

Hypogeusia and hyposmia with topical 5-fluorouracil treatment



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INTRODUCTION

5-Fluorouracil is a chemotherapy medication used to treat a number of systemic cancers. For patients receiving it intravenously to treat malignant neoplasms, common adverse effects include fatigue, nausea, loss of appetite, ulcers, and a metallic taste.¹ In addition to treating the aforementioned cancers, fluorouracil can also be used topically to treat actinic keratoses. Adverse effects for fluorouracil cream typically comprise erythema at the site of application, as well as crusting, burning, and irritation.² However, additional systemic adverse effects can occur with fluorouracil cream, particularly when it is applied over a larger surface area. These adverse effects include diarrhea, nausea, fever or chills, and rashes. The systemic adverse effects of fluorouracil cream, which resemble those of intravenous 5-fluorouracil, encourage dermatologists to limit the surface area to which patients apply the cream. Here, we report a unique case of hypogeusia and what is to our knowledge the first case of hyposmia with the topical use of fluorouracil.*

CASE PRESENTATION

A 53-year old woman presented with a pink, telangiectatic papule on her nasal dorsum that she reported as being present for approximately 1 month. To rule out malignancy, a shave biopsy was performed. The pathology revealed a traumatized actinic keratosis, at least, which extended to the deep margin. Given that extent, the patient was

prescribed fluorouracil 5% cream and was instructed to spot treat the area twice daily for 3 weeks once the biopsy site healed. 5-Fluorouracil was preferred to cryotherapy because the lesion was in an area of cosmetic concern. The patient reported following treatment as directed and denied applying the cream to any other areas of skin. At her follow-up appointment, she retrospectively noted that she had “felt unwell” during treatment, experiencing nausea and malaise, although she continued therapy as prescribed. She noted that during the final week of treatment, she had “unpleasant” disturbances to her sense of taste and smell. She began to have a metallic taste in her mouth, and her food lacked flavor. She was unable to taste foods such as pesto and bacon. When showering, she was unable to smell her fragranced soap. Despite the reported adverse effects, she consistently applied the medication for the 3-week duration. She reported that her nausea subsided the day after she concluded treatment. One week after the treatment ended, her normal sense of taste and smell returned. At her follow-up visit, her nasal dorsum was smooth, with mild residual post-inflammatory erythema, without clinical signs of remaining actinic keratosis or malignancy.

DISCUSSION

5-Fluorouracil is a fluoropyrimidine analog and a chemotherapy medication used to treat a number of cancers, including colorectal, esophageal, gastric, and anal cancer.³ Belonging to the chemotherapy class known as antimetabolites, it is involved in the inhibition of the pathway to building thymidine, one of the nucleotides that form DNA. Specifically, it enters malignant cells and binds to thymidylate synthetase and disrupts the mitotic process of the cell. By preventing the formation of thymidine in

*We concluded that this was the first reported case of hyposmia with topical fluorouracil use, according to a literature search of publications in *Journal of the American Academy of Dermatology* and PubMed archives. Search terms included “topical fluorouracil,” “hyposmia,” “anosmia,” “dysosmia,” and “smell alterations.” Articles published after 1970 were considered.

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cancer cells, 5-fluorouracil is able to damage the DNA structure of the cell and prevent cancerous cells from rapidly dividing.

This case report demonstrates a unique adverse reaction to a commonly prescribed medication in dermatology. Despite applying 5-fluorouracil cream to a limited surface area, the patient exhibited systemic adverse effects, which is more often observed when the cream is applied to multiple lesions over a larger surface area.⁴ In addition, the patient reported significant disturbances in taste and smell. These adverse effects have been frequently documented in patients receiving fluorouracil intravenously for systemic cancers. Although there has been a reported case of a metallic taste in the mouth after topical 5-fluorouracil use, the dysgeusia resolved on its own after 4 days.⁵ In the current case, the patient not only reported a metallic taste but also a partial loss of taste, one that lasted until 1 week after treatment. Manufacturers of topical fluorouracil do not list alterations to smell as an adverse effect, nor to our knowledge are there any other reported cases of dysosmia with topical application of fluorouracil. This suggests that the patient experienced adverse effects of 5-fluorouracil similar to that of individuals receiving chemotherapy intravenously, rather than topically.

It may be relevant to determine whether the patient possesses dihydropyrimidine dehydrogenase enzyme deficiency. This enzyme is the rate-limiting step in the catabolism of fluorouracil; thus, it plays a major role in determining the amount of 5-fluorouracil available for anabolism. As a result, individuals who have dihydropyrimidine dehydrogenase deficiencies can experience fluoropyrimidine toxicity, whose symptoms can include diarrhea, mucositis, myelosuppression, neurotoxicity, and death.^{6,7} Dihydropyrimidine dehydrogenase deficiency has been shown to be responsible for at least 50% of toxicity reactions related to 5-fluorouracil treatment in cancer patients.³ Considering this finding, as well as the suggestion that 3% to 5% of the general population possesses a partial dihydropyrimidine dehydrogenase deficiency, testing prospective systemic cancer patients for the enzyme deficiency should be considered. Although a number of tests have been developed to determine dihydropyrimidine dehydrogenase deficiency,⁸ they remain

expensive and inconvenient for clinicians to regularly use in their practice, but they would allow physicians to assess cancer patients on an individual level and determine the most appropriate treatment option for them while reducing the risk of adverse reactions to treatment. The rarity of toxicity reactions in topical use of 5-fluorouracil may make testing for dihydropyrimidine dehydrogenase deficiency in dermatology less appropriate. However, the adverse reaction observed in this patient, who applied the cream only to a solitary precancerous lesion on her nasal dorsum, raises the question of the potential for toxicity reactions in topical 5-fluorouracil application. Although underlying dihydropyrimidine dehydrogenase deficiency may account for the adverse reaction to topical 5-fluorouracil in this patient, her adverse effects of hypogeusia and hyposmia have not been previously reported, to our knowledge. These observations should encourage dermatologists to consider their patients' history of tolerance to systemic 5-fluorouracil chemotherapy and to extensively discuss symptoms of toxicity with patients before prescribing the medication, including alterations of taste and smell.

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