



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.

Letters should be submitted via our online submission system, available at the Manuscript Central website: <http://mc.manuscriptcentral.com/jrheum> For additional information, contact the Managing Editor, The Journal of Rheumatology, E-mail: jrheum@jrheum.com

Longterm Anti-Tumor Necrosis Factor- α 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 population¹. Traditional and nontraditional risk factors including systemic inflammation, effects of several antirheumatic treatments, and increased insulin resistance contribute to the atherogenesis in RA². Insulin resistance plays an important role in the development and progression of atherosclerotic lesions in patients with autoimmune rheumatic diseases, including RA³. 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 condition⁴. 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)⁵.

Tumor necrosis factor- α (TNF- α) 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- α treatment reduces RA disease activity and also improves insulin sensitivity, although the latter effect remains controversial^{6,7}. Two independent groups have also recently reported an independent association of insulin resistance with atherosclerosis in RA^{8,9}. 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- α 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 (μ U/ml) \times fasting plasma glucose (mmol/l)/22.5; and the Quantitative Insulin Sensitivity Check Index (QUICKI) using the formula: $1/\log$ insulin (μ U/ml) + \log glucose (mg/dl)^{10,11}. Measurements were made on blood samples collected before the administration of the TNF- α 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 ± 0.9 vs 3.5 ± 0.6) and then to Week 24 (2.1 ± 0.5) ($p < 0.01$ for both), in patients with anti-TNF- α treatment, and not significantly in nontreated RA patients (controls) from baseline to Week 12 (4.4 ± 0.8 vs 3.3 ± 0.4) and to Week 24 (2.8 ± 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- α treatment.

Table 1. Baseline characteristics of patients with active RA.

Characteristic	RA Patients with Anti-TNF- α , n = 38	Etanercept Treated Patients, n = 20	Infliximab Treated Patients, n = 18	RA Patients without Anti-TNF- α (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 ² , \pm SD	24.1 \pm 2.2	24.8 \pm 1.8	24.2 \pm 0.5	23.9 \pm 1.1

