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LETTERS

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Variant mannose-binding lectin genotypes and outcome in early versus late rheumatoid arthritis: comment on the article by Ip et al

To the Editor:

Recently, we showed that variant mannose-binding lectin (MBL) genotypes were associated with radiographic outcome in Danish patients with rheumatoid arthritis (RA) (1). Therefore, it was with great interest that we read that our results have now been confirmed in a study of Southern Chinese patients (2). Ip and colleagues reported that a variant MBL genotype was found significantly more often in patients with erosive disease (52 of 127) than in those with nonerosive disease (16 of 84) ($P = 0.001$) (2). Their results also confirmed that serum MBL levels do not vary with disease activity (3). The mean duration of RA in the Chinese patients was ~7 years; therefore, the number of patients in this population who had early RA may be too small for separate statistical analysis.

It would be interesting if Ip et al compared the relative risk of developing erosions in RA patients with low-producing MBL genotypes who had early-stage disease (e.g., duration <3 years) with that in similar patients who had later-stage RA. Neither our study cohort nor the Chinese study cohort was an inception cohort; i.e., both studies included patients with disease of varying duration. This design may introduce a bias, because RA patients with severe or permanent symptoms are more likely to seek medical attention than are those with milder or fluctuating symptoms. Therefore, many patients with mild RA may be included in an inception cohort, while patients with later stages of disease are more likely to be part of a major cohort from which patients with mild RA may have withdrawn. Consequently, a study group comprising patients who had established RA but varying disease duration at the time of inclusion would be more homogeneous than an inception cohort. It could be hypothesized that in both the Danish and Chinese noninception cohorts (1,2), MBL-sufficient patients with mild RA never presented for evaluation and thus were not included. Therefore, the difference in outcome between MBL-sufficient and MBL-insufficient patients may have been smaller than it would have been in an inception cohort.

The data shown in Figure 1 support the above hypothesis. As illustrated, 140 RA patients from the Danish cohort (1) are divided into 2 groups, 1 comprising 79 patients with short disease duration (<3 years) at the time of inclusion and 1 comprising 61 patients with longer disease duration (4–26 years). In 15 patients with MBL insufficiency and short duration of disease, the relative risk (RR) of radiographically evident erosion occurring in subsequent years was 4.1 ($P < 0.0001$), whereas in 9 patients with MBL insufficiency and longer disease duration the RR was 1.8 ($P = 0.17$). Furthermore, although the gene frequencies did not differ between the 140 RA patients and the background population, the frequency of homozygous variant genotypes in the 79 patients with short disease duration was higher than that in the background population (6.3% versus 2.8%).

Two recent inception cohort studies of arthritis patients from early-arthritis clinics showed significant associations between variant MBL genotypes and radiographic progression (4) and between low serum levels of MBL and radiographic progression (5) within the first year after onset of RA. These results confirm that studies including only patients with recent-onset disease are probably more sensitive for detecting differences than are studies including patients with long-term disease.

The optimum prognostic study is probably based on a population of patients with early RA. Because such studies are few and are followed for only a limited period of time, it is currently necessary to investigate less optimum study popula-

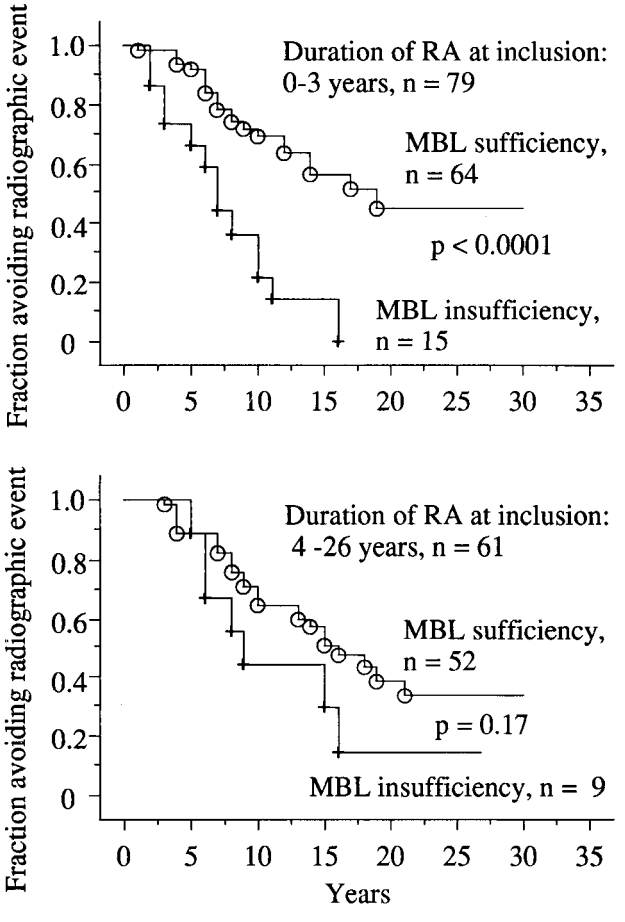

Figure 1. Kaplan-Meier plots of radiographic events, defined as the occurrence of 30% of maximal radiographic destruction, in rheumatoid arthritis (RA) patients grouped according to mannose-binding lectin (MBL) sufficiency (normal genotype or heterozygous genotype with high-expressive promoters) or MBL insufficiency (homozygous variant genotype or heterozygous genotype with low-expressive promoters).

tions in order to get information about the long-term prognosis. However, this should be done with care, and the influence of possible selection bias on the results should always be discussed in detail.

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Reply

To the Editor:

We thank Graudal and colleagues for their comments. We also read with interest the preliminary data that they presented, which showed that the relative risk for development of erosive disease among patients with MBL insufficiency is higher in those with recently diagnosed RA than in those with disease of longer duration. This finding is indeed in accordance with our previous observations.

