Refractory Adult Primary Autoimmune Neutropenia that Responded to Alemtuzumab

Anu R. Neerukonda¹, Fengshuo Lan², Theodore Gabig³ and Takeshi Saraya³

Abstract

Primary autoimmune neutropenia (P-AIN) is an extremely rare disease. The most effective treatment for primary P-AIN is a granulocyte colony-stimulating factor; however, no curative treatment has been reported. We herein report a case of an adult P-AIN patient with a relatively mild medical history (irrespective of the severe neutropenia) who showed a sustained hematological response over seventeen months after the initiation of treatment with subcutaneous Alemtuzumab.

Key words: primary autoimmune neutropenia, adult, Alemtuzumab

Introduction

Although several cases of primary autoimmune neutropenia (P-AIN) have been reported in infants (1) and a few cases have been reported in adults (2), limited data exists regarding effective treatment strategies for patients in whom conventional treatment has failed. Bux et al. (1) reported numerous cases of P-AIN in children and Killick et al. (2) reported the course of a patient with severe autoimmune neutropenia in whom transient responses occurred after treatment with corticosteroids, granulocyte-colony stimulating factor (G-CSF), and antilymphocyte globulin. Their report noted that no patients showed any response to azathioprine, the intravenous injection of immunoglobulin (IVIG), or cyclosporine but that a sustained hematologic response was achieved with Alemtuzumab. We herein present a case of a patient with P-AIN which was refractory to several treatments but in whom a significant response was achieved with the subcutaneous administration of Alemtuzumab.

Case Report

A 35-year-old Caucasian man in good health presented with gingival and rectal pain. An examination revealed a rectal fissure on exam. After laboratory testing revealed an absolute neutrophil count of zero, he was treated with G-CSF, Filgrastim (1-3), which achieved a transient response. He was readmitted a year later with total white blood cell count of 700 cells/μL, an absolute neutrophil count of 0, a hemoglobin level of 14.2 g/dL, and a platelet count of 358,000/μL. He had multiple readmissions that year for cellulitis and acute febrile illnesses. At these readmissions, the patient was treated with Filgrastim and the treatment achieved a transient response. The patient had no history of alcohol, tobacco or intravenous drug use and no family history of autoimmune disease or periodic fever syndromes. The results of a polymerase chain reaction (PCR), which was performed in the diagnostic evaluation of the patient, revealed that the patient was negative for Hepatitis B, Hepatitis C, HIV 1/2, Cytomegalovirus, Parvovirus B19 IgM and IgG antibodies and no serologic markers for Epstein-Barr virus (EBV) (including viral capsid antigen, early antigen and EBV nuclear antigen) were detected. Flow cytometry of the peripheral blood leukocytes and a T cell receptor gene rearrangement analysis revealed that the patient was negative for large granular cell leukemia and clonal disease, respectively. Anti-nuclear antibody and rheumatoid factor tests were negative. A high cytoplasmic-antineutrophil cytoplasmic antibody (c-ANCA) titer was detected (up to 1:1,280). The titer of proteinase-3/myeloperoxidase immunoglobulin G (PR-3/ MPO IgG) was also elevated. The presence of

¹Department of Medicine, SUNY Stony Brook University Hospital, USA, ²Department of Medicine, Division of Hematology/Oncology, SUNY Stony Brook University Hospital, USA and ³Department of Respiratory Medicine, Kyorin University Hospital, Japan

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Correspondence to Dr. Takeshi Saraya, sara@yd5.so-net.ne.jp
anti-neutrophil cytoplasmic antibodies was confirmed by an indirect granulocyte immunofluorescence test (GIFT) and a granulocyte agglutination test (GAT) (1). Granulomatosis with polyangiitis (GPA) and other systemic vasculitic syndromes were ruled out by chest imaging/CT and a skin biopsy of the right calf. The absence of airway, kidney, joint, skin, mucosa, and central nervous system involvement made the diagnosis of systemic lupus erythematosus (SLE), Felty’s syndrome, GPA or other vasculitic syndromes less likely. The patient’s bone marrow aspirate revealed normal karyotype and normal cellularity with maturation arrest at the myelocyte stage (Fig. 1). The marrow aspirate revealed occasional hypolobulated megakaryocytes (Fig. 2), which have been described in the setting of chronic idiopathic neutropenia; however the morphologic criteria for myelodysplastic syndrome or large granular lymphocyte syndrome were not met. Based on the positive findings of both direct and indirect GIFT and GAT, the patient was diagnosed with P-AIN.

