Dear Editor,

Lepra reactions are the immune reactions of leprosy. They can be divided into type 1, type 2 (erythema nodosum leprosy [ENL]), and type 3 reactions (Lucio phenomenon). The typical clinical characteristics of ENL are crops of tender and erythematous papuloplaques accompanied by constitutional symptoms. Here, we reported a case of ENL with generalized eruptions studded with pustules that was misdiagnosed as antiphospholipid syndrome (APS) due to the presence of immunoglobulin (Ig)M isotypes of antiphospholipid (aPl) antibodies.

A 24-year-old Indonesian woman presented with painful eruptions on the trunk and limbs for 5 months. Four years ago, she experienced her first spontaneous abortion. Six months later, when she was pregnant again, asymptomatic erythematous papuloplaques developed on her calves, which subsided partially after delivery. APS was suspected after her second spontaneous abortion, following the detection of IgM isotypes for both anti-cardiolipin (aCL antibody; 13 U/mL) and anti-beta-2 glycoprotein antibodies (anti-b2GP1 antibody; 338 U/mL). Prednisolone (10 mg daily), aspirin (100 mg daily), and hydroxychloroquine (100 mg twice a day) were prescribed. She had no pregnancy morbidity, but experienced a gradual onset of numerous tender erythematous papuloplaques and nodules with pustules on her trunk and four limbs (Figure 1A–C), accompanied by fever, chills, and malaise 6 months after the regular treatments for suspicious APS. Therefore, the treatments were discontinued. Laboratory evaluation revealed leukocytosis (13,600/uL) with prominent neutrophilia (78.4%) and high CRP (184.3 mg/dL). The rapid plasma regain was negative, and histopathology of the pustular lesion showed granulomatous inflammation with massive intra-epidermal and intradermal neutrophil infiltrates with foamy macrophages containing globi (Figures 2A and 2B). Intradermal nerve bundles were also involved (Figure 2C), and numerous bacilli were found by Fite staining, but not by ordinary acid-fast staining (Figure 2D). Lepromatous leprosy was diagnosed. One month after the initiation of multidrug therapy (MDT) with thalidomide, prednisolone, dapsone, clofazimine, and rifampicin, serology revealed that the patient was negative for aPL antibodies. Her skin lesions resolved with residual postinflammation hyperpigmentation at the end of MDT for 1 year.

ENL is an inflammatory condition of leprosy that most commonly occurs in patients with a high bacterial index or after starting MDT and other highly bactericidal drugs, including ofloxacin. None of the drugs used by the presenting case for the suspicious aPL syndrome had been reported to induce ENL. In fact, steroids were one of the elements included in ENL treatments.

Constitutional symptoms, including fever and malaise, are common. Neutrophils are the signature cells, with clinical presentation potentially resembling erythema nodosum, showing crops of painful papulonodules. However, pustular lesions have rarely been reported. Dave et al first reported one case of ENL with multiple pustules after switching from World Health Organization (WHO)-
MDT to ofloxacin-aided MDT. Histopathology revealed intradermal granulomata with a prominent neutrophilic infiltrate, which encroached into the epidermis to form an abscess. Nine years later, Adhe et al. analyzed the clinical and histopathologic presentation of 64 leprosy cases, reporting that three of 42 patients with type 2 reactions presented clinically with pustules and lesions showing intra-epidermal neutrophils pathologically. The authors concluded that the dense collection of neutrophils in the epidermis and dermis was probably responsible for the clinical pustules in ENL lesions. In 2014, Ghorpade reported another case of ENL with generalized pustules after treatment with WHO multibacillary-MDT for 3 months. Histology of a biopsy from one pustular lesion showed a prominent inflammatory infiltrate with numerous neutrophils and foamy cells in the dermis. Furthermore, the neutrophilic infiltrate extended into the perforated epidermis to form subcorneal pustules. It was suspected that inflammatory damage may cause the release of cytokines, damaging the basement membrane and dermal collagen, and thereby inducing perforating channels. Pustular ENL is a rare manifestation that is possibly triggered by initiation of therapy, pregnancy, or parturition to induce the formation of immune complexes that release cytokines to damage normal dermal structures with the influx of neutrophils.

This case was suspected to have APS based on the presence of the IgM isotype of the b2GP1 antibody and the aCL antibody, although she did not meet the revised Sapporo classification criteria for APS due to inadequate clinical evidence of thrombosis. aPL antibodies were reportedly associated with leprosy. Sene et al. reported that the mean prevalence of aCL and anti-b2GP1 antibodies in lepromatous or borderline leprosy was ~43% and ~45%, respectively. Ribeiro et al. compared the frequency of antiphospholipid antibodies according to isotype distribution in healthy controls, leprosy patients, and a group of primary APS patients. Increased levels of aPL antibodies were observed in leprosy patients and the APS group. In contrast to APS, the predominant isotype in leprosy was IgM rather than IgG. One study reported 77 of 158 leprosy patients with positive aPL, with 31 of them maintaining high titers of IgM aPL antibodies 5 years later. However, two studies had failed to show the clinical or statistical evidence correlating the presence of aPL antibodies in leprosy to any thrombotic event. Whether the aPL antibodies in leprosy increase the risk of thrombosis needs further clarification. Therefore, the benefits of anticoagulants or antithrombotic agents were unclear. Leu247Val and Trp316Ser single-nucleotide polymorphisms were suspected to represent genetic risk factors for anti-b2GP1 antibody production in multibacillary leprosy patients. Baeza et al. discovered a positive correlation between anti-mycolic- non-bilayer arrangements and aCL antibodies in leprosy patients, suggesting that antibodies to non-bilayer lipid arrangements may represent the pathogenic mechanism in lepromatous leprosy.

In conclusion, the presence of aPL antibodies in leprosy, especially the IgM isotype, is not only a coincidence, but also represent a genetic predisposition and pathogenic process. Clinicians should bear in mind the possibility of pustular-eruption development in patients with ENL, and leprosy should be included in differential diagnosis in the presence of IgM isotype-aPL antibodies.

Kang-Ling Kuo, Chun-Bing Chen, Ming-Hui Chi
Department of Dermatology, Chang Gung Memorial Hospital, Keelung Branch, Keelung, Taiwan

Tseng-tong Kuo
Department of Pathology, Chang Gung Memorial Hospital, Taipei, Taiwan

* Corresponding author. Department of Pathology, Chang Gung Memorial Hospital, 199 Tun Hua North Road, Taipei 105, Taiwan.
E-mail address: ttkuo@cgmh.org.tw (T.T. Kuo).

References


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Figure 2 Histopathology is consistent with lepromatous leprosy. (A) Parakeratosis with neutrophilic infiltrates (hematoxylin and eosin stain; original magnification: 400×). (B) Massive infiltrate of neutrophils and presence of foamy macrophage with globs (hematoxylin and eosin stain; original magnification: 400×). (C) Neutrophils, lymphocytes, foamy macrophages, and globs aggregate around a nerve bundle (hematoxylin and eosin stain; original magnification: 400×). (D) Fite staining reveals the presence of numerous acid-fast bacilli in macrophages (Fite staining; original magnification: 400×).