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Case Report: Etoposide Induced Skin Rash in Small Cell Lung Carcinoma

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Abstract

Introduction: Etoposide is a semisynthetic podophyllotoxin derivative that is active against several solid and hematologic malignancies. The adverse effect of this chemotherapeutic agent includes nausea, vomiting, abdominal pain, hair loss, and dizziness [3-7]. On rare occasions, individuals taking this medication have been recorded to have pruritus, rash, and hives. In this case report, we describe a patient who presented with an erythematous macular rash following the administration of Etoposide and Carboplatin after being recently diagnosed with small cell lung cancer.

Case presentation: A 72-year-old Caucasian male recently diagnosed with small cell lung cancer was admitted to our hospital for acute right-sided pleuritic chest pain. Upon further evaluation, he was noted to have diffuse eruptions of pruritic erythematous macular rash 3 weeks following his first dose of chemotherapy which consisted of Etoposide and Carboplatin. The chemotherapy regimen was held following this discovery, and the patient was started on fluocinonide 0.05% BID.

Conclusion: This case represents the rare adverse effect of skin eruptions following the administration of a chemotherapeutic regimen containing Etoposide and Carboplatin for the treatment of small cell lung cancer.

Keywords: Etoposide; Small cell lung carcinoma; Erythroderma; Macular rash; Chemo radiotherapy.

Introduction

Lung cancer is the second most common cancer diagnosed in the United States. In 2018, 218 520 diagnoses were made and 142 080 people died [1]. Small Cell Carcinoma of the Lung (SCLC) represents one of the majorly prevalent subtypes of primary lung cancers, encompassing approximately 15% of all lung cancer diagnoses [2]. In the context of the treatment protocol for SCLC, chemotherapy remains the main modality of treatment [3]. SCLC has poor prognosis, with data showing an overall 5-year survival rate less than 5% [4]. In the context of SCLC, chemoradiotherapy protocols that utilize Etoposide and Carboplatin in tandem with radiotherapy lead to clinically significant therapeutic advantage to patients, with studies showing the 5-year survival rate can reach as high as 25% [5].

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The mechanism of action of these chemotherapy agents varies and adverse reactions can be harsh. Clinicians need to carefully weigh the costs and benefits of employing a particular chemotherapy protocol before proceeding. In terms of chemotherapy for SCLC the chemotherapeutic agents used routinely in extensive disease cases are Carboplatin and Etoposide. Previously reported adverse effects are hematological and gastrointestinal in nature [6]. The presence of dermatological adverse reactions with this chemoradiotherapy protocol for SCLC remains to be further established, as at the present time in the literature only 4 cases of Etoposide induced rash in patients undergoing chemotherapy for SCLC [7].

The purpose of this case report is to bring to light the presence of dermatological consequences secondary to Carboplatin and Etoposide chemotherapy in the treatment of small cell lung cancer. Here we describe the case of a 72-year-old male patient with recently diagnosed SCLC that developed a rash following exposure to Etoposide and Carboplatin based chemotherapy.

Case presentation

A 72-year-old man with small cell lung cancer of the left upper lung lobe developed an erythematous, macular rash 3 weeks after his first cycle of chemotherapy. The rash was confluent in nature and present on the arms, legs, and chest (Figure 1. Panel A-C). The patient presented to clinic due to right sided chest pain secondary to a congestive heart failure exacerbation, at this time the rash was noted to be present on his body extensively.

The patient had a past medical history of hypertension, chronic obstructive pulmonary disease, coronary artery disease with six stent placements, congestive heart failure with preserved ejection fraction, and colon cancer with hemicolectomy 3 years prior. The patient's medications at the time included fluticasone propionate/salmeterol 100 mcg qd, Incruse Ellipta (Umeclidinium) 62.5 mcg qd, Albuterol 90 mcg qd, apixaban 5 mg q12, atorvastatin 40 mg qd, and metoprolol ER 50 mg q12. The patient has a 80-pack-year smoking history.

As part of the chemotherapy protocol, 20 days prior to the emergence of the rash, the patient received chemotherapy with Etoposide and Carboplatin. Specifically, the patient received Carboplatin and Etoposide on day 1 of chemotherapy, and on day 2 received just Etoposide. This was followed by radiotherapy Monday-Friday for 3 consecutive weeks. The patient was set to undergo another round of chemotherapy on the 21st day following the first chemotherapy session, but the emergence of the rash led to the cessation of the chemotherapy.

A rash emerged with lesions that were raised, pruritic, erythematous, macular, and confluent in nature. The patient had been prescribed topical corticosteroid cream that was causing the lesions to dry out and flake off the top. Dermatology was consulted, and their impression was that the rash was an adverse reaction to medication, specifically Etoposide. The plan moving forward was to hold chemotherapy, continue topical steroids specifically fluocinonide 0.05 BID, consider the addition of systemic steroids, and use oral antihistamines as needed.

