VIA MEDICA

CASE REPORT

Adam Kowalczyk[1], Barbara Radecka[1, 2]

[1]Department of Oncology with Daily Unit, Tadeusz Koszarowski Cancer Center in Opole, Poland
[2]Department of Oncology, Institute of Medical Sciences, University of Opole, Poland

Stevens-Johnson syndrome in breast cancer patient treated with ribociclib

Address for correspondence:
Dr hab. n. med. Barbara Radecka
Department of Oncology with Daily Unit,
Tadeusz Koszarowski Cancer Center
in Opole, Poland
ul. Katowicka 66A, 45–061 Opole, Poland
e-mail: barbara.s.radecka@gmail.com

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ABSTRACT

Introduction. Ribociclib is a cyclin-dependent kinase (CDK) inhibitor, widely used in patients with different types of cancer. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe immunologic skin reactions that lead to epidermal necrolysis followed by exfoliation with life-threatening consequences.

Case presentation. We present a case of a patient with metastatic breast cancer with SJS-like skin reaction during treatment with ribociclib and letrozole. The patient presented skin changes, typical clinical symptoms (with Nikolsky sign), and destruction of the epithelium by forming blisters and abscesses on pathological examination. The lesions covered about 30% of the skin surface, and they were scored as grade 4 according to CTCAE v. 5.0. After ribociclib discontinuation and supportive management, a gradual improvement of skin lesions was observed.

Conclusion. We present this case as there are only a few case reports on ribociclib-related Stevens-Johnson syndrome in the literature, and clinicians should be aware of the risk of this side effect.

Key words: ribociclib, breast cancer, Stevens-Johnson syndrome, toxic epidermal necrolysis

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Established facts and novel insights

Established facts

- Ribociclib, an oral CDK inhibitor, is more increasingly used in daily clinical practice.
- Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) could be life-threatening conditions.
- The sudden onset of bullous skin lesions should prompt immediate drug discontinuation, close monitoring, and dermatological evaluation.

Novel insights

- Cancer patients treated with ribociclib should be educated and closely monitored, even if they are in good general health state.
- Histopathological examination of samples taken during a biopsy of skin from the affected area is feasible and could diagnose SJS or TEN and introduce early treatment.

Introduction

Ribociclib is a cyclin-dependent kinase (CDK) inhibitor, indicated in the treatment of patients with HR+/HER2– breast cancer in combination with aromatase inhibitor/fulvestrant, with proven significant improvement in progression-free/overall survival [1–3].

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe immunologic skin reactions that may lead to epidermal necrolysis followed by exfoliation, with life-threatening consequences, such as loss of the skin barrier, dehydration, and possible multi-organ failure. They are differentiated based on body surface area affected (less than 10% is SJS, and more than 30% is TEN). Mortality is proportional to the extent of the skin damage and can exceed 40% in TEN patients [4].

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Although the rash is a common side effect associated with the use of ribociclib, bullous skin lesions of sudden onset were not reported in clinical trials.

We present a case of a patient with metastatic breast cancer with SJS-like skin reaction during treatment with ribociclib and letrozole.

Case report

A 67-year-old female patient was diagnosed with moderately differentiated, HER2-negative, stage IV (cT4cN1M1) breast cancer with lung, skin, and Th11 metastases.

Palliative spine irradiation and bisphosphonates were used in supportive treatment, and ribociclib and letrozole were commenced one month later. The medical history revealed compensated hypothyroidism, with chronic thyroid hormone supplementation and smoking (approx. 40 pack-years).

Two weeks after starting ribociclib treatment, skin dryness and an erythematous maculopapular rash appeared with a dark or purple tinge in the middle of the lesions located on the face, arms, and trunk. It was accompanied by a burning pain, sore and dry throat, and feeling dry eyes. After a few days, the rash turned into hemorrhagic blisters with accompanying epidermal shedding. There were erosions on the oral mucosa, making drinking and eating difficult. The treatment was continued, and the patient did not report to the doctor until the second treatment cycle was started. Then the intensity of lesions decreased for several days. The patient denied introducing new hygiene measures, changing detergents, or taking new medications or altenative medicines. The patient complained of painful skin sensations and itchiness. Pruritus grade 2, according to CTCAE v. 5.0, was diagnosed. Physical skin examination revealed small, partially confluent papules, erosions at the site of ruptured serous blisters, lesions with scabs in both mouth corners, and single erosions on the oral mucosa (Fig. 1A, B). Nikolsky sign, e.g. dislodgement of the intact superficial epidermis by a shearing force was also observed. The lesions covered about 30% of the skin surface, which was qualified as grade 4 according to CTCAE v. 5.0. The patient remained in a good general condition (PS = 1 according to ECOG).