Figure 1 shows the number of patients with erosive and nonerosive RA according to serum MBL level. Because RA is a progressive disease, some patients who originally present with nonerosive disease will develop radiographically apparent erosive lesions; thus, the proportion of patients with erosive arthritis will become higher with longer duration of followup. This will further strengthen our observation that MBL insufficiency is a prognostic marker for erosive RA. Our hypothesis

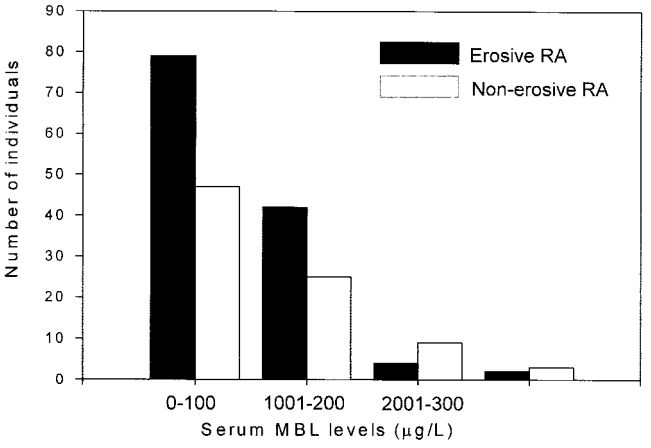

Figure 1. Number of patients with erosive and nonerosive rheumatoid arthritis (RA) according to serum levels of mannose-binding lectin (MBL).

is supported by 2 recent studies reported by Jacobsen et al (Jacobsen S, Madsen HO, Klarlund M, Jensen T, Skjødt H, Jensen KE, et al. The influence of mannose binding lectin polymorphisms on disease outcome in early polyarthritis. J Rheumatol 2001;28:935–42) and Saevarsdottir et al (Saevarsdottir S, Vikingsdottir T, Vikingsson A, Manfredsdottir V, Geirsson AJ, Valdimarsson H. Low mannose binding lectin predicts poor prognosis in patients with early rheumatoid arthritis: a prospective study. J Rheumatol 2001;28:728–34).

We agree with Graudal and associates that an inception cohort with a long duration of followup is needed to properly delineate the association between MBL insufficiency and severity of RA. Such a cohort study is currently being set up within our unit. We believe that the data obtained from this upcoming study will further confirm our hypothesis that MBL insufficiency is associated with poor outcome in RA.

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Association of Fcγ receptor IIIA polymorphism with rheumatoid arthritis: comment on the article by Morgan et al

To the Editor:

We read with interest the recent article by Morgan et al (1), which indicated that the Fcγ receptor type IIIA (FcγRIIIA)–158V allele was associated with an increased risk of developing rheumatoid arthritis (RA). The authors also reported that the association was more marked in patients with nodular RA, suggesting that the FcγRIIIA-158 polymorphism may be a useful marker for severe RA.

We recently reported a similar study with quite different results (2). Our cohort comprised 117 patients with RA and 142 unrelated healthy control subjects, all of whom were Caucasians from southern Spain. We observed that the overall distribution of FcγRIIIA genotypes in RA patients was significantly different from that in the control group ($P = 0.023$, by chi-square test from 3×2 contingency table). In addition, an overrepresentation of the FcγRIIIA-158FF genotype in the patients was observed (for 158FF versus non-158FF $P = 0.01$, odds ratio [OR] 1.98, 95% confidence interval [95% CI] 1.16–3.4). In contrast to Morgan et al, we did not find an association between FcγRIIIA alleles or genotypes and any disease manifestation.

It is generally accepted that in association studies, valid conclusions can be drawn only if the population studied is homogeneous. In our opinion, the UK Caucasians and the North Indians/Pakistanis are very different populations in terms of genetics and, therefore, it is not appropriate to combine these groups for genetic association studies. For instance, in the study by Morgan et al, the shared epitope was present in 55% of UK Caucasian controls but in only 17% of North Indian/Pakistani controls. Curiously, these figures are very different from the previously reported frequency of the shared epitope in an Indian population (37.6%) (3). On the other hand, the frequency of nodular disease in UK Caucasians (31%) was clearly greater than that in North Indians and Pakistanis (4%), suggesting a clinical heterogeneity of the disease in both populations.

According to Morgan et al, the reported association between FcγRIIIA alleles and RA susceptibility and severity was confirmed in 2 distinct ethnic groups. However, it should be noted that, according to our analysis, there was no statistically significant difference in allele frequencies in the North Indian/Pakistani cohort ($P > 0.05$, OR 1.50, 95% CI 0.98–2.28). It is also worth noting that the difference between the overall FcγRIIIA genotype distribution (3×2 contingency tables) of the control subjects and that of both UK Caucasian and North Indian/Pakistani RA patient was not statistically significant. Moreover, no individual FcγRIIIA genotype was associated with RA in either population. Morgan et al observed that the increase of the FcγRIIIA-158V allele was statistically significant in North Indian and Pakistani RA patients but not in UK Caucasian patients ($P > 0.05$, OR 1.62, 95% CI 0.97–2.72).

Morgan and colleagues also reported an association between FcγRIIIA-158V/F polymorphism and nodular disease in UK Caucasians and suggested that this association is a marker of RA severity. Nevertheless, it is worth mentioning that they determined the association between FcγRIIIA alleles and nodular disease by comparing RA patients with nodules and healthy controls. In our opinion, the comparison should have been made between patients with and patients without nodules. Of note, no statistically significant difference in the FcγRIIIA allele or genotype distribution is observed when this type of analysis is performed.

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Reply

To the Editor:

We thank Nieto et al for their interest in our study, which demonstrated an association between FcγRIIIA and RA in both UK Caucasian and North Indian/Pakistani cohorts (1). We welcome the opportunity to discuss the differences in analytic and genotyping approaches used in our respective studies (2), which may contribute to the different results.

In our study, the 2 cohorts of RA patients were recruited from the same district general hospitals, and local population control subjects were recruited from the same geographic area as the RA patients. We presented the results for each ethnic group separately and in combination. Because of the major ethnic differences in the various Indian/Pakistani populations, recruitment of our patients and controls was restricted to individuals from the states of Kashmir, Punjab, Haryana, Himachial, Pradesh, or Delhi. Individuals from these areas are of Aryan descent and differ from southern Indians, who are of Dravidian descent. The Arya arrived in India in approximately 1500 BC and are believed to be from the Caspian region or the southern steppes of Russia, and, therefore, they have a degree of genetic similarity with white Europeans (3). The FcγRIIIA allele frequencies of the UK Caucasian and North Indian/Pakistani cohorts varied by only 1%. We therefore also combined data across the 2 ethnic groups, which increased the power for detecting an association between the FcγRIIIA-158F/V polymorphism and RA. Table 1 presents genotypic data for the combined group, both with and without adjustment for ethnicity, using the Mantel-Haenszel method for combining risk estimates across strata (4). There was no evidence against homogeneity of the odds ratios, and one can see that the results with and without adjustment are almost identical, confirming the acceptability of combining these data. Nieto and colleagues thought that the

