

HLA–DPB1 associations differ between DRB1*03 positive anti-Jo-1 and anti-PM-Scl antibody positive idiopathic inflammatory myopathy

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Objective. The HLA 8.1 ancestral haplotype (HLA-B*08/DRB1*03/DQA1*05/DQB1*02) is associated with adult/juvenile idiopathic inflammatory myopathy (IIM), but confers a greater strength of association in patients possessing anti-Jo-1 or anti-PM-Scl antibodies. The HLA–DPB1 gene is centromeric to other HLA class II loci and separated by a recombination hotspot. We investigated whether HLA–DPB1 associations differ between anti-Jo-1 and anti-PM-Scl antibody-positive IIM cases.

Methods. Two hundred and thirty-three adult IIM patients (73% females, 49.4 ± 13.6 years) with PM ($n=89$), DM ($n=88$) and myositis associated with another CTD ($n=55$) and 85 juvenile DM patients (75% females, 6.2 ± 3.6 years) were compared with 678 UK Caucasian controls. Patients/controls were genotyped for HLA–DPB1 and DRB1 alleles. Myositis-specific and associated antibodies were identified in cases using immunoprecipitation.

Results. HLA–DPB1*0101 was associated with IIM overall [22 vs 13% controls, corrected probability (P_{corr}) = 2×10^{-03} ; odds ratio (OR) 2.0; 95% CI 1.4, 2.9], PM ($P_{\text{corr}} = 7 \times 10^{-03}$; OR 2.5; 95% CI 1.5, 4.4) and anti-Jo-1 ($P_{\text{corr}} = 3 \times 10^{-5}$; OR 4.1; 95% CI 2.1, 7.8). No significant DPB1*0101 difference was present between anti-PM-Scl cases and controls. The HLA–DPB1*0101 association in IIM overall cases was dependent on the presence of DRB1*03. A number of HLA–DRB1*03/DPB1 haplotypes were identified, but only DRB1*03/DPB1*0101 was associated with anti-Jo-1 antibody-positive cases.

Conclusions. The HLA–DRB1*03/DPB1*0101 haplotype is a risk factor for anti-Jo-1 antibody-positive IIM. Thus, although DRB1*03 is strongly associated with possession of either anti-Jo-1 or anti-PM-Scl, differing antibody associations are observed at the HLA–DPB1 locus.

KEY WORDS: Myositis, Polymyositis, Dermatomyositis, Autoantibodies, Immunogenetics, HLA, MHC, HLA–DPB1, HLA–DRB1, Haplotype.

Introduction

The idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of rare autoimmune diseases characterized by acquired proximal muscle weakness, inflammatory cell infiltrates in muscle biopsies and the presence of circulating myositis-specific/associated autoantibodies (MSA/MAAs). The aetiopathogenesis of IIM is likely to be due to both genetic and environmental factors and their interactions [1]. IIM are commonly classified according to traditional clinical sub-group status: PM, DM, myositis overlapping with another CTD (myositis/CTD-overlap) and juvenile IIM, the most common type of the latter being juvenile DM (JDM). However, IIM studies suggest that case stratification is more appropriate when undertaken according to MSA/MAA, as the detected antibody and clinical phenotype are closely associated [2–4].

For instance, patients with anti-histidyl-tRNA synthetase (Jo-1) antibodies, or other anti-aminoacyl-tRNA synthetases, may present with the ‘anti-synthetase syndrome’, comprising fever, myositis, arthritis, RP, ‘mechanic’s hands’ and an increased

likelihood for the development of interstitial lung disease (ILD), irrespective of whether the traditional clinical sub-group is PM or DM [5]. Patients with anti-PM-Scl antibodies may, like those with anti-Jo-1, also present with myositis, RP and ILD, but as part of a sclerodermatous overlap spectrum [6].

It is well recognized that the MHC confers a major genetic contribution for a variety of autoimmune diseases. Candidate gene studies have suggested an association of HLA–DRB1*0301 and HLA–DQA1*0501 in adult and juvenile Caucasian IIM, with increased risk of these alleles in patients possessing anti-Jo-1 or anti-PM-Scl antibodies [2, 5, 7–11]. These alleles form part of a conserved, Caucasian haplotype known as the HLA 8.1 ancestral haplotype containing A1/B8/Cw7/DRB1*03/DQA1*05/DQB1*02, predisposing to a wide range of autoimmune diseases [12, 13]. The term ‘haplotype’ refers to closely linked alleles present on one chromosome that are inherited together *en bloc* and ‘ancestral’ emphasizes that the haplotype has been inherited with little, or no, change from a common ancestor through meiotic cross-overs. The resulting non-random assortment of alleles at neighbouring loci in such conserved haplotypes is known as linkage disequilibrium (LD).

