



#### INSTRUCTIONS FOR LETTERS TO THE EDITOR

Editorial comment in the form of a Letter to the Editor is invited. The length of a letter should not exceed 800 words, with a maximum of 10 references and no more than 2 figures or tables; and no subdivision for an abstract, methods, or results. Letters should have no more than 4 authors. Financial associations or other possible conflicts of interest should be disclosed.

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### Longterm Anti-Tumor Necrosis Factor- $\alpha$ Treatment in Patients with Refractory Rheumatoid Arthritis: Relationship Between Insulin Resistance and Disease Activity

To the Editor:

Patients with rheumatoid arthritis (RA) experience increased mortality rates, with cardiovascular disease as the most important cause of death compared to the general population<sup>1</sup>. Traditional and nontraditional risk factors including systemic inflammation, effects of several antirheumatic treatments, and increased insulin resistance contribute to the atherogenesis in RA<sup>2</sup>. Insulin resistance plays an important role in the development and progression of atherosclerotic lesions in patients with autoimmune rheumatic diseases, including RA<sup>3</sup>. Obesity and increased RA disease activity have been found to be associated with increased insulin resistance, whereas suppression of disease activity results in a marked reduction of this last condition<sup>4</sup>. Studies have found that suppression of RA disease activity with conventional disease modifying agents resulted in improvement in insulin sensitivity (and its associated cardiovascular risk factors)<sup>5</sup>.

Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) is a well defined proinflammatory cytokine with a wide range of activities including initiation and amplification of the inflammatory cascade both in RA and in atherogenesis. Studies found that anti-TNF- $\alpha$  treatment reduces RA disease activity and also improves insulin sensitivity, although the latter effect remains controversial<sup>6,7</sup>. Two independent groups have also recently reported an independent association of insulin resistance with atherosclerosis in RA<sup>8,9</sup>. We assessed whether longterm treatment with etanercept or infliximab may result in reduction of insulin resistance in patients with refractory RA and whether there are relationships between insulin resistance and disease activity.

In a prospective study 38 consecutive female patients with RA fulfilling the American College of Rheumatology 1987 criteria were analyzed (Table 1). All patients showed active disease as defined by the Disease Activity Index (DAS), using a 28-joint score (DAS28 > 3.2) at baseline; they were nonresponders or did not tolerate at least 2 previous disease modifying antirheumatic drugs. Patients received TNF- $\alpha$  blockers (etanercept, n = 20, 25 mg twice weekly; infliximab, n = 18, 3 mg/kg at 0, 2, 6 weeks, and every 8 weeks thereafter), stable doses of nonsteroidal antiinflammatory drugs, prednisolone (< 7.5 mg/day), and methotrexate (MTX; 10 mg/week) during the study. Patients were excluded from the study if they had a history of blood hypertension, diabetes mellitus, or endocrine or metabolic disorders, as well as current treatment with drugs that might influence glucose metabolism or lipid-lowering agents. A control group included 20 women with RA with stable therapy (prednisone < 7.5 mg/day and MTX 10 mg/week). Concentrations of plasma glucose and serum insulin (Abbott, Chicago, IL, USA) were evaluated using a microparticle enzyme immunoassay on the AxSYM system (for insulin). Insulin resistance was estimated by the homeostasis model assessment for insulin resistance (HOMA) using the following formula: fasting serum insulin ( $\mu$ U/ml)  $\times$  fasting plasma glucose (mmol/l)/22.5; and the Quantitative Insulin Sensitivity Check Index (QUICKI) using the formula:  $1/\log$  insulin ( $\mu$ U/ml) +  $\log$  glucose (mg/dl)<sup>10,11</sup>. Measurements were made on blood samples collected before the administration of the TNF- $\alpha$  blockers and after 12 and 24 weeks from the starting dosage. Body weight and body mass index (BMI) were assessed at each visit, when blood samples were collected. The changes observed before and after etanercept or infliximab were assessed by paired t-test for normally distributed data and Wilcoxon's signed-rank test for non-normally distributed data.

The study showed that BMI remained unchanged throughout the study period, whereas DAS28 score decreased significantly from baseline to Week 12 ( $4.8 \pm 0.9$  vs  $3.5 \pm 0.6$ ) and then to Week 24 ( $2.1 \pm 0.5$ ) ( $p < 0.01$  for both), in patients with anti-TNF- $\alpha$  treatment, and not significantly in nontreated RA patients (controls) from baseline to Week 12 ( $4.4 \pm 0.8$  vs  $3.3 \pm 0.4$ ) and to Week 24 ( $2.8 \pm 0.6$ ;  $p < 0.01$ ). At baseline and after 12 weeks no significant differences for the HOMA index or for the QUICKI were observed between the groups with or without anti-TNF- $\alpha$  treatment.

Table 1. Baseline characteristics of patients with active RA.

Characteristic	RA Patients with Anti-TNF- $\alpha$ , n = 38	Etanercept Treated Patients, n = 20	Infliximab Treated Patients, n = 18	RA Patients without Anti-TNF- $\alpha$ (controls), n = 20
Mean age, yrs (range)	51 $\pm$ 4 (45–68)	52 $\pm$ 3 (45–64)	51 $\pm$ 6 (51–68)	50 $\pm$ 7 (46–69)
IgM rheumatoid factor-positive, n (%)	35 (92)	19 (95)	16 (88)	16 (80)
Mean duration of disease, mo, $\pm$ SD	84 $\pm$ 32	80 $\pm$ 22	88 $\pm$ 28	77 $\pm$ 24
ESR, mm/h, $\pm$ SD	48 $\pm$ 26	50 $\pm$ 21	46 $\pm$ 22	50 $\pm$ 18
CRP, mg/dl, $\pm$ SD	18 $\pm$ 6	20 $\pm$ 6	16 $\pm$ 9	18 $\pm$ 2.2
DAS28 joint score, $\pm$ SD	4.8 $\pm$ 0.9	4.7 $\pm$ 0.8	4.8 $\pm$ 0.9	5.4 $\pm$ 2.2
HAQ score, $\pm$ SD	1.6 $\pm$ 0.6	1.6 $\pm$ 0.8	1.6 $\pm$ 0.6	1.5 $\pm$ 0.9
BMI, kg/m <sup>2</sup> , $\pm$ SD	24.1 $\pm$ 2.2	24.8 $\pm$ 1.8	24.2 $\pm$ 0.5	23.9 $\pm$ 1.1

