 가능</td>
</tr>
<tr>
<td>권협통/신장 이상</td>
<td>-</td>
<td>혈관 혼합 통반</td>
</tr>
</tbody>
</table>
Treatment (medical)

- Corticosteroids
- Cyclophosphamide (oral or iv)
- MTX
- Azathioprine
- Rituximab (anti-CD20 monoclonal antibody)
- Anti-TNF agents
- ± Plasmapheresis

5-yr survival rate

<table>
<thead>
<tr>
<th>GPA (WG)</th>
<th>mean survival</th>
<th>mean survival</th>
<th>75% remission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 months</td>
<td>12.5 months</td>
<td>75% remission</td>
</tr>
</tbody>
</table>

• Prednisolone 1mg/kg
• Cyclophosphamide 100mg/d PO
Treatment of ANCA Associated Vasculitis

- Mild disease
  - No evidence of organ/life-threatening manifestations

- Moderate to severe disease (organ/life-threatening)
  - Active glomerulonephritis, Pulmonary hemorrhage,
    Cerebral vasculitis, Progressive neuropathy, Orbital pseudotumor,
    GI bleeding, Pericarditis, Myocarditis

<table>
<thead>
<tr>
<th>Induction of remission (3-6mo)</th>
<th>Maintenance (≥12-18mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate ~Severe</td>
<td>GC + CYC (oral or iv) or MTX or AZA</td>
</tr>
<tr>
<td>Mild</td>
<td>GC + Rituximab</td>
</tr>
</tbody>
</table>

GC, glucocorticoids; CYC, cyclophosphamide; MTX, methotrexate; AZA, azathioprine

Plasmapheresis

- Severe active & rapidly progressive renal disease
- Severe pulmonary hemorrhage
  - eg. life threatening or ventilatory dependent
- Concurrent anti-GBM antibody disease
  - usually when the Scr is > 5.7 mg/dL

- In a meta-analysis of 9 trials.
  - The addition of plasma exchange to standard care decreased the pooled risk of ESRD or death (RR 0.8, 95% CI, 0.65-0.99)

### Treatment (interventions in TA)

- Angioplasty
- Cerebral hypoperfusion
- Renovascular hypertension
- Limb claudication
- Aneurysms
- Valvular insufficiency

### Summary

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diagnosis</th>
<th>的特点</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large</td>
<td>Takayasu arteritis</td>
<td>&lt;50 yrs., 동양, stroke, renovascular hypertension</td>
</tr>
<tr>
<td>Giant cell (temporal) arteritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>Polyarteritis Nodosa</td>
<td>Visceral/digital artery involve, HBV(1) No GN, No granuloma, No ANCA</td>
</tr>
<tr>
<td>Small (arteritis, capillaries)</td>
<td>Microscopic polyangiitis</td>
<td>ANCA-associated:</td>
</tr>
<tr>
<td></td>
<td>Granulomatosis with polyangiitis (Wegener's granulomatosis)</td>
<td>(few or no immune deposits)</td>
</tr>
<tr>
<td></td>
<td>Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)</td>
<td>Pul. hemorrhage, ILD, No granuloma</td>
</tr>
<tr>
<td></td>
<td>IgA vasculitis (H-S purpura)</td>
<td>Upper respiratory (destructive: nasal septal perforation, saddle nose, subpulm. stenosis)</td>
</tr>
<tr>
<td></td>
<td>Cryoglobulinemic vasculitis</td>
<td>Pul. hemorrhage, Cavitary lung lesion</td>
</tr>
<tr>
<td></td>
<td>Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)</td>
<td>Upper respiratory (sinusitis, nasal polyp) Asthma, allergic rhinitis Pul. infiltrates (non-fixed) Eosinophilia (blood/tissue)</td>
</tr>
<tr>
<td></td>
<td>Immune complex</td>
<td>IgA1 Skin, Gl, Arthritis, GN (IgA)</td>
</tr>
<tr>
<td></td>
<td>Cryoglobulin</td>
<td>Skin, GN, nerve</td>
</tr>
<tr>
<td></td>
<td>GN, (Lung)</td>
<td>Anti-C1q Urticaria, C, Complement, GN, Arthritis, Obstructive pulmonary disease, Ocular</td>
</tr>
</tbody>
</table>

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통풍의 진단과 치료

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이 창 훈

Introduction

痛風
Epidemiology

\[ \text{Spearmen's rho} = 0.426 \quad P < 0.001 \]

\[ \text{Age (yr)} \]

\[ \text{Waist circumference (cm)} \]

\[ \text{Systolic Blood Pressure (mmHg)} \]

\[ \text{Diastolic Blood Pressure (mmHg)} \]

\[ \text{Triglycerides (mg/dL)} \]

\[ \text{Cholesterol (mg/dL)} \]