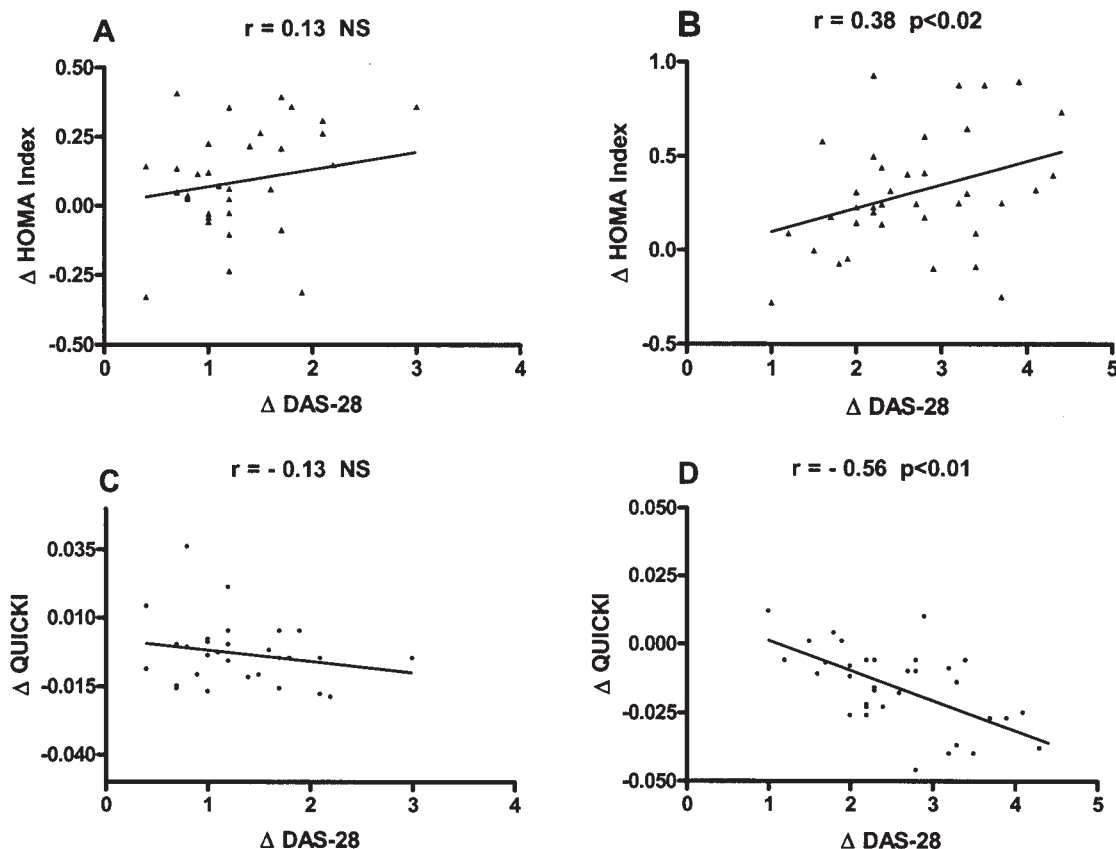


Figure 1. Correlations between changes in DAS28 and HOMA index (A, B) and the QUICKI (C, D) after 12 weeks (A, C) and 24 weeks (B, D) of therapy with anti-TNF- α blockers.

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- α 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- α . In this study, changes in insulin resistance were significantly associated with changes in disease activity in treated patients, as shown by Dessein, *et al*^{4,8}. A recent study by Gonzalez-Gay, *et al* showed a percentage reduction in the HOMA index immediately after infliximab infusion¹². 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- α 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^{4,8}. Thus, our results seem to show that different longterm anti-TNF- α treatments improve both disease activity and insulin resistance.

These results suggest that longterm use of TNF- α 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.

BRUNO SERIOLO, MD; CARMELA FERRONE, MD; MAURIZIO CUTOLO, MD, Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine and Medical Specialities, University of Genova, Genova, Italy. Address reprint requests to Prof. B. Seriole, Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine and Medical Specialities, University of Genova, Viale Benedetto XV, no. 6, 16132 Genova, Italy. E-mail: seriolo@unige.it

REFERENCES

1. Solomon DH, Karlson EW, Rimm EB, et al. Cardiovascular morbidity and mortality in patients with rheumatoid arthritis. *Circulation* 2003;107:1303-07.
2. Van Doornum S, McColl G, Wicks IP. Accelerated atherosclerosis. An extraarticular feature of rheumatoid arthritis? *Arthritis Rheum* 2002;46:862-73.
3. Seriole B, Paolino S, Ferone C, Cutolo M. Effects of etanercept or infliximab treatment on lipid profile and insulin resistance in patients with refractory rheumatoid arthritis. *Clin Rheumatol* 2007;26:1799-800.
4. Dessein PH, Stanwix AE, Joffe BI. Cardiovascular risk in rheumatoid arthritis versus osteoarthritis: acute phase response-related decreased insulin sensitivity and high-density lipoprotein cholesterol as well as clustering of metabolic syndrome features in rheumatoid arthritis. *Arthritis Res* 2002;4:R5.
5. Dessein PH, Joffe BI, Stanwix AE. Effects of disease modifying agents and dietary intervention on insulin resistance and dyslipidemia in inflammatory arthritis: a pilot study. *Arthritis Res*

2002;4:R12.

6. Dessein PH, Joffe BI, Stanwix A, Botha AS, Moomal Z. The acute phase response does not fully predict the presence of insulin resistance and dyslipidemia in inflammatory arthritis. *J Rheumatol* 2002;29:462-6.
7. Seriole B, Paolino S, Ferrone C, Cutolo M. Impact of long-term anti-TNF α treatment on insulin resistance in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2007; (in press).
8. Dessein PH, Norton GR, Woodiwiss AJ, et al. Independent role of conventional cardiovascular risk factors as predictors of C-reactive protein concentrations in rheumatoid arthritis. *J Rheumatol* 2007;34:681-8.
9. Chung CP, Oeser A, Solus JF, et al. Prevalence of the metabolic syndrome is increased in rheumatoid arthritis and is associated with coronary atherosclerosis. *Atherosclerosis* 2007 Jan 29; Epub ahead of print.
10. Bonora E, Kiechl S, Willeit J, et al. Prevalence of insulin resistance in metabolic disorders. The Bruneck Study. *Diabetes* 1998;47:1643-9.
11. Dessein PH, Stanwix AE, Joffe BI, et al. Quantitative Insulin Sensitivity Check Index: a simple accurate method for assessing insulin sensitivity in humans. *J Clin Endocrinol Metab* 2000;85:2402-10.
12. Gonzalez-Gay MA, De Matias M, Gonzalez-Juanatey C, et al. Anti-tumor necrosis factor- α blockade improves insulin resistance in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2006;24:83-6.