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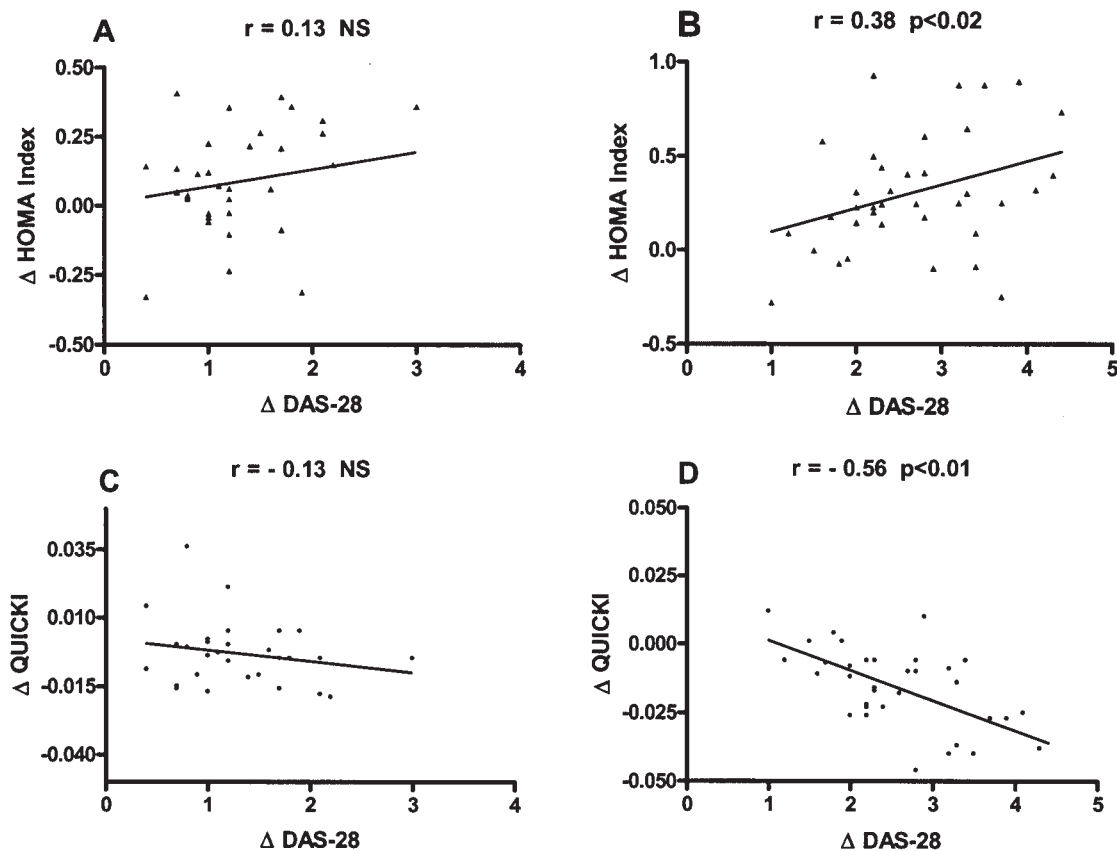


Figure 1. Correlations between changes in DAS28 and HOMA index (A, B) and the QUICKI (C, D) after 12 weeks (A, C) and 24 weeks (B, D) of therapy with anti-TNF- $\alpha$  blockers.

However, after 24 weeks from baseline, a significant decrease of the HOMA index (1.445 vs 1.733;  $p < 0.01$ ) and a significant increase of the QUICKI (0.361 vs 0.378;  $p < 0.01$ ) were found in RA patients who had anti-TNF- $\alpha$  treatment. Interestingly, no differences were found between RA patients treated with either infliximab or etanercept, and no significant changes were observed in the RA control group. The changes in HOMA index and QUICKI from 0 to 12 weeks showed no significant correlations with DAS28. By contrast, changes in DAS28 from 0 to 24 weeks were significantly associated with the HOMA index ( $p < 0.02$ ) and the QUICKI ( $p < 0.01$ ; Figure 1), and the changes in DAS28 were not significantly associated with insulin resistance in patients not treated with anti-TNF- $\alpha$ . In this study, changes in insulin resistance were significantly associated with changes in disease activity in treated patients, as shown by Dessein, *et al*<sup>4,8</sup>. A recent study by Gonzalez-Gay, *et al* showed a percentage reduction in the HOMA index immediately after infliximab infusion<sup>12</sup>. Our longterm study confirmed that the reduction of the HOMA index (20% at Week 24) was progressive in all RA patients treated with anti-TNF- $\alpha$  therapy, with no difference for the 2 different TNF blockers (etanercept and infliximab). These changes were associated with a decrease in disease activity. Our findings are consistent with observations by Dessein, *et al* that high C-reactive protein concentrations were associated with insulin resistance and that the QUICKI was not different in RA patients compared with healthy controls<sup>4,8</sup>. Thus, our results seem to show that different longterm anti-TNF- $\alpha$  treatments improve both disease activity and insulin resistance.

These results suggest that longterm use of TNF- $\alpha$  blockers might also interfere with some of the mechanisms implicated in development of atherosclerosis and might reduce the cardiovascular risk profile in patients with RA.

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### **Dramatic Improvement Following Interleukin 1 $\beta$ Blockade in Tumor Necrosis Factor Receptor-1-Associated Syndrome (TRAPS) Resistant to Anti-TNF- $\alpha$ Therapy**

*To the Editor:*

Tumor necrosis factor (TNF) receptor-1-associated-syndrome (TRAPS) is a chronic inherited autoinflammatory disorder. Typical features of TRAPS include recurrent fever, myalgia, rashes, and joint and abdominal pain associated with autosomal dominant mutations in the gene encoding the 55 kDa TNF receptor. Based upon a physiological rationale<sup>1</sup>, treatment with the p75 TNFR-Fc fusion protein etanercept has been found to be successful in many cases<sup>2</sup>. However, not all patients seem to benefit from anti-TNF- $\alpha$  therapy<sup>3</sup>. We describe dramatic improvement with interleukin 1 $\beta$  (IL-1 $\beta$ ) blockade in a French patient with TRAPS who had failed to respond to anti-TNF- $\alpha$  therapy.

A 26-year-old woman was followed for recurrent fever with persistent subcutaneous inflammation of the trunk or limbs. The onset of recurrent fever was noted at age 3 years. Stereotypic attacks occurred several times a year, lasting for 3 to 20 days. The fever was usually high-grade, with chills and sweats. Erythema with pain and swelling in a limb, together with stiffness in an adjacent joint, was frequent. This process moved distally down the limb during progression. There was no residual joint damage. Abdominal pain was also frequent, sometimes accompanied by diarrhea. The patient's family originated from the county of Normandy in France. Her grandfather had a similar history of sudden attacks between the ages of 30 and 55, consisting of high-grade fever, abdominal pain, and swelling and painful erythema in the trunk or limbs. The diagnosis of TRAPS was made in February 1999 when a missense mutation, C30S, was characterized in the first extracellular N-terminal cysteine-rich domain (CRD1) of the 55 kDa TNF receptor superfamily 1A (C30S TNFRSF1A mutation)<sup>4</sup>.

