Problem Solving in Rheumatology

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Abbreviations

ABD	adynamic bone disease
ACE	angiotensin-converting enzyme
ACR	American College of Rheumatology
ADAMTS	a disintegrin and metalloproteinase with thrombospondin motif
ADFR	Activate, Decrease osteoclast activity, Free of treatment and Repeat
ADP	adenosine diphosphate
ADR	adverse drug reaction
AMP	adenosine monophosphate
ANA	antinuclear antibody
ANCA	anti-neutrophil cytoplasmic antibodies
ANF	antinuclear factor
AP	alkaline phosphatase
AP-1	activator protein-1
APPROVe	Adenomatous Polyp Prevention on Vioxx study
APS	antiphospholipid syndrome
AS	ankylosing spondylitis
ASC	apoptosis-associated speck-like protein
ATP	adenosine triphosphate
B19	parvovirus B19
BASMI	British Ankylosing Spondylitis Metrology Index
BMD	bone mineral density
BMI	body mass index
BP	blood pressure
BPs	bisphosphonates
C5	fifth cervical segment
c-ANCA	cytoplasmic anti-neutrophil cytoplasmic antibody
CCB	calcium channel blocker
CCTG	cytosine-cytosine-thymine-guanine
CCL2	monocyte chemoattractant protein-1 (see also MCP-1)
CCP	cyclic citrullinated peptide
CDSN	corneodesmin
CEP	circulating endothelial precursor
cGMP	cyclic guanosine monophosphate
CHB	congenital heart block
CI	confidence interval
CIM	critical illness myopathy
CK	creatine kinase
CKD	chronic kidney disease
CKD-MBD	CKD-mineral and bone disorder
CLASS	Celecoxib Long-term Arthritis Safety Study
Clc-l	chloride channel
CMC	carpometacarpophalangeal
CNS	central nervous system
CORE	Continuing Outcomes Relevant to Evista
COX	cyclooxygenase
COX-1	cyclooxygenase-1
COX-2	cyclooxygenase-2
CPEO	Chronic Progressive External Ophthalmoplegia
CPPD	calcium pyrophosphate dihydrate
CREST	Calcinosis; Raynaud's phenomenon; Esophageal dysmotility; Sclerodactyly, Telangiectasia
CRP	C-reactive protein
CSS	Churg–Strauss syndrome
CT	computed tomography
CTG	cytosine-thymine-guanine
CTGF	connective tissue growth factor
CTS	carpal tunnel syndrome
CTLA4-Ig	cytotoxic lymphocyte-associated antigen linked to immunoglobulin
CVD	cardiovascular disease
CXR	chest X-ray
D3	1,25-dihydroxy-vitamin D_3
DC	dendritic cell
DD	Dupuytren's disease
DEXA	dual-energy X-ray absorptiometry
DHA	docosahexaenoic acid
DHEA	dehydroepiandrosterone
DIL	drug-induced lupus
DIP	distal interphalangeal
DISH	diffuse idiopathic skeletal hyperostosis
DLCO	diffusing capacity for carbon monoxide
DM	dermatomyositis
DM1	myotonic dystrophy type 1

