Erythema multiforme occurring during concomitant chemoradiation for anal canal cancer: a case report

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ABSTRACT

Background: Multimodality treatment is the mainstay of therapy for patients with locally advanced squamous cell anal cancer. This consistes of concurrent radiation and chemotherapy (including fluoropyrimidines and mitomycin). Several adverse skin reactions are associated with fluoropyrimidines.

Case Presentation: Here, we describe the occurrence of an erythema multiforme in a patient treated with radiotherapy and concomitant mitomycin C and capecitabine for anal cancer.

Conclusion: We underline the potential cutaneous drug-induced toxicity during pelvic radiotherapy with capecitabine.

Keywords: Anal canal cancer, erythema multiform, chemoradiation, capecitabine, case report.

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Background

Erythema multiform (EM) represents an immune-mediated condition characterized by a severe rash with appearance of distinctive target-like lesions. The rash is often pruritic and associated with erosions or bullae, rarely involving the mucosae. The clinical course of EM is typically a self-limited condition resolving within weeks without significant sequelae, and treatment is symptomatic.

Various factors have been implicated in the pathogenesis of EM, the most common being infection, in particular the herpes simplex virus [1]. Other potential triggers are drugs and vaccines, such as anticonvulsants, antibiotics, and allopurinol. Moreover, underlying malignancy, autoimmune diseases and radiotherapy (RT) have all been associated to the cases of EM. In our case report, we describe the occurrence of an EM in a patient treated with concomitant chemoradiation (CRT) for locally advanced squamous cell anal cancer (SCAC) and we provide a glimpse into the literature.

Case Presentation

In March 2018, a 64-years old woman presented with a local relapse of a previously diagnosed SCAC treated with surgical resection. No regional lymph node or visceral metastatic involvement was seen at staging thoracic and abdominal computer tomography scan. Her medical history included epilepsy and gastro-esophageal reflux for which she continued her usual medication (valproic acid 500 mg daily, pantoprazole 40 mg daily).

Accordingly, we decided to treat the patient with concomitant CRT. RT was delivered in 1.5 Gy/fraction up to 42 Gy for planning target volume (PTV) II (pelvis, perineum and bilateral groin lymph nodes) and 1.8 Gy/fraction up to 50.4 Gy for PTV I (boost), respectively. The treatment plan was developed using the Varian Eclipse planning system (version 12, Varian Medical System, Palo Alto, CA), and RT was delivered with VMAT/RapidArc technique (Varian Medical System, Palo Alto, CA) with two arcs of six MV photon beams generated by a True Beam linear accelerator. Concomitant chemotherapy consisted in the administration of mitomycin (MMC) (single dose of 12 mg/m^2 on day 1 through iv bolus injection) and capecitabine (CAP) (825mg/m2 bid orally, 5 days per week concomitant with RT).

On day 7 from the beginning of CRT, the RT was transiently disrupted for 5 days due to the occurrence of grade 2 leuko-thrombocytopenia and diarrhea, whereas CAP was permanently interrupted after 2 weeks of concomitant treatment for protracted grade 3 neutropenia.

After 12 days of cessation of CAP and whilst on RT, the patient experienced multiple, progressive, symmetrical, and itchy maculo-papular lesions involving the extensor surfaces of limbs and the thorax in association with skin edema (Figure 1). In addition, a grade 2 perineal radiation dermatitis occurred and completely resolved 2 weeks later. The patient reported no fever, pulmonary, or gastrointestinal symptoms.

The last day of RT the generalized rash evolved into annular erythematous plaques strictly limited on chest and limbs (Figure 2). No signs of toxic epidermal necrolysis (TEN) neither Stevens-Johnson syndrome (SJS) were present. Biochemical analyses were normal, including hepatic and renal function.

A punch skin biopsy revealed basal layer vacuolization and perivascular lymphocyte-rich inflammatory infiltrate with the presence of eosinophils (Figure 3). Based on these findings, the diagnosis of drug-induced EM was made.

The patient was counseled to avoid sun exposure, and topical emollients, steroids and urea-based lotions were recommended.

Cutaneous manifestations fully resolved 2 weeks later from diagnosis of EM.

Discussion

Concurrent CRT is the mainstay of therapy for patients with locally advanced SCAC. High rates of disease free survival, overall survival, and locoregional control have been reported with RT delivered with concomitant administration of MMC and 5-fluorouracil (5-FU) [2]. CAP is an oral prodrug shown to be equivalent to 5-FU when given concurrently with RT in the neoadjuvant setting for locally advanced rectal adenocarcinoma and thus provides an attractive alternative to 5-FU by avoiding the need for intravenous access and inpatient stay [3].