She was initially treated with colchicine that was ineffective. From February 1999 to November 1999, self-medication by short courses of steroids attenuated the intensity and diminished the duration of the attacks. Continuous oral prednisone treatment was then tried to prevent relapses, which occurred when daily dose was under 20 mg. Over the last 8 years her

condition had deteriorated, with increasing frequency and severity of attacks and chronic anemia. From December 2000 to March 2005, she was successively treated with etanercept, infliximab, and azathioprine, with no benefit. Clinical and biological remission was never achieved and C-reactive protein (CRP) had never normalized. The only way to reduce the intensity of attacks was to maintain prednisone at a minimal level of 20–25 mg (0.4 mg/kg) daily.

As a beneficial response to IL-1 $\beta$  blockade had been suggested in TRAPS<sup>3</sup>, treatment with daily subcutaneous injections of 100 mg anakinra was initiated in November 2006. The last attack had occurred 2 weeks before. At this time, the patient was treated with 20 mg daily oral prednisone. Blood tests showed a white blood cell count of 14,000 (85% neutrophils), CRP 75 mg/l, and hemoglobin 11.1 g/dl. Urinalysis was normal. From the day anakinra was started, she had no more clinical symptoms. CRP decreased to normal baseline values within 3 weeks and has remained in the normal range (Figure 1).

Inflammatory cytokine production was assessed before and under therapeutic IL-1 $\beta$  blockade. Release of IL-1 $\beta$  and TNF- $\alpha$  was measured from Ficoll-isolated unstimulated peripheral blood mononuclear cells as described<sup>5</sup>. A normal TNF- $\alpha$  level was observed both before (active disease) and under anakinra (inactive disease). Circulating levels of IL-1 $\beta$  were under the detection threshold in both situations (data not shown). A mutation search was performed on genomic DNA after polymerase chain reaction amplification of exon 3 of CIAS1 gene as described<sup>6</sup>. No mutation was detected.

Besides minor reactions at injection site, anakinra was well tolerated. Prednisone could be stopped after 3 months of anakinra treatment. At 9 months, the patient remains in complete clinical and biological remission.

TRAPS is a rare autoinflammatory autosomal dominantly inherited condition associated with mutation of the 55 kDa TNFRSF1A. TRAPS usually shows a response to high doses of oral prednisone. However, the initial response may wane with time. Immunomodulators such as azathioprine, methotrexate, and cyclosporin have been tried, with disappointing results<sup>3</sup>. After the discovery of the genetic basis of TRAPS, anti-TNF- $\alpha$  treatment was introduced<sup>2</sup>. Not all patients benefit from this therapy, however. In our patient, both etanercept and infliximab failed to give satisfactory control of the disease<sup>7</sup>. Corticosteroids attenuated the intensity of attacks but did not diminish disease activity as assessed by the recurrence of attacks and the sustained high CRP blood level. The impact of the disease on the quality of life, corticosteroid-associated morbidity, and the potential occurrence of amyloidosis all emphasize the need to search for a novel treatment strategy in TRAPS. A dramatic improvement caused by the recombinant human IL-1 $\beta$  receptor antagonist was observed in our patient with TRAPS.

More than 40 different TNFRSF1A mutations have been identified<sup>8</sup>. Some patients do not express the TRAPS phenotype although they carry TRAPS-associated mutations. In addition, a previous study reported patients with symptoms highly suggestive of TRAPS with none of the mutations in the TNFRSF1A gene known to date<sup>9</sup>. Obviously, the genetic heterogeneity of TRAPS may affect treatment response. The TNFRSF1A receptor is a membrane protein with 4 cysteine-rich extracellular domains, a transmembrane domain, and a ~70-residue intracellular "death domain" involved in signal transduction<sup>10</sup>. Accordingly, our patient was known to have the C30S mutation that affects the CRD1 of TNFRSF1A<sup>4</sup>. Although the proinflammatory effects of TNF- $\alpha$  seemed to be mediated predominantly through binding of TNFRSF1A<sup>1</sup>, failure of anti-TNF- $\alpha$  therapy suggests that inflammation does not depend only on TNF- $\alpha$ -TNFRSF1A interaction, and that other mechanisms might be involved in the pathogenesis of TRAPS.

A beneficial response to anakinra in TRAPS has been reported<sup>3</sup>. Both this report and ours point to the role of IL-1 $\beta$  in the pathogenesis of TRAPS. Interestingly, efficacy of anakinra has recently been reported in other inherited autoinflammatory disorders, such as the cryopyrin-associated periodic syndromes (CAPS)<sup>11,12</sup>. CAPS include syndromes previously thought to be distinct — familial cold autoinflammatory syndrome,

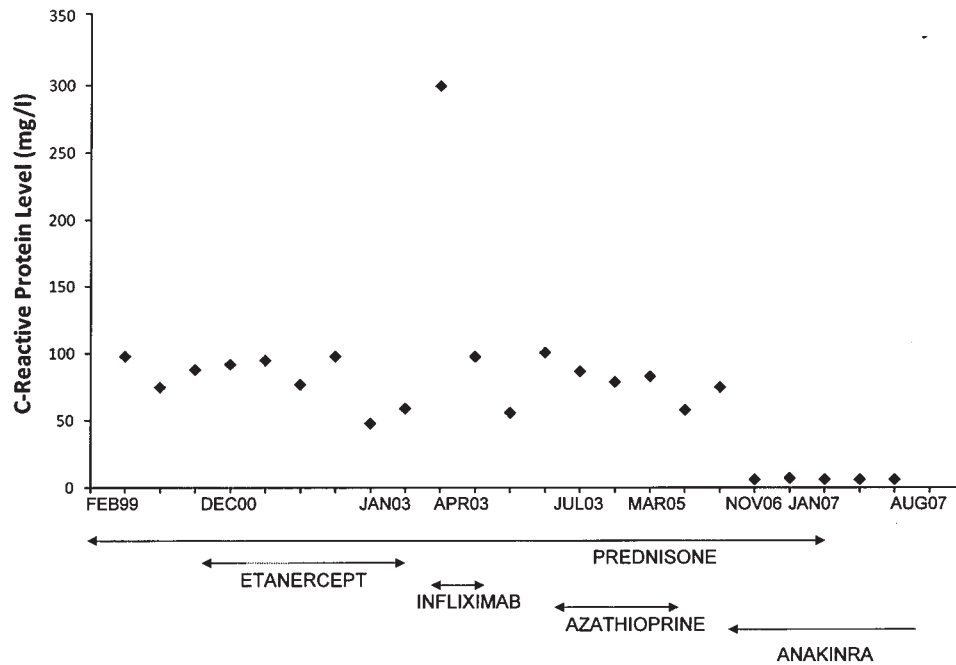


Figure 1. Treatment course and CRP blood levels in a patient with TRAPS from February 1999 to August 2007.

Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease — now linked to mutations in the CIAS1 gene<sup>13</sup>. The protein encoded by CIAS1 belongs to the inflammasome, a protein complex that contains cysteine-aspartate proteases involved in the proteolytic cleavage of IL-1<sup>14</sup>. Hence, mutations in CIAS1 ultimately result in overproduction of IL-1 $\beta$ . Because our observation suggests that IL-1 $\beta$  could play a key role in the pathogenesis of TRAPS, we hypothesized the coexistence of 2 different autoinflammatory disease genes, meaning both mutations of the CIAS1 and TNFRSF1A genes in our patient. However, the plasma level of IL-1 $\beta$  was under the detection threshold and we failed to find any mutation in the exon 3 of CIAS1.

Our observation suggests that IL-1 $\beta$  blockade with anakinra is safe and effective in controlling TRAPS refractory to anti-TNF- $\alpha$  agents.

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## Neither Cell-Surface Nor Soluble CD154 Levels Are Associated with Coronary Artery Disease in Systemic Lupus Erythematosus

To the Editor:

Kiani and colleagues recently presented data suggesting that soluble CD154 in the blood is not associated with atherosclerosis in systemic lupus erythematosus (SLE)<sup>1</sup>. Although they referenced our earlier work in abstract form<sup>2</sup>, we also previously reported similar findings of a lack of association between soluble CD154 levels and subclinical atherosclerosis in another large cohort of patients with SLE<sup>3</sup>. In our study, subclinical atherosclerosis was measured as coronary artery calcification by electron beam computed tomography (EBCT). In our cohort, as in Kiani's, soluble CD154 was not associated with cardiovascular risk factors, including cholesterol level, homocysteine level, and hypertension. Additionally, it was not associated with high-sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), a disease activity index (SLEDAI), or a damage index (Systemic Lupus International Collaborating Clinics-DI) ( $p > 0.40$  for all comparisons). Therefore, both studies suggest that soluble CD154 levels do not confer an independent risk for atherosclerosis seen in SLE.

We also now report a lack of a difference of surface CD154 expression levels on activated CD4 T cells from SLE patients with or without coronary artery disease. Although soluble CD154 levels may not compound the risk for atherosclerosis in SLE, it is possible that increased surface CD154 present on activated SLE CD4 T cells<sup>4,5</sup> may participate. We investigated surface CD154 levels on activated CD4 T cells from SLE patients with and without coronary atherosclerosis.

Twenty patients with SLE were studied. Ten patients with evidence of atherosclerotic cardiovascular disease (ASCVD) as determined by coronary artery calcification with EBCT (Group I) were compared to 10 patients without evidence of ASCVD (Group II, SLE controls; Table 1). Peripheral blood samples were drawn, and CD4 T cells were isolated by negative selection<sup>6</sup>, with comparable percentages of CD4 T cells in both

groups following isolation (Table 2). CD4 T cells were analyzed by flow cytometry immediately *ex vivo* and 5 and 20 hours after polyclonal activation *in vitro*, for cell-surface CD154 expression, as well as for CD25 and CD69 activation controls, as described<sup>7</sup>. There were no differences in CD154 expression between the 2 SLE cohorts at any of the timepoints examined before or after CD4 T cell activation (Table 2). Moreover, CD25 and CD69 levels were comparable, and only minimal CD69 levels *ex vivo* were statistically significantly different (Student t test) between the groups (Table 2). Thus, surface CD154 levels on freshly isolated peripheral blood CD4 T cells or cells activated *ex vivo* were unlikely to contribute to the differences seen in ASCVD in the 2 SLE cohorts.

Several recent studies including ours have begun to explore the risk factors involved in increased atherosclerosis in patients with SLE<sup>3,8,9</sup>. It is also clear that surface and soluble CD154 levels are increased in patients with SLE<sup>6</sup>. Moreover, it is now apparent that CD154 levels contribute to atherosclerosis and coronary artery disease in the general population<sup>10</sup>. Nevertheless, our results suggest that neither soluble CD154<sup>3</sup> nor CD4 T cell surface levels of CD154 (Table 2) account for the differences seen among SLE patients with or without ASCVD. CD154 may still serve as an attractive target of therapy<sup>11</sup>, but it is unlikely that CD154 levels will help in risk assessment for atherosclerosis in patients with SLE.

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Table 1. SLE patients with coronary artery calcification by EBCT (odd-numbered patients) matched for age and race with patients with SLE with coronary artery calcification (even-numbered patients).

Patient	Race	Age, yrs	Raw CAC Score	% Rank EBCT	Disease Duration, yrs	SLEDAI Score	hs-CRP, mg/l (0-3)
1	AA	45	17.28	> 90	4	8	1.83
2	AA	44	0	< 25	21	4	236.29
3	AA	58	238.26	> 90	23	12	1.29
4	AA	60	0	< 25	6	0	3.91
5	AA	50	359.72	> 90	25	6	1.87
6	AA	51	0	< 25	3	0	10.9
7	AA	47	87.16	> 90	15	0	0.62
8	AA	49	0	< 25	16	4	33.2
9	AA	39	23.72	> 90	13	0	1.51
10	AA	38	0	< 25	7	2	7.58
11	AA	49	438.02	> 90	23	4	0.34
12	AA	48	0	< 25	0.5	2	0.3
13	AA	36	230.53	> 90	18	0	4.55
14	AA	35	0	< 25	20	9	11.8
15	Asian	34	24.75	> 90	4	4	0.92
16	Asian	30	0	< 25	10	4	0.53
17	Cauc	50	64.98	> 90	24	0	2.99
18	Cauc	50	0	< 25	11	0	3.13
19	Cauc	49	191.59	> 90	31	10	0.6
20	Cauc	52	0	< 25	0.08	6	1.06

% rank EBCT = CAC percentile rank compared to age and sex matched controls. CAC: coronary artery calcification, AA: African American, Cauc: Caucasian, EBCT: electron beam computed tomography, SLEDAI: SLE Disease Activity Index, hs-CRP: high-sensitivity C-reactive protein.

Table 2. CD154 fluorescence-activated cell sort results in SLE patients with and without atherosclerosis.

