

Selected publications from peruvian rheumatologists

Graciela S. Alarcón, MD, MPH
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Introduction

The contribution to medicine of the rheumatologist whose bios have been described in the previous chapter of this book span different aspects of the practice of medicine in general and of rheumatology in particular; some of these rheumatologists have played important roles in the development of teaching programs at their respective medical schools while others have done it at the medical school level. Still others are recognized for their research efforts which can be attested in refereed publications. In this section, we are presenting a selection of the best articles that these Peruvian rheumatologists have published. This compilation has been done utilizing PubMed the electronic search engine of the National Library of Medicine in the US; although we have tried to be as objective as possible in the selection of these articles some subjectivity may have involuntarily permeated. Perhaps we have failed to select the papers which are closer to the authors' hearts; if that is the case we ask them for their forgiveness.

A very short introductory comment precedes each of the selected articles (only one representative abstract from the selected articles is being reproduced for each of these authors).

EDUARDO ACEVEDO-VÁSQUEZ

Dr. Acevedo's group was the first one to bring attention to the fact that the tuberculin skin test (PPD) is not appropriate for the screening of latent tuberculosis infection in patients with rheumatoid arthritis. This information is of great relevance in view of the fact that this test is being increasingly used for this purpose prior to initiation of biologic therapy in these patients.

Ponce de Leon D, **Acevedo-Vásquez E**, Sanchez-Torres A, Cucho M, Alfaro J, Perich R, Pastor C, Harrison J, Sanchez-Schwartz C. Attenuated response to purified protein derivative in patients with rheumatoid arthritis: study in a population with a high prevalence of tuberculosis.

Division of Rheumatology, Hospital Nacional Guillermo Almenara Irigoyen, EsSalud, Lima; Universidad Mayor Nacional de San Marcos, Lima, Peru.

BACKGROUND: The purified protein derivative (PPD) skin test is the only widely used method which detects latent tuberculosis infection (LTBI) and is dependent on a normal T cell function. In rheumatoid arthritis (RA) the T cell function is altered, which may result in an inability to develop an adequate PPD reaction. **OBJECTIVES:** To evaluate the response to PPD in patients with RA and to compare it with that of control subjects. **METHODS:** 112 patients with RA and 96 healthy controls were studied. PPD 5 U was applied using the Mantoux method, and skin reaction was measured at 72 hours. The reaction was considered negative for PPD <5 mm. **RESULTS:** There were no significant differences in age, sex, history of bacille Calmette-Guerin vaccination, or tuberculosis contact between the two groups. The median size of the PPD induration in the patients with RA was significantly less than that in the control group (4.5 v 11.5 mm, $p < 0.01$). 79 (70.6%) patients with RA compared with 25 (26%) of the control group had a negative reaction to PPD ($p < 0.01$), a response not influenced by disease activity or duration of disease in the patients with RA. **CONCLUSION:** A PPD skin test is not an appropriate test for recognising LTBI in patients with RA in our population.

PMID: 16100342 [PubMed - indexed for MEDLINE]

GRACIELA S. ALARCÓN

This study is one of the most recent publications from the LUMINA cohort, a long-term study of lupus outcome sponsored by the National Institute of Health (USA) in Hispanic, African-American, and Caucasian populations afflicted with this disease. It clearly shows that socioeconomic-demographic (age, ethnicity, health insurance) and behavioral/psychological (abnormal illness-related behaviors among others) variables are important mediators of high levels of disease activity in SLE over its course, in contrast with what occurs early in the disease in which genetic factors are important. This cohort has contributed to our understanding of the role played by non-genetic factors in the course and outcome of SLE among minority population groups in the US.

Alarcon GS, Calvo-Alen J, McGwin G, Uribe AG, Toloza SM, Roseman J, Fernandez M, Fessler BJ, Vila L, Ahn C, Tan FK, Reveille JD. Systemic lupus erythematosus in a multiethnic cohort: LUMINA XXXV. Predictive factors of high disease activity over time. *Ann Rheum Dis.* 2006 Jan 31; [Epub ahead of print]

The University of Alabama at Birmingham, United States.

Purpose: To ascertain the predictive factors of high levels of disease activity in systemic lupus erythematosus (SLE). **Patients and METHODS:** SLE patients (ACR criteria), inverted exclamation markY 16 years of age, inverted exclamation markU5 years of disease, of Hispanic (Texas and Puerto Rico), African American and Caucasian ethnicity were included. The outcome was high disease activity at any one time [SLAM-R > 10]. A basic multivariable model (age, gender, ethnicity, health insurance, social support, abnormal illness-related behaviors, helplessness and prior disease activity) was first examined. Additional models were built by including other variables. **RESULTS:** Five hundred and forty four patients (100 Hispanics - Texas, 94 Hispanics - Puerto Rico, 199 African Americans, 161 Caucasians) and 2366 visits were analyzed; 47% of the patients and 29% of the visits met the high disease activity definition [more common among African Americans (72.0 %) and Hispanics - Texas (71.3 %) than Caucasians (43.9 %) and Hispanics - Puerto Rico (31.9 %)]. Variables found to predict high levels of disease activity were Hispanic - Texas and African American ethnicities, lack of health insurance, helplessness, abnormal illness-related behaviors and poor social support; age was negatively associated with it. African admixture and anti-dsDNA antibodies also predicted high levels of disease activity as did prior disease activity. None of the HLA variables were retained in the models. **CONCLUSIONS:** Socioeconomic-demographic (age, ethnicity, health insurance), behavioral/psychological variables are important mediators of high levels of disease activity in SLE over its course. Interventions aimed at modifiable factors may substantially improve SLE outcomes.

