A Rare Case of Ibrutinib-Induced Panniculitis in a Patient with Chronic Lymphocytic Leukemia

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Background

Ibrutinib is an oral Bruton tyrosine kinase (BTK) inhibitor that was FDA approved in 2016 as first-line therapy for the treatment of chronic lymphocytic leukemia (CLL).[1,2] Prior to the introduction of ibrutinib, traditional CLL therapy consisted of chemotherapy, often with anti-CD20 antibody rituximab, alone or in combination.[1] The exact mechanism of ibrutinib efficacy for CLL is not clearly understood, but it is thought to be related to the inhibition of B-cell-receptor signaling, slowing proliferation and decreasing survival of malignant cells.[1] Commonly reported side effects of ibrutinib include neutropenia, anemia, thrombocytopenia, early lymphocytosis, joint pain, nausea, self-limited rash, fatigue, pyrexia and hemmorhage.[2] Few reports have described inflammatory panniculitis as a side effect of ibrutinib therapy. We present this case as a compelling diagnostic dilemma and describe panniculitis as an emerging side effect of ibrutinib.

Case Presentation

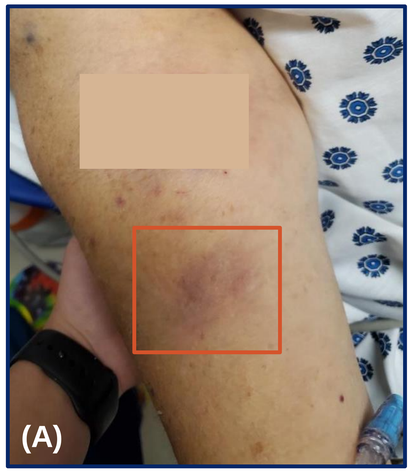
- **CC:** Weakness
- **HPI:** 61-year-old morbidly obese female presenting to the hospital for 3-5 days of weakness, malaise, nausea and decreased appetite. She also complained of painful “cellulitis” that presented on her right arm that morning. She followed closely with an oncologist outpatient. Patient was recently diagnosed with new myelodysplastic syndrome via bone biopsy and was initiated on daily ibrutinib immunotherapy as well as chemotherapy 2 weeks ago by her oncologist. Her last chemotherapy session was 5 days ago. The CLL was previously treated with IVIG, completed 5 months ago.
- **PMH:** CLL (diagnosed 1998) on immunotherapy and chemotherapy, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease s/p 2 stents, hyperlipidemia
- **ROS:** Denies chills, night sweats, headache, chest pain, shortness of breath, vomiting, diarrhea, and abdominal pain, joint pain.
- **FH:** Hypertension, congestive heart failure
- **SH:** Divorced, lives alone locally. Former smoker, 25 pack-years. Denies alcohol, IV drug use
- **Allergies:** Penicillin (hives)
- **Vitals:** T 38.7, HR 93, RR 18, BP 112/66, 94% O2 RA
- **PE:** Well-circumscribed, purpuric papulonodules on the proximal bilateral arms. Warm to touch with palpable underlying nodularity. Surrounding skin normal temperature.
- **Labs:** WBC 21.6k/μL; ALC 12.7k/μL; Hgb 7.3; Plt 120

Acknowledgement

We would like to acknowledge the patient for allowing us to participate in her care and for graciously permitting us to learn from her case.

Clinical Course

- The patient was admitted for sepsis rule out and appropriate imaging and cultures were performed. Broad-spectrum antibiotics were started. The patient was continued on home medications including daily ibrutinib.
- CT scan revealed 8 mm peripheral lung nodule in the left lower lobe, two hypodense hepatic lesions and retroperitoneal/ extraperitoneal lymphadenopathy. Lung nodule, liver lesions and lymphadenopathy unchanged from prior imaging.
- Infectious disease and hematology/oncology were consulted. Consultants deem lung nodule unable to be biopsied and advise continued antibiotic therapy to cover infectious etiologies.
- **Hospital day 1:** The patient continued to complain of severe tenderness to palpation of nodules. Reported new, similar rash on the bilateral anterior thighs. Physical exam revealed warm, well-circumscribed, purpuric rash with underlying nodularity scattered linearly across the bilateral thighs.
- Punch biopsy of the skin was performed on the right medial thigh. Histopathology revealed acute inflammation of fibroadipose tissue. Negative for acid fast bacilli or fungal organisms on AFB and GMS stains.
- **Hospital day 2:** Ibrutinib was held, and patient was initiated on 4 mg methylprednisone daily + ibuprofen as needed for pain.
- **Hospital day 3-6:** Patient reported rapid regression of rash (B) and tenderness resolved. Fungal antibody panel negative. Leukocytosis downtrended.
- **Hospital day 7:** Rash resolved. Patient discharged home with close follow-up with her oncologist. Subsequently lost to follow-up.



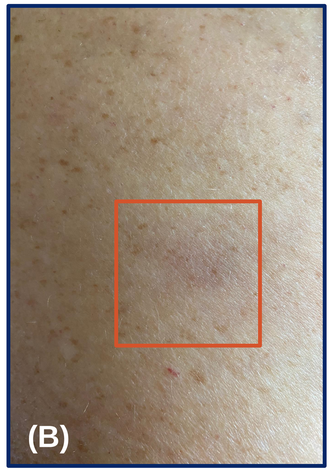


Figure (A): Tender, purpuric papulonodule of the right arm, hospital day 1

Figure (B): Near resolution of right arm rash, hospital day 5

Patient identifiers removed.

Discussion

Panniculitis is inflammation of the subcutaneous fat classified as septal or lobular, with or without vasculitis.[3] The most common cause of panniculitis is erythema nodosum.[3] The differential diagnosis for panniculitis is broad, including malignant, paraneoplastic, infectious, autoimmune and iatrogenic causes.[4] Additionally, patients with lymphoid malignancy commonly manifest with cutaneous toxicity.[4]

Ibrutinib-induced panniculitis is a newly described, rare entity. Most patients experience onset of symptoms within 3 weeks of medication induction.[4] Clinical presentation is consistent with erythematous, firm nodules and plaques, usually on the proximal extremities.[4] Histological features shows lobar infiltrate with inflammatory cells including lymphocytes, neutrophils and eosinophils.[5] The mechanism for this entity is thought to be due to ibrutinib binding to cellular kinases beyond BTK, initiating an adaptive immune response.[5] As such, many cases experience reappearance of lesions when steroids are tapered, requiring maintenance therapy.[4] Other reports relate regression within weeks of drug discontinuation with quick relapse when medication was resumed.[6] Few are symptomatically managed with ibuprofen only.[4,7] However, for the comfort of our patient, steroid therapy was started in conjunction with ibrutinib cessation, so the cause of clinical regression cannot be distinguished.

Our case highlights a diagnostic challenge in an immunosuppressed female with known malignancy on chemotherapy and novel immunotherapy. Thus, infectious, malignant and drug-induced etiologies were important diagnostic factors in clinical decision-making.

Conclusion

- Few reports of panniculitis during ibrutinib therapy have been described. We add to the literature a case of panniculitis caused by novel therapy which quickly remitted with low-dose steroids.
- Because the differential for panniculitis remains broad, clinician awareness of this rare entity may help optimize patient care and mitigate cost by preventing unnecessary workup.

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