Dramatic Improvement Following Interleukin 1 β Blockade in Tumor Necrosis Factor Receptor-1-Associated Syndrome (TRAPS) Resistant to Anti-TNF- α 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 rationale¹, treatment with the p75 TNFR-Fc fusion protein etanercept has been found to be successful in many cases². However, not all patients seem to benefit from anti-TNF- α therapy³. We describe dramatic improvement with interleukin 1 β (IL-1 β) blockade in a French patient with TRAPS who had failed to respond to anti-TNF- α 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)⁴.

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 β blockade had been suggested in TRAPS⁵, 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 β blockade. Release of IL-1 β and TNF- α was measured from Ficoll-isolated unstimulated peripheral blood mononuclear cells as described⁵. A normal TNF- α level was observed both before (active disease) and under anakinra (inactive disease). Circulating levels of IL-1 β 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 described⁶. 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 results³. After the discovery of the genetic basis of TRAPS, anti-TNF- α treatment was introduced². Not all patients benefit from this therapy, however. In our patient, both etanercept and infliximab failed to give satisfactory control of the disease⁷. 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 β receptor antagonist was observed in our patient with TRAPS.

More than 40 different TNFRSF1A mutations have been identified⁸. 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 date⁹. 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 transduction¹⁰. Accordingly, our patient was known to have the C30S mutation that affects the CRD1 of TNFRSF1A⁴. Although the proinflammatory effects of TNF- α seemed to be mediated predominantly through binding of TNFRSF1A¹, failure of anti-TNF- α therapy suggests that inflammation does not depend only on TNF- α -TNFRSF1A interaction, and that other mechanisms might be involved in the pathogenesis of TRAPS.

A beneficial response to anakinra in TRAPS has been reported³. Both this report and ours point to the role of IL-1 β 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)^{11,12}. CAPS include syndromes previously thought to be distinct — familial cold autoinflammatory syndrome,

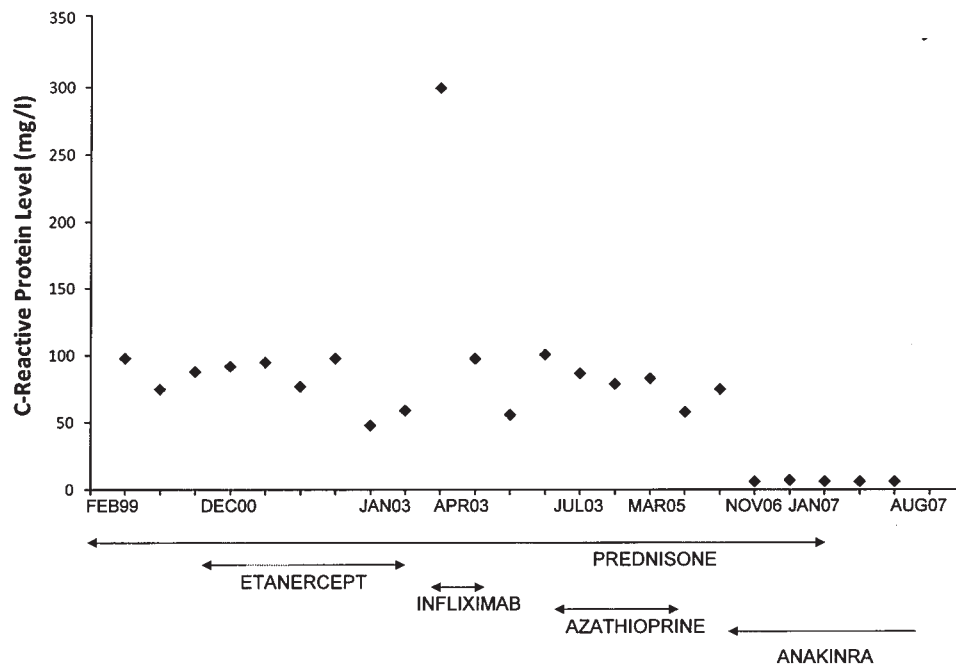


Figure 1. Treatment course and CRP blood levels in a patient with TRAPS from February 1999 to August 2007.

Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease — now linked to mutations in the CIAS1 gene¹³. The protein encoded by CIAS1 belongs to the inflammasome, a protein complex that contains cysteine-aspartate proteases involved in the proteolytic cleavage of IL-1¹⁴. Hence, mutations in CIAS1 ultimately result in overproduction of IL-1 β . Because our observation suggests that IL-1 β 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 β was under the detection threshold and we failed to find any mutation in the exon 3 of CIAS1.

