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Concomitant Chemoradiotherapy Using Carboplatin and Etoposide-induced Cutaneous Vasculitis in a Patient with Small Cell Lung Cancer

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ABSTRACT Drug-induced vasculitis occurs after drug exposure and consequent inflammation of small blood vessels which can lead to damage of affected tissue. Rare cases of drug-induced vasculitis during chemotherapy or concomitant chemoradiotherapy have been described in the literature. Our patient was diagnosed with stage IIIA (cT4N1M0) small cell lung cancer (SCLC). Four weeks after the application of the second cycle carboplatin and etoposide (CE) chemotherapy, the patient developed cutaneous vasculitis and rash on the lower extremities. CE chemotherapy was discontinued and symptomatic therapy with methylprednisolone was administered. On prescribed corticosteroid therapy, there was an improvement in local finding. After completion of chemoradiotherapy, the patient continued treatment with four cycles of consolidation chemotherapy with cisplatin (six cycles of chemotherapy in total). Clinical examination verified further regression of the cutaneous vasculitis. Elective radiotherapy of the brain was performed after completion of consolidation chemotherapy treatment. The patient was clinically monitored until disease relapse. Subsequent lines of chemotherapy for platinum-resistant disease were administered. The patient died seventeen months after diagnosis of SCLC. To our knowledge, this is the first described case of a patient who developed vasculitis of lower extremities during concomitant administration of radiotherapy and CE chemotherapy as a part of the primary treatment for SCLC.

KEY WORDS: vasculitis, skin diseases, chemoradiotherapy, lung neoplasms, treatment outcome

INTRODUCTION

Vasculitis can occur in two forms, as primary vasculitis when the cause is unknown or secondary vasculitis when the cause is a drug or underlying disease. Drug-induced vasculitis occurs after drug exposure and consequent inflammation of small blood vessels, which can lead to damage of affected tissue (1). Rare cases of drug-induced vasculitis during chemotherapy or concomitant chemoradiotherapy have been

described in the literature. To our knowledge, this is the first described case of a patient who developed vasculitis of the lower extremities during concomitant administration of radiotherapy and carboplatin and etoposide (CE) chemotherapy as a part of the primary treatment for small cell lung cancer (SCLC).

CASE REPORT

A 64-year-old female patient was diagnosed with stage IIIA (cT4N1M0) SCLC in May 2019. Due to newly-diagnosed hypertension and decreased creatinine clearance, the combination of carboplatin (area under the curve (AUC)=5) intravenously, instead of cisplatin, and etoposide (intravenous etoposide on day 1 and oral etoposide on days 2 and 3) was administered. After the application of the first cycle of carboplatin and etoposide chemotherapy only, patient had no cutaneous adverse events.

After 21 days, treatment was continued with the second cycle of CE chemotherapy concomitantly with thoracic radiotherapy. Four weeks after the application of the second cycle of CE chemotherapy during concomitant chemoradiotherapy, the patient developed cutaneous vasculitis and rash of the lower extremities.

Dermatological examination revealed petechiae, ecchymoses, and some hemorrhagic bullous lesions throughout the circumference of the lower legs in a symmetrical arrangement, with a transition to the upper legs (Figure 1, A).

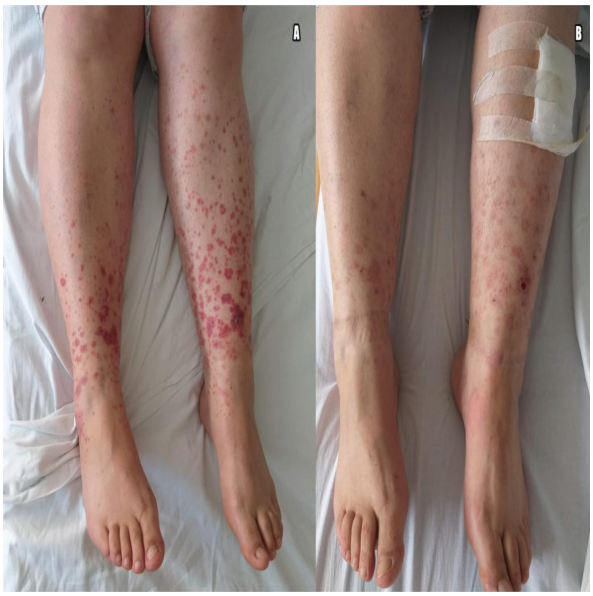

Figure 1. Skin lesions on the lower extremities very suggestive of cutaneous vasculitis (A) and their regression after discontinuation of chemotherapy and inclusion of corticosteroids (B).

