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Topical application of 5-fluorouracil 5 percent cream associated with severe neutropenia: discussion of a case and review of systemic reactions after topical treatment with 5-fluorouracil

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Abstract

5-fluorouracil, a fluoropyrimidine antineoplastic drug, is used to topically treat actinic keratoses. Local skin reactions to the medication are common and anticipated. However, severe adverse events from topical 5-fluorouracil are rare and unexpected. A 69-year-old man with a lower lip actinic keratosis developed severe neutropenia on day 11 of topical 5-fluorouracil treatment — after 14 applications. After receiving a subcutaneous injection of filgrastim, his neutrophil count normalized. The PubMed database was used to search the following terms: agranulocytosis, cream, 5-fluorouracil, granulocytopenia, neutropenia, severe, systemic, topical, and toxicity. The papers, and relevant cited references, generated were reviewed. Systemic reactions to topical 5-fluorouracil included angioedema, melanonychia, neurologic conditions (such as acute cerebellar syndrome, headaches, and peripheral neuropathy exacerbation), taste alteration, and systemic toxicity requiring hospitalization (including severe neutropenia). One of the individuals (a man with severe neutropenia and other symptoms) also had a deficiency of dihydropyrimidine dehydrogenase, the enzyme that catalyzes the rate-limiting step in 5-fluorouracil metabolism. Evaluation for dihydropyrimidine dehydrogenase deficiency is not routinely performed in patients receiving systemic or topical 5-fluorouracil. Also, the incidence of potentially severe 5-fluorouracil-induced toxicity associated with topical application of the drug may be greater than documented.

Keywords: agranulocytosis, cream, 5-fluorouracil, granulocytopenia, neutropenia, severe, systemic, topical, toxicity

Introduction

5-fluorouracil is a fluoropyrimidine anticancer drug [1]. Severe neutropenia is defined as an absolute neutrophil count of less than 500 cells/mm^3 and may be associated with a moderate to severe risk of infection [2, 3]. A man who developed severe neutropenia after initiating topical treatment with 5-fluorouracil 5% cream is described and systemic reactions to topical 5-fluorouracil are reviewed [1-25].

Case Synopsis

A 69-year-old man presented for evaluation of skin lesions on his face and lower lip of at least three months' duration. He had no personal history of non-melanoma skin cancer and no personal or family history of melanoma. He had several medical problems including Bell palsy, benign prostatic hyperplasia, depression, erectile dysfunction, gout, herpes zoster, hypothyroidism, and sleep apnea. Medications, each of which he had been taking for more than two months, included azelastine nasal spray, colchicine, ferrous sulfate, fluticasone propionate nasal spray, lansoprazole levothyroxine, multivitamin, tadalafil, terazosin, and ubiquinone.

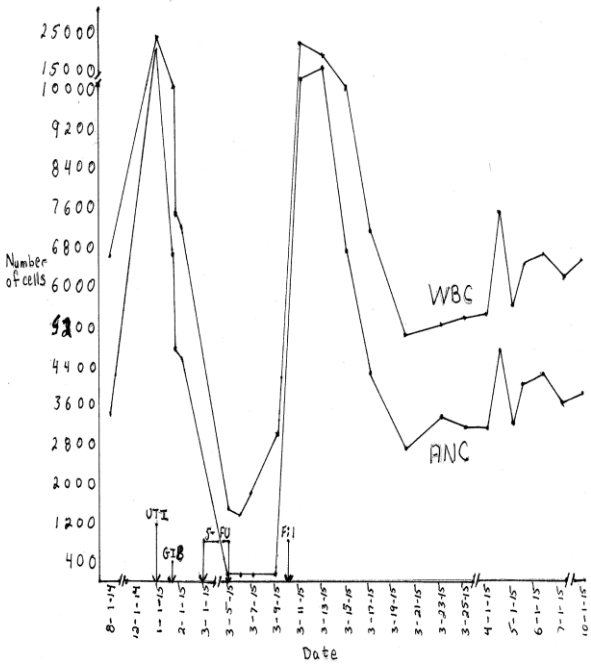

Figure 1. *Topical 5-fluorouracil 5% cream-associated severe neutropenia: chronology of white blood cell count and absolute neutrophil count. The dates are on the X-axis and the number of cells are on the Y-axis. Abbreviations: ANC, absolute neutrophil count; Fil, filgastrin (480 micrograms subcutaneously administered); 5-FU, 5-fluorouracil 5% cream (topically administered); GIB, gastrointestinal bleed; UTI, urinary tract infection; WBC, white blood cells.*

Cutaneous examination of his face showed keratotic plaques on his forehead and a 10×6mm scaly plaque on the left side of his lower lip. The diagnosis, based on clinical presentation, was actinic keratoses and actinic cheilitis, respectively. He previously had actinic keratoses on his right dorsal hand that had been treated with cryotherapy using liquid nitrogen; he was not pleased with this treatment and requested an alternative therapy for his current lesions.

