

# Resolution of eosinophilia and elevated immunoglobulin E with ibrutinib for chronic lymphocytic leukemia



Eosinophilia can be categorized as mild (500–1,500 eosinophils/ $\mu$ L), moderate (1,500–5,000 eosinophils/ $\mu$ L), or severe ( $\geq$ 5,000 eosinophils/ $\mu$ L), with hypereosinophilia referring to an eosinophil count of 1,500 or more eosinophils/ $\mu$ L.<sup>1</sup> Rarely, eosinophilia is associated with hematologic disorders that produce eosinophilopoietic cytokines.<sup>2</sup> We describe a case of eosinophilia and elevated immunoglobulin E (IgE) in a 61-year-old gentleman who was subsequently diagnosed with B-cell chronic lymphocytic leukemia (B-CLL). His eosinophilia and immunoglobulin E (IgE) levels declined significantly after initiating ibrutinib therapy for B-CLL.

A 61-year-old man developed pruritic papules on his scalp, where he received botulinum toxin injections for chronic migraine headaches. He was evaluated in the dermatology clinic, where a complete blood count was obtained for his pruritus. He had eosinophilia to 13%, an absolute count of 975 eosinophils/ $\mu$ L, and elevated IgE of 15,513 kU/L. The patient had no prior history of atopy or rashes. Repeat levels remained elevated (Fig 1), which prompted further testing. A thorough evaluation of infectious, autoimmune, and allergic causes was unrevealing (eTable 1). His evaluation included human immune deficiency virus, parasite serologies, antineutrophil cytoplasmic antibody (ANCA) screen, immunoglobulin levels, allergic bronchopulmonary aspergillosis screen, environmental allergy immunoCAP testing, serum electrophoresis, and FIP1-like-1–platelet-derived growth factor receptor- $\alpha$  testing on peripheral blood. Because hematological malignancies can cause elevated eosinophils and IgE levels, lymphocyte phenotyping was obtained. The only identified abnormality was a monoclonal B cell population on peripheral blood flow cytometry (CD5+, CD19+, CD23+, CD10–, CD20+, and dim lambda light chain restricted). He was referred to a hematology clinic and diagnosed with B-CLL, but treatment was not initiated, because he was asymptomatic. No eosinophilic organ involvement was found based on laboratory findings, echocardiogram, and multiple radiographic imaging studies. The pruritic lesions on his scalp were localized to the botulinum injection sites and attributed to mild folliculitis and scalp dysesthesia. He was started on scheduled fexofenadine 180 mg daily, doxepin 20 mg nightly, and clindamycin lotion for scalp pruritus. Eventually, he discontinued clindamycin lotion and doxepin, but continued fexofenadine daily. His rash resolved shortly after his initial visit to dermatology, before starting ibrutinib therapy.

One year later, he developed night sweats, fatigue, and cervical lymphadenopathy. Positron emission tomography scans demonstrated new hypermetabolic bilateral cervical and supraclavicular lymphadenopathy. A lymph node biopsy showed a clonal interfollicular B cell infiltrate consistent with CLL. A bone marrow biopsy showed hypercellular bone marrow with 20% involvement by a non-Hodgkin B-cell lymphoma. The c-KIT D816V mutation testing from bone marrow was normal. These biopsy specimens were consistent with B-CLL, and ibrutinib was started at 420 mg daily. The CD19+ and CD5+, CD19+, CD23+, CD10–, CD20+, and dim lambda light chain–restricted lymphocyte counts decreased (Fig 1A and 1B). His constitutional symptoms improved with therapy, and both his eosinophilia and his IgE level decreased (Fig 1C and 1D).

During the observation period before starting ibrutinib, the patient's eosinophil levels fluctuated. The first time his levels decreased was after prednisone use for an emphysema flare. The

second time occurred after his excisional lymph node biopsies after receiving general anesthesia, although no clear correlation was determined. The third time his levels normalized after a viral illness. His eosinophilia returned after each episode until ibrutinib was started, suggesting that his CLL was the primary cause of his eosinophilia.

His eosinophil levels have remained normal for over 1 year since starting therapy. The ibrutinib treatment will be continued until disease progression. He developed muscle spasms that were attributed to the ibrutinib and treated with baclofen. He continues to be followed by Hematology and Immunology.

Eosinophilia is associated with several hematologic malignancies, including Hodgkin's lymphoma (HL), non-Hodgkin's lymphoma (NHL), and leukemia.<sup>3</sup> A recent retrospective study shows that NHL is the most common eosinophilia-associated lymphoma, whereas CLL is the most common leukemia diagnosed in patients with peripheral eosinophilia. Hematologic malignancies are more common in patients with hypereosinophilia than in those with simple eosinophilia.<sup>3</sup> Correlation between the degree of eosinophilia and disease burden suggest that malignant cells are producing eosinophilopoietic cytokines. Th2 cytokines likely play a role, because they are involved in B-cell proliferation and survival, Ig class switching to IgG4 and IgE, and eosinophil differentiation, proliferation, and activation. These cytokines include interleukin (IL)–4, IL–5, IL–6, IL–9, IL–10, and IL–13.<sup>4</sup> Of these, IL–4 and IL–5, which are critical for IgE production and eosinophilopoiesis, respectively, are of interest in this case.

