Why common things are common: the tale of non-gonococcal urethritis

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Common things are common perhaps because they reflect common pathophysiological principles. Non-gonococcal urethritis (NGU) is a common problem. In 1998 over 520 000 episodes of NGU were reported from genitourinary medicine clinics in England.1 Systematic reviews on its pathogenesis and treatment are long overdue. In their absence it might be useful to list some of what we do know about the aetiology and associations of this common and enigmatic problem.

We know that 30–50% of men with NGU have a persistent inflammation,2 and that even after a course of currently recommended antibiotic therapy the inflammatory stimulus remains for several weeks (months?) in the urethra after chlamydial and non-chlamydial NGU.3 We know that chlamydia is isolated from approximately half of patients presenting with their first episode of NGU but less frequently afterwards4 and that the proportion with chlamydia negative NGU have apparently increased over the past few years.5 The evidence that some cases of chlamydia negative urethritis are associated with Mycoplasma genitalium is now difficult to refute.6 A similar role for Ureaplasma urealyticum remains debatable,7 and other organisms may account for a further small percentage of other cases.8

We know from three separate studies that male contacts of women with bacterial vaginosis (BV) have NGU.9-11 We also know that in women BV is associated with plasma cell endometritis,12 13 premature delivery of the fetus,14 and increased proinflammatory cytokines in cervical secretions.15 Moreover, the presence of anaerobes may potentiate damage to the fallopian tubes in pelvic inflammatory disease.16

We know that men with urethritis of whatever cause (chlamydia, non-chlamydia, or gonococcal) have a greater in vitro lymphocyte proliferative response to chlamydia than controls without urethritis,17 suggesting that in the presence of mucosal inflammation memory T cells may be activated through as yet unknown mechanisms with cross reactivity to chlamydial antigens. We are not too surprised by this since we have long known that sterile urethritis (and conjunctivitis) follows infection by a variety of seemingly unrelated micro-organisms at other mucosal sites.18

We know that chlamydia causes its damage predominantly through immunological mechanisms19 with a role for the ubiquitous 60 kD heat shock protein (hsp 60) family suggested20 and refuted.21 We also know that in humans untreated chlamydia can be cleared from tissues.22 Finally, although we do have a good human model for studying chlamydial induced tissue damage in the eye, important and lasting genital tissue damage occurs in the female fallopian tube—a relatively inaccessible organ. Hence, most of our information on genital damage by chlamydia comes from animals—with the guinea pig model being the most useful.23 Yet data derived from animal models may not be applicable to humans.

It seems reasonable to suggest that NGU might prove a useful model to study not only the mechanisms for the chlamydial inflammatory process but also the mucosal inflammatory response in general. The organ is relatively accessible, and when inflamed its secretions contain sufficient lymphocytes24 and macrophages25 to study phenotype, cell surface markers, and perhaps cytokine profiles. The lymphocytes are also viable and can be grown in culture from men with urethritis and from controls (without urethritis)26 allowing in vitro studies of lymphocyte responses to antigenic stimuli to be performed.

I would propose a hypothesis that at least some cases of non-chlamydial NGU are caused by mechanisms that may involve immune stimulation by one or more components of the vaginal microflora in BV. This hypothesis is open to testing and might provide clues to the immunological damage caused by chlamydia and other organisms in the female genital tract. NGU combines a common condition with an accessible organ. I am surprised so little attention is paid to it.


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