Good syndrome, bad problem

Bianca Martinez and Sarah K. Browne*

Immunopathogenesis Section, Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA
*Correspondence: brownesa@niaid.nih.gov

Edited by:
Arjun Rajan, National Cancer Institute, USA

Reviewed by:
Ronan Kelly, Johns Hopkins, USA

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A commentary on

Three difficult cases: the challenge of autoimmune, immunodeficiency and recurrent infections in patients with Good’s syndrome
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Good syndrome (GS), which is classically defined as the triad of thymoma, immunodeficiency, and hypogammaglobulinemia, was first characterized by Robert Alan Good, a pioneer in the field of immunodeficiency diseases, who recognized the crucial role that the thymus plays in the development of the immune system (1). The definition of this entity remains vague, in part because of the protean immunological manifestations of thymic epithelial neoplasms. How the thymus influences the precise balance of immune reactivity that is so critical to both host-defense and self-tolerance remains to be fully understood. Accordingly, immunologic manifestations because of thymic epithelial tumors can range from nothing to severe autoimmunity, immunodeficiency, or both, the spectrum of which is wide and patient-specific (Table 1). Further, patients may have opportunistic infection without gross immunologic lab abnormalities (2), and conversely, may have relatively few problems, despite an abnormal immune profile (3). Nevertheless, we can look to the immunology and infectious complications in individual patients, to identify where their immune defects are most concentrated and how to go about treating them.

The critical role that the thymus plays in T cell education likely explains the observation of coincident autoimmunity and immunodeficiency in thymoma, reflecting T cells that are both over-reactive to self and under-responsive to pathogens. The importance of the T cell in directing B cell responses is also apparent in the immunopathology of thymoma. Consistent with T cell immunodeficiency, patients with thymoma can develop pneumocystis pneumonia, cytomegalovirus, mucocutaneous candidiasis, varicella zoster reactivation (both localized and systemic), Kaposi’s sarcoma, and progressive multifocal leukoencephalopathy, cryptococcosis, and non-tuberculous mycobacteria (2, 4, 5). Under scoring the B cell component of this disease, the cardinal manifestation of GS is hypogammaglobulinemia. In fact, the most prominent clinical characteristics of GS includes an increased susceptibility to sinopulmonary bacterial infections with encapsulated organisms (Haemophilus influenzae and Streptococcus pneumoniae), which is clearly associated with hypogammaglobulinemia. Even outside classical GS, a tendency toward B cell dysfunction is apparent in the observation that anti-acetylcholine receptor autoantibody-associated myasthenia gravis is the most frequent autoimmune complication of thymoma (6). B cell lymphopenia is also common and in some cases has even led to the initial diagnosis of thymoma (7, Allergy and Asthma Proceedings). Together, these observations underscore the complex interrelatedness of T and B lymphocyte biology.

Another potential mechanism of infection susceptibility is presence of anti-cytokine autoantibodies (2, 8–10). It is clear that anti-cytokine autoantibodies are an important and emerging mechanisms of adult-onset immunodeficiency (11) and can be responsible for severe opportunistic infection in previously healthy adults (12, 13). Interestingly, mucocutaneous candidiasis has been seen in association with anti-IL-17 and anti-IL-22 autoantibodies in autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) syndrome (14, 15), caused by a Mendelian deficiency of the autoimmune regulator (AIRE) gene. AIRE is critical for the negative selection of autoreactive T cells in the thymus (16) and likely explains much of the profound and diverse autoimmune phenomena that are typical of APECED. This compelling link between autoimmunity and immunodeficiency may also be relevant to thymoma where defective AIRE expression has been recognized (17), as has a predisposition to mucocutaneous candidiasis in association with anti-IL-17 and IL-22 autoantibodies (2, 14).

Immunological evaluation can include an assessment of quantitative immunoglobulins, as well as B and T lymphocyte subsets. If the clinical presentation points to antibody deficiency, a vaccine challenge may help evaluate the patient’s ability to generate an appropriate humoral response, which can be impaired even with relatively normal IgG levels. Testing for anti-cytokine autoantibodies is done in specialized laboratories on a research basis.