PMID: 16439440 [PubMed - as supplied by publisher]

- Clinical, immunogenetic and outcome features of Hispanic systemic lupus erythematosus patients of different ethnic ancestry. *Lupus*. 2003;12(5):377-85. PMID: 12765301 [PubMed - indexed for MEDLINE]
19. Bastian HM, Roseman JM, McGwin G Jr, **Alarcon GS**, Friedman AW, Fessler BJ, Baethge BA, Reveille JD; LUMINA Study Group. Lupus in Minority populations: Nature vs nurture. Systemic lupus erythematosus in three ethnic groups. XII. Risk factors for lupus nephritis after diagnosis. *Lupus*. 2002;11(3):152-60. PMID: 12004788 [PubMed - indexed for MEDLINE]
 20. **Alarcon GS**, McGwin G Jr, Bartolucci AA, Roseman J, Lisse J, Fessler BJ, Bastian HM, Friedman AW, Reveille JD; LUMINA Study Group. Lupus in Minority Populations, Nature versus Nurture. Systemic lupus erythematosus in three ethnic groups. IX. Differences in damage accrual. *Arthritis Rheum*. 2001 Dec;44(12):2797-806. PMID: 11762940 [PubMed - indexed for MEDLINE]
 21. **Alarcon GS**, McGwin G Jr, Bastian HM, Roseman J, Lisse J, Fessler BJ, Friedman AW, Reveille JD. Systemic lupus erythematosus in three ethnic groups. VII [correction of VIII]. Predictors of early mortality in the LUMINA cohort. LUMINA Study Group. *Arthritis Rheum*. 2001 Apr;45(2):191-202. Erratum in: *Arthritis Rheum* 2001 Jun;45(3):306. PMID: 11324784 [PubMed - indexed for MEDLINE]
 22. Zuniga R, Ng S, Peterson MG, Reveille JD, Baethge BA, **Alarcon GS**, Salmon JE. Low-binding alleles of Fcγ receptor types IIA and IIIA are inherited independently and are associated with systemic lupus erythematosus in Hispanic patients. *Arthritis Rheum*. 2001 Feb;44(2):361-7. PMID: 11229467 [PubMed - indexed for MEDLINE]
 23. Zhang J, Roschke V, Baker KP, Wang Z, **Alarcon GS**, Fessler BJ, Bastian H, Kimberly RP, Zhou T. Cutting edge: a role for B lymphocyte stimulator in systemic lupus erythematosus. *J Immunol*. 2001 Jan 1;166(1):6-10. PMID: 11123269 [PubMed - indexed for MEDLINE]
 24. **Alarcon GS**, Friedman AW, Straaton KV, Moulds JM, Lisse J, Bastian HM, McGwin G Jr, Bartolucci AA, Roseman JM, Reveille JD. Systemic lupus erythematosus in three ethnic groups: III. A comparison of characteristics early in the natural history of the LUMINA cohort. LUPus in Minority populations: Nature vs. Nurture. *Lupus*. 1999;8(3):197-209. PMID: 10342712 [PubMed - indexed for MEDLINE]
 25. **Alarcon GS**, Roseman J, Bartolucci AA, Friedman AW, Moulds JM, Goel N, Straaton KV, Reveille JD. Systemic lupus erythematosus in three ethnic groups: II. Features predictive of disease activity early in its course. LUMINA Study Group. Lupus in minority populations, nature versus nurture. *Arthritis Rheum*. 1998 Jul;41(7):1173-80. PMID: 9663472 [PubMed - indexed for MEDLINE]
 26. Reveille JD, Moulds JM, Ahn C, Friedman AW, Baethge B, Roseman J, Straaton KV, **Alarcon GS**. Systemic lupus erythematosus in three ethnic groups: I. The effects of HLA class II, C4, and CR1 alleles, socioeconomic factors, and ethnicity at disease onset. LUMINA Study Group. Lupus in minority populations, nature versus nurture. *Arthritis Rheum*. 1998 Jul;41(7):1161-72. PMID: 9663471 [PubMed - indexed for MEDLINE]
 27. Calvo-Alen J, Bastian HM, Straaton KV, Burgard SL, Mikhail IS, **Alarcon GS**. Identification of patient subsets among those presumptively diagnosed with, referred, and/or followed up for systemic lupus erythematosus at a large tertiary care center. *Arthritis Rheum*. 1995 Oct;38(10):1475-84. PMID: 7575697 [PubMed - indexed for MEDLINE]
 28. Reveille JD, Bartolucci A, **Alarcon GS**. Prognosis in systemic lupus erythematosus. Negative impact of increasing age at onset, black race, and thrombocytopenia, as well as causes of death. *Arthritis Rheum*. 1990 Jan;33(1):37-48. PMID: 2302266 [PubMed - indexed for MEDLINE]
 29. Mikuls TR, Saag KG, Curtis J, Bridges SL Jr, **Alarcon GS**, Westfall AO, Lim SS, Smith EA, Jonas BL, Moreland LW; CLEAR Investigators. Prevalence of osteoporosis and osteopenia among African Americans with early rheumatoid arthritis: the impact of ethnic-specific normative data. *J Natl Med Assoc*. 2005 Aug;97(8):1155-60. PMID: 16173331 [PubMed - indexed for MEDLINE]
 30. Bridges SL Jr, Hughes LB, Mikuls TR, Howard G, Tiwari HK, **Alarcon GS**, McNicholl JM, Moreland LW. Early rheumatoid arthritis in African-Americans: the CLEAR Registry. *Clin Exp Rheumatol*. 2003 Sep-Oct;21(5 Suppl 31):S138-45. Review. PMID: 14969066 [PubMed - indexed for MEDLINE]
 31. Kremer JM, **Alarcon GS**, Weinblatt ME, Kaymakcian MV, Macaluso M, Cannon GW, Palmer WR, Sundry JS, St Clair EW, Alexander RW, Smith GJ, Axiotis CA. Clinical, laboratory, radiographic, and histopathologic features of methotrexate-associated lung injury in patients with rheumatoid arthritis: a multicenter study with literature review. *Arthritis Rheum*. 1997 Oct;40(10):1829-37. Review. PMID: 9336418 [PubMed - indexed for MEDLINE]
 32. **Alarcon GS**, Kremer JM, Macaluso M, Weinblatt ME, Cannon GW, Palmer WR, St Clair EW, Sundry JS, Alexander RW, Smith GJ, Axiotis CA. Risk factors for methotrexate-induced lung injury in patients with rheumatoid arthritis. A multicenter, case-control study. Methotrexate-Lung Study Group. *Ann Intern Med*. 1997 Sep 1;127(5):356-64. PMID: 9273826 [PubMed - indexed for MEDLINE]
 33. Bluhm GB, Sharp JT, Tilley BC, **Alarcon GS**, Cooper SM, Pillemer SR, Clegg DO, Heyse SP, Trentham DE, Neuner R, Kaplan DA, Leisen JC, Buckley L, Duncan H, Tuttleman M, Li S, Fowler SE. Radiographic results from the Minocycline in Rheumatoid Arthritis (MIRA) Trial. *J Rheumatol*. 1997 Jul;24(7):1295-302. PMID: 9228128 [PubMed - indexed for MEDLINE]
 34. Reveille JD, **Alarcon GS**, Fowler SE, Pillemer SR, Neuner R, Clegg DO, Mikhail IS, Trentham DE, Leisen JC, Bluhm G, Cooper SM, Duncan H, Tuttleman M, Heyse SP, Sharp JT, Tilley B. HLA-DRB1 genes and disease severity in rheumatoid arthritis. The MIRA Trial Group. Minocycline in Rheumatoid Arthritis. *Arthritis Rheum*. 1996 Nov;39(11):1802-7. PMID: 8912501 [PubMed - indexed for MEDLINE]
 35. **Alarcon GS**, Tracy IC, Strand GM, Singh K, Macaluso M. Survival and drug discontinuation analyses in a large cohort of methotrexate treated rheumatoid arthritis patients. *Ann Rheum Dis*. 1995 Sep;54(9):708-12. PMID: 7495340 [PubMed - indexed for MEDLINE]
 36. McDaniel DO, **Alarcon GS**, Pratt PW, Reveille JD. Most African-American patients with rheumatoid arthritis do not have the rheumatoid antigenic determinant (epitope) Ann Intern Med. 1995 Aug 1;123(3):181-7. PMID: 7598299 [PubMed - indexed for MEDLINE]

