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Title: Interferon: the invisible link between COVID-19 and BCGitis female protection?

Letter to the Editor

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Interferons: the invisible link in the physiopathology of COVID-19 and BCGitis?

Abstract

Gender distribution of COVID-19 severity is unbalanced. Higher mortality rates are reported in men (60-70% deaths in men).

We reviewed 243 BCGitis cases reported in the literature. The M/F ratio in BCGitis is 49:1 and is not fully explained by the higher incidence of bladder cancer among males, neither by anatomical reasons. We discuss the M/F ratio in BCGitis in the light of immune system differences among different genders, with a focus on interferon response (higher in females).

Letter to the editor

Dear editor,

Facing the COVID-19 pandemic we were intrigued by the difference of incidence and disease severity between males and females (60-70% of deaths occurring in men). This disparity remains significant even after age stratification in all age groups (postmenopausal women vs age-matched men), suggesting a partially hormone-independent mechanism.

Coincidentally, during the last month we were reviewing the infectious complications of Bacillus Calmette-Guerin (BCG) bladder instillation. BCG is used for non-muscle

invasive bladder cancer (NMIBC) after standard surgical treatment: surprisingly, among 243 BCGitis cases reported in the literature, only 3 were female.

The higher number of BCGitis in men has been justified so far considering the worldwide M/F ratio for bladder cancer (3.5:1) [1]. In addition, for anatomical reasons, traumatic catheterization is more common in males, potentially providing a wider port of entry for systemic BCG dissemination [2]. However, these two issues are not strong enough to justify the overwhelming unbalanced gender ratio found in BCGitis (M/F 49:1).

BCG acts against NMIBC mainly by stimulating non specific immune response and a torrent of Th-1 cytokines, including IFN-γ [4]. IFN-γ plays a role against intracellular infection by pathogens such as *M. tuberculosis* and *M. bovis* [3]. A reduced level of IFN-γ has been observed in men, both prior than after surgery [5].

BCG used as a tubercular vaccine is generally administered to young patients and induced IgG and IFNγ generally diminish with age if a booster dose is not given [3]. On the contrary, BCG used as immune therapy for non muscle invasive bladder cancer is administered to adult elderly patients, and according to the schedule of the treatment the instillations are repeated periodically resulting in a more sustained immune response.

Constitutional differences in male and female immune systems have long been described. The underlying biological mechanisms are not fully understood. They are supposed to result from steroid hormones secreted by gonads and/or different cytokines response.

With regard to steroid hormones, *in vivo* studies [6–8] reported a protective role of estrogens against respiratory infections. For instance, high levels of 17β-estradiol are related to better clinical outcomes in mice infected with Influenza A [6].

Inflammatory immune responses, as well as the number and activity of innate immune cells, are higher in females. Human studies demonstrated that plasmacytoid dendritic cells of female exhibit increased expression of interferon (IFN)-α, following toll-like receptor (TLR)-7 stimulation [9]. Furthermore, TLR associated genes that activate IFN pathway are significantly upregulated in female after vaccinations [10].

To be kept in mind, both *in vitro* and *in vivo* studies demonstrated the efficient role of IFNs against SARS-CoV [11,12].

In light of the above, we hypothesize that major susceptibility of male gender to COVID-19 and to BCG infection might share a common interferon-centred physiopathological basis that needs to be deeply investigated (Fig. 1).

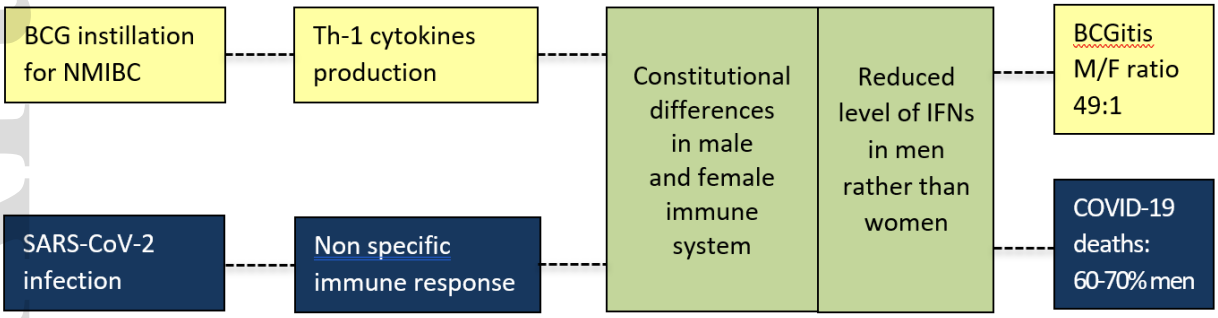

Figure 1. Schematic diagram of the hypothesized common mechanism for gender disparity in BCGitis and COVID-19.

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