Due to skin damage and the suspicion of SJS, ribociclib was discontinued, whereas letrozole was maintained. An elevated amount of neutral fluids, antihistamines, and close monitoring were recommended. According to the patient's report, the intensity of skin lesions on the visit day was slightly lower compared to the first days after their appearance. For this reason, calcineurin inhibitors were not introduced.

The comprehensive differential diagnosis was performed, including laboratory tests to exclude active and chronic HBV, HCV, and *Mycoplasma pneumoniae* infections. A history of Chlamydia pneumoniae infection

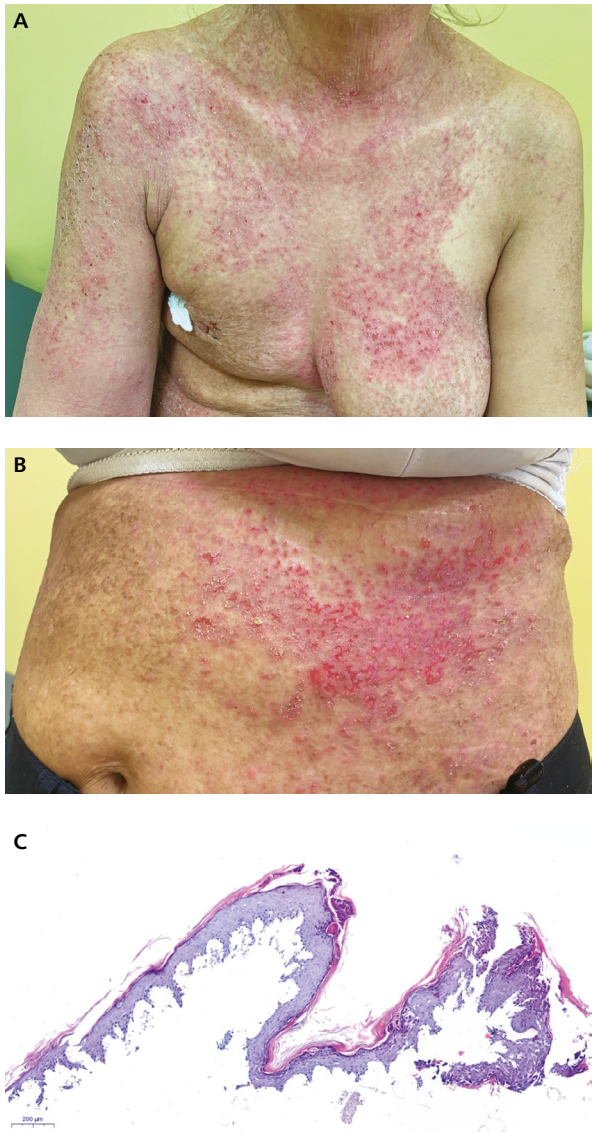

Figure 1. Skin lesion 2 weeks after symptoms onset (A, B) and pathological examination of skin biopsy (C)

was confirmed. The skin biopsies from the affected areas were performed (4 weeks after the first dermal symptoms). The histopathological examination revealed destruction of the epithelium with forming blisters and abscesses (Fig. 1C).

A gradual improvement of skin lesions was observed in the next few weeks, and it was decided to discontinue treatment with ribociclib and to continue monotherapy with letrozole.

Discussion

SJS and TEN are extremely rare (1–2 cases per million per year), life-threatening mucocutaneous reactions most commonly attributed to drug hypersensitivity.

