Arthritis Care & Research
Vol. 68, No. 3, March 2016, pp 285–287
DOI 10.1002/acr.22663

EDITORIAL

Incomplete Systemic Lupus Erythematosus: Early Diagnosis or Overdiagnosis?

MANUEL F. UGARTE-GIL[1] AND GRACIELA S. ALARCÓN[2]

We read with great interest the article published recently in *Arthritis Care & Research* by Costenbader and Schur (1), and with this editorial we would like to offer additional insights and views. While we fully agree with the fact that autoimmunity does not occur overnight, that autoantibodies may be present years before any clinical manifestation of lupus ensues (2), and that in lupus disease manifestations may evolve over a variable time period (days to years), we also think that in the clinical setting we must be exceedingly careful about the name we give to those individuals who eventually may (or may not) evolve into a defined systemic lupus erythematosus (SLE) phenotype. In fact, the majority of these "possible" patients will never develop SLE (3–7). The authors cite work conducted at their own institution in which they followed 264 "potential SLE" patients. Over a mean ± SD of 6.3 ± 4.3 years, 21% of these patients progressed to SLE, 18% definitively did not have SLE, and the remaining 61% remained as "potential SLE" (8). The 21% is not too dissimilar from the percentages cited by different authors when studying patients grouped under different headings such as undifferentiated connective tissue disease, incomplete lupus, pre-lupus, latent lupus, and incomplete lupus, among others (3–7,9,10). The problem in our view with coining the term "potential SLE" is 2-fold. First, since the majority of these individuals is not going to develop SLE, attaching the term SLE to their diagnosis (even with the qualifier "potential") may bring unnecessary anxiety to the patient (and his/her family), who will be expecting the disease to emerge any time. Second, this diagnosis may be transmitted erroneously to other providers (primary care or emergency care) from whom these patients may seek help for a number of different ongoing or new manifestations and who, being less knowledgeable about lupus than the specialists, may inappropriately interpret potential SLE as being SLE; this may lead to the use of medications with serious potential side effects and even irreversible damage. For example, among 476 patients referred to an autoimmune disease center, 203 patients had received a misdiagnosis; of those, 137 patients were diagnosed at the center as either having positive antinuclear antibodies (ANAs) or fibromyalgia. Among these patients, 39 had received glucocorticoids, and more than half of them had received >15 mg/day with some receiving a very high dosage (60 mg/day) (11). Unfortunately, we have witnessed such mishaps numerous times over the years with regrettable consequences.

We certainly favor identifying patients who will evolve into SLE early in the disease course, but the "million dollar question" is: How do we distinguish them from the bulk of patients that will never develop SLE? Since we lack specific biomarkers, we rely on the presence of some classical clinical or laboratory features. In fact, various authors have recognized malar rash (4), discoid lupus (9), proteinuria (7), abnormal urinalysis (7), anti-Sm (9), and anti–double-stranded DNA (4,10) as indicating the onset of SLE when studying patients within this undefined category. Perhaps the most controversial laboratory finding is that of ANA positivity. In a study we conducted more than 2 decades ago, we searched for the records of patients with an International Classification of Disease (ICD) code of 710.0 (SLE), who had less than 5 years of disease duration and who lived in Alabama (8). Of the 140 patients identified, only 16% had in fact unequivocal SLE, while 58% had a related diagnosis (antiphospholipid syndrome, cutaneous lupus) or were unclassifiable. It is important to note that there were 37 patients (26.4%) who had fibromyalgia-like symptoms (arthralgias, myalgias, fatigue, depression, and sleep disturbances). Certainly these poorly defined clinical manifestations had prompted obtaining an ANA test that showed a positive finding and that was, very likely, the reason for these patients receiving the 710.0 ICD code. In still another (recent) study, 232 patients, in whom an ANA test had been the reason for a referral to a rheumatologist, were studied. The positive predictive value for a diagnosis of lupus in this study was 2.1% and for a lupus-related disorder was 9.1%; in the large majority of these patients, the test had been ordered because of the presence of widespread pain. These authors concluded that the

[1]Manuel F. Ugarte-Gil, MD: Hospital Nacional Guillermo Almenara Irigoyen, EsSalud and Universidad Científica del Sur, Lima, Perú; [2]Graciela S. Alarcón, MD, MPH, MACR: University of Alabama at Birmingham and Universidad Peruana Cayetano Heredia, Lima, Perú.

