Autoimmune Progesterone Dermatitis

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Objectives
- At the end of this lecture the participant will be able to:
  - Define autoimmune progesterone dermatitis and differentiate it from other forms of allergic or non-allergic dermatitis
  - Discuss the proposed immunopathogenesis of autoimmune progesterone dermatitis
  - Determine best approach to evaluate and treat patients with autoimmune progesterone dermatitis

Conflicts of interest
- Novartis - research
- Dyax, Viropharma, CSL Behring, Shire - research, consulting and speaking
- Pharmaing - research
- Journal of Asthma - Editor in Chief

Autoimmune Progesterone Dermatitis (APD):
Definition
- A spectrum of dermatologic presentations with or without systemic anaphylaxis
- Cyclic in nature
- Triggered during the luteal phase of menstruation

Prevalence
- Unknown
- Rare
  - 71 References in Pub Med
  - all reports are cases or case series
- First case of cyclic urticaria related to menses reported by Geber et.al. 1921
- First case of pre-menstrual cyclic urticaria reported by Guy et.al. 1951

Menstrual Cycle

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Progesterone Function and Structure

- Progesterone is the principal hormone of the corpus luteum.
  - Also found in the ovaries, placenta, adrenals and peripheral veins.
- Derived from cholesterol: its major metabolite is pregnenolone which is made in the liver.
- Dramatic rise in progesterone 24-48 hours prior to ovulation.
- Prepares the uterus for implantation of the ovum.
- Synthetic progesterones are made by adding or modifying side chains.
  - Most derived from 19-nortestosterone, 17a-hydroxyprogesterone or acetate progestin.

Immunopathogenesis

- Type I mediated
  - Immediate skin testing to progesterone
- Type II mediated
  - Basophil or mast cell activation (positive and negative responses)
- Type III mediated (immune complex)
  - Circulating immunoglobulin directed against 17-hydroxyprogesterone was found to have an IgG fraction containing a progesterin binding component with high affinity for 17-hydroxyprogesterone (Cheesman K., et al., 1982; 20:50-51).
- Treatment with corticosteroids for 2 months reduced the IgG concentration to normal
- Type IV mediated
  - Delayed skin test responses

Immunopathogenesis Continued

- Paradoxically, evidence for an autoimmune mechanism is scant.

Potential Mechanisms for Sensitization

- Possible that synthetic oral contraceptives or hormonal supplements are dissimilar enough to induce antibody responses in susceptible individuals.
  - Not all women with APD have had exposure to exogenous progesterone agents.
  - Steroid cross sensitization (Schoenmakers et al. Contact dermatitis 1992; 26:159-162).
  - Rise in endogenous progesterone levels to a critical level where the susceptible female reacts.

Proposed Immunopathogenesis of Progesterone Sensitive Anaphylaxis

- Anaphylactoid reactions
- Premenstrual
- Catamenial

Presentations of Autoimmune Progesterone Dermatitis

Anaphylactoid reactions
- Dermatologic/mucosal reactions
- Eczema
- Erythema multiforme
- Stephens-Johnson syndrome
- Fixed drug eruptions
- Foliculitis
- Vesiculobullous reactions
- Urticaria
- Urticaria and angioedema

*More than one of these presentations can occur together.*
Catamenial Anaphylaxis
- Varies from APD by timing of symptoms
  - Begins at the start of the menstrual flow
  - Continues throughout the menstrual flow
  - Symptoms stop when menstrual flow stops
- Endometrial derived mediators such as PGF2α may leak into the blood causing these reactions
  - Indomethacin has helped in some cases
- Skin and intramuscular hormone tests are usually negative
- Symptoms resolve with BSO

Sex Hormones and Urticaria
- Estrogens are considered enhancers of humoral immunity
- Progesterone and androgens are natural immune suppressors
- Altered sex hormones can lead to immune deregulation and genesis of autoimmunity
- Modulate mast cell activity
  - Estrogen enhances histamine release
  - Progesterone and testosterone inhibit mast cell activation
- Can have progesterone-induced or progesterone-responsive urticaria
- Estrogen induced urticaria or dermatitis
  - Daily and unremitting; peaks pre-menstrually

Patterns of Symptomatology
- Symptoms begin 3-10 days in the premenstrual phase and end 1-2 days into the menstrual flow
  - Symptoms can persist throughout the menstrual cycle or occur randomly during the cycle
- Onset of APD is variable:
  - Can begin before pregnancy and women during pregnancy; has been reported to result in spontaneous abortions in some cases
  - Can occur during pregnancy with or without later premenstrual recurrences
  - Can occur post-partum as the menstrual cycle is regularizing