Possible mechanisms for eosinophilia with Th2 cytokines have been extensively studied in HL.<sup>4</sup> Overproduction of Th2 cytokines, particularly IL–5 and IL–13, has been demonstrated in HL. IL–5 messenger RNA is strongly expressed by Reed Sternberg (RS) cells from HL with eosinophilia.<sup>5</sup> RS cells express IL–13 and its receptor, and antibody-mediated neutralization of IL–13 causes dose-dependent reduction of growth in RS cell lines,<sup>6</sup> suggesting that IL–13 functions as an autocrine growth factor. IL–13 also induces production of chemokines such as eotaxin, a chemoattractant for eosinophils; eotaxin expression correlates with tissue eosinophilia.<sup>7</sup> Similar to HL, T-cell–derived cytokines are thought to play an important role in proliferation and survival of B cells in CLL.

B-CLL is characterized by accumulation of clonal CD5+ lymphocytes that are highly resistant to apoptosis. IL–4 has been identified as a key cytokine in B-CLL that increases expression of anti-apoptotic proteins Bcl–2 and PI–3 kinase.<sup>8</sup> T cells and B cells from B-CLL patients have higher levels of cytoplasmic IL–4, and IL–4 receptor expression is increased in CLL B-cells compared with normal B cells, suggesting an autocrine or paracrine pathway for IL–4.<sup>9</sup> Anti-IL–4 monoclonal antibodies significantly reduce resistance to apoptosis.<sup>9</sup> Although the mechanism for eosinophilia in B-CLL has not yet been studied extensively, possibly IL–4 promotes production of IgE in addition to cell survival. In contrast, IL–5 has been found to induce apoptosis in B-CLL cells, and the presence of IL–4 significantly reduces the level of apoptosis induced by IL–5.<sup>10</sup> A source of IL–5 in B-CLL has not been identified.

The elevated IgE in our patient was thought to be secondary to the malignant cells overproducing cytokines such as IL–4 that influence B-cell immunoglobulin synthesis through a similar mechanism as the eosinophilia. Many of the same cytokines are involved in eosinophilic differentiation and Ig class switching from IgM to IgE, and B-CLL can trigger a Th2 profile and produce cytokines such as IL–4.<sup>4,9</sup> However, no serum or tumor cells from our patient are available for cytokine analysis.

Our case demonstrates that B-CLL can present with eosinophilia and elevated IgE that correlates with disease burden. Resolution of