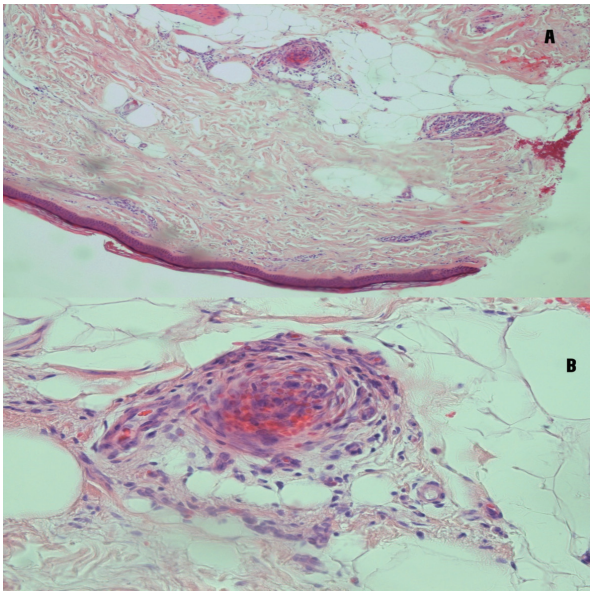

Figure 2. Skin biopsy. Histopathological finding of post-chemotherapy vasculitis in the dermis and subcutis, original magnifications ×100 (A). Higher magnification shows damage to the vessel wall by inflammatory infiltrate, original magnification ×400 (B).

Bilateral perimalleolar edema was also verified. The patient had an increased sensitivity to pain. Laboratory findings showed elevated an erythrocyte sedimentation rate (ESR) and were negative for: anti-double stranded DNA (anti-dsDNA), anti-neutrophil cytoplasmic antibody (ANCA): C-ANCA or proteinase 3 (PR3) ANCA and perinuclear (P) ANCA or myeloperoxidase (MPO) ANCA, extractable nuclear antigen

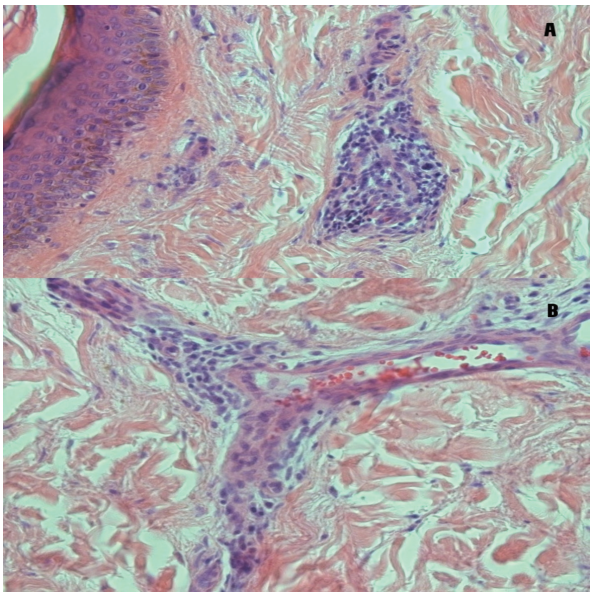

Figure 3. Skin biopsy. Histopathological finding of post-chemotherapy vasculitis, the intense inflammatory cell infiltrate in the blood vessels wall and surrounding connective tissue in dermis, original magnifications ×400 (A, B).

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(ENA) profile, beta-2 glycoprotein 1 IgG antibodies, and cardiolipin IgG antibodies.

A skin biopsy was performed. The histopathological finding showed a slightly acanthotic epidermis and mixed inflammatory infiltrate composed of plasma cells, lymphocytes, and polymorphonuclear cells in the underlying papillary dermis (especially around the wall of small blood vessels) (Figure 2 and Figure 3).

CE chemotherapy was discontinued, and symptomatic therapy with methylprednisolone was administered. Concomitant radiotherapy was continued. On prescribed corticosteroid therapy, there was an improvement of local findings and reduction of pain and perimalleolar edema (Figure 1, B).

After completion of chemoradiotherapy, the patient continued treatment with four cycles of consolidation chemotherapy with cisplatin (six cycles of chemotherapy in total).

Clinical examination verified further regression of cutaneous vasculitis of the lower extremities. Control computed tomography (CT) of the thorax showed significant regression of the primary lung tumor. After completion of treatment with consolidation chemotherapy, elective radiotherapy of the brain was performed. Three months after verified cutaneous vasculitis, complete regression of cutaneous vasculitis on the lower extremities was achieved.

After that, the patient was clinically monitored until disease relapse. Subsequent lines of chemotherapy for platinum-resistant disease were administered to the patient. The patient died in October 2020, seventeen months after diagnosis of SCLC.

