Table 1 Comparison of RA characteristics across Mediterranean and northern European countries

Characteristics	Lebanon (current survey)	Greece ¹	Italy ^{8,9}	Spain ³	France ¹⁰	UK ¹	Norway ²	Lithuania ²
Patients (n)	97	108	200	788	1109	107	201	201
Mean age (years)	52.2		55.3	61	56.7		55.9	55.9
Sex (% women)	87		81	71.3	77.3		83	83
Mean disease duration (years)	9.2		12.5	10	10.6		12.7	11.9
Tender joints (n), mean	6.9	6.8		3	7.2	15	6.6	12.6
Swollen joints (n), mean	4.4	4		4	4.9	8.9	7.8	4.7
DAS28 score, mean (SD)	3.6 (1.0)			3.4 (1.2)	4.51 (1.55)		4.4 (1.4)	5.3 (1.0)
Patients with typical lesions (%)	76	63	84		78	95		
HAQ score, mean (SD)			1.71	1.6 (0.4)	1.32 (0.77)			
MHAQ score, mean (SD) [scale]	0.66 (0.47) [0–3]						1.6 (0.5) [1–4]	2.3 (0.8) [1–4]
Patients with EAMs (%)	18	20.4	40.9	36.2	8.4	65–71	62	59
Patients ever receiving DMARDs (%)	100		89				90	94
Patients currently receiving DMARDs (%)	98			72	82.1			
Patients receiving oral steroids (%)	66		75		72			

DAS28, 28 joint disease activity score; HAQ, Health Assessment Questionnaire score; MHAQ, modified Health Assessment Questionnaire score; EAMs, extra-articular manifestations; DMARD, disease modifying antirheumatic drug.

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Accepted 13 September 2005

Published Online First 21 September 2005

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Pulmonary nodules as initial manifestation of primary Sjögren's syndrome

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Ann Rheum Dis 2006;**65**:685–687. doi: 10.1136/ard.2005.042069

A 66 year old white woman was referred to us for further evaluation of pulmonary nodules. Her medical history was as follows: in July 2001 multiple pulmonary nodules were recorded on a chest x ray examination as well as computed tomographic (CT) scan (fig 1). Cancer of unknown origin with multiple lung metastases was suspected. The patient showed no pulmonary symptoms at any time, was a non-smoker, and had not been exposed to any environmental toxins. She underwent an intensive search for the primary tumour, but all investigations were unsuccessful. Thus anterolateral thoracotomy was performed for histological evaluation of the nodules, which were classified as disseminated rheumatoid nodules (fig 2).

On presentation at our clinic, the patient reported extreme dryness of mouth and eyes, as well as Raynaud's phenomenon. She did not have any history of fever, night sweats, weight loss, thrombosis, arthralgias, or morning stiffness.

Clinical examination at that time (November 2001) showed extreme dryness of mouth and eyes, confirmed by pathological Saxon and Schirmer tests. There was no evidence of parotid swelling or enlarged lymph nodes. No tender or swollen joints, no functional deficits or joint deformities, no subcutaneous rheumatoid nodules or rashes were documented on clinical examination.

Laboratory values were as follows: rheumatoid factor was strongly positive with 156 U/ml (normal <20 U/ml). Indirect immunofluorescent assay for antinuclear antibodies on Hep-2 cells showed a titre of 1/640, and serological testing was positive for anti-SSA and anti-SSB antibodies; antibodies against Sm, RNP/Sm, U1-snRNP, Scl-70, Jo-1, CENP-B, dsDNA, and histones were negative, as were antineutrophil cytoplasmic antibodies. The C3 and C4 complement fractions and C reactive protein were in the normal range.

Figure 1 Chest x ray (A) of the patient in 2001 (depicting multiple pulmonary nodules) and chest CT scan (B).

Figure 2 Histology of the nodules (haematoxylin and eosin staining, magnification $\times 2.5$).

Serum electrophoresis showed polyclonal hypergamma-globulinaemia with a γ globulin fraction of 24%. IgG was raised at 22.6 g/l (normal 7–16 g/l); IgA and IgM were within the normal range.

An x ray examination of the hands and feet showed no pathological finding; in particular, no signs of destructive lesions were seen.

Symptomatic treatment of the sicca syndrome and Raynaud's phenomenon was started and led to good relief of the symptoms. In addition, steroid treatment was started and gradually tapered to a low dose of 5 mg prednisolone/day. The patient has been seen regularly as an outpatient during the past 4 years. She has not developed any clinical signs or symptoms of rheumatoid arthritis (RA) since her first visit in November 2001 and a recently repeated Tc^{99m} scintigraphy again showed no signs of arthritis. Remarkably, the size and number of the pulmonary nodules has been stable since then.

Disseminated pulmonary nodules as a primary manifestation of a disease present a challenge for the clinician because a wide range of differential diagnoses have to be considered^{1–3} (box 1). In this case histological analysis finally showed the typical features of rheumatoid nodules.