He decided to initially treat his lower lip actinic cheilitis with topical 5-fluorouracil 5% cream, once daily for one week and then twice daily for up to two additional weeks; the forehead lesions would be treated afterwards. He began daily treatment on February 26, 2015. He had no difficulties during the first seven days and began twice-daily application of 5-fluorouracil cream to the left lower lip lesion; the treatment site became inflamed. With regard to his general health, he was asymptomatic. After the morning application of 5-fluorouracil cream on the eleventh day, he had a routine follow up complete blood cell count performed since he had recently experienced a blood loss-related anemia secondary to nonsteroidal anti-inflammatory drug overuse.

A baseline complete blood cell count in August 2014 revealed 6,600/mm^3 white blood cells (normal = 4,000 to 10,000) of which 3,400 were neutrophils (normal = 1,600 to 7,000; **Table 1**). In December 2014, he had been experiencing severe headaches and began taking ibuprofen several times each day. On December 30, 2014, he had a urinary tract infection and prostatitis that was treated with oral antibiotics; his leukocyte (23,500/mm^3) and absolute neutrophil (20,100/mm^3) counts were both elevated.

He had an acute gastrointestinal bleed on January 20, 2015, secondary to the ibuprofen he had been continually taking and his hemoglobin fell from 12.8 gm/dL on December 20, 2014 to 5.8 gm/dL on January 20, 2105. He received a blood transfusion. The following day, his leukocyte and absolute neutrophil counts were both normal (7,500/mm^3 and 4,700/mm^3, respectively). He was started on iron and a proton pump inhibitor. His complete blood cell counts were monitored after approximately one week (January 30, 2015) and then after about one month (March 5, 2015).

His white blood cell count was 1,500/mm^3 and there were less than 100 neutrophils on March 5, 2015 following his fourteenth application of 5-fluorouracil cream; his hemoglobin was 12.1 gm/dL. He was evaluated in the emergency center. He was found to be afebrile and microscopic examination of his peripheral smear showed no evidence of leukemia or dysplasia. The most probable etiology for his sudden onset of isolated neutropenia was exposure to a new toxin or medication, most likely 5-fluorouracil. Therefore, not only his topical 5-fluorouracil 5% cream, but also all of his oral medications, except for levothyroxine and terazosin, were discontinued. He was admitted to the hospital overnight. He remained afebrile (with his temperature being less than 100.4° Farenheit) and was discharged the next day.

Three days later, March 9, 2015, he developed new partial vision loss in his left eye. At that time his

Table 1. *Results of serial complete blood cell counts.*

Date	WBC[a] (per mm^3)	ANC[b] (per mm^3)	Hemoglobin[c] (g/dL)	Hematocrit[d] (%)	Platelets[e] (per mm^3)
8-14-14	6,600	3,400	13.7	39.6	170,000
12-30-14	23,500	20,100	12.8	38.0	157,000
1-20-15	10,100	6,600	5.8	17.0	159,000
1-21-15	7,500	4,700	8.0	23.2	126,000
1-30-15	7,200	4,500	10.1	29.9	295,000
3-05-15	1,500	<100	12.1	36.8	192,000
3-06-15	1,400	<100	12.0	35.8	186,000
3-07-15	1,800	<100	12.3	36.0	178,000
3-09-15	3,000	100	12.2	36.1	190,000
3-11-15	21,800	12,600	12.5	37.6	186,000
3-13-15	18,700	15,100	12.4	36.7	176,000
3-15-15	10,000	6,700	12.4	37.0	146,000
3-17-15	7,100	4,200	12.9	38.8	137,000
3-20-15	5,000	2,700	12.3	36.0	130,000
3-23-15	5,200	3,300	12.1	35.9	149,000
3-25-15	5,300	3,100	12.0	34.9	155,000
4-02-15	5,400	3,100	12.2	37.1	158,000
4-16-15	7,500	4,700	12.4	36.6	147,000
4-28-15	5,600	3,200	12.5	37.4	165,000
5-13-15	6,400	4,000	12.6	36.8	157,000
6-09-15	6,600	4,200	11.4	33.4	142,000
7-20-15	6,100	3,600	12.4	36.0	140,000
9-24-15	6,500	3,800	13.6	39.6	171,000