JUAN ANGULO-SOLIMANO

This collaborative work between Peruvian and Swedish investigators in which Dr. Angulo played a leadership role, is the first one demonstrating that a polymorphism of tumor necrosis factor is associated with rheumatoid arthritis in a non-white population.

Castro F, Acevedo E, Ciusani E, **Angulo JA**, Wollheim FA, Sandberg-Wollheim M. Tumour necrosis factor microsatellites and HLA-DRB1*, HLA-DQA1*, and HLA-DQB1* alleles in Peruvian patients with rheumatoid arthritis. *Ann Rheum Dis.* 2001 Aug;60(8):791-5.

OBJECTIVE: To study the association between rheumatoid arthritis (RA) and HLA and tumour necrosis factor (TNF) polymorphism in Peruvian mestizo patients in comparison with ethnically similar controls. **METHODS:** Seventy nine patients with RA and 65 ethnically matched healthy controls were genotyped for HLA-DRB1, HLA-DQA1, HLA-DQB1, and TNFalpha and TNFbeta alleles using PCR amplification. Clinical severity was assessed as mild, moderate, or severe in 35 of the patients. **RESULTS:** TNFalpha6 showed the strongest association with disease susceptibility. The TNFalpha6 allele was more common in patients than in controls ($p < 0.0076$) and the proportion of patients with at least one copy of this allele was greater ($p < 0.015$, relative risk 2.35). Among the HLA-DRB1* alleles with the shared epitope sequence, only the DRB1*1402 allele was significantly increased in patients compared with controls ($p < 0.0311$), as was the proportion of patients with at least one copy of this allele ($p < 0.0232$, relative risk 2.74). In contrast, the overall frequency of alleles with the shared epitope was not different in patients and controls. The haplotype HLA-DRB1*1402-DQB1*0301-DQA1*0401 was significantly more common in patients. TNFalpha6 was more common in patients whether or not they had this haplotype. None of the 11 patients lacking the TNFalpha6 allele had severe disease. **CONCLUSIONS:** This study shows for the first time that TNF gene polymorphism is associated with susceptibility to RA in a non-white population. TNFalpha6 and HLA-DRB1*1402 independently conferred significantly increased risk in Peruvian mestizo patients.