Our observation suggests that IL-1 β blockade with anakinra is safe and effective in controlling TRAPS refractory to anti-TNF- α agents.

KARIM SACRÉ, MD; BENOIT BRIHAYE, MD; OLIVIER LIDOVE, MD; THOMAS PAPO, MD, Internal Medicine Department; MARIE-ANNICK POCIDALO, MD, PhD, Immunology Department, Bichat Hospital; LAURENCE CUISSET, PhD; CATHERINE DODÉ, PhD, Human Molecular Genetics Department, Cochin Hospital, Paris, France. Address reprint requests to Prof. T. Papo, Internal Medicine Department, Bichat Hospital, 46 rue Henri Huchard, 75018, Paris, France. E-mail: thomas.papo@bch.aphp.fr

REFERENCES

- McDermott MF, Aksentijevitch I, Galon J, et al. Germline mutations in the extracellular domains of 55kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. *Cell* 1999;97:133-44.
- Drewe E, McDermott EM, Powel PT, Isaacs JD, Powel RJ. Prospective study of anti-tumour necrosis factor receptor superfamily 1B fusion protein, and case study of anti-tumor necrosis factor receptor associated periodic syndrome (TRAPS): clinical and laboratory findings in a series of seven patients. *Rheumatology Oxford* 2003;42:235-9.
- Simon A, Bodar EJ, van der Hilst JCH, et al. Beneficial response to interleukin-1 receptor antagonist in TRAPS. *Am J Med* 2004;117:208-10.
- Dode C, Papo T, Fieschi C, et al. A novel missense mutation (c30s) in the gene encoding tumor necrosis factor receptor 1 linked to autosomal-dominant recurrent fever with localized myositis in a French family. *Arthritis Rheum* 1999;43:1535-42.
- Saito M, Fujisawa A, Nishikomori R, et al. Somatic mosaicism of CIAS1 in a patient with chronic infantile neurologic cutaneous articular syndrome. *Arthritis Rheum* 2005;52:3579-85.
- Dode C, Le Dû N, Cuisset L, et al. New mutations of CIAS1 for Muckle Wells syndrome and familial cold urticaria: a novel mutation underlies both syndromes. *Am J Hum Genet* 2002;70:1498-506.
- Jacobelli S, Andre M, Alexandra JF, Dode C, Papo T. Failure of anti-TNF therapy in TNF-receptor-1-associated periodic syndrome (TRAPS). *Rheumatology Oxford* 2007;46:1211-2.
- Infervers database. The Registry of Familial Mediterranean Fever and Hereditary Autoinflammatory Disorders Mutations. Touinou I, editor. Internet. Available from: <http://fmf.igh.cnrs.fr/infervers>. Accessed November 23, 2007.
- Aganna E, Hammond L, Hawkins PN, et al. Heterogeneity among patients with tumor necrosis factor receptor-associated periodic syndrome phenotypes. *Arthritis Rheum* 2003;48:2632-44.
- Banner DW, D'Arcy A, Janes W, et al. Crystal structure of the soluble human 55kd TNF receptor-human TNFb complex: implication for TNF receptor activation. *Cell* 1993;73:431-55.
- Hawkins PN, Lachmann HJ, Aganna E, McDermott MF. Spectrum of clinical features in Muckle-Wells syndrome and response to anakinra. *Arthritis Rheum* 2004;50:607-12.
- Hoffman HM, Rosengren S, Boyle DL, et al. Prevention of cold-associated acute inflammation in familial cold autoinflammatory syndrome by interleukin-1 receptor antagonist. *Lancet* 2004;364:1779-85.
- Arostegui JJ, Aldea A, Modesto C, et al. Clinical and genetic heterogeneity among Spanish patients with recurrent autoinflammatory syndromes associated with the CIAS1/PYPAF1/NALP3 gene. *Arthritis Rheum* 2004;50:4045-50.
- Neven B, Callebaut I, Prieur AM, et al. Molecular basis of the spectral expression of CIAS1 mutations associated with phagocytic cell-mediated autoinflammatory disorders CINCA/NOMID, MWS, and FCU. *Blood* 2004;103:2809-15.