Table 1. Association of Fcγ receptor IIIA (FcγRIIIA) with rheumatoid arthritis*

Population, genotype	OR (95% CI, *P*)	*P* for trend of odds
UK Caucasian†		
FcγRIIIA-158FF	1.0	
FcγRIIIA-158FV	1.50 (0.89–2.52, 0.13)	0.03
FcγRIIIA-158VV	2.18 (0.96–4.96, 0.06)	
North Indian/Pakistani†		
FcγRIIIA-158FF	1.0	
FcγRIIIA-158FV	1.86 (1.06–3.27, 0.03)	0.04
FcγRIIIA-158VV	1.84 (0.66–5.13, 0.23)	
Combined ethnic group†		
FcγRIIIA-158FF	1.0	
FcγRIIIA-158FV	1.65 (1.12–2.41, 0.01)	0.003
FcγRIIIA-158VV	2.09 (1.10–3.95, 0.02)	
Combined, adjusting for ethnicity†		
FcγRIIIA-158FF	1.0	
FcγRIIIA-158FV	1.65 (1.13–2.43, 0.01)	0.003
FcγRIIIA-158VV	2.04 (1.08–3.88, 0.03)	
Spanish Caucasian‡		
FcγRIIIA-158VV	1.0	
FcγRIIIA-158FV	0.79 (0.37–1.70, 0.55)	0.04
FcγRIIIA-158FF	1.65 (0.76–3.61, 0.20)	

* Statistical analysis was performed with Stata statistical software, version 6.0, 1999 (Stata Corporation, College Station, TX). OR = odds ratio; 95% CI = 95% confidence interval.
† Ref. 1
‡ Ref. 2

frequency of the "shared epitope" in our North Indian/Pakistani population was low at 17%. However, this percentage actually compares well with previously reported frequencies of 19.6–24% in this ethnic group (5–7). Therefore, the "shared epitope" frequency of 35% quoted by Nieto et al is (8) at variance with much of the published literature.

Nieto and colleagues analyzed our data using a method different from the one that we used and obtained distinctly different results. First, they calculated a borderline odds ratio for the association of FcγRIIIA alleles in our North Indian/Pakistani cohort ($P = 0.05$). We chose not to calculate odds ratios from our allele data, however, because it is not immediately obvious how the relative odds of an allele occurring in patients and controls translate into a statement about the risk of a disease (9). In contrast, odds ratios derived directly from genotypic data are easier to interpret. Our report and that of Nieto et al also highlight the fact that 2×3 genotypic table analyses are not straightforward in that a variety of methods are available for their interpretation (9). Neither Nieto et al nor our group tested an a priori hypothesis specifying the FcγRIIIA-158F or V allele as the putative risk allele in RA, and data were therefore analyzed according to the genotyping results.

Sasieni (9) has suggested that an appropriate method for analyzing genetic case–control data is to calculate odds ratios for homozygotes for the putative disease-associated allele (FcγRIIIA-158V from our data, FcγRIIIA-158F from the data of Nieto et al) and for heterozygotes, using homozygotes for the alternative allele as the reference group. Under a dominant model the odds ratios for homozygotes and heterozygotes would be equal, under a codominant model (in which each allele contributes to disease risk) a trend in odds ratios would be expected, and under a recessive model the odds ratio for heterozygotes would be 1.0.

We applied Sasieni's approach to both our own data and those of Nieto et al (Table 1). Our own data best fit a codominant model and, in our original publication, we presented data for carriage of the FcγRIIIA-158V allele and for homozygosity of the FcγRIIIA-158V allele. The data presented by Nieto et al are most consistent with a recessive model, with the apparent decreased risk of disease in the heterozygotes interpreted as being attributable to sampling variation. The odds ratios presented by Nieto et al therefore compare the FcγRIIIA-158FF genotype with a reference group consisting of heterozygotes and FcγRIIIA-158VV homozygotes, showing a difference that is just significant at the 1% level. The fact that a recessive model was used to analyze their data must be considered when interpreting their results.

In our UK Caucasian group with nodular RA, both carriage of the FcγRIIIA-158V allele (OR 2.2, 95% CI 1.0–5.1, $P = 0.004$) and homozygosity for the FcγRIIIA-158V allele (OR 4.4, 95% CI 1.5–12.9, $P = 0.004$) were associated with RA. We accept that our results for the North Indian and Pakistani cohort just failed to reach significance for an association of homozygosity of the FcγRIIIA-158V allele with nodular RA (OR 14.8, 95% CI 1.2–179.7, $P = 0.05$). As we stated in our report, however, of the 4 patients in this cohort who had nodules, 3 carried the FcγRIIIA-158V allele, 2 of whom were homozygous.

The most appropriate control group for this type of analysis depends on the hypothesis being tested. The primary objective of our study was to determine if the FcγRIIIA-158V/F polymorphism was associated with RA, not to study parameters of RA severity. In this context, we thought that a comparison between the subset of patients with nodular RA, which may represent a different etiopathogenic RA group, and the control population was most appropriate. In fact, analysis of RA patients with and those without nodules demonstrated that homozygosity for FcγRIIIA-158V was associated with the presence of nodules in the UK Caucasian RA patients (OR 3.6, 95% CI 1.1–11.8, $P = 0.03$) and showed a trend toward significance in the North Indian/Pakistani cohort (OR 10.3, 95% CI 0.8–129.6, $P = 0.09$ [data not shown]).

