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CASE REPORT

The Role of Skeletal Radiology and the Limits of Serologic Assays in Distinguishing among the Causes of Inflammatory Arthritis

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Abstract

Radiologic findings are important for the diagnosis and treatment of inflammatory joint disease.

Current classification criteria utilize different serological findings, such as anti-citrullinated-peptide antibodies (ACPA) and rheumatoid factor (RF), as well as clinical findings, for diagnosis of rheumatoid arthritis (RA). The presence of erosions allows diagnosis, even if serological criteria are not fulfilled. However, the pertinent erosions are not clearly defined.

Previous studies have shown different patterns of radiographic changes in RA patients, possibly representing different mechanisms of damage. The association between different damage patterns and serological findings is not known.

This study explores the association between serological factors and radiographic findings in patients with a clinical diagnosis of RA, RF-/ACPA-positive and negative, and spondylarthropathy, from a single centre. Anonymized radiographs were evaluated blindly, assessing presence of osteopenia, marginal and subchondral erosions, peri-erosional sclerosis, joint surface crumbling, and joint fusion. Radiological diagnosis was then correlated with serological findings.

193 patients were studied (RA/spondylarthropathy 151/42). Age and disease duration did not differ significantly between the groups. Subchondral and wrist erosions were significantly more common in clinically-diagnosed RA patients. RF, but not ACPA, was associated with metacarpal-carpal and metatarsal-tarsal erosions. Generally, no serological or clinical parameter could reliably predict radiological changes in patients with peripheral arthritis, neither those findings associated with RA, nor those rather associated with spondylarthropathy.

This study suggests that serology alone is unable to predict the mode of radiological damage in patients with peripheral inflammatory joint disease. To prevent confounding, further studies into arthritis pathophysiology should therefore take both radiological and serological findings into account.

Introduction

Radiologic findings play a central role in the diagnosis, treatment, and prognosis of inflammatory joint disease. The ACR/EULAR classification criteria, the most recent classification criteria for rheumatoid arthritis (RA), permits that the criteria may be bypassed if erosions are present [1]. For the current psoriatic arthritis (PsA) classification criteria, radiographic change is one of the five criteria, of which the patient must fulfill > 3 [1]. For PsA, radiographic findings are clearly defined, whereas the 2010 ACR/EULAR publication for diagnosis of RA does not define 'erosive disease' precisely.

Expansion of the diagnostic criteria for rheumatoid arthritis and deletion of exceptions increases sensitivity, but at the expense of specificity [2-5]. The result has been a tendency [6-8] to group all individuals with a predominantly non-axial inflammatory arthritis in this rheumatoid arthritis category [9]. Two decades later, modification of criteria included the caveat: "Absence

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of an alternative diagnosis that better explains the synovitis", which, even if one assumes, that RA despite its heterogeneity is a single entity, puts great reliance on the diagnostic skills of the evaluating individual and their perspectives of disease. The major confounding factors appear to be spondyloarthropathy and calcium pyrophosphate deposition disease and occasionally, gout [10-12], which share some characteristics with rheumatoid arthritis. It is suggested that rheumatoid arthritis be recognized on the basis of marginally distributed, symmetrical polyarticular erosions, in the absence of axial (odontoid disease-excepted) involvement, to avoid failure to distinguish it from these different diseases [5,12-15]. Alternatively, subchondral erosions and peripheral joint fusion teleologically might be considered results of a process variant from those producing marginal erosions or in which periarticular (or peri-erosional) bone are lost.

Another approach to RA classification has been serologically-based. Historically, serology-based practitioners have used presence or absence of rheumatoid factor as defining whether an individual is suffering from rheumatoid arthritis [16]. However, rheumatoid factor is elevated in other connective tissue disorders, other forms of inflammatory arthritis, malignancy, chronic infections (e.g., endocarditis, rheumatic fever, tuberculosis, syphilis, viral disease, parasitic disease), rheumatic fever, pulmonary fibrosis, sarcoidosis and chronic renal disease), as well as among healthy elderly [17,18]. The tradeoff between sensitivity and specificity results in a titer cutoff that has a 5% false positive result. The former impression that presence of rheumatoid factor has specificity for diagnosis of a specific variety of inflammatory arthritis probably derives from lumping of all inflammatory arthritis as rheumatoid [19]. Adding anti-citrullinated peptide antibody status to such assessments produces additional perspectives [20], but specificity for specific clinical patterns or radiologic findings requires further analysis.