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)¹. Although they referenced our earlier work in abstract form², 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 SLE³. 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^{4,5} 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 selection⁶, 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 described⁷. 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^{3,8,9}. It is also clear that surface and soluble CD154 levels are increased in patients with SLE⁶. Moreover, it is now apparent that CD154 levels contribute to atherosclerosis and coronary artery disease in the general population¹⁰. Nevertheless, our results suggest that neither soluble CD154³ 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 therapy¹¹, but it is unlikely that CD154 levels will help in risk assessment for atherosclerosis in patients with SLE.

JOAN M. VON FELDT, MD, Associate Professor of Medicine; SHERIF LATIF, MD; ANNA GENIN, MD, PhD, Rheumatology Division, The University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, RANDY Q. CRON, MD, PhD, Associate Professor of Pediatrics, University of Alabama, Birmingham, Alabama, USA. E-mail: vonfeldt@mail.med.upenn.edu

REFERENCES

1. Kiani A, Mahoney JA, Petri M. Soluble CD154 is not associated with atherosclerosis in systemic lupus erythematosus. *J Rheumatol* 2007;34:969-72.

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.

		Group I		Group II		p, t-test
	Time, h	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.

- Scalzi LV, Cron RQ, Von Feldt JM. Correlation of increased soluble CD40 ligand levels and coronary artery calcification in SLE patients [abstract]. *Arthritis Rheum* 2002;Suppl 49:S55.
- Von Feldt JM, Scalzi LV, Cucchiara AJ, et al. Homocysteine levels and disease duration independently correlate with coronary artery calcification in patients with systemic lupus erythematosus. *Arthritis Rheum* 2006;54:2220-7.
- Desai-Mehta A, Lu L, Ramsey-Goldman R, Datta SK. Hyperexpression of CD40 ligand by B and T cells in human lupus and its role in pathogenic autoantibody production. *J Clin Invest* 1996;97:2063-73.
- Koshy M, Berger D, Crow MK. Increased expression of CD40 ligand on systemic lupus erythematosus lymphocytes. *J Clin Invest* 1996;98:826-37.
- Cron RQ. CD154 transcriptional regulation in primary human CD4 T cells. *Immunol Res* 2003;27:185-202.
- Cron RQ, Bandyopadhyay R, Genin A, et al. Early growth response-1 is required for CD154 transcription. *J Immunol* 2006;176:811-8.
- Roman MJ, Shanker BA, Davis A, et al. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003;349:2399-406.
- de Leeuw K, Freire B, Smit AJ, Bootsma H, Kallenberg CG, Bijl M. Traditional and non-traditional risk factors contribute to the development of accelerated atherosclerosis in patients with systemic lupus erythematosus. *Lupus* 2006;15:675-82.
- Vishnevetsky D, Kiyanista VA, Gandhi PJ. CD40 ligand: a novel target in the fight against cardiovascular disease. *Ann Pharmacother* 2004;38:1500-8.
- Toubi E, Shoenfeld Y. The role of CD40-CD154 interactions in autoimmunity and the benefit of disrupting this pathway. *Autoimmunity* 2004;37:457-64.

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

To the Editor:

The level of interferon- α (IFN- α), a type I interferon, is correlated with both disease activity and severity of systemic lupus erythematosus (SLE)¹. 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 apoptosis². IRF5-knockout mice showed reduction of proinflammatory cytokines, including interleukin 6 (IL-6), IL-12, and tumor necrosis factor- α ³.

Studies conducted in different populations in Europe, USA, and Argentina, with both case-control design and investigations involving nuclear families⁴⁻⁷, 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 SLE⁴⁻⁷. The T allele of rs2004640 was found to generate a 5' splice-donor site for an alternative exon 1, exon 1b⁵, whereas rs10954213 locates in a polyadenylation site and affects the expression level as well as a transcript variant on 3'UTR⁶. Finally, an insertion/deletion determines the use of the precise isoforms to be expressed by patients with SLE⁷.

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 cohorts⁵. 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 mutations⁸. 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 reported⁹.

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 date⁵ (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- α ^{6,7}. It was also found to be weakly associated with risk for SLE^{6,7}. This SNP was located on an overtransmitted haplotype in the UK SLE nuclear families⁶, as well as SLE trios from Spain and Denmark⁷. 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^{6,7}. 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^{6,7}. 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 cohorts⁷, 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.