Last, we would like to draw attention to the differing FcγRIIIA allele frequencies in our control populations. Although this difference could be attributable to the distinct ethnic groups studied, Table 2 summarizes the literature on this point. FcγRIIIA-158F/V genotyping is problematic because of the high sequence homology with FcγRIIIB. We chose to genotype this polymorphism by direct sequencing, because, in our hands, conventional assays produced inconsistent results, particularly when the DNA quality was poor, as reported by another group (10). One striking feature when comparing the FcγRIIIA-158F/V allele frequencies in published control populations (Table 1) is that there are 2 clusters, with the frequency of the V allele being in the range of either 0.27–0.33 or 0.41–0.47. This clustering could represent genuine interethnic differences, although whenever the same group previously analyzed 2 ethnically diverse populations, similar allele frequencies for each ethnic group were obtained (1,10–14). Loss of assay specificity for FcγRIIIA over FcγRIIIB would result in an overrepresentation of the FcγRIIIA-158V

Table 2. Comparison of allele and genotype frequencies and the method of analysis for published control populations*

Population studied	Allele frequency		Genotype frequency			Assay technique	Ref.
	F	V	FF	FV	VV		
North Indian and Pakistani	0.73	0.27	0.52	0.41	0.07	Direct sequencing	Morgan et al (1)
UK Caucasian	0.72	0.28	0.52	0.39	0.09	Direct sequencing	Morgan et al (1)
Japanese	0.72	0.28	0.54	0.36	0.10	ARMS-PCR	Sugita et al (10)
US Caucasian	0.70	0.30	0.50	0.39	0.11	ASO	Lehrnbecher et al (11)
Dutch Caucasian	0.67	0.33	0.43	0.47	0.10	ARMS-PCR	Dijstelbloem et al (14)
US African	0.67	0.33	0.42	0.50	0.08	ASO	Lehrnbecher et al (11)
Spanish Caucasian	0.59	0.41	0.32	0.54	0.14	RFLP: *Rsa* I + *Sty* I	Nieto et al (2)
Dutch Caucasian	0.57	0.43	0.32	0.51	0.17	RFLP: *Nla* III	Koene et al (15)
US ethnically diverse	0.56	0.44	0.26	0.61	0.13	ARMS-PCR	Wu et al (12)
US African	0.56	0.44	0.34	0.44	0.22	RFLP: *Nla* IV	Oh et al (16)
Korean	0.53	0.47	0.20	0.66	0.14	ARMS-PCR	Salmon et al (13)

* ARMS-PCR = amplification-refractory mutation screening–polymerase chain reaction; ASO = allele-specific oligonucleotide; RFLP = restriction fragment length polymorphism.

allele caused by sequence homology. We are the only group that has directly sequenced large cohorts for this polymorphism, and we have obtained the lowest V allele frequencies. Indeed, when we genotyped a subset of our controls using conventional amplification-refractory mutation screening–polymerase chain reaction, this method resulted in an apparent V allele frequency of 0.40.

In summary, the differences between our results and those obtained by Nieto et al may reflect the different analytic strategies and models used and possibly also the genotyping methods. Further studies in our laboratory are currently under way to determine the role of FcγRIIIA in RA susceptibility in larger RA populations and in different aspects of RA pathogenesis and severity. We are also addressing the possible influence of other FcγR located in the same gene cluster on chromosome 1.

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Effect of etanercept on tenosynovitis and nodules in rheumatoid arthritis

To the Editor:

In recent years, it has been shown that tumor necrosis factor α (TNFα) plays an important role in the pathogenesis of

rheumatoid arthritis (RA). TNFα blockers represent a new generation of treatments for both RA and juvenile RA (JRA). These agents induce a rapid and sustained decrease in symptoms and slow progression of joint damage in both disorders (1–4).

The efficacy of disease-modifying antirheumatic drugs (DMARDs) for the treatment of extraarticular manifestations of RA (e.g., tenosynovitis, rheumatoid nodules) has not yet been demonstrated. Some reports are encouraging, such as that of the beneficial effect of etanercept in a patient with rheumatoid lymphedema (5).

Etanercept, a recombinant human soluble TNF receptor, is a dimeric fusion protein resulting from the association of the human p75 TNF receptor and the Fc portion of IgG1. It belongs to the family of TNFα blockers. We attempted to determine whether etanercept has efficacy in either the treatment of the extraarticular features of RA or prevention of their occurrence.

We assessed 82 patients with RA and 5 with JRA (70 female, 17 male). The median age was 51 years (range 7–76), and the median duration of RA was 11 years (range 2–32). Rheumatoid factor was positive in 64 patients. The median number of previously used DMARDs was 5 (range 1–10). We examined all patients for the presence of tenosynovitis and rheumatoid nodules on day 0, before treatment with etanercept was started. We then observed the evolution of tenosynovitis and rheumatoid nodules during a 6-month period.

All patients received 25 mg of etanercept subcutaneously twice a week. They were seen once monthly during the first 3 months and then once every 3 months. The presence or absence of tenosynovitis and rheumatoid nodules was systematically registered.

When etanercept treatment began, 66% of the 87 patients who were assessed had tenosynovitis. After 90 days of treatment, some or all tenosynovitis disappeared in 23% of these patients, new tenosynovitis appeared in 7%, and in 2% of patients tenosynovitis disappeared from some sites but appeared in others. No change was observed in the remaining 68% of patients.

On day 180, 73 patients were available for assessment, 57 of whom had tenosynovitis on day 90. In contrast to the findings on day 90, no change was observed in 87% of these patients, 8% had either less or no increase in tenosynovitis, new tenosynovitis appeared in 4%, and in 1% of patients tenosynovitis disappeared in some sites but appeared in new ones.

Throughout the study period, no new rheumatoid nodules appeared, and none disappeared. On day 0 and on day 180, 22 nodules were observed in 10 patients. Overall, after 6 months of etanercept treatment, very few patients had a change in their tenosynovitis assessment, and no one had a change of rheumatoid nodule status.

Although tenosynovitis disappeared in some patients at the beginning of etanercept therapy, this occurrence was probably independent of treatment, because tenosynovitis could simultaneously disappear from one site and appear at other locations in the same individuals. In the majority of cases, etanercept was not efficacious for tenosynovitis, and surgery remains the only possibility for helping people who are handicapped by this disorder.

Nodules neither appeared nor disappeared during treatment, and we can conclude similarly that their evolution might be completely independent of treatment. However, in contrast with methotrexate, which can induce rheumatoid nodules (6,7), etanercept seemed to have neither an efficacious nor a deleterious effect on nodules. Currently, no DMARD has proven efficacy for the treatment of spontaneously occurring rheumatoid nodules. Apparently, only colchicine, hydroxychloroquine, and D-penicillamine can reduce nodules induced by methotrexate, and only in some cases (8,9). Surgery is also disappointing, because nodules often recur.

No other extraarticular manifestation of RA appeared in our patients during the period of assessment. The role of etanercept for the treatment of other extraarticular features of RA remains to be elucidated.

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How frequently and how soon should we screen our patients for the presence of antimalarial retinopathy?