Pulmonary rheumatoid nodules are detected in only 1% of patients with RA on chest radiographs, while they are found in 22% of subjects on high resolution CT.⁴ They often correlate with the presence of subcutaneous nodules and are mostly asymptomatic.^{4,5}

However, although most frequently found in RA, rheumatoid nodules are not specific for this disease. Subcutaneous rheumatoid nodules have also been described in connective tissue diseases—for example, in 5–7% of patients with

Box 1 Differential diagnosis of pulmonary nodules

Malignant tumours
Bronchial carcinoma
Metastases
Pulmonary lymphoma

Benign tumours
Hamartoma
Chondroma

Infections
Tuberculosis
Bacterial infections
Fungal infections

Autoimmune diseases
Sarcoidosis
Rheumatoid arthritis
Wegener's granulomatosis
Churg-Strauss syndrome
Goodpasture syndrome

Rare causes
Myeloidosis
Connective tissue diseases (SS, SLE, PM/DM)

systemic lupus erythematosus and systemic sclerosis.⁶ In addition, rheumatoid nodules have occasionally been reported in association with Sharp's syndrome and dermatomyositis.

To our knowledge, this is the first case in which pulmonary rheumatoid nodules have been reported in a patient with primary Sjögren's syndrome (SS). Their occurrence can be explained by the same pathophysiological mechanism as in RA.

Pulmonary manifestations other than nodules were found to be present in about 10% of patients with SS, with most patients developing interstitial lung disease such as lymphocytic interstitial pneumonia or more rarely pseudolymphoma.⁷ Our observation of pulmonary rheumatoid nodules in primary SS further enlarges the spectrum of potential pleuropulmonary manifestations in patients with primary SS.

ACKNOWLEDGEMENTS

We thank Professor Dr Heine, Institute of Pathology, Schweinfurt, for providing the histological pictures.

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Competing interest: None

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Accepted 2 October 2005

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Lack of association between ankylosing spondylitis and a functional polymorphism of *PTPN22* proposed as a general susceptibility marker for autoimmunity

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Ann Rheum Dis 2006;**65**:687–688. doi: 10.1136/ard.2005.046094

Ankylosing spondylitis (AS) is a common chronic rheumatic disease whose aetiology arises as a result of the contribution of environmental factors and a strong genetic component.¹ One crucial point in the pathogenesis of the disease is the regulation of T cell response.² Recently, it has been shown that the functional 1858 C/T polymorphism of *PTPN22*, the gene that encodes a lymphoid-specific protein tyrosine phosphatase (LYP), is associated with several autoimmune diseases (ADs), supporting the hypothesis that common aetiopathological pathways are shared by different ADs.³ LYP has a key role as a negative regulator of T cell activation.⁴ It seems that the single nucleotide polymorphism (SNP) 1858 C/T disrupts the interaction between LYP and Csk, probably leading to an overactivated T cell response.⁵

Taking into account the functional relevance of the *PTPN22* 1858 C/T polymorphism, and its association with a wide range of ADs, this study aimed at investigating for the first time the possible implication of the SNP for susceptibility to AS.

A total of 197 patients with AS meeting the modified New York criteria for AS⁶ were recruited from Hospital Virgen de las Nieves (Granada, Spain) and Hospital Xeral-Calde (Lugo, Spain). A total of 551 blood bank donors and bone marrow donors were included as healthy controls. All the subjects were of white Spanish origin. Samples were genotyped for *PTPN22* 1858C→T variants as previously described.⁷ Statistical analysis to compare allelic and genotypic distributions was performed by χ^2 test using Statcalc program (Epi Info 2002; Centers for Disease Control and Prevention, Atlanta, GA, USA).

We found no statistically significant differences after comparing allele and genotypic frequencies of *PTPN22* 1858C→T between patients with AS and controls (table 1).

In addition, comparison of genotypes carrying the T allele (CT+TT v CC) between patients with AS and controls did not reach statistically significant skewing.

Similarly, no statistically significant differences were found when we stratified patients with AS according to HLA-B27 status (data not shown).

The lack of association that we show here might be due to a false negative, given our underpowered sample size. Because of this, we cannot completely exclude a weak effect of this polymorphism in AS and further investigations in different populations are required.

Recent studies of the *PTPN22* 1858C/T polymorphism have reported a lack of association with some ADs.⁸ The lack of association with these ADs may indicate a common aetiological mechanism that is different from the associated ADs. It has been proposed that the susceptibility of the polymorphism may predispose individual subjects to autoimmunity by promoting the generation of autoantibodies that contribute to disease onset and progression.⁹ The existence of humoral abnormalities in *PTPN22* knockout mice strengthens the hypothesis that autoantibody production is a prominent feature of the ADs that are associated with *PTPN22*.¹⁰ Based on that, the lack of autoantibody production in AS might explain the negative association between *PTPN22* 1858C/T polymorphism and this condition.

In conclusion, the lack of association of *PTPN22* with some ADs emphasises that susceptibility factors for AD are not shared among all ADs.

This work was supported by Plan Nacional de I+D (grant SAF03-3460) and in part by Junta de Andalucía, grupo CTS-180. We thank Ma Paz Ruiz and Sonia Morales for excellent technical assistance.

Table 1 Allele and genotype frequencies of the *PTPN22* 1858C→T polymorphism in 197 patients with AS and 551 healthy controls

	Patients with AS (%)	Healthy controls (%)	p Value*	OR (95% CI)
C/C	166 (84.3)	462 (83.8)	0.89	1.03 (0.65 to 1.65)
C/T	28 (14.2)	84 (15.2)	0.72	0.92 (0.56 to 1.5)
T/T	3 (1.5)	5 (0.9)	0.47	1.69 (0.32 to 8.17)
C	360 (91.4)	1008 (91.5)	0.95	0.99 (0.64 to 1.52)
T	34 (8.6)	94 (8.5)	0.95	1.01 (0.66 to 1.55)

*3×2 contingency table, overall p value = 0.73.