DM2	myotonic dystrophy type 2
DMARD	disease-modifying antirheumatic drug
DMOAD	disease-modifying osteoarthritis drug
DMPK	myotonic dystrophy protein kinase
dsDNA	double-stranded DNA
EBV	Epstein–Barr virus
EDTA	ethylenediaminetetraacetic acid
EEG	electroencephalogram
EGF	epidermal growth factor
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMG	electromyography
ENA	extractable nuclear antigen
eNOS	endothelial nitric oxide synthase
EPA	eicosapentaenoic acid
ESR	erythrocyte sedimentation rate
ET	endothelin
FA	fatty acid
FBC	full blood count
FDG-PET	(18)-F-fluorodeoxyglucose-positron emission tomography
FGF	fibroblast growth factor
FKBP-12	12 kDa FK506-binding protein
FMS	fibromyalgia syndrome
FVC	forced vital capacity
FSH	follicle-stimulating hormone
GAIT	Glucosamine/chondroitin Arthritis Intervention Trial
GCA	giant cell arteritis
GDM	gestational diabetes
GFR	glomerular filtration rate
GI	gastrointestinal
GMP	guanosine monophosphate
GSD	glycogen storage disease
GTP	guanosine triphosphate
GVHD	graft-versus-host disease
H_2RA	histamine H_2 receptor antagonist
HBA_1C	glycosylated haemoglobin
HBO_2	hyperbaric oxygen
HDL	high-density lipoprotein
HELLP	Haemolytic anaemia, Elevated Liver enzymes, Low Platelets
HIV	human immunodeficiency virus
HLA	human leukocyte antigen (genetic designation for human major histocompatibility complex)
HNPP	hereditary neuropathy with liability to pressure palsies
hnRNP	heterogeneous nuclear ribonucleoprotein
HPRT	hypoxanthine phosphoribosyltransferase
HRCT	high-resolution computed tomography
HRT	hormone replacement therapy
HSP	Henoch-Schönlein purpura
HTLV-1	human T-lymphotropic virus type 1
IBD	inflammatory bowel disease
IBM	inclusion body myositis
IFN	interferon
Ig	immunoglobulin
IGF-1	insulin-like growth factor-1
Iκβ	inhibitor of kappa-beta
IL	interleukin
IL-1ra	interleukin-1 receptor antagonist
IMPDH	inosine monophosphate dehydrogenase
IMT	intima-media thickness
INR	International Normalized Ratio
IP	inflammatory polyarthritis
IU	International Units
JSN	joint space narrowing
LBP	low back pain
LDL	low-density lipoprotein
LFA-1	lymphocyte function-associated antigen-1
LFT	liver function test
LIFE	Losartan Intervention for Endpoint reduction
LJM	limited joint mobility
LORA	late-onset RA
LRP-5	LDL receptor-related protein-5
LUMINA	Lupus in minorities: nature versus nurture
LH	luteinizing hormone
MCP	metacarpophalangeal
MCP-1	monocyte chemoattractant protein-1 (see also CCL2)
MCTD	mixed connective tissue disease
MELAS	Myopathy, Encephalopathy, Lactic Acidosis and Stroke
MERRF	Myoclonic Epilepsy with Ragged Red Fibres
MI	myocardial infarction
MMF	mycophenolate mofetil
MMP	matrix metalloproteinase
MORE	Multiple Outcome of Raloxifene Evaluation
MPA	microscopic polyangiitis

MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
MSA	myositis-specific antibodies
MTOR	mammalian target of rapamycin
MTP	metatarsophalangeal
MUA	manipulation under anaesthesia
NALP	pyrin domain-containing proteins sharing structural homology with NODs
NCS	nerve conduction studies
NFAT	nuclear factor of activated T lymphocytes
NF-κB	nuclear factor-κ-beta
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of Health
NO	nitric oxide
NOD	nucleotide-binding and oligomerization domain proteins
NOS	nitric oxide synthase
NOS-2	inducible nitric oxide synthase
NOS-3	endothelial nitric oxide synthase (eNOS)
NSAID	non-steroidal anti-inflammatory drug
OA	osteoarthritis
OCP	oral contraceptive pill
25(OH)D	25-hydroxy-vitamin D
OPG	osteoprotegerin
OR	odds ratio
PADAM	partial androgen deficiency in aging men
PADI	peptidylarginine deaminase
PAH	pulmonary artery hypertension
PAN	polyarteritis nodosa
p-ANCA	perinuclear anti-neutrophil cytoplasmic antibody
PCR	polymerase chain reaction
PCT	plasma procalcitonin
PDGF	platelet-derived growth factor
PET	positron emission tomography
PG	prostaglandin
PGI_2	prostacyclin
PIP	proximal interphalangeal
PM	polymyositis
PM/DM	polymyositis/dermatomyositis
PMR	polymyalgia rheumatica
PP	pyrophosphate
PPAR	peroxisomal proliferator-activated receptor
PPI	proton pump inhibitor
PPRP	5′phosphoribosyl 1-pyrophosphate
PRIMO	Prediction of Muscular Risk in Observational conditions
PsA	psoriatic arthritis
PTH	parathyroid hormone
PTNP22	protein tyrosine phosphate non-receptor type 22
PUFAs	polyunsaturated fatty acids
QALY	quality-adjusted life year
RA	rheumatoid arthritis
RANK	receptor activator of NF-κB
RANKL	receptor activator of NF-κB ligand
RCT	randomized controlled trial
REM	rapid eye movement
RF	rheumatoid factor
RISC	RNA-induced silencing complex
RNA	ribonucleic acid
RNP	ribonucleoprotein
ROD	renal osteodystrophy
ROS	reactive oxygen species
RR	relative risk
RS3PE	remitting seronegative symmetric synovitis with pitting oedema
RUTH	Raloxifene Use for The Heart
SAPHO	Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis
SE	shared epitope
SELENA	Safety of Estrogens in Lupus Erythematosus National Assessment
SERM	selective oestrogen receptor modulator
SHBG	sex hormone binding globulin
SI	sacroiliac
sIL-6R	soluble receptor for IL-6
SJC	swollen joint count
SLC22A4	solute carrier family 22 A4
SLE	systemic lupus erythematosus
Sm	Smith antigen
SOBOE	shortness of breath on exertion
SOTI	Spinal Osteoporosis Therapeutic Intervention
SPARC	secreted protein acidic and rich in cysteine
SPECT	single photon emission computed tomography
SRP	signal recognition particle
SRRR	sibling recurrence risk ratio
SS	Sjögren's syndrome
SSc	systemic sclerosis
ssDNA	single-stranded DNA