Abbreviations: ANC, absolute neutrophil count; dL, deciliter; gm, grams; mm, millimeter; WBC, white blood cells; /, per; %, percent; <, less than
[a]The WBC reference range of normal is 4,000 to 10,000 cells/mm^3.
[b]The ANC reference range of normal is 1,600 to 7,000 cells/mm^3.
[c]The hemoglobin reference range of normal is 13.7 to 17.5 g/dL.
[d]The hematocrit reference range of normal is 40.0 to 50.0%.
[e]The platelet reference range of normal is 140,000 to 370,000 platelets/mm^3.

leukocyte count of 3,000/mm^3 and absolute neutrophil count of 100/mm^3 were both low. Ophthalmology examination was performed and a retinal detachment was diagnosed. Laser surgery was urgently necessary and to prevent potential bacterial and fungal infections associated with severe neutropenia; he subcutaneously received 480 micrograms of filgrastim on March 10, 2015. His retina surgery was successfully performed on March 11, 2015. At that time he had 21,800 white blood cells/mm^3 of which 12,800/mm^3 were neutrophils.

His leukocyte count returned to 5,000/mm^3 cells, with 2,700 neutrophils, by March 20, 2015. Subsequently, it progressively increased to 6,600 leukocytes with 4,200 absolute neutrophils by June 9, 2015. Beginning in May 2015, the systemic medications he had previously been taking were re-started and he did not develop neutropenia. He declined testing to evaluate for dihydropyrimidine dehydrogenase deficiency.

Case Discussion

5-Fluorouracil-background

5-fluorouracil is an antineoplastic agent. It is used as a component of therapy for patients being treated for colorectal carcinoma. A topical preparation,

Table 2. *Systemic reactions to topical 5-fluorouracil.*

Systemic reaction	Ref
Angioedema	[9]
Melanonychia (following treatment of periungual verruca)	
Diffuse nail pigmentation of both the treated and untreated digits	[10]
Transverse pigmented nail bands of only some of the treated distal digits	[11]
Neurologic	
Acute cerebellar syndrome	[12]
Headache	[13]
Peripheral neuropathy exacerbation	[14]
Systemic toxicity (requiring hospitalization)	
Occlusive therapy-associated	[16]
Severe neutropenia	CR
Severe neutropenia (and other symptoms)	[17, 18]
Taste alteration	
Medicinal taste	[4]
Metallic taste	[8]

Abbreviations: CR, current report

varying in strength from 2% to 5% and formulated in either a solution or cream, can be used for the treatment of actinic keratoses [1, 4].

5-Fluorouracil-systemic absorption

Systemic absorption of 5-fluorouracil occurs after topical application. After 5-fluorouracil was applied to intact skin, a small percentage of the dose (approximately 6%) was absorbed systemically [5]. However, when equal dose per unit area of 5-fluorouracil was applied to diseased skin, the absorption was 15 percent to 75 percent greater than in healthy skin [6].

5-fluorouracil-mechanism of action

Inhibition of thymidylate synthase is the main mechanism of action for 5-fluorouracil. Dihydropyrimidine dehydrogenase — which is encoded by the *DPYD* gene — is the enzyme that catalyzes the first and the rate-limiting step in fluorouracil metabolism by converting it to the non-cytotoxic dihydrofluorouracil. Deficiency of dihydropyrimidine dehydrogenase enzyme does not allow for normal metabolism of 5-fluorouracil and can be associated with increased risk of severe and potentially life-threatening drug-associated toxicity, such as neutropenia [1, 22, 23].

Dihydropyrimidine dehydrogenase deficiency

Dihydropyrimidine dehydrogenase deficiency is found in 3 percent to 5 percent of Caucasians. Individuals who have one copy of a non-functional *DPYD* variant are considered to be intermediate metabolizers and people with a combination of two non-functional dihydropyrimidine dehydrogenase subtypes are poor metabolizers. Oncology patients in whom a decreased dihydropyrimidine dehydrogenase activity has been diagnosed usually receive a reduction in their dose of 5-fluorouracil [22, 24].

