Panniculitis in Patients Undergoing Treatment With the Bruton Tyrosine Kinase Inhibitor Ibrutinib for Lymphoid Leukemias

Ibrutinib is an oral inhibitor of Bruton tyrosine kinase (BTK) with marked activity in several B-cell malignant neoplasms. Commonly reported adverse events include diarrhea, infection, fatigue, arthralgias, pyrexia, hypertension, and neutropenia. Grade 1 and 2 rashes have been described but are generally self-limited and not treatment limiting. To our knowledge, panniculitis, an inflammation of the subcutaneous adipose tissue, has not yet been described during ibrutinib therapy. We describe 5 patients who developed panniculitis during ibrutinib treatment for lymphoid leukemias.

Methods | We conducted an institutional review board–approved retrospective medical record review to identify patients with ibrutinib-associated panniculitis at a single academic center. Due to its retrospective nature, the study was

Table. Patient Characteristics and Clinical Course

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Leukemia Diagnosis/Genetic Subtype</th>
<th>Prior Therapy (Months Prior to Starting Ibrutinib 420 mg Orally Daily)</th>
<th>Onset of Panniculitis</th>
<th>Clinical Findings at Onset</th>
<th>Histologic and Microbiologic Findings</th>
<th>Abnormal Bloodwork Results at Time of Panniculitis</th>
<th>Therapeutic Response</th>
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</thead>
<tbody>
<tr>
<td>1/F/70s</td>
<td>CLL, 8 y; complex karyotype; FISH +del11q; +del17p; IGVH unmutated</td>
<td>Bendamustine and rituximab (5); high-dose methylprednisolone + rituximab (3)</td>
<td>Day 8</td>
<td>Predominantly lobular panniculitis with a septal component.</td>
<td>Superficial, perivascular, and interstitial infiltrate composed of lymphocytes, neutrophils, histiocytes, eosinophils, and keratinocytes. Negative Gram, GMS stains</td>
<td>WBC count, 36 200/μL; ANC, 27.9 K/μL; CD4+ 1247/μL; IgG, 249.0 mg/dL</td>
<td>Remitted with prednisone 20 mg daily; relapsed once after complete taper; ultimately gained good control with 5 mg prednisone daily</td>
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<tr>
<td>2/F/50s</td>
<td>CLL, 3 y; complex karyotype, including del17p</td>
<td>Fludarabine and rituximab (6); high-dose methylprednisolone + rituximab (1)</td>
<td>Day 1</td>
<td>Multiple painful nodules on calves, with some coalescence. Warm to touch with some edema proximal to ankles</td>
<td>Lobular and septal panniculitis. Superficial and perivascular predominantly lymphohistiocytic infiltrate with small, loosely defined granulomas and rare eosinophils. Microbiologic analysis NA</td>
<td>WBC count, 9.8 K/μL; ANC, 3200/μL; CD4+, 480/μL; ANC, 6000/μL; IgG, 526.0 mg/dL</td>
<td>Treated with ibuprofen and naproxen, as patient declined steroids. Waking and waning course throughout remainder of treatment to date.</td>
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<tr>
<td>3/M/40s</td>
<td>HCL, 6 y; BRAF V600E+</td>
<td>Cladribine (80); rituximab (10)</td>
<td>Day 22</td>
<td>Purpuric warm patches over proximal and distal legs underlying nodularity; erythematous, warm patches over bilateral arms. Moderately painful</td>
<td>Predominantly lobular panniculitis. Superficial and perivascular infiltrate composed of neutrophils, histiocytes, and rare eosinophils. Gram stain results equivocal; GMS stain results negative. Negative bacterial and fungal cultures.</td>
<td>WBC count, 3400/μL; ANC, 1870/μL; CD4+, 631/μL; ANC, 1870/μL; IgG, 571 mg/dL</td>
<td>Remitted with prednisone 20 mg daily; relapsed once after complete taper; ultimately gained good control with 10 mg prednisone daily tapered over months</td>
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<tr>
<td>4/F/50s</td>
<td>CLL, 7 y; normal karyotype</td>
<td>Fludarabine, cyclophosphamide, and rituximab (29)</td>
<td>Day 8</td>
<td>Well-circumscribed, firm, light pink, subcutaneous nodules on medial thighs bilaterally, stomach, and right arm.</td>
<td>Lobular and septal panniculitis with necrosis. Superficial and perivascular infiltrate composed of lymphocytes, neutrophils, histiocytes, and leukocytoclasis. Focal intraepidermal necrotic keratinocytes observed. Negative results on Gram, GMS, acid-fast, and Fite stains.</td>
<td>WBC count, 96 500/μL; ANC, 90 700/μL; CD4+, NA; ANC, 4830/μL; IgG, 909 mg/dL</td>
<td>Remitted with prednisone 20 mg daily and flared when held. Sustained improvement after gradual taper over cycle 1</td>
</tr>
<tr>
<td>5/F/70s</td>
<td>CLL, 17 y; genetic risk stratification unknown</td>
<td>Fludarabine, mitoxantrone, and dexamethasone (168); fludarabine, cyclophosphamide, and rituximab (120); fludarabine, bendamustine; bendamustine (35); fludarabine and mitoxantrone (30); lenalidomide (12)</td>
<td>Approximatively 60 d from restarting drug after 90-d hiatus</td>
<td>Scattered painful nodular rash over upper and lower extremities with associated purpura</td>
<td>Predominantly lobular and septal panniculitis. Infiltrate composed of lymphocytes, neutrophils, histiocytes, and abundant eosinophils. Cutaneous involvement by CLL/SLL observed. Negative GMS and periodic acid-Schiff stain results.</td>
<td>WBC count, 133 300/μL; ANC, 130 600/μL; CD4+, NA; ANC, 2660/μL; IgG, 356 mg/dL</td>
<td>Treated symptomatically with ibuprofen</td>
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</table>

Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CLL, chronic lymphocytic leukemia; FISH, fluorescence in situ hybridization; GMS, Grocott methenamine silver; HCL, hairy cell leukemia; IgG, immunoglobulin G; NA, not available; SLL, small lymphocytic lymphoma; WBC, white blood cell.

SI conversion factors: To convert WBC count, ALC, and ANC to billions per liter, multiply by 0.001; to convert IgG to grams per liter, multiply by 0.01.

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conducted under a waiver of informed consent. Cases were identified among patients receiving ibrutinib treatment for lymphoid leukemia after cross-referencing skin biopsies consistent with panniculitis. Medical records were abstracted from an electronic medical record, and all biopsies were reviewed by a single dermatopathologist (A.A.G.).

**Results** | Five patients were identified (Table), all of whom developed isolated painful, nodular rashes, primarily on the extremities, while receiving ibrutinib (Figure, A and B). Histopathologic analysis demonstrated a lobular and septal panniculitis, frequently with superficial and perivascular mixed inflammatory infiltrate and prominent leukocytoclasis (Figure, C and D). Three patients received oral prednisone in low, tapering doses. Gradual tapering of the prednisone dose resulted in sustained resolution of the rash in 1 patient (case 4) but recurrence after discontinuation of corticosteroid use in the remaining 2, both of whom required sustained maintenance therapy. Among patients not receiving steroids, the rash was either relapsing and remitting (case 2) or persistent (case 5).

**Discussion** | Cutaneous eruptions are common among patients with lymphoid malignant neoplasms. The differential diagnosis is broad, including infectious, immunologic, paraneoplastic, and iatrogenic etiologies. Panniculitides have been reported in association with use of some chemotherapeutics, although primarily neutrophilic and more typical in myeloid disorders. Because panniculitis may mimic extensive atypical purpura, which is common during ibrutinib treatment, biopsy may be required for diagnosis. Careful clinicopathologic evaluation, including tissue culture for bacterial, fungal, and acid-fast organisms, is important.

Although our patients differed by diagnosis, treatment history, and immune status, they generally presented with painful erythematous nodules involving the extremities early in the course of ibrutinib therapy. Diagnosis of this unique entity is aided by its distinct pattern of distribution, absence of systemic symptoms, and histopathological pattern of lymphohistiocytic, lobular panniculitis with prominent leukocytoclasis and occasional eosinophils. Use of low-dose systemic corticosteroids resulted in complete resolution of cutaneous manifestations. The rash has yet to prove treatment limiting, but patients may require sustained low-dose prednisone therapy for suppression while receiving ibrutinib. Use of nonsteroidal anti-inflammatory drugs may mitigate symptoms.

