

at the time of clonal evolution in our case. Our case report described an entire course of disease in one patient, where Ph-positive AML develops on the wheels of PNH in known cases of AA. BCR-ABL is considered a class I mutation in reference to AML and provides proliferation advantage to neoplastic clones [10]. Co-existing cytogenetic and molecular events may determine the preexisting illness in the form of AA, MDS, or de novo leukemia. In our case, the patient refused treatment or molecular workup that might have provided insight into the BCR-ABL transcript type or other coexisting mutations.

The availability of SNP array karyotyping, exome sequencing, and next-generation sequencing in clinical labs has increased the momentum for the search for predictors of clonal evolution in AA. Cytogenetic abnormalities including -7/del 7q are associated with increased risk of progression to MDS/AML [12], while DNMT3A and ASXL1 mutations are good molecular predictors. These factors are also reported at variable frequencies in age-related clonal hematopoiesis. Hence, the application of this information in predicting prognosis and tailoring treatment is still not part of clinical practice. Our interesting case suggests that molecular and genetic events in AA, MDS, and AML are complex and overlapping.

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Response of multifocal acquired demyelinating sensorimotor neuropathy associated with atypical chronic lymphocytic leukemia to rituximab therapy

TO THE EDITOR: Paraproteinemic peripheral neuropathy (PPN) refers to peripheral neuropathy (PN) associated with and considered to be mediated by a monoclonal protein in the serum+urine [1]. About 4% patients with PN have an associated monoclonal gammopathy (MG) [2]. An assemblage of MG (<3 g/dL), small clonal population of bone marrow (BM) plasma cells (PCs) (<10%), and absence of myeloma defining events defines monoclonal gammopathy of undetermined significance (MGUS). The prevalence of MGUS in general population is about 0.7%, and it increases with age (3.2% in >50 yr and 5.3% in >70 yr) [3]. Therefore, both PN and MGUS may co-exist; ascribing pathogenicity of M-protein in such cases relies on demonstrating neurological improvement with treatment being targeted at the underlying clone secreting the implicated paraprotein. Recently, the term monoclonal gammopathy of clinical sig-

nificance (MGCS) was introduced to describe the potentially organ-toxic properties of M-protein. Typically, the M-protein in MGCS is “small” and does not meet the diagnostic criteria for “large” clonal disorders such as multiple myeloma (MM) and Waldenstrom’s macroglobulinemia (WM) [4]. Such cases were earlier considered MGUS, undermining the potential pathogenicity of these proteins. Therefore, PPN without any evidence of MM or WM could be redefined as monoclonal gammopathy of neurological significance (MGNS). The current report describes a rare association of multifocal acquired demyelinating sensorimotor neuropathy (MADSAM) with a B-cell chronic lymphoproliferative disorder (B-CLPD) and its rapid response to rituximab. We intend to substantiate the broader concept of MGNS.

A 76-year-old man presented to our hospital with a 3-month history of insidious onset of weakness involving both the upper limbs, with associated numbness up to the elbows. Weakness progressed gradually to involve both the lower limbs. Patient could not stand unsupported after 1 month. The patient’s clinical history was negative for diabetes, hypertension, alcohol intake, and autoimmune disorder. General examination revealed bilateral wrist drop and wasting of bilateral thenar and hypothenar eminences. Neurological exam was remarkable for bilateral distal upper limb hypotonia, areflexia, impaired vibration, and proprioception. The examination of motor system of the lower limbs was essentially normal; however, distal vibration and proprioception were impaired up to the knees. The cranial nerve exam was normal. The liver (4 cm) and spleen (2 cm) were palpable per abdomen. Blood tests showed the