Despite sharing many clinical features and the HLA 8.1 ancestral haplotype, patients with anti-Jo-1 or anti-PM-Scl antibodies are considered to have distinct IIM clinical phenotypes and prognoses [2]. We hypothesize that genetic variations not usually considered as part of the 8.1 ancestral haplotype may be involved in serotype/phenotype differences between anti-Jo-1 and PM-Scl antibody-positive IIM cases. The HLA–DPB1 gene lies at the centromeric end of the MHC and is separated from other HLA class II loci by one or more recombination hotspots [14]. This separation will weaken the degree of LD between HLA–DPB1 and other class II loci, e.g. DR and DQ. The aim of this study was to investigate whether differing HLA–DPB1

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associations may be observed in anti-Jo-1 and anti-PM-Scl antibody-positive cases.

Patients and methods

Subjects

DNA was available from 318 UK Caucasian IIM cases. Adult IIM patients ($n=233$), aged ≥ 18 years of age at disease onset, were recruited through the UK Adult Onset Myositis Immunogenetic Collaboration, (AOMIC) [5]. JDM patients ($n=85$) were recruited to the UK and Ireland JDM National Registry and Repository [11, 15]. All adult PM/DM and JDM cases had probable or definite disease according to Bohan and Peter [16]. For adult myositis/CTD-overlap cases, use of diagnostic criteria is problematic, as myositis is often diagnosed less rigorously in the context of another CTD (likely reflecting the lack of expertise of electromyography and muscle histology in UK non-teaching centres). Thus, 12 of the 56 (21%) myositis/CTD-overlap patients were included if they fulfilled all of the following: (i) met published criteria for their primary CTD [17–21] or MCTD [22]; (ii) possessed at least two of four Bohan and Peter criteria (proximal muscle weakness, elevated muscle enzymes, characteristic myopathic electromyographic changes, diagnostic muscle biopsy); and (iii) possessed at least one MSA/MAA. The remaining 44 myositis/CTD-overlap patients all fulfilled criteria for their primary disease/MCTD and probable/definite myositis according to Bohan and Peter [16, 23]. A standardized clinical data collection form, detailing demographics and individual clinical details, was used.

Controls

One thousand five hundred and forty-two UK Caucasian control subjects were recruited from blood donors and general practitioner registers, as previously described [5]. Of these, 678 were available for HLA-DPB1 and DRB1 typing. An additional 864 control samples were typed for DRB1. The study was approved by the local research ethics committee (North West Multi-centre Research Ethics Committee, number 98/8/86) and informed consent was obtained according to the Declaration of Helsinki.

Autoantibody typing

Serum was obtained from patients for determination of MSAs: anti-synthetases: -Jo-1, -PL-7, -PL-12, -EJ, -OJ, -KS, -Zo; anti-Mi-2, anti-SRP, anti-p155/140 and MAAs: anti-PM-Scl, anti-Ku, anti-U1-RNP, anti-U3-RNP using radio-immunoprecipitation, as previously described in adult [5, 24] and juvenile [11] IIM. The presence of anti-small ubiquitin-like modifier 1 activating enzyme (SAE) was also determined [25].

Genotyping

DNA was extracted from peripheral whole blood samples obtained from both cases and controls using a standard phenol-chloroform method. Cases were broad-typed for HLA-DRB1 and high-resolution-typed for DPB1, using a commercially available PCR-sequence-specific oligonucleotide probe typing system (Dynal Biotech, Hamburg, Germany).