Case Study #1
- 29 year old presents with 6 months of pruritic vesicular eruptions on her palms and soles which are very painful and disabling
- Treatment with over the counter topical corticosteroids, antifungals and antihistamines not effective
- Eruptions were cyclic in nature occurring just prior to her menses and clearing without treatment as the menses began
- Attacks were getting progressively worse
- Has been on oral contraceptives in the past

APD: Dermatologic Manifestations

Case Study #1 Continued
- Work-up:
  - Titration intra-cutaneous skin testing to progesterone using Candida as a control in conjunction with positive histamine and negative saline controls
  - Skin testing of a nurse in the clinic was also performed as a negative control
  - Immediate and delayed reactions to the skin test after 20 minutes and 48 hours, respectively were observed for the patient but not the nurse
Case Study #1

- Patient started on conjugated estrogens (Premarin 1.25mg/day)
  - Referred to gynecologist for breast and pelvic exams
- Follow up demonstrated no lesions during her entire menstrual cycle

Case Study #2

- 26 year old G2P2Ab0 female presents with relapsing itchy skin rash on her lower extremities
- Initial diagnosis insect bite
- Subsequently diagnosed as pityriasis lichenoides chronica and then erythema multiforme
- Unresponsive to topical corticosteroids and UVB phototherapy

Case Study #2 Continued

- Several years later she re-presented with a marked flare up of the skin eruption 2 days post-partum
- She was asymptomatic throughout pregnancy
- She has been given a depot progesterone contraception injection resulted in severe pruritic bullous lesions on the limbs and trunk which took several months to flare
- Further questioning revealed the eruptions were always worse in the 2 weeks preceding menses
- A biopsy of the lesion was taken

Case Study #2: Skin Biopsy of Pruritic Bullous Lesion

- Figure 1: Histological examination of skin biopsy showing典型 change consistent with the diagnosis of pityriasis lichenoides chronica
Case Study #2

- Prick testing to progesterone in ethyl oleate 50mg/ml diluted with sterile saline to 1mg/ml was negative.
- Intracutaneous testing with 0.1ml of 1mg/ml solution was result in a 3mm papule at 15 minutes; unclear whether significant reaction or irritant
- Skin test papule resolved after 24 hours but she had a severe flare-up of the skin eruption lasting several weeks
- During her fourth pregnancy the rash cleared entirely but recurred 10 days post-partum
- Buserelin (a gonadotropin releasing antagonist) nasal spray 150ug one spray to each nostril tid resulted in rapid resolution of the rash
- Four months after discontinuation of the buserelin, the rash reoccurred

Internal Medicine

Case Study #2

- Learning points
  - Diagnosis of APD can be difficult to make
  - Patients don’t always offer a history of peri-menstrual exacerbations
  - Physicians must always include in their history questions regarding temporal relationship of rashes to menses
  - The clinical presentation is very variable
  - Intracutaneous testing with progesterone is very challenging

Internal Medicine

Clinical Presentation and Histology Is Very Variable

- Erythematous scaly papules on the face
- An inflammatory infiltration with a focus of multinucleated giant cells is observed under an epidermis showing irregular atrophy (80 x 200)

Internal Medicine

APD Misdiagnosed As Allergic Contact Dermatitis

Internal Medicine

Case Study #3

APD Presenting As Cyclic Urticaria/Angioedema, Dermatitis and Anaphylaxis

- 26 year old female with 6 month history of urticaria vulgaris and polycyclic erythematous disease presents with facial angioedema, bronchoconstriction and hypotension within 2 days of starting Ortho-Novum 777 (norethindrone + ethinyl estradiol) prescribed to prevent the recurrence of rupturing cysts
  - The OC was discontinued for 1 week and restarted 2 weeks later resulting in a similar reaction
  - Three subsequent reactions over a 2 month period each with increasing intensity and duration
- History revealed the occurrence of premenstrual urticaria with angioedema
- Skin prick testing to progesterone, 5α-pregnandiol, estradiol, norethindrone and ortho-Novum 777 were negative
- Leukocyte histamine release demonstrated positive response to 5α-pregnandiol which decreased four months after discontinuing OC
- Condition completely resolved after several years of treatment with nafarelin

Internal Medicine

Histopathology of a Petechial Lesion Associated With Autoimmune Progesterone Dermatitis (APD)

*Note perivascular accumulation of lymphocytes in the dermis (black arrows). This finding is nonspecific but is consistent with either a drug reaction or APD.

