AB014. Bone marrow dyscrasias in autoimmune regulator deficiency: lessons from thymoma and autoimmune polyendocrinopathy-candidiasis ectodermal dystrophy

Laercio DaSilva[1], Shannon Swift[1], Susan Sansone[1], Eva Szabo[1,2], Chen Zhao[1], Christine Feierabend[1], Nisha Patel[3], Sebastian Ochoa[4], Michail S. Lionakis[4], Arun Rajan[1,5], Meredith McAdams[1]

[1]Thoracic and GI Malignancies Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA; [2]Lung and Upper Aerodigestive Cancer Research Group, Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA; [3]Hematology Section, Department of Laboratory Medicine, National Institutes of Health Clinical Center, Bethesda, MD, USA; [4]Fungal Pathogenesis Section, Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy & Infectious Diseases, National Institutes of Health, Bethesda, MD, USA; [5]Center for Immuno-Oncology, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA

Correspondence to: Meredith McAdams, MD. Thoracic and GI Malignancies Branch, Center for Cancer Research, National Cancer Institute, 10 Center Drive, Building 10, Room 4E-5330, Bethesda, MD 20892, USA. Email: meredith.mcadams@nih.gov.

Background: The autoimmune regulator (AIRE) gene plays a crucial role in the development of immunological self-tolerance. Primary mutations can lead to autoimmune polyendocrinopathy-candidiasis ectodermal dystrophy (APECED) whereas decreased expression can be seen in thymomas, both of which are associated with autoimmunity and acquired immunodeficiency. Here we characterize the differences between bone marrow (BM) dyscrasias arising in the setting of primary versus acquired AIRE deficiency.

Methods: We conducted a retrospective review of patients with thymoma or APECED and identified cases with disease or treatment-related biopsy-confirmed BM dyscrasias. We describe clinicopathologic features, management, and outcomes.

Results: Between January 2011 and December 2022, 16 patients [thymoma (n=10); APECED (n=6)] had sufficient data for inclusion. The median age at thymoma diagnosis was 42 (range, 28–72) years, 6 were female, most had World Health Organization (WHO) subtype B histology (B1 n=2, B2 n=2, B2/B3 n=3, B3 n=1, unknown n=2), and 40% (4/10) had a history of paraneoplastic autoimmunity. In contrast, median age at APECED diagnosis was 6 (range, 3–10) years, 4 were female, and 83% (5/6) had 5 or more manifestations of the syndrome. At BM dyscrasia diagnosis, the median age was 48 (33–75) years in thymoma and 25 (range, 3–58) years in APECED, median hemoglobin nadir was 6.9 (range, 5.5–8.3) gm/dL for thymoma and 7.3 (range, 5.0–8.1) gm/dL for APECED, and all patients were red blood cell transfusion dependent. Among patients with thymoma, 70% (7/10) were receiving thymoma-directed therapy. Seven patients presented with anemia alone, 2 with anemia and transfusion-dependent thrombocytopenia, and 1 with anemia and neutropenia. Diagnostic marrows revealed severe erythroid hypoplasia/aplasia alone (n=5), concurrent megakaryocytes hypoplasia/aplasia (n=2), and concurrent decrease in mature granulocytes (n=1). In patients with APECED, 5 presented with anemia alone, and 1 presented with anemia and transfusion-dependent thrombocytopenia. Marrows revealed erythroid hypoplasia/aplasia alone (n=5) and concurrent megakaryocytic aplasia (n=1). Abnormal CD8+ T-cell lymphocytosis was noted in BMs from both thymoma and APECED. Lymphocytic infiltrates were seen in all cases involving >1 cell line and 6 of 10 cases involving erythroid hypoplasia/aplasia alone. Various immunosuppressive treatment approaches were trialed in these patients. Among patients with thymoma, no responses were seen with prednisone (0/3) or intravenous immunoglobulin (0/3). Treatment with cyclosporine A (CsA) achieved transfusion-independence in all patients (8/8), 3 of whom had failed at least one prior line of immunosuppression. In contrast, among APECED patients, no responses were observed with CsA (0/2) or various other immunosuppressive strategies including prednisone (0/1), intravenous immunoglobulin (0/2), rituximab (0/2), mycophenolate mofetil (0/1), tacrolimus (0/2), and antithymocyte globulin (0/2). Responses were only seen with alemtuzumab (4/4), 3 of whom had failed at least one prior line of immunosuppression, and hematopoietic cell transplantation (1/1). Post-CsA BMs in 2 patients with thymoma revealed reduction of lymphoid aggregates and normalization of previously absent cell lines.

Conclusions: AIRE deficiency, both primary and acquired, can be associated with clinically significant, transfusion-

dependent BM dyscrasias with potentially serious long-term complications. T-cell directed therapy appears effective and spares patients' toxicities seen with alternative immunosuppressive agents.

Keywords: Thymoma; autoimmune polyendocrinopathy-candidiasis ectodermal dystrophy (APECED); marrow dyscrasia; cyclosporine

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://med.amegroups.com/article/view/10.21037/med-23-ab014/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective analysis was performed under protocols 14-C-0105 and 11-I-0187 (NCT02146170 and NCT01386437, respectively), which are approved by the NIH Institutional review board and in which patients included in this study were enrolled after providing informed consent.

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