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Case Report

Cutaneous leukocytoclastic vasculitis in a patient treated with carboplatin for uterine carcinoma

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Cutaneous leukocytoclastic vasculitis (LCV) is a histopathological term used to refer to inflammation of the small vessels, including arterioles, capillaries and postcapillary venules, in the skin. The main morphological features of LCV are fibrinoid necrosis of the vessel wall with mainly neutrophilic infiltration and leukocytoclasis. LCV can be idiopathic or triggered by several causes, such as medications, underlying infection and malignancies. IgA vasculitis is a type of LCV with IgA-dominant immune deposits in the vascular wall. We report a rare case of skin-limited IgA vasculitis after treatment with carboplatin in a patient with uterine cancer. To our knowledge, this is the first reported case of LCV (in our case, skin-limited IgA vasculitis) connected to carboplatin treatment. A 57-year-old patient with uterine carcinoma was treated with surgery. Afterwards, she received postoperative chemotherapy with pegylated liposomal doxorubicin (PLD) in combination with carboplatin. When the disease progressed, the patient received carboplatin monotherapy; after the third round of carboplatin therapy, she developed IgA vasculitis of the skin without systemic involvement. Chemotherapy with carboplatin was discontinued. She was treated symptomatically, and after six months, the skin lesions resolved and had not reappeared as of her last visit. Carboplatin can induce LCV, and clinicians should be aware of this potential effect for the proper management of affected patients.

Keywords

Vasculitis; Leukocytoclastic; Cutaneous; Carboplatin

1. Introduction

Leukocytoclastic vasculitis is a histopathological term indicating inflammation of small vessels. If limited to the skin, it usually presents as purpura and haemorrhage and predominantly affects the lower leg area, although it can also affect other parts of the skin [1]. It can also be a secondary manifestation caused by many factors, such as autoimmune diseases, malignancies, underlying infections, collagen-vascular disorders and drugs. Medications are estimated to be the cause of 10-15% cases of LCV. Drug-induced vasculitis may be associated with antibodies against drug-related haptens, direct drug toxicity affecting vessel walls, auto-antibodies reacting with endothelial cells, or a cytokine-mediated reaction to the vascular endothelium [1, 2]. Carboplatin is one of the most commonly used anti-cancer drugs. It forms reactive platinum complexes that cause intra- and inter-strand cross-linkages of DNA molecules within the cell. This modifies the DNA structure and inhibits DNA synthesis [3]. To our knowledge, no cases of LCV related to carboplatin have been reported in the literature. In this article, we describe an exceedingly rare case involving a 57-year-old woman with skin-limited IgA LCV during carboplatin treatment for uterine carcinoma that resolved after treatment discontinuation.

2. Case

A 57-year-old, Caucasian, non-smoking woman with arterial hypertension and stable angina pectoris was diagnosed with poorly differentiated uterine endometrioid carcinoma (FIGO IV) in 2016. She was treated with laparoscopic surgery (removal of the uterus with both adnexa and partial pelvic lymphadenectomy). The resection was not radical because of the metastatic disease-a local macroscopic residual tumour remained above the vagina. Imaging with scintigraphy and bone X-ray revealed metastases in her spine and ribs. Postoperatively, she was treated with six cycles of chemotherapy with carboplatin and pegylated liposomal doxorubicin from December 2016 to May 2017. She also received denosumab subcutaneously every 4 weeks for her bone metastases and radiotherapy of the painful bone metastases (5×4 Gy to the 10^{th} thoracic vertebra). Partial response of the disease was achieved. After discontinuation of chemotherapy, she continued denosumab therapy. She had no known allergy to drugs, and for the whole treatment time, she received ranolazine and bisoprolol for her concomitant diseases.

Six months after discontinuation of chemotherapy, progression of the disease with new lung and abdominal lymph node metastases was observed. A multidisciplinary team recommended second-line chemotherapy with carboplatin as monotherapy. She received three cycles of carboplatin (the cumulative dosage of carboplatin was 2.050 mg). Aside from carboplatin, the patient received no new medications. At the end of March 2018, 22 days after the last carboplatin administration, she presented with itching and macular eruptions affecting both lower legs (Fig. 1). She was referred to the der-

Fig. 1. Leukocytoclastic vasculitis at the time of presentation (March 2018).