Discussion

Medication induced drug rash is not a new phenomenon, as many drugs have been associated with causing rashes in patients. Among chemotherapeutic agents, Etoposide induced drug rash is not well documented in the literature with only 4

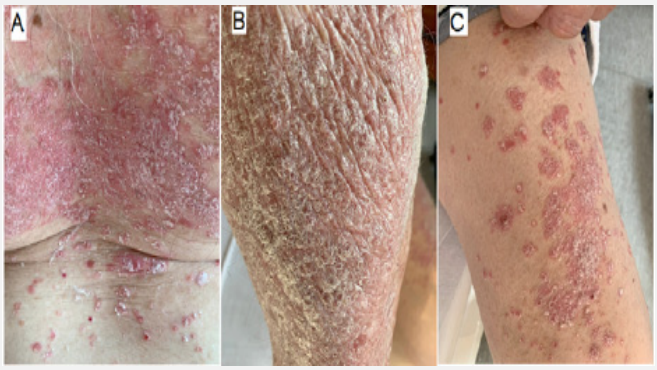

Figure 1: Panel **A, B**, and **C** show the erythematous macular raised rash 3 weeks following chemotherapy exposure. Lesions are red, raised, and confluent. Older lesions are crusted, drying out, and flaking off. Panel A is shows the chest, Panel B shows the left arm, and Panel C shows the left anterior thigh.

other cases in the literature available. In one case series, it is reported that Etoposide induced a diffuse erythematous rash consisting of macules and papules 5-9 days following the initiation of Etoposide and resolved spontaneously in 3 weeks. In that instance histological examination of the skin rash was done which showed a pattern of epidermal maturation that was disturbed with enlarged keratinocytes with clear cytoplasm and dyskeratotic cells that were arrested at metaphase of the cell cycle [7].

Etoposide is a semisynthetic podophyllotoxin derivative that functions by targeting Topoisomerase II, which is an enzyme that unwinds and removes knots from DNA by causing double-stranded breaks in the double helix [8]. Etoposide stabilizes these double stranded breaks which are transient intermediates of the Topoisomerase II enzyme. The accumulation of these intermediates overwhelms the cell and triggers apoptosis [9]. Adverse effects are limited to alopecia and gastrointestinal adverse reactions including nausea, vomiting, and stomatitis [10]. Hypersensitivity reactions are rarer with Etoposide but that can include flushing, bronchospasm, cyanosis, hypertension and hypotension [11]. Etoposide is a topoisomerase II inhibitor, and thereby arrests cells as they go from S to G2 of the cell cycle. This mechanism of action directly explains the pathogenesis behind the most common forms of adverse reaction-alopecia and gastrointestinal distress. In the case of chemotherapy induced alopecia, the mitotic activity of the cells at the time of insult is directly related to the degree of hair loss- when matrix keratinocytes are in their proliferative anagen phase they are highly sensitive to chemical insult and rapidly undergo apoptosis leading to alopecia, conversely when they are in the catagen and telogen phase they are not affected because this is their mitotically inactive phase [12]. This logic can be extended to explain Etoposide's role in the pathogenesis of rash seen in Figure1. The body's skin is constantly regenerating from the stratum basale layer of the epidermis, and it takes approximately 4 weeks for a cell to grow and mature from the stratum basale layer of the epidermis to the uppermost stratum corneum and stratum lucidum layers [13]. Under this logic Etoposide induced drug rash should be a more prevalent adverse reaction, however the literature only shows a handful of such cases and fails to provide an explanation as to why rates are not higher. Therefore, this remains an area for further exploration.

It is interesting to see how the time frame for the maturation of skin cells from the deepest to most superficial layer of the epidermis correlates with the time frame that it took for

the rash to emerge in the patient in this case report. The fact that it took 20 days following Etoposide chemotherapy administration to cause the observed rash supports this relation. The Etoposide chemotherapy likely led to cell cycle arrest for the cells in the stratum basale layer of the epidermis. As this layer of cells migrated superficially, they failed to undergo the normal sequence of cell cycle events that are seen in cells of the stratum granulosum and corneum, leading to the observed macular erythematous rash present diffusely on this patient's chest, arms, and legs.

Conclusion

In this case report we have highlighted one specific case of Etoposide induced skin rash. The rash presented several weeks after the initiation of chemotherapy, and the best explanation for this can be related to the time it takes for the deep epidermal cell layers to mature up to the superficial layers. This data is important in raising awareness so that further research can be done to determine the mechanism by which chemotherapy regimen contain Etoposide induces the onset of skin rash, and in extension why this phenomenon emerges in a small subset of patients exposed to this chemotherapeutic regimen. In the case of small cell lung cancer, Carboplatin and Etoposide dual chemotherapy with adjunctive radiotherapy remains the mainstay of disease management. Overall, the benefits of treatment outweigh the risks for most patients, but it is important to have a strong knowledge base of the potential adverse effects that may emerge.

Declarations: Patient consent for this case report was obtained in line with HIPAA policies, including consent for publication of patient images. All data are as is reported and available in this case report inclusively. The authors acknowledge no competing interests or outside funding for this case report.

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