Fixed Drug Eruption Late in the Course of Capecitabine Therapy

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ABSTRACT – A fixed drug eruption (FDE) is a toxic skin effect thought to be caused by delayed cell-mediated hypersensitivity to a pharmaceutical agent. We report herein the first known patient with possible capecitabine-induced FDE that appeared relatively late in the course of adjuvant therapy for rectal cancer. The temporal association with capecitabine use and prompt disappearance after capecitabine discontinuation make this relationship probable. Knowledge about this dermatologic skin effect seen with oral fluoropyrimidines should avoid unnecessary diagnostic workup and provide the necessary patient reassurance.

Introduction

Fixed drug eruptions represent toxic skin effects caused by delayed cell-mediated hypersensitivity to various pharmaceutical agents. They are often described as drug-induced development of one or more annular/oval erythematous patches. We report herein a fixed drug eruption with capecitabine use, occurring late in the course of adjuvant therapy for rectal cancer.

Case Report

A 49-year old male presented for cycle 10 of adjuvant chemotherapy for rectal cancer in May 2015. A physical examination revealed an oval erythematous patch on the level of the medial malleolus of his left foot. Per the patient, the rash was slightly tender but nonpruritic, and started at 12 weeks of capecitabine-oxaliplatin therapy.

The patient's medical history included clinical stage IIIC (T3N2bM0) rectal cancer diagnosed in August 2014. He was treated with capecitabine followed by combined capecitabine-radiation therapy in the neo-adjuvant setting. Except for a mild radiation dermatitis, he did not have any skin reactions. He had an excellent response to this therapy, followed by surgery in December 2014. Pathology showed pT3N0M0 poorly differentiated tumor with clear margins. He then received 12 cycles of chemotherapy with XELOX (oxaliplatin 130mg/m^2 IV every three weeks and capecitabine 1500mg orally twice daily 2/3 weeks) in the adjuvant setting from February to July 2015.

The patient denied any known allergies. His current medications included only the chemotherapy agents capecitabine and oxaliplatin. He denied using any vitamin/mineral supplements or other complementary therapies. On review of systems, the patient reported mild fatigue. He denied fevers, night sweats, weight loss, shortness of breath, cough, chest pain, nausea, vomiting, diarrhea, hematochezia, melena, other skin lesions, or excessive sun exposure.

Physical examination was significant for an oval erythematous patch on his medial malleolus of his left foot (Figure 1A). The rash was well-circumscribed and measured 5 cm in the largest diameter. There was no ulceration, purulence, or bleeding. The lesion was minimally tender but not warm to palpation. Nikolsky sign was negative. There was no desquamation of the palms or soles. There were no mucocutaneous ulcers,

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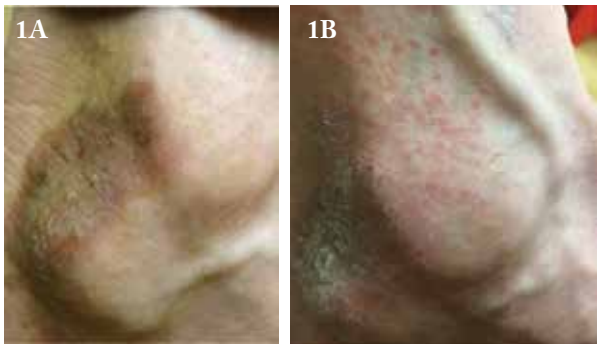
petechiae, ecchymoses, or other lesions on a complete skin examination. The patient had no abnormalities on a fundoscopic examination. The pharynx had a normal appearance, without exudates and erythema. The rest of the physical examination was within normal limits. Laboratory panel showed normal values for hemoglobin, white blood cells, platelets, liver function tests, blood glucose, and electrolyte panel. Antinuclear antibody titers were within normal limits.

Based on the appearance of the lesion, the patient and family were counseled that the lesion would likely disappear after completion of therapy. Indeed, three weeks after completion of the adjuvant chemotherapy, fading of the intensity and decrease in size of the lesion was noted. A near-complete resolution of the lesion was documented three weeks later (Figure 1B). The patient was followed as an outpatient for the next six months. There has been no recurrence of either rash or cancer at the time of writing this report.