STAT1	signal transducer and activator of transcription-1
sTNFR	soluble receptor for TNF
SSRI	selective serotonin reuptake inhibitor
TB	tuberculosis
TBF	thermal biofeedback
TGF-β	transforming growth factor-β
Th1	T helper 1 cells
Th2	T helper 2 cells
TIMP	tissue inhibitor of metalloproteinase
TJC	tender joint count
TLR	Toll-like receptor
TKA	total knee arthroplasty
TMV	turnover, mineralization and volume
TNF	tumour necrosis factor
TNFR2	TNF-α receptor type 2
TRAP	tartrate-resistant acid phosphatase
TROPOS	Treatment Of Peripheral Osteoporosis Study
TSH	thyroid-stimulating hormone
TxA_2	thromboxane A_2
U1RNP	uracil-rich 1 ribonucleoprotein
UA	uric acid
U/E	urea and electrolytes
UDP	uridine diphosphate
UK	United Kingdom
US	United States
UV	ultraviolet light
VDR	vitamin D receptor
VEGF	vascular endothelial growth factor
VIGOR	Vioxx Gastrointestinal Outcomes Research study
WBC	white blood cell
WHO	World Health Organization
WOMAC	Western Ontario and McMaster Universities
XO	xanthine oxidase

SECTION ONE 01

General Rheumatology and Soft Tissue Rheumatism

01 New onset painful joints
02 An acutely swollen/hot joint
03 Painful shoulders – rotator cuff and frozen shoulder
04 Tennis elbow and golfer's elbow
05 Carpal tunnel syndrome and other entrapment neuropathies
06 Fibromyalgia syndrome
07 Plantar fasciitis

PROBLEM

01 New Onset Painful Joints

Case History

June is a 32-year-old tour guide with an eight-week history of painful stiff hands and difficulty walking in the mornings. The symptoms usually last for 90 minutes. For the last six weeks she has been using diclofenac 50 mg bd with moderate benefit. Her mother has rheumatoid arthritis treated with methotrexate.

What additional history will help to determine a diagnosis?

What is the relevance of her family history?

What aspects of the examination will be particularly relevant?

Which investigations should be performed?

Background

History

Obtaining a clear history of June's symptoms will assist greatly in narrowing your initial differential diagnosis as a prelude to examination and investigations. Open questions that encourage the person to start with their initial symptoms provide chronology and the pattern of progression. Gentle prompting can, towards the end of consultation, be supplemented with specific questions. As you listen to the story, you will be assessing the impact of the symptoms on the individual's life and its components of family, work and leisure. Specifically:

- Are symptoms related to a musculoskeletal problem?
- Was there an identified trigger or precipitant?
- What has been the pattern or progression of symptoms?
- Are there features of systemic illness or inflammatory disease?
- Has anything helped the problem?