His neutropenia transiently improved (each time) with the administration of Rituximab (375 mg/m², three doses, once every three weeks) (4, 5) together with cyclosporine (6) and methylprednisolone (100 mg, intravenously, weekly), IVIG (1, 2) (2 g/kg, weekly) and Filgrastim (5 μg/kg, subcutaneously, weekly, for 6 months), after which his neutropenia became minimally responsive. His treatment was then changed to methotrexate (10 mg, weekly) with Filgrastim (5 μg/kg, daily), which achieved a moderate response for approximately 2 years until he presented with intractable left upper quadrant pain from splenomegaly. A splenectomy was then performed after the administration of a 23-valent pneumococcal vaccine. The surgical pathology revealed non-specific reactive lymphoid hyperplasia. Post-splenectomy, his neutrophil counts rose significantly, but decreased to 500/μL after 4 months despite the continuation of Filgrastim injections.

Based on the study of Willis et al., in which Campath-1H was used intravenously in the treatment of autoimmune cy-
topenias (7), a decision was made to administer a modified regimen of Alemtuzumab [10 mg (fixed dose), subcutaneously] 5 days a week for 2 weeks. The patient’s neutrophil count rose and his response was sustained for over seventeen months until his death from a motor vehicle accident. In the 17 months after the initiation of Alemtuzumab therapy, he was hospitalized 4 times for cellulitis or fever compared with 9, 5 and 6 times in the three preceding years.

Discussion

P-AIN, which has an estimated frequency of 1:100,000, is a rare disorder which predominantly occurs in early childhood. P-AIN is characterized by neutropenia due to the peripheral destruction of neutrophils by antibodies directed against neutrophil antigens (HNAs) (8). Primary AIN is usually diagnosed based on the exclusion, the criteria include: 1) the reduced production of neutrophils (without congenital or acquired diseases other than AIN); 2) sequestration (without hypersplenism [vascular or tissue pools]), 3) increased peripheral destruction such as septicemia (9).

As shown in our case, adult P-AIN patients, 35% of whom have been shown to be positive for antineutrophil autoantibodies, have a relatively mild medical history, irrespective of their severe neutropenia (10). This is a clinical clue to the diagnosis of P-AIN (11). In contrast to cases of P-AIN that occur in infancy/childhood (1), the adult disease has a chronic course and spontaneous remission is unusual (2). Bux et al. reported numerous cases of P-AIN in infants and established the criteria to confirm its diagnosis by the detection of anti-neutrophil antibodies with a granulocyte immunofluorescence test (GIFT) and a granulocyte agglutination test (GAT). We performed both of these tests to establish a diagnosis of P-AIN after other etiologies had been excluded. In the present case, it was hypothesized that the patient’s splenomegaly occurred due to the phagocytosis of antibody-sensitized neutrophils by macrophages/histiocytes.

AIN can be caused by granulocyte-specific antibodies. Most of the autoantibodies are directed against the FcγIIb and the leukocyte adhesion molecule CD11b/CD18 (1). Although the direct causal relationship between AIN and ANCA remains unclear, previous reports suggest the possibility of ANCA-related neutropenia via complement-mediated cytotoxicity (12) or phagocytosis (13), which may have affected the neutrophil count of our patient.

ANCA and neutropenia have also been reported in other autoimmune diseases such as autoimmune hepatitis, primary sclerosing cholangitis, and Sjögren’s syndrome in the absence of vasculitis (14). The significance of lupus anticoagulant in the development of AIN in our patient also remains to be elucidated.

Although no curative strategy exists for primary P-AIN, the most effective treatment for primary AIN is G-CSF (3). According to Palmblad et al., a number of patients with severe P-AIN have demonstrated transient responses to Filgrastim, corticosteroids, or antilymphocyte globulin, whereas treatment with Cyclosporine, Azathioprine and IVIG has been shown to be unsuccessful (15). Alemtuzumab is the only therapeutic agent that has been shown to induce a sustained response (2, 15). Alemtuzumab is a humanized IgG1k monoclonal antibody that recognizes the CD52 antigen on human lymphocytes, monocytes, macrophages, eosinophils, dendritic cells and natural killer cells. Alemtuzumab causes cell lysis via complement or antibody-dependent cellular cytotoxicity as well as by directly acting on the T lymphocytes, which play an important role in controlling the expansion of antibody producing autoreactive B-cell clones (15). In the case of our patient, who had refractory P-AIN, Alemtuzumab was effective in maintaining stable neutrophil counts and reducing neutropenia-related hospitalizations.

The present case demonstrated that Alemtuzumab is potentially a novel treatment option for patients with refractory P-AIN. However, Alemtuzumab therapy should only be considered in patients who have failed multiple conventional, less toxic treatments due to the high risk of infectious complications.

The authors state that they have no Conflict of Interest (COI).

References

