Review

Dermatology in a multidisciplinary approach with infectious disease and obstetric medicine against COVID-19

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ABSTRACT

The care for patients infected with COVID-19 requires a team approach, and dermatologists may collaborate with other specialties, especially infectious disease (ID) and obstetrics and gynecology (ObGyn), at every stage of the infection process. A broad spectrum of cutaneous manifestations may occur early in COVID-19 infection, making appropriate dermatologic identification critical for an early diagnosis. There is prognostic value in appropriately identifying different types of COVID-19–associated skin manifestations, which have been linked to disease severity. Such observations emanated from dermatology research, especially large series and international registries of cutaneous manifestations relating to COVID-19, and impact COVID-19 care provided by most health care providers. Also, research based on international registries of skin reactions from the COVID-19 vaccines has an impact across disciplines. An increased risk for severe illness from COVID-19 is encountered during pregnancy, and dermatologists’ role is to urge ObGyn and other clinicians to monitor and educate pregnant patients about the potential for eruptions as a manifestation of COVID-19. ID and ObGyn experts indicate that teledermatology enhanced the interaction among health care providers and improved COVID-19 care. More than 40% of all dermatology consultations at a tertiary care hospital were done via teledermatology. Future collaborative research involving dermatology and specialties, such as ID and ObGyn, could help delineate guidelines for dermatology consultations in patients infected with COVID-19 and determine cases appropriate for teledermatology.

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Contents

Introduction ......................................................... 641
Cutaneous manifestations related to COVID-19 ................................................. 641
Overview .......................................................... 641
Pernio-like and acral lesions ............................................... 641
Maculopapular eruptions ................................................ 642
Urticarial eruptions .................................................. 642
Vasculitis ............................................................. 642
Livedo-like lesions .................................................... 642
Pathophysiology of cutaneous manifestations related to COVID-19 ..................... 642
Skin reactions to COVID-19 vaccines ........................................... 643
Infectious disease perspectives .............................................. 643

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Obstetrics and gynecology perspectives ................................................................. 643
Conclusion .............................................................................................................. 644
Declaration of Competing Interest ................................................................. 644
Funding .................................................................................................................. 644
Study approval .................................................................................................... 644
References ............................................................................................................. 644

What is known about this subject in regard to women and their families?
• Differences in immunological responses to COVID-19 have been observed between women and men, but whether there are sex differences in the spectrum or severity of skin eruptions associated with the disease is not yet known.
• Skin manifestations of COVID-19 can occur during pregnancy and may be the presenting sign of the disease. Early diagnosis of COVID-19 is crucial during pregnancy because of increased risk for severe disease among pregnant women and increased maternal and fetal/neonatal complications.

What is new from this article as messages for women and their families?
• There is a prognostic value in identifying different types of COVID-19 associated skin eruptions, which have been linked to disease severity.
• Although COVID-19 associated skin eruptions have been reported in pregnant patients, their prognostic value is unknown in this population.
• A multidisciplinary approach including dermatology, infectious disease medicine, and obstetrics and gynecology is essential to optimize care in many patients with COVID-19.

Introduction

Dermatologists have played an important role in COVID-19 prevention and the judicious management of skin disease during this critical period (Bhargava et al., 2021c; Goldust et al., 2020a; Goren et al., 2020a). They served on the frontline in several parts of the globe (Bhargava et al., 2020b; Zheng and Lai, 2020). Most importantly, dermatologists have been focusing on demystifying skin manifestations related to COVID-19, as well as diagnosing and treating adverse effects of a plethora of drugs that have been used to treat the disease (Bhargava et al., 2021c; Galván Casas et al., 2020). Additionally, they have been involved in the management of occupational diseases caused by personal protective equipment (Bhargava et al., 2020a, 2021b; Goldust et al., 2020b). Furthermore, dermatologists have assessed the risks associated with using systemic immunosuppressants and immunomodulators for inflammatory skin disease during the pandemic (Price et al., 2020; Sadoughifar et al., 2020).