Internal Medicine
Inhibition Experiments 3 Months After Stopping OCPs

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<th>Concentration (ng/mL)</th>
<th>Progesterone</th>
<th>Alone (control)</th>
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<td>0.03</td>
<td>91</td>
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<td>84</td>
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Interaction Between Progesterone And IgE Membrane

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Diagnosis of APD

- History
  - Cyclical skin lesions related to the menstrual cycle
  - Onset usually in adult life after menarche, but can occur or worsen during pregnancy
  - Symptoms start 3-10 days before premenstrual phase and cease 1-2 days into the menses

- Physical examination
  - Presentation of skin rash in different morphological forms
  - In vivo or in vitro testing:
    - A positive progesterone skin test?
    - A positive oral/intramuscular challenge to progesterone?
    - Demonstration of a circulating antibody to progesterone?
    - Basophil degranulation tests?

Diagnostic Testing

- **ELISA**
  - Optimization of these assays requires that a conjugated preparation of progesterone rather than a progesterone hapten be used
- **Skin testing** using aqueous preparations of progesterone preferred
  - Positive skin tests typically occur within 30 minutes consistent with an early phase response (Type I immune response)
  - Delayed reactions with erythema and induration peak at 24 and 48 hours consistent with late-phase response (Type IV immune response)
  - More recent studies using progesterone skin testing to diagnose APD have used high progesterone concentrations and were performed without appropriate solvent controls or did not establish subcutaneous levels in normal controls

Conclusions: Skin testing and immunoassays are not standardized and therefore not reliable as predictors for progesterone induced hypersensitivity

Use Of An Autologous Serum Skin Test For Diagnosis Of APD

A
Other Diagnostic Tests

- Passive transfer of serum was performed from a patient with APD to a naïve patient
  - A wheal and flare response was observed at the site injected with serum after challenge
  - Provocation with IM progesterone or oral progesterone challenge can induce a cutaneous and/or systemic anaphylactic reaction
  - Could result in severe cutaneous or systemic reaction so should be done with caution
  - Degranulation of rabbit basophils (indirect basophil degranulation test) or morphologic alteration of rat mast cells in the present of the patient’s serum and progesterone
- Not standardized and low positive predictive value
- Indirect immunofluorescence studies have demonstrated progesterone

Alas in some patients

Algorithmic Approach To Evaluate Progesterone Induced Anaphylaxis

- Female patient with suspected anaphylaxis
- Progesterone challenge
- Positive
- Treatment
- Negatives
- Other evaluation
- Food
- Hardware
- Medications
- Otophobic

Treatment Options For APD

- Oral Contraceptives (OCs): Usually used in initial therapy
  - Not effective in long-term therapy
  - May cause other endometrial abnormalities

- Antihistamines: Low efficacy in the progesterone vapume.
  - Oral: Histamine 2 receptor blockers
  - Nasal: Antihistamines

- Glucocorticoids: Effective on oral progesterone
  - May be used to control severe APD

- Tamsulosin: Can control symptoms of prostatic hyperplasia

- Bosentan: Can control symptoms of prostatic hyperplasia

APD Treated With Oophorectomy

- 42 year-old female with recurrent anaphylaxis to progesterone. Attempted Oophorectomy, 1.5 months post-op
  - No recurrence of attacks

APD: Painful Papules That Resolved Spontaneously

- 29 year-old female with recurrent papules for 6 months
  - Lesions began one week post-op, side of the incision

- Several months later the development intermittent outbreaks of painful papules, papules 1–2 cm in diameter

- Several months after resolution of papules, papules 1–2 cm in diameter

- Rapidly involved right papular lemon, red papular lesions

- Histology: Silvery granulomatous inflammatory foci of lymphoid/epithelioid cells

- Intracutaneous testing to 100 µg of progesterone solution (10 µg/ml) at 48 hours after onset of symptoms

- Positively tested at 48 hours

- Patient declined treatment with oral progesterone

- Patient developed symptoms of pain and tenderness in abdomen

Conclusions

- APD has a distinct onset during the luteal phase before menses
  - Can manifest as many dermatologic conditions with or without anaphylaxis

- Clinical presentation is quite variable
  - Skin or without anaphylaxis

- Histology is often non-specific

- Diagnostic testing has limitations: unmet need

- Treatment to suppress gonadotropin releasing hormone or having a TAH with BSO are most effective