Statistical analyses

Contingency tables were used to compare the overall allelic distributions between the myositis subtypes and controls, and exact probabilities calculated using the CLUMP program [26]. Individual HLA phenotypic associations were derived from 2×2 contingency tables using the chi-squared test, or two-tailed Fisher's exact test where individual cells valued five or less. Where significant, data were expressed as odds ratios (ORs) with exact

95% CIs. Point-wise P -values were corrected using the Bonferroni correction, by multiplying the uncorrected P -value by the number of alleles tested (DPB1 = 23; DRB1 = 14). 'Possible' associations were defined as significant before a Bonferroni correction was applied. Due to the large number of corrections that would have to be applied, uncorrected probabilities are presented for haplotype associations. LD was calculated using both D' and pairwise r^2 values. HLA-DRB1/DPB1 haplotypes were estimated and constructed using the expectation/maximization algorithm, using HelixTree (version 3.1.2, Golden Helix, Bozeman, MT, USA). Haplotypes were also imputed from missing data, to maximize statistical power. The analyses were also repeated after stratification for myositis serology. Unless otherwise stated, the statistical package Stata (release 9.2, Stata Corp., College Station, TX, USA) was used to perform statistical analysis.

Results

Demographics

Two hundred and thirty-three adult IIM patients (73% females, 49.4 ± 13.6 years): PM ($n=89$), DM ($n=88$), myositis associated with another CTD (myositis/CTD-overlap, $n=56$) and 85 JDM patients (75% females, 6.2 ± 3.6 years) were analysed.

HLA associations

A significant difference was noted between IIM overall cases and controls for the HLA-DPB1 and DRB1 loci ($P=0.002$ for both). However, after stratification by clinical or serological sub-groups, no overall significant differences were noted in comparison to controls for the DPB1 locus. HLA-DPB1*0401 was the most frequent allele in controls (65%). The frequency of HLA-DPB1*0101 was increased in IIM cases overall compared with controls. DPB1*0101 was a significant risk factor in IIM cases overall, in adult PM, and a possible risk factor in JDM, in comparison with controls (Table 1). After multiple corrections were applied, no further significant DPB1 associations were noted. A relative predispositional effect test [27] was performed to evaluate residual effects in other minor alleles which may have otherwise been masked by HLA-DPB1*0101. After allowing for the presence of HLA-DPB1*0101, no evidence for other allelic association was found.

Detailed analyses of our HLA-DRB1 results in the adult IIM and JDM clinical sub-groups have been reported previously [5, 11]. For comparison purposes, DRB1*03 associations are presented with the univariate DPB1 data (Table 1). Strong associations were observed in PM and myositis-CTD/overlap cases, explained by the presence of anti-Jo-1 and PM-Scl antibodies (and lack of the non-DRB1*03-associated antibodies, e.g. anti-Mi-2 and -p155/140) in these groups.

The frequency of HLA-DPB1*0101 homozygosity in IIM cases was no different to that seen in controls [3/71 (4%) IIM cases vs 5/94 (5%) controls]. No differences were observed either in adults or juveniles when data were stratified above or below median age of onset. No interaction was observed between gender and HLA-DPB1 status.

Serological associations

To further investigate disease associations, the data were stratified by MSA/MAA status. Due to the similarities noted for HLA-genotype-serological associations between juveniles and adults [11], these cohorts were combined together in the ensuing analysis. A strong association was noted between DPB1*0101 and anti-Jo-1 antibody-positive cases (Table 1). Given the strong and shared association of HLA-DRB1*03 in anti-Jo-1 or anti-PM-Scl positive cases (Table 1) [5, 10], a similar magnitude of association in anti-PM-Scl antibody-positive cases for HLA-DPB1*0101 may have been expected. However, no significant difference was

TABLE 1. HLA-DRB1*0101 and DRB1*03 associations in IIM clinical and anti-Jo-1/PM-Scl sub-groups vs controls

Group	n	HLA-DRB1*0101 associations			HLA-DRB1*03 associations		
		%	P_{corr}	OR (95% CI)	%	P_{corr}	OR (95% CI)
Controls	676	12.7	—	—	28.8	—	—
IIM overall	311	22.5	2×10^{-03}	2.0 (1.4, 2.9)	53.7	7×10^{-13}	2.0 (1.4, 2.8)
PM	88	27.3	7×10^{-03}	2.5 (1.5, 4.4)	59.1	2×10^{-07}	3.5 (2.2, 5.8)
DM	88	20.5	0.05	1.8 (0.94, 3.2)	44.3	0.04	2.0 (1.2, 3.2)
CTD/overlap	55	18.2	NS	1.5 (0.66, 3.2)	70.9	2×10^{-09}	6.0 (3.2, 11.8)
JDM	80	22.5	NS	2.0 (1.1, 3.6)	46.2	0.01	2.1 (1.3, 3.5)
Jo-1	51	37.3	3×10^{-05}	4.1 (2.1, 7.8)	88.2	4×10^{-17}	18.5 (7.7, 53.7)
PM-Scl	33	15.2	NS	1.2 (0.36, 3.3)	97.0	4×10^{-15}	78.9 (12.9, 3219)