Dermatological research helped evaluate the prevalence and types of cutaneous manifestations related to COVID-19, as well as their duration and association with disease severity. The creation of international registries on skin manifestations related to COVID-19 was a major contribution (Freeman et al., 2020a; McMahon et al., 2021b). Also, dermatologists have investigated the role of androgens in COVID-19. An observational study reported that 71% of Caucasian males admitted to two Spanish hospitals for COVID-19 were diagnosed with androgenetic alopecia. This prevalence was higher than would be expected in the general population (Goren et al., 2020b). Findings of several subsequent studies led to the hypothesis that antiandrogen drugs might have a protective effect against severe COVID-19 (Goren et al., 2021). This research paves the way for future clinical research investigating antiandrogen drugs to treat COVID-19.

COVID-19 care requires a team approach, and dermatologists may collaborate with other specialties, especially infectious disease (ID) medicine and obstetrics and gynecology (ObGyn), at every stage of the infection process. Perspectives of ID experts are included in this article. ObGyn providers have collaborated with dermatologists on COVID-19 care, especially because cutaneous manifestations of COVID-19 present a diagnostic challenge in pregnant patients. In this article, we present a comprehensive overview of the dermatology contributions to COVID-19 care and research. Also, we comment on the interface and potential collaboration between dermatology and other specialties, especially ID and ObGyn, in COVID-19 care and research.

Cutaneous manifestations related to COVID-19

Overview

Soon after the spread of COVID-19 worldwide, reports of cutaneous manifestations related to the disease appeared (Recalcati, 2020). In an early study of patients with COVID-19 in Italy, 20.4% developed cutaneous manifestations, ranging from erythematous rash to widespread urticaria (Recalcati, 2020). However, in a meta-analysis, cutaneous manifestations had a prevalence rate of 5.69% among patients with COVID-19 (Rajan et al., 2020).

A broad spectrum of cutaneous manifestations has been detected in patients with COVID-19. Some of the most common manifestations include acral lesions, maculopapular eruption, and urticarial eruption. Less common manifestations include vasocclusive, such as fixed livedo racemosa, retiform purpura, acral ischemia, and erythema multiforme-like eruptions (Daneshgaran et al., 2020). Most manifestations precede other COVID-19 symptoms; however, chilblain-like eruption may develop late in the disease process, and vesicular and maculopapular eruptions and acral lesions may occasionally predate COVID-19 symptoms. Papulosquamous lesions last a median of 20 days, which is the longest duration of all cutaneous manifestations in a registry of cases (McMahon et al., 2021b). Pernio-like lesions last a median of 15 days. The study concluded that urticarial and morbilliform eruptions were relatively ephemeral, whereas papulosquamous and pernio-like eruptions were longer-lasting. Associations between the type of symptom and COVID-19 severity have been observed, with vasculitic (palpable purpura) and livedo racemosa-like patterns being associated with high severity and chilblain-like pattern with asymptomatic status (Marzano et al., 2021).

Pernio-like and acral lesions

There have been a large number of reports of acral pernio-like (pseudo-chilblain) lesions associated with COVID-19, especially among younger populations, unrelated to cold exposure. Pernio-like was the most frequent lesion identified (40.4% of cases) in a systematic review (Daneshgaran et al., 2020). In an international registry, pernio-like lesions accounted for 18% of cutaneous
manifestations among patients with laboratory-confirmed COVID-19 (Freeman et al., 2020a). In an earlier study of the same registry, pernio-like lesions accounted for 63% of dermatologic manifestations among patients with suspected or confirmed COVID-19, although most cases were in patients with suspected COVID-19 without confirmatory testing (Freeman et al., 2020b). Most pernio-like lesions occur in the feet (>80%), with smaller percentages on both the feet and hands or only the hands (Freeman et al., 2020b; Piccolo et al., 2020).

Debate exists surrounding the legitimacy of the association between acral pernio-like lesions and COVID-19. In two case series of patients presenting with pernio-like lesions during the COVID-19 pandemic, one including children only and the other adults, none of the patients tested positive for COVID-19 (Caselli et al. 2020; Herman et al. 2020). However, a case-control study comparing patients with pernio-like lesions versus controls found a significant positive odds ratio of positive IgG against the receptor-binding domain of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein (odds ratio: 3.40; 95% confidence interval, 1.25–9.22; p = .0162) in cases compared with controls (Ortega-Quijano et al., 2021).

