Annals of Hematology (2019) 98:2443–2445
https://doi.org/10.1007/s00277-019-03780-1

LETTER TO THE EDITOR

Autoimmune hemolytic anemia in refractory hairy cell leukemia on dabrafenib and trametinib

Damond Barrick Ng[1] · Gary Schiller[1,2] · Edward Ha[1,3]

Received: 22 July 2019 / Accepted: 5 August 2019 / Published online: 13 August 2019

Dear Editor,

Hairy cell leukemia (HCL) is a rare, indolent B cell malignancy characterized by bone marrow infiltration, splenomegaly, pancytopenia, and neoplastic cells morphologically with cytoplasmic "hair-like" projections [1]. Analogous to other B cell disorders, autoimmune diseases have been reported in HCL; however, autoimmune hemolytic anemia (AIHA) has seldom been reported [2, 3].

We report a 74-year-old man with refractory HCL on dabrafenib/trametinib who presented with fatigue, dyspnea, dark red urine, and dizziness exacerbated by hot showers. He was diagnosed with HCL at the age of 53 years and treated with cladribine resulting in a complete response (CR) that lasted 15 years before requiring reinduction. Three years later, the patient was enrolled in a moxetumomab pasudotox trial for refractory HCL, but his bone marrow persistently exhibited disease after six cycles. Sustained partial remission was achieved while on dabrafenib/trametinib trial for 1.5 years prior to admission (Fig. 1a). While on the study, he developed pallor without splenomegaly. Baseline assessment was significant for hemoglobin 6.6 g/dL, LDH 1497 U/L, reticulocyte count 20.85%, and undetectable haptoglobin. DAT demonstrated 3+ IgG and negative C3d, confirming warm AIHA. He did not have any antecedent infection, antibiotic use, or significant medication changes. Peripheral smear revealed atypical lymphocytes with characteristic projections, normocytic anemia, and absence of Heinz bodies. Flow cytometry of peripheral blood demonstrated monotypic lambda restricted B cells (0.7%) that co-expressed CD11c and CD103. Flow cytometry on marrow aspirate showed 3–5% infiltration with the same monoclonal population. Of note, the *BRAF V600E* mutation was absent and a previously identified DNMT3a mutation was unchanged from 2 years prior (Fig. 1b).

Dabrafenib/trametinib was discontinued, and our patient was started on prednisone (1 mg/kg). Steroid therapy and three units of blood were unsuccessful in decelerating hemolysis; intravenous immunoglobulin (IVIG, 1 g/kg) was administered for 2 days, which led to a gradual decrease in transfusion dependency and hemoglobinuria resolution. Rituximab was considered but not recommended as it would result in trial exclusion. Hemolysis markers and hemoglobin normalized by 6 weeks post-discharge on prednisone. Our patient was not restarted on dabrafenib/trametinib and remains asymptomatic without recurrence of AIHA.

To our knowledge, this is the first reported case of warm AIHA in the setting of dabrafenib/trametinib therapy for refractory HCL. Though possibly due to HCL, a non-clonal process is favored with the absence of *BRAF V600E*, stable *DNMT3a* mutation, and down-trending bone marrow infiltration (Fig. 1b). *BRAF V600E* is present in active and residual post-treatment disease but is not identified in CR [4, 5]. Mutations in *DNMT3a* are non-specific changes in hematopoietic processes and are not associated with B cell lymphomas [6]. In patients on dabrafenib/trametinib for longer than 36 months, the incidence of adverse events was highest in the first 6 months with no reported events after 30 months in 20% of cases [7]. The incidence of AIHA with ongoing dabrafenib/

✉ Damond Barrick Ng
dng@mednet.ucla.edu

[1] David Geffen School of Medicine, University of California, Los Angeles, 10833 Le Conte Avenue, Los Angeles, CA 90095, USA

[2] Division of Hematology/Oncology, Department of Medicine, University of California, Los Angeles, Los Angeles, CA, USA

[3] Department of Medicine, University of California, Los Angeles, Los Angeles, CA, USA

