involvement, and all had improvements in their symptoms. Other patients who had cutaneous and neurological involvement also had symptomatic improvements. The treatment was tolerated well, with only one patient discontinuing therapy because of headache. The performance status improved in 75% of patients, and the median survival for the cohort was 24 months. It is likely that etanercept had an effect on AL amyloidosis, but appropriate response assessment using free light chains and cardiac biomarkers was not available.

To our knowledge, this is the first report of a patient with AL amyloidosis and symptoms related to GI involvement responding to therapy with adalimumab. Tumor necrosis factor-α could play a role in the pathophysiology of AL amyloidosis. In our patient, diarrhea and severe abdominal pain improved dramatically after receiving a total dose of 80 mg of adalimumab subcutaneously. The effectiveness of this agent could be investigated further in phase II/III trials in patients with refractory AL amyloidosis.

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Identification of a Novel ZBTB20-JAK2 Fusion by Mate-Pair Sequencing in a Young Adult With B-Lymphoblastic Leukemia/Lymphoma

To the Editor: B-lymphoblastic leukemia/lymphoma (B-ALL), BCR-ABL1–like (for expansion of gene symbols, search use tool at www.genenames.org) is a provisional entity in the revised 2017 World Health Organization classification. This entity is characterized by a gene expression profile similar to BCR-ABL1 fusion–positive B-ALL but lacks the BCR-ABL1 fusion.1,2 The BCR-ABL1–like subtype is observed in approximately 20% to 25% of B-ALL cases in adolescents and young adults (15-39 years) and is associated with aggressive leukemia with a high risk of relapse and death, although the discovery of kinase-activating fusions suggests these tumors may be amenable to tyrosine kinase inhibitor (TKI) therapy.1,3 In approximately 5% of cases of pediatric BCR-ABL1–like B-ALL and more frequently in adolescent and young adult cases, JAK2 rearrangements occur and result in constitutive activation of the JAK-STAT (Janus kinase–signal transducers and activators of transcription) signaling pathway and may respond to TKI therapy.2,4 To date, over 20 JAK2 gene fusion partners have been identified.2,5 Herein, we report identification of a novel JAK2 gene fusion partner in a young adult with newly diagnosed B-ALL that we characterized using mate-pair sequencing.

Report of Case A 33-year-old woman presented with malaise, dyspnea, and a 3-week history of worsening fatigue. She had an elevated white blood cell count of 43.8 × 10^9/L, anemia (hemoglobin level, 6.6 g/dL [to convert to g/L, multiply by 10.0], and thrombocytopenia (platelet count, 9 × 10^9/L). The peripheral blood smear revealed circulating nucleated red blood cells and blasts. Concurrent eosinophilia (absolute eosinophil count, 5.7 × 10^9/L) and dysplastic changes in the neutrophil lineage were also noted. Bone marrow examination revealed variably sized blasts (57% of total nucleated cells)
FIGURE. Conventional chromosome, fluorescence in situ hybridization, and mate-pair sequencing results. A, Representative karyogram demonstrating t(3;9)(q13;p24). This clone was observed in 19 of 20 metaphase cells analyzed. B, Representative interphase and metaphase nuclei showing a JAK2 rearrangement using a JAK2 break-apart fluorescence in situ hybridization probe, indicated by single red and green signals. The single fusion signal indicates a single intact JAK2 gene region. C, Junction plot demonstrating a translocation between the ZBTB20 gene (intron 4, NM_001164342) at 3q13.31 and the JAK2 gene (intron 18, NM_004972) at 9p24.1. This translocation is predicted to create an in-frame chimeric gene consisting of exons 1 through 4 of ZBTB20 and exons 19 through 25 of JAK2. D, Sanger sequencing confirmation of the fusion breakpoint. E, Schematic diagram showing ZBTB20-JAK2 chimeric protein structure.
with scant basophilic cytoplasm and indistinct nucleoli as well as increased eosinophils and precursors (20% of total nucleated cells). Flow cytometry revealed an increased blast population positive for CD34, CD19, CD10, CD45 (partial dim), CD13 (partial), HLA-DR, CD38, and CD66c (partial) and negative for CD3, CD15, CD16, CD33, CD117, CD2, CD7, CD56, CD36, CD64, CD20, and CD9. This immunophenotypic profile confirms a B-lineage acute leukemia. Genomic characterization was performed on the diagnostic bone marrow aspirate specimen. FLT3 mutation/internal tandem duplication was absent. Conventional chromosome analysis identified an apparently balanced t(3;9)(q13:p24) in 19 of 20 metaphases analyzed (Figure A), and B-ALL panel fluorescence in situ hybridization studies confirmed a suspected JAK2 rearrangement at 9p24 (Figure B) and also revealed a cryptic heterozygous JAK2F1 deletion at 7p12 in approximately 90% of interphase nuclei. In order to identify the JAK2 fusion partner, we performed mate-pair sequencing as previously described. Mate-pair sequencing identified a t(3;9)(q13.31;p24.1) with breakpoints located within intron 4 of ZBTB20 (NM_001164342) and intron 18 of JAK2 (NM_004972) that was predicted to create an in-frame chimeric fusion consisting of exons 1 through 4 of ZBTB20 and exons 19 through 25 of JAK2 (Figure C).  

