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Atypical chronic lymphocytic leukemia (CLL) with polyglandular autoimmune endocrinopathy (PGA) type II – a complex profile

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A 77-year-old woman presented with marked fatigue and anemia in August 2012. She had a significant past history of type 2 diabetes or latent autoimmune diabetes of adults (LADA), hypertension, chronic atrial fibrillation, Hashimoto's thyroiditis associated hypothyroidism and Addison's disease. She was diagnosed with iron deficiency anemia in 2009 and was treated with oral iron supplements. In July 2012, she was hospitalized due to low blood pressure and fatigue. She had hemoglobin of 7 gm/dL and she received 2 units of packed red blood cells (PRBC) transfusion. A bone marrow (BM) biopsy (performed at an outside hospital) revealed a CD5+ lymphoproliferative disorder and dysmegakaryocytic hyperplasia. The patient was referred to our hospital for further evaluation. Her physical examination was within normal limits. Her hemoglobin was 11.1 g/dL, white blood cell count (WBC) 5.2 K/ μ L, platelet count 443 K/ μ L and mean corpuscular volume (MCV), reticulocyte and differential counts were normal. Her beta2 microglobulin was 2.4 mg/L (normal range – NR) (0.7–1.8), serum ferritin 260 ng/ml (NR – 13–150), and serum lactate dehydrogenase (LDH), liver and renal function tests, direct antiglobulin test, serum vitamin B12, folate and methylmalonic acid levels were normal. Her anti-nuclear antibody (ANA) titres were strongly positive by immunofluorescence method showing nucleolar and speckled patterns. A repeat BM biopsy showed – cellularity 20%, increased small lymphocytes with an interstitial and nodular distribution (Figure 1 A–B; H&E 60 $\times$ and 500 $\times$ magnification), and 50% of cellularity with few dysplastic megakaryocytes and mild erythroid hypoplasia. Flow cytometry of BM aspirate demonstrated a discrete population of lambda light chain restricted aberrant B-cells, positive for CD19, CD5, CD20 bright, CD200, FMC-7 and dim CD23 expression (Figure 1 C–E; flow cytometry dot plots of CD20, FMC-7 and CD23). BM cytogenetics showed normal female karyotype (18 metaphases), +8 in one and 5q- in one metaphase. *JAK2V617F* mutation test was negative. A whole body Positron emission tomography (PET) scan did not show any active lymphadenopathy. Based on these findings the patient was suspected to have a low grade myelodysplastic syndrome (MDS) with anemia of chronic disease and CD5-positive B-cell lymphoproliferative disorder without

peripheral lymphocytosis. Prior to her presentation to us the patient was receiving oral steroids (replacement dose of hydrocortisone and fludrocortisone). She was treated empirically with tapering doses of steroids and received supportive care for 3–4 weeks. She was then hospitalized due to pneumonia and congestive heart failure (CHF). Her hemoglobin was 9.4 g/dL with normal blood cell count and slightly elevated MCV of 104 FL. A repeat BM examination showed increased lymphocytic infiltration (40% of cellularity) with an interstitial and nodular pattern. Immunophenotype was similar to the previous BM aspirate. Immunohistochemistry for cyclinD1, SOX-11 and CD34 was negative while PAX-5 staining was positive. BM cytogenetics showed diploid female karyotype in 18 metaphases, +8 in one and 5q- in one metaphase on conventional cytogenetic analysis. Fluorescent in situ hybridization (FISH) study showed trisomy 12, deletion of a D13S319 locus and a minor clone with trisomy 14. FISH test for IGH@/CCND1 gene rearrangement and BCL3 gene was negative. Somatic hyper mutation testing and VH gene sequencing of the BM showed 4.7% mutated immunoglobulin heavy chain variable region (IGHV) and VH 3–74 gene usage. Simultaneously, a full endocrine work up revealed elevated level of thyroid stimulating hormone (TSH) 17.11 μ IU/ml (NR 0.27–4.2), HbA1C of 6.5%, antithyroglobulin antibody 400 IU/ml (NR <40), anti 21-hydroxylase antibody 8 U/ml (NR <1). Levels of free T4 (FT4) 1.53 ng/ml (NR 0.93–1.7), blood glucose, electrolytes, thyroid peroxidase, antiovarian, liver kidney microsomal (LKM) antibodies, 25 hydroxy vitamin D, luteinizing hormone (LH), follicular stimulating hormone (FSH), estradiol and thyroid stimulating immunoglobulin were normal. Anti-islet cell antibody and adrenocorticotrophic (ACTH) hormone levels were not performed.

