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Systemic 5-fluorouracil induced lupus erythematosus: a review of the literature

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Abstract

Drug-induced subacute cutaneous lupus erythematosus (SCLE) is the most common subtype of drug-induced systemic lupus erythematosus and has been associated with more than 100 drugs. It presents weeks to months after initiation of the culprit medication. The eruption is typically in a photodistribution and it is marked by positive serology to anti-Ro (SSA) antibody. Systemic 5-fluorouracil (5-FU) is a less-common culprit of drug-induced SCLE and its occurrence is likely dependent on exposure to ultraviolet light. Herein, we present a review of drug-induced lupus induced by the pyrimidine analog, 5-FU, and its prodrugs, capecitabine and uracil-tegafur. The search was carried out using the following terms: (PubMed: keywords included drug-induced lupus, 5-fluorouracil, subacute cutaneous lupus erythematosus, capecitabine, uracil-tegafur, discoid lupus, systemic lupus erythematosus).

Keywords: drug-induced lupus, 5-fluorouracil, subacute cutaneous lupus erythematosus, capecitabine, uracil-tegafur, discoid lupus, systemic lupus erythematosus

Introduction

The list of drugs with the potential to trigger drug-induced lupus erythematosus is mounting and understanding the timeline and presentation of

these cases might help us better understand how to care for these patients. An antineoplastic drug, which is also a pyrimidine analogue, 5-fluorouracil (5-FU), has been linked to drug-induced subacute cutaneous lupus erythematosus (SCLE) when administered systemically. Murine studies have demonstrated a clear link between 5-FU, ultraviolet B (UVB) radiation, and development of lupus-like lesions on the skin, suggesting that UVB light may play an integral role in the pathogenesis of this disease process [1]. A recent review found that overall, there was an increase of 12.6% in the reporting of drug-induced lupus secondary to the chemotherapeutic class of drugs between 2009 and 2016, suggesting that the incidence of chemotherapy-induced lupus is on the rise [2]. We present a review of the literature relating to systemic 5-FU-induced lupus erythematosus to highlight the cutaneous side effects that can occur with pyrimidine analog antimetabolites.

Table 1 summarizes all known reported cases of lupus erythematosus induced by either 5-FU or its prodrugs, capecitabine and uracil-tegafur. Cases with a prior history of systemic lupus erythematosus (SLE) or SCLE were excluded. Most cases of 5-FU-induced lupus occur in females with an average age of 67 years (median 67 years; range 49-78 years). This is consistent with a previous review of drug-induced SCLE, in which

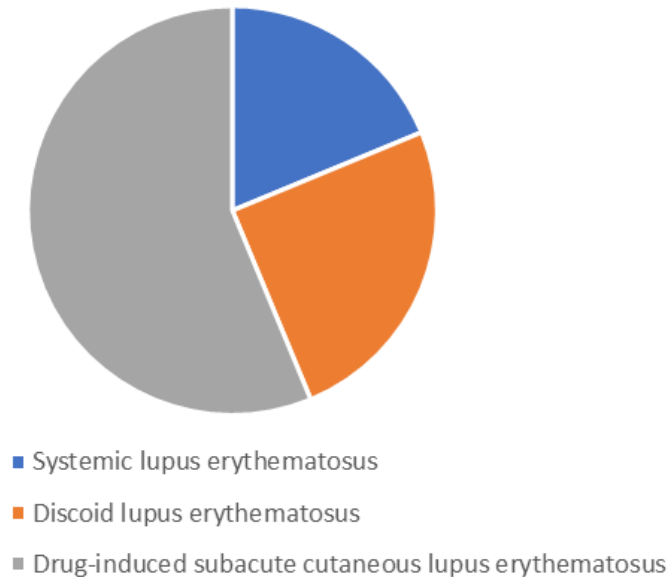


Figure 1. Lupus subtype induced by 5-fluorouracil/capecitabine/uracil-tegafur. A graphical representation of the frequency of lupus subtypes induced by 5-fluorouracil and its analogues. Most cases of drug-induced lupus erythematosus secondary to 5-fluorouracil and its analogues result in the subacute cutaneous lupus phenotype.

authors reported most cases occurred in females with a mean age of 59 years [2]. In the current series, SCLE represents the most common phenotype of drug-induced systemic lupus erythematosus, which can be seen in **Figure 1**. It manifests as erythematous annular plaques in sun-exposed areas and commonly is associated with a positive anti-Ro antibody (**Figure 2**). Most cases of SCLE occur within days to weeks after

exposure to drug and resolve within 3 months. Topical corticosteroids, photoprotection, and discontinuation of the culprit drug are generally the mainstays of treatment. A few patients were also treated with hydroxychloroquine and/or systemic steroids. One case of 5-FU induced SCLE recurred when capecitabine was administered [3]. The most common underlying cancers reported were breast cancer and colorectal cancer.