following: hemoglobin, 124 g/L; white cell counts, $16.30 \times 10^9/L$ (lymphocytes-80%); and platelet counts, $89 \times 10^9/L$. Peripheral blood smear showed presence of small-medium sized lymphocytes and smudge cells. Prolymphocytes were not seen. Organ chemistries, including serum vitamin B12, red cell folate, and C-reactive protein levels were normal. Serum lactate dehydrogenase was slightly elevated (283 U/L; normal, <250 U/L). Viral markers [hepatitis B surface antigen, anti-hepatitis C virus (HCV) and anti-human immunodeficiency virus (HIV) serology, Epstein-Barr virus, and Cytomegalovirus DNA] were negative. BM biopsy showed interstitial infiltration by small-medium sized mature lymphocytes with scant cytoplasm and clumped chromatin. Flow cytometry (FCM) of BM aspirate showed increased clonal B-lymphocyte phenotype: CD45+, CD19+, CD20+, FMC-7+, CD200+, CD38+, CD5-, CD23-, CD10-, CD11c-, CD25-, CD103-, and CD123-. Morphology and immunophenotype were consistent with a diagnosis of atypical chronic lymphocytic leukemia (aCLL) (Fig. 1). BM cytogenetics revealed normal karyotype. Serum and urine protein electrophoresis and immunofixation were negative. Serum free light chain (sFLC) levels were as follows: kappa, 90.0 mg/L (3.30–19.40 mg/L); lambda, 25.90 mg/L (5.71–26.30 mg/L); and ratio, 3.47 (0.26–1.65). Immunoglobulin profile was normal [IgG, 8.9 g/L (6.6–16.9 g/L); IgM, 0.32 g/L (0.37–2.58 g/L); and IgA, 1.2 g/L (1.03–5.91 g/L)]. 18Fluoro-2-deoxy-d-glucose positron emission tomography-computed tomography (18FDG PET-CT) scan failed to show any abnormality. Nerve conduction study (NCS) was consistent with the diagnosis of multifocal acquired demyelinating

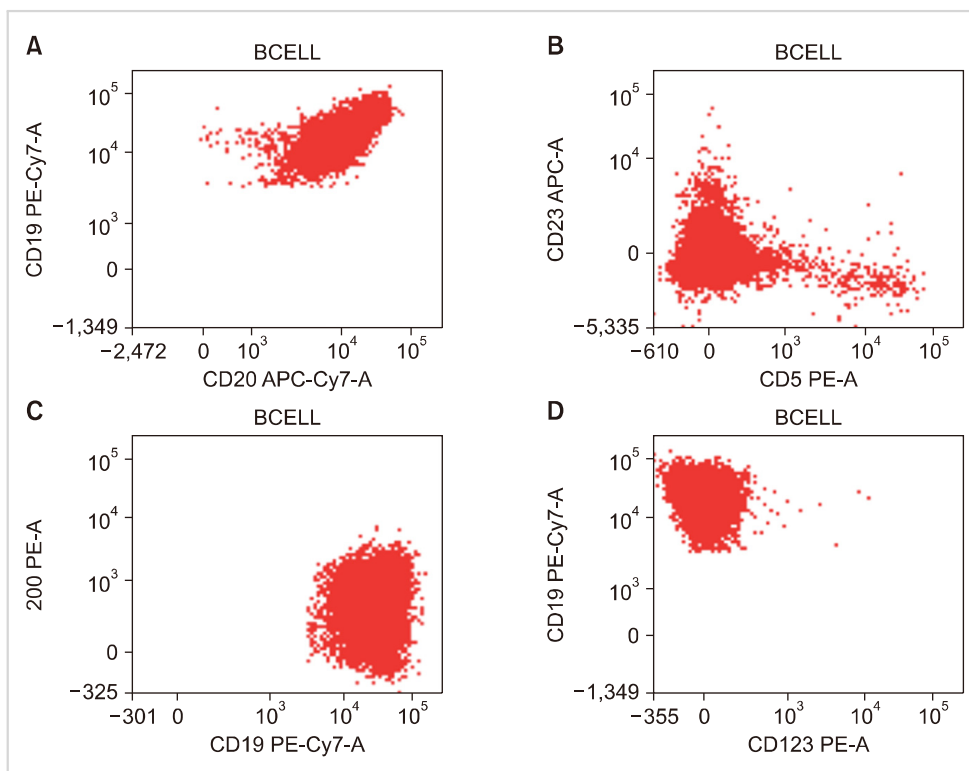


Fig. 1. Flow cytometry plots showing gated clonal B-cells (A) dual positivity for CD19 and CD20, (B) dual negativity for CD5 and CD23, (C) positivity for CD200, and (D) negativity for CD123, consistent with B-CLPD (atypical CLL).