For RA, the enormous significance of erosive disease (allowing a definite RA diagnosis, independent of other findings), together with the poor definition of what actually constitutes erosive disease, means that further research into the discriminative ability of radiological damage is needed. Also, the link between serologic findings such as ACPA and RF, and radiological damage is tenuous, at best.

The problem is further compounded by the variability

of RA itself, both concerning serology, therapeutic response [21,22] and long-term prognosis [23,24]. Several studies have shown differences between several "subtypes" of RA, both concerning joint distribution [25-27] and bone morphology [27]. The results, however, are not entirely consistent [28].

Several different modes of damage are attributed to RA [29], including erosions, periarticular osteopenia, ankylosis, periarticular ossification [30], and carpal dissolution [31]. It is not known whether these findings are specific for RA, and if they are dependent on other characteristics such as RF or ACPA status.

It is conceivable that different modes of damage are visible manifestations of specific pathophysiological processes, independent of serology. If that is the case, then further research could enable 'targeted' interventions, choosing a therapeutic agent suited to the patient's form of disease.

This study aims to investigate the prevalence and discriminatory ability of different radiographic characteristics, concerning marginal or subchondral erosions, joint crumbling, MCC and MTT joint erosions or peripheral joint fusion.

Methods

The clinical data base (EMIL, itc-ms.de, Marburg, Germany) was utilized to identify individuals treated at the Würzburg University rheumatology clinic from with hand X-rays. The study was approved by the ethics department of the Würzburg University clinic. All X-ray images had been obtained for clinical indications. No additional radiographs were performed for this study. Patient pseudonymization was performed on-site, no sensitive data were transmitted during the study. Given the retrospective study design, anonymized X-rays and absence of transmission of sensitive data, written patient consent was not required.

Patients were initially divided on the basis of clinical diagnosis into two groups (spondyloarthropathy and RA), with the latter divided according to rheumatoid factor (RF) presence or absence (Table 1). The RF positive subset was further subdivided according to presence or absence of anti-cyclic citrullinated peptide (CCP) antibodies. As all CCP-positive individuals were also rheumatoid factor positive, there was no RF-negative/CCP-positive comparison group. Age and sex were recorded for each group. Clinical diagnosis was performed by trained rheumatologists in a regular context.

Table 1: Patient characteristics. Data given as mean (range), except where noted.

Patient group	Total	RA (ACPA+/RF+)	RA (ACPA-/RF+)	RA (ACPA-/RF-)	SpA
n (M/W)	193 (60/133)	56 (18/38)	39 (9/30)	56 (17/39)	42 (16/26)
Age	59 (28-86)	61 (37-79)	66 (32-86)	62 (37-84)	49 (26-70)
Disease Duration	13 (0-54)	14 (0-31)	17 (1-54)	10 (0-49)	9 (0-31)

Clinical diagnosis of RA was based on fulfilment of the 2010 ACR/EULAR criteria for RA [32]. Clinical diagnosis of spondyloarthropathy was based on the current classification criteria for psoriatic arthritis and axial spondyloarthritis [33].

Rheumatoid factor (RF) was determined by the RF-II test (Roche Diagnostics GmbH, Mannheim, Germany). CCP were determined by the EliA CCP Well test (Phadia AB, Uppsala, Sweden). Tests were considered positive when above upper limit of normal (ULN) (16 IU/ml and 10 U/ml, respectively).

Anterior-posterior and oblique hand/wrist radiographs were anonymized for confidentiality. Radiographs were evaluated by a single blinded study group member (BMR), assessing general osteopenia and reactive new bone formation. Each joint individually for periarticular osteopenia, marginal and subchondral erosions, peri-erosional sclerosis, joint surface crumbling or accretion/calcification and joint fusion. The goal of this study was to assess the fundamental components of bone/joint assessment, rather than the individual joint extent as suggested by mathematical coding systems (e.g., Sharp/von der Heijde scoring system) [34].

Radiologic diagnoses were based on presence or absence of marginal or subchondral erosions, joint crumbling, metacarpal-carpal joint (MCC) and metatarsal-tarsal (MTT) joint erosions or peripheral joint fusion. The diagnosis of RA was based on the presence of polyarticular, marginally distributed erosions, axial skeleton (atlanto-axial junction excepted) sparing and absent joint fusion [5,35]. A diagnosis of spondyloarthropathy was based on the presence of axial joint disease, joint fusion, or peripheral, predominantly subchondral erosions and reactive new bone formation [10,35]. The diagnosis of calcium pyrophosphate deposition disease diagnosis was based on recognition of a calcified sheet (reflecting onto the articular surface), radiocarpal articular surface indentation, or calcific concretions at the joint surface margins [11,35]. The diagnosis of gout was based on recognition of sharply defined erosions with new bone formation producing a space-occupied appearance with overhanging edge [12,35]. Radiologic alterations in the four groups were compared to assess specificity of both serological and radiological findings.