Chronic cutaneous lupus erythematosus is the second-most common subtype occurring with systemic administration of 5-FU and its analogues (**Table 2**). It tends to have a slower onset (months to years) and resolves over months. There is variable antinuclear antibody positivity in these cases. Systemic lupus erythematosus is the least common subtype to occur, with an onset of days to months and it tends to resolve within days to weeks. Antibody status was only reported for one of the cases, which had positive antinuclear antibody, anti-Smith, anti-Ro, and anti-La antibodies.

Discussion

Drug-induced lupus erythematosus was first reported by Hoffman, et al. in 1945 and was attributed to sulfadiazine treatment [4]. Drug-induced lupus erythematosus can be classified into systemic drug-induced lupus erythematosus, drug-induced SCLE, and chronic cutaneous drug-



Figure 2. Drug-induced subacute cutaneous lupus erythematosus. **A)** Erythematous annular plaques on the upper back, **B)** chest, and **C)** upper extremities.

induced lupus erythematosus, similar to idiopathic lupus erythematosus. Drug-induced SCLE and chronic cutaneous drug-induced lupus erythematosus are the forms which present with cutaneous involvement. The concept of drug-induced SCLE was introduced in 1985 by Reed, et al. and was associated with hydrochlorothiazide [5]. Now, drug-induced SCLE is known to be the most common drug-induced lupus erythematosus subtype [6]. In fact, the occurrence of a drug as a cause of or as an exacerbating factor represents about 20% of newly diagnosed cases of SCLE [4]. Drugs associated with SCLE are typically photosensitizing agents and the most common culprits are hydrochlorothiazide, calcium channel blockers, and angiotensin-converting enzyme inhibitors [7]. Reports of drug-induced SCLE related to proton pump inhibitors and chemotherapy agents are increasing [2]. Less commonly, SCLE is associated with terbinafine, immunomodulators, and biologics [2].

The pathogenesis of drug-induced lupus erythematosus is likely an interaction of genetic predisposition, drug biotransformation, and epigenetic dysregulation [7]. Regarding 5-FU-induced SCLE, 5-FU is postulated to damage the basal layer of the epidermis, which may predispose these cells to the effects of UVB light [1]. Interestingly, mouse models of 5-FU-induced

SCLE found that 5-FU alone without concomitant ultra-violet light (UVB) did not induce significant changes either clinically or histologically [8]. It has also been postulated that these chemotherapeutic agents translocate SSA/Ro to the surface of basal keratinocytes in a manner similar to UVB light [8, 9]. This observation suggests that the effects of UVB on keratinocytes damaged by 5-FU are integral in the pathogenesis of 5-FU-induced SCLE.

Conclusion

There are many drugs that can induce lupus erythematosus in a variety of patients. In our review we looked at patients who had different subtypes of lupus erythematosus and the majority exhibited cutaneous manifestations induced by systemic administration of drugs such as 5-FU, capecitabine, and uracil-tegafur. Our findings showed that the most common lupus subtype induced by these drugs is SCLE (56% of cases) and the least common was SLE (19% of cases). In most cases, the condition subsided with discontinuation of the culprit medication, photoprotection, and topical corticosteroids.

Potential conflicts of interest

The authors declare no conflicts of interests

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Table 1. Summary of drug-induced lupus erythematosus caused by 5-fluorouracil and its analogues.

Dem	Lupus Subtype	Cancer Diagnosis	Drug	Morphology	Distribution	Antibodies U/ml	Onset Rash	TRR	TRA	TX	Ref
49 year-old female	SCLE	Breast cancer	capecitabine	Annular red scaly patches	Neck, chest, upper arms, forearms, hands	Histone: Positive (2.3) Smith: Negative dsDNA: Negative Antinuclear antibody: 640 Ro: Positive(>8) La: (Not available)	2 weeks	4-6 weeks	Not available	Topical steroid Photoprotection	[8]
50 year-old female	SCLE	Colon cancer	capecitabine	Annular red itchy eruption	Areas exposed to sunlight	Histone: Not available Smith: Not available dsDNA: Not available Antinuclear antibody: Not available Ro: Positive La: Not available	4 months	Not available	Not available	Hydroxychloroquine Oral prednisone	[9]
54 year-old female	SLE	Breast cancer	capecitabine	Not available	Face, chest	Histone: Not available Smith: Not available dsDNA: Not available Antinuclear antibody: Not available Ro: Not available La: Not available	4 days	11 days	Not available	Not available	[10]
58 year-old female	DLE	Rectal cancer	capecitabine	Not available	Face	Histone: Negative Smith: Not available dsDNA: Negative Antinuclear antibody: 160 Ro: Negative La: Negative	3 months	2 months	Not available	Not available	[11]
64 year-old female	SCLE	Colon Cancer	5-fluorouracil	Red scaly plaques	Face, neck, forearms, hands	Histone: Negative Smith: Not available dsDNA: Negative Antinuclear antibody:160 Ro: Positive (27.2) La: Not available	2 weeks	2 weeks	Not available	Topical steroid Photoprotection	[12]