They most frequently occur after administration of antibiotics, anticonvulsants, allopurinol, some non-steroidal anti-inflammatory drugs, and sertraline [5]. However, some infections (*Mycoplasma pneumoniae, Herpes simplex, hepatitis B and hepatitis C virus, Chlamydophila pneumoniae*) have been also reported as potential etiologies. Observational studies have shown an increased risk of SJS/TEN-related mortality and morbidity in patients with active cancer (relative risk, RR = 2.7), especially for hematological malignancies [6]. Therefore identifying SJS/TEN risk factors in this group of patients is particularly important. The previous publications highlighted the effect of immunosuppression, exposure to drugs triggering SJS/TEN (including antibiotics, immunomodulating drugs, cytotoxic agents), active neoplastic process, and their combination. The diagnosis is usually based on recent drug exposure that increases the risk of SJS or infection with *Mycoplasma pneumoniae*, as well as the presence of target-like skin lesions with central necrosis and mucosal involvement. Management of SJS and TEN consists in identifying the causative factors (discontinuing the suspected drug), inhibiting the reaction, if possible, and introducing intensive supportive care. As this is an extremely rare condition, the recommended algorithms are based on case series descriptions and therefore could be not definitive.

Currently, there are three CDK4/6 inhibitors approved for use in patients with advanced breast cancer. They are usually well-tolerated, and the most common side effect is neutropenia, which occurs in one to three quarters of patients (grade 3 or 4) but is usually asymptomatic and does not increase the risk of infection. Serious non-hematological adverse reactions are rare with a low treatment discontinuation rate. In clinical trials with CDK4/6 inhibitors, only rash and alopecia were reported among skin abnormalities. The prevalence of these skin lesions was similar for all discussed CDK4/6 inhibitors, with all-grade rash in < 20% of patients, and grades 3/4 in < 1% patients [2, 7].

A search of available medical literature databases found 4 case reports of SJS in patients treated with CDK4/6 inhibitors, including one case with simultaneous radiotherapy [8–11]. They described the varying degree of skin lesion severity, from only moderate to extensive, hemorrhagic mucous lesions, including rapid course and development of full-symptom life-threatening shock within several hours. Only in one case, the diagnosis of SJS was supported by a histopathological examination. The treatment included calcineurin inhibitor, glucocorticoids, and etanercept, an antibody against tumor necrosis factor α (TNF-α). One patient required hospitalization in a burn unit, and another one in an intensive care unit where drugs leading to hemodynamic stabilization and broad-spectrum empirical antibiotic therapy were administered. The authors of one report also highlighted the coexistence of psoriatic arthritis in a patient in remission.

A case of a female patient who underwent radiotherapy in the supraclavicular area while using palbociclib is of special interest [10]. She had a grade 3 (according to CTCAE, v.4.0) post-radiation esophageal and skin reactions, which resulted in hospitalization and intravenous hydration. In pivotal studies with CDK4/6 inhibitors, radiotherapy was continued to treat painful bone lesions, but anti-CDK4/6 treatment was stopped during radiotherapy. However, a synergistic effect of CDK4/6 inhibitor and radiotherapy is possible, enhancing G1-phase arrest of cell cycle and increasing cells' susceptibility to radiation during treatment with CDK4/6 inhibitors. Clinical trials with these combinations are ongoing [12].

In the presented case, radiotherapy was completed a month before ribociclib treatment. It involved a small area of skin on the back, so in our opinion, it had no effect on the SJS occurrence. The medical history and additional tests did not identify any other causes of SJS. We would like to highlight the feasible and useful skin biopsy. Although it did not reveal the typical lymphocyte infiltrations, the microscopic picture with features of epithelium destruction helped us to confirm the diagnosis and introduce specific treatment. CDK 4/6 inhibitors are well tolerated and become an established treatment option for patients with advanced breast cancer. However, it should not be forgotten that every drug can cause side effects, with serious and even life-threatening consequences. Pharmacovigilance is especially valuable in relation to recently introduced drugs to improve knowledge and reduce safety-related risks. Finally, the greater awareness of the risk of side effects, the more rational the management, which is of special importance in heavily treated cancer patients.

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Statement of ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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Author contributions

AK — concept, draft manuscript preparation, decision about submission of the manuscript.

BR — concept, manuscript review, acceptance of final version, decision about submission of the manuscript.

Conflict of interest

Fees from: AstraZeneca, AMGEN, BMS, Gilead, Lilly, Merck, MSD, Novartis, Pfizer, Pierre-Fabre, Roche, Servier.

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