Address correspondence to Graciela S. Alarcón, MD, MPH, MACR, 1 Lakeside Drive, Apartment 602, Oakland, CA 94612. E-mail: galarcon@uab.edu.

Submitted for publication May 27, 2015; accepted in revised form July 7, 2015.

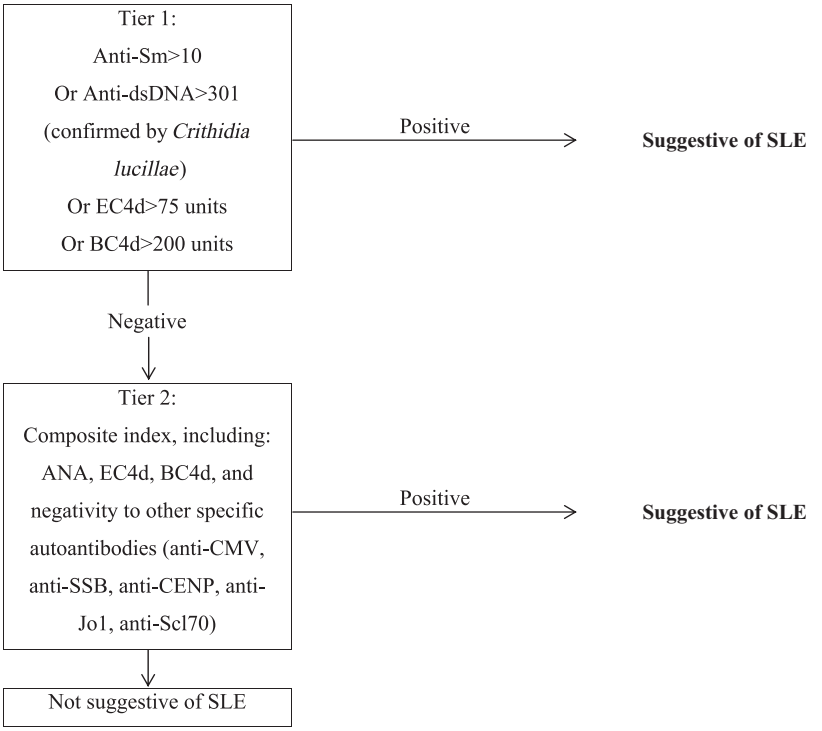

Figure 1. Two-tier methodology for the diagnosis of systemic lupus erythematosus (SLE). Anti-dsDNA = anti–double-stranded DNA; EC4d = erythrocyte cell-bound complement (C4d); BC4d = B cells cell-bound complement (C4d); ANA = antinuclear antibodies; anti-CMV = anti–mutated citrullinated vimentin; anti-CENP = anti–centromere extractable nuclear antigen. Modified from ref. 15.

very low positive predictive values they had observed were related to the low pretest probabilities of lupus and lupus-related disorders in these patients (12). Finally, in the 2013 *Choosing Wisely* communication from Yazdany et al, the testing of ANA and subserologies were the ancillary studies of greatest concern to rheumatologists. The work of Qaseem et al of not testing patients with nonspecific symptoms such as fatigue or myalgia or fibromyalgia for ANA (13) is echoed by Yazdany et al in this pivotal communication (14).