PMID: 11454644 [PubMed - indexed for MEDLINE]

1. Castro F, Acevedo E, Ciusani E, **Angulo JA**, Wollheim FA, Sandberg-Wollheim M. Tumour necrosis factor microsatellites and HLA-DRB1*, HLA-DQA1*, and HLA-DQB1* alleles in Peruvian patients with rheumatoid arthritis. *Ann Rheum Dis.* 2001 Aug;60(8):791-5. PMID: 11454644 [PubMed - indexed for MEDLINE]
2. **Angulo JM**, Sigal LH, Espinoza LR. Coexistent minocycline-induced systemic lupus erythematosus and autoimmune hepatitis. *Semin Arthritis Rheum.* 1998 Dec;28(3):187-92. Review. PMID: 9872479 [PubMed - indexed for MEDLINE]

TOMÁS BOCANEGRA

In this paper which was published when Dr. Bocanegra was a trainee of Dr. Luis Espinoza at the University of South Florida in Tampa, the mechanism by which reactive arthritis may ensue in the context of infestation with *Taenia saginata* and *Strongyloides stercoralis* is reported.

Bocanegra TS, Espinoza LR, Bridgeford PH, Vasey FB, Germain BF.

Reactive arthritis induced by parasitic infestation: *Ann Intern Med.* 1981 Feb;94(2):207-9

Arthritis developed in two patients during the course of parasite infestation with *Strongyloides stercoralis* and *Taenia saginata*, respectively. The joint involvement was polyarticular and symmetrical but seronegative and nonerosive radiologically. We found evidence of abnormal humoral immunity to the parasites, immune complexes in serum and synovial fluid, and immunoglobulin deposits in the synovia. Nonsteroidal anti-inflammatory agents proved ineffective but specific antiparasitic treatment resulted in resolution of the symptoms and immunologic abnormalities. Our findings provide further documentation of the interaction between the body's immune system and parasites and suggest that arthritis induced by parasitic infestation may be mediated by immune complex formation in susceptible hosts.

PMID: 7469214 [PubMed - indexed for MEDLINE]

1. Gotuzzo E, Alarcon GS, **Bocanegra TS**, Carrillo C, Guerra JC, Rolando I, Espinoza LR. Articular involvement in human brucellosis: a retrospective analysis of 304 cases. *Semin Arthritis Rheum.* 1982 Nov;12(2):245-55. PMID: 6101216 [PubMed - indexed for MEDLINE]
2. Espinoza LR, Vasey FB, Espinoza CG, **Bocanegra TS**, Germain BF. Vascular changes in psoriatic synovium. A light and electron microscopic study. *Arthritis Rheum.* 1982 Jun;25(6):677-84. PMID: 7092966 [PubMed - indexed for MEDLINE]
3. **Bocanegra TS**, Vasey FB. Musculoskeletal syndromes in parasitic diseases. *Rheum Dis Clin North Am.* 1993 May;19(2):505-13. Review. PMID: 8502785 [PubMed - indexed for MEDLINE]
4. Alarcon GS, **Bocanegra TS**, Gotuzzo E, Espinoza LR. The arthritis of brucellosis: a perspective one hundred years after Bruce's discovery. *J Rheumatol.* 1987 Dec;14(6):1083-5. Review. No abstract available. PMID: 3325640 [PubMed - indexed for MEDLINE]
5. Alarcon GS, Gotuzzo E, **Bocanegra TS**, Castaneda O, Calvo A, Carrillo C, Go RC, Acton RT, Barger BO. Familial studies in human brucellosis. *Tissue Antigens.* 1985 Jul;26(1):77-9. No abstract available. PMID: 3862265 [PubMed - indexed for MEDLINE]
6. Espinoza LR, Bridgeford P, Lowenstein M, **Bocanegra TS**, Vasey FB, Germain BF. Polymyalgia rheumatica and giant cell arteritis: circulating immune complexes. *J Rheumatol.* 1982 Jul-Aug;9(4):556-60. PMID: 6215486 [PubMed - indexed for MEDLINE]
7. **Bocanegra TS**, Espinoza LR, Bridgeford PH, Vasey FB, Germain BF. Reactive arthritis induced by parasitic infestation. *Ann Intern Med.* 1981 Feb;94(2):207-9. PMID: 7469214 [PubMed - indexed for MEDLINE]
8. Bridgeford PH, Lowenstein M, **Bocanegra TS**, Vasey FB, Germain BF, Espinoza LR. Polymyalgia rheumatica and giant cell arteritis: histocompatibility typing and hepatitis-B infection studies. *Arthritis Rheum.* 1980 Apr;23(4):516-8. No abstract available. PMID: 7370065 [PubMed - indexed for MEDLINE]

OSWALDO CASTAÑEDA-JIMENEZ

This is one of the first studies to critically evaluate the American College of Rheumatology preliminary criteria for remission in rheumatoid arthritis. The criteria were found to be highly specific in both patient groups but the sensitivity of the criteria was lower in the American than in the Peruvian patients. This is an important study in view of the high remission rates encountered nowadays with the use of biologic compounds.