Maculopapular eruptions

Maculopapular eruptions make up to 44% of skin manifestations in an international registry of dermatologic manifestations in patients with confirmed or suspected COVID-19 (Freeman et al., 2020a). In a large Spanish cohort, patients with COVID-19 accounted for 47% of all cutaneous manifestations, but only 21.3% in a systematic review (Danesgharan et al., 2020). Maculopapular eruptions associated with COVID-19 have been observed to follow morbilliform, purpuric, erythema multiforme-like, pityriasis rosea-like, erythema elevatum diutinum-like, and perifollicular patterns (Catala et al., 2020). Of these, generalized morbilliform eruptions have been most frequently observed (Catala et al., 2020).

Urticarial eruptions

Urticarial eruptions were first reported in relation to COVID-19 in an Italian study in which they accounted for 16.7% of skin manifestations among hospitalized patients with COVID-19 (Recalcati, 2020). In a larger study conducted in Spain, 19% of patients with suspected or confirmed COVID-19 presented with urticarial eruption (Galvan Casas et al., 2020). The presentation of urticarial eruptions is variable. In a meta-analysis including 202 cases of urticarial eruptions associated with COVID-19, the differential diagnoses included urticaria, urticarial vasculitis, idiopathic plantar hidradenitis, and neutrophilic dermatosis (Algaadi, 2020). Urticarial eruptions are mainly distributed on the trunk or in a generalized pattern, but have been also observed in facial and acral regions (Algaadi, 2020). COVID-19–associated urticarial rash has been successfully treated with antihistamines and systemic and topical steroids (Algaadi, 2020). However, COVID-19–related urticaria may be difficult to distinguish from idiopathic urticaria and urticarial eruptions triggered by other infections, foods, drugs, and emotional stress (Antia et al., 2018).

Vasculitis

Cutaneous vasculitis has been observed in patients with COVID-19, although not commonly. In an international registry of dermatologic manifestations in patients with confirmed or suspected COVID-19, palpable purpura and vasculitis accounted for 1.4% of manifestations (Freeman et al. 2020b). Several cases of cutaneous small vessel vasculitis in patients with COVID-19 have been documented, often accompanied by palpable purpura (Dominguez-Santas et al., 2020; Mayor-Ibarguren et al., 2020; Schenker et al., 2021; Tahir et al., 2020). More specifically, leukocytoclastic vasculitis in patients with COVID-19 has been observed in both children and adults (Irají et al., 2020; Kumar et al., 2021). Henoch-Schonlein purpura associated with COVID-19 infection has been reported (AliGhozzi and AlKhayyat, 2021).

Livedo-like lesions

Livedo-like lesions related to COVID-19 are relatively uncommon. A review study reported that vascular eruptions resembling livedo or purpura accounted for only 4% of skin manifestations and occurred mainly in elderly patients (Marzano et al., 2021). In an international registry of dermatologic manifestations in patients with confirmed or suspected COVID-19, livedo reticularis-like lesions and livedo racemosa accounted for 3.5% and 0.6% of manifestations, respectively (Freeman et al. 2020b). In a Spanish cohort, 6% of patients with suspected or confirmed COVID-19 presented with livedo-like lesions or necrosis, whereas in a French observational study, only 1 of 14 patients with COVID-19 and cutaneous symptoms displayed livedo-like lesions (Bouaziz et al., 2020; Galvan Casas et al., 2020).

Pathophysiology of cutaneous manifestations related to COVID-19

The pathologic mechanisms that cause skin lesions in patients with COVID-19 have not been adequately elucidated. To enter cells, the spike protein of SARS-CoV-2 binds to the cell membrane angiotensin-converting enzyme 2 (ACE2) receptor and the transmembrane protease serine 2 (ACE2) receptor and the transmembrane protease serine 2 expressed on the surface of human cells (Hoffmann et al., 2020). ACE2 receptor expression has been observed in skin tissues, particularly in keratinocytes, as well as in the testes, kidneys, colon, and lungs (Xue et al., 2021). A direct pathogenic effect of SARS-CoV-2 via ACE2 receptor in the epidermis, leading to acantholysis and dyskeratosis causing visible cutaneous manifestations of infection, has been proposed (Mahe et al., 2020). Upregulation of bradykinin, a potent vasodilator typically degraded by ACE2, results in increased vascular permeability and may be involved in edematous and/or urticarial-like lesions (Kroupouzos, 2021). Activation of bradykinin receptors has a proinflammatory effect that may contribute to COVID-19 disease severity and lead to inflammatory cutaneous manifestations, such as pernio-like lesions (Ehrenfeld et al., 2006; Kenne et al., 2019).