sensory and motor (MADSAM) neuropathy. Cerebrospinal fluid (CSF) examination was normal. Autoimmune panel, including antinuclear antibody, anti-neutrophil cytoplasmic antibodies, and PN antibody panel (anti-GM1, GM2, GM3, GD1a, GD1b, GT1b, GQ1b, MAG) were negative. Abdominal fat pad biopsy did not reveal any amyloid deposits. Serum cryoglobulins were not detected. FCM of peripheral blood identified a normal subset of regulatory T-cells (Tregs). Patient was treated with rituximab monotherapy (375 mg/m²/wk ×4 doses). He experienced marked improvement in his neurological function, beginning after the first rituximab dose. He could stand and walk unsupported and had about 80% improvement in hand grip at the end of fourth rituximab dose. However, neuropathy progressed 2 weeks later, and he failed to respond to intravenous immunoglobulin treatment. Treatment with high-dose methylprednisolone (MPS, 1 gm/day ×3 days) halted the neurological worsening. Reassessment after MPS therapy suggested regression of organomegaly, absence of clonal B-cells in the peripheral blood and BM aspirate by FCM, and normalization of sFLC. Maintenance rituximab (every 2 months) resulted in an ongoing neurological improvement.

Mechanistically, M-protein can inflict PN either 1) directly, by means of tissue deposition and consequent neurological impairment, or 2) indirectly, by acting as an autoantibody directed against peripheral nerve antigens [1]. Whilst the former category includes amyloidosis-associated PN and cryoglobulinemic neuropathy (CN), the latter is exemplified by (a) distal acquired demyelinating symmetric neuropathy (DADS, IgM-MG, anti-MAG antibody), (b) chronic inflammatory demyelinating polyneuropathy (CIDP, IgG/IgA-MG), (c) chronic ataxic neuropathy with ophthalmoparesis, M-protein, cold agglutinins, and disialosyl ganglioside antibodies syndrome (CANOMAD syndrome, usually IgM-MG), and (d) polyneuropathy, organomegaly, endocrinopathy, monoclonal disorder, and skin changes (POEMS syndrome, vascular endothelial growth factor-mediated) [1, 5]. Association of MADSAM with MG has not been described [6]. CLL-like morphology, a low Matutes score, and CD200-positivity supported the diagnosis of aCLL in this case [7, 8]. Follicular lymphoma was unlikely because of CD10-negativity, and CD200-positivity excluded mantle cell and marginal zone lymphoma. Absence of plasmacytic differentiation and CD200-positivity argued against lymphoplasmacytic lymphoma (LPL). Absence of hairy cell markers excluded hairy cell leukemia [8, 9]. An abnormal sFLC ratio might not necessarily imply monoclonality and could happen in the setting of renal impairment or polyclonal FLC increase secondary to infection and inflammation [10]. Normal renal function test and immunoglobulin levels made these possibilities unlikely in our case. After exclusion of the polyclonal causes, abnormal sFLC ratio could suggest monoclonality, even if results of serum/urine electrophoresis and immunofixation are negative [11]. Our patient had B-CLPD (aCLL), evidence of monoclonality (abnormal sFLC ratio), and clinical and electrophysiological findings, suggesting

