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CASE REPORT

**Treating Melanoma in Situ During a Pandemic with Telemedicine and a Combination of Imiquimod, 5-Fluorouracil, and Tretinoin**

William J. Nahm • Eran C. Gwillim • Evangelos V. Badiavas • Anna J. Nichols • Robert S. Kirsner  
• Laurence H. Boggeln • John T. Shen

W. J. Nahm

New York University Grossman School of Medicine; New York, NY

E-mail: [william.nahm@nyulangone.org](mailto:william.nahm@nyulangone.org)

E. C. Gwillim • E. V. Badiavas • A. J. Nichols • R. S. Kirsner

2: Dr. Phillip Frost Department of Dermatology & Cutaneous Surgery, University of Miami Miller School of Medicine; Miami, FL

A. J. Nichols • R. S. Kirsner

Sylvester Comprehensive Cancer Center; Miami, FL

L. H. Boggeln

Department of Family Medicine, Western University School of Medicine; Pomona, CA

L. H. Boggeln

5: Department of Family Medicine, UHS Southern California Medical Education Consortium; Temecula, CA

J. T. Shen

Shen Dermatology; Temecula, CA

## **ABSTRACT**

The recent coronavirus disease 2019 (COVID-19) pandemic has created a quandary for the physician in the evaluation and treatment of cutaneous skin cancers, particularly with melanomas. At the onset of the pandemic, many planned medical and surgical visits for skin cancers were postponed. Physicians and patients have had to balance the risk of exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with that of worsening morbidity and mortality due to delays in skin cancer treatments. We present a male patient who had two melanoma-in-situ (MISs) that were treated during the COVID-19 pandemic with a combination of topical imiquimod 5% cream, 5-fluorouracil 2% solution, and tretinoin 0.1% cream. The successful treatments occurred without in-person visits and with the aid of telemedicine. Although surgery is the standard for the treatment of melanoma in situ, this case demonstrates an effective viable treatment modality for MIS during a pandemic situation.

## **DIGITAL FEATURES**

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**Key Words:** COVID-19; Fluorouracil; Imiquimod; Melanoma-in-situ; SARS-CoV-2; Skin Cancer; Telemedicine; Topical Therapy; Tretinoin

## **Key Summary Points**

- The COVID-19 pandemic has created a delay in access to treatment of cutaneous skin cancers, including melanomas.
- Two melanoma-in-situ (MISs) were treated with a topical combination of imiquimod 5% cream, 5-fluorouracil 2% solution, and tretinoin 0.1% cream (IMI/5-FU/TRET) without in-person office visits and with a store-and-forward telemedicine application.
- The use of IMI/5-FU/TRET with telemedicine is a useful option to manage and treat MIS remotely during the time of a pandemic.

## INTRODUCTION

During the coronavirus disease of 2019 (COVID-19) pandemic, the National Comprehensive Cancer Network, numerous medical organizations, and physicians have proposed delaying localized treatments for skin cancers, including melanomas [1, 2]. Physicians, who were conditioned to treating cutaneous cancers expeditiously, had to weigh the benefits of early cancer treatment for their patients versus potentially exposing them to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3, 4]. The pandemic also ushered in the wide-spread adoption and acceptance of using telemedicine modalities for medical care by physicians and patients [5]. Although this shift in healthcare delivery has allowed patients to practice social distancing and avoid in-person visits, there are many limitations in terms of medical care, especially with skin cancer treatments [6-8]. Although melanoma-in-situ (MIS) is typically treated via surgical excision, reports have shown that topical imiquimod, 5-fluorouracil, and certain retinoids used as a mono or dual therapy have been effective treatments for melanoma and MIS [9-14]. We present a patient who had two effective treatments of MISs in a pandemic setting with a combination of topical imiquimod 5% cream, 5-fluorouracil 2% solution, and tretinoin 0.1% cream. During the treatment phase, the patient had no person-to-person medical visits and was monitored with a telemedicine app.

## CASE REPORT

A 66-year-old male physician had two biopsy-proven MISs on the left forearm (1.2 cm irregular pigmented patch) (Figures 1a; 2a; 2b) and left upper arm (6 mm asymmetric brown colored macule) diagnosed before the COVID-19 pandemic. He reported being a non-smoker but had a history of asthma with occasional bouts of acute bronchitis. His medications included theophylline and an albuterol inhaler. The patient (Fitzpatrick skin type I) also had an extensive sun-exposure history as a child and presented with multiple keratinocyte carcinomas (KCs) and actinic keratoses in adulthood. In the past, he had successful treatments of his KCs with the triple combination approach of topical imiquimod 5% cream, 5-fluorouracil 2% solution, and tretinoin 0.1% cream.

