Use of etanercept in management of tyrosine kinase-inhibitor-induced erythema nodosum

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INTRODUCTION

Erythema nodosum (EN) can occur in patients receiving tyrosine kinase inhibitors (TKI), and it resolves with cessation of the offending drug. Sometimes, the medication can be continued and the EN suppressed by systemic corticosteroids.[1] We present an instance of TKI-induced EN in a patient with chronic myeloid leukemia (CML) that was refractory to oral and intralesional corticosteroids but was successfully treated with etanercept, allowing for resumption of targeted chemotherapy.

Abbreviations used:

CML: chronic myeloid leukemia
EN: erythema nodosum
TKI: tyrosine kinase inhibitors
TNF: tumor necrosis factor

CASE REPORT

A 63-year old man with a 15-year history of *BCR-ABL*–positive CML was admitted for worsening painful nodules on his lower extremities of 3 months' duration that began following treatment with ponatinib, a multi-TKI that targets the *BCR-ABL* mutation.[2] The patient had been treated with imatinib and nilotinib with poor response. He exhibited a great response to ponatinib but had to stop the drug after 8 months because of severe side effects of arthralgias and biopsy-proven EN complicated by ulceration. The EN did not resolve with trials of alternative TKIs like bosutinib and dasatinib, suggesting a class effect. During these trials, his *BCR-ABL* also increased, mandating a switch back to ponatinib.

Physical examination found erythematous, deep, tender nodules on his shins without warmth or evidence of infection, clinically consistent with EN. Biopsy of a lesion on patient's right leg found septal panniculitis (Fig 1), consistent with a diagnosis of EN.

The patient was initially well treated with serial intralesional triamcinolone injections. Repeated courses of pulse systemic steroids were used with waning improvement over time. Based on normal baseline G6PD, dapsone was tried with some improvement in his symptoms. During therapy, the patient had worsening anemia that was felt to be caused by nonsteroidal anti-inflammatory drug–related gastrointestinal bleeding. Repeat testing of G6PD found G6PD deficiency. In light of a concern for worsening anemia, dapsone was discontinued. We were uncomfortable with a trial of hydroxychloroquine because of relative contraindication in patients with G6PD deficiency.

After hospitalization for progressive, uncontrolled, painful EN, ponatinib was discontinued. Unsuccessful outpatient therapy with colchicine, prednisone, and saturated solution of potassium iodide alongside leg elevation and local compression prompted a trial of etanercept, 50 mg subcutaneously biweekly. Three days after the first injection of etanercept—while still on a prednisone taper—the patient reported improvement of his lesions and

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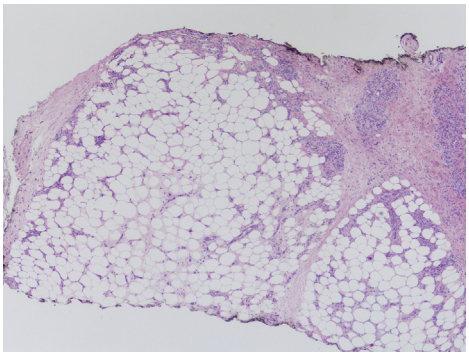

Fig 1. Histopathology of subcutaneous nodule on right leg. (Original magnification: ×4.)

pain. The prednisone was fully tapered off 12 days after initiation of etanercept.

After 2 weeks, the patient reported sustained clinical improvement; physical examination did not find any deep nodules on palpation. The decision was made to restart ponatinib at 15 mg daily.

Etanercept, 50 mg once weekly, permitted dosing of ponatinib, 15 mg, without recurrence of EN. Upon dose escalation to ponatinib, 30 mg, breakthrough EN while on weekly etanercept necessitated the addition of prednisone, 15 to 20 mg with EN control. Five months later, his *BCR-ABL* on polymerase chain reaction has continued to decrease while on this regimen.

DISCUSSION

The pathogenesis of EN may involve immune complex deposition in the septal venules of the subcutaneous fat, neutrophil chemotaxis with resulting reactive oxygen species formation, tumor necrosis factor (TNF)-α production, and granuloma formation.[3-6]

In 2001, Labunski et al[7] speculated a link between dysregulation of TNF-α production and granuloma formation supported by the strong correlation between the polymorphism in the TNF-α promoter region and sarcoidosis-associated EN. In 2003, Chodorowska et al[8] found that TNF-α serum concentrations were significantly more elevated in patients with drug-induced cutaneous reactions, including EN, than those of controls. More recently, Vavricka et al[9] found that TNF-α was overexpressed in skin biopsies from EN.

Etanercept has been reported to ameliorate idiopathic EN.[10] Our case demonstrates a similar observation with TKI-induced EN. Given the dramatic improvement after 1 month of biweekly etanercept, 50 mg, and continued—albeit imperfect—response on 50 mg weekly in the face of TKI dose escalation, we believe etanercept is an effective treatment option for TKI-induced EN.

The use of anti—TNF-α agents in CML is controversial. In vitro studies suggest that TNF-α has an inhibitory effect on CML cell lines[11]; however, one patient with rheumatoid arthritis complicated by CML had a 2-log reduction in *BCR-ABL* after administration of infliximab.[12] Our patient did not experience worsening of his CML on etanercept but did experience resolution of therapy-restricting EN. The use of etanercept in lieu of high-dose prednisone affords the benefits of long-term steroid sparing and, in this case, has enabled sustained control of CML with otherwise intolerable TKI therapy.

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