MADSAM. Workup for amyloidosis and cryoglobulinemia was negative. Negative PN antibody panel was consistent with MADSAM [6]. Autoimmune manifestations including PN are well known in CLPD [12]. Normal Tregs and a negative autoimmune panel argued against this possibility. Absence of neural thickening or enhancement on 18FDG PET-CT scan and normal CSF analysis make consideration of neurolymphomatosis unlikely. Either direct toxicity or autoantibody property of kappa light chains could have been responsible for PN in our case. Rapid clinical response seen with single agent rituximab, paralleled by decline in clonal B-cells and normalization of sFLC indicates MG-driven neural damage. Clinical response deepened with maintenance rituximab, possibly suggesting ongoing clonal eradication with possible neural regeneration. Recently, Chen *et al.* [13] described 5 patients with IgM-paraprotein related PN, with identifiable B-cell clones in the BM. Responsiveness to rituximab suggested potential significance of B-cell clones as the underlying cause of the pathogenesis of PN. Identification of clone secreting M-protein (B-cells, PC, and LPL cells) is of paramount significance as clone-directed therapy (rituximab-based regimens for B-cell clone, bortezomib, or lenalidomide-based regimens for PC clone, and either of the two regimens for LPL-clone) improves clinical outcomes of MGCS, including monoclonal gammopathy of renal significance [3, 4]. Although PN has been reported in about 2.2% cases of CLL, response of PN to rituximab monotherapy has not been described. Moreover, occurrence of PN in a patient with aCLL has not been reported [14]. Since data for clone-directed therapy in PPN is most robust in POEMS syndrome and DADS (anti-MAG neuropathy) [5], the current report widens the spectrum of PPN; thus, we propose the term “MGNS” for PPN unrelated to MM and WM. Presence of MG in a case of PN must trigger a search for an underlying clone as timely initiation of clone-directed therapy could possibly improve neurological outcome.

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Large granular lymphocytes (LGL) in primary Sjögren syndrome (pSS): immunophenotype and review on the pathological role of T cells in pSS

TO THE EDITOR: Primary Sjögren syndrome (pSS) is a chronic autoimmune systemic disease that mainly affects the exocrine glands, causing severe inflammation with accompanying destruction of the gland. It is also characterized by systemic symptoms and laboratory findings of polyclonal B-lymphocyte activation, hypergammaglobulinemia, and positive autoantibodies. Its pathophysiology is not yet fully understood; genetic factors seem to play a relatively minor role, while environmental ones, most likely infections, contribute to disease onset and progression by activation of the innate and adaptive immune systems. Although the role of B cells in the disease is better characterized, little is known about the involvement of T cells in pSS [1-3].

We report a case of a pSS patient who was followed up at our hematology unit for monoclonal CD8+ T lymphocytosis. We have discussed the immunophenotype of CD8+ T lymphocytes and reviewed the involvement of pathological CD8+ T lymphocytes in pSS.

Case report

In September 2012, a 39-year-old woman was referred to our outpatient service because of unexplained lymphocytosis, mild anemia, and thrombocytopenia. Together with the lymphocytosis, the patient developed xerophthalmia and xerostomia with anti-nuclear, extractable nuclear antigen, and Ro-SSA antibody positivity. A diagnosis of pSS was made following salivary gland biopsy. Clinical evaluation showed slight dryness of the mouth and eyes with no alterations to the spleen, liver, and lymph nodes. The tests performed on September 22, 2012 were significant for $9.61 \times 10^9/L$ leukocytes, $8.19 \times 10^9/L$ lymphocytes, $106 \times 10^9/L$ platelets, and 11.8 g/dL hemoglobin; normal liver and kidney function values were seen with a slight polyclonal rise in the immunoglobulin dosage. In addition, hepatitis markers (A, B, and C serology) and parasitological stool assays were negative.

Therefore, to investigate a possible lymphoproliferative disorder, bone marrow and imaging studies were carried out. Bone marrow biopsy showed an interstitial and often intra-sinusoidal infiltration by small-medium sized CD8+ T lymphocytes, which had partial CD5 expression. However, no other sites appeared to be involved since a total body CT examination showed no adenopathies or liver or spleen enlargement.

Flow cytometric analyses were performed in the peripheral blood and bone marrow samples using a FacsCanto II cytometer (BD Biosciences, Franklin Lakes, NJ, USA) equipped with three lasers (405, 488, 633 nm). A total of