Discussion

FDEs represent round/oval, well-demarcated, dusky, erythematous plaques that may evolve into edematous plaques, with or without accompanying vesicles.[1] They tend to recur on the same skin area after reexposure to the drug. Several pharmaceutical agents have been linked with occurrence of FDEs (Table).[2] Although fluoropyrimidines may cause several cutaneous reactions and hand-foot syndrome, we are not aware of any case reports in the literature linking capecitabine use with a FDE.

Figure 1. A. Well-Demarcated, Oval-Shaped Dusky Erythematous Plaque on the Medial Aspect of the Left Foot near the Malleolus. B. Near-Complete Resolution of the Lesion Six Weeks after Capecitabine Discontinuation.



At the present time, fluoropyrimidines form the backbone of chemotherapy regimens for colorectal cancer.[3] Capecitabine is a prodrug of 5-fluorouracil (5-FU), developed as an oral agent that would mimic the action of infusional 5-FU and overcome the inconvenience of IV administration. Capecitabine is metabolized to 5-FU through three activation steps. Thymidine phosphorylase, the enzyme that mediates the final step of capecitabine activation, is expressed in higher concentrations in tumor tissues than in normal ones. This allows for selective activation of the drug in the tumor tissue and less systemic toxicity.[4]

Hand-foot syndrome, also known as palmar-plantar erythrodysesthesia, features numbness, tingling, pain, redness, or blistering of the palms and soles. It represents the most common dermatologic side effect of capecitabine, affecting up to 60% patients taking the drug.[5] Other dermatologic side effects of capecitabine include nonspecific dermatitis (23% – 31%) and nail disorders (4%).[6] Alopecia, erythematous rash, pruritus, eruptive multiple lentigo maligna-like lesions, radiation recall dermatitis, pyogenic granulomas, photoeruption, hyperpigmentation, and inflammatory responses in actinic keratoses have also been described with capecitabine.[6] In addition, a case of leopard-like vitiligo and another case of subacute cutaneous lupus erythematosus have been reported.[6,7]

For the first time, we report a FDE in a patient with rectosigmoid cancer being treated with capecitabine. This lesion appeared relatively late in the course of adjuvant therapy. Nonetheless, its temporal association with capecitabine use and prompt disappearance after capecitabine discontinuation make this relationship at least probable. Differential diagnoses in our case included paraneoplastic rash as the patient had advanced rectosigmoid cancer. However, the patient had no evidence of residual malignancy after surgery. In addition, the skin lesion resolved after discontinuation of the offending agent, making paraneoplastic lesions unlikely. The only other agent the patient was taking,

Table. Drugs Known to Cause Fixed Drug Eruptions.

Cotrimoxazole	Tetracycline	Metamizole	Phenylbutazone
Paracetamol	Acetylsalicylic Acid	Mefenamic Acid	Metronidazole
Tinidazole	Chlormezanone	Amoxicillin	Ampicillin
Erythromycin	Belladonna	Griseofulvin	Phenobarbitone
Diclofenac Sodium	Indomethacin	Ibuprofen	Diflunisal
Pyrantel Pamoate	Clindamycin	Allopurinol	Albendazole

oxaliplatin, had been linked with anaphylaxis but not with localized skin reactions. Allergic contact dermatitis and mycosis fungoides did not fit the clinical scenario, given the lack of contact with new antigens to support the former, and the response to capecitabine discontinuation arguing against the latter. No clinical or serological evidence to support a collagen vascular disease was found, and no sun exposure occurred to induce a local phototoxic reaction in this patient.

Awareness of the possibility of fixed drug reactions with capecitabine and other fluoropyrimidines is important for several reasons. Firstly, several fluoropyrimidines are currently being used for the therapy of gastrointestinal (GI) cancers. Secondly, several newer oral fluoropyrimidines are in the pipeline and will soon join the armamentarium against GI malignancies. The last but not least, expanding knowledge about this dermatologic skin effect should avoid unnecessary diagnostic workup and provide the necessary patient reassurance.

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