Alarcon GS, **Castañeda O**, Ferrandiz M, Krumdieck CL, Koopman WJ. Efficacy and safety of 10-deazaaminopterin in the treatment of rheumatoid arthritis. A one-year continuation, double-blind study. *Arthritis Rheum.* 1992 Nov;35(11):1318-21.

Department of Medicine, University of Alabama, Birmingham 35294.

OBJECTIVE. To determine the long-term safety and efficacy of 10-deazaaminopterin (10-DAM) in the treatment of rheumatoid arthritis (RA). **METHODS.** A 1-year continuation of an initial 15-week randomized, double-blind clinical trial of 10-DAM and methotrexate (MTX). **RESULTS.** 10-DAM (n = 10) and MTX (n = 8) had comparable safety and efficacy profiles. One 10-DAM-treated and 2 MTX-treated patients experienced transient side effects; 1 MTX-treated patient experienced recurrent nausea and discontinued MTX. **CONCLUSION.** 10-DAM appears to be as beneficial and This is one of the first studies to critically evaluate the American College of Rheumatology preliminary criteria for remission in rheumatoid arthritis. The criteria were found to be highly specific in both patient groups but the sensitivity of the criteria was lower in the American than in the Peruvian patients. This is an important study in view of the high remission rates encountered nowadays with the use of biologic compounds as safe as MTX for the treatment of RA.

PMID: 1445448 [PubMed - indexed for MEDLINE]

1. Berrocal A, Gotuzzo E, Calvo A, Carrillo C, **Castañeda O**, Alarcon GS. Sternoclavicular brucellar arthritis: a report of 7 cases and a review of the literature. *J Rheumatol.* 1993 Jul;20(7):1184-6. Review. PMID: 8371214 [PubMed - indexed for MEDLINE]
2. Alarcon GS, **Castañeda O**, Ferrandiz M, Krumdieck CL, Koopman WJ. Efficacy and safety of 10-deazaaminopterin in the treatment of rheumatoid arthritis. A one-year continuation, double-blind study. *Arthritis Rheum.* 1992 Nov;35(11):1318-21. PMID: 1445448 [PubMed - indexed for MEDLINE]
3. Alarcon GS, **Castañeda O**, Nair MG, Ferrandiz M, Koopman WJ, Krumdieck CL. Controlled trial of methotrexate versus 10-deazaaminopterin in the treatment of rheumatoid arthritis. *Ann Rheum Dis.* 1992 May;51(5):600-3. PMID: 1616322 [PubMed - indexed for MEDLINE]
4. Gotuzzo E, Seas C, Guerra JG, Carrillo C, Bocanegra TS, Calvo A, **Castañeda O**, Alarcon GS. Brucellar arthritis: a study of 39 Peruvian families. *Ann Rheum Dis.* 1987 Jul;46(7):506-9. PMID: 3662637 [PubMed - indexed for MEDLINE]

CECILIA P. CHUNG-NAKANDAKARI

Since joining Vanderbilt University, Dr. Chung has studied the risk factors associated with the development of accelerated atherosclerosis in patients with lupus and rheumatoid arthritis (RA). In this article, Dr. Chung and her collaborators studied 141 patients with RA (70 with early disease and 71 with established disease) and 86 normal subjects for the presence of coronary calcifications as a measure of atherosclerosis (more frequent and severe in patients than in controls). Risk factors for this outcome included smoking, disease duration and elevated sedimentation rate suggesting that in patients with RA (and probably other chronic inflammatory disorders) traditional and disease-related risk factors need to be taken into consideration to improve the outcome of patients with RA.

Chung CP, Oeser A, Raggi P, Gebretsadik T, Shintani AK, Sokka T, Pincus T, Avalos I, Stein CM. Increased coronary-artery atherosclerosis in rheumatoid arthritis: relationship to disease duration and cardiovascular risk factors.

Vanderbilt University School of Medicine, Nashville, Tennessee 37232-6602, USA.

OBJECTIVE: To compare the prevalence and severity of coronary-artery atherosclerosis in patients with early and established rheumatoid arthritis (RA) and controls. **METHODS:** Electron-beam computed tomography was used to measure the extent of coronary-artery calcification in 227 subjects, of whom 70 had early RA, 71 had established RA, and 86 were controls. Coronary-artery calcification calculated according to the Agatston calcium score was compared in patients and controls, and its relationship to clinical characteristics was examined. Adjusted odds ratios (ORs) were obtained with the use of proportional odds logistic regression models to determine independent associations of early and established RA and coronary-artery calcification. **RESULTS:** Calcium scores were higher in patients with established RA (median 40.2, interquartile range [IQR] 0-358.8) compared with those with early disease (median 0, IQR 0-42.6) and controls (median 0, IQR 0-19.2) ($P = 0.001$). Coronary-artery calcification occurred more frequently in patients with established RA (60.6%) than in patients with early RA (42.9%) and control subjects (38.4%) ($P = 0.016$). The OR for the likelihood of having more severe coronary-artery calcification (defined as an Agatston score >109) in patients with established disease was 3.42 ($P = 0.002$) after adjusting for cardiovascular risk factors. Among patients with RA, smoking (OR 1.02, $P = 0.04$) and an elevated erythrocyte sedimentation rate (OR 1.02, $P = 0.05$) were associated with more severe coronary-artery calcification after adjustment for age and sex. **CONCLUSION:** The prevalence and severity of coronary calcification is increased in patients with established RA and is related, in part, to smoking and an increased erythrocyte sedimentation rate.

