Blinatumomab-associated vasculitis

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Key words: blinatumomab; chemotherapy; cutaneous adverse dermatopathology; medium vessel vasculitis; pharmacology; reaction.

INTRODUCTION

Blinatumomab is the first-in-class bispecific T-cell engager antibody approved for the treatment of refractory acute lymphoblastic leukemia (ALL).[1,2] It simultaneously binds endogenous $CD3^+$ cytotoxic T cells and $CD19^+$ B cells, resulting in T-cell–mediated serial lysis of normal and malignant B cells. Although studies have been conducted into the incidence and severity of adverse events, cutaneous vasculitis has not been reported thus far.

Abbreviation used:

ALL: acute lymphoblastic leukemia

CASE REPORT

A 14-year-old Chinese boy with Li Fraumeni syndrome and ALL underwent chemotherapy (Malaysia-Singapore Acute Lymphoblastic Leukaemia 2010 Study [MASPORE 2010] protocol) with re-induction twice with 6-mercaptopurine, methotrexate, and bortezomib. When he did not achieve remission, the decision was made to start him on intravenous blinatumomab (5 $\mu g/m^2/d$ for days 1 through 7 inclusive, increased to 15 $\mu g/m^2/d$ from day 8 onward). On day 15 of his treatment regimen, tender lesions developed on both feet associated with swelling.

Physical examination found 2 erythematous nodules on the dorsum of his right foot and a similar lesion on the dorsum of his left foot (Fig 1). The lesions were tender on palpation, slightly warm, and blanchable. There were no other mucocutaneous lesions noted. He was otherwise well, and systemic examination was unremarkable. Results of laboratory testing, including full blood count, renal function, liver enzymes, and urinalysis, were within normal ranges. The initial differential diagnoses were disseminated fungal infections and immune/hypersensitivity reactions such as vasculitis. Histopathologic examination found vasculitic changes of the medium-sized blood vessels. The inflammatory infiltrate within the blood vessel walls were predominantly histiocytic with significant karyorrhexis, and there was presence of a few scattered $CD3^+$ T cells (Fig 2). Both $CD4^+$ and $CD8^+$ T cells were present. There were no $CD20^+$ and $PAX5^+$ B cells noted. Tissue biopsy findings for bacterial and fungal cultures were negative; acid-fast bacilli smear and cultures were also normal.

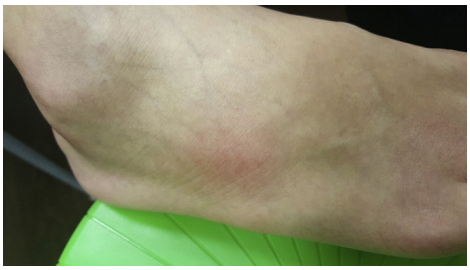

Fig 1. Erythematous, tender nodule on the lateral aspect of the dorsum of the right foot.

Blinatumomab was withheld, and the erythema and pain resolved completely 1 week later. After a multidisciplinary discussion with his oncologists, the decision was made to restart blinatumomab at a lower dose (5 $\mu g/m^2/d$) 23 days after his first infusion, as the drug was regarded as critical to

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Funding sources: None.
Conflicts of interest: None declared.

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JAAD Case Reports 2017;3:395-7.
2352-5126