Cases and controls only included here where samples were typed for both HLA-DRB1 and DPB1. Numbers stated for cases and controls refer to percentages of patients with individual genetic phenotypes. Statistical comparisons are vs controls. P_{corr} : corrected probability.

TABLE 2. HLA-DRB1*03/DPB1 haplotype frequencies in anti-Jo-1 and PM-Scl sub-groups vs controls

Haplotype	Controls 2n=3084	Jo-1 2n=112			PM-Scl 2n=72		
		%	OR (95% CI)	P	%	OR (95% CI)	P
DRB1*03-DPB1*0101	4.6	17.8	4.5 (2.6, 7.6)	3×10^{-10}	6.0	1.2 (0.32, 3.3)	NS
DRB1*03-DPB1*0401	3.7	21.9	7.5 (4.4, 12.3)	2×10^{-21}	20.8	6.9 (3.5, 12.7)	4×10^{-13}
DRB1*03-DPB1*0201	1.8	2.7	1.5 (0.3, 4.7)	NS	9.0	5.8 (2.2, 13.5)	5×10^{-4}
DRB1*03-DPB1*0402	1.8	1.2	0.5 (0.01, 2.9)	NS	7.9	4.9 (1.7, 11.9)	3×10^{-3}
DRB1*03-DPB1*0301	1.7	2.7	1.6 (0.3, 5.1)	NS	7.5	4.3 (1.3, 11.3)	9×10^{-3}

Cases and controls included here where samples were typed for either HLA-DRB1 or DPB1. Numbers stated for cases and controls refer to percentages of patients with individual genetic haplotypes. Due to large number of possible HLA-DRB1-DPB1 haplotypes, P-values are not corrected. Statistical comparisons are vs controls.

noted in the frequency of HLA-DRB1*0101 between anti-PM-Scl antibody-positive cases (15%) and controls (13%). Indeed, after allowing for the presence of anti-Jo-1, HLA-DRB1*0101 was no longer a significant risk factor in IIM after multiple corrections were applied (19% IIM vs 13% controls; $P=0.007$; OR 1.7; 95% CI 1.1, 2.5). A significant difference at HLA-DRB1*0101 was noted between anti-Jo-1 and PM-Scl positive cases when the two antibody-positive populations were compared directly with each other (37% Jo-1 vs 15% PM-Scl; $P=0.03$; OR 3.3; 95% CI 1.01, 12.7). All cases possessing other anti-synthetase antibodies (anti-OJ, $n=3$; anti-PL-7, $n=1$) carried one copy of DPB1*0401.

LD

To assess the relationship between the HLA-DRB1 and DPB1 loci, an LD plot was created for the control group. As assessed by D' , a high degree of LD was present within alleles of each locus. HLA-DRB1*03, the allele associated with highest risk for IIM, exhibited the greatest LD with DPB1*0101 ($D'=0.67$) and DPB1*0401 ($D'=0.48$). Using the r^2 value, only weak correlation was noted, between DRB1*03 and DPB1*0101 ($r^2=0.18$).

Adjustment for HLA-DRB1*03

To ascertain whether HLA-DRB1*0101 exerted an effect independent of HLA-DRB1*03, a multivariate logistic regression model was created, including both DRB1*03 and DPB1*0101 as outcomes. After adjusting for HLA-DRB1*03, HLA-DRB1*0101 was no longer a significant risk factor for IIM cases overall or for any of the clinical/serological sub-groups vs controls (data not shown). Fifty-eight of the 71 (82%) cases with HLA-DRB1*0101 were also HLA-DRB1*03 positive. In the anti-Jo-1 antibody sub-group, where HLA-DRB1*0101 appeared to be a strong risk factor, it was noted that each of 19 anti-Jo-1/DPB1*0101 positive cases also possessed at least one copy of DRB1*03. Furthermore, in the absence of HLA-DRB1*0101, HLA-DRB1*03 remained a significant risk factor in IIM overall cases (46% cases vs 22%

controls; $P=5 \times 10^{-11}$; OR 2.9; 95% CI 2.1, 4.1) and anti-Jo-1 antibody positive cases (81% cases vs 22% controls, $P=1 \times 10^{-11}$; OR 15.9; 95% CI 5.9, 45.8).