Increased vascular permeability combined with complement activation by SARS-CoV-2 could also contribute to cutaneous manifestations of COVID-19. In a case series, significant deposits of terminal complement components C5b-9, C4d, and mannose binding lectin-associated serine protease 2 consistent with sustained, systemic activation of complement pathways was observed in retiform purpura (Magro et al., 2020). Other authors suggested that an overactive immune response may be driving cutaneous manifestations of COVID-19. The release of proinflammatory cytokines, often called a cytokine storm, could reach the skin and stimulate dermal inflammatory cells, thus triggering erythematous and urticarial eruptions (Kaya et al., 2020). In a case series, robust interferon signaling and inflammation characterized by pronounced histiocytic infiltration was detected in samples of pernio-like lesions (Magro et al., 2020).

To our knowledge, sex differences in the incidence and presentation of cutaneous manifestations related to COVID-19 have not been reported. Interestingly, sex differences in the immune response to COVID-19 have been reported. In a study of patients with moderate COVID-19 who had not received immunomodulatory medications, male patients had higher plasma levels of innate immune cytokines and a more robust induction of nonclassical
monocytes, whereas female patients mounted significantly more robust T-cell activation (Takahashi et al., 2020). Also, in a prospective study of hospitalized patients with COVID-19, the levels of several cytokines, particularly IL-4, were higher in male than in female patients, but the difference did not reach significance (Petrey et al., 2021). Based on these immunologic findings, cutaneous manifestations of COVID-19 might disproportionately affect males or females, or at different points in disease progression. However, data are insufficient, and further research on sex differences in COVID-19–related cutaneous manifestations is warranted.

Skin reactions to COVID-19 vaccines

Dermatologists have studied skin reactions observed after COVID-19 vaccination that helped ease public anxiety. A major contribution was the establishment of a registry that included 414 cases of skin reactions after an mRNA vaccine (McMahon et al., 2021a). Delayed large local reactions (i.e., >4 days after the first vaccination dose) were most common, followed by local injection site reactions, urticarial eruptions, and morbilliform eruptions. Delayed local reactions developed a median of 7 days after the first vaccine dose, primarily after the Moderna vaccine (94%), and resolved within 3 to 4 days (McMahon et al., 2021a). Forty-three percent of patients with first-dose reactions experienced a second-dose recurrence. Less common reactions included pernio/chilblains, cosmetic filler reactions, zoster, herpes simplex flares, and pityriasis rosea-like reactions. Some dermatologic reactions to mRNA vaccines, such as pernio/chilblains, mimicked SARS-CoV-2 infection itself (Lopez et al., 2021; McMahon et al., 2021a).

Most patients in the registry who developed first-dose reactions did not have a second-dose reaction, and serious adverse events (e.g., severe allergic reaction) did not develop in any patients. None of the first-dose urticaria or angioedema reports occurred on the day of vaccination; therefore, these would not be classified as immediate hypersensitivity. The presence of a cutaneous reaction to the first vaccine dose, when it appears >4 hours after injection, is not a contraindication to receiving the second dose (McMahon et al., 2021a). Most reactions resolved without medical intervention. The data provided by this dermatologist-facing registry-based study provide reassurance to clinicians tasked with counseling patients who have experienced a delayed cutaneous arm reaction after their first mRNA vaccine dose.

Infectious disease perspectives

COVID-19 is a protean disease and often requires a team approach for both the diagnosis and management of the infection and its complications. In this regard, ID physicians and dermatologists may collaborate at every stage of the infection process. Importantly, cutaneous manifestations may occur early during COVID-19 infection, making appropriate dermatologic identification critical for early diagnosis. Although most patients have cutaneous signs at the same time as or after systemic symptoms, skin manifestations can be the presenting sign of COVID-19 infection in a significant percentage of patients, as high as 10% to 17% in some reports (Galvan Casas et al., 2020; Visconti et al., 2021; Young and Fernandez 2020; Zhao et al., 2020).