In short, while we share Costenbader and Schur's suggestion that (as in rheumatoid arthritis [RA]) there is an unmet need to recognize individuals at high risk of, or in the process of, developing SLE due to the presence of genetic or environmental factors, we think these terms should be used with extreme caution to avoid their misuse in those who will never develop SLE. In understanding SLE, we lag behind RA for which extensive literature is now available to identify individuals who are to develop RA. However, as our understanding of the pathophysiology of SLE advances, our ability to identify this subgroup of patients within those referred for the evaluation of possible SLE using specific biomarkers will be a welcome development. Whether the 2-tier methodology testing proposed by Putterman et al (Figure 1) in which cell-bound complement (C4d) activation products on erythrocyte (EC4d) and B cells (BC4d) and several other autoantibodies could really be of help in identifying these patients remains to be determined (15).

AUTHOR CONTRIBUTIONS

Both authors were involved in drafting the article or revising it critically for important intellectual content, and both authors approved the final version to be published.

REFERENCES

1. Costenbader KH, Schur PH. We need better classification and terminology for "people at high risk of or in the process of developing lupus." Arthritis Care Res (Hoboken) 2015;67:593–6.
2. Arbuckle MR, McClain MT, Rubertone MV, Scofield RH, Dennis GJ, James JA, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. N Engl J Med 2003;349:1526–33.
3. Greer JM, Panush RS. Incomplete lupus erythematosus. Arch Intern Med 1989;149:2473–6.
4. Vila LM, Mayor AM, Valentin AH, Garcia-Soberal M, Vila S. Clinical outcome and predictors of disease evolution in patients with incomplete lupus erythematosus. Lupus 2000;9:110–5.
5. Stahl-Hallengren C, Jonsen A, Nived O, Sturfelt G. Incidence studies of systemic lupus erythematosus in Southern Sweden: increasing age, decreasing frequency of renal manifestations and good prognosis. J Rheumatol 2000;27:685–91.
6. Swaak AJ, van de Brink H, Smeenk RJ, Manger K, Kalden JR, Tosi S, et al. Incomplete lupus erythematosus: results of a multicentre study under the supervision of the EULAR Standing Committee on International Clinical Studies Including Therapeutic Trials (ESCISIT). Rheumatology (Oxford) 2001;40:89–94.
7. Al Daabil M, Massarotti EM, Fine A, Tsao H, Ho P, Schur PH, et al. Development of SLE among "potential SLE" patients seen in consultation: long-term follow-up. Int J Clin Pract 2014;68:1508–13.

8. 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;38:1475–84.
9. Calvo-Alen J, Alarcon GS, Burgard SL, Burst N, Bartolucci AA, Williams HJ. Systemic lupus erythematosus: predictors of its occurrence among a cohort of patients with early undifferentiated connective tissue disease: multivariate analyses and identification of risk factors. J Rheumatol 1996;23:469–75.
10. Danieli MG, Fraticelli P, Salvi A, Gabrielli A, Danieli G. Undifferentiated connective tissue disease: natural history and evolution into definite CTD assessed in 84 patients initially diagnosed as early UCTD. Clin Rheumatol 1998;17:195–201.
11. Narain S, Richards HB, Satoh M, Sarmiento M, Davidson R, Shuster J, et al. Diagnostic accuracy for lupus and other systemic autoimmune diseases in the community setting. Arch Intern Med 2004;164:2435–41.
12. Abeles AM, Abeles M. The clinical utility of a positive antinuclear antibody test result. Am J Med 2013;126:342–8.
13. Qaseem A, Alguire P, Dallas P, Feinberg LE, Fitzgerald FT, Horwitch C, et al. Appropriate use of screening and diagnostic tests to foster high-value, cost-conscious care. Ann Intern Med 2012;156:147–9.
14. Yazdany J, Schmajuk G, Robbins M, Daikh D, Beall A, Yelin E, et al, and the American College of Rheumatology Core Membership Group. Choosing wisely: the American College of Rheumatology's top 5 list of things physicians and patients should question. Arthritis Care Res (Hoboken) 2013;65:329–39.
15. Putterman C, Furie R, Ramsey-Goldman R, Askanase A, Buyon J, Kalunian K, et al. Cell-bound complement activation products in systemic lupus erythematosus: comparison with anti-double-stranded DNA and standard complement measurements. Lupus Sci Med 2014;1:e000056.