HLA-DRB1/DPB1 haplotypes

To further examine whether the DPB1 locus could discriminate the shared DRB1*03 Jo-1/PM-Scl association, haplotypes were constructed across HLA-DRB1 and DPB1 for these serological sub-groups. The most common haplotype in the control group was HLA-DR2/DPB1*0401, frequency 10%. Significant associations for IIM were only observed here in haplotypes containing HLA-DRB1*03, thus a summary of the DRB1*03/DPB1 haplotypes is presented in Table 2. HLA-DRB1*03/DPB1*0101 was a significant risk factor in IIM overall cases vs controls (haplotype frequency 8% IIM vs 5% controls, $P=2 \times 10^{-04}$; OR 1.8; 95% CI 1.3, 2.4) and showed a greater strength of association in anti-Jo-1 antibody positive cases (Table 2). After excluding anti-Jo-1 antibody cases from the analysis, this haplotype lost significance. HLA-DRB1*03/DPB1*0401 conferred risk with a greater strength of association in IIM cases overall (13% IIM vs 4% controls, $P=1 \times 10^{-24}$; OR 3.9; 95% CI 2.9, 5.2), and also in both anti-Jo-1 and PM-Scl antibody groups. Even after exclusion of cases with either or both these antibodies, HLA-DRB1*03/DPB1*0401 remained a significant risk factor for IIM vs controls (data not shown). The frequency of HLA-DRB1*03/DPB1*0401 was still increased in the cohort of IIM cases that were negative for recognized MSA/MAA by immunoprecipitation ($2n=124$; 8%). Although the MSA/MAA negative group was not significantly different compared with the control group, due to loss of statistical power from stratification, this suggests that HLA-DRB1*03/DPB1*0401 is increased in IIM regardless of serological status. Three other haplotypes containing HLA-DRB1*03 were associated with anti-PM-Scl antibody positive cases, suggesting that a characteristic DPB1 haplotype cannot be identified for anti-PM-Scl antibody-positive patients.

Discussion

This is the first analysis of the HLA–DPB1 locus in a cohort of UK Caucasian adult and juvenile IIM patients. The findings start to dissect out why two distinct serological sub-groups, anti-Jo-1 and -PM-Scl, both share a strong association with the HLA class II allele DRB1*03 (and thus the 8.1 ancestral haplotype). HLA–DPB1*0101 is a risk factor for the development of anti-Jo-1 antibody-positive IIM, although this allele shares LD with, and is dependent upon, the presence of DRB1*03. It is interesting to note that despite the strong relationship of HLA–DRB1*03 with anti-PM-Scl, the frequency of HLA–DPB1*0101 is not increased in this antibody sub-group.

Construction of HLA–DRB1*03/DPB1 haplotypes appears to further explain the relationship of DPB1 with IIM. The HLA–DRB1*03/DPB1*0101 haplotype only confers risk for anti-Jo-1 antibody-positive cases. The HLA–DRB1*03/DPB1*0401 haplotype confers strong risk across the whole IIM cohort and is prominent in cases that are negative for recognized MSA/MAA. The PM-Scl/DRB1*03 association is shared across multiple DRB1*03/DPB1 haplotypes, thus a characteristic DPB1 haplotype cannot be identified for anti-PM-Scl antibody positive patients. Thus, in addition to the ‘generic’ genetic risk conferred by possession of HLA–DRB1*03, other MHC polymorphisms, not so far investigated, may be involved in clinical phenotype features related to antibody production.