	Time, h	Group I		Group II		p, t-test
		Mean	SD	Mean	SD	
Activation marker		% Positive Activation				
CD154	0	11.04	9.76	9.76	12.45	0.65
	5	83.66	6.40	85.4	9.14	0.62
	20	81.71	6.21	82.65	6.57	0.58
CD69	0	2.15	1.30	1.53	0.75	0.03*
	5	92.98	2.31	92.79	4.73	0.89
	20	96.36	2.57	97.88	1.20	0.06
CD25	0	41.87	16.13	45.56	13.94	0.50
	5	48.36	23.20	54.75	28.66	0.28
	20	92.03	7.63	93.7	3.60	0.59
		Mean Fluorescence Intensity				
CD154	0	63.11	51.96	97.5	108.16	0.34
	5	1147.80	291.39	1179.71	303.15	0.75
	20	663.78	268.98	641.06	196.91	0.75
CD69	0	276.92	249.23	359.5	299.14	0.36
	5	668.97	101.07	671.96	137.46	0.95
	20	1376.33	205.41	1406.94	306.03	0.87
CD25	0	116.77	29.11	122.45	40.89	0.72
	5	89.67	25.11	93.81	27.29	0.61
	20	559.42	122.19	541.64	61.09	0.69
% CD4+	0	81.58	5.93	83.51	13.41	0.67

Group I: SLE patients with EBCT coronary calcification > 90%; Group II: SLE patients with EBCT coronary calcification < 25%. EBCT: electron beam computed tomography. \* Significantly different.

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## Association of a Haplotype of IRF5 Gene with Systemic Lupus Erythematosus in Chinese

To the Editor:

The level of interferon- $\alpha$  (IFN- $\alpha$ ), a type I interferon, is correlated with both disease activity and severity of systemic lupus erythematosus (SLE)<sup>1</sup>. Activation of transcription factors, the IFN regulatory factors (IRF) 3, 5, and 7, can modulate the expression of type I IFN genes, and play an important role in inflammation, immunity, and apoptosis<sup>2</sup>. IRF5-knockout mice showed reduction of proinflammatory cytokines, including interleukin 6 (IL-6), IL-12, and tumor necrosis factor- $\alpha$ <sup>3</sup>.

Studies conducted in different populations in Europe, USA, and Argentina, with both case-control design and investigations involving nuclear families<sup>4-7</sup>, have reported that the IRF5 gene is a strong susceptibility candidate for SLE. In these studies single-nucleotide polymorphisms (SNP) rs2004640, rs2070197, and rs10954213 have been reported to be associated with susceptibility to SLE<sup>4-7</sup>. The T allele of rs2004640 was found to generate a 5' splice-donor site for an alternative exon 1, exon 1b<sup>5</sup>, whereas rs10954213 locates in a polyadenylation site and affects the expression level as well as a transcript variant on 3'UTR<sup>6</sup>. Finally, an insertion/deletion determines the use of the precise isoforms to be expressed by patients with SLE<sup>7</sup>.

However, most of the cohorts studied involve Caucasians, and indeed the only other cohort studied, in Argentina, showed a lower T allele frequency for rs2004640 than other cohorts<sup>5</sup>. It is well known that replication of association in other populations, especially in much different populations, can garner the most reliable evidence for validation of an association, although it is not a requirement for an unambiguous replication. It was also shown in animal models that genetic background plays a key role in the penetrance of genetic mutations<sup>8</sup>. We studied the potential involvement of IRF5 in SLE in a Chinese population, to test whether the association of IRF5 with SLE holds true in a population with a different genetic background.

Our study included 444 patients with SLE and 410 healthy Hong Kong Chinese blood donors. This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. All SLE patients met the revised American College of Rheumatology criteria for SLE and gave informed consent. DNA was extracted and SNP rs2004640, rs2070197, and rs10954213 were genotyped by sequencing as reported<sup>9</sup>.

The genotype frequencies of SNP rs2004640 and rs10954213 in IRF5 were in Hardy-Weinberg equilibrium. Indeed, we found that the Chinese population has a much lower minor allele frequency in rs2004640 than any other population studied to date<sup>5</sup> (Table 1). For the control group, the proposed detrimental T allele represents only 26% in our population compared to frequencies between 44% and 56% in other populations. Despite the differences in allele frequencies, the association with SLE susceptibility by the T allele showed the same trend compared to all other cohorts studied, with increased risk in bearers of the GT genotype for SLE and even greater risk in TT genotype individuals (odds ratios 1.23 and 1.83, respectively), although they failed to reach significance after correction for age and sex, probably due to the sample size limit in the study (Table 1).

The A allele of SNP rs10954213 was located in a AATAAA polyadenylation signal and was reported to correlate with a shorter mRNA form and higher overall mRNA level, particularly when cells were stimulated with IFN- $\alpha$ <sup>6,7</sup>. It was also found to be weakly associated with risk for SLE<sup>6,7</sup>. This SNP was located on an overtransmitted haplotype in the UK SLE nuclear families<sup>6</sup>, as well as SLE trios from Spain and Denmark<sup>7</sup>. Our result showed that allele A of SNP rs10954213 has a lower frequency in the Chinese population. Further, we found a lower A allele frequency in the

SLE patients compared to the control group, which is different from the findings from other populations<sup>6,7</sup>. However, consistent with the trio data from UK, Spain, and Denmark, the TA haplotype formed by the 2 SNP was much higher in SLE patients than in controls in our population (Table 2). Haplotypes were constructed by the 2 SNP using the expectation-maximization (EM) algorithm with permutation. The overall difference in haplotype frequencies was found to be significant between SLE patients and controls ( $p < 0.0001$ ). The TA haplotype (21.9%) was overrepresented in patients compared to controls (16%). For the GA haplotype, the frequency decreased from 34.3% in controls to 25.8% in SLE patients; this is different from studies in other populations, in which the GG haplotype was the undertransmitted allele<sup>6,7</sup>. Our result is consistent with the notion that mutation(s) that occurred on the TA haplotype before the separation of the Chinese and Caucasian populations may be associated with susceptibility to SLE.

Another SNP in the 3'UTR region of this gene but upstream of rs10954213, rs2070197, shown to have the strongest association with SLE susceptibility in studies in the European and Argentinian cohorts<sup>7</sup>, was found to be nonpolymorphic in our Chinese population as genotyped from 190 individuals comprising equal numbers of SLE patients and controls. The similarities and the differences between the populations composed of mainly Caucasians and our Chinese population seem to indicate that there are other undiscovered mutations in this gene conferring risk for SLE disease, and the differences in different populations may be caused by differences in linkage disequilibrium in this region between the populations.