Arthritis Research & Therapy (2015) 17:59
Pathophysiology

* Purine (adenine, guanine) final metabolite \( \Rightarrow \) uric acid

* Monosodium urate have low solubility limit (380 \( \mu \text{mol/L} \))
  - 6.8mg/dL at 37°C

* Acidified urine converted urate to low solubility (pKa 5.75)

---

Pathophysiology

* In tissue, low solubility

  : dehydration state, low temperature, low pH,

  low presence of extracellular matrix protein

  ➢ Night
  ➢ MTP joint
  ➢ Osteoarthritic joint
제22차 대한류마티스학회 연수강좌 - 개원의를 위한 증례 중심의 류마티스 질환 치료지침

Pathophysiology

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Clinical features

- Asymptomatic hyperuricaemia
  Episodes of acute attacks of gout with asymptomatic intervals
  Chronic gouty arthritis

- Most often affect first MTP joint – podagra

- Midtarsal, ankles, knees, and arms

- Often have a second attack within 6 months to 2 years
Classical podagra (Pous, foot)+(agra, a seizure)
- Explosive, sudden onset
- Awakens from sleep
- Hot, dusty red, tender joint
- Skin: resemble bacterial cellulitis
- Fever, Leukocytosis, ESR, CRP 증가
- 관절통이 수일 내지 14일 이내 자연 소실

증례 1
- 56세 남자
- 우측 염지발가락 발적 및 부종
- 내원 전날 회식 후 새벽부터 통증, 응급실 방문
- 2년 전부터 같은 증상으로 2-3번 개인의원 주사 치료 후 바로 호전
- 사회력: 맥주 2병/ 주3회, 30갑년 흡연
- 고혈압-Thiazide, losartan 복용 중
- ESR:CRP : 55mm/Hr : 11.7mg/L
- BUN/Cr : 21/1.1
- Uric acid : 9.8mg/dL
진단 및 치료

- 급성 통풍, 고혈압
  - Intra-articular triamcinolone 40mg
  - Colchicine 0.6mg BID, Naproxen 500mg BID

- 증상 호전 7일 후 부터
  - Allopurinol 100mg + colchicine 0.6mg
Classical podogra

- general practitioner supposed gout in 98% of cases
- correct diagnosed only in 77% of cases

Diagnostic value of serum uric acid

<table>
<thead>
<tr>
<th></th>
<th>Elevated uric acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with positive result</td>
<td>75~90%</td>
</tr>
<tr>
<td>Prevalence of positive result in normal persons</td>
<td>~5%</td>
</tr>
<tr>
<td>Disease prevalence</td>
<td>0.5~9%</td>
</tr>
<tr>
<td>Likelihood of disease if result is positive</td>
<td>5~10%</td>
</tr>
<tr>
<td>Likelihood of disease if result is positive and joint pain is present</td>
<td>30~34%</td>
</tr>
</tbody>
</table>
통풍의 확진 - polarized light microscope

관절액 검사의 정확도
- negatively birefringent intra- and extracellular crystals
  - Sensitivity 85%
  - Specificity 100%
- Sensitivity; 63-78%
  - Specificity; 93-100%
  - positive likelihood ratio (+LR) is 14
- 25%; false negative ratio
- Coexisting septic arthritis

Curt Open Rheumatol. 2006;15(2):171
Ann Rheum Dis. 2002;61:491-8
J Rheumatol. 1986;13(3):604
확진: 통풍 결절 (Tophi)

확진Dual Energy CT (DECT)
- 비침습적으로 요산침착확인
- 진단 및 치료 모니터링
- dual-energy
  - two X-ray sources
  - two levels simultaneously;
  - 80 kV and 140 Kv
Dual Energy CT (DECT)

DECT sensitivity & specificity

- sensitivity and specificity
  - 0.90 (95% CI 0.76 - 0.97)/ 0.83 (95% CI 0.68 - 0.93)

- All false negative patients; acute, recent-onset gout

- All false positive patients - advanced knee osteoarthritis

- 위양성
  - Nailbed
  - skin
  - Submillimeter sized tophi
Imaging

- Gout
  - Punched-Out Erosions
- Gout
  - Sclerotic Overhanging Edges

통풍의 초음파 소견
- 이중 윤곽신호 (double contour sign)
  - 관절연골표면에 요산결정이 침착되어 초음파음영이 이중으로 보임

- hyperchoic spots in the synovial fluid

- Doppler signal; increased blood flow sign
  - knees and MTP joints are the most frequent affected sites (in 93% of patients)
  - six-minute US examination of four joints (knees and the 1st MTPs)
    - detection of HCA or DC sign in 97% of cases

Clin Exp Rheumatol 2012; 30: 830-837
이중 윤곽신호 (double contour sign)