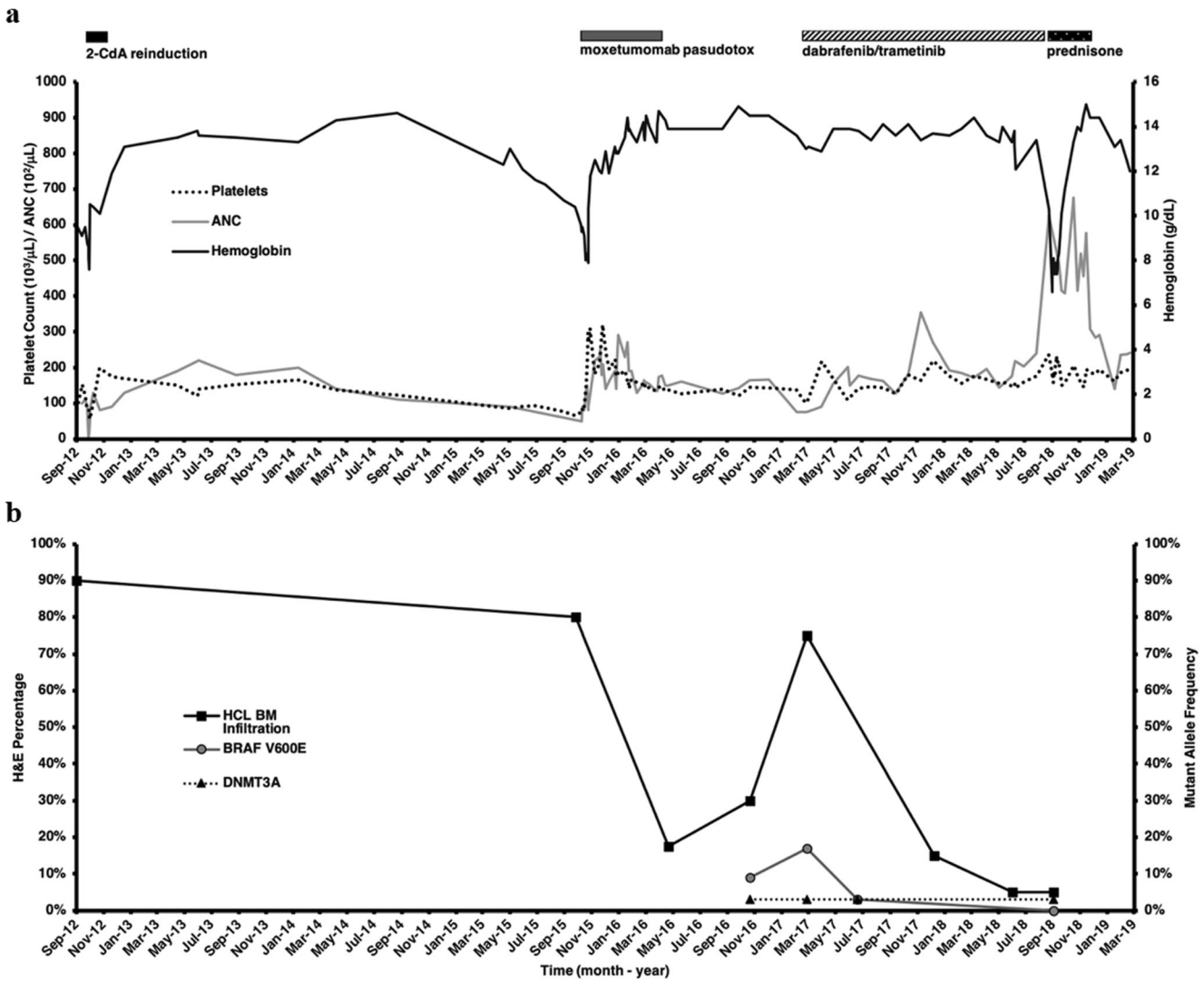

Fig. 1 Progression of HCL with treatment course and peripheral blood counts. The case presented occurred on September 2018. **a** Absolute neutrophil count (ANC), platelet count, and hemoglobin over multiple treatment modalities since cladribine (2-CdA) reinduction at 0.14 mg/kg in October 2012. Initial 2-CdA course (0.09 mg/kg) administered after diagnosis in August 1997. **b** HCL involvement in bone marrow, assessed by hematoxylin and eosin (H&E) stain with mutant allele frequencies reported via hematologic malignancy sequencing panel. At HCL diagnosis, bone marrow showed 65% infiltration

trametinib clinical trials in refractory HCL should be determined and its prognostic relevance investigated. This is also the first report of warm AIHA in the setting of established HCL successfully treated with steroids and IVIG. Domingo et al. described the first case of warm AIHA preceding HCL diagnosis [2]. Two reports described AIHA treatment in HCL with cladribine and interferon-alpha, respectively [8, 9]. This case contributes to the accumulating reports of autoimmune hematologic conditions associated with HCL and provides insight into treatment of refractory disease.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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