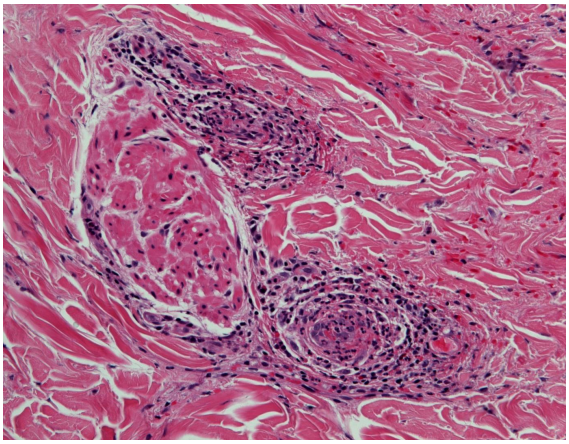

Fig. 2. Fibrinoid necrosis of small vessels in the dermis with neutrophilic infiltration, leukocytoclasia and erythrocytes extravasation.

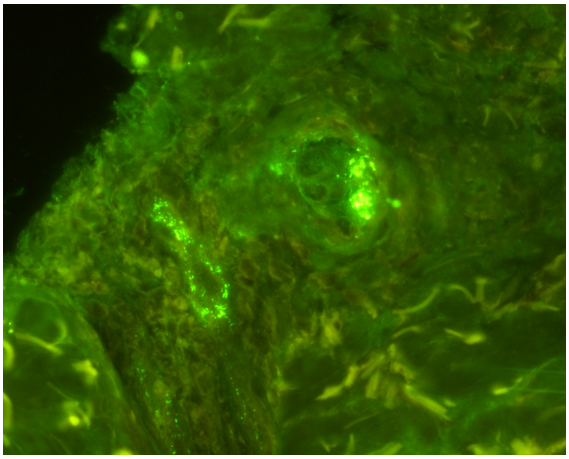

Fig. 3. Deposition of IgA in the dermal vessel wall.

matology clinic, where the first differential diagnoses were Henoch-Shönlein purpura without systemic involvement or possible paraneoplastic rash. Her laboratory tests were normal, except for light monocytosis (14.7%) and a C-reactive protein level of 12 (normal range up to 5 mg/L). The dermatologist prescribed corticosteroid cream and oral antihistamines. Biopsy of the skin lesion was performed for evaluation by light microscopy and further direct immunofluorescence. Histological evaluation revealed fibrinoid necrosis of the small vessels in the dermis with neutrophilic infiltration and leukocytoclasis, followed by extravasation of erythrocytes (Fig. 2). Direct immunofluorescence imaging showed mainly deposits of IgA (Fig. 3) in the vessel walls, complement C3 and fibrin, suggesting IgA vasculitis. Serum tests for anti-neutrophil cytoplasmic antibody (ANCA) and cryoglobulin were negative. An infectious workup was performed to rule out other causes of LCV. Treatment with carboplatin was discontinued, and the patient received further symptomatic therapy with corticosteroid cream and oral antihistamines. She continued denosumab therapy every 4 weeks without interruption. On the 25^{th} of September 2018, she had a standard examination, which revealed that her skin rash had completely resolved (Fig. 4). Afterwards, the patient was treated with radiation of painful bone lesions, and she continued denosumab therapy. Due to deterioration of her performance status, no new chemotherapy treatment was administered. At the time of reporting this case, the patient is receiving the best supportive care. No recurrence of the rash was found as of her last visit in June 2020. Fig. 5 shows her skin ten months after the development of LCV.

3. Discussion

Leukocytoclastic vasculitis is a histopathological term used to describe a variety of types of small vessel vasculitis and mainly refers to the skin, although there are types of vasculitis that can affect other regions of the body. By using the positive results from direct immunofluorescence examination, we may categorize the type of LCV based on the detection of immune complex deposits in the vessel wall [2, 4]. LCV presents approximately seven to ten days after exposure to the causative agent. In our case, this time was slightly longer, as our patient presented with skin lesions 22 days after carboplatin administration.

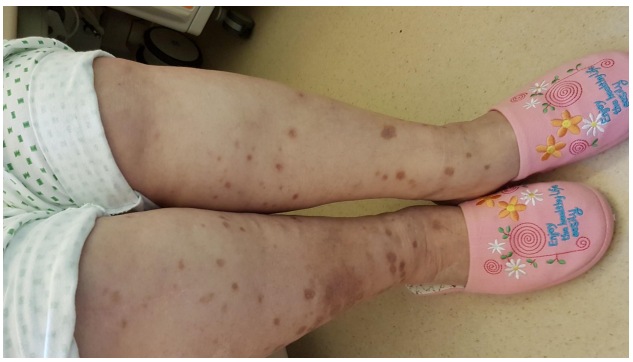

Fig. 4. Skin lesions three months after the 1st presentation (September 2018).