Whereas the mechanism underlying ibrutinib-associated panniculitis has not been fully elucidated, its histopathologic features are reminiscent of a localized adaptive cellular immune response against a novel hapten epitope. It is conceivable that ibrutinib-conjugated peptides are presented to host immune cells via major histocompatibility complex, leading to a T-cell–driven immune response and bystander tissue destruction.

Whereas ibrutinib was designed to bind and inhibit BTK, the drug binds a broad range of cellular kinases at therapeutic doses, including the inducible T-cell kinase. Inhibition of inducible T-cell kinase may modulate cellular immunity, potentially contributing to the development of panniculitis. Furthermore,
inhibition of BTK downregulates expression of myriad downstream signaling molecules, most prominently PLCγ2, some mutations in which seem to mediate ibrutinib resistance. Interestingly, a clinically similar eruption—a lymphohistiocytic infiltrate with eosinophils responsive to corticosteroids—has been described in patients with mutations in the PLCγ2 gene.6

In conclusion, treatment of lymphoid leukemias with the BTK inhibitor ibrutinib can lead to development of a panniculitis, which may be induced by drug-induced immune modulation. Previously uncharacterized, this painful rash typically occurs early during drug exposure and responds well to systemic corticosteroid use; however, low-dose maintenance therapy may be necessary to prevent recurrence.

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Author Contributions: Drs Fabbro and Jones had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Drafting of the manuscript: Fabbro, Smith, Gru, Jones.
Critical revision of the manuscript for important intellectual content: All authors. Administrative, technical, or material support: Fabbro, Gru, Jones.
Study supervision: Fabbro, Gru, Jones.
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Table 1. Characteristics of mCRC Cases Involving the Axilla Reported in the Literature

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Primary Site</th>
<th>Axillary LAN</th>
<th>Presentation of Axillary LAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/78</td>
<td>Left colon</td>
<td>Left</td>
<td>Swollen left axillary node noted on CT</td>
</tr>
<tr>
<td>2/M/49</td>
<td>Left colon</td>
<td>Left</td>
<td>Large axillary mass approaching 10 cm in diameter on physical examination</td>
</tr>
<tr>
<td>3/F/72</td>
<td>Left colon</td>
<td>Left</td>
<td>Patient-discovered, confirmed on examination</td>
</tr>
<tr>
<td>4/F/46</td>
<td>Left colon</td>
<td>Left</td>
<td>Palpable 1-cm lump on right breast examination; FNA cytology</td>
</tr>
<tr>
<td>5/M/52</td>
<td>Right colon</td>
<td>Left</td>
<td>&quot;Firm, rubbery, painless&quot; axillary LAN measuring 4 cm on physical examination</td>
</tr>
<tr>
<td>6/M/70</td>
<td>Right colon</td>
<td>Left</td>
<td>Left axillary lymph node metastasis detected on imaging</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomographic scan; FNA, fine-needle aspiration biopsy; LAN, lymphadenopathy; mCRC, metastatic colorectal cancer.

Axillary Lymph Node Involvement, a Unique Pattern of Metastasis in BRAF-Mutant Colorectal Cancer

Axillary lymph nodes (axLNs) are a virtually unheard of site of metastasis in patients with metastatic colorectal cancer (mCRC). Our search of the National Library of Medicine’s PubMed database identified only 6 case reports,1-6 each describing 1 patient with axLN metastasis of primary colorectal cancer (Table 1).

Methods | Initially, we identified 3 cases of axLN metastasis clinically in patients with CRC, and all were noted to have BRAF-mutant mCRC. Since late 2008, all mCRCs in our institution have been sequenced for KRAS and BRAF mutations. We therefore identified all cases with BRAF mutation between 2008 and 2012 and reviewed clinical and radiology records for evidence of axLN metastases. For a comparison group, we performed a computerized search for patients with mCRC whose tumors were genotyped in 2011 and identified the first 100 sequential cases with wild-type BRAF.

All cases were reviewed for axillary lymphadenopathy on imaging studies in the absence of additional primary malignant neoplasms to describe the frequency of axLN larger than 1 cm in these patients. Appropriate Memorial Sloan Kettering Cancer Center institutional review board and/or privacy board waivers were obtained for this review.

Results | Three patients identified during their clinical course had biopsy confirmation of CRC metastases to the axilla. Patient 1, a woman in her 30s, presented with mCRC involving the peritoneum and ovaries treated with complete cytoreduction. She developed a rapid recurrence in the peritoneum, LNs, and pleura, with concurrent increase in size and number of left...