After his diagnosis of two MISs, the patient was instructed to see a surgical oncologist for the removal of both lesions. Due to the onset of the pandemic, which created a lack of available surgical appointments, he could not address both his MISs and had to resort to telemedicine. With the reality of these restrictions, unwillingness to have visits that could risk SARS-CoV-2 exposure, and concerns about having melanomas, the patient requested an alternative treatment that required no in-person interaction. After extensive consideration of the higher risks of undergoing non-surgical therapies and being fully informed of all options, the patient opted for a topical therapy protocol. The treatment involved a combination of 1/5 packet of imiquimod 5% cream, one drop of 5-fluorouracil 2% solution, and 1/5 of a pea-sized quantity of tretinoin 0.1% cream applied to each of his MISs with a bandage overnight. Although the patient was instructed to use 30 applications within a 42-day period, the patient completed his treatment protocols over 30 days. During these treatments, the patient employed a store-and-forward app (DermTRAC; Winchester, CA), which allowed him to report his progress and side-effects of treatment (Figure 1b) and receive customized medical instructions. Although the patient had a moderate amount of oozing, erythema, crusting, scaling, and burning in both treatment areas (Figure 1b), the patient could tolerate the cutaneous side-effects and compliantly use the topical medications. Three months after the conclusion of his treatment and ease of pandemic restrictions, the patient followed up with his dermatologist and had two tangential whole-lesional site biopsies, both demonstrating dermal cicatrix and absence of MIS (Figure 2c).

## DISCUSSION

Although the standard treatment of MIS is a surgical modality, the pandemic period warranted a non-surgical approach. Many medical organizations also recommended the delay of skin cancer treatments during the pandemic, but some reports expressed dissenting opinions about delaying the evaluation and treatment of pigmented lesions [1, 15-17]. Studies have demonstrated the efficacy of topical treatments of melanoma or MIS solely with imiquimod [8-10, 14, 18-24], imiquimod and 5-fluorouracil [11], and imiquimod and tazarotene [12]. Although tazarotene has been shown to have efficacy against MIS while tretinoin does not [13, 25], the use of the triple combination with tretinoin was chosen over the combination with tazarotene as a treatment. In the authors' experience, patients with skin Type I and a history of extensive sun damage background displayed unacceptable amounts of inflammation with a tazarotene combination therapy. Other patients with MIS who have darker skin types and less past sun exposure may do well with the latter combination.

Imiquimod is thought to act through the innate immune system as a Toll-like receptor 7 and 8 agonist that can inhibit the proliferation of human melanocytes [26] and induce proapoptotic effects in melanoma cells [27, 28]. Additionally, through their distinct mechanisms of action, 5-fluorouracil (anti-metabolite) [11] and imiquimod (immune system enhancement) [9, 10] are thought to provide synergistic antitumor effects. Imiquimod stimulates the production of numerous inflammatory cytokines that upregulate the enzyme thymidine phosphorylase, which is accountable for converting 5-fluorouracil to its functional end product [29, 30]. This synergism, combined with the proposed penetration enhancement with retinoids [12] and chemoprevention offered by tretinoin, could result in the use of less medication, fewer side-effects, improved clearance, and shorter duration of treatment.

Since the amount of inflammation is an essential measure of the treatment's efficacy and a potential cause for discontinuation of therapy, the use of the store-and-forward app is an indispensable tool for monitoring and guiding the patient's treatment course. The app determines whether the patient, based on screening questions, is eligible to start the treatment. The app will ask questions that screen for illness, fever, pregnancy status, etc. Although the patient can submit medical journal visits with template model photography at any time during their subscription service (Figure 1b), the patient is prompted by email once a week to submit a journal visit. The app then allows for the transformation of the images and sequentially displays images for the physician to view in an efficient manner (Figure 1b). The symptoms are aggregated and graded with a proprietary numerical score that allows the physician to gauge the severity of symptoms. Based on the symptoms, the patient, prompted through the app, will continue treatments, cease or delay treatments, and/or use steroids to abate symptoms. Since some symptoms of COVID-19 can mimic the flu-like syndrome of imiquimod [31], app-based decision making is an important part of the treatment. In general, imiquimod mostly induces mild to moderate symptoms, but severe flu-like syndromes can occur [32]. Previous reports using the same treatment regimen (imiquimod, 5-fluorouracil, and tretinoin) on individual keratinocyte carcinomas also demonstrate that treatments induce mostly mild to moderate symptoms [33, 34].