To our knowledge, this is the first report of a patient who developed an EM during concurrent CRT with CAP for a SCAC tumor.

Several adverse skin reactions are associated with CAP, including hand-foot syndrome, nail and nail fold reactions, subacute cutaneous lupus erythematosus and lichenoid drug eruption [4]. None of these adverse events occurred in our case.

Furthermore, MMC, an antibiotic used as antineoplastic agent in various cancer types (bladder, esophageal, and anal) was also administered the first day of therapy by systemic route. However, there are no reports of cutaneous adverse reactions due to MMC in literature, at the exception of exfoliative dermatitis following intravesical therapy [5].

On the other hand, RT is a well-known cause of dermatitis affecting the skin of the irradiated volume in approximately 90% of patients. The acute reactions, such as erythema, moist desquamation, pigmentation changes, and ulceration usually disappear in 1 month time, while the late effects can occur after months/years and including telangiectasias, fibrosis, and necrosis in the irradiated volume [6].

Concomitant chemotherapeutic drugs, such as anthracyclines, taxanes, and antimetabolites (including CAP) are risk factors for radiation dermatitis but they rather

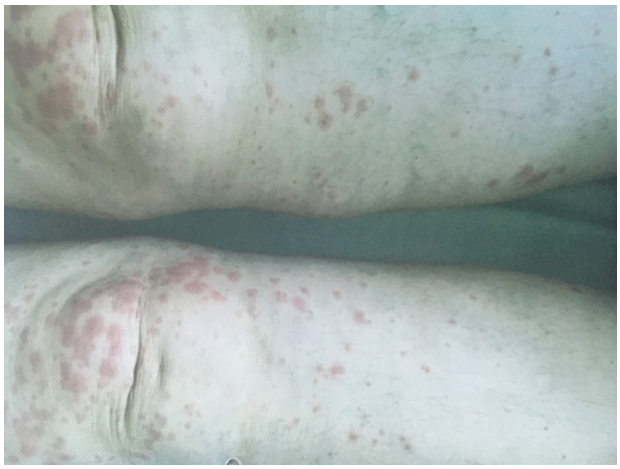

Figure 1. *Cutaneous rash on lower extremities 2 weeks after cessation of capecitabine and whilst being on radiotherapy.*

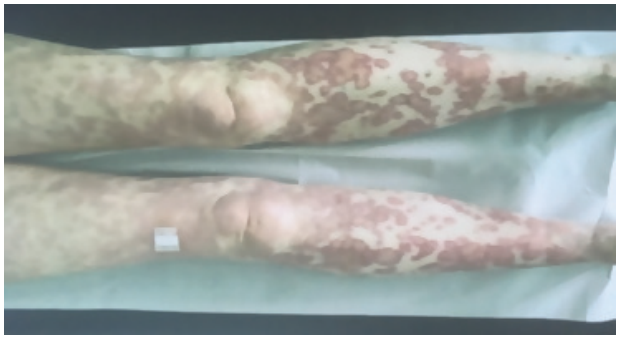

Figure 2. *Evolution of skin reaction to an erythema multiforme at the end of RT.*

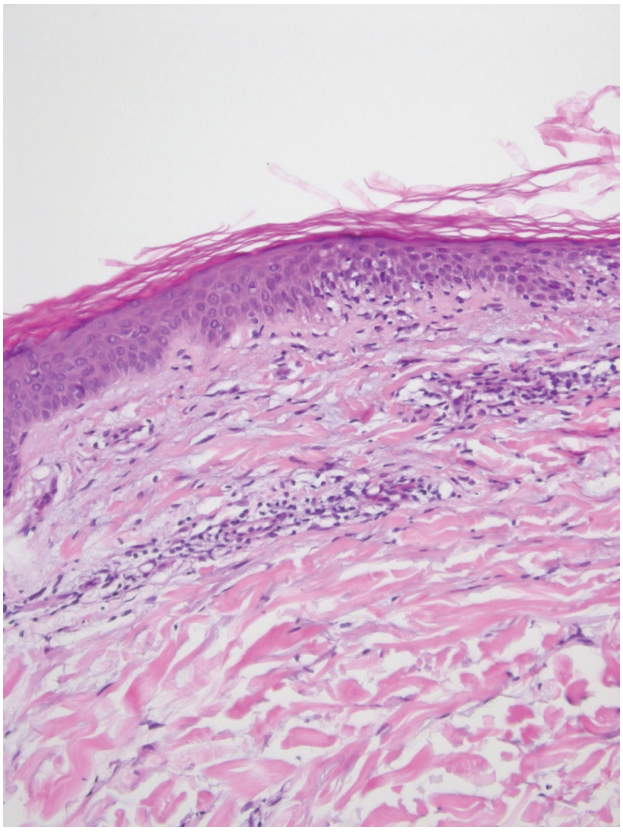

Figure 3. *Evidence of basal layer vacuolization and perivascular lymphocyte-rich inflammatory infiltrate.*

induce the radiation recall phenomenon [7]. This is an acute inflammatory reaction triggered by antineoplastic agents confined to previously irradiated areas. Our patient had never received radiotherapy in the past, thus this alternative diagnosis was rejected.