HO-ON SIU, MPhil; WANLING YANG, PhD, Department of Paediatrics and Adolescent Medicine; CHAK-SING LAU, MD; TAK-MAO CHAN, MD; RAYMOND WOON-SING WONG, MD, Department of Medicine; WILFRED HING-SANG WONG, MMedSci; YU-LUNG LAU, MD, Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China; MARTA E. ALARCON-RIQUELME, MD, Department of Genetics and Pathology, Unit of Medical Genetics, Rudbeck Laboratory, Uppsala University, Uppsala, Sweden. Address reprint requests to Prof. Y-L. Lau, The University of Hong Kong, Paediatrics and Adolescent Medicine, Room 117, 1/F, New Clinical Building, Queen Mary Hospital, Hong Kong. E-mail: lauylung@hkucc.hku.hk

REFERENCES

1. Banchereau J, Pascual V. Type I interferon in systemic lupus erythematosus and other autoimmune diseases. *Immunity* 2006;25:383-92.
2. Honda K, Yanai H, Takaoka A, Taniguchi T. Regulation of the type I IFN induction: a current view. *Int Immunol* 2005;17:1367-78.
3. Takaoka A, Yanai H, Kondo S, et al. Integral role of IRF-5 in the gene induction programme activated by Toll-like receptors. *Nature* 2005;434:243-9.
4. Sigurdsson S, Nordmark G, Goring HH, et al. Polymorphisms in the tyrosine kinase 2 and interferon regulatory factor 5 genes are associated with systemic lupus erythematosus. *Am J Hum Genet* 2005;76:528-37.
5. Graham RR, Kozyrev SV, Baechler EC, et al. A common haplotype of interferon regulatory factor 5 (IRF5) regulates splicing and expression and is associated with increased risk of systemic lupus erythematosus. *Nat Genet* 2006;38:550-5.
6. Cunningham Graham DS, Manku H, Wagner S, et al. Association of IRF5 in UK SLE families identifies a variant involved in polyadenylation. *Hum Mol Genet* 2007;16:579-91.
7. Kozyrev SV, Lewen S, Reddy PM, et al. Structural insertion/deletion variation in IRF5 is associated with a risk haplotype and defines the precise IRF5 isoforms expressed in systemic lupus erythematosus. *Arthritis Rheum* 2007;56:1234-41.
8. Kotzin BL. Susceptibility loci for lupus: a guiding light from murine models? *J Clin Invest* 1997;99:557-8.
9. Kong EK, Chong WP, Wong WH, et al. p21 gene polymorphisms in systemic lupus erythematosus. *Rheumatology Oxford* 2007;46:220-6.

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^{1,2}. 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 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 ^{99m} 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^{3–11}. Involvement of the axial skeleton is rare, but is often symptomatic⁹. The thoracolumbar location appears as the most frequent site. Cervical involvement was found in 9 other cases (Table 1)^{12–20}, 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.

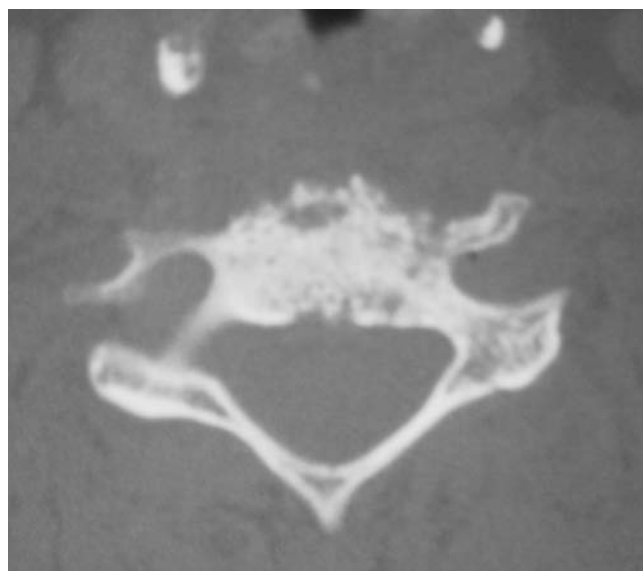


Figure 2. Case 1. CT scan of C4 shows sclerotic lesion of the vertebral body.

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^{12,17,20}, like ours, plain radiography showed sclerotic lesions of cervical vertebrae, and scattered lytic and sclerotic areas in one case¹⁵. This pattern is unusual, but has also been described in the lumbar vertebra^{6,19} and pelvic bones¹¹.

The possibility of fracture of an involved vertebral body is mentioned by Engle and Cooney¹⁷ on C5, or destruction of the vertebral body and loss of intervertebral disc¹⁶.

