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Case Report

Copanlisib-Associated Skin Toxicity: A Peculiar Case of Copanlisib-Induced Skin Rash in a Patient with Refractory Follicular Lymphoma

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ABSTRACT

Background: Phosphatidylinositol 3-kinase (PI3K) is an essential target in lymphoid tumors therapy. Copanlisib is a novel class of medication that targets PI3K and used for the treatment of relapsing or refractory B-cell lymphomas.

Case Presentation: A 42-year-old woman presents to our hospital for worsening abdominal pain. Examination pertinent for axillary lymphadenopathy, and abdominal ascites. CT chest, abdomen and pelvis reported multiple lung nodules, pleural effusions, extensive retroperitoneal lymphadenopathy, and peritoneal carcinomatosis. Lymph node and bone marrow biopsies confirmed B-cell follicular lymphoma and fluorescent in situ hybridization (FISH) testing was positive for translocation t(14:18). Her disease was refractory to multiple chemotherapy regimens. Thus, initiated copanlisib therapy with a remarkable response, but the patient developed a diffuse maculopapular rash and skin biopsy-proven to be drug rash. Therefore, copanlisib was discontinued.

Conclusion: Here, we report a case of a middle-aged woman who developed a rash after the fifth cycle of copanlisib therapy. This case report will create awareness of evolving possible side effects in this novel chemotherapeutic agent.

Introduction

Phosphatidylinositol 3-kinase (PI3K) signaling is crucial for the proliferation, angiogenesis, and survival of malignant Lymphoid B cell malignancies [1-4]. Therefore, targeting PI3K comprise a novel class of agents that are effective for treating lymphoid malignancies [2]. Copanlisib is an intravenous pan-class I PI3K inhibitor; approved by the US-FDA in September 2017 for the treatment of adults with relapsing or refractory indolent B-cell lymphomas after two prior therapies with rituximab and alkylating agents [1-6]. Pan-PI3K inhibitors are a new class of agents to join the present oncologists' armamentarium, and community oncologists are still getting familiarized with their clinical use. We present a case of severe drug toxicity secondary to copanlisib therapy.

Case Report

A 42-year-old morbidly obese, previously healthy, Hispanic woman presented to our hospital for a four-month history of worsening abdominal distension. On examination, the patient found to have abdominal ascites and an enlarged 9.0x 9.0 cm right axillary lymph node without clinically palpable peripheral lymph nodes, liver, or spleen.

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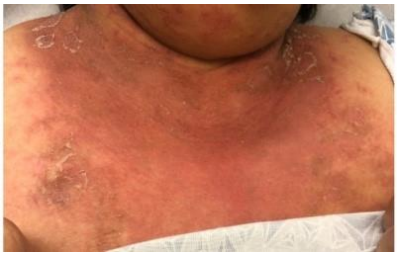
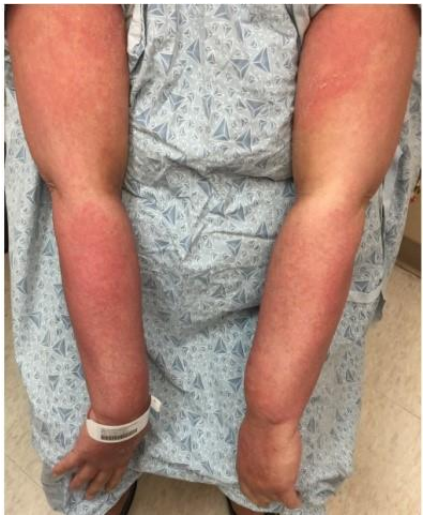
Laboratory studies were unremarkable. Initial chest x-ray (CXR) and computed tomography (CT) scan done at that time reported multiple bilateral lung nodules, largest measuring 1.9 x 1.6 cm with moderate bilateral pleural effusions. CT abdomen and pelvis showed extensive retroperitoneal lymphadenopathy, peritoneal carcinomatosis. Lymph node and bone marrow biopsies confirmed low-grade B-cell follicular lymphoma with translocation t(14:18) on fluorescent in situ hybridization (FISH) testing and CD10, CD19, CD20, CD23 positive cells with CD5 negativity on flow cytometry.

The patient was subsequently started on RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) therapy, but had an anaphylactic reaction to rituximab, and the drug was discontinued. The patient received various chemotherapy regimens over the next four years, including CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), ICE (Ifosfamide, Carboplatinum, and Etoposide), bendamustine therapy, GEMOX (Gemcitabine with Oxaliplatin) and Lenalidomide. There was never any Richter's transformation to diffuse large B cell lymphoma upon progression biopsies.

As the patient did not have health insurance, a hematopoietic stem cell transplant was not an option. Hence, initiated copanlisib therapy. She had a great response to treatment, but after the fifth cycle, the patient developed a diffuse, erythematous, covering more than 80% of her body surface area and including her arms, legs, neck, chest, and groin, sparing the face. She did have annular lesions on her legs with central scaling. Affected skin areas were warm and swollen with some induration. She did not have any oral or ocular involvement (Figure 1). This was a grade 3 toxicity by Common Terminology Criteria for Adverse Events (CTCAE). Skin biopsy showed superficial perivascular dermatitis with eosinophils consistent with drug eruption (Figure 2). Copanlisib was permanently discontinued, and the patient was given oral prednisone 40 mg daily for four days, and in a month, the rash had resolved entirely (Figure 3).