To the Editor:

In 1996, the American College of Rheumatology published guidelines for monitoring drug therapy for rheumatoid arthritis (RA) (1). Baseline and subsequent frequent (every 6–12 months) ophthalmologic examinations were recommended to monitor patients receiving hydroxychloroquine (HCQ) therapy. Since then, the need to monitor HCQ therapy so closely has been called into question (2–4). It has been argued that, given the fact that HCQ retinal toxicity occurs preferentially in elderly patients receiving HCQ in a daily dosage of >6.5 mg/kg body weight and only after a given time period (4 years of treatment), such frequent examinations are not necessary. In addition, these examinations may not be cost effective, given the large number of patients that must be examined in order to detect a single case of antimalarial retinopathy. This caveat may apply particularly to young patients who are receiving a dosage lower than that noted above.

Bienfang et al (5) have made a compelling argument for not relaxing these guidelines (6,7). They recently described 6 patients with HCQ retinopathy, all of whom had regularly received ophthalmologic followup at a large academic health center. These cases involved members of a patient population that had been screened every 6 months for HCQ toxicity over a 25-year period by one ophthalmologist, who examines ~120 patients annually for HCQ toxicity. The mean daily dosage of HCQ given to these 6 patients had not exceeded the threshold dosage of 6.5 mg/kg body weight. Early detection of this retinopathy is quite important, since no long-lasting visual impairment (8) occurs if HCQ is discontinued immediately after the lesion (premaculopathy) is detected.

The following case report documents the early occurrence of antimalarial retinopathy in a young woman who received less than the above-mentioned threshold dosage of HCQ for a relatively short period of time. This case further reinforces the need to maintain the existing ACR guidelines for monitoring this complication.

The patient was a 35-year-old African American woman weighing 296 pounds (134.5 kg) in whom systemic lupus erythematosus (SLE) was diagnosed. She had both mucocutaneous and articular manifestations of SLE and positive serologic findings. Therapy with HCQ (400 mg/day, ~3 mg/kg body weight) was started. Prior to initiation of HCQ therapy, the patient had a baseline ophthalmologic evaluation, with normal results. She returned 3 months later, and significant improvement of her articular and mucocutaneous symptoms was noted. The patient missed her next 2 appointments for rheumatologic examination and 1 for ophthalmologic evaluation. She presented again 9 months after beginning treatment with HCQ; she reported feeling good and had no overt evidence of ocular toxicity. At this time, she was again told that she needed to have her eyes examined. By the time the ophthalmologic evaluation was finally performed (a month after her visit to the rheumatologist), she had started to note some difficulty reading printed material but had no other ocular symptoms. Typical "bull's eye" lesions were observed, and HCQ was discontinued.

In short, the data presented and reviewed do not support relaxing the guidelines on ophthalmologic monitoring in patients with rheumatic diseases who are receiving antimalarial therapy. Neither a low dose of HCQ, short duration of therapy, nor young age precludes the occurrence of antimalarial retinopathy (1,8–10). It is tempting to speculate that antimalarial retinopathy is more common in patients with SLE than in those with RA or juvenile RA, but neither the literature nor our own experience may allow us to reach such a conclusion at this time.

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Distinguishing congenital from acquired heart block: comment on the article by Julkunen and Eronen

To the Editor:

Drs. Julkunen and Eronen's report (1) on the high prevalence of "autoimmune" clinical symptoms (especially sicca syndrome) in mothers of children with congenital heart block (HB) is an additional contribution to the somewhat confusing distinction between congenital and acquired HB (2). In their study, mothers of children with HB detected after the newborn period did not have clinical features of autoimmune diseases (1). Serologic differences between these 2 groups are well known: maternal antibodies to Ro/SSA are essential for congenital HB (3,4), whereas most of the mothers of children in the acquired HB group are seronegative, suggesting 2 forms of HB in children (5).

Anti-Ro/SSA–positive mothers of children with postnatally detected HB with (2,6) or without (5,7) clinical symptoms of an autoimmune disorder are difficult to categorize.

The anti-Ro/SSA status of the mothers studied by Julkunen and Eronen was not reported, and this element could add to our understanding on the subject. In a previous study from the same group (8), all 33 mothers of children with congenital HB were found to be anti-Ro/SSA positive and the clinical findings were similar to those reported in the comparable group in the present study (1). However, in that former study, no mothers of children with "late onset" HB were serologically studied.

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Reply

To the Editor:

We agree with Dr. Hübscher that the distinction between congenital HB (CHB) and acquired isolated HB has been (and still is) somewhat confusing. We have defined isolated HB as the absence of intracardiac anatomic malformations considered to be causally related to HB (1). Cardiac malformations included in our present study were hemodynamically insignificant muscular ventricular septal defect, secundum atrial septal defect, patent ductus arteriosus, mild-degree pulmonary valve stenosis, and mild-to-moderate mitral valve regurgitation. CHB was defined as HB diagnosed during pregnancy or at birth; all children had complete HB.

Isolated CHB using the above definitions is practically always associated with antibodies to SSA/Ro and/or SSB/La (2). Pathologic studies suggest that these antibodies cross the placenta and damage the fetal conduction system by fibro-fatty replacement of the atrial connections to the atrioventricular node. However, there are rare cases of seronegative isolated CHB, which may be caused by mass lesions of the conducting system, e.g., fibroma, rhabdomyoma, or hemangioma of the atrial cavity (3).

What is the etiology and pathogenesis of isolated HB diagnosed after the newborn period but before the age of 16 years? We suspect, as Hübscher et al point out in their study (4), that most of the cases previously diagnosed in early infancy are congenital, and this is explained by failure to make the diagnosis during pregnancy. Nowadays, however, late detection of isolated CHB is rare because of the wide use of fetal ultrasound examinations. Another explanation for late detection of isolated CHB is the possible progression of first- or second-degree HB to third degree after birth (5) (one such case was also noted in our series). In addition, there are reports of dilated cardiomyopathy developing after birth as a manifestation of neonatal lupus (1,6). The above findings are interesting and suggest an ongoing immunologic injury in selected affected hearts.

Data on the etiopathogenesis of truly acquired isolated HB in children are limited. There are occasional reports of atrioventricular block associated with myocarditis, endocarditis, inherited or acquired collagen diseases, different medications, and rare environmental exposures (7).

In our present study, there were 54 children (and their mothers) with isolated HB diagnosed after the newborn period but before the age of 16 years. Some mothers of these children had clinical features suggesting an underlying autoimmune disease. In the majority of the cases, however, we could not find any overt etiology or explanation for the HB in these children during the clinical followup or by examining the hospital case records. In 16 of the 54 children, the HB was diagnosed between 0 and 1 years of age, in 27 children between 1 and 5 years of age, and in 11 children after the age of 5 but before the age of 16. Forty-eight of the mothers of the 54 children are still alive. We hope that the determination of antibodies to SSA/Ro and SSB/La in these mothers could add to our understanding of the etiopathogenesis of isolated "acquired" HB.

