

Autoimmune Progesterone Dermatitis Herpetiformis and the Gluten-Sensitive

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Description

The morphology of these lesions is variable and includes erythema multiforme, urticaria, eczematous patches, angioedema, papulopustular/papulovesicular lesions, stomatitis, folliculitis, Stevens-Johnson syndrome, vesiculobullous reactions, dermatitis herpetiformis-like rash, and mucosal lesions. The lesions can be localized or generalized, and are most commonly found on the face, but have also been reported on the body, hands, and mucosa of the oropharynx. Vulvovaginal APD has also been reported as well. Symptoms correlate with progesterone levels and occur during the luteal phase of the menstrual cycle and resolve 1-2 days after menstruation. The pathogenesis of APD is unknown. It may occur in women with a previous history of exogenous progesterone intake, suggesting that synthetic progesterone may induce a crossreaction against the endogenous hormone, or rarely with exposure to endogenous progesterone during menarche or pregnancy as an autoimmune reaction. The diagnosis is made with appropriate clinical history as well as confirmation with an intradermal skin test to progesterone, intramuscular and oral challenge with progesterone, or detection of circulating antibodies to progesterone. In many cases detection of antibodies to progesterone has been reported to be negative, and therefore this is not essential for making a diagnosis. The other criterion for diagnosing APD is prevention of progesterone-induced skin eruption by inhibiting ovulation. APD should be differentiated from recurrent eczemas. Differential diagnosis and treatment of recurrent eczema.

APD is caused by a reaction to the endogenous production of progesterone, and thus treatment modalities are generally based on drugs that suppress ovulation. Antihistamine therapy is usually unsuccessful and high doses of steroids are needed to suppress symptoms. At present, the first-line therapy is COC. Other medical options are GnRH analogs, tamoxifen, danazol, and conjugated estrogens. Because of the adverse side effects of these drugs, long-term use is limited. For cases that are unresponsive to medical treatment, bilateral oophorectomy is recommended; however, this is only for those who no longer desire fertility. In some patients, the disorder completely resolves spontaneously. Other therapeutic agents, such as azathioprine, hydroxychloroquine, dapsone, or cyclosporine, have also been described in the literature. However, their use is limited because they appear ineffective or have significant side

effects. In our cases, treatment with the GnRH analog and COC pills was effective. The long-term use of GnRH analogs induces some side effects, and therefore we prescribed the drug for only 3 months. Symptoms disappeared with the treatment in all the cases. Two months after cessation of therapy, the patients still had no skin lesions.

Unique Clinical Presentation of APD

Atopic dermatitis (AD) is a chronic relapsing systemic skin disorder characterized by an intense pruritus and the development of eczematous lesions to particular sites. It usually begins before one year of age, and fades after childhood in 80–90% of the cases. Adult-onset has been observed as well. The adult form of the disease is more severe, and associated with a high morbidity. It is the most common skin condition showing up to 20% lifetime prevalence in some countries. AD has a substantial effect on the quality of life, and is associated with several comorbidities such as an increased IgE-dependent allergic sensitization (“the atopic march”), increased infection rates, mental disorders, and the development of some autoimmune diseases. AD shows a strong genetic predisposition associated with epidermal barrier dysfunction and type 2 immune responses. The severity of the disease has been associated with allergen sensitization and IgE levels as well as with the prevalence of autoreactive IgE. Dupilumab, which is a monoclonal antibody targeting the IL-4R α chain, is approved to treat moderate to severe symptoms in children from six years old to adults, and is currently evaluated in toddlers from six months to five years old. Dupilumab efficiency supports how critical IL-4 and/or IL-13 are for the development of AD. However, AD pathogenesis is complex and seem to result from an interplay between an altered epidermal function, the microbiota, allergen sensitization, and the immune system.

Iatrogenic Autoimmune Progesterone

Epidermal inflammation and barrier dysfunction are associated with an altered lipid composition, an increased pH, and a reduced secretion of antimicrobial peptides (AMP) in the skin of AD patients. These factors are important for the homeostasis of the skin commensal microbiome. In AD, a decreased diversity of the skin microbiome has been observed at lesional sites. As antibiotic treatment, or a germ-free

environment, promotes IgE secretion, a peripheral basophilia, and the development of allergic responses, commensals are considered to protect from atopy. A dysbiosis allows the expansion of the opportunistic commensal *Staphylococcus aureus* over other species. Other members of the *Staphylococcus* sp. have been shown to secrete specific AMPs to keep *S. aureus* in check in healthy individuals. *S. aureus* colonization is frequent in AD patients and is associated with the severity of the disease both in adults and children. It could be a secondary cause of AD, and of the chronification of the disease since dysbiosis and *S. aureus* colonization occur after the first AD symptoms in infants. Indeed, *S. aureus* and other bacteria found on the skin of AD patients (such as *Roseomonas mucosa*) induce a skin barrier dysfunction and an IgE secretion after inoculation on the skin of rodent AD models, while a healthy microbiome is protective. Furthermore, *S. aureus* products alone can induce an epidermal barrier dysfunction and skin inflammation, the development of specific IgE, skin mast cell activation, and eosinophils and basophils recruitment, which supports the fact

that *S. aureus* colonization is an integrant part of the AD pathogenesis.

Most patients have a reaction to the intradermal injection test with an aqueous suspension or aqueous alcohol solution of progesterone. Positive skin test results with progesterone have shown immediate reactions, usually urticarial, within 30 min, delayed reactions, with erythema and induration peaking at 24–48 h, and reactions with features of both the immediate and delayed types. Other helpful investigations include indirect basophil degranulation test, indirect immunofluorescence for IgG, which binds rat corpus luteum, and provocative testing with intramuscular or oral progesterone (10–20 mg and 10 mg, respectively) in the first half of the menstrual cycle. In the presence of negative progesterone testing, estrogen dermatitis should be considered and intradermal testing with estrone (0.1 ml at 1 mg/ml) should be carried out. A positive reaction may be seen immediately or after several hours, and should persist for more than 24 hours.