PMID: 16200609 [PubMed - indexed for MEDLINE]

LUIS R. ESPINOZA

Dr. Espinoza's group was one of the first to call attention to the rheumatic manifestations occurring in the context of infections with the Human Immunodeficiency Virus (HIV). In this landmark article, his group studied 100 consecutive patients infected with HIV; in addition to report the high frequency of musculoskeletal and rheumatic manifestations in these patients, his group was the first one to report the syndrome of severe intermittent oligoarthralgias, usually requiring more than NSAIDs to control them.

Berman A, **Espinoza LR**, Diaz JD, Aguilar JL, Rolando T, Vasey FB, Germain BF, Lockey RF. Rheumatic manifestations of human immunodeficiency virus infection. *Am J Med.* 1988 Jul;85(1):59-64.

Department of Internal Medicine, University of South Florida College of Medicine, Tampa 33612.

PURPOSE: The prevalence and characteristics of the rheumatic and extra-rheumatic manifestations of human immunodeficiency virus (HIV) infection were determined in a prospective manner. **PATIENTS AND METHODS:** One hundred one patients with HIV infection were consecutively interviewed and examined. The prevalence of autoantibodies and their association with rheumatologic symptoms were also determined. **RESULTS:** The musculoskeletal system was involved in 72 patients. Thirty-five patients had arthralgias, 10 had Reiter's syndrome, two had psoriatic arthritis, two had myositis, and one had vasculitis. Also found were two previously unreported syndromes. The first, occurring in 10 patients, consisted of severe intermittent pain involving less than four joints, without evidence of synovitis, of short duration (two to 24 hours), and requiring therapy (ranging from nonsteroidal antiinflammatory drugs to narcotics). The second, occurring in 12 patients, consisted of arthritis (oligoarticular in six patients, monoarticular in three patients, and polyarticular in three patients) involving the lower extremities and lasting from one week to six months. The synovial fluid of five patients (three with arthritis, one with Reiter's syndrome, and one with psoriatic arthritis) was sterile and inflammatory. **CONCLUSION:** Musculoskeletal complications are common in advanced stages of HIV infection. Persons in a high-risk group for HIV infection who manifest oligoarthritis with or without any other extra-articular manifestation suggestive of Reiter's syndrome or other form of spondyloarthropathy should be tested for HIV.

PMID: 3260453 [PubMed - indexed for MEDLINE]

23. **Espinoza LR**, Aguilar JL, Espinoza CG, Cuellar ML, Scopelitis E, Silveira LH. Fibroblast function in psoriatic arthritis. I. Alteration of cell kinetics and growth factor responses. *J Rheumatol.* 1994 Aug;21(8):1502-6. PMID: 7983654 [PubMed - indexed for MEDLINE]
24. Lopez LR, Santos ME, **Espinoza LR**, La Rosa FG. Clinical significance of immunoglobulin A versus immunoglobulins G and M anti-cardiolipin antibodies in patients with systemic lupus erythematosus. Correlation with thrombosis, thrombocytopenia, and recurrent abortion. *Am J Clin Pathol.* 1992 Oct;98(4):449-54. PMID: 1415024 [PubMed - indexed for MEDLINE]
25. **Espinoza LR**, Zakraoui L, Espinoza CG, Gutierrez F, Jara LJ, Silveira LH, Cuellar ML, Martinez-Osuna P. Psoriatic arthritis: clinical response and side effects to methotrexate therapy. *J Rheumatol.* 1992 Jun;19(6):872-7. PMID: 1404123 [PubMed - indexed for MEDLINE]
26. Jara LJ, Gomez-Sanchez C, Silveira LH, Martinez-Osuna P, Vasey FB, **Espinoza LR**. Hyperprolactinemia in systemic lupus erythematosus: association with disease activity. *Am J Med Sci.* 1992 Apr;303(4):222-6. PMID: 1562038 [PubMed - indexed for MEDLINE]
27. Berman A, Reboredo G, Spindler A, Lasala ME, Lopez H, **Espinoza LR**. Rheumatic manifestations in populations at risk for HIV infection: the added effect of HIV. *J Rheumatol.* 1991 Oct;18(10):1564-7. PMID: 1765982 [PubMed - indexed for MEDLINE]
28. Martinez-Osuna P, Wallach PM, Seleznick MJ, Levin RW, Silveira LH, Jara LJ, **Espinoza LR**. Treatment of the eosinophilia-myalgia syndrome. *Semin Arthritis Rheum.* 1991 Oct;21(2):110-21. PMID: 1749939 [PubMed - indexed for MEDLINE]
29. Seleznick MJ, Silveira LH, **Espinoza LR**. Avascular necrosis associated with anticardiolipin antibodies. *J Rheumatol.* 1991 Sep;18(9):1416-7. PMID: 1757948 [PubMed - indexed for MEDLINE]
30. Martinez-Osuna P, **Espinoza LR**. On the treatment of the eosinophilia-myalgia syndrome. *Arch Intern Med.* 1991 Jun;151(6):1239. No abstract available. PMID: 2043034 [PubMed - indexed for MEDLINE]
31. **Espinoza LR**, Jara LJ, Silveira LH, Martinez-Osuna P, Zwolinska JB, Kneer C, Aguilar JL. Anticardiolipin antibodies in polymyalgia rheumatica-giant cell arteritis: association with severe vascular complications. *Am J Med.* 1991 Apr;90(4):474-8. PMID: 2012088 [PubMed - indexed for MEDLINE]
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RAFAEL GRAU

In this important article, Dr. Grau delivers a critical review of the clinical characteristics, diagnostic basis, differential diagnosis and pathogenic pathways of the pseudovasculitic syndromes. This article is "a must reading" for all those interested in the study of vasculitis

Grau R. Pseudovasculitis: mechanisms of vascular injury and clinical spectrum. *Curr Rheumatol Rep.* 2002 Feb;4(1):83-9.

