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Anticytokine autoantibodies – association with infectious manifestations

Background

Autoantibodies (AAbs) to cytokines are increasingly being recognized as potential contributors to acquired immune deficiency, immune dysregulation and autoimmunity [1, 2]. These AAbs may mediate a variety of infectious manifestations depending on the cytokine they target, although definite causality has not been established in all cases. Examples of cytokines that are associated with infectious manifestations are interferon gamma (IFNγ), interleukin 17 (IL-17) and granulocyte macrophage colony stimulating factor (GM-CSF), among others. Anti-cytokine AAbs are not always associated with disease and they can be detected in healthy individuals [3]. However, the presence of high titer, neutralizing anti-cytokine AAbs in the appropriate clinical context may be considered clinically significant.

Interferon gamma

IFNγ is one of the key cytokines involved in host defense against intracellular pathogens such as mycobacteria. The central role of IFNγ in generation of protective immunity to mycobacterial infections and infections with other intracellular organisms is highlighted by the fact that genetically inherited disorders of the IFNγ pathway, including IFNGR1, IFNGR2 and STAT1 lead to overwhelming infections with intracellular organisms of low pathogenicity such as the *Mycobacterium bovis* Bacille Calmette-Guérin (BCG)vaccine, or nontuberculous mycobacterial (NTM) species [4]. These infections manifest early in childhood. In adults, however, such infections are rare and are generally associated with an immune deficient state, such as HIV infection or immunosuppression following transplant.

In 2004, the first case of an acquired immune deficiency due to high titer, neutralizing AAbs to IFNγ was described [5]. This patient presented with extra-pulmonary, treatment refractory NTM infection. Since then numerous reports have documented the association of anti-IFNγ AAbs with intracellular infections in otherwise healthy, immune competent individuals [6-8]. Although extra-pulmonary, disseminated, NTM infections formed the majority of such cases, isolated NTM empyema and infections with *Salmonella typhi*, cytomegalovirus, *Toxoplasma gondii* and *Varicella zoster* [9, 10] have been reported as well.

Patients that present with this autoimmune phenomenon that may contribute to an immune deficient state are, in general, otherwise healthy and not obviously immune compromised. The majority of patients documented to date are of Southeast Asian origin, strongly suggesting an inherited predisposition to development of these AAbs. Indeed, anti-IFNγ AAbs have been shown to be strongly associated with HLA-DRB1*16:02 and HLA-DQB1*05-02 [7]. However, the recent identification of anti-IFNγ AAbs associated infections in non-Asian patients [10, 11] suggest that this phenomenon may be more wide spread and is perhaps influenced by other, as yet unidentified, genetic and/or environmental factors.

AAbs to IFNγ have been demonstrated by the ability of patient's plasma to inhibit phosphorylation of STAT1 in normal monocytes stimulated with IFNγ [12], as well as by binding studies to evaluate antibody titer. It is essential to demonstrate the functionality of these antibodies, since healthy individuals may show evidence of low titer anti-IFNγ AAbs with little to no neutralizing activity *in vitro*. Additionally, at least one patient has been identified by an initial indeterminate Quantiferon Gold In-tube result since the high titer, neutralizing anti- IFNγ AAbs in plasma interfere with the detection of IFNγ in mitogen-stimulated whole blood.

Interleukin-17

Chronic mucocutaneous candidiasis (CMC) is a clinical syndrome characterized by recurrent or persistent superficial skin, nail and mucosal infection with Candida organisms, usually *C. albicans* [13]. Patients with significantly impaired cellular immunity (HIV, primary T cell immune deficiency), or those on immunosuppressants or antibiotics are predisposed to mucosal candidiasis [13, 14].

Anti-IL-17 AAbs have been shown to be associated with CMC and have been noted in patients with APECED (Autoimmune Polyendocrinopathy, Candidiasis-Ectodermal Dystrophy) [15, 16]. While the presence of these AAbs may not provide a complete explanation for the susceptibility to CMC in these patients, it is also known that TH17 cells (CD4 T cells producing IL-17) are important for robust, protective immune responses against fungal infections. Thus, neutralizing anti-IL-17 AAbs may dampen protective IL-17 mediated responses, thereby increasing susceptibility to fungal infections.

Granulocyte Macrophage Colony Stimulating Factor

Granulocyte-macrophage colony-stimulating factor (GM-CSF) promotes the proliferation and maturation of neutrophils and macrophages. The critical role of GM-CSF in macrophage development and function is evident from studies conducted in GM-CSF deficient mice [17]. Alveolar macrophages in these mice were unable to clear pulmonary surfactant, resulting in lung pathology that closely resembled Pulmonary Alveolar Proteinosis (PAP), a rare lung disease in humans.

PAP may be primary (genetic) or acquired [18]. The acquired form is due to the presence of neutralizing autoantibodies to GM-CSF, found both in bronchoalveolar lavage fluid and plasma of PAP patients. Alveolar macrophages from these patients show impaired phagocytic and killing function, providing potential explanations for the over-representation of opportunistic pathogens such as *Mycobacterium avium* complex, *Cryptococcus sp., Nocardia sp.* and *Aspergillus sp.* in PAP patients [19]. Cryptococcus meningitis associated with anti-GM-CSF AAbs has been documented to precede PAP in seven cases [20]. AAbs to GM-CSF are not always associated with PAP; in fact, AAbs to GM-CSF have been noted in five otherwise immunocompetent patients with disseminated Nocardia infection [21]. Such clinical presentations have expanded the spectrum of clinical situations in which AAbs to GM-CSF should be evaluated as the possible cause of autoimmunity leading to an immune deficient state, and therefore increased susceptibility to infection.

AAbs to GM-CSF in these patients are of high titer and functional, as demonstrated by their ability to neutralize GM-CSF induced STAT5 phosphorylation.

Laboratory Diagnosis and Therapeutic Intervention

Evaluation of AAbs to cytokines should be considered in immune competent patients presenting with infections due to opportunistic pathogens or organisms of low pathogenicity. Because anti-cytokine AAbs may be present in healthy individuals, it is important to evaluate the titer of the AAbs as well as functionality of the AAbs by conducting in-vitro studies to demonstrate their ability to neutralize their cognate cytokine's activity. In general, laboratory testing includes binding assays, such as ELISA, to demonstrate the antibody titer as well as flow cytometry based assays to evaluate the ability of the AAbs to inhibit signals induced by their cognate cytokine.

Treatment of patients with anti-cytokine AAbs (IFNγ and GM-CSF) focuses on management of the clinical manifestations or elimination of the neutralizing activity of the AAbs. Anti-mycobacterial, anti-fungal or other appropriate anti-microbial therapeutic strategies are employed for management of infectious manifestations, and strategies such as whole lung lavage is utilized in the case of PAP. Elimination of the AAbs has been attempted with plasmapheresis. Exogenously administered GM-CSF to overcome the inhibitory effects of anti-GM-CSF AAbs has been effective in a subset of PAP patients [22, 23]. Finally, immunomodulatory therapy such as rituximab to eliminate B cells and thereby the AAbs has been employed in patients with anti-IFNγ AAbs with varying levels of success [6, 24].

Because of the association of disseminated, treatment refractory infections with anti-cytokine AAbs, it is important to evaluate patients presenting with such clinical manifestations for the presence anti-cytokine AAbs. Demonstrating these AAbs in the appropriate clinical context may then suggest immune modulatory treatment options to supplement traditional management of the infections.

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