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The difficulties in establishing a birth order or maternal age effect in ankylosing spondylitis: comment on the article by Baudoin et al

To the Editor:

In this letter, I offer some grounds for suggesting why it will be difficult to establish that there is a birth order effect in ankylosing spondylitis (AS), supposing that one actually does exist. Baudoin et al (1) reported an increased risk of AS among first-born siblings versus others in sibships. If these authors are correct, this is an important result and will almost certainly have implications for the etiology of the disease. However, I previously noted a flaw in their demonstration (2). AS is a condition that usually develops in adulthood. So, at a given time in any sibship, the first-born has a greater chance than other siblings to have been diagnosed with AS simply because the first-born has lived through more of the risk interval. Some of the authors responded (3) with the observation that the median age of their patients and siblings was 52 years, and that 90% of patients with AS have been diagnosed by that age.

This argument is not decisive. Therefore, I suggest a method by which the authors might strengthen their argument. For each of their siblings who is (so far) unaffected, a probability (p) that ultimately he or she will develop AS may be estimated. For sibling i, this probability is given by the product of 2 individual probabilities, $p_i = p_1 p_2$, where p_1 is the sex-specific sibling recurrence risk for AS, and p_2 the probability that a case is not diagnosed until after the age of sibling i. All these p_i values may be treated as expected frequencies and pooled with the appropriate observed frequencies of cases, and the result may be retested for a birth order effect. However, even when such adjustment has been made, the result may be subject to reservations, as will be later explained.

Moreover, there is another point that should be considered by the authors. They used a 1-tailed test. As I understand it, their justification for doing so is that some other diseases that they liken to AS (i.e., multiple sclerosis and rheumatoid arthritis) have been associated with birth order effects. The argument is questionable. However, because the grounds themselves are false, this need not detain us. There are no *conclusive* grounds for supposing that these 2 latter diseases are subject to birth order effects. The claim with regard to rheumatoid arthritis is based on a letter by Sayeeduddin et al (4). This letter reports a study in which the data were uncorrected (as indicated above) for future diagnoses of (mainly younger-born) siblings. Moreover, the claim was based on the test of Haldane and Smith (5), which has the same flaw as that in the test of Greenwood and Yule (6) (described below). Last, in other studies, higher rates of rheumatoid arthritis have been described in *later*-born men (7) and women (8). With regard to multiple sclerosis, there has been a brisk, but inconclusive, discussion of the possibility of a birth order effect. The last 2 studies (known to me) reported no such effect (9,10).

The test for a birth order effect used by Baudoin et al (1) is derived from that of Greenwood and Yule (6). On the occasion of the presentation of their test to a meeting of the Royal Statistical Society, Yule (who later became coauthor of the standard volumes on advanced statistics) expressed doubt about the validity of the test, which was later to be widely (and indiscriminately) used. Eighty-seven years later, his words are worth noting. "Mr Yule . . . thought they both (viz himself and Greenwood) felt, after the conclusion of their work, very doubtful as to the possibility of definitely proving the existence of a real differential incidence of any character in order of birth. The whole question seemed so open to fallacious possibilities in different directions." One of the grounds for Yule's doubt was that central to the test is the notion that if one ascertains a subject from a sibship of size n, then he or she has equal probabilities (1/n) of being first-, second-, . . . nth born. This is intuitively appealing but is subject to logical qualification, and empiric testing has shown it to be false under very general circumstances (11,12). Part of the explanation lies in the fact that population birth rates change across time.

None of the foregoing discussion should be taken to imply that there is no birth order effect in AS, simply that it will be difficult to demonstrate if there actually is one. At first, it might be thought that it would be useful, instead, to concentrate on maternal age rather than birth order. Baudoin et al (1) report a significant maternal age effect. However, one is again faced with the problem of the currently unaffected siblings who will later be diagnosed with the disease. In general, they are younger and thus later-born than the present cases. So, when diagnosis is finally complete in the ascertained sibships, mean maternal age will be higher than estimated at present.

As I see it, there are 2 solutions to the present problem. 1) Because of the established flaw in the Greenwood-Yule test (6), investigators could take the (admittedly more expensive) provision of ascertaining, in addition to their sample of cases, a control group of healthy, unaffected individuals who would be matched for age. The mean birth orders and maternal ages could then be tested for significant contrasts. If such a control group is ascertained, there seems no logical requirement to wait until all of the unaffected siblings have passed the maximum age of onset. 2) Alternatively, it would be possible to wait until the maximum age of onset and then estimate, for each affected case, his or her "expected" birth order, based on population mean birth order for the case's year of birth.

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Reply

Dr. James suggests that the observed effect of birth order in AS might be due to the possibility that the younger siblings may not yet have developed AS. Despite the relatively high age of the patients included, as was described in our reply, this issue still might be considered to be confounding in the observation that the risk of AS in first-born siblings is increased compared with that in later-born siblings. Although, in theory, Dr. James is right, we consider the confounding effect negligible, because the probability that one of the younger siblings of our group did not yet pass the proper age for diagnosis is very small. Also, the later-born siblings in our study had a lower median age at diagnosis compared with the first-borns (see Table 1 in our study). Moreover, the fact that these siblings had an older brother or sister with AS increases the awareness for detection of the disease in these relatives, which makes detection in an earlier stage possible. When limiting the analysis to families with only 2 children, the number of first-born siblings with AS still outweighed the expected number of later-born siblings with AS, as was shown in Table 2 of our study. In families with 2 children, 26 first-born children with definite AS were found, whereas 20 were expected ($\chi^2 = 3.6$, $P = 0.029$, by 1-sided test).

Another concern of Dr. James was the fact that 1-tailed testing was based on false arguments. Our hypothesis was primarily based on an observation in an animal model that the risk of ankylosing enthesopathy was increased in earlier-born offspring in mice (Weinreich S, Hoebe B, Ivanyi P. Maternal age influences risk for HLA-B27 associated ankylosing enthesopathy in transgenic mice. Ann Rheum Dis 1995;54:754–6). This was the main argument for why we used 1-sided testing to determine whether first-born siblings had an increased risk of AS. Two-sided testing would have also resulted in a significant increase, for all sibship sizes together. We do agree, however, that the results of studies on the effect of birth order in related autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis, are conflicting, as was mentioned in Dr. James' discussion of our article.