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Pseudovasculitis, vasculitis-like syndromes, or mimics of vasculitis represent a heterogeneous collection of disorders that are capable of simulating a vasculitic disorder. Some conditions such as cardiac myxomas, cholesterol embolization, and fibromuscular dysplasia are more apt to cause confusion, but numerous other conditions can do so also. Inappropriate diagnosis leads to delay or absence of proper management and exposure to potentially deleterious treatment modalities such as corticosteroids and cytotoxic agents. The diagnosis of a pseudovasculitic disorder requires a high index of suspicion and should always be part of the differential diagnosis of vasculitis. The endothelium is thought to be pivotal in vascular injury; much has been learned using in vitro human umbilical vein endothelial cell cultures. Application of this knowledge to human disease and to vasculitic disorders and their imitators is still premature.

PMID: 11798987 [PubMed - indexed for MEDLINE]

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RAQUEL M. HICKS

Dr. Hicks had the privilege of being member of the team who reported the first community-wide outbreak of Kawasaki syndrome in the USA (Hawaii). Herein, this group reported that patients with Kawasaki syndrome, compared to the general population of the island, were more likely to be of Japanese ancestry, to have a high-income, and possibly a history of respiratory infection in the preceding month (44%).

Dean AG, Melish ME, **Hicks R**, Palumbo NE. An epidemic of Kawasaki syndrome in Hawaii. *J Pediatr.* 1982 Apr;100(4):552-7.

A community-wide outbreaks of Kawasaki syndrome, apparently the first in the United States, occurred in Hawaii in the first half of 1978. Twenty-seven of the 33 cases were subjected to intensive epidemiologic and microbiologic study. Patients with Kawasaki syndrome, compared to the general population, more often had Japanese ancestry, high-income status, and possibly a history of respiratory infection in the preceding month (44%). *Staphylococcus aureus* was not found in high frequency in the patients (15%), and viral cultures and serologic studies, immune electron microscopy, and guinea pig and primate inoculation did not reveal a causative microorganism. Febrile illnesses in guinea pigs inoculated with a skin biopsy specimen should not be further passaged.

PMID: 7062202 [PubMed - indexed for MEDLINE]

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LUIS JAVIER JARA

This recently published article by Dr. Jara's group emphasizes the seriousness of the primary antiphospholipid syndrome as recruitment of additional organ systems over the course of relatively few years occurs in the majority of these patients despite standard treatment (oral anticoagulation).

Medina G, Vera-Lastra O, Angeles U, **Jara LJ**. Mono-organic versus multi-organic involvement in primary antiphospholipid syndrome. *Ann N Y Acad Sci*. 2005 Jun;1051:304-12.

Research Division, Hospital de Especialidades Centro Medico La Raza, Seris y Zaachila S/N Col. La Raza, México, CP. 02990. luis_jara_quezada@hotmail.com.

The prevalence of mono-organic and multi-organic involvement during long-term follow-up in patients with primary antiphospholipid syndrome (pAPS) was investigated. We studied 60 pAPS patients followed up at least 5 years. Patients with associated systemic lupus erythematosus were excluded. All patients received oral anticoagulant therapy. A diagnosis of mono-organic involvement was considered when one organ was affected exclusively, and multi-organic involvement was considered when two or more organs became affected during follow-up. Average age at diagnosis was 32.9 +/- 12.4 years, 40 subjects were female and 20 male, and mean disease evolution totaled 11.5 +/- 4.5 years. The mean number of clinical events was 3.75 +/- 1.87. Among patients, immunoglobulin G anticardiolipin (IgM aCL) titers totaled 50 +/- 40.3 IgG phospholipid units, and IgM aCL titers totaled 47.3 +/- 35.4 IgM phospholipid units. The most frequent clinical manifestations at study onset were deep venous thrombosis, stroke, pulmonary thromboembolism, fetal loss, and pre-eclampsia. At the beginning of follow-up, 46 patients had mono-organic involvement and 14 had multi-organic involvement ($P = 0.0001$). In contrast, at the end of the study, only 8 patients still had mono-organic involvement, leading to deep venous thrombosis ($n = 3$), stroke ($n = 3$), and retinal thrombosis ($n = 2$) ($P = 0.0001$). Kaplan-Meier analysis showed that the probability of remaining with mono-organic involvement decreased throughout the cumulative years, especially during the first 3. The hazard risk ratio for developing multi-organic involvement was 1.47 patients per year. In conclusion, PAPS is a chronic disorder with unpredictable clinical course and multi-organic involvement, especially during the first years. The conversion to multi-organic involvement supports the concept that pAPS is a systemic autoimmune disease.

PMID: 16126972 [PubMed - in process]

SERGIO JIMENEZ

This is a comprehensive clinical and laboratory analyses of a fairly large number of patients (n=9) afflicted with a recently recognized disorder- nephrogenic fibrosing dermopathy. Findings from this study suggest that the fibrotic process affects not only the dermis, but also the subcutaneous tissues, fascia, and other organs, including striated muscles, heart, and lungs. The authors go on to conclude that this is a systemic fibrosing process, and suggest that "dialysis-associated systemic fibrosis" is a better name for this disorder.