- DC sign and hyperechoic aggregates
- sensitivity/specificity (84.6% / 83.3%)
- high positive / good negative predictive values (92% / 71%)

Ann Rheum Dis 2014; 73: 1522-1528
감별진단

- Cellulitis
- 재발성 류마티즘 (Palindromic rheumatism)
- Septic arthritis
- 가성 통풍 (Calcium Pyrophosphate Deposition)
- Osteomyelitis

증례 2

- 37세 남자
- 6개월 전 부터 손을 먹고 난 다음날 갑작스런 왼쪽 팔목, 오른쪽 팔꿈치, 압통, 부종, 발적
- RF(-), anti-CCP Ab(-), HLA B27(-), uric acid 7.4
- NSAIDs, steroid, colchicine – dramatic response
통풍의 임상적 진단

미국 류마티스학회 1977년 급성 통풍 관절염 분류기준
(11개 항목 중 6개 이상)

1. 1번 이상의 급성 관절염
2. 염증이 하루 내 최대 발전
3. 단관절염 발작
4. 관절 위에 발적(홍조)
5. 1st MTP joint 침범
6. 한쪽 1st MTP 침범
7. 한쪽 발목(tarsal) 침범
8. 발작동안 관절액 미생물 배양 음성
9. 고요산 혈증
10. 방사선 사진에서 비대칭성 관절 부종
11. 방사선 사진에서 골마라운드 피질하낭증(subcortical cyst)

sensitivity (0.70~0.80) , specificity (0.64~0.78)

J Rheumatol 2013;40;356-358

Gout Clinical Dx
관절액 검사 없이 진단법

Table 4. Clinical Scores of the Final Diagnostic Rule After Transforming the Regression Coefficients Shrunken by the Bootstrap Method

<table>
<thead>
<tr>
<th>Predefined Variable</th>
<th>Regression Coefficient After Shrinkage</th>
<th>Clinical Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>1.01</td>
<td>2.0</td>
</tr>
<tr>
<td>Previous patient-reported arthritis attack</td>
<td>0.95</td>
<td>2.0</td>
</tr>
<tr>
<td>Onset within 1 d</td>
<td>0.03</td>
<td>0.5</td>
</tr>
<tr>
<td>Joint redness</td>
<td>0.40</td>
<td>1.0</td>
</tr>
<tr>
<td>MP1 involvement</td>
<td>1.25</td>
<td>2.5</td>
</tr>
<tr>
<td>Hypertension or ≥ 1 cardiovascular diseases</td>
<td>0.72</td>
<td>1.5</td>
</tr>
<tr>
<td>Serum uric acid level ≥ 8.88 mmol/L</td>
<td>1.85</td>
<td>3.5</td>
</tr>
<tr>
<td>Maximum score</td>
<td>6.21</td>
<td>13.0</td>
</tr>
</tbody>
</table>

MSU 결정 양성률
8점 이상 : 82.5%

Arch Intern Med 2010;170:1120-1126
**2015 미국 유럽 류마티스학회 통풍 새 분류기준**

- 적용기준
  - 적어도 한번 말초관절/윤활낭에 종창, 통증 또는 압통 이 있던 환자를 대상

- 통풍 진단 충분 기준
  - MSU 결정이 있으면 바로 진단 가능

<table>
<thead>
<tr>
<th>영역</th>
<th>기준</th>
<th>카테고리</th>
<th>점수</th>
</tr>
</thead>
<tbody>
<tr>
<td>입상영역</td>
<td>1) 침범양상</td>
<td>발목/두족골</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2) 발작의 특징</td>
<td>제1 중족지관절</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3) 발작의 시간경과</td>
<td>한차례</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>4) 입상적 통풍결절</td>
<td>두차례</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>세차례</td>
<td>3</td>
</tr>
<tr>
<td>검사실영역</td>
<td>5) 혈청요산</td>
<td>한차례 전형적인</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>재발성</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>양성</td>
<td>4</td>
</tr>
<tr>
<td>영상영역</td>
<td>6) 초음파 이중음파신호 또는 이중뇌</td>
<td>발목/두족골</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>CT에서 요실헬형성물</td>
<td>제1 중족지관절</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>7) 단순방사선사진의 특징적 골미란</td>
<td>한차례</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>재발성</td>
<td>4</td>
</tr>
</tbody>
</table>

*MSU crystal 검사에서 음성인 경우 2점 감점
* 전체 점수의 합이 8점 이상인 경우 통풍으로 분류
통풍 분류기준 설명

1. 체질양상: 제1중족지관절과 발목관절은 단관절염 또는 소수관절염 부분으로 발현

2. 발작 특징: 체질한 관절 위에 발적(홍조)이 있고 만지거나 압력을 주었을 때 전디지 못하고 걷거나 관절을 이용하기 힘들

3. 발작 시간 경과: 전형적인 발작은 24시간 이내 통증이 최고 초에 이르고 14일 이내 발작이 해소되며 발작간에는 처짐과 같이 열증이 완전 해소됨