Regarding clinical scenarios of drug-induced LCV, the following observations can be made. Female patients are more affected than male patients (8.8 : 1 F : M). Typical symptoms of drug-induced LCV are skin rash in 41-51%, fever in 46%,

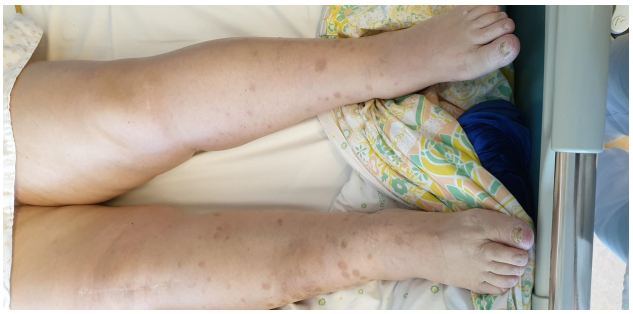

Fig. 5. Skin lesions 10 months after the 1st presentation.

arthralgia in 36-43% and renal manifestations in 57% of cases. Skin lesions are usually self-limiting and resolve in 3-4 weeks. In our case, skin lesions resolved over a longer period without other organ involvement. Approximately 6% of patients have serological evidence of ANCA positivity, which was not present in our case [5].

Histopathological findings in LCV, when evaluated > 48 h after the first manifestation of the disease, include fibrinoid necrosis of the vessel wall with predominant neutrophilic infiltration, nuclear debris around disrupted vessels, endothelial swelling, and erythrocyte extravasation [6]. Direct immunofluorescence imaging is recommended for the detection of immune deposits in the vessel walls.

Direct comparison to other data in the literature is not possible in this case since there are no reported cases of carboplatin-induced LCV. We found similarities between our case and others related to different drugs. Namely, Lee *et al.* reported a case of LCV caused by another anti-cancer drug, everolimus. The patient presented with no systemic manifestations of vasculitis and did not receive any immunosuppressive therapy, but he needed skin grafting [4]. Our colleagues Grasic *et al.* presented a similar case with everolimus connected to LCV, where the patient needed only treatment discontinuation and local measures, as in our case [7]. Quintanliha *et al.* published a case of LCV in a patient with laryngeal carcinoma who developed LCV after the first dose of cisplatin. The authors concluded that cisplatin was the most likely cause of LCV since the time between the first exposure and the development of the symptoms was in accordance with the literature (12 days), and the lesion regressed when no new exposure to the agent occurred [2]. This could also explain our case, since LCV developed 22 days after carboplatin administration, resolution after corticosteroid therapy was seen, and the patient did not experience LCV on any other treatment. Our case complements the one by Quintanliha *et al.*, demonstrating that LCV may occur after exposure to platinum agents.

The clinical picture and skin biopsy of our patient revealed typical features of LCV, and direct immunofluorescence imaging was suggestive of IgA vasculitis. Usual treatment for drug-related LCV is prompt discontinuation of the causative drug. In many patients, this leads to the resolution of symptoms. In more severe cases, other treatments were successfully used, such as corticosteroids, cyclophosphamide, plasmapheresis and azathioprine [5]. Fortunately, for our patient, after discontinuation of carboplatin chemotherapy and symptomatic treatment with corticosteroid ointment, her condition resolved without major consequences. Our patient received concomitant treatment with denosumab due to bone metastases before and during LCV without interruptions. Since LCV resolved during denosumab treatment, we believe it is highly unlikely that LCV was associated with denosumab.

To our knowledge, this is the first case report of LCV development most likely caused by carboplatin treatment. LCV related to drugs is a rare treatment complication and can easily be erroneously diagnosed as other skin conditions. Describing such rare cases can raise awareness among treating physicians so they can perform the correct diagnostic tests and start the correct treatment as soon as possible.

Author contributions

All authors contributed to manuscript writing, M.R. wrote the final manuscript, B.G. and E.S. provided informed consent and patient data, M.Z. provided microscopic figures, E.S. initiated and coordinated procedures.

Ethics approval and consent to participate

The patient has consented to the publication of her case and our institution's Ethics committee has approved this case report-the documents were added.

Acknowledgment

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Conflict of interest

The authors have no conflicts of interest in connection with the submitted material.

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