Our results verified that, although there were very different allele frequencies compared to those reported from European and Argentinian

Table 1. Genotype associations of SNP rs2004640 and rs0954213 with SLE.

	Cases, N = 444 (%)	Controls, N = 410 (%)	p	p*	OR (95% CI)
Genotype					
rs2004640			0.043	0.161	
GG	216 (48.7)	225 (54.9)			Reference
GT	174 (39.2)	154 (37.6)			1.23 (0.83–1.81)
TT	54 (12.2)	31 (7.6)			1.83 (0.94–3.56)
rs10954213			0.096	0.123	
AA	109 (24.6)	98 (23.9)			Reference
AG	206 (46.4)	217 (52.9)			0.98 (0.62–1.54)
GG	129 (29.1)	95 (23.2)			1.54 (0.91–2.61)
Allele					
rs2004640			0.016	0.056	
G	606 (68.2)	604 (73.7)			1.32 (0.99–1.77)
T	282 (31.8)	216 (26.3)			
rs10954213			0.302	0.108	
A	424 (47.8)	413 (50.4)			1.24 (0.96–1.61)
G	464 (52.3)	407 (49.6)			

\* Adjusted by sex and age.

Table 2. Haplotype associations of SNP rs2004640 and rs10954213 with SLE, using E-M algorithm with permutation. Values are percentages (95% confidence interval).

Haplotype	SNP		Cases, N = 444	Controls, N = 410
	rs2004640	rs10954213		
1	G	A	25.8 (22.9–28.7)	34.3 (31.7–37.6)
2	G	G	42.4 (39.1–45.6)	39.3 (35.9–42.7)
3	T	A	21.9 (19.2–24.6)	16.0 (13.5–18.5)
4	T	G	9.8 (7.9–11.8)	10.3 (8.2–12.4)

Overall frequencies of the haplotypes were significantly different between cases and controls ( $p < 0.0001$ ).

cohorts, the TA haplotype from SNP rs2004640 and rs10954213 was over-represented in our patients with SLE. Replication of the association of IRF5 with risk of SLE in a population with a different genetic background further supports the involvement of this gene in SLE disease. The functional changes of the gene in our patients remain to be elucidated, and it will be interesting to see whether different polymorphisms and functional changes are contributing to disease susceptibility in different populations.

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## Inaugural Cervical Vertebral Sarcoidosis

To the Editor:

Sarcoidosis is a multisystem disease of unknown origin, occurring especially in young adults. While involvement of virtually every tissue and organ has been described, the usual sites are lymph nodes, liver, spleen, lungs, skin, and the uveo parotid region. Diagnosis is supported by clinical and radiological manifestations and histological features consisting of widespread, noncaseated epithelioid cell granuloma. The precise incidence of bone marrow involvement is not known, but bone lesions are identified in 1% to 13% of patients during the course of the disease<sup>1,2</sup>. Bone lesions often involve small bones of the hands and feet. Vertebral lesions are sel-

dom reported, located mainly at the dorsolumbar level. We describe 2 cases of cervical bone lesion revealing the features of the disease.

*Case 1.* From the beginning of 1992, a 38-year-old Black woman had mechanical lumbar pain with weight loss, anorexia, and asthenia. Laboratory data showed only inflammation [erythrocyte sedimentation rate (ESR) 76 mm/h]. Radiographs showed dense and heterogeneous lesions involving the skull and cervical spine. Magnetic resonance imaging (MRI) showed abnormal signal of C1, C2, C4, C5, and C6 vertebral bodies (Figure 1).

Since tuberculosis, neoplasia, or lymphoma could readily be suggested, surgical biopsy of C4 and C5 vertebral bodies was performed for diagnosis. Histological studies rendered a conclusion of nonspecific intensive osteofibrosis. The patient was then admitted to our department in May 1993 because of persistence of symptoms and occurrence of pulsatile headache, neck pain, wrist arthralgias, and pelvic pain. Physical examination was unremarkable; there was neither lymph node enlargement nor hepatosplenomegaly.

Laboratory data showed persistent elevated ESR (70 mm/h), microcytic anemia, and hypergammaglobulinemia. The serum and urine calcium and phosphorus concentrations and the angiotensin-converting enzyme (ACE) were normal. Chest radiograph was normal. Pelvic radiograph showed mild, bilateral osteosclerotic lesions of the iliac edge of the sacroiliac joint. Skull and cervical lesions consisted of dense and heterogeneous areas confirmed by computed tomography scan (Figure 2). The rest of the skeleton was normal. A technetium <sup>99m</sup> bisphosphonate bone scan showed disseminated uptake in the skull, the cervical spine, the fifth lumbar vertebral body, and the iliac bone.

Bone marrow aspiration was normal. Bilateral posterior iliac crest biopsies disclosed follicular lesions without necrosis or giant cells, consistent with the diagnosis of sarcoidosis.

She was then treated with prednisone at starting dosage of 1 mg/kg/day with decreasing regimen over several weeks. All aching resolved within 3 months. A 1-year followup displayed radiologic regression of the skull location of the disease. Steroid treatment was stopped.

*Case 2.* A 42-year-old Caucasian man was admitted in June 1993 because of cervical pain with bilateral irradiation to shoulders and arms, and finger dysesthesiae. There was no fever or weight loss. The physical examination was unremarkable. Cervical spine radiograph showed lesions of the C6 vertebral body with a lattice-like pattern (Figure 3). Chest radiograph was normal. Electromyographic investigation showed bilateral C6 radicular nerve lesions. MRI revealed a hyposignal with a T1-weighted sequence of the C6 vertebral body sparing both adjacent disks (Figure 4). Surgical biopsy of C6 was performed for diagnosis.

Histological study showed epithelioid and giant cellular follicular lesions, without necrosis. These lesions were consistent with diagnosis of tuberculosis or sarcoidosis. He was discharged home without treatment since pain was relieved spontaneously and investigations remained negative.

In June 1994, he was readmitted due to relapsing pain. There was no change in physical examination. ESR, hemoglobin, white blood cell count, and serum and urine calcium and phosphorus levels were normal. Different cultures revealed no *Mycobacterium tuberculosis*. ACE level was increased to 50.7 nmol/ml/min (normal 15–25 nmol/ml/min).

Chest radiograph at this time showed bilateral interstitial infiltration mainly involving the upper fields. Pulmonary function investigations were normal. Alveolar lavage disclosed CD4 lymphocyte alveolitis. Bone involvement then was retrospectively referred to diagnosis when typical lung sarcoidosis was discovered. He was treated with an initial prednisone regimen of 60 mg/day and was doing well after 9 months of followup. Steroid treatment was then stopped.