4. 임상적 통풍 결정: 석회분말(Chalk)과 같은 것이 배출되거나 흔히 파부 밑에 결절처럼 보일 수 있으며, 전형적으로 귀, 발굽지 윤활감, 손가락, 인대 등에 나타남

통풍 분류기준 설명

5. 혈청 요산: 요산저하제를 복용하고 있지 않을 때 측정하되, 발작 시작시점에서 4주 떨어져 측정(즉, 발작이 없는)하는 것이 이상적. 적응할 수 있다면 이런 상황에서 다시 측정할. 측정시기와 상관 없이 가장 높은 수치를 적용함

6. 초음파 이중윤향신호 또는 이중에너지 CT 요산 첨착소견: 관절연골표면의 요산결정 첨착이 초음파에서 보이거나 이중에너지 CT에서 깃상과 요산을 다른 색깔로 표현하여 관절 주위의 사이에 요산첨착을 영상으로 확인함

7. 단순방사선사진에서 골미란 경호된 영(osteitis)과 돌출모서리(overhanging edge)를 갖는 cortical bony defect가 보임. 골관절염과 관련된 소견을 배제하기 위해 원위 수지관절(DIP)은 제외함.
### Criteria sensitivity & specificity

<table>
<thead>
<tr>
<th>Criteria set (ref.)</th>
<th>Area under the curve*</th>
<th>Sensitivity at published threshold</th>
<th>Specificity at published threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR/EULAR criteria</td>
<td>0.95</td>
<td>0.97</td>
<td>0.89</td>
</tr>
<tr>
<td>ACR/EULAR criteria (clinical-only)</td>
<td>0.89</td>
<td>0.85</td>
<td>0.78</td>
</tr>
<tr>
<td>ACR 1977 criteria (full) (9)</td>
<td>0.83</td>
<td>1.00‡</td>
<td>0.51‡</td>
</tr>
<tr>
<td>ACR 1977 (survey) (9)</td>
<td>0.83</td>
<td>0.84‡</td>
<td>0.62‡</td>
</tr>
<tr>
<td>Rome (12)</td>
<td>0.95</td>
<td>0.97</td>
<td>0.78§</td>
</tr>
<tr>
<td>Rome (clinical) (12)</td>
<td>NA</td>
<td>0.77§</td>
<td>0.78§</td>
</tr>
<tr>
<td>New York (13)</td>
<td>0.83</td>
<td>1.00‡</td>
<td>0.78§</td>
</tr>
<tr>
<td>New York (clinical) (13)</td>
<td>NA</td>
<td>0.79‡</td>
<td>0.78§</td>
</tr>
<tr>
<td>Mexico (11)</td>
<td>0.84</td>
<td>1.00‡</td>
<td>0.44‡</td>
</tr>
<tr>
<td>Mexico (clinical) (11)</td>
<td>NA</td>
<td>0.95</td>
<td>0.44‡</td>
</tr>
<tr>
<td>Netherlands (10)§</td>
<td>0.87</td>
<td>0.95</td>
<td>0.59</td>
</tr>
</tbody>
</table>

*Area under the curve: higher values indicate better sensitivity. Sensitivity and specificity values indicate the model's performance in predicting the presence or absence of a condition, respectively.
통풍의 치료

- 급성통풍발작 (1+2+3 사용가능)
  1. NSAIDs : 최대용량의 소염진통제 or Cox-2 i 사용
  2. Colchicine : 처음 0.6mg 2T, 1시간 후 1T, 이후 12시간 간격으로 1T
  3. Corticosteroid
     - 1,2관절 침범시 – *intra-articular* triamcinolone
     - 다관절, 연부조직까지 침범
       - 경구 prednisolone 10-30mg/d, 3일 후 감량하면서 5-10일 후 중단
       - Methylprednisolone 20-60mg IV for 1-5days

- 근육주사 : triamcinolone acetonide 60mg, 이후 경구

⇒ 급성통풍이 해소될 때까지
만성통풍 치료 시기

- 년 2회 이상 급성통풍 발생 이후 부터 투여

- Tophi 가 임상적 또는 방사선 소견으로 보일 때

- 요산 과잉성이 증명되었을 때

- 고요산혈증과 요산 결석이 있을 때

- 고요산혈증과 신기능장애나 CHF 가 있을 때

_Nat Rev Rheumatol_ 2010;6:30-38
만성통풍 예방

- 생활습관변화와 함께: 체중조절(내장비만), 수분섭취, 젤주, 금연, 요거토, 야채

- 급기: 골경, 내장, 선지, 과두당 시립 음료수, 주류

- 요산저하제(최소 6개월 이상, 목표치 달성 후 3개월까지)
  - 알로퓨리놀 (100mg 부터, HLA B*5801, CKD 3 주의)
  - 페북소타트 (신기능 장애 용량 조절 없음, 간 대사)
  - Benzbramaronе (2차 억제, 요산배설제)