Statistical analysis was performed by Chi square and Fisher exact tests to assess comparability of groups as to sex, age and disease duration, as well as the relationship of rheumatoid factor and CCP serology to presence of MCC/MTT joint involvement, subchondrally-distributed erosions, wrist-limited joint distribution of erosions, peripheral joint fusion, peripheral joint fusion and combinations thereof, as well as for the presence of arthritis mutilans.

Results

The study population (Caucasian) consisted of 60 males and 133 females (Table 1). There were 44 males and 107 females with RA; 16 males and 26 Females with spondyloarthropathy (Chi square = 1.2303, n.s.).

Table 2: Patient characteristics for different radiological changes. Data given as mean and range.

	Crumbling			Fusion		
	# (M/W)	Age	Disease duration	# (M/W)	Age	Disease duration
ACPA+/RF+	10 (2/8)	60 (43-73)	15 (5-20)	13 (1/12)	59 (44-79)	16 (4-30)
ACPA-/RF+	4 (1/3)	69 (62-74)	18 (14-24)	7 (2/5)	60 (32-79)	30 (14-54)
ACPA-/RF-	9 (2/7)	73 (57-83)	8 (1-17)	7 (1/6)	60 (41-78)	17 (2-49)
SpA	1 (0/1)	61	0	1 (0/1)	61	0
Total	24 (5/19)	67 (43-83)	12 (0-24)	28 (4/24)	59 (32-79)	19 (0-54)

	Osteopenia			Marginal Erosions		
	# (M/W)	Age	Disease duration	# (M/W)	Age	Disease duration
ACPA+/RF+	25 (8/17)	67 (50-82)	16 (2-31)	8 (1/7)	56 (38-82)	15 (4-31)
ACPA-/RF+	17 (1/15)	69 (32-87)	15 (3-32)	4 (1/3)	67 (57-75)	17 (1-32)
ACPA-/RF-	15 (4/11)	70 (53-83)	10 (1-38)	7 (0/7)	49 (37-69)	11 (2-19)
SpA	6 (3/3)	43 (25-59)	9 (0-27)	3 (1/2)	47 (34-68)	8 (2-16)
Total	63 (17/46)	66 (25-87)	14 (0-49)	22 (2/20)	55 (34-82)	13 (1-31)

	Subchondral Erosions			Peri-erosional sclerosis		
	# (M/W)	Age	Disease duration	# (M/W)	Age	Disease duration
ACPA+/RF+	7 (0/7)	61 (38-82)	15 (4-31)	9 (2/7)	59 (44-71)	18 (13-31)
ACPA-/RF+	4 (1/3)	59 (36-74)	25 (18-32)	5 (2/3)	62 (36-75)	14 (1-27)
ACPA-/RF-	3 (0/3)	60 (41-83)	9 (4-17)	5 (0/5)	58 (37-74)	10 (2-17)
SpA	1 (0/1)	40	6	1 (1/0)	68	16
Total	15 (1/14)	59 (36-83)	16 (5-32)	20 (5/15)	60 (37-74)	15 (1-31)

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The age average age for individuals diagnosed with RA was 64, ranging from 32 to 86, compared to 49, ranging from 26-70 for spondyloarthropathy (Table 2). Individuals diagnosed as having RA were not significantly older than those with spondyloarthropathy (t test = 0.8364, n.s.) nor had disease of longer duration (average 13 versus 9) (t test = 0.56744, n.s.).

Among individuals clinically diagnosed as having RA, 56 were positive for RF and CCP; 39 RF, only for RF; and 56, negative for both. Sex ratios were indistinguishable (Chi square = 0.9288, n.s.).

Statistical analysis (Table 3) revealed significantly less seropositivity among individuals with no radiologic signs of inflammation/erosive disease. Both rheumatoid factor and antibodies to CCP were present significantly more often among individuals with subchondral erosions or erosions limited to wrists. Sixteen of twenty individuals with erosive disease of wrists were positive for rheumatoid factor; nine, for CCP antibodies. Rheumatoid factor, but not antibodies to CCP, was present significantly more often in those with MCC/MTT erosions.

All individuals with subchondral erosions, joint fusion and MTT/MCC joint involvement were both rheumatoid factor and CCP antibody positive. Five of seven with just joint fusion and MCC/MTT involvement were positive for rheumatoid factor; thee for CCP antibodies.