**Discussion** The ZBTB20 protein is a member of the BTB (Broad complex, Tramtrack, Bric-a-brac)—ZF (zinc finger) family that acts primarily as transcriptional repressors and is involved in a variety of biological processes, including chromatin remodeling, development, differentiation, and tumor formation. ZBTB20 is expressed in a number of different hematopoietic lineages, including dendritic cells, monocytes, T cells, and B cells. Within the B lineage, ZBTB20 is expressed in peritoneal B1 cells, germinal center B cells, and in long-lived bone marrow plasma cells. In B1 cells, ZBTB20 is highly expressed and promotes BLIMP1 expression and terminal B-cell differentiation, although PAX5 has also been shown to bind to the ZBTB20 promoter, suggesting that it may down-regulate ZBTB20 expression in immature B cells. Aberrant ZBTB20 expression has been demonstrated in certain human B-cell lymphoma cell lines, suggesting that dysregulated expression could lead to tumorigenesis. However, whether loss of normal ZBTB20 function contributes to tumorigenesis of this B-ALL requires further investigation.

We predict that the ZBTB20-JAK2 fusion could function in a similar manner to other chimeric JAK2 fusions such as BCR-JAK2, PCM1-JAK2, and ETV6-JAK2. In each of these fusions, it is thought that the JAK2 fusion partner promotes dimerization leading to constitutive activation of the JAK2 tyrosine kinase. The BTB domain of ZBTB20 is a highly conserved, hydrophobic region that mediates homodimerization as well as interaction with corepressors and chromatin remodelers, while the ZF domain confers specificity of DNA binding (Figure E). In the ZBTB20-JAK2 fusion identified in this patient, the N-terminal BTB domain is fused to the C-terminal tyrosine kinase domain of JAK2 (Figure E). Therefore, we hypothesize that the BTB domain facilitates dimerization of the chimeric fusion protein leading to transphosphorylation and activation of the JAK2 kinase domain, thus resulting in downstream receptor signaling and STAT pathway activation.

The clinical presentation of our case shares similarities with malignancies harboring the PCM1-JAK2 fusion. PCM1-JAK2—positive neoplasms are clinically heterogeneous, and patients may present with myeloproliferative neoplasms, myelodysplastic syndrome, acute myeloid leukemia, and primary or secondary B- and T-cell leukemias and lymphomas. In addition to JAK2 rearrangements, these neoplasms often present with eosinophilia and have been grouped within the category of

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myeloid/lymphoid neoplasms with eosinophilia and PDGFRα, PDGFRβ, and FGFR1 gene rearrangements as a provisional entity in the revised 2017 World Health Organization classification. It has been suggested that ETV6-JAK2 and BCR-JAK2 may also be variants of this entity. Interestingly, our case had concurrent peripheral blood and bone marrow eosinophilia, suggesting that this newly described JAK2 fusion partner, ZBTB20, may also be a variant within myeloid/lymphoid neoplasms with associated eosinophilia.

Although the ZBTB20-JAK2 fusion has not been reported in the literature, other rearrangements involving JAK2 have been associated with BCR-ABL1—like B-ALL and are associated with higher rates of treatment failure and death compared with standard-risk ALL patients. The genomic landscape of BCR-ABL1—like ALL is further complicated by the presence of genetic alterations in lymphoid transcription factors, including IKZF1, which may further accelerate disease progression. In one recent study, 15% of BCR-ABL1—like B-ALL cases harbored either an ABL-class fusion or an activating kinase fusion of the JAK-STAT pathway. Of these cases, approximately 70% had a co-occurring IKZF1 deletion, which is an independent unfavorable prognostic factor. Accordingly, we identified a concomitant heterozygous deletion of IKZF1 in our patient harboring the ZBTB20-JAK2 fusion, and several ongoing prospective studies are examining the impact of the addition of TKI to high-risk combination chemotherapy regimens in this patient population. Although our patient’s current status is unknown, the cytogenetic abnormalities discussed herein would render a poor prognostic outlook and high risk for relapse for this patient. Ongoing prospective studies are examining the role for the addition of TKI to high-risk chemotherapeutic regimens for patients in this group.

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Drs Peterson, Blackburn, Baughn, and Greipp contributed equally to this work. Author contributions: Mr Webley and Ms Pearce provided technical support and analyzed raw data; Drs Peterson, Blackburn, Baughn, and Greipp wrote the manuscript; Drs Peterson, Blackburn, Vasmatis, Smadbeck, Bieliauskas, Reichard, Ketterling, Baughn, and Greipp interpreted data, provided critical review, and approved the final submitted manuscript.

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Chikungunya Virus Infection—Associated Psoriatic Arthritis?

To the Editor: Chikungunya, an Aedes mosquito—transmitted alphavirus with 3 main lineages, circulated in Africa and Asia and recently swept through the Americas. After an incubation period of 3 to 7 days, chikungunya-infected persons may present with fever, arthralgia, myalgia, headache, and rash; arthralgia may persist for weeks or longer. Predictors of persistent symptoms include age more than 40 years, severity at