To date, there is no evidence that radiotherapy alone can induce EM while it seems that combining chemo-radiation can give rise to its apparition. In this regard, there have been sporadic reports of 5-FU inducing EM, with or without associated RT [8,9]. EM has also been observed with the use of another 5-FU prodrug, tegafur (TS-1) [10]. Since both CAP and TS-1 are enzymatically metabolized to fluorouracil, this would suggest that the EM seen with 5-FU prodrugs is related to the 5-FU itself rather than metabolites of the prodrug.

Interestingly, potential causes for development of EM are also drugs other than chemotherapeutics, such as anticonvulsants, antibiotics and allopurinol. Our patient assumed valproic acid and pantoprazole at time of treatment. While proton pump inhibitors are not related to EM, we cannot exclude that concomitant use of valproic acid during CRT acted as a trigger for the cutaneous reaction. Indeed, the combination of RT and antiepileptic drugs can induce EM. The association of EM with phenytoin and cranial radiation has been described in the so-called ‘’EMPACT” syndrome [11]. To our knowledge, however, there are no reports of EM induced by pelvic RT and anticonvulsant therapy.

The appearance of the EMPACT syndrome is somewhat similar to what our patient has exhibited. An immediate skin reaction wasn’t detected after CAP exposure. It is believed that the rash requires some days to appear because of the accumulation of active metabolites or immune complexes rather than the active compound. Surprisingly in our patient, the cutaneous manifestations did not occur within the irradiated volume but involved other areas of the body (extremities, thorax, and dorsum). This is not the first case to report the absence of cutaneous rash within RT fields [12]. It could be speculated that this phenomenon is caused by RT-induced local immunosuppression due to reduction of lymphocytes, or as a result of the modification of the cutaneous microvasculature.

Some pathophysiologic mechanisms could explain the onset of the EM in our patient. First of all, RT can enhance the primary antibody response by depleting the function of T-suppressor cells [13], and this mechanism could be responsible for the development of hypersensitivity reactions to drugs, whether it’s CAP or valproic acid or both. In addition, inflammatory cytokines induced by RT, such as kinins and histamine, could increase vascular permeability and facilitate the migration of the new antigen into the circulation, causing an immune response.

SJS and TEN have been taken into consideration in the differential diagnosis in our case. However, the cutaneous biopsy findings as well as the absence of mucosal involvement have made these entities less plausible. Finally, the drug-induced sweet syndrome (acute febrile neutrophilic dermatosis) has been taken into account. Nonetheless, histologically this syndrome does not typically display the vacuolar changes that were observed in our patient’s biopsy specimen, represented by a dense neutrophilic infiltrate [14]. Moreover, our patient exhibited neither systemic symptoms nor laboratory alterations typically associated to this syndrome.

In conclusion, we believe that our patient presented a radiotherapy-induced EM, triggered by concomitant drugs (CAP and valproic acid). For this reason, clinicians should be aware of potential cutaneous drug-induced toxicity during pelvic RT to cause EM. This case also underlines the importance of careful history and examination of co-medication that could influence CRT strategies.

List of Abbreviations

CAP	Capecitabine
CRT	Concurrent chemoradiation
EM	Erythema multiforme
MMC	Mitomycin
PTV	Planning target volume
RT	Radiotherapy
SCAC	Squamous cell anal cancer
SJS	Stevens-Johnson syndrome
TEN	Toxic epidermal necrolysis
5-FU	5-fluorouracil

Consent for publication

Informed consent was obtained from the patient to publish this case in a medical journal.

Ethical approval

Ethical approval is not required at our institution for publishing a case report in a medical journal.

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Summary of the case

1	**Patient (gender, age)**	Female, 67
2	**Final Diagnosis**	Erythema multiforme induced by drug
3	**Symptoms**	Cutaneous reaction
4	**Medications**	Capecitabine
5	**Clinical Procedure**	Chemo-radiotherapy
6	**Specialty**	Oncology