ORIGINAL ARTICLE

Thymic Epithelial Tumor-Associated Cytopenia: A 10-Year Observational Study in France

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ABSTRACT

Introduction: Thymic epithelial tumor (TET)-associated cytopenia is rare but difficult to treat.

Methods: We performed a multicenter, retrospective study of TET and associated forms of cytopenia in France. Cases were collected by the French National Reference Center for Autoimmune Cytopenia and the French National Thymic Malignancy Interest Group (Réseau Tumeurs Thymiques et Cancer) and through a call for cases by the French Society of Internal Medicine.

Results: Thirty-six cases were recorded between 2002 and 2014 and followed up for a median of 38 months (interquartile range, 23–106 months). Thirty-two patients underwent surgery for TET, and 14 of the latter were in complete remission at last follow-up. Cytopenia can occur before, simultaneously, or after diagnosis of TET. The most common types of cytopenia were pure red cell aplasia (in 30% of cases) and Good syndrome (GS) (also in 30% of cases). Eleven patients displayed two or more episodes of cytopenia. Eighteen patients received steroids as their first-line treatment, leading to a complete response in nine. Other first-line treatments (cyclosporine and rituximab) were less effective but should be considered as treatment options. Infections developed in 84% of the patients with GS; this did not appear to be related to the presence or

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absence of immunosuppressive treatment or chemotherapy. Eight patients died during the follow-up period (two died of cytopenia and five of infections).

Conclusions: The optimal treatment for TET-associated cytopenia has not been clearly defined and the outcome does not appear to be correlated with TET progression. For GS, prophylactic immunoglobulin replacement therapy and prophylactic antibiotic therapy can be recommended.

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Keywords: Thymic epithelial tumor; Pure red cell aplasia; Good syndrome; Infectious complications

Introduction

Thymic epithelial tumors (TETs), including both thymoma and thymic carcinoma, are rare: the overall incidence in the United States is 0.15 per 100,000 person-years. These tumors can be classified according to the extent of the disease (e.g., using the Masaoka-Koga staging system, as modified in 1994) and/or the histologic findings (e.g., using the World Health Organization local histologic classification of thymic tumors, as updated in 2004). Thymic epithelial tumors are frequently associated with parathymic diseases (including autoimmune manifestations); myasthenia gravis is the most frequent condition and affects between 30% and 50% of patients with TET.[1]

Thymic epithelial tumor–associated cytopenia has also been reported (it was first described in the 1980s) but is far less common than myasthenia gravis.[2] Pure red cell aplasia (PRCA) is defined as severe, normochromic, normocytic anemia associated with reticulocytopenia and the absence of erythroblasts in otherwise normal bone marrow[3]; it is reportedly the second most frequent autoimmune disease in patients with TET. A Japanese series described the diagnosis of 41 cases of PRCA over a 16-year period.[4] Other types of cytopenia have been described, albeit usually as case reports; they include immune thrombocytopenia,[5] autoimmune agranulocytosis,[6] autoimmune hemolytic anemia,[7] and Good syndrome (GS).[1] The latter is a puzzling entity observed in 5% of patients with TET[1]; it features a combination of B lymphopenia, variable CD8 and CD4 T-cell counts, hypogammaglobulinemia, and susceptibility to infections. The mechanisms underlying GS have not been determined. Other cases of cytopenia in patients with TET may be variously related to pernicious anemia (also known as Biermer anemia) and hypothyroidism.

The treatment of the rare, autoimmune forms of cytopenia is not as well codified as that of GS. Similarly, long-term outcomes in TET-associated, autoimmune forms of cytopenia have not been extensively described. We therefore decided to collect data on French cases of TET-associated cytopenia over a 10-year period and to describe the patients' characteristics, treatments, and outcomes.

Methods

Cases were identified in three settings: those diagnosed at the French National Reference Center for Autoimmune Cytopenia, those recorded after a national call from the French Society of Internal Medicine, and those reviewed since January 2012 in the tumor board by the French National Thymic Malignancy Interest Group (RYTHMIC [Réseau Tumeurs Thymiques et Cancer]). Data concerning TET (date of diagnosis, histologic characteristics, treatments, and outcome) and autoimmune cytopenia (date of diagnosis, type, clinical manifestations, and outcome) were collected retrospectively.

The date of TET diagnosis was considered to be the date of histologic confirmation or (if biopsy or surgery was not performed) the date on which the thymic tumor was discovered. Thymic epithelial tumors were classified according to both the modified Masaoka-Koga staging system and the 2004 World Health Organization classification.[1]

Members of the RYTHMIC network performed a systematic, histopathological review of all cases included in the present analysis. The study was approved by the Internal Review Board of Gustave Roussy, and the authors observed strict accordance with the Helsinki Declaration guidelines.

For descriptive purposes, the study results are expressed as a median (interquartile range [IQR]) or a number (percentage). Continuous variables were compared using the Mann-Whitney test and categorical variables were compared using a chi-square test or Fisher's exact test.

Definitions

The response to TET treatment was defined in accordance with the RECIST criteria: a complete response (CR) corresponded to the disappearance of all target lesions; a partial response (PR) corresponded to at least a 30% decrease in the sum of the target lesions' diameters (relative to the value before treatment); progressive disease (PD) was defined as an increase in the sum of the target lesions' diameters of at least 20% (relative to the lowest value recorded for each individual patient during the study); and stable disease (SD) was defined as all cases not meeting the criteria for a CR, PR, or PD (relative to the lowest value recorded for each individual patient during the study and with at least 1 year between the first and last evaluation).[8]

Cases of autoimmune cytopenia (PRCA, immune thrombocytopenia, autoimmune hemolytic anemia, and

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