Jimenez SA, Artlett CM, Sandorfi N, Derk C, Latinis K, Sawaya H, Haddad R, Shanahan JC. Dialysis-associated systemic fibrosis (nephrogenic fibrosing dermopathy): study of inflammatory cells and transforming growth factor beta1 expression in affected skin. *Arthritis Rheum.* 2004 Aug;50(8):2660-6.

Division of Rheumatology, Thomas Jefferson University, Philadelphia, Pennsylvania 19107-5541, USA.

OBJECTIVE: Nephrogenic fibrosing dermopathy (NFD) is a newly recognized cutaneous fibrotic disorder occurring in individuals with end-stage renal disease (ESRD). The aim of the present study was to describe the clinical and histopathologic features of 9 new cases and to characterize the inflammatory cells and expression of transforming growth factor beta1 (TGFbeta1) in affected skin. **METHODS:** Clinical and laboratory assessments, including serology and pulmonary function studies, were performed in 9 patients undergoing long-term dialysis (8 hemodialysis; 1 peritoneal dialysis) for ESRD of diverse etiologies. Skin, fascia, striated muscles, lungs, and heart were examined by histopathology. Inflammatory cells were characterized by immunophenotyping using specific monoclonal antibodies. TGFbeta1 expression was determined by in situ hybridization. **RESULTS:** All patients displayed cutaneous features resembling both systemic sclerosis and diffuse fasciitis, with severe loss of motion and flexion contractures in multiple joints. Six patients displayed woody induration of the muscles of the legs, thighs, and forearms. Five of the 6 patients with lung involvement had a reduced diffusion capacity for carbon monoxide on pulmonary function testing. Marked elevations of the erythrocyte sedimentation rate and/or C-reactive protein level were found in 6 patients. Antinuclear antibodies were present at low titers in 4 patients. Histopathologic studies indicated that in addition to the dermis, the fibrotic process affected the subcutaneous tissue, fascia, striated muscles, lungs, and myocardium. Large numbers of CD68+/factor XIIIa+ dendritic cells and increased expression of TGFbeta1 were found in affected skin and muscle. **CONCLUSION:** Our findings indicate that the fibrotic process of NFD affects not only the dermis, but also the subcutaneous tissues, fascia, and other organs, including striated muscles, heart, and lungs. We therefore believe this is a systemic fibrosing process, and we suggest that dialysis-associated systemic fibrosis would be a better term for the condition.

PMID: 15334482 [PubMed - indexed for MEDLINE]

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ISAIAS SPILBERG

Our prematurely departed compatriot was involved in the study of the pathogenesis of gout. In this classic paper Spilberg and collaborators from Washington University demonstrated the occurrence of an acute inflammatory response in the joint cavities of rabbits administered monosodium urate-derived chemotactic factor suggesting that this is the mechanism by which acute gout occurs in humans

Spilberg I, Rosenberg D, Mandell B. Induction of arthritis by purified cell-derived chemotactic factor: role of chemotaxis and vascular permeability. *J Clin Invest.* 1977 Mar;59(3):582-5.

The injection of monosodium urate-induced chemotactic factor into the joint cavities of rabbits induces an acute inflammatory response that resembles the one produced by monosodium urate crystals. The leukocyte accumulation induced by the factor was not accompanied by a measurable increase in vascular permeability as measured by appearance of ¹²⁵I-albumin in the joint cavity. When histamine was injected into the joints, a marked increase in vascular permeability but no leukocytosis above control levels was observed. The above results suggest that the cell-derived factor is primarily responsible for the accumulation of cells seen in the acute inflammation induced by monosodium urate crystals.

PMID: 838864 [PubMed - indexed for MEDLINE]

PETER STASTNY

This landmark article describes the association between HLA-Dw4 (*HLA-DRB1*04* per current nomenclature) with rheumatoid arthritis; numerous studies around the world have been conducted since to determine if this association, which he described in white patients with seropositive disease held true in patients with seronegative disease and/or from other ethnic groups. It also marks the beginning of our understanding of the genetic basis for the occurrence (and severity) of this disease.

Stastny P. Association of the B-cell alloantigen DRw4 with rheumatoid arthritis. *N Engl J Med.* 1978 Apr 20; 298(16):869-71.

Previous testing of patients with rheumatoid arthritis showed that one HLA-D type, Dw4, occurred more frequently than in normal controls. B-cell alloantigens closely related to HLA-D can now be identified by a simple serologic procedure. Using this test, I studied 80 white patients with erosive, rheumatoid-factor-positive rheumatoid arthritis. The B-cell alloantigen HLA-DRw4 occurred in 70 per cent of 54 patients, as compared to 28 per cent of the 68 normal controls (*P* less than 10⁻⁵). Both groups were also tested for the HLA-A, B and C antigens and for HLA-D. HLA-Dw4 occurred in 54 per cent of the patients and 16 per cent of the controls (*P* less than 10⁻⁵). Small differences observed in several of the HLA-A and B antigens were not statistically significant. The results indicate that rheumatoid arthritis in whites is associated with genes of the HLA-D region and that immunogenetic factors linked to HLA have a role in its pathogenesis.

PMID: 147420 [PubMed - indexed for MEDLINE]

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