Technetium ^{99m} 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 reactions²⁰. The intensity of the signal is enhanced with contrast medium²¹. 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^{14,16}; 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^{15,17-20}. In other circumstances^{14,16}, 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 surgery¹⁵ is recommended in these cases. Vertebral biopsy appears to be the most pertinent procedure (our second case and Jelinek, *et al*²⁰), 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 ¹²	23	M	C	C2-C5 dorsolumbar, pelvis, ribs	0	0	0		
Zimmerman ¹³	34	M	L	C2-skull	+	0	Tetraparesia	P	Surgery
Stump ¹⁴	14	M	L	C6 ribs, sternum lumbar	+	+	0	Lymph node biopsy	Corticosteroids
Perlman ¹⁵	27	M	L+C	C3, C4, C5, rib, lumbar	0	0	Tetraplegia	P + vertebral biopsy	Corticosteroids + surgery
Cutler ¹⁶	26	F	L + disc	C6, C7, rib	+	+	Neuralgia C7	Vertebral biopsy	Corticosteroids
Engle ¹⁷	26	M	C + fracture	C4, C5, C6	+	0	Tetraparesia	P + vertebral biopsy	Corticosteroids + surgery
Jager ¹⁸	59	M	L	C3, dorsal, pelvis	+	0		P	Corticosteroids
Bushara ¹⁹	40	M		C4 (MRI), lumbar	+	0	Tetraparesia	P	Corticosteroids
Jelinek ²⁰	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^{14,16,18-20}, or in combination with surgery^{15,17} in cases of severe neurological complication (tetraparesia). This emphasizes the need of an established diagnosis. In some cases with lumbar involvement, colchicine⁶ or methotrexate¹⁰ 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 instability⁹.

There is scant information about radiological development of the sclerotic changes of vertebral sarcoidosis. However, cases described by Young and Laman¹² 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*¹⁵, 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.

DANIEL WENDLING, MD, PhD, Head, Department of Rheumatology; HÉLÈNE DESMURS, MD, Department of Rheumatology, Department of Internal Medicine; FRANÇOISE ROYER, MD, Department of Rheumatology; HELDER GIL, MD; JEAN-LOUIS DUPOND, MD, Department of Internal Medicine, University Teaching Hospital, Franche-Comté University, Besançon, France. Address reprint requests to Prof. D. Wendling, Department of Rheumatology, CHU J. Minjoz, Bld. Fleming, F-25030 Besançon, France. E-mail: dwendling@chu-besancon.fr

REFERENCES

- Neville E, Carstairs LS, James DG. Bone sarcoidosis. *Ann NY Acad Sci* 1976;278:475-87.
- Resnick D, Niwayama G. Sarcoidosis. In: Resnick D, Niwayama G, editors. *Diagnosis of bone and joint disorders*. 2nd ed. Philadelphia: W.B. Saunders; 1988:4011-32.
- Baldwin DW, Robert JC, Croft HE. Vertebral sarcoidosis. A case report. *J Bone Joint Surg Am* 1974;56:629-32.
- Brodey PA, Pripstein S, Strange G, Kohout ND. Vertebral sarcoidosis. A case report and review of the literature. *AJR Am J Roentgenol* 1976;126:900-2.
- Bundens DA, Rochtine GR. Sarcoidosis of the spine. *Spine* 1986;11:209-12.
- De Bandt M, Grossin M, Kahn MF. Vertebral sarcoidosis with condensing pseudo-Paget's disease [French]. *Rev Rhum Mal Ostéoartic* 1992;59:359-60.
- Golzarian J, Matos C, Golstein M, Stallenberg B, Depierreux M, Struyven J. Case report: Osteosclerotic sarcoidosis of spine and pelvis: plain film and magnetic resonance imaging findings. *Br J Radiol* 1994;67:401-4.
- Mijiyawa M, Fereres M, Deutsch JP, Awada H, Dougados M, Amor B. Pelvi-rachidian involvement in sarcoidosis. Case report. Review of the literature. *Rev Rhum Mal Ostéoartic* 1989;56:529-32.
- Tzagarakis GP, Papagelopoulos PJ, Sapkas GS, Tsarouchas JK. Surgical management for instability and paraplegia caused by spinal sarcoidosis. *Spine* 1998;23:1711-4.
- Mana J, Gomez-Vaquero C, Dorca J, Pujol R. Vertebral and rib sarcoidosis: longterm clinical remission with methotrexate. *Clin Rheumatol* 1999;18:492-4.
- Franco M, Passeroni C, Tieulie N, Verdier JF, Benisuy D. Longterm radiographic follow-up in a patient with osteosclerotic sarcoidosis of the spine and pelvis. *Rev Rhum Engl Ed* 1998;65:586-90.
- Young DA, Laman ML. Radiodense skeletal lesions in Boeck's sarcoid. *AJR Am J Roentgenol* 1972;114:553-8.
- Zimmerman R, Leeds NE. Calvarial and vertebral sarcoidosis. *Radiology* 1976;119:384.
- Stump D, Spock A, Grossman H. Vertebral sarcoidosis in adolescents. *Radiology* 1976;121:153-5.
- Perlman SG, Damergis J, Witorsch P, Cooney FD, Gunther SF, Barth WF. Vertebral sarcoidosis with paravertebral ossification. *Arthritis Rheum* 1978;21:271-6.
- Cutler SS, Sankaranarayanan G. Vertebral sarcoidosis. *JAMA* 1978;240:557-8.
- Engle EA, Cooney FD. Tetraplegia secondary to cervical sarcoidosis. *J Neurosurg* 1979;50:665-7.
- Jager J, Andriessen MP, Van Ingen J. Bone lesions mimicking disseminated malignancy after remission of thoracic sarcoidosis. *Netherlands J Med* 1990;36:204-6.
- Bushara KO, Petermann G, Wacławik AJ, Brown WD, Schutta HS. Sarcoidosis of the spinal cord with extensive vertebral involvement: a case report. *Comput Med Imaging Graphics* 1995;19:443-6.
- Jelinek JS, Mark AS, Barth WF. Sclerotic lesions of the cervical spine in sarcoidosis. *Skeletal Radiol* 1998;27:702-4.
- Rua-Figueroa I, Gantes MA, Erausquin C, Mhaidi H, Montesdeoca A. Vertebral sarcoidosis: clinical and imaging findings. *Semin Arthritis Rheum* 2002;31:346-52.