- 요산저하제 시작과 함께 colchicine 0.6mg 또는 저장량 NSAIDs (Naproxen 250mg)를 3개월 정도 같이 처방

2012 ACR guidelines
*Arthritis Care Res 2012;64:1431–46, 47-61

Treatment : Urate-lowering therapy

- Purine nucleotide metabolism
- Xanthine oxidase inhibitors
- Allopurinol, oxyphenol, levetiracetam

- Xanthine
- Uric acid
- Alkalization
- Dietary modification
- Urate excretion
- Renal excretion
- Gastrointestinal tract excretion

- Uricosuric
- Probenecid, benzbromarone, IRAAS54

- Inflammation inhibitors
- Non-steroidal anti-inflammatory drugs (NSAIDs), anakinra, leflunomide, et al.
Treatment; Febuxostat

- Non-purine selective xanthine oxydase inhibitor

- Prophylaxis continued for at least 6 months

- To

  : intolerant to allopurinol (Allopurinol hypersensitivity Synd)
  : not controlled gout with other urate-lowering agent
  : renal insufficiency (but, Ccr >30ml/min)
Target of urate lowering treatment

- 2006 EULAR, 2010 Japan, 2012 ACR guidelines; 6mg/dL
- 2007 BSR guideline; 5mg/dL
- In tophaceous gout, lower 6mg/dL

- Too low?
  - Uric acid; antioxidant, beneficial to the brain
  - Low level associated with Parkinson or Alzheimer’s Ds
  - J or U-shaped assoc with mortality in CKD pts

New drugs?

- RDEA-594 (Lesinurad)
- Is Drug interaction?
- Effectiveness?
- Side effect?

Promising treatment
Take home message

- 통풍은 새로운 분류기준, 초음파, X-ray, DECT로 진단할 수 있다.

- Cellulitis, palindromic rheumatism, Septic arthritis와 감별 진단해야 한다.

- 급성기에는 NSAIDs, Colchicine, Steroid로 치료한다.

- 만성 통풍은 allopurinol, febuxostat, benzbromarone으로 요산농도가 4-6mg/dl 되도록 유지한다.
골관절염의 진단과 치료

가톨릭대학교 의과대학 류마티스내과
윤 종 현

Osteoarthritis (OA)

- Failure of the diarthrodial joint
- Radiographic OA
  - Joint space narrowing
- Symptomatic OA
  - Pain
  - Functional limitation
- 가장 흔한 관절염
- 고령인구에서 장애의 가장 흔한 원인
- 생산성 저하(일을 할 수 없는 날)의 가장 많은 원인
Hand OA 진단 기준

ACR criteria for Hand OA

Clinical
1. Hand pain, aching or stiffness for most days of prior month
2. Hard tissue enlargement of ≥ 2 of 10 selected hand joints
3. MCP swelling in ≤ 2 joints
4. Hard tissue enlargement of ≥ 2 DIP joints
5. Deformity of ≥ 1 of 10 selected hand joints

OA is present if the items present are: 1, 2, 3, 4 or 1, 2, 3, 5

* 10 selected hand joints: bilateral 2nd & 3rd PIP joints, 2nd & 3rd DIP joints, 1st CMC joints

Heberden’s node  Bouchard’s node

Hand OA

• Spur
• Joint space narrowing
Hip OA 진단기준

ACR criteria for Hip OA

Clinical and radiographic
1. Hip pain for most days of the prior month
2. ESR ≤ 20 mm/h
3. Radiograph femoral and/or acetabular osteophyte
4. Radiograph hip joint-space narrowing

OA is present if the items present are: 1, 2, 3 or 1, 2, 4 or 1, 3, 4

Knee OA 진단기준

ACR criteria for knee OA

Clinical
1. Knee pain for most days of prior month
2. Crepitus on active joint motion
3. Morning stiffness ≤ 30 min in duration
4. Age ≥ 38 years
5. Bony enlargement of the knee on examination

OA is present if the items present are: 1, 2, 3, 4 or 1, 2, 5 or 1, 4, 5

Clinical and radiographic
1. Knee pain for most days of prior month
2. Osteophytes at joint margins (radiograph)
3. Synovial fluid typical of OA (laboratory)
4. Age ≥ 40 years
5. Morning stiffness ≤ 30 min
6. Crepitus on active joint motion