Pain and loss of function are primary presenting symptoms, but do not always coexist. Individuals differ in their descriptors of pain, its intensity and its impact. You will be told when the problem began and where. Is the pain in a joint; in a related joint structure such as tendon, ligament or bursa; or in a bone? What is the nature of the pain; when does it occur; and what is the effect of movement? Malignant pain is usually a dull, deep ache within a bone, occurring at night or when resting. Similar symptoms may occur with Paget's disease or with a fracture. Differentiators of inflammatory from non-inflammatory/mechanical joint pain are summarized in Table 1.1.

Table 1.1 Differentiators of joint pain

Inflammatory pain	Non-inflammatory/mechanical pain
• Pain and stiffness predominant in morning and at end of day • Stiffness greater than 30 minutes • Symptoms lessen with activity • Pain does not improve with rest • Localized erythema, swelling, tenderness • Systemic features – fatigue, weight loss	• Short-lived joint stiffness • Pain worsens with activity • Pain improves with rest

Localization of pain requires clarification as to whether symptoms are recreated by contact or movement in the area, or whether the pain is referred from another site. Referred pain occurs when sensory perception externalizes nociceptive input from the sclerotome or myotome of an affected structure to the relevant dermatome. Table 1.2 shows common referred pain patterns.

Onset of symptoms following trauma supports mechanical disruption of a joint, disruption of a joint's surrounding capsule and ligaments, or fracture. Less obvious triggers to explore are infections (Table 1.3), vaccinations (Rubella) and recent travel. A tactful approach is required when soliciting information on genitourinary symptoms or a

Table 1.2 Common presentations of referred pain

Area pain experienced	Origin of pain
Shoulder	Cervical spine
Biceps and lateral upper arm	Shoulder and rotator cuff
Groin, inner knee	Hip
Lateral thigh, buttock	Trochanteric bursa

Table 1.3 Common infections associated with arthritis

Viral	Gastrointestinal	Genitourinary
Hepatitis B, C	*Salmonella typhimurium*	*Chlamydia trachomatis*
Rubella	*Shigella flexneri*	
Parvovirus	*Yersinia enterocolitica*	
Arbovirus*	*Campylobacter jejuni*	

*Serology should be tested according to exposure.

history of a new sexual partner, as it is not obvious to a patient with arthritis as to why you would be asking such questions.

A comprehensive family history is a key part of every clinical history. A familial pattern of a specific diagnosis such as rheumatoid arthritis (RA), ankylosing spondylitis or systemic lupus erythematosus (SLE) highlights that diagnosis, and may also raise related diagnoses that are particularly relevant for seronegative spondyloarthritides such as psoriasis or inflammatory bowel disease.

Examination

Examination identifies the pattern and number of joints involved and extra-articular features (Table 1.4). Features of inflammation are sought: temperature, pulse and blood pressure are measured, and an assessment is made of localized erythema and warmth, tenderness, inflammation obscuring the joint margins, and reduced function. You should distinguish monoarthritis from oligoarthritis (≤4 joints) and polyarthritis (>4 joints), whether these joints are large or small, and whether there is spinal (particularly sacroiliac) involvement. Distal to the wrist and ankle there are at least 56 joints, so that as the number of joints increases, the greater the probability is of involvement of both hands and feet and of the pattern becoming increasingly 'symmetrical'. Fingernails are assessed for pitting or onycholysis suggestive of psoriasis. The scalp, umbilicus, natal cleft and extensor surfaces of knee and elbow should be inspected. The presence of a malar rash or photosensitive rash in a young woman suggests SLE.

Investigations

Investigations serve to:

- Confirm or refute a diagnostic possibility

Table 1.4 Patterns of arthritis

Pattern	Monoarthritis	Inflammatory spinal disease Sacroiliitis	Asymmetrical large joint arthritis	Symmetrical small joint arthritis (MCP, PIP, MTP)	DIP hands
Differential diagnosis	Trauma	Ankylosing spondylitis	Psoriatic arthritis	RA	Inflammatory OA (if involves PIP and 1st CMC)
	Haemophilia Septic Gout Pseudogout	Psoriatic arthritis IBD	Reactive arthritis IBD	SLE Psoriatic arthritis	Psoriatic arthritis
Further investigations	X-ray Aspirate for crystals and culture	Review personal and family history HLA-B27	Review personal and family history Examine for conjunctivitis and urethritis, and scalp and buttocks for psoriasis	Examine rheumatoid nodules Skin rashes, serositis or mucositis	X-ray hands
		X-ray lumbar spine and SI joints	Infection screen	Urinalysis RF, CCP antibodies, ANA X-ray hands and feet	

ANA, antinuclear antibodies; CCP, cyclic citrullinated peptides; CMC, carpometacarpophalangeal; DIP, distal interphalangeal; IBD, inflammatory bowel disease; MCP, metacarpophalangeal; MTP, metatarsophalangeal; OA, osteoarthritis; PIP, proximal interphalangeal; RA, rheumatoid arthritis; RF, rheumatoid factor; SI, sacroiliac; SLE, systemic lupus erythematosus.