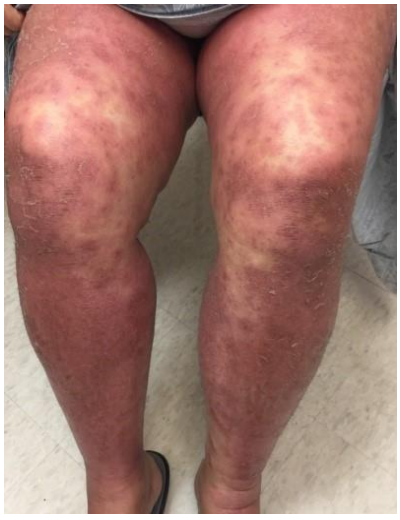


Figure 1: Diffuse erythematous rash.

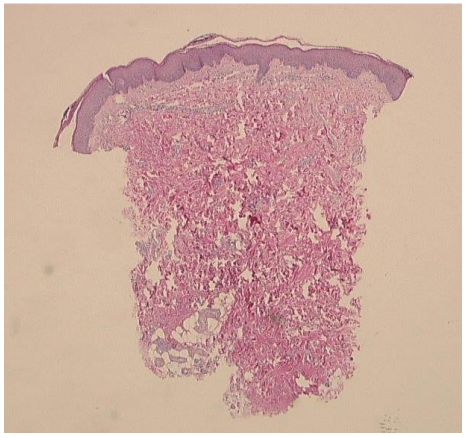


Figure 2A: Section of the epidermis showing hyperkeratosis and parakeratosis with no significant spongiosis.

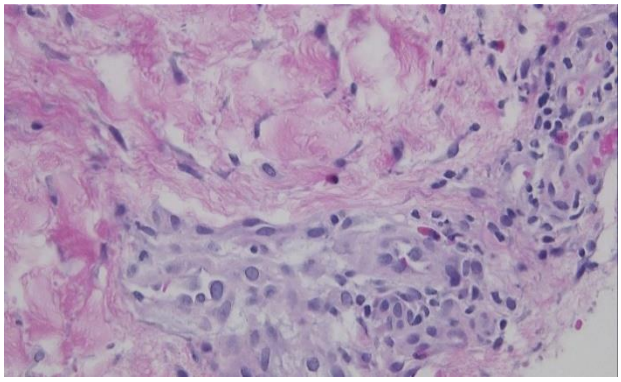


Figure 2B: There is evidence of superficial perivascular mixed cell inflammatory infiltrate with eosinophils, slightly increased dermal edema and focal vacuolar change. The findings are consistent with drug eruption.

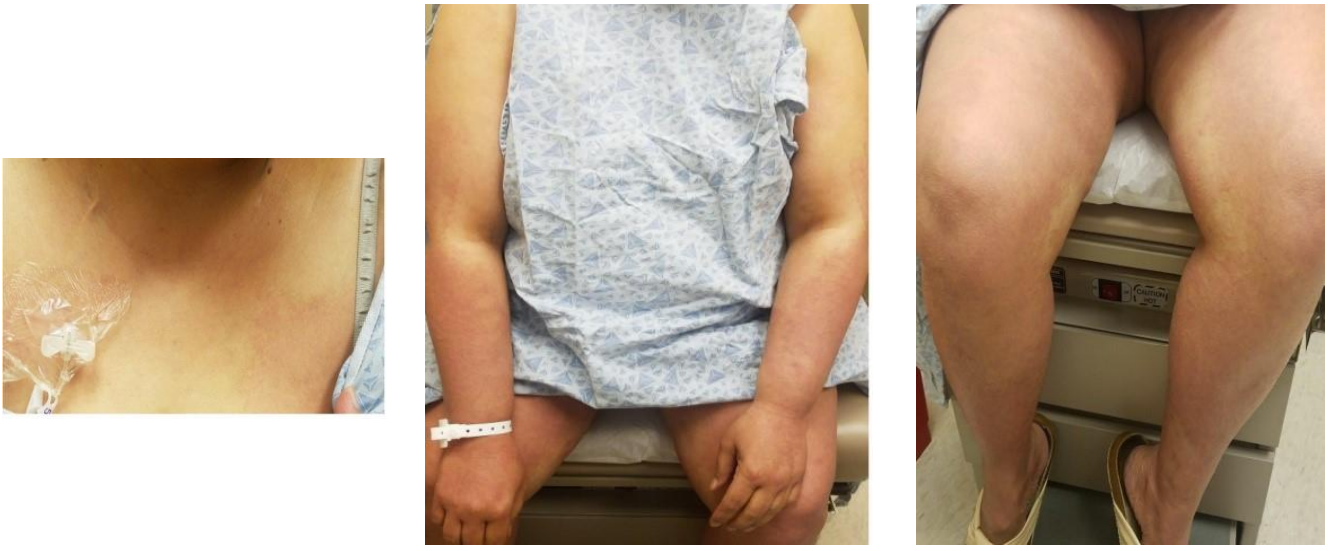


Figure 3: Rash resolved.