The doubts expressed by Dr. James that the statistical methods we used were not in accordance with the rules of the renowned statistician, Mr. Yule, have, in our opinion, small grounds. One of the possible biases concerns the change in population birth rates across time. However, we had the opportunity to include families with a large variation in numbers of children per family. The increase in AS in first-born siblings was observed in the small (2 or 3 children) as well as in the large (>3 children) families (see Table 4 in our study).

We agree that performing additional, prospective studies to test whether our hypothesis is correct would indeed be very interesting, but would take a very long time. However, to compare the maternal age at birth of a large group of AS patients with the maternal age at birth of age-matched controls would give us a clue as to whether birth order and/or maternal age influence the risk of AS.

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Somatization does not fit all fibromyalgia patients: comment on the article by Winfield

To the Editor:

Dr. Winfield is to be congratulated for his thoughtful editorial on fibromyalgia syndrome (FMS) and its related bio-psycho-social aspects (Winfield JB. Does pain in fibromyalgia reflect somatization? Arthritis Rheum 2001;44:751–3). He correctly points out that patients with FMS have many physical findings related to biologic abnormalities that strongly correlate with increased pain states. They include hyperalgesia, allodynia, abnormal temporal summation of second pain, neuroendocrine abnormalities, and abnormal activation of pain-related brain regions. He also emphasized the important fact that many FMS patients are distressed and often lack adequate coping skills. Although current evidence indicates that the definition of FMS selects for patients who show signs of maladaptation, the FMS criteria have nevertheless been very helpful for research purposes. The same may be true for

somatization. This diagnosis relies on the lack of clinical findings in patients with otherwise-characteristic physical symptoms. When applied to FMS patients, however, one obviously has to neglect the presence of at least one abnormal clinical finding, i.e., mechanical hyperalgesia (tender points). At this time, we have conclusive evidence that many chronic pain patients, including FMS patients, have detectable neurologic abnormalities that relate to abnormal central pain processing. The cause for these pathologic changes, however, is still unknown. Nevertheless, many of us who study FMS agree that the pain these patients experience is real and deserves our attention. The diagnosis of somatization should therefore focus our attention on those patients who need more help with the bio-psycho-social aspects of their pain experience.

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Gouty tophi in a pancreatic pseudocyst

To the Editor:

Gout represents a disease caused by uric acid deposition and is characterized by acute gouty arthritis, tophi formation, and uric acid nephrolithiasis. Tophi, deposits of sodium urate monohydrate crystals that usually occur in and around the joints, are rarely observed in patients without a history of gouty arthritis (1). Ectopic uric acid deposition, with tophi occurring in tissue other than periarticular, subcutaneous, or renal tissue, is extremely rare and has been found in the heart, spine, eye, and larynx (2,3). We now report the first case of inflammatory tophaceous deposits within a pancreatic pseudocyst.

The patient, a 39-year-old Hispanic man, was transferred to our medical center for surgical drainage of an infected pancreatic pseudocyst. Five months before admission, he developed acute alcoholic pancreatitis, and 2 large pancreatic pseudocysts were found 2 months later. The patient had previously been healthy and was taking no medications. He denied any history of arthritis, kidney stones, gall stones, or neurologic impairment but reported that his grandfather had a history of gout. At the time of transfer, the patient had nausea, abdominal pain, and daily low-grade fever. He had been taking broad-spectrum antibiotics for 4 weeks prior to admission to the hospital. A helical computed tomography scan performed at the previous facility revealed a large (5×5 cm) pseudocyst with pockets of air in the body of the pancreas. Another large pseudocyst (7×5 cm) was visualized in the tail of the pancreas.

On admission to our hospital, physical examination revealed a well-developed, well-nourished man with normal vital signs. The abdomen was soft and nondistended. There was mild tenderness in the epigastric area, without rebound or guarding. Musculoskeletal examination revealed no tophi or synovitis.

The patient underwent surgical drainage and debridement of the infected pancreatic pseudocyst. Intraoperatively, a copious amount of milky-colored fluid was drained from the pseudocyst. The cyst also contained dense, cheesy, necrotic material. Pathologic examination of the necrotic material revealed fat necrosis and saponification, with aggregates of crystals (Figure 1A). Examination of the cystic fluid under polarized microscopy revealed abundant negatively birefringent needle-shaped crystals consistent with gout (Figure 1B). Biochemical analysis of the cystic fluid confirmed that it was uric acid. Complete blood cell count, renal function, and electrolyte levels were within normal limits. The patient had normal findings on thyroid function tests and no monoclonal gammopathy. Multiple blood cultures were negative. Laboratory studies of blood and 24-hour urine specimens were obtained after he had received total parenteral nutrition (TPN) for more than 3 days. His serum uric acid level was very low at 2 mg/dl (normal 3.8–8.9), whereas the urinary uric acid level was in the low-normal range at 261 mmoles/24 hours (normal 250–750). The quantity of uric acid in the urine was higher than expected in conjunction with a serum uric acid level of <2 mg/dl.

The patient continued to have nausea and epigastric pain, and repeat drainage and examination revealed abundant uric acid crystals. Based on these findings, therapy with