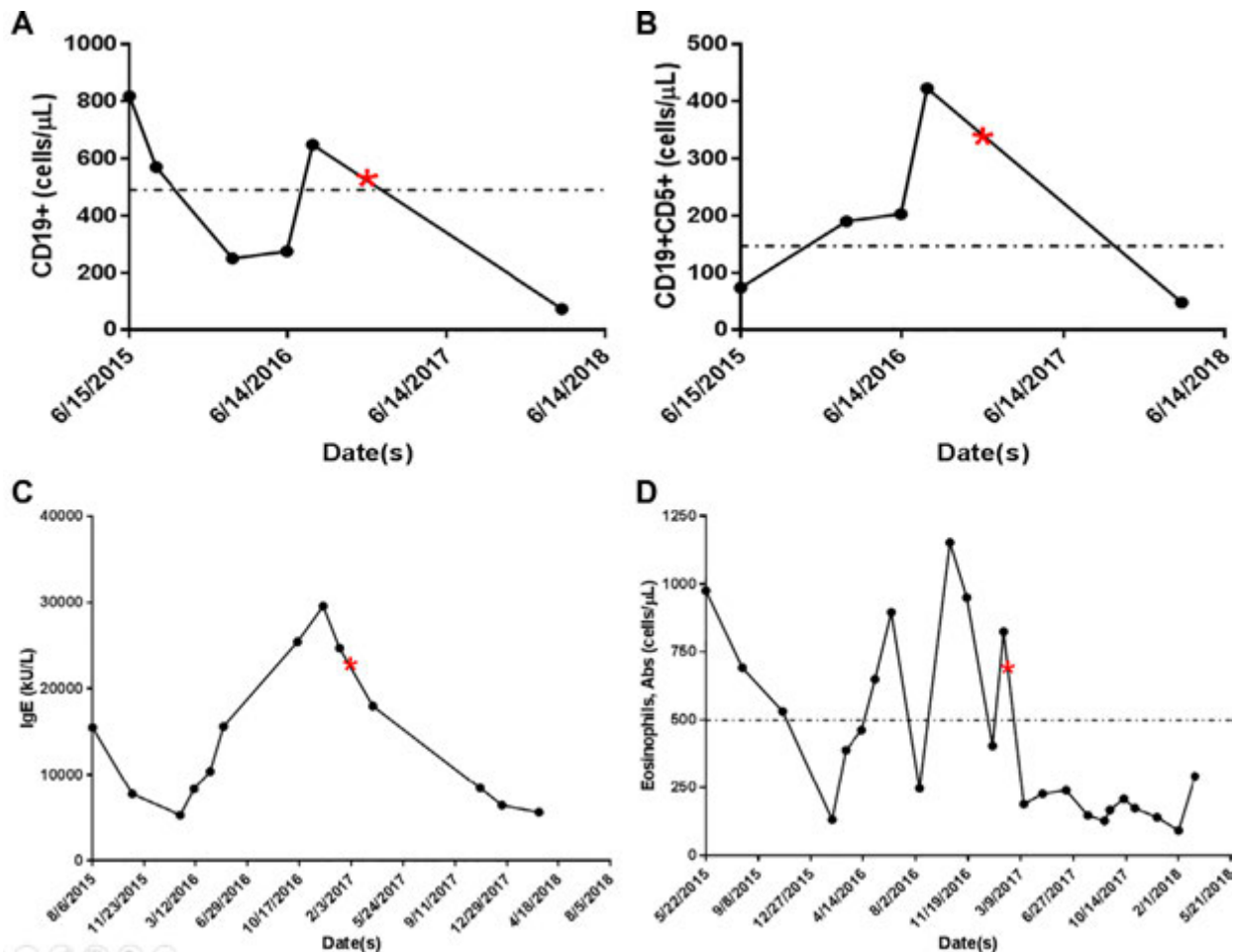


**Figure 1.** CD19+ cells (A), CD19+CD5+ cells (B), IgE level (C), and absolute eosinophil count (D) over time. All levels decreased after initiation of ibrutinib in February of 2017 (marked with asterisks). The normal threshold for the CD19+ cells, CD19+CD5+ cells, and absolute eosinophil count was denoted by the dashed line.

eosinophilia and elevated IgE with ibrutinib suggests that they are part of a B-cell–induced Th2 response. Overproduction of Th2 cytokines has been demonstrated in HL with eosinophilia, and a similar mechanism may explain eosinophilia in B-CLL. Further study of cytokine production by B-CLL malignancies may explain the findings of eosinophilia and elevated IgE in our patient.

#### Supplementary Data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.anai.2018.07.007>.

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**eTable 1**  
The Initial Laboratory Evaluation

| Laboratory findings              | Measured values    | Reference range    |
|----------------------------------|--------------------|--------------------|
| <b>General</b>                   |                    |                    |
| Eosinophils %                    | 13.0               | 0%-5%              |
| Abs eosinophils                  | 975 cells/ $\mu$ L | 0-1 cells/ $\mu$ L |
| Alanine aminotransferase (ALT)   | 22.0               | 0-34 U/L           |
| Aspartate aminotransferase (AST) | 28.0               | 0-34 U/L           |
| Alkaline phosphatase             | 62.0               | 30-130 U/L         |
| Total bilirubin                  | 0.3                | <1.20              |
| TSH                              | 3.1                | 0.3-4.2 $\mu$ U/mL |
| <b>Infectious</b>                |                    |                    |
| Strongyloides antibody, IgG      | 0.0                | <1.49              |
| Norovirus                        | Not detected       |                    |
| Ova + parasite                   | Negative           |                    |
| Cryptosporidium antigen          | Negative           |                    |
| Giardia antigen                  | Negative           |                    |
| Cyclospora                       | Negative           |                    |
| HIV antigen/antibody             | Nonreactive        |                    |
| Hepatitis B                      | Negative           |                    |
| Hepatitis C                      | Negative           |                    |
| <b>Immunology</b>                |                    |                    |
| Tryptase                         | 9.0                | <11.5 ng/mL        |
| IgE                              | 15,513.0           | 0-115 kI/L         |
| IgG                              | 1,120.0            | 700-1,600 mg/dL    |
| IgG1                             | 509.0              | 382-929 mg/dL      |
| IgG2                             | 592.0              | 241-700 mg/dL      |
| IgG3                             | 77.0               | 22-178 mg/dL       |
| IgG4                             | 63.9               | 4.0-86 mg/dL       |
| IgA                              | 183.0              | 70-400 mg/dL       |
| IgM                              | 72.0               | 40-230 mg/dL       |
| C3                               | 85.0               | 81-145 mg/dL       |
| C4                               | <10                | 16-39 mg/dL        |
| PDGFRA and B                     | Negative           |                    |
| ANA                              | <1:80              | <1:80              |
| C-ANCA                           | Negative           |                    |
| P-ANCA                           | Negative           |                    |
| Atypical P-ANCA                  | Negative           |                    |
| dsDNA antibody                   | <12.3              | <30 IU/mL          |
| Rheumatoid factor                | <15.9 IU/mL        |                    |
| Tissue transglutaminase          | <1.9               | <20 CU             |

Abbreviations: TSH, thyroid-stimulating hormone; Ig, immunoglobulin; HIV, human immune deficiency virus; PDGFRA, platelet-derived growth factor receptor- $\alpha$ ; PDGFRB, platelet-derived growth factor receptor- $\beta$ ; ANA, antinuclear antibody; C-ANCA, cytoplasmic antineutrophil cytoplasmic antibodies; P-ANCA, perinuclear antineutrophil cytoplasmic antibodies; dsDNA, double-stranded DNA.