- Monitor for known complications of the disease process or proposed treatment
- Document a parameter that changes with disease activity or treatment

The latter includes the inflammatory markers erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), which are non-specific markers. Whenever the possibility of a septic joint is considered, obtaining aspirate and culture from the joint is mandatory. Aspirated fluid is collected into a sterile container and an ethylenediaminetetraacetic acid (EDTA)-containing tube to enable a cell count, and is sent with a request for Gram staining, polarized light microscopy, culture and sensitivity, and cell count and differential cell count. If there will be a significant delay in the sample reaching the laboratory, fluid can be inoculated into a blood culture system.

The early signs and symptoms of RA are not always typical. RA is characterized as autoimmune partly on the basis of the presence of rheumatoid factor (RF), an autoantibody (usually immunoglobulin M [IgM]) targeting the Fc portion of IgG. Its sensitivity is low, ranging from 60%–80%, and specificity is lower, the antibody being frequently present in other connective tissue diseases, which limits the diagnostic utility.

Recent Developments

1 RF is present in 70% of RA cases but is not specific, occurring in 5% of healthy individuals, and globally is more associated with chronic infection than rheumatic diseases. Non-RF antibodies were first described in the 1960s, with the target

epitopes now identified as citrulline residues, which are arginine residues modified by peptidylarginine deaminase (PADI). Assays are now available for the detection of antibodies to cyclic citrullinated peptides (anti-CCP antibodies), which are highly sensitive and specific for RA and are a poor prognostic marker of joint erosion, vasculitis and rheumatoid nodules.[1] The specificity of anti-CCP in RA is >90% with sensitivity of 33%–87%. When combined with IgM-RF, anti-CCP has positive predictive value of >90% for RA.[2] A study of undifferentiated polyarthritis found that 93% of subjects positive for anti-CCP at first clinic visit progressed to RA compared to 25% who were anti-CCP negative.[3]

2 Smoking increases the risk of RA 2–4 fold and also influences the manifestations of the disease – with increased RF positivity and erosive disease, nodularity and vasculitis – similar to the findings noted with anti-CCP antibodies. Smoking may break immune tolerance by creating neo-epitopes on IgG and thus leading to RF development. Recent work has shown that smoking is associated with increased citrullination. The subsequent citrullinated antigens bind with more affinity to the HLA-DR4 shared epitope subtypes, leading to increased risk of RA.[4]

Conclusion

Persistent arthropathy in a younger patient necessitates both accurate diagnosis and effective management. A working knowledge of local infectious triggers is required, with supplemental knowledge of the likely pathologies based on age and gender. History and examination need to include potential exposure to infectious triggers, along with personal and family history. Examination will confirm or exclude significant joint inflammation, and provide information on its pattern and severity (number of joints and functional impact). Targeted investigations will narrow the diagnosis, with the urgent investigation being exclusion of septic arthritis if there is clinical suspicion.

Further Reading

1 Mimori T. Clinical significance of anti-CCP antibodies in rheumatoid arthritis. *Intern Med* 2005; **44**: 1122–6.

2 Schellekens GA, Visser H, De Jong BAW *et al.* The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. *Arthritis Rheum* 2000; **43**: 155–63.

3 van Gaalen FA, Linn-Rasker SP, van Venrooij WJ *et al.* Autoantibodies to cyclic citrullinated peptides predict progression to rheumatoid arthritis in patients with undifferentiated arthritis: a prospective cohort study. *Arthritis Rheum* 2004; **50**: 709–15.

4 Gorman JD. Smoking and rheumatoid arthritis: another reason just to say no. *Arthritis Rheum* 2006; **54**: 10–13.