1, 2 or 1, 3, 5, 6 or 1, 4, 5, 6
Knee OA

- Osteophyte
- Joint space narrowing
- Subchondral bony sclerosis

Kellgren-Lawrence (K/L) grading system in Knee X-ray

Grade 1  Grade 2  Grade 3  Grade 4
Kellgren-Lawrence (K/L) grading system in Knee X-ray

- Grade 1: possible osteophytes and doubtful narrowing of joint space narrowing
- Grade 2: definite osteophyte and possible joint space narrowing
- Grade 3: definite osteophyses, moderate diminution of joint space narrowing
- Grade 4: large osteophytes, greatly impaired joint space, severe sclerosis and bony deformity

관절 연골의 영상

MRI

초음파
치료

- 목표:
  - Reducing pain
  - Maintaining mobility
  - Minimizing disability

골관절염에서 관절통의 원인

<table>
<thead>
<tr>
<th>원인</th>
<th>기전</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovium</td>
<td>Inflammation</td>
</tr>
<tr>
<td>Subchondral bone</td>
<td>BM edema (Medullary hypertension), microfracture</td>
</tr>
<tr>
<td>Osteophyte</td>
<td>Stretching of periosteal nerve endings</td>
</tr>
<tr>
<td>Ligaments</td>
<td>Stretch</td>
</tr>
<tr>
<td>Capsule</td>
<td>Inflammation, distention</td>
</tr>
<tr>
<td>Muscle</td>
<td>Spasm</td>
</tr>
</tbody>
</table>
# Osteoarthritis and Cartilage

OARSI guidelines for the non-surgical management of knee osteoarthritis

T.E. McAlindon 1, R.R. Bannuru 1, M.C. Sullivan 1, N.K. Arden 1, F. Berenbaum 1, S.M. Bierma-Zeinstra 2, G.A. Hawker 1, Y. Henrotin 2, R. Hunter 3, K. Kawaguchi 1, K. Kwok 2, S. Lohmander 1, F. Rana 1, E.M. Roos 4, M. Underwood 1

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2 OARSI Rheumatoid Arthritis Research Unit, University of Oxford, Oxford, UK
3 Pierre and Marie Curie University Paris 6, Paris, France
4 AP-HS St. Vincent Hospital, Bordeaux, France

OARSI (Osteoarthritis Research Society International) is a worldwide organization of professionals in the field of osteoarthritis. The purpose of this session is to present the OARSI guidelines for the non-surgical management of knee osteoarthritis.

## Table 1

<table>
<thead>
<tr>
<th>OA joint type</th>
<th>Knee-only OA: Symptomatic OA in one or both knees only.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple-joint OA</td>
<td>Symptomatic OA of the knee(s) in addition to other joints (e.g., hip, hand, spine, etc.).</td>
</tr>
</tbody>
</table>

### Co-morbidities

- **No co-morbidities:** The individual with OA has no pertinent co-morbid health concerns.
- **Co-morbidities:** The individual with OA has any of the following pertinent co-morbid health concerns: diabetes; hypertension; CV disease; renal failure; Gastrointestinal (GI) bleeding; depression; or physical impairment limiting activity, including obesity.

#### Moderate co-morbidity risk

The individual with OA has any of the following pertinent co-morbid health concerns: diabetes; advanced age; hypertension; CV disease; renal failure; GI complications; depression; or physical impairment limiting activity, including obesity.

#### High co-morbidity risk

The individual with OA has any of the following pertinent co-morbid health concerns: diabetes; advanced age; hypertension; CV disease; renal failure; GI complications; depression; or physical impairment limiting activity, including obesity.

* Defines a clinical sub-phenotype. Recommendations refer to treatment of the knee(s) in such individuals.

1 For Oral NSAIDs (both non-selective and selective COX-2 inhibitors). Further stratification of risk categories was considered necessary for these treatments given the important safety implications and substantial availability of safety data.
OARSI Guidelines for the Non-surgical Management of Knee OA

Core Treatments
Appropriate for all individuals:
- Land-based exercise
- Weight management
- Self-efficacy and education
- Strength training
- Water-based exercise

Recommended Treatments*
Appropriate for the following OA types:

**Knee-only OA without co-morbidities**
- Biomechanical Interventions
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Topical NSAIDs
- Walking Cane
- Oral COX-2 inhibitors
- Osteoarthritis medication
- Anti-inflammatory drugs
- Non-steroidal anti-inflammatory drugs

**Knee-only OA with co-morbidities**
- Biomechanical Interventions
- Walking Cane
- Oral anti-inflammatory drugs
- Oral COX-2 inhibitors
- Osteoarthritis medication
- Anti-inflammatory drugs
- Non-steroidal anti-inflammatory drugs

**Multi-joint OA without co-morbidities**
- Biomechanical Interventions
- Walking Cane
- Oral COX-2 inhibitors
- Oral NSAIDs
- Osteoarthritis medication
- Anti-inflammatory drugs
- Non-steroidal anti-inflammatory drugs

**Multi-joint OA with co-morbidities**
- Biomechanical Interventions
- Walking Cane
- Oral COX-2 inhibitors
- Oral NSAIDs
- Osteoarthritis medication
- Anti-inflammatory drugs
- Non-steroidal anti-inflammatory drugs

*OARSI does not recommend referral for consideration of open or arthroscopic surgery if non-surgical treatment modalities are not effective.