Fewer than 50 cases of vertebral sarcoidosis have been reported<sup>3-11</sup>. Involvement of the axial skeleton is rare, but is often symptomatic<sup>9</sup>. The thoracolumbar location appears as the most frequent site. Cervical involvement was found in 9 other cases (Table 1)<sup>12-20</sup>, 7 men and 2 women, with





**A** **B**  
 Figure 1. Case 1. MRI scan of the cervical spine. A. Hyposignal of C1, C2, C4, C5, C6 in T1-weighted sequence. B. Moderate hypersignal in T2 sequence.

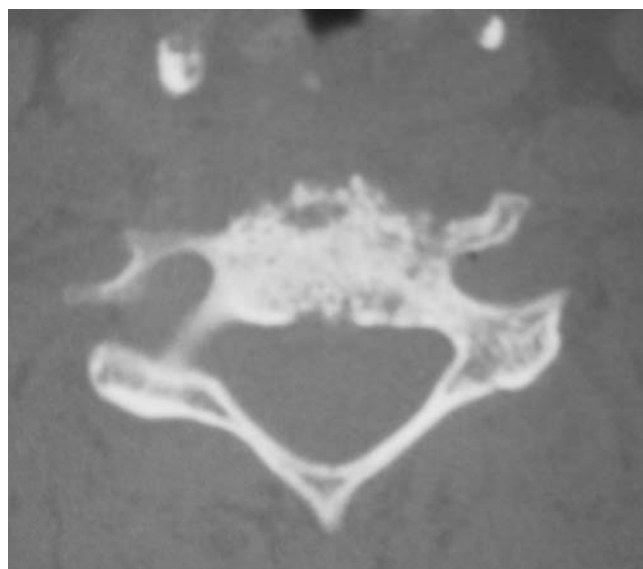


Figure 2. Case 1. CT scan of C4 shows sclerotic lesion of the vertebral body.

ages ranging from 14 to 59 years. The related clinical symptoms were pain in 7 cases, and possibility of neurological complications in 5 cases (4 tetraparesia and one cervicobrachial neuralgia, like our second case). In 7 cases, cervical involvement was part of a multifocal bone disease (skull, lumbar spine, ribs), like our first case.

Radiologically, the vertebral lesion appeared lytic in most of the cases. In several cases<sup>12,17,20</sup>, like ours, plain radiography showed sclerotic lesions of cervical vertebrae, and scattered lytic and sclerotic areas in one case<sup>15</sup>. This pattern is unusual, but has also been described in the lumbar vertebra<sup>6,19</sup> and pelvic bones<sup>11</sup>.

The possibility of fracture of an involved vertebral body is mentioned by Engle and Cooney<sup>17</sup> on C5, or destruction of the vertebral body and loss of intervertebral disc<sup>16</sup>.

Technetium <sup>99m</sup> bone scintigraphy shows increased uptake in affected bones, and may reveal asymptomatic lesions, but it is nonspecific. MRI reveals a usually hypointense signal on T1-weighted sequences, and variable intensity of signal on T2-weighted sequences, mostly hyperintense in the example of lytic sarcoid lesions, and iso- or hypointense in osteoblastic reactions<sup>20</sup>. The intensity of the signal is enhanced with contrast medium<sup>21</sup>. MRI is very sensitive to detect bone infiltration revealing lesions with normal radiographs, but is not specific in sarcoidosis.

A diagnosis may be facilitated in case of typical chest radiograph findings such as hilar lymphadenopathy<sup>14,16</sup>; but this may appear later in the disease development, as in our second case.

In some cases, cervical bone involvement has occurred in patients with established or previous diagnosis of sarcoidosis<sup>15,17-20</sup>. In other circumstances<sup>14,16</sup>, this vertebral location is inaugural, as in our 2 cases, or may represent an isolated bone involvement, as in our case 2. Nevertheless, due to absence of specificity of MRI, as discussed, and the possibility of many differential diagnoses (including bone metastases, lymphomas, mastocytosis, condensing myeloma, SAPHO syndrome) and infections in cases of disc space narrowing and soft tissue involvement in lytic or sclerotic lesions, histological confirmation by biopsy or during surgery<sup>15</sup> is recommended in these cases. Vertebral biopsy appears to be the most pertinent procedure (our second case and Jelinek, *et al*<sup>20</sup>), but may fail to reveal a



Figure 3. Case 2. Plain radiograph shows moderate condensing changes of the vertebral body of C6.



Figure 4. Case 2. MRI scan shows hypointense signal of C6 in T1-weighted sequence.

Table 1. Fewer than 50 cases of vertebral sarcoidosis have been reported.

Study	Age, yrs	Sex	Rx	Topography	Pain	Inaugural	Neurological Complications	Diagnosis	Treatment
Young <sup>12</sup>	23	M	C	C2-C5 dorsolumbar, pelvis, ribs	0	0	0		
Zimmerman <sup>13</sup>	34	M	L	C2-skull	+	0	Tetraparesia	P	Surgery
Stump <sup>14</sup>	14	M	L	C6 ribs, sternum lumbar	+	+	0	Lymph node biopsy	Corticosteroids
Perlman <sup>15</sup>	27	M	L+C	C3, C4, C5, rib, lumbar	0	0	Tetraplegia	P + vertebral biopsy	Corticosteroids + surgery
Cutler <sup>16</sup>	26	F	L + disc	C6, C7, rib	+	+	Neuralgia C7	Vertebral biopsy	Corticosteroids
Engle <sup>17</sup>	26	M	C + fracture	C4, C5, C6	+	0	Tetraparesia	P + vertebral biopsy	Corticosteroids + surgery
Jager <sup>18</sup>	59	M	L	C3, dorsal, pelvis	+	0		P	Corticosteroids
Bushara <sup>19</sup>	40	M		C4 (MRI), lumbar	+	0	Tetraparesia	P	Corticosteroids
Jelinek <sup>20</sup>	39	F	C	C3, C5	+	0		P + vertebral biopsy	Corticosteroids

C: condensing, L: lytic, P: previously established.

specific lesion as in our first case. Also notable is the possibility of finding those characteristic features in iliac crest biopsies.

Treatment is based upon steroid use alone, with good clinical results as in our 2 cases<sup>14,16,18-20</sup>, or in combination with surgery<sup>15,17</sup> in cases of severe neurological complication (tetraparesia). This emphasizes the need of an established diagnosis. In some cases with lumbar involvement, colchicine<sup>6</sup> or methotrexate<sup>10</sup> have been used successfully.

The response to treatment is difficult to assess, due to the paucity of cases. Surgical treatment is required in the presence of progressive neurologic deterioration and spinal instability<sup>9</sup>.