64 year-old female	DLE	Lung cancer	uracil-tegafur	Not available	Face	Histone: Not available Smith: Not available dsDNA: Negative Antinuclear antibody: 80 Ro: Negative La: Negative	7 months	2 months	2 months	Not available	[13]
64 year-old male	SCLE	Esophageal cancer	5-fluorouracil	Annular red plaques	Photo-exposed	Histone: Negative Smith: Not available dsDNA: Negative Antinuclear antibody: 320 Ro: Negative La: Positive	3 weeks	1 month	Not available	Topical steroid Photoprotection	[14]
50 year-old female	SCLE	Colon cancer	capecitabine	Annular red itchy plaques	Face, chest, arms	Histone: Negative Smith: Not available dsDNA: Not available Antinuclear antibody: 1280 Ro: Positive La: Not available	3 weeks	2 weeks	Not available	Hydroxychloro- quine Oral prednisone	[15]
67 year-old female	SCLE	Colon cancer	capecitabine	Annular red patches	Face, forearms, hands	Histone: Not available Smith: Not available dsDNA: Not available Antinuclear antibody: 320 Ro: Positive(200) La: Not available	6 weeks	Not available	Not available	Oral prednisone	[16]
68 year-old female	SLE	Colon cancer	capecitabine	Not available	Not available	Histone: Not available Smith: Not available dsDNA: Not available Antinuclear antibody: Not available Ro: Not available La: Not available	Not available	Not available	Not available	Hydroxychloro- quine Methylpredni- solone	[17]
70 year-old female	DLE	Colon Cancer	uracil-tegafur	Annular Scaly pink/ violaceous/ red scaly plaques	Face	Histone: Not available Smith: Not available dsDNA: Negative Antinuclear antibody: 40 Ro: Positive(217.6) La: Positive (40.4)	6 months	3 weeks	Still elevated at 6 months	Not available	[7]

72 year-old female	SCLE	Gastric cancer	capecitabine	Red, indurated papules and plaques	Face, neck, chest, arms, hands	Histone: Not available Smith: Not available dsDNA: Not available Antinuclear antibody: 2560 Ro: Positive (240) La: Positive(320)	1 month	3 months	Not available	Methylpredni-solone	[18]
74 year-old female	SCLE	Colon Cancer	capecitabine	Red annular scaling lesions	Face, arms, hands, feet	Histone: Negative Smith: Not available dsDNA: Negative Antinuclear antibody: 1000 Ro: Positive La: Positive	2 weeks	2 weeks	Not available	Hydroxychloro-quine Topical steroid Retinoid	[19]
77 year-old female	SCLE	Gastric cancer	5-fluorouracil	Red scaling plaques	Face, chest, forearms, hands	Histone: Negative Smith: Not available dsDNA: Negative Antinuclear antibody: Not available Ro: Positive (82.7) La: Negative	7 days	6 weeks	Not available	Topical steroid Photoprotection	[20]
78 year-old female	SCLE	BRCA	capecitabine	Annular red scaling plaques	Face, neck, upper back, forearms	Histone: Negative Smith: Not available dsDNA: Negative Antinuclear antibody: 640 Ro: Positive (4.93) La: Negative	10 days	3 weeks	Not available	None	[21]
78 year-old female	DLE	Gastric Cancer	uracil-tegafur	Annular Scaly pink/ violaceous/ red scaly plaques	Face	Histone: Not available Smith: Not available dsDNA: Positive (19) Antinuclear antibody: 2560 Ro: Positive(256) La: Positive(7)	30 months	6 months	Still elevated at 6 months	Not available	[7]

78 year-old male	SLE	Pancreatic cancer	uracil-tegafur	Erythema and blisters	Face	Histone: Not available Smith: Positive (23.3) dsDNA: Negative Antinuclear antibody: 640 Ro: Positive (129) La: Positive (207)	4 months	2 weeks	6 months	Topical steroid	[22]
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Dem – Demographics; dsDNA – double-stranded DNA; Ro – Anti-Sjögren's-syndrome-related antigen A; La – Anti-Sjögren's-syndrome-related antigen B; DLE – Discoid lupus erythematosus; anti-histone antibodies Histone); Smith – anti-Smith antibodies; Ref – References; SCLE – Subacute cutaneous lupus erythematosus; SLE – Systemic lupus erythematosus; TRA – Time to resolution of antibodies; TRR – Time to resolution of rash; TX – Treatment

Table 2. Types of drug-induced lupus erythematosus induced by 5-fluorouracil and its analogues.

	SLE	DLE	SCLE
5-fluorouracil			✓
Capecitabine	✓	✓	✓
Uracil-tegafur	✓	✓	