T.C. McKelvie et al. / Osteoarthritis and Cartilage 20 (2014) S1-S2

비약물적 치료

- 체중 조절
- 운동
- 생체공학 보조기
- 열치료
체중 조절

- 과체중인 무릎 OA환자는 체중 감량으로 통증과 활동제한이 개선됨
- 20주 동안 체중의 5% 감량 권장

유도

- 무릎 OA에서 통증과 활동력 개선 효과가 약하게 단기간 동안 지속됨
- “타이치”가 무릎 OA에서 통증과 활동력개선에 매우 긍정적인 효과가 있을
- 스트레칭, 관절운동범위 능동 운동, 유산소운동, 근력강화 등을 종합적으로 시행할 권장
수증 운동

- 삶의 질과 기능 개선 효과가 증가되도록 단기간 지속됨
- 무릎과 골관절 OA에서 통증 개선효과는 약함

[그림: 삶의 질과 기능 개선의 향상]

근력강화 운동

- Moderate effect sizes for reducing pain & improving physical function.
- Resistance-based lower limb & quadriceps strengthening exercises

[그림: 근력강화 운동의 향상]
생체공학 교정기 및 보조기

- 무릎 교정기와 발목 보조기가 통증, 강직, 신체 기능 개선 및 약물 용량 감량에 도움이 될 수 있음
- Lateral wedge insoles

<table>
<thead>
<tr>
<th>Biomechanical interventions</th>
<th>Treatment Appropriateness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee-only OA without co-morbidities</td>
<td>Appropriate</td>
</tr>
<tr>
<td>Knee-only OA with co-morbidities</td>
<td>Appropriate</td>
</tr>
<tr>
<td>Multi joint type OA without co-morbidities</td>
<td>Appropriate</td>
</tr>
<tr>
<td>Multi joint type OA with co-morbidities</td>
<td>Appropriate</td>
</tr>
</tbody>
</table>

LEVEL OF EVIDENCE: SII of RCTs and non-randomized clinical trials
QUALITY OF EVIDENCE: Fair
ESTIMATED EFFECT SIZE FOR PAIN OR FUNCTION: Not available

약물 요법

- SYSADOAs
- Acetaminophen
- NSAIDs
  - Naproxen, Celecoxib, Aceclofenac, Meloxicam
- Duloxetine
- Opioid
  - Tramadol
- Intraarticular injection
  - Hyaluronan
  - Glucocorticoid
- Local application
  - Capsaicin cream
  - NSAID patch or cream
Acetaminophen

- Systematically evaluated 1st choice
- Relieves symptoms
- Use caution (>3 g/day), avoid with gastrointestinal, cardiovascular, respiratory, and renal disorders.

![Graph showing benefit and risk scores for Acetaminophen (Paracetamol) in different types of OA with and without co-morbidities.]

Treatment Appropriateness:
- Appropriate
- Uncertain

Level of evidence: SR and meta-analysis of RCTs
Quality of evidence: Good
Estimated Effect Size for Pain (SMD): 0.18 (0.11–0.25)

Association Between Drug Exposure & Upper/Lower GI Hospitalization

<table>
<thead>
<tr>
<th>Drug Exposure Category</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonusers of PPIs</td>
<td></td>
</tr>
<tr>
<td>Acetaminophen ≤3 g/day</td>
<td>Referent</td>
</tr>
<tr>
<td>Acetaminophen &gt;3 g/day</td>
<td>1.20 (1.03–1.40)</td>
</tr>
<tr>
<td>Acetaminophen and tNSAIDs</td>
<td>2.55 (1.98–3.28)</td>
</tr>
<tr>
<td>tNSAIDs</td>
<td>1.63 (1.44–1.85)</td>
</tr>
<tr>
<td>Users of PPIs</td>
<td></td>
</tr>
<tr>
<td>Acetaminophen ≤3 g/day</td>
<td>0.95 (0.81–1.11)</td>
</tr>
<tr>
<td>Acetaminophen &gt;3 g/day</td>
<td>1.16 (0.94–1.43)</td>
</tr>
<tr>
<td>Acetaminophen and tNSAIDs</td>
<td>2.15 (1.35–3.40)</td>
</tr>
<tr>
<td>tNSAIDs</td>
<td>1.07 (0.82–1.39)</td>
</tr>
</tbody>
</table>