There has been extensive controversy in the delay of the treatment of melanomas during the pandemic. The National Comprehensive Cancer Network recommends that during a pandemic, treatments can be delayed for up to 3 months with T0 to T1 cutaneous melanomas if

there is no obvious residual lesion present after histological biopsy. They also recommend delaying treatments of cutaneous melanomas in patients with greater than or equal to T2 disease for up to 3 months if biopsy margins are negative [1]. Others have differing opinions about diagnosing and treating melanomas in that they would perform wider excisions but delay sentinel node biopsies and only perform procedures in an outpatient setting, which would limit the risks for in-patient hospitalization [35]. The European Society for Medical Oncology suggests that all patients being treated for advanced melanomas obtain swabbings for SARS-CoV-2 but continue with surgery, radiation treatments, chemotherapy, or immunotherapy [4]. Some dermatology departments have stressed that delays in detecting and treating melanomas can lead to increased health costs, morbidity, and mortality [3]. The British Association of Plastic Reconstructive and Aesthetic Surgeons recommends that melanoma treatments should not notably change from current established high standards [36], while some dermatologists have called for an entire cessation of non-emergent dermatological care during the pandemic [2].

Although we are recommending a treatment paradigm for melanoma using teledermatology that follows guidelines and demonstrates cost-efficiency and ethical compliance, the diagnosis of melanoma with teledermatology may be difficult and has not been conclusively proven [16, 37, 38]. The diagnosis of melanomas de novo may be enhanced dramatically with teledermoscopy [39], but patients may not be able to obtain such equipment during a pandemic. The ability to transform images and utilize template model photography may be of great benefit in telemedicine, but patients contribute to a poor diagnosis by being untrained in medical photography. Therefore, telemedicine may be better suited for following and treating a cutaneous melanoma rather than diagnosing one.

Our patient, who was relatively healthy with a couple of risk factors (age and asthma) for severe symptoms with COVID-19, was an ideal candidate for this treatment protocol. This treatment regimen may be even more warranted for patients with multiple risk factors for developing dangerous symptoms with COVID-19, such as significantly advanced age, lung problems, weakened immune system, cancers, chronic kidney or liver disease, certain blood disorders, heart disease, diabetes, and obesity [40-44].

## **CONCLUSIONS**

This treatment paradigm with store-and-forward technology complies with pandemic guidelines, decreases risk of COVID-19 exposure to patients and medical staff, demonstrates cost-effectiveness, and provides accurate details about inflammation. Moreover, this is the first reported case of MIS being treated with telehealth, a lack of in-person visits, and topical treatments. It is an example of how to manage MIS remotely during a pandemic crisis until an in-person visit is possible.

Informed consent was obtained from the patient for publication of the article, including clinical photographs.

Pre-typeset version

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### **Authorship**

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

### **Disclosures**

William Nahm, Eran Gwillim, Evangelos Badiavas, Anna Nichols, Robert Kirsner, Laurence Boggeln have nothing to disclose. John Shen serves as a consultant for DirectResponse Medicine.

### **Compliance with Ethics Guidelines**

Informed consent was obtained from the patient for publication of the article, including clinical photographs.

### **Data Availability**

Data sharing does not apply to this article, as no data sets were generated or analyzed during the current study.

Pre-typeset Version

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### Figure Legends

Figure 1. a) Clinical image of melanoma in situ on the left forearm. b) Dashboard of the store-and-forward app (DermTRAC) demonstrating a side bar with numerical scoring of patient reported treatment-related adverse events (0-none, 1 minimal, 2-mild, 3-moderate, 4-severe) and sum total in colored numbers of scores based upon patient-answered questions of adverse event. There is also a date of visit journal submission under each score. Right side of screen showing transformed images of treated melanoma in situ on the left forearm. In the sequential images during treatment, there is a demonstration of erythema, oozing, and ulceration.

Figure 2. a) Hematoxylin and eosin staining of melanoma in situ of the left forearm. There is a mildly thickened epidermis with atypical melanocytes at all levels of the epidermis organized in a pagetoid pattern. Single cells have an expanded cytoplasm with a dusty tan pigment and enlarged nuclei. Some of the nuclei have a single nucleolus. There is no evidence of dermal invasion. b) Immunoperoxidase stain for Melan-A highlights the melanocytic cells of the melanoma in situ. c) Tangential biopsy of the left forearm post-treatment with imiquimod, 5-fluorouracil and tretinoin revealed only a dermal cicatrix.