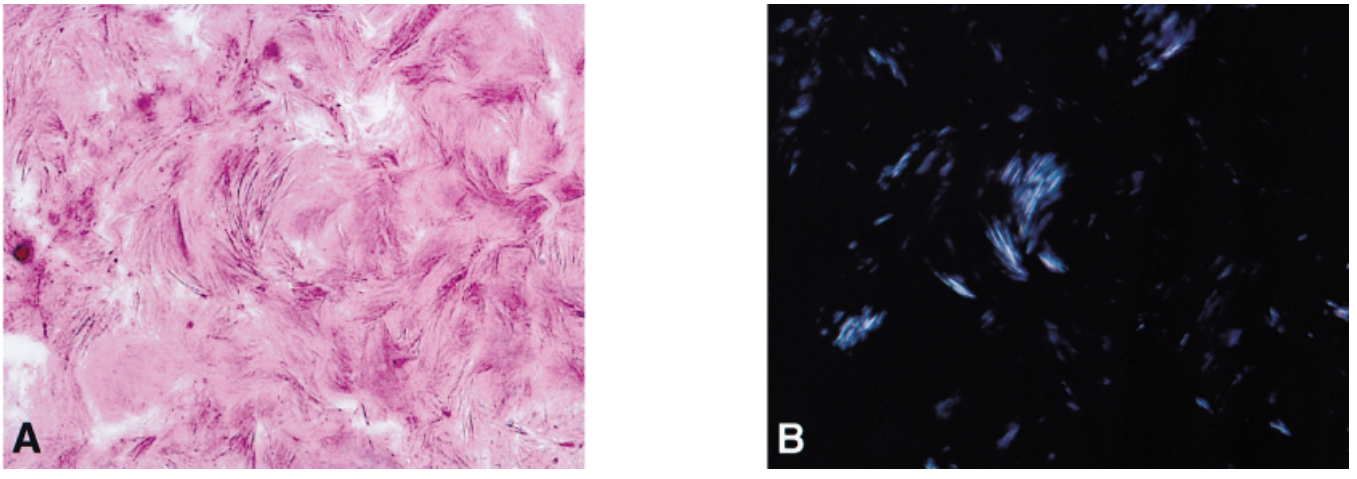

Figure 1. A, High-power photomicrograph of a gouty pancreatic pseudocyst with aggregates of urate crystals (hematoxylin and eosin stained). **B,** Polarized microscopic view showing needleshaped birefringent crystals.

uricosuric agent, sulfinpyrazone 200 mg orally twice a day, was started to determine whether a defect in tubular reabsorption of urate was causing his serum uric acid level to be low while the urinary level was normal. TPN was discontinued, and he resumed oral food intake. Seven days after initiation of sulfinpyrazone therapy, 24-hour urinary uric acid secretion increased to 612 mmoles, suggesting that reabsorption of uric acid by renal tubules was probably normal. His serum uric acid level also increased, to 3.7 mg/dl, despite sulfinpyrazone treatment. He has had no recurrence of pancreatitis or symptoms of gout during a followup period of 3 months.

We hypothesize that the following factors contributed to the gouty pseudocyst: 1) increased systemic uric acid production secondary to ethanol abuse, 2) a probable defect in renal tubular secretion of uric acid, and 3) possible increased uric acid production by the pancreas or pancreatic pseudocyst due to tissue ischemia associated with pancreatitis. It is likely that the numerous crystals present in the pseudocysts contributed to inflammation in that tissue. Therefore, it would be interesting to know if urate crystals could be identified in pancreatic pseudocysts of other patients, because introduction of urate-lowering therapies might be useful in preventing subsequent attacks of pancreatitis in such individuals.

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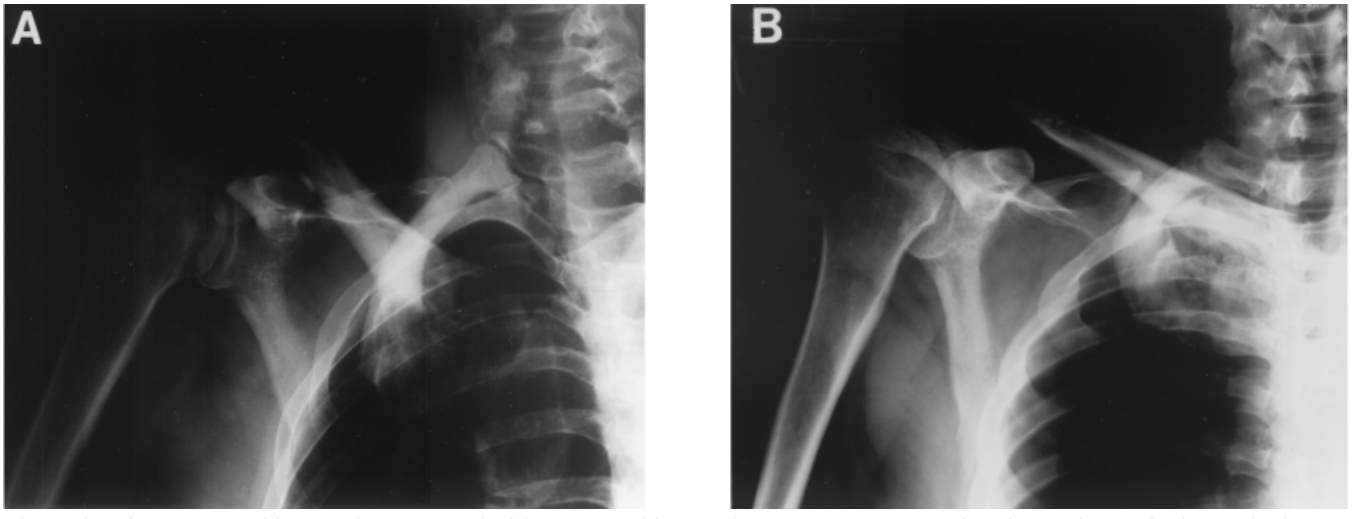
Clinical Images: Unrecognized SAPHO syndrome as a rare cause of chronic anterior chest pain



The patient is a 62-year-old man who presented with a 27-year history of recurrent upper anterior chest pain. He had consulted many physicians, and numerous complete evaluations had been performed, without a conclusive diagnosis. Results of routine laboratory tests, including erythrocyte sedimentation rate and C-reactive protein level, were within normal ranges. HLA–B27, antinuclear antibodies, and rheumatoid factor were negative. The physical examination findings at the time of presentation were normal except for distention of the sternoclavicular joints. The patient reported that these joints had repeatedly become swollen for periods of several days during previous years. There were no abnormalities of the skin, nails, or eyes. On intensive questioning, the patient also reported having recurrent skin rashes restricted to the palms of the hands and soles of the feet. Radiography of the sternoclavicular joints revealed typical findings of SAPHO syndrome, with cortical thickening and expansion of the sternal ends of the clavicles (**A**) and sternoclavicular hyperostosis (**B**). The acronym SAPHO (synovitis, acne pustulosis, hyperostosis, osteitis) describes a clinical entity of musculoskeletal disorders, in particular hyperostosis involving the bones and joints of the anterior chest wall in association with various dermatologic conditions such as palmoplantar pustulosis or other patterns of psoriasis and severe acne. As this case illustrates, it may be underrecognized, because skin manifestations may be mild or absent and the courses of skin and bone manifestations are often not parallel. Awareness of this clinical entity and thorough history-taking and examination will allow correct and early diagnosis of the syndrome.

Monika A. Reuss-Borst, MD
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