Am J Gastroenterol 2008;103:872-882
경구 비선택적 NSAID

- 심각한 위장관, 심혈관 및 신장 부작용의 위험을 고려해야 함
- 최소 용량, 제한된 기간 동안 사용 권장

Celecoxib

- 상부위장관 부작용의 위험이 비선택적 NSAID에 비해 상대적으로 낮다 (RR 0.23, 95% CI: 0.07-0.76).
- 심혈관 부작용은 상대적으로 높다.
Figure 1. Pooled estimates of the relative risk (RR) and 95% confidence interval (95% CI) of upper gastrointestinal bleeding/perforation associated with the use of individual nonsteroidal antiinflammatory drugs (NSAIDs) and total NSAID use from published studies since 1990. P values are for the heterogeneity test results; n values are the number of studies. * = reported in studies published after 2000.
Duloxetine

• 만성 통증 완화에 효과가 있다.
• 임상시험에서 Duloxetine군에서 16.3%의 환자들이 부작용으로 중도 포기 (위약군은 5.6%가 부작용으로 포기).
• 부작용: 오심, 입마음, 출혈, 피로, 변비, 식욕 저하, 다한증

Duloxetine Benefit and Risk Scores

Knee-only OA without co-morbidities
Knee-only OA with co-morbidities
Multi-joint type OA without co-morbidities
Multi-joint type OA with co-morbidities

Treatment Appropriateness

Level of evidence: SR and meta-analysis of RCTs
Quality of evidence: Fair
Estimated Effect Size for Pain: Not available.
지구 마약성 진통제 (Opioids)

- **Tramadol**: 무릎과 골관절 OS에 통증이 약간 개선되는 효과
- **Codeine**: 중등도의 개선 효과
- **Oxycodone**: 경미에서 중등도의 개선 효과
- **Morphine**: 약간 개선되는 효과

임상시험에서 위약군에 비해 4배 많은 수의 환자들이 부작용으로 중도 포기 (RR 4.05, 95% CI: 3.06-5.38), 심각한 부작용이 3배 많이 발생 (RR 3.35, 95% CI: 0.83-13.56).

<table>
<thead>
<tr>
<th>Oral Opioids</th>
<th>Treatment Appropriateness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kneen-only OA without co-morbidities</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Kneen-only OA with co-morbidities</td>
<td>Uncertain</td>
</tr>
<tr>
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</tr>
<tr>
<td>Multi-joint type OA with co-morbidities</td>
<td>Uncertain</td>
</tr>
</tbody>
</table>

**Level of evidence**: SR and meta-analysis of RCTs. **Quality of evidence**: Good.
**Estimated Effect Size for Pain**: N/A, N/A.

다양한 코르티코이드 관절내 주사

- 단기간 동안 강한 통증 개선 효과
- 허루안 주사에 비해 강력한 효과

<table>
<thead>
<tr>
<th>Intra-articular Corticosteroid Benefit and Risk Scores</th>
<th>Treatment Appropriateness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kneen-only OA without co-morbidities</td>
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</tr>
<tr>
<td>Kneen-only OA with co-morbidities</td>
<td>Appropriate</td>
</tr>
<tr>
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<tr>
<td>Multi-joint type OA with co-morbidities</td>
<td>Appropriate</td>
</tr>
</tbody>
</table>

**Level of evidence**: SR and meta-analysis of RCTs. **Quality of evidence**: Good.
**Estimated Effect Size for Pain**: N/A, N/A.
히루안 관절내 주사
무릎 OA 통증을 경미하게 개선시키는 효과가 24주 동안 지속됨

SYSADOAs (Symptomatic slow-acting drugs for OA)
- Glucosamine sulfate (Rotapharm),
- Chondroitin 4&6 sulfate
- Diacerein
- Avocado-soybeanunsaponifiable (ASU)
Avocado soybean unsaponifiables (ASU)
무릎 OA 통증 경미한 개선 효과가 기대됨 (메타 분석)

Diacerein
단기간 동안 경미한 통증 개선 효과

211
**Glucosamine**

- **Crystalline glucosamine sulfate (Rottapharm) kannani wirak e bihe se tongtong og kem geen ganein jokwa (Cochrane Database Syst Rev 2000;2:CD002368.)**

- **NIH-funded RCT (GAIT study) he nehe tongtong ganei se wirak og chayi a gineh.**

**Chondroitin**

**GAIT jeryu ne dafa hantzaso.**

---

**References:**
- M. K. et al. (2013). Osteoarthritis and Cartilage 21, 156.
Take Home Massage

- 치료 목표:
  - Reducing pain
  - Maintaining mobility
  - Minimizing disability

- 비약물적 치료: 운동, 체중 감량
- 동반된 질환에 따른 약물 선택
- 약물 부작용의 위험을 줄이자