http://dx.doi.org/10.1016/j.jdcr.2017.01.017

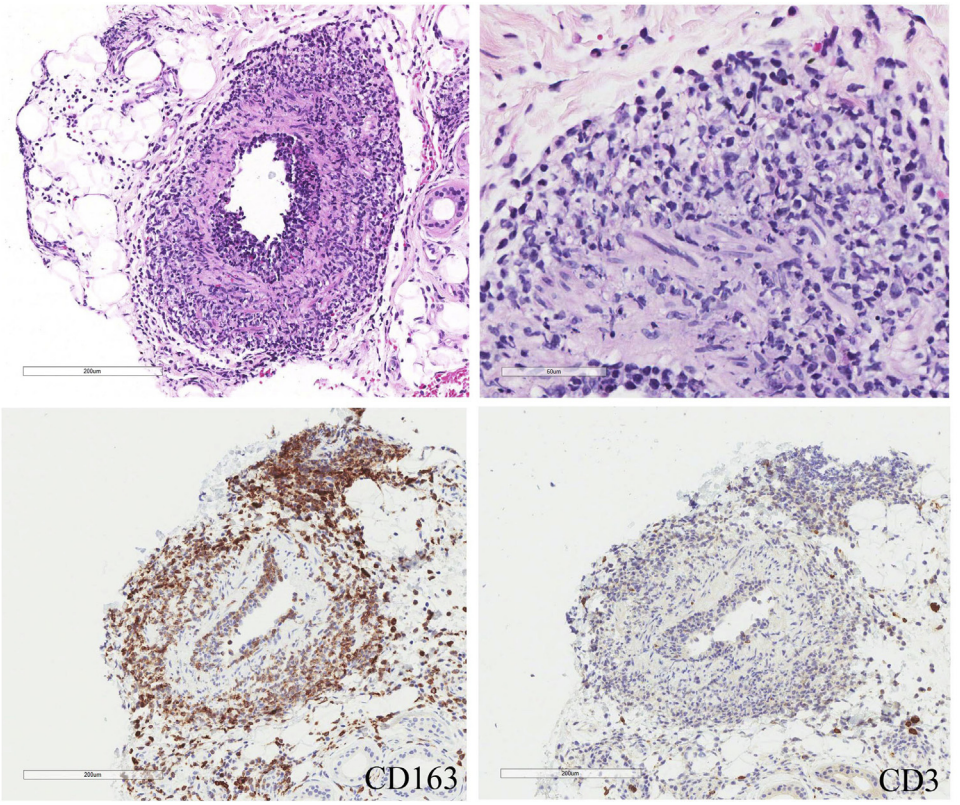

Fig 2. Hematoxylin-eosin–stained section of skin biopsy shows vasculitic changes in medium-sized blood vessel. High-power image of the same blood vessel (above right) shows significant amount karyorrhexis. The inflammatory infiltrate is composed predominantly of histiocytes ($CD163^+$ cells) with few scattered $CD3^+$ T cells.

achieve remission. The patient remained well, and 1 week later, the dose of blinatumomab was increased to 10 $\mu g/m^2/d$ with no further development of vasculitic nodules.

DISCUSSION

From 2014 to 2015, a multicenter phase 2 study of 189 patients with ALL treated with 2 cycles of blinatumomab was conducted to evaluate the efficacy and safety profile of this drug.[3] All except one patient (99%) experienced an adverse event. The most common adverse effects were pyrexia (113 [60%] patients), headache (65 [34%]), febrile neutropenia (53 [28%]), peripheral edema (49 [26%]), nausea (46 [24%]), hypokalemia (45 [24%]), constipation (39 [21%]), and anemia (38 [20%]). Four (2%) patients had disseminated intravascular coagulation during the study. Three (2%) patients had grade 3 cytokine release syndrome. Twenty-three (12%) patients had fatal adverse events, mainly infection related and possibly related to blinatumomab treatment. There were no reported cases of vasculitis.

Subsequently, blinatumomab was also studied in pediatric patients with relapsed/refractory pre-B ALL in a phase I/II clinical trial.[4] Patients received blinatumomab for 4 weeks by continuous intravenous infusion followed by a 2-week treatment-free period (for up to 5 cycles). Patients had dose escalations of 5, 15, and 30 $\mu g/m^2$ /d and stepwise dosing of 5 to 15 or 15 to 30 $\mu g/m^2/d$. The adverse events reported in this study were similar to those from adult patients with relapsed/refractory B-cell precursor ALL who received body surface area–based dosing.

This is the first reported case of blinatumomab-associated medium-vessel vasculitis to our knowledge. Hypersensitivity reactions induced by monoclonal antibodies are type III hypersensitivity reactions. The mechanisms underlying drug-induced hypersensitivity reactions are still incompletely understood, but cellular and humoral immune processes are implicated. Although cutaneous vasculitis (usually a small-sized vessel vasculitis) associated with the tumor necrosis factor-α inhibitor, infliximab, in the treatment of arthritis is well known, this condition is rarely seen after monoclonal antibody–based cancer therapy.

That the vasculitis may resolve with temporary withdrawal of the drug suggests that vasculitis may

be a reversible side effect for which careful monitoring must be done. To date, the patient had tolerated the re-introduction of blinatumomab, albeit at a lower dose. It is extremely crucial to balance both the need to achieve remission in otherwise refractory/relapsed ALL patients with the need to avoid adverse events such as vasculitis that may contribute to significant morbidity or mortality. Long-term longitudinal studies are necessary to evaluate blinatumomab's safety profile, especially as it is a first-in-class biologic agent.

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