Importantly, timely diagnosis of skin lesions can help with COVID-19 diagnosis and management. Consultation with dermatology is useful because COVID-19–related rashes can be similar to other viral exanthems or even medication-related reactions (Tan et al., 2021; Young and Fernandez 2020). Of note, one instructive study collected photographs of rashes from patients with a positive SARS-CoV-2 test or typical COVID-19 symptoms and had four dermatologists independently assess whether the rash was COVID-19 related. All four dermatologists agreed on the classification 82% of the time, and three of four agreed 96% of the time, indicating high diagnostic precision among the dermatologists (Visconti et al., 2021).

There is also prognostic value in appropriately identifying different types of COVID-19–associated skin manifestations, which have been linked to disease severity (Naderi-Azad and Vender, 2021). The presence of skin findings itself does not appear correlated with severity, but there are prognostic implications with specific types of skin lesions. Vascular lesions, such as acral ischemia or livedoid eruptions, tend to affect older patients and are associated with increased intensive care unit admissions and mortality (Young and Fernandez, 2020). On the other hand, pseudo-chilblain lesions were the most common in young adults and had the highest survival rates among patients with COVID-19 and cutaneous manifestations (Galvan Casas et al., 2020; Jamshidi et al., 2021; Lai et al., 2020; Young and Fernandez 2020). Both vascular and pseudo-chilblain lesions can present on acral surfaces but are on opposite sides of the spectrum in terms of predicting disease progression and severity (Tan et al., 2021).

In addition to diagnosis and clinical evaluation, the management of skin lesions also often requires a group approach. For example, antihistamines have been used for urticaria-like lesions and systemic glucocorticoids for vascular lesions (Jamshidi et al., 2021; Rahimi and Tehranchinia 2020; Tan et al., 2021). Taken in their totality, we see that due to the multi-system effects of COVID-19, a multidisciplinary approach is often needed to optimize care. In fact, patients with COVID-19 can make up a significant portion of inpatient dermatology consultations. One study found that >30% of dermatology consultations at a tertiary care hospital were for patients with COVID-19, and >40% of all dermatology consultations were done via telemedicine (Bhargava et al., 2021a; Trinidad et al., 2020; Uzuncakmak et al., 2020).

Teledermatology, which has become increasingly common since the start of the pandemic, can both increase access to dermatologic care for inpatients and reduce the risk of infection spread (Bhargava et al., 2020c; Trinidad et al., 2020). However, teledermatology has been linked to lower rates of diagnostic certainty, necessitating follow-up in-person consultations for as many as 25% of patients in one study (Rogers et al., 2021). Future research with collaboration by dermatology and ID could help further delineate guidelines for dermatology consultations in patients with COVID-19 and determine cases appropriate for teledermatology.

Obstetrics and gynecology perspectives

Pregnant women are more susceptible to viral respiratory infections due to immunologic and physiological adaptations of pregnancy (Dotters-Katz and Hughes, 2020). The influenza pandemic of 2009 showed that pregnant women experienced a higher mortality rate compared with nonpregnant women of the same age (Mosby et al., 2011). Two recently published multinational cohort studies have confirmed that COVID-19 infection during pregnancy is also associated with substantial increases in severe maternal and neonatal morbidity and mortality (Brandt et al., 2021; Villar et al., 2021). Pregnant women are at an increased risk for severe illness from COVID-19 compared with nonpregnant women due to altered physiology, increased susceptibility to infections, and compromised immunological functions during gestation (Dashraath et al., 2020). There is also an increased risk of preeclampsia, preterm birth, and other fetal complications that are possibly related to cytokine dysregulation (Alberca et al., 2020). Hence, it is most important for all clinicians who encounter pregnant women to be able to diagnose this condition promptly.

As described, cutaneous manifestations of COVID-19 infection are frequently present in our patients. It is important that there is an effective dialogue and avenue of communication between
ObGyn and dermatology because the onset of COVID-19–related cutaneous manifestations may be the earliest clue to the presence of systemic manifestations of the viral syndrome, and prompt recognition can help improve maternal and fetal outcomes in this context. Also, herpes zoster may be a sign of COVID-19 infection during pregnancy (Elsaei et al., 2020). This observation validates the link between pregnancy and a higher risk of COVID-19 complications. Dermatologists’ role is to urges clinicians to monitor and educate pregnant patients about the potential for rashes, such as herpes zoster, as a symptom of COVID-19 infection.