Twelve of 32 individuals radiologically-diagnosed as having RA were positive for rheumatoid factor, 17 of whom were also positive for CCP antibodies. Forty-five of 63 individuals radiologically-diagnosed as having spondyloarthropathy were positive for rheumatoid factor; 24 of whom were also positive for CCP antibodies.

Two of four individuals radiologically diagnosed with gout were positive for rheumatoid factor, one of whom was also positive for CCP antibodies.

Discussion

In this study, we find no serological or clinical parameter that can reliably predict radiological changes in patients with peripheral arthritis. This does not only apply to changes typical for RA, such as marginal erosions and periarticular osteopenia, but also for lesions that are rather considered to be associated with peripheral spondyloarthritis, such as joint fusion and subchondral erosions.

Radiological findings suggestive of SpA were also found in ACPA positive, RF positive individuals and in those fulfilling the 2010 ACR/EULAR criteria.

While RF and CCP were more common among individuals with radiographs diagnostic for a specific arthritis than in those with normal X-rays (Table 3), the prevalence did not vary among them. Seropositivity in individuals with subchondral erosions, MCC/MTT localization of erosions or presence of peripheral joint fusion was indistinguishable among the groups, but significantly greater than those without such findings. Both RF and CCP were more common in individuals with subchondral erosions than in the rest of the sample. Rheumatoid factor was slightly more prevalent among individuals with peripheral joint fusion.

Seropositivity was significantly greater among individuals with any of the above-named radiologic alterations than in those without such findings. Examining specific (e.g., radiologic changes limited to the wrist) and combinations of diagnostic components

Table 3: Relation of serologic positivity to radiologic alterations.

Involvement (#)	RF positivity (p value)	CCP positivity (p value)
No inflammation-relatable radiologic alteration (48)	7 Chi square = 30.6717 (< 0.0001)	3 Chi square = 20.3910 (< 0.0001)
MCC/MTT (45)	32 Chi square = 11.249 (< 0.001)	21 Chi square = 0.153 (n.s.)
Subchondral erosion (57)	41 Chi square = 13.670 (< 0.001)	23 Chi square = 14.220 (< 0.0001)
Peripheral joint fusion (30)	20 Chi square = 4.350 (< 0.03)	12 Chi square = 1.029 (n.s.)
Arthritis mutilans (8)	6 Fisher exact = 0.124 (n.s.)	6 Fisher exact = 0.208 (n.s.)
Marginal erosions (22)	12 Chi square = 0.334 (n.s.)	8 Chi square = 1.9429 (n.s.)
Erosions only wrists (20)	16 Chi square = 141.5391 (< 0.00001)	9 Chi square = 72.4142 (< 0.00001)
Subchondral erosions + Fusion + MCC/MTT (9)	9 Fisher exact (< 0.00001)	7 Fisher exact (< 0.00001)
Fusion + MCC/MTT (7)	5 Fisher exact (< 0.00001)	3 Fisher exact (< 0.00001)
Subchondral erosions + Fusion	8 Chi square = 101.9613 (< 0.00001)	5 Chi square = 58.1568 (< 0.00001)

(Table 2 and Table 3) revealed these findings to be significantly more likely to have positive serologies.

The association of these findings with greater seropositivity suggests that these derive from a different process than producing marginal erosions. Radiologic recognition is critical and perhaps more pertinent to patient care than diagnoses based on serologies. Although radiologic alterations have major implications in clinical decision making related to the aggressiveness of therapeutic intervention [36], there is an additional consideration: Occupational therapy efforts are essential to prevent/reduce loss of range of motion in individuals with spondyloarthropathy, in contrast to RA, in which primary efforts are directed to physical therapy intervention to prevent/reduce deformities.

These findings indicate that the correlation between serological tests and modes of radiological damage is weak. Previous studies have shown biomechanical differences between radiological manifestations leading to subchondral erosions and joint fusion compared to marginal erosions [37,38]. Given these findings, investigation (e.g., using cytokine or proteomic parameters or biopsies) into the underlying pathophysiological processes causing radiological damage in RA should segregate individuals not only according to serological findings, but also according to specific radiological signs.

Prospectively, a multidimensional approach, taking articular as well as extraarticular phenomena into account, could enable a deeper understanding of the inflammation process - or processes - associated with chronic peripheral arthritis. This could lead to a reassessment of the current classification paradigm, in which serology and radiographic findings are viewed independently, and which arguably does not do justice to the complexity of the disease. A more differentiated classification system might lead to a therapeutic approach in which serological and radiographic findings are all taken into account, and therapy is tailored for the specific findings of the individual patient.

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