These investigations led us to a working diagnosis of atypical CLL with dim CD23 expression^{1,2}, trisomy 12 and polyglandular autoimmune syndrome type II (PGA-II) or Schmidt syndrome³. Features which favored the diagnosis of atypical CLL were dim CD23, bright CD20, positive FMC-7, CD5, CD19 and CD200 positive lymphocytes with trisomy 12. Mantle cell lymphoma was ruled out by lack of cyclin D1 and negative FISH for IGH@/CCND1. PGA-II was diagnosed based on the autoimmune Addison's disease and Hashimoto's thyroiditis. The patient is under observation for his atypical CLL, and is treated with steroid and thyroxine replacements for the polyendocrinopathy. The cause of anemia in this patient could be multifactorial ranging from iron deficiency to nutritional to anemia of chronic disease. We do not believe that a single clone of trisomy 8 and del5q in conventional karyotyping could be clonal but since there was mild megakaryocytic dysplasia and anemia, an initial impression of low risk MDS was rendered. Since the patient has atypical CLL and trisomy 12 which can be associated with t(14;19)⁴ a BM FISH test was performed which was negative for t(14;19).

Patients with CLL are prone to develop hemic (hemolytic anemia, thrombocytopenia, neutropenia) and non-hemic autoimmune diseases such as rheumatoid arthritis, vasculitis, systemic lupus erythematosus^{5,6}. Anecdotal case reports have reported on patients with CLL and autoimmune endocrine disease such as hashimoto's thyroiditis or non-hemic autoimmune disorders; however a mechanistic relationship between CLL and the development of autoimmune endocrine disorders is never established. In one study it was shown that CD5+ CLL cells stimulate the autoreactive T helper cells via aberrant Rh antigen presentation and promote autoimmune hematological manifestations in patients with CLL⁷.

Our patient has early Rai stage atypical CLL with trisomy 12. Presence of autoantibodies to 21-hydroxylase and thyroglobulin confirmed the diagnosis of autoimmune polyendocrinopathy. Polyglandular autoimmune syndrome type II (PGA-II) also known as Schmidt's syndrome, is characterized by the combination of autoimmune Addison's disease with autoimmune thyroid Disease and/or Type 1 Diabetes (T1D). Primary hypogonadism, vitilago, grave's disease, myasthenia gravis and celiac disease are also observed in this syndrome. PGA-II is a complex multigenic disease, seen in adult females. It has been demonstrated that risk of PGA-II is increased in the presence of HLA-DR3/DQ2 and DRB1*0404 genes⁸. CTLA-4 gene polymorphism is also associated with PGA-II^{9, 10}. One study has also demonstrated that polymorphism of MIC-A gene (major histocompatibility complex class I chain related genes) is strongly associated with autoimmune Addison's disease. It is now considered that concomitant presence of both MIC-A5.1 and HLA-DR3/DQ2 is a strong genetic risk factor for PGA-II endocrinopathy⁸. Soluble MIC-A is one of the ligands for Natural killer (NK) group 2 member D (NKG2D) receptor. NKG2D ligand-receptor axis plays a role in immune surveillance in various cancers and autoimmune diseases. NKG2D receptors and ligands play an important role in antitumor immunity¹¹. NKG2D receptors are expressed on NK cells, gamma delta T cells and cytotoxic CD8+ T cells. These receptors can provide co-stimulatory signals to T cells and cause cytolysis or cytokine production. One study has shown that blockage of NKG2D receptor by a monoclonal antibody prevented the development of type 1 diabetes in mouse model.¹² Elevated levels of NKG2D ligand such as MIC-A correlate with disease progression in different cancers (e.g. multiple myeloma)¹³. In one study, plasma levels of NKG2D ligands (MIC-A and B, ULBP2) were shown to be significantly higher in patients with CLL (n=98)¹⁴. However, NKG2D receptor expression was not significantly higher in CLL patients than the healthy controls. NKG2D receptor is encoded on chromosome 12 in humans¹⁵. In this patient we have hypothesized that CLL with trisomy 12 and PGA-II may have a mechanistic relationship via NKG2D ligand receptor axis. We speculate that since our patient has trisomy 12, this may lead to overexpression of NKG2D receptors and we know that CLL patients can have elevated MIC-A levels. Furthermore, MIC-A5.1 allele which predisposes to autoimmune Addison's disease may also encode for a soluble ligand. Therefore we speculate that an overexpression of NKG2D ligand and receptor axis might be responsible for the pathogenesis of both CLL as well as PGA-II in this patient. Further studies are needed to evaluate the relevance of NKG2D-MIC-A axis among atypical and typical CLL patients with trisomy 12 and the association with autoimmune endocrinological and non-endocrinological disorders. Exploitation of NKG2D-MIC-A axis might be of potential therapeutic relevance in patients with CLL.

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Figure-1. (A–E) – Histopathological features and flow cytometry dot plots of bone marrow (BM) biopsy and aspirate

A–B) Hameatoxylin and eosin (H&E) staining of bone marrow showing interstitial and nodular infiltration by small and mature lymphocytes – (60 and 500× magnification) **C–E)** Dot plots from the bone marrow aspirate originating from CD5 and CD19 positive lymphocyte population (not shown) showing bright CD20, FMC-7 and dim to negative CD23 expression suggestive of atypical CLL.