

Recurrent Vulvovaginal Candidiasis – Allergy or Immune Deficiency?

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Key Words

Candida · Allergy · Vulvovaginal · Immunodeficiency

Recurrent vulvovaginal candidiasis (RVVC) is a common and distressing clinical disorder affecting 3–5% of women, variably considered to be a hypersensitivity or an immune deficiency disorder. The pathogenesis remains confused due to inconsistent results from often poorly constructed studies, with a failure to confirm specific IgE antibody, or depressed T lymphocyte function [1]. A positive outcome of immunotherapy has been used to support both hypotheses. No previous study, however, has taken account of the profound immunomodulatory effects of sex hormones and glucocorticoids on the regulation of mucosal immunity in the female reproductive tract. The aim of this study was to re-examine the question of ‘allergy or immune deficiency’ within the context of the variable hormonal environment of the female reproductive tract, by contrasting results obtained in the follicular and luteal phases of the menstrual cycle.

Thus, 28 premenstrual women with RVVC and 25 controls were studied, noting cycle phase. No significant difference in usage of oral contraceptives was recorded. Only 1 subject gave a positive immediate hypersensitivity to injected antigen (a control subject). No difference was noted in incidence in delayed hypersensitivity when tested with 1,000 PNU of *Candida albicans* antigen. The level of the T

lymphocyte proliferative response to *Candida* antigen (1.6 and 0.4 µg/ml) without reference to cycle was less in RVVC ($p < 0.003$ and < 0.03 , respectively), though no difference was noted with PPD and PHA. IFN- γ production in these cultures was less in RVVC with both *Candida* ($p < 0.05$) and PPD ($p < 0.03$) stimulation; IL-4 production was not detected in either group. When results were controlled for phase, T cells from RVVC obtained in the follicular phase gave less proliferation ($p < 0.008$) and IFN- γ ($p < 0.01$), only with stimulation with *Candida* antigen. There was no significant difference in proliferation or cytokine production between phases in the control group.

While a more broad-based deficiency of circulating antigen-reactive TH₁ cells was detected, the major difference between groups was a profound reduction in *Candida*-specific TH₁ cells. No evidence of immediate hypersensitivity to *Candida* antigen was detected in RVVC. The consistent difference between results dictated by cycle phase (and presumably hormonal balance) accounts for the variability in uncontrolled published results of T lymphocyte defects in RVVC. The presence of a defect restricted to the follicular phase of the menstrual cycle in RCCV patients suggests the primary defect is one of pool size rather than a suppressive effect on TH₁ cells. These TH₁ cells are likely to be derived from the mucosa-associated lymphoid tissue (in particular the Peyer’s patch) with their target the mucosa of the reproductive tract. Recruitment of Peyer’s patch-derived B lymphocytes into cervical mucosa is oestrogen-dependent [2]. A similar effect of oestrogen on T lymphocytes would ac-

count for the pool dynamics observed in this study. The similar level of cutaneous delayed hypersensitivity to *Candida* antigen in RVVC in both the follicular and luteal phase would be consistent with a selective effect of oestrogen on the mucosa of the reproductive tract.

It is concluded that RVVC is not an IgE-mediated hypersensitivity disorder, but rather a mucosal immune deficiency due to a reduction in the pool of mucosa-targeted TH₁ lymphocytes. Clinical manifestations appear in the reproductive system, which is the only region subject to phasic restriction of lymphocyte recruitment. Reduction of T lymphocyte recruitment below a critical level required to control *C. albicans* colonisation is likely to occur at times of low oestrogen, accounting for the premenstrual occurrence of clinical episodes. The more broad-based T lymphocyte defect is consistent with the clinical association with other disorders of immunoregulation. A logical approach to management would be to drive Peyer's patch production of antigen-specific mucosa-targeting TH₁ cells by oral immunisation.

References

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