DISCUSSION AND CONCLUSIONS

CE chemotherapy is often used in the primary treatment of SCLC (2). Cases of vasculitis caused by carboplatin or etoposide or concomitant chemoradiotherapy have been described in the literature (3-5), but to our knowledge no case of vasculitis caused by the combined action of carboplatin and etoposide has been described so far.

Cutaneous vasculitis is an inflammation of the small blood vessels of skin caused by the infiltration of inflammatory cells (1). The diagnosis of cutaneous vasculitis is established on the basis of the clinical picture, laboratory findings, and histopathological findings of the biopsy of cutaneous lesions.

Based on clinical, laboratory, and histopathological findings, the presentation in our case showed a similarity with the manifestation of carboplatin-induced cutaneous vasculitis that occurred during the treatment of uterine cancer reported by Rajer *et al.* (3).

Although drug-induced vasculitis most commonly occurs a few days after drug exposure, a time delay in the manifestation of the cutaneous vasculitis and other presentations in our case are similar to those published by Rajer *et al.* (3).

Indeed, the appearance of rash with cutaneous lesions on both lower legs, laboratory-negative tests for ANCA, and biopsy-proven deposits of inflammatory cells in blood vessels are common.

If ANCA and anticardiolipin antibodies are verified by serum tests, the clinical outcome can be serious (6). In our case, ANCA and anticardiolipin antibodies were negative. After discontinuation of carboplatin chemotherapy during concomitant chemoradiotherapy treatment and inclusion of symptomatic corticosteroid therapy, complete regression of symptoms was observed three months later.

In 2007, Turken *et al.* published a case report about oral etoposide-induced leukocytoclastic vasculitis in a patient with lung adenocarcinoma. Ten days after the initiation of oral etoposide chemotherapy, the patient developed maculopapular eruptions on his hands, arms, and legs. Histological examination revealed leukocytoclastic vasculitis. After cessation of etoposide, vasculitis decreased in severity over time (4).

Corella *et al.* reported on cutaneous vasculitis associated with gemcitabine therapy. A patient with non-small cell lung carcinoma (NSCLC) was treated with gemcitabine and carboplatin combination chemotherapy (7). Since the authors did not find a link between carboplatin and skin toxicity by searching the literature at the time of publication, they concluded that gemcitabine was the cause of skin vasculitis based on previously published papers on this topic.

One of the development mechanisms of cutaneous vasculitis may be mediated through the immune system by the formation and deposition of the immune complex between antibodies and neoantigens in blood vessels, either cell-mediated or by the direct action of antibodies with tumor or endothelial cells in blood vessels (8). Although drug-induced vasculitis most commonly occurs a few days after drug exposure, in our case vasculitis developed after 4 weeks of drug administration combined with radiotherapy. A possible explanation for this is the release of a larger amount of neoantigen caused by the combined antitumor action of chemotherapy and radiotherapy. In fact, the patient had no adverse treatment events after one cycle of carboplatin and etoposide chemotherapy.

Additionally, our patient did not have a relapse of cutaneous vasculitis when she was subsequently treated with other cytostatics, including cisplatin, combination of cyclophosphamide, doxorubicin, and vincristine (CAV protocol), irinotecan, and docetaxel.

Paraneoplastic syndrome may cause cutaneous vasculitis in 10% of solid tumors (6). Since SCLC is the most common cancer associated with paraneoplastic syndrome in real clinical practice, it is difficult to determine the actual cause of cutaneous vasculitis. Since the exclusion of CE chemotherapy and the use of corticosteroids resulted in complete regression of symptoms, which no longer appeared in the further course of the disease, paraneoplastic syndrome was excluded as the cause of cutaneous vasculitis in the present case.

Our case showed that cutaneous vasculitis, as an extremely rare drug-induced side effect, can also occur due to the combination of carboplatin and etoposide chemotherapy during concomitant chemoradiotherapy treatment, and timely identification and treatment is important to improve patient outcomes.

ABBREVIATIONS

SCLC: Small cell lung cancer; **CE:** Carboplatin and etoposide; **AUC:** Area under the curve; **ESR**: Erythrocyte sedimentation rate; **anti-dsDNA**: Anti-double stranded DNA; **ANCA**: Anti-neutrophil cytoplasmic antibody; **PR3:** Proteinase 3; **P:** Perinuclear; **MPO:** Myeloperoxidase; **ENA:** Extractable nuclear antigen; **CT:** Computed tomography; **NSCLC:** Non-small cell lung carcinoma; **CAV:** Cyclophosphamide, doxorubicin and vincristine

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