Evaluation for dihydropyrimidine dehydrogenase deficiency is not routinely performed in oncology patients receiving systemic 5-fluorouracil [1, 23, 25]. Indeed, testing recommendations for patients receiving topical 5-fluorouracil are not addressed in the package insert [4]. Although dihydropyrimidine dehydrogenase deficiency was suspected in the reported patient, *DPYD* gene testing could not be performed.

Local reactions to topical 5-fluorouracil

Topical 5-fluorouracil causes inflammation of the areas treated; development of an irritant dermatitis at the sites of application and photosensitivity are

common adverse events. Erosions and secondary bacterial infection may also occur. Less commonly, reports of allergic contact dermatitis, conjunctivitis, exacerbation of rosacea and seborrheic dermatitis, herpes simplex virus reactivation, onycholysis, and telangiectasia formation, have been described [4, 7, 8].

Systemic reactions to topical 5-fluorouracil

Systemic reactions to topical 5-fluorouracil are rare (**Table 2**), [4, 8-18]. They include angioedema, melanonychia, neurologic conditions, systemic toxicity, and taste abnormalities. All these side effects can occur in patients receiving systemic 5-fluorouracil [8, 10, 12, 14, 16, 17, 19].

Angioedema

A 71-year-old man with actinic keratoses on his chest was prescribed 0.5% 5-fluorouracil cream; initially he applied it as prescribed. However, he then began to apply the cream several times a day. After nine days, he developed pruritus and swelling of both hands. He had a near syncopal episode on treatment day 11 and was treated with diphenhydramine, triamcinolone, and prednisone. He returned to the emergency department the following day with significant dysphonia and swelling of not only his lower lip but also his hands bilaterally. The topical 5-fluorouracil cream and his oral lisinopril (the angiotensin converting enzyme inhibitor he had been taking for two years) were discontinued, but he continued his daily metformin. He was treated with intravenous corticosteroids and prescribed oral prednisone. The pruritus and swelling resolved over two to three days without recurrence of the symptoms [9].

Melanonychia

Diffuse nail pigmentation of both the treated and untreated digits following treatment of periungual verruca

A 69-year-old woman with periungual warts on her left third and fourth fingers was treated topically with 0.5 percent 5-fluorouracil (Verrumal, which also contained 10 percent salicyclic acid and 8 percent dimethysulphoxide); in addition, the fingers received soft radiation (500 radiation absorbed dose, 12 Kilovolts) initially and after two weeks. Follow up, after seven weeks of treatment showed: (1) transverse pigmented streaks on the left third and fourth fingers and (2) diffuse dark brown pigmentation, which partially obliterated the lunula of the nails of all fingers. The left third and fourth fingernails shed and the pigment on the other nails resolved after 16 weeks. Recurrent warts were treated with 5 percent 5-fluorouracil (Efudex) cream; pigmentation only appeared on the treated fingernails [10].

Transverse pigmented nail bands of only some of the treated distal digits following treatment of periungual verruca

A 32-year-old woman with periungual and subungual warts affecting the first-to-fourth fingers of both hands and the left toe was initially treated with 25% podophyllin and salicylic acid twice daily plus curettage. The residual warts were then treated with 5-fluorouracil under occlusion twice daily and 20 percent urea. Follow up, after one month, showed a grayish transverse discoloration — along and parallel to the lunula — on the left hand second finger and the left great toe. The warts and the pigmentation persisted after another month of treatment; the topical therapy was discontinued [11].

Neurologic conditions

Acute cerebellar syndrome

A man in his 60s developed severe headaches and awoke each morning with marked unsteadiness on his feet, altered coordination in gait, and dizziness after 3.5 weeks of twice daily application of fluorouracil cream to his scalp. All symptoms resolved eight hours after stopping treatment. Dihydropyrimidine dehydrogenase deficiency deficiency was excluded [12].

Headache

Patients received topical fluorouracil cream for up to 28 days: either 0.5 percent, 1 gram daily (11 patients) or 5 percent, 1 gram twice daily (ten patients). Two patients in each group developed headache [13].

