Who Will Develop Pemphigus Foliaceus?

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Pemphigus foliaceus (PF), an autoimmune blistering disorder, is characterized by the development of superficial cutaneous blisters in a seborrheic distribution, without mucosal involvement. Autoantibodies target the desmoglein 1 (Dsg1) antigen expressed on the surface of keratinocytes located in the superficial levels of the epidermis (Mahoney *et al.*, 1999), and both sporadic PF and endemic PF can occur. Endemic PF, referred to as fogo selvagem (FS), is endemic to specific areas of the world, most notably Brazil, although it has also been described in Tunisia and Colombia (Abreu-Velez *et al.*, 2003). Both genetic and environmental factors appear to play a role in the development of FS. Certain human leukocyte antigen (HLA) types appear to be at greatest risk: the HLA-DRB1*0102, HLA-DRB1*0404, and HLA-DRB1*1402 alleles ($P < 0.005$, relative risk, 14; Moraes *et al.*, 1997). It has been hypothesized that the disease may be triggered by a local environmental agent(s) such as *Simulium* (a hematophagous insect), causing a cross-reactive anti-Dsg1 antibody response that leads to FS (Diaz *et al.*, 2004).

Endemic PF is of special interest, beyond its clinical impact on those affected, because it can serve as a model for organ-specific immune disease with both genetic and environmental components. FS appears to be caused by isotype-restricted, pathogenic anti-Dsg1 autoantibodies that are predominantly IgG4 (Warren *et al.,* 2003) and that increase in concentration in serum upon progression from preclinical to clinical disease.

Development of a predictive test for PF would benefit those at high risk, and it could also serve as an investigative tool. In an effort to develop such a test, Qaqish *et al.* (2009, this issue) used Dsg1 enzyme-linked immunosorbent assay in a study of 214 patients with FS and 261 healthy controls, randomly divided into training (50%), validation (25%), and test (25%) sets. IgG4 was found to be the best predictor of FS, with a sensitivity of 92% and specificity of 97%. The positive predictive value of this test in the endemic region of Brazil (which has an FS prevalence of 3%) was 49%. This was then validated by testing 11 patients with FS before and after clinical disease onset, as well as 60 Japanese patients with PF.

Through the following questions, we examine this paper in greater detail. For brief answers, please refer to http://network.nature.com/group/jidclub.

REFERENCES

Abreu-Velez AM, Hashimoto T, Bollag WB, Tobon Arroyave S, Abreu-Velez CE, Londono ML *et al.* (2003) A unique form of endemic pemphigus in northern Colombia. *J Am Acad Dermatol* 49:599–608

Diaz LA, Arteaga LA, Hilario-Vargas J, Valenzuela JG, Li N, Warren S *et al.* (2004) Anti-desmoglein-1 antibodies in onchocerciasis, leishmaniasis and Chagas disease suggest a possible etiological link to fogo selvagem. *J Invest Dermatol* 123:1045–51

Mahoney MG, Wang Z, Rothenberger K, Koch PJ, Amagai M, Stanley JR (1999) Explanations for the clinical and microscopic localization of lesions in pemphigus foliaceus and vulgaris. *J Clin Invest* 103:461–8

Moraes M, Fernandez-Vina M, Lazaro A, Diaz Filho L, Friedman H, Rivitti E *et al.* (1997) An epitope in the third hypervariable region of the DRB1 gene is involved in the susceptibility to endemic pemphigus foliaceus (fogo selvagem) in three different Brazilian populations. *Tissue Antigens* 49:35–40

Qaqish BF, Prisayanh P, Qian Y, Andraca E, Li N, Aoki V *et al.* (2009) Development of an IgG4-based predictor of endemic pemphigus foliaceus (fogo selvagem). *J Invest Dermatol* 129:110–8

Warren S, Arteaga L, Rivitti E, Aoki V, Hans-Filho G, Qaqish B *et al.* (2003) The role of subclass switching in the pathogenesis of endemic pemphigus foliaceus. *J Invest Dermatol* 120:104–8

QUESTIONS

1. Describe pemphigus foliaceus.

2. How is a predictive test developed, and how does the population affect the development and utility of these tests?

3. What were the findings of this study?

4. What may be the clinical implications of this article?

5. What further studies could be performed?

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