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Is Tunisian Endemic Pemphigus Foliaceus A Real Entity, Or Should These Cases Be Reclassified With Other Autoimmune Blistering Disease?

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Opinion

Endemic pemphigus foliaceus, also called South American Endemic Pemphigus Foliaceus (SAPF), has been described in Brazil, Peru, Venezuela, Paraguay, and French Guyana; the disorder presents primarily in native Indian and African descendants living in rural areas [1]. In general, SAPFs present similar sex predilection and familiar clustering [1]. In Colombia, a new variant of EPF exists in El Bagre (El Bagre EPF) [1]. In a 1988 study in Tunisia (which did not state whether it was retrospective or not), Sfax hospital reported 22 cases with pemphigus from the southern area of Tunis [2]. They reported autoimmune blistering diseases (ABDs) in 19 females (six presented with the disorder during pregnancy, and eight were post-partum breast feeding) as well as three males [2]. The authors stated that the age at presentation varied between 19 and 60 years, with an average age of 30 years [2]. Seventy percent (70%) of the cases began by the age of 31, and 90% by the age of 45 [3]. The authors also cited a case of pemphigus vulgaris (PV) following radiation for skin carcinoma at the age of 60. Pruritus was reported preceding the rash in 14 cases [2]. The authors documented nine cases of mucosal involvement, and one case of likely mucous membrane pemphigoid [MMP] was recorded [2]. The histologic findings showed spongiosis in two cases, including intraepithelial eosinophils and neutrophils [2]. The authors later suggested that seven cases could represent PV, six cases could represent pemphigus foliaceus (PF), six cases could represent seborrheic pemphigus (PS), two cases could represent pemphigus herpetiformis (HP), and one case could represent pemphigus vegetans [2]. Later, a 1993 study at the University Hospital of Sousse in Tunisia reported 20 cases of Tunisian Endemic pemphigus Foliaceus (TEPF), all of which involving young women seen from November 1985 through January 1987 [3]. The 1993 report claimed that pregnancy, postpartum, and/or breastfeeding conditions were present in

several of the patients [3]. Later, in a 1995 report [4], similar authors emphasized the term TEPF, avoiding classification of their patient disorders as pemphigoid gestationis (PG) or other rashes presenting in pregnancy or postpartum states [4]. In the 1993 [3] and 1995 [4] studies, differential diagnoses including drug-induced pemphigus and herpetiformis-type drug-induced pemphigus were not considered [3,4]. Moreover, few comments were offered about the presence of IgA intercellular staining (ICS) between epidermal keratinocytes and/or immunofluorescence [IF] staining at the basement membrane zone (BMZ) described in several of the patients [3,4]. In summary, despite the presence of pregnancy and postpartum conditions reported in selected patients in the 1993 and 1995 studies, the authors did not review differential diagnoses involving pregnancy and postpartum conditions and/or other causes of blistering diseases (BD) [5]. The first author of this letter (Amav) traveled to France in 1999 to compare the reactivity of TEPF to those with El Bagre-EPF in a laboratory that supposedly held TEPF samples; to her surprise, no sample was available for this comparison. Supposedly the 1995 study samples had been sent there. Further, Amav contacted multiple times by email three authors on TEPF (Masmoudi [HM], Abida [OA], Masmoudi [AM]) raising these issues, but received no answer. Also, HM, OA, AM, and their other coauthors never discussed the presence of ICS using IgA, nor BMZ staining with IgG and C3 using IF [1, 3, 4]. No communication was received regarding differential diagnoses including IgA pemphigus triggered by medications, other ABDs and/or BDs caused by infectious, or other possible triggers. In 2013 [6], HM, OA, AM and others, including Drs. Stanley and Amagai (experts in ABDs), evaluated autoantibodies from healthy Tunisians and found that they reacted with the C-terminal extracellular domains of unmatured Dsg1 (pre-Dsg1) using immunoblotting (IB) [5]. They concluded that anti-Dsg1 antibodies from healthy Tunisians do not show ICS, in contrast to those from PF and or SAPF patients [6]. In lay terms, this finding contradicts the hypothesis that PF, PS, and SAPF antibodies are explicitly directed against the mature N-terminal extracellular expressed domain (mature form of Dsg1, and not the pre-Dsg1, unmature form) [7]. Dr. Morini, who was part of the TEPF original study [3], made only one comment on this matter, calling the disorder "Tunisian pemphigus." Neither Dr. Souissi nor Dr. Jomaa published further on TEPF. Later, in 1999, Dr. Pascal (an expert on ABDs) and colleagues examined Tunisian samples from 30 patients supposedly with TEPF using IB and immune electron microcopy (IEM), plus six with PV [8]. Overall, 7/30 TEPF sera were classified as PF (they bound to the 160 kDa/Dsg1 by IB; 2/6 PV sera bound to the 130 kDa Dsg3). IB and IEM showed that 24/30 PF sera contained IgG1, IgG3, or IgG4 antibodies binding to a 185-kDa polypeptide localized on the desmosomal plaque [8]. The multiple publications by HM, OA, AM and their coworkers are clearly in contrast with others (which are referral centers for dermatological diseases) [8]. In 2011 [9], the presence of linear IgA bullous dermatosis (LAD) was described in Tunisian children [9]. Also in 2011, a larger study focusing on the incidence of ABD cases seen during an 11-year period (1997–2007) reported 174 patients, (16.3 cases/year) with pemphigus, the most common ABD (53%); the majority were PV (61%) and 36% PF, followed by bullous pemphigoid (BP) in 41 patients (mostly younger males with occasional elderly patients) [9], PG in 18, LAD in 11, dermatitis herpetiformis in nine patients, and CP and epidermolysis bullosa acquisita in two patients and one patient, respectively. They a1so reported single cases of pemphigus herpetiformis, paraneoplastic pemphigus, and IgG/IgA pemphigus [9]. Of 174 patients, 110 were female (63%) and 64 male (37%), with a female-to-male ratio of 1:7 [9]. Pemphigus vegetans was observed in 10 patients, representing 17.8% of the PV group. [9]. Epidemiologically noteworthy differences between SAPF and TEPF include the following.

a. Geographic: SAPF develops in low-income areas of the South American Amazonian humid areas near rivers and within the flight range of hematophagous insects [1-4, 8, 10]. In contrast, TEPF occurs in rural areas with dry coasts in central Tunisia.
b. Affected age groups: SAPF mostly affects children, adolescents, and young adults (except in El Bagre-EPF, mostly affecting males older than 25) [1]. TEPF seems to affect young women (reports varied) [1-3, 9].
c. The presence of familial cases: well-documented in SAPF [1, 10], although there is only one report in TEPF [11].
d. In TEPF, clusters of cases occur in olive fields, Turkish baths, in bovine workers, and with the use of traditional cosmetics [12]. SAPF occurs in association with bites from hematophagous insects, proximity to rivers and creeks, deforestation, and road construction [1, 10].
e. Additionally, female/male population demographics are clearly different in SAPF compared with the areas of "endemicity" in TEPF, where females are more common than males [13].

For all the above reasons, we respectfully question the endemicity of TEPF. Furthermore, we invite the above three TEPF authors (HM, OA, AM) to further document field studies, including addressing infectious factors, and to answer the above questions regarding TEPF.

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