Peripheral neuropathy exacerbation

A 70-year-old man with neuropathy (numbness and burning of plantar feet and toes) attributed to alcohol developed exacerbation of his symptoms with increased alcohol consumption, severe weather

changes, topical tanning solutions (containing dihydroxyacetone), and topical 5-fluorouracil (Efudex) cream. His symptoms were worse after 21 days of topical 5-fluorouracil treatment and subsequent rechallenge. There were no symptoms with topical imiquimod cream. Dihydropyrimidine dehydrogenase deficiency was excluded [14].

Systemic toxicity

Occlusive therapy-associated requiring hospitalization

Chemowraps, using 5-fluorouracil 5% cream under Unna wrap, have been performed on extremities as a novel off-label use of 5-fluorouracil to reduce actinic keratoses and as an adjuvant to definitive surgery for squamous cell carcinoma. One group of investigators treated over 200 patients with this method. They observed no serious adverse events and only reported side effects in two patients: contact allergy to 5-fluorouracil, and hair loss [15].

A 64-year-old woman developed symptoms (fever and chills, nausea and vomiting, diarrhea, abdominal pain, and generalized pain and discomfort) and signs (liver toxicity and erythematous skin rash) of systemic 5-fluorouracil toxicity after repeat treatment of occlusive therapy with topical 5% 5-fluorouracil cream to her legs. In addition, she developed inflammation of actinic keratoses on her face and arms — sites that had not been treated with topical 5-fluorouracil. Dihydropyrimidine dehydrogenase deficiency was excluded; all symptoms and signs resolved after oral prednisone (beginning at 60 milligrams and tapered over eight days), cephalexin and morphine [16].

Severe neutropenia (requiring hospitalization)

Neutropenia is an abnormally low concentration of neutrophils in the blood. It can be acute and transient or chronic. Acute severe neutropenia, sometimes referred to as agranulocytosis, is often caused by a drug received by the affected individual [20, 21]. Severe neutropenia secondary topical 5-fluorouracil, similar to the patient described in this report, has previously been described in a man with profound dihydropyrimidine dehydrogenase deficiency [17, 18].

A 76-year-old man presented with not only severe neutropenia, but also other systemic symptoms. He was only treating a basal cell carcinoma on his scalp with 5% 5-fluorouracil (Efudex) cream twice daily when he presented after seven days with severe abdominal pain, bloody diarrhea, vomiting, fever, chills, severe stomatitis, and erythematous skin rash. He had severe neutropenia (600 white blood cells with 120 neutrophils), thrombocytopenia (57,000 platelets). Colonoscopy confirmed severe inflammatory colitis. He had profound dihydropyrimidine dehydrogenase deficiency. His previous state of health returned after three weeks of total parenteral nutrition and broad-spectrum antibiotics [17, 18].

The patient in the current report was a 69-year-old man who developed severe neutropenia (1,500 white blood cells with less than 100 neutrophils) after the fourteenth application (day 11) of 5 percent 5-fluorouracil cream to a single actinic keratosis on his lower lip. He declined dihydropyrimidine dehydrogenase testing. He required retinal surgery and received 480 micrograms of filgrastim five days later; his white blood cell count and neutrophil count promptly increased and subsequently stabilized to pretreatment counts.

Taste abnormalities

Medicinal taste

A medicinal taste following topical application of 5-fluorouracil has been listed as an adverse reaction (in the gastrointestinal section) in the manufacturer's package insert and label information for the medication [4].

Metallic taste

A 64-year-old woman had a 4 mm squamous cell carcinoma in situ on her right external naris. She elected twice daily topical treatment with 5% fluorouracil for six weeks. After three days, she developed a constantly present metallic taste in her mouth. She continued the therapy; the dysgeusia persisted for four days before spontaneously resolving without further sequelae during or following the remainder of her treatment [8].

Conclusion

Topical 5-fluorouracil is a frequently used modality for the management of actinic keratoses. Local skin

reactions to the medication are common and anticipated. In contrast, systemic adverse events secondary to the topical application of 5-fluorouracil are rare and unexpected. The reported patient only treated a small area of his lower lip for a total of 14 topical applications of 5-fluorouracil 5% cream. He was asymptomatic when his severe neutropenia was detected during a routine follow up for blood loss-related anemia. Therefore, the incidence of potentially severe 5-fluorouracil-induced toxicity associated with topical application of the drug may be greater than documented.

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