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 WG¹ and are a presenting sign in 10% of all patients². 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 disease³. 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 WG¹. 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 observed¹. 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 palsy⁴⁻¹⁰. 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.

MOTOHISA YAMAMOTO, MD; HIROKI TAKAHASHI, MD; CHISAKO SUZUKI, MD; YASUHIISA SHINOMURA, MD, First Department of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan. Address reprint requests to Dr. M. Yamamoto, First Department of Internal Medicine, Sapporo Medical University School of Medicine, South 1- West 16, Chuo-ku, Sapporo, Hokkaido, 0608543, Japan. E-mail: mocha@cocoa.plala.or.jp

REFERENCES

1. Barksdale SK, Hallahan CW, Kerr GS, Fauci AS, Stern JB, Travis WD. Cutaneous pathology in Wegener's granulomatosis. A clinicopathogenic study of 75 biopsies in 46 patients. *Am J Surg Pathol* 1995;19:161-72.
2. Patten SF, Tomecki KJ. Wegener's granulomatosis: Cutaneous and oral mucosal disease. *J Am Acad Dermatol* 1993;28:710-8.
3. Burrows NP, Lockwood CM. Antineutrophil cytoplasmic antibodies and their relevance to the dermatologist. *Br J Dermatol* 1995;132:173-81.
4. Fahey JL, Leonard E, Churg J, Godman G. Wegener's granulomatosis. *Am J Med* 1954;17:168-79.
5. Stuckey SL, Smart PJ. Wegener's granulomatosis: parotid involvement and associated pancreatitis with C.T. findings. *Australas Radiol* 1992;36:343-6.
6. Lustmann J, Segal N, Markitzu A. Salivary gland involvement in Wegener's granulomatosis. *Oral Surg Oral Med Oral Pathol* 1994;77:254-9.
7. Berge S, Niederhagen B, von Lindern JJ, Appel T, Reich H. Salivary gland involvement as an initial presentation of Wegener's disease. A case report. *Int J Oral Maxillofac Surg* 2000;29:450-2.
8. Saravanappa N, Bibas A, Singhal A, Davis JP. Unilateral parotid swelling as initial manifestation of Wegener's granulomatosis. *J Otolaryngol* 2000;29:396-7.
9. Bucolo S, Torre V, Montemagno A, Beatrice F. Wegener's granulomatosis presenting with otologic and neurologic symptoms: clinical and pathological correlations. *J Oral Pathol Med* 2003;32:438-40.
10. Chegar BE, Kelley RT. Wegener's granulomatosis presenting as unilateral parotid enlargement. *Laryngoscope* 2004;114:1730-3.

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.