There is scant information about radiological development of the sclerotic changes of vertebral sarcoidosis. However, cases described by Young and Laman<sup>12</sup> not treated with steroids demonstrated no changes at 1-year followup. This was also the result in our 2 observations for the cervical ver-

tebral location, whereas we observed radiographic reduction of the sclerotic changes of the skull under steroid treatment in our case 1. However, in the case described by Perlman, *et al*<sup>15</sup>, after 1 year without steroids, radiological followup disclosed disease progression, with anterior erosion of the body of C5 and dense anterior bridging paravertebral ossification of C3-C4 at the time of neurological complications.

We conclude that spinal sarcoidosis is rare, especially affecting the cervical spine. This bone lesion may lead to neurological complications revealing the disease. Due to the numerous possibilities in differential diagnosis, particularly in a case with sclerotic changes, histologic proof is required to make the diagnosis. Management with steroids may be effective when there are neurologic symptoms. However, with bone destruction leading to instability, or progressive neurologic symptoms, surgical intervention is required.

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## Facial Cutaneous and Parotid Gland Involvement in Wegener's Granulomatosis

To the Editor:

Wegener's granulomatosis (WG) is defined as an aseptic, necrotizing, granulomatous inflammation and vasculitis affecting the upper and lower respiratory tract and kidneys. Less common manifestations involve the skin, central nervous system, eye and orbit, heart, breast, gastrointestinal tract, spleen, and urogenital tract. Salivary gland involvement in WG is also uncommon. We describe a case with more extensive and rapidly progressive involvement of facial skin and bilateral parotid glands.

A 62-year-old Japanese man with a 4-year history of bronchial asthma was treated by his family doctor using inhaled steroid and bronchodilators. Continuous high fever, arthralgia of the fingers and knees, and neuropathy of the lower limbs developed, so he was admitted to hospital in April 2003. Computed tomography (CT) showed pulmonary infiltration in right lower lobe. Blood examination revealed eosinophilia and positive results for myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA). Initial diagnosis was Churg-Strauss syndrome and treatment was initiated with prednisolone 30 mg/day, but he was transferred to our hospital due to complications of headache, dysphagia, and hoarseness in May 2004. Otolaryngeal examination revealed cranial nerve IX and X and bilateral recurrent nerve palsy due to hypertrophic pachymeningitis, which was identified on gadolinium-enhanced magnetic resonance imaging. He also displayed saddle nose and severe sinusitis, and WG was diagnosed following biopsy of nasal mucosa. Prednisolone 60 mg/day and cyclophosphamide were started after high-dose intravenous methylprednisolone therapy. Most symptoms resolved immediately, although dysphagia and hoarseness remained. Cyclophosphamide was changed to azathioprine due to transient leukopenia, and continuous use of prednisolone 15 mg/day and azathioprine helped to achieve a comfortable life at home. In January 2007, he suddenly developed high fever, and reported a gradually enlarging area of prickly pain on the face, particularly around the eyes and ears (Figure 1A). CT of the face revealed severe swelling of bilateral parotid glands (Figure 2). Biopsy of facial skin identified predominant granulomatous inflammation with some leukocytoclastic vasculitis. He was readmitted and treated with 50 mg/day prednisolone and low-dose cyclophosphamide. Facial swelling including the parotid glands gradually improved (Figure 1B).

Cutaneous manifestations occur in 40%–50% of diagnosed cases of WG<sup>1</sup> and are a presenting sign in 10% of all patients<sup>2</sup>. These manifestations are often seen in systemic type WG, but can appear as an initial manifestation or develop later. The activity of skin lesions appears to closely





Figure 1. A. Second admission. Severe swelling is present around the eyes, and the patient was unable to fully open his eyes. B. After treatments for 1 month. Enlargement of the face gradually improved.



Figure 2. Enhanced CT of the face shows bilateral parotid glands were severely swollen, with inflammation.

parallel disease activity in other organ systems and is indicative of active systemic disease<sup>3</sup>. Typical lesions include palpable purpura, necrotizing

ulcerations, papules, subcutaneous nodules, petechia, or vesicles, distributed symmetrically over the elbows, knees, and sometimes buttocks. Skin lesions on face are very rare. Barksdale, *et al* reported histopathologic features for 75 cutaneous biopsies from 46 patients with WG<sup>1</sup>. Biopsies were subdivided into histological groups that included leukocytoclastic vasculitis (31%), granulomatous inflammation (19%), nonspecific ulceration (4%), superficial dermal and epidermal necrosis without inflammation (2.7%), erythema nodosum (2.7%), granuloma annulare (1%), chronic inflammation (31%), and acute inflammatory lesions without vasculitis (9%). Barksdale, *et al* mentioned that no convincing examples of granulomatous vasculitis had been observed<sup>1</sup>. A specimen of skin lesion revealed granulomatous inflammation and leukocytoclastic vasculitis in our case, but not in the same vessels. Granulomatous vasculitis might have been present in the cutaneous lesion. Why granulomatous vasculitis is difficult to detect on skin biopsy warrants examination.

Salivary gland involvement in WG is also uncommon. Only 19 cases with WG involving parotid glands have been described. Characteristically, parotid gland swelling is initially asymptomatic, but gradually causes facial pain with skin lesion and ear discomfort. Cases can be uni- or bilateral, and the submandibular gland can also be involved. According to these reports, specimens of swollen parotid gland exhibit chronic inflammation or vasculitis with granuloma. Surprisingly, 7 cases (35%) displayed complications of neuropathy, including facial nerve palsy<sup>4-10</sup>. This represents a higher frequency than seen in typical generalized WG, but the relationship between involvement of parotid gland and nerve dysfunction remains unclear. In unilateral parotid lesions, neuropathy often presents ipsilaterally. Parotiditis tends to present as an initial manifestation of WG, but occurred about 4 years after the appearance of WG. The appearance of parotid involvement may thus correlate with disease activity of WG.

Prognosis of the patient with WG involving cutaneous tissue or the



parotid gland is highly dependent on early diagnosis. Some patients have developed severe systemic organ dysfunction. A high rate of clinical remission from WG is possible with early start of treatment using glucocorticoids and cyclophosphamide.

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## Correction

Yigit S, Bagci H, Ozkaya O, Ozdamar K, Cengiz K, Akpolat T. MEFV Mutations in Patients with Familial Mediterranean Fever in the Black Sea Region of Turkey. *J Rheumatol* 2008;35:106-13. The correct title should be "MEFV Mutations in Patients with Familial Mediterranean Fever in the Black Sea Region of Turkey: Samsun Experience"; the correct institution of Prof. K. Ozdamar is Osmangazi University. We regret the errors.