With respect to IIM, the HLA–DPB1 locus has previously been investigated in 750 Japanese patients screened for autoantibodies. The results showed that 21 were anti-Ku antibody positive, all of whom possessed HLA–DPB1*0501 [28]. However, no HLA–DPB1 association was found in a further Japanese study of anti-KS antibody positive IIM patients [29]. The HLA–DPB1 locus has also been investigated in small numbers of other autoimmune diseases. In a UK Caucasian SSc population, HLA–DPB1*1301 was associated with anti-topoisomerase antibody positivity [30]. HLA–DPB1*0402 is a reported protective factor in type 1 diabetes [31]. HLA–DPB1*0201 is associated with juvenile idiopathic and adult RA [32, 33]. A recent adult RA study performed careful 1:1 matching of 372 cases and 372 controls by DRB1 genotype, to remove the effect of alleles in this gene [34]. In this population, associations were reported in the centromeric MHC, in regions containing the DOB1, TAP2, DPB1 and COL11A2 genes.

A number of points require discussion. As demonstrated in the study by Lee *et al.* [34], other genes lie in the centromeric MHC which we have not tested for here, may confer susceptibility for IIM or alter phenotypic disease expression. Furthermore, to account for the effects of the 8.1 ancestral haplotype in IIM, matching of controls and cases would provide further information, although conditional logistic regression analysis has allowed us to discern the relationship between DRB1 and DPB1. We have not assessed the relationship between DPB1 and other HLA class II loci, e.g. DQ, due to the limited genotyping of the control group used in the current study to date. A lack of statistical power may have influenced our data meaning that associations after stratification were not detected, i.e. a type II error. We are however, confident that the observed univariate associations would hold up to a type I error after application of a conservative Bonferroni correction. No other confirmation studies are currently available in a Caucasian population, thus our results must be interpreted in this context.

Our data suggest that there may be an additional disease susceptibility signal for anti-Jo-1 antibody positive cases in the centromeric MHC region. In anti-PM-Scl antibody positive cases, no individual DPB1 allele is related to the strong HLA–DRB1*03 association observed for this antibody, other than the generic DRB1*03-DPB1*0401 IIM association. An accurate location of all disease susceptibility genes for these and other antibodies cannot be ascertained from this existing data and

will require fine mapping studies and further careful analyses in large-scale collaborative studies. Future whole-genome association studies in IIM may allow for a more comprehensive analysis of the MHC region.

In conclusion, we have demonstrated that in HLA–DRB1*03 positive UK Caucasian adult and juvenile IIM, the HLA–DPB1*0101 allele is a risk factor for possession of anti-Jo-1 antibodies, but not for anti-PM-Scl antibodies. Thus, although DRB1*03 is strongly associated with possession of either antibody, HLA–DPB1 appears to genetically discriminate between these serological sub-groups.

Rheumatology key messages

- The HLA–DRB1*03/DPB1*0101 haplotype confers susceptibility for anti-Jo-1 antibody-positive IIM.
- Although HLA–DRB1*03 is strongly associated with possession of anti-Jo-1 or anti-PM-Scl, differing associations are observed at HLA–DPB1.

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Clinical Vignette

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Cystic swelling of the acromioclavicular joint: an unusual complication of gout

A 79-year-old man with a history of type 2 diabetes, congestive cardiac failure and a prior history of gout was admitted with acute-onset pain and swelling affecting his left wrist, elbow and shoulder. Examination revealed acute synovitis of the wrist and elbow and a tender soft tissue swelling overlying the acromioclavicular (AC) joint, but no visible tophi. Investigations revealed an elevated uric acid at 690 $\mu\text{mol/l}$, creatinine was 128 $\mu\text{mol/l}$ and CRP 293 mg/dl. An X-ray (Fig. 1) revealed a radio-opaque cystic swelling surrounding the left AC joint, with spiculation of the lateral border of the clavicle. A total of 5 ml of chalky fluid was aspirated from the AC joint, the microscopy of which revealed abundant uric acid crystals. The patient was treated with colchicine 500 μg twice daily, and prednisolone 10 mg, and the AC joint was injected with 20 mg of depomedrone, providing complete relief of his symptoms.

Gout affecting the shoulder and the AC joint in particular is exceedingly uncommon, and to our knowledge a cystic swelling of this joint visible on plain radiography has not been previously reported. Spiny outgrowths, termed 'porcupine shoulder' have been reported previously [1], but are more typical of erosive damage in the feet.

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Fig. 1. An AP radiograph of the left shoulder, showing a cystic opacity surrounding the acromioclavicular joint with spiculation of the lateral border of the clavicle.

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