Treatment of infection generally focuses on targeted antimicrobial therapy. In the case of recurrent sinopulmonary infections
Table 1 | Immunologic abnormalities reported in thymoma.

| Laboratory features | Abnormality/activity | Clinical associations | Management Comments |
|---------------------|----------------------|----------------------|---------------------|
| **LYMPHOCYTE SUBSETS** | | | |
| CD20+ B cells | Decreased in peripheral blood (2, 3) | Immunodeficiency | Consider vaccine challenge to evaluate ability to mount antibody response | May be independent of hypogammaglobulinemia |
| CD20+/CD27+ memory B cells | Decreased in peripheral blood (2) | Unknown, often in setting of total B cell lymphopenia | Therapy targeting clinical manifestations | As above |
| CD4+ T cells | May be increased or decreased in peripheral blood (2, 3) | Elevated levels associated with autoimmunity | Therapy directed at clinical manifestations; consider secondary prophylaxis if history of opportunistic infection | The accumulation of CD8+CD45RA+ T cells can be used to monitor clinical stages of immunodeficiency in thymoma (19) |
| CD8+ T cells | May be increased or decreased in peripheral blood (2, 3) | Elevated levels associated with immunodeficiency | Therapy targeting clinical manifestations | As above |
| CD16+ or CD56+ NK cells | May be increased or decreased in peripheral blood (2, 3) | Unknown | No specific therapy indicated | Low or dysfunctional NK cells associated with herpes virus infection |
| **IMMUNOGLOBULINS (Ig)** | | | |
| IgG | May be increased or decreased in peripheral blood (2, 3) | Recurrent bacterial sinopulmonary infections | If there is an inadequate antibody response, or history of severe or recurrent infection, immunoglobulin replacement therapy may be started (18) | Even if immunoglobulins normal or high, consider vaccine challenge to evaluate ability to mount antibody response, particularly if history of severe or recurrent infections (18) |
| IgA | May be increased or decreased in peripheral blood (2, 3) | Unknown | No specific therapy indicated | None |
| IgM | May be increased or decreased in peripheral blood (2, 3) | Unknown | No specific therapy indicated | None |
| **ANTI-CYTOKINE AUTOANTIBODIES** | | | |
| Anti-IFNα | Prevents IFNα-induced pSTAT-1 and pSTAT-4 in vitro (2) | Unknown | IFNα given to one patient with disseminated zoster | Associated with one case of disseminated severe varicella zoster infection in patient without thymoma; thymoma patients may have disseminated or localized varicella reactivation |
| Anti-IFNβ | Prevents IFNβ-induced pSTAT-1 in vitro (2) | Unknown | No specific therapy indicated | One case of activating anti-IFNβ autoantibodies (unpublished data) |
| Anti-IFNω | Prevents IFNω-induced pSTAT-1 (unpublished data) | Unknown | No specific therapy indicated | Autoantibodies against type I IFNs common in APECED suggesting etiologic role of gene AIRE for origin of some anti-cytokine autoantibodies |
| Anti-IL1α | Prevents PHA-induced IFNγ production by T cells (2) | Unknown | No specific therapy indicated | Can be seen in normal hosts (12) |

(Continued)
associated with hypogammaglobulinemia, intravenous immunoglobulin (IVIg) can be an effective prophylactic measure. IVIg has also been used to augment the immune response in the case of CMV infection (5). It can also be effective in treating anti-acetylcholine receptor-associated myasthenia gravis, although the mechanistic explanation for this benefit remains elusive. Secondary prophylaxis could be considered in patients under certain circumstances such as those who have had pneumocystis pneumonia.

A better understanding of the underlying immunological defects in thymoma will enhance therapeutic options, such as primary prophylaxis or immunomodulation. Furthermore, despite the futility of their primary immunologic lesion (the neoplastic thymic epithelial cells), patients with thymoma can demonstrate fascinating clinical overlaps with many other diseases, from rheumatologic, hematologic, and pulmonary disorders, to primary and congenital immunodeficiency, and far beyond. Thus, understanding thymoma, as Dr. Good so astutely recognized in decades past, will provide an important opportunity that should not be missed, to improve care of these complex patients, and to shed light on fundamental principals of human immunology.

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