Health care providers who care for pregnant women are accustomed to routinely examining the skin to look for signs of clinical conditions, such as viral illnesses, atopic eruption of pregnancy, polymorphic eruption of pregnancy (PEP), intrahepatic cholestasis of pregnancy, pemphigoid gestationis, and impetigo herpetiformis—a number of these skin conditions are associated with adverse maternal and especially fetal outcomes (Mehta et al., 2016). The hormonal and immune changes of gestation could affect COVID-19 cutaneous manifestations (Proietti et al., 2020). A case of PEP that developed simultaneously with SARS-CoV-2 manifestations of fever, headache, and diarrhea in a patient with COVID-19 prompted speculation that PEP could be a COVID-19 manifestation (Proietti et al., 2020). The authors suggested that a hypersensitivity reaction against viral antigens as a possible pathogenetic mechanism in their case. Erythematous and papular skin eruption associated with SARS-CoV-2 infection has been documented in a pregnant woman, but at the time of review, no case reports or studies have reported on the prognostic value of skin lesions in pregnant women with COVID-19 (Oropeza Chavez et al., 2021). Further investigation is required, and ongoing collaboration between dermatology and obstetric medicine is essential to such research.

During the ongoing COVID-19 pandemic, a number of routine clinical obstetric visits were switched to telehealth visits. This made routine examination a lot more difficult, but a number of women experienced cutaneous manifestations that were visible to the clinician via videoconferencing. On a number of occasions, dermatology expertise was sought very soon afterward to confirm whether the cutaneous manifestations were related to COVID-19. A successful collaboration between dermatology and ObGyn on a COVID-19–related eruption that presented during the immediate postpartum period was reported (Paolina et al., 2020). A number of patients also presented with unexplained cutaneous manifestations to the emergency department of the specialty maternity hospital Women & Infants of Rhode Island during the pandemic. Once again, dermatological expertise was extremely valuable in differentiating between possible COVID-19 manifestations versus other diagnoses as previously listed. Dermatology consultations helped optimize obstetric care greatly in these patients.

ObGyn providers should promptly provide the relevant obstetric or gynecological history to dermatologists to facilitate the appropriate diagnosis of a skin eruption. This is particularly useful for teledermatology consultations where the dermatologist may not have access to detailed ObGyn history data (Betancourt et al., 2020). ObGyn may also provide information about a pregnant patient’s COVID-19 vaccination status, as well as any recent exposures to SARS-CoV-2, that can aid the dermatologist in establishing a diagnosis of a skin eruption.

Furthermore, ObGyn providers encounter a number of nonpregnant patients in their practice. Women with polycystic ovarian syndrome (PCOS) have an increased risk of COVID-19 infection compared with those without PCOS (Subramanian et al., 2021). The hallmarks of PCOS are insulin resistance and hyperandrogenism, and hyperandrogenic women reportedly experienced more severe COVID-19 symptoms (Cadeigiani et al., 2021). A possible explanation is related to hyperandrogenism, which is associated with increased ACE-2 receptor expression (La Vignera et al., 2020). Nevertheless, a recent report showed no evidence of increased risk of COVID-19 infection, hospitalization, or mortality in women with acne vulgaris, PCOS, or hirsutism (Yale et al., 2021). However, the study provided no clear data on the clinical symptoms for which patients were hospitalized. Ongoing collaboration between dermatology and gynecology may provide insight into the role of sex hormones on disease incidence and severity that will contribute to a better understanding of at-risk populations (Yale et al., 2021).

Conclusion

Dermatologists have played an important role in COVID-19 prevention and the judicious management of skin disease during the pandemic. They have focused on demystifying skin manifestations related to COVID-19 infection and conducted prolific research in this field. A multidisciplinary approach with ID and ObGyn is essential to optimize care in patients with COVID-19.

Declaration of Competing Interest

The authors have no conflicts of interest. Eletherios Mylonakis was involved in clinical trials on COVID-19. These trials were supported by Regeneron, NIH, and SciClone Pharmaceuticals, Inc. All funds were to the institution, and Eletherios Mylonakis received no direct funds.

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