Discussion

Patients with refractory or relapsed follicular lymphoma are treated based on the clinical presentation and the individual's initial chemotherapy response [1, 7]. Most patients manifest with advanced disease at diagnosis. Patients most commonly initiated with rituximab-based chemotherapeutic regimens [8, 9]. The need for more effective therapeutic options with more tolerable side effects has led to the introduction of targeted chemotherapeutic agents. In a phase II study by Dreyling et al., 142 patients with relapsed or refractory indolent lymphoma to two or more lines were enrolled to receive copanlisib therapy. In this study, researchers found a significant favorable response to copanlisib treatment with a manageable safety profile and low rates of severe adverse events in this patient population [1]. The major PI3K isoforms include PI3K-delta (PI3Kδ), is involved in B-cell proliferation and survival, and PI3K-alpha (PI3Kα) is involved in disease relapse. Overexpression of these subunits has been shown to predict worse outcomes and is a cause of relapse and cancer resistance in B-cell malignancies, including follicular lymphoma.

Therefore, novel therapies to target PI3K to treat lymphoid malignancy has been developed [2, 3]. Copanlisib provides an excellent intravenously administered agent, approved as a third-line therapy of refractory follicular lymphoma. It has an inhibitory activity that predominantly targets PI3Kα and PI3Kδ isoforms. It appears to be well tolerated with low rates of adverse events. It is suggested that targeting alfa PI3K isoform may be responsible for the copanlisib unique toxicity profile [6]. The most common reported adverse events to include hypertension in up to half of the cases, hyperglycemia and diarrhea in up to a third of the cases, and lung infection in up to 20% of cases. Other potential complications include diarrhea, colitis, pneumonitis, transaminitis, neutropenia, anemia, lymphopenia, fever, and fatigue. It is found that almost all patients experience at least one adverse event, and about half the patients treated with copanlisib develop grade 3 toxicity [1-6]. The most common dermatological toxicities of copanlisib include maculopapular and exfoliative pruritic rash and dermatitis [3]. The mechanism for which skin toxicity occurs remains unknown.

Conclusion

Decision to interrupt treatment, adjust the dose or discontinue treatment is guided by the severity and persistence of symptoms [3]. This case conveys an important message to bring attention to this severe and unique severe skin toxicity and helps guide its management.

REFERENCES

1. Dreyling M, Santoro A, Mollica L, Leppä S, Follows GA et al. (2017) Phosphatidylinositol 3-Kinase inhibition by copanlisib in relapsed or refractory indolent lymphoma. *J Clin Oncol* 35: 3898-3905. [Crossref]
2. Seiler T, Hutter G, Dreyling M (2016) The Emerging Role of PI3K Inhibitors in the Treatment of Hematological Malignancies: Preclinical Data and Clinical Progress to Date. *Drugs* 76: 639-646. [Crossref]
3. Mensah FA, Blaize JP, Bryan LJ (2018) Spotlight on copanlisib and its potential in the treatment of relapsed/refractory follicular lymphoma: evidence to date. *Onco Targets Ther* 11: 4817-4827. [Crossref]
4. Rodon J, Dienstmann R, Serra V Tabernero J (2013) Development of PI3K inhibitors: lessons learned from early clinical trials. *Nat Rev Clin Oncol* 10: 143-153. [Crossref]
5. Greenwell IB, Flowers CR, Blum KA, Cohen JB (2017) Clinical use of PI3K inhibitors in B-cell lymphoid malignancies: Today and tomorrow. *Expert Rev Anticancer Ther* 17: 271-279. [Crossref]
6. Cheson BD, O'Brien S, Ewer MS, Goncalves MD, Farooki A et al. (2019) Optimal Management of Adverse Events from Copanlisib in the Treatment of Patients With Non-Hodgkin Lymphomas. *Clin Lymphoma Myeloma Leuk* 19: 135-141. [Crossref]
7. Sehn LH, Goy A, Offner FC, Martinelli G2, Caballero MD et al. (2015) Randomized Phase II Trial Comparing Obinutuzumab (GA101) With Rituximab in Patients With Relapsed CD20+ Indolent B-Cell Non-Hodgkin Lymphoma: Final Analysis of the GAUSS Study. *J Clin Oncol* 33: 3467-3474. [Crossref]
8. Rummel MJ, Niederle N, Maschmeyer G, Banat GA, von Grünhagen U et al. (2013) Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-

cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet* 381: 1203-1210. [Crossref]

9. Rummel M, Kaiser U, Balser C, Stauch M, Brugger W et al. (2016) Bendamustine plus rituximab versus fludarabine plus rituximab for patients with relapsed indolent and mantle-cell lymphomas: a multicentre, randomised, open-label, non-inferiority phase 3 trial. *Lancet Oncol* 17: 57-66. [Crossref]