Reflectance confocal microscopy examinations of COVID-19 vaccination sites: A prospective observational study

Reflectance confocal microscopy (RCM) provides cellular-level insights into cutaneous pathology in vivo and is used to guide both diagnosis and management. The COVID-19 vaccine is the first messenger RNA vaccine in widespread use. Because a variety of cutaneous reactions associated with the COVID-19 vaccination have been reported,[1] there may be value in identifying characteristic cellular features using RCM following vaccination. In this study, we used RCM to observe changes in the skin following COVID-19 vaccination.

A convenience sample of 8 health care workers were enrolled. Before the COVID-19 vaccine was administered, participants had a circle drawn on the deltoid region with a marking pen where they subsequently requested the vaccine be injected. RCM images were captured using the Vivascope 1500 device (Caliber I.D.) at the baseline before vaccination, 1 and 2 weeks after the first vaccine dose, and 1 week after the second vaccine dose. Confocal mosaics (8 mm × 8 mm) and image stacks at 0.003 mm increments to a depth of 0.25 mm were taken. The presence of common RCM cellular features[2,3] was assessed from each individual's set of images by 2 expert confocalists (AAM and MC) who were blinded to the time-point but not to the study objectives. Discrepancies were resolved by consensus. After the third imaging session, patients completed a survey about which vaccine they had received and whether they had experienced commonly reported vaccine side effects.

Eight individuals with a median age of 43.5 years (range, 25-56 years) participated, with half receiving the Pfizer vaccine and the other half receiving the Moderna vaccine. After the first dose, all patients had newly appreciated disruption and an infiltrate of small rounded cells in the stratum corneum, focal disruption in the stratum spinosum and dermal-epidermal junction, and cell clusters in the dermis (Fig 1). Other notable features included necrotic keratinocytes in the stratum spinosum and vertical vascular structures in the dermis (Supplementary Fig 1, available via Mendeley at https://doi.org/10.17632/j8nkcbpjjk.1). Features observed 2 weeks after the first dose and 1 week after the second dose were similar to those observed 1 week after the first dose, although they occurred less frequently (Fig 1).

Our study has identified characteristics that may be associated with the epidermal and superficial dermal immune response to the COVID-19 vaccine (Fig 2). The limitations of this study include the small sample size, convenience sample of health care workers, and limited blinding of reviewers. A major limitation of our study includes the lack of a control assessment, as we were unable to differentiate these findings from those associated with needle wound puncture. However, the chronicity of our findings and the similarities in features with those identified in a recent RCM study of graft-versus-host-disease suggest that our findings may be secondary to the local immune response to the vaccine.[4] Future studies investigating the COVID-19 other messenger RNA vaccines should consider these criteria and investigate these findings further. RCM vaccination-site evaluation may have prognostic value, as implementing this methodology may present a way to proactively identify vaccine nonresponders.

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		Number of Patients with Specified Characteristic (*n=8*)				
Layer of the Skin	RCM Feature	Features present at baseline *n (%)*	**Week 1** Change from Baseline 1 week after Dose 1	**Week 2** Change from Baseline 2 weeks after Dose 1	**Week 5** Change from Baseline 1/2 week(s) after Dose 2	Change in Features between Week 1 and Week 5
Stratum Corneum	Small Rounded Cells	0 (0%)	+8	+7	+5	-3
	Disruption	0 (0%)	+7	+5	+3	-4
	Dendritic Cells	0 (0%)	+3	+2	+1	-2
	Impetigination	0 (0%)	+1	0	0	-1
	Parakeratosis	0 (0%)	0	0	0	0
Stratum Granulosum/Spinosum	Focal Disruption	0 (0%)	+8	+6	+5	-3
	Necrotic Keratinocytes	0 (0%)	+6	+4	+2	-4
	Atypical Honeycombing	0 (0%)	+4	+3	+2	-2
	Exocytosis	0 (0%)	+4	0	0	-4
	Dissaranged	0 (0%)	+3	+2	+2	-1
	Atypical Cobblestoning	0 (0%)	+1	0	0	-1
	Dyskeratosis	0 (0%)	+1	+1	0	-1
	Typical Cobblestoning	8 (100%)	-1	-1	-3	-2
	Typical Honeycombing	7 (87.5%)	-3	-2	-2	+1
Stratum Basalis/DEJ	Focally Disrupted	0 (0%)	+8	+6	+5	-3
	Periadnexal inflammation	0 (0%)	+7	+5	+3	-4
	Elongated/Streaming Cells	0 (0%)	+4	+2	+1	-3
	Uniformly Populated	6 (75%)	+1	+2	0	-1
	Cellular Atypia	0 (0%)	+1	+1	+1	0
	Irregular Papillae	0 (0%)	+1	+1	0	-1
	Rounded Melanocytes	2 (25%)	0	-1	-2	-2
	Dendritic Melanocytes	0 (0%)	0	+1	+1	+1
	Pleomorphic Melanocytes	0 (0%)	0	0	0	0
	Periadnexal Necrosis	1 (12.5%)	0	-1	-1	-1
	Regular Papillae	7 (87.5%)	0	0	0	0
	Edged Papillae	6 (75%)	0	0	-1	-1
	Non-Edged Papillae	2 (25%)	0	+1	0	0
	Meshwork	0 (0%)	0	0	0	0
	Widely Disrupted	1 (12.5%)	-1	-1	-1	0
	Architecture Preserved	8 (100%)	-4	-2	-3	+1
Dermis	Cell Clusters	0 (0%)	+8	+5	+2	-6
	Small Round Bright Cells	1 (12.5%)	+7	+6	+4	-3
	Vertical Vascular Structures	0 (0%)	+6	+6	+6	0
	Thin Vascular structures	4 (50%)	+4	+4	+3	-1
	Linear Vascular Structures	2 (25%)	+4	+3	+4	0
	Enlarged vascular structures	0 (0%)	+3	+1	+1	-2
	Amorphous Collagen	2 (25%)	+3	+4	+3	0
	Plump Bright Cells	0 (0%)	+1	0	+1	0
	Small Stellate Cells	0 (0%)	+1	0	0	-1
	Junctional thickening	0 (0%)	+1	0	0	-1
	Reticulated Collagen	7 (87.5%)	+1	+1	-1	-2
	Thickened Collagen	0 (0%)	+1	0	+1	0
	Bundled Collagen	1 (12.5%)	0	-1	-1	-1

Fig 1. Changes in reflectance confocal microscopy features observed after the administration of the first and second COVID-19 vaccine doses.

Key words: confocal microscopy; COVID-19 vaccine; medical dermatology; optical imaging; vaccine response.

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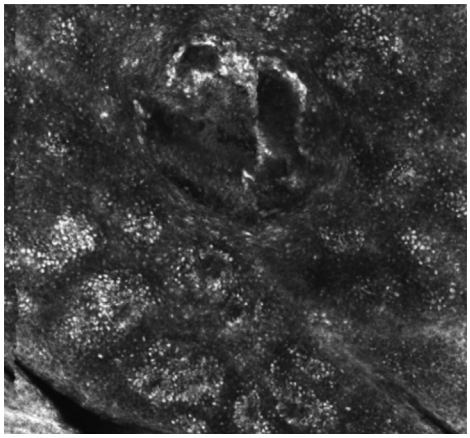

Fig 2. Representative reflectance confocal microscopy image of focal disruption of the dermal-epidermal junction, and small rounded cells on confocal imaging of the vaccine administration site.

Conflicts of interest

None disclosed.

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