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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Alejandro A. Gru, MD
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Letters

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/51*</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 axLNs 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

axLNs. Chest wall biopsy adjacent to the axilla confirmed mCRC and identified BRAF V600E mutation.

Patient 2, a woman in her 60s, developed recurrent disease in the retroperitoneal LNs and lungs with concurrent left axillary lymphadenopathy after resection of a stage I, BRAF V600E-mutated colon cancer. She was resistant to all standard therapies and developed bulky, uncomfortable, left axLNs as large as 3 cm. Biopsy of the axLNs confirmed mCRC, and she underwent palliative resection.

Patient 3, a woman in her 70s, developed left axLN involvement as the only site of metastasis within 6 months of resection of a node-positive colon tumor. Biopsy of the axLNs confirmed mCRC and identified BRAF V600E mutation. The patient progressed through chemotherapy and developed bulky left axLNs with involvement of the left breast and dermis, clinically mimicking an inflammatory breast cancer. Subsequent breast biopsy, however, again showed mCRC.

An additional 100 patients with CRC were identified with known BRAF-mutant tumors sequenced at our institution between 2008 and 2012. On review of the 100 sequential BRAF-mutant cases, 6 additional patients had suspect axillary lymphadenopathy on imaging; axLNs were larger than 1.4 cm on CT, progressed on serial imaging, and were fluorodeoxyglucose (FDG) avid where positron emission tomographic (PET) scans were performed (Table 2). In a comparison group of 100 sequential wild-type BRAF cases, no patients had axLNs that progressed on serial imaging. One patient had an enlarged axLN to 1.3 cm on CT that was not FDG avid and did not progress.

Discussion | Our data reveal a unique pattern of metastatic spread of BRAF-mutant mCRC, a particularly aggressive subset of mCRC, and extend our understanding of BRAF-mutant mCRC as a distinct subset of CRC. We identified 9 cases with likely axLN metastases from CRC, an exceedingly rare site of metastatic involvement in this disease. Several patients in our series developed axillary involvement in the setting of chest wall, skin, or breast involvement, suggesting initial spread and then local extension. Interestingly, overexpression of BRAF-activated long non-coding RNA found in specimens from patients with BRAF-mutant CRC has recently been correlated with increased LN metastasis through induction of epithelial-mesenchymal transition.9 Our data suggest that axLN evaluation should be included in the physical examination of patients with BRAF-mutant mCRC, and this area should be scrutinized when considering these patients for curative-intent resection.

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Conflict of Interest Disclosures: None reported.


COMMENT & RESPONSE

Truthfulness of More Optimistic vs Less Optimistic Messages for Patients With Advanced Cancer

To the Editor | Tanco et al1 report that physicians delivering a more optimistic message are perceived by patients with advanced cancer as being more compassionate and trustworthy. Patients may perceive a more optimistic message as a sign of their physician’s compassion and trustworthiness because they need to protect themselves from devastating news in order to carry

### Table 2. Characteristics of Patients With BRAF-Mutant Metastatic Colorectal Cancer and Axillary Lymphadenopathy Suggestive of Metastasis

<table>
<thead>
<tr>
<th>Patient No./Sex/ Age at Dx, y</th>
<th>Mutation</th>
<th>Primary Site</th>
<th>Stage at Dx</th>
<th>Axillary LNs</th>
<th>Presentation of Axillary LNs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/21</td>
<td>V600E</td>
<td>Right colon</td>
<td>IV</td>
<td>Bilateral</td>
<td>CT (1.8 cm)</td>
</tr>
<tr>
<td>2/F/72</td>
<td>V600E</td>
<td>Right colon</td>
<td>IV</td>
<td>Left</td>
<td>CT (1.4 cm); focal hypermetabolism on PET (SUV, 3.1)</td>
</tr>
<tr>
<td>3/M/65</td>
<td>V600E</td>
<td>Left colon</td>
<td>IV</td>
<td>Left</td>
<td>CT (1.8 cm); focal hypermetabolism on PET (SUV, 15.1)</td>
</tr>
<tr>
<td>4/F/48</td>
<td>V600E</td>
<td>Left colon</td>
<td>III</td>
<td>Left</td>
<td>CT (1.5 cm)</td>
</tr>
<tr>
<td>5/F/62</td>
<td>V600E</td>
<td>Right colon</td>
<td>III</td>
<td>Bilateral</td>
<td>CT (2.1 cm)</td>
</tr>
<tr>
<td>6/F/42</td>
<td>V600E</td>
<td>Right colon</td>
<td>IV</td>
<td>Left</td>
<td>CT (2.9 cm); focal hypermetabolism on PET (SUV, 2.1); palpable on PE (3 cm)</td>
</tr>
</tbody>
</table>

Abbreviations: Dx, diagnosis; LNs, lymphadenopathy; PE, physical examination; PET, positron emission tomography; SUV, standardized uptake value. *For CT, the largest axillary lymph node dimension is noted in parentheses.