Extra Pulmonary TB

Although the lung in pulmonary TB is the most common site for Mycobacterium tuberculosis infections, dissemination of mycobacteria from a primary lung infection to other organs can occur when alveolar macrophages become infected with bacteria following phagocytosis. Mycobacteria have evolved adaptive mechanisms to evade destruction in macrophages and can survive in vacuoles. Migration of activated macrophages to secondary lymphoid tissue for antigen presentation to CD4+ helper T cells can facilitate spread of mycobacteria to other tissues such as the pleura, liver, lymph nodes, spleen, gut, bone marrow, brain and the urogenital tract. In immunocompetent hosts, mycobacterial dissemination to other tissues is usually controlled. However, due to the testis being an immune privileged site, it is likely that intracellular mycobacteria may have a survival advantage in this tissue.

In the related case study, our patient was previously infected with pulmonary TB, which was treated but possibly sub-optimally. His history was incomplete and opened questions to whether previous treatment was curative. It is possible that our patient was latently infected with TB and we assume that reactivated mycobacteria disseminated to the testes.

Pathophysiology

We outline below the main points about the pathology of extra-pulmonary testicular TB. Following infection of the testicular macrophages located in the interstitial space of the testis with
mycobacteria, the infected cells promote an immune response which results in the formation of a granuloma. This serves to sequester infected cells at the centre surrounded by predominantly CD4+ helper T cells. The infected macrophages can fuse to form foamy macrophage giant cells, which are thought to result from mycolic acid products released from infected cells. A sheath of collagen fibres produced by fibroblasts then surrounds the cells.

In the immune-privileged testis, Th1 immune responses are suppressed and it is thought that this suppression promotes mycobacterial survival because CD8+ T cells which are required to kill intracellular bacteria are not recruited. Th1 helper T cells provide essential cytokine activation signals to CD8+ cytotoxic T cells. The build up of recruited macrophages and T cells is thought to result in progressive testicular swelling and disruption of sperm production. As noted in our patient there was development of gradual testicular enlargement. Whether this resulted in infertility is not known, as the patient originally became infected with TB after having children.

**Immune privileged sites**

Apart from the testis, other immune privileged sites include the eye, brain and placenta and are so-called because of mechanisms of immune tolerance that operate to protect the tissues from immune-mediated damage. The following discussion we will focus on the testis.

**Blood-testis barrier**

In the testis at the onset of puberty, new antigens are expressed during spermatogenesis and risk provoking an immune response because their development occurs after immune tolerance has been established. Mechanisms must therefore be in place to protect them. This is achieved in part
by segregation of antigens in the seminiferous tubules from immune cells in the interstitial space by a layer of Sertoli cells connected by impermeable tight junctions which form a blood-testis barrier. However this physical barrier cannot account for all immune suppression in the testis because it is incomplete in the region called the rete testis, thus allowing for some exposure to antigen. Thus other forms of immune suppression mechanisms are in place.

Immune evasion

The primary goal of immune suppressive mechanisms in the male testis is to circumvent destruction of testicular cells or disruption of sperm production. Mechanisms known to operate in the protection of sperm cells from attack by cytotoxic immune cells such as natural killer cells and CD8+ cytotoxic T cells involve lack of expression of classical [simple_tooltip content='HLA']

HLA is Human Leukocyte Antigen which is part of the Major Histocompatibility Complex (MHC) which are a set of genes that, in part, direct T cell mediated immunity. There are two classes of MHC that are involved with directing T cell immunity: class I present peptides to CD8+ T cells and class II present peptides to CD4+ T cells. The peptides presented by either classes of MHC are derived from either “self” (own proteins) or from invading pathogens. HLA are one of the most polymorphic genes, meaning that many variants exist and the pairs of inherited genes create a unique set of immune responses in each person. HLA are known to be associated with different diseases and with transplantation compatibility/ incompatibility.

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] HLA[ E and G receptors. Sertoli cells also express cell surface ligands FasL and PD-L1 which promote apoptosis in activated T cells following engagement with their respective Fas and PD-1 receptors. In addition, Sertoli cells which are support cells, inhibit T cell proliferation by mediating depletion of tryptophan with IDO (indolamine 2,3-dioxygenase). Lack of tryptophan inhibits protein synthesis in activated T cells.

**Immune deviation**

In the testis, cytokine production following activation of antigen presenting cells such as macrophages is skewed towards a "Th2-like" immunoregulatory /immunosuppressive profile. Activated macrophages produce IL-10 and very little IL-12. IL-12 is the cytokine required to stimulate T-cells to differentiate into pro-inflammatory Th1 IFN-g and **IL-2** secreting cells. Th1 helper T cells necessary to provide activation signals to CD8+ cytotoxic T cells. IL-10 is also a potent inhibitor of Th1 helper T cells and antagonize the production of IFN-g production. Additionally, Sertoli cells secrete Activin A that inhibits activated macrophages from producing pro-inflammatory cytokines such as **IL-6** and TNF-a. Sertoli cells also secrete TGF-b that inhibits activated T cells from differentiating into cells with a Th1 phenotype. Finally, Leydig cells produce large quantities of testosterone which also has immunosuppressive properties. Due to the local production of testosterone in the testis, testosterone levels can be up to 10 fold greater than observed on blood.