

# The Oldest New Finding in Atopic Dermatitis

## Subclinical Miliaria as an Origin

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**Importance:** In 1947, Sulzberger and colleagues published a micrograph of a blocked acrosyringium in a patient with atopic dermatitis (AD), believing that it had a large role in the disease process. Lacking appropriate probes, they could not confirm the finding.

**Objective:** To confirm the observations by Sulzberger et al on the blockage of sweat ducts in AD in pathologic specimens.

**Design and Setting:** Biopsy specimens diagnostic of various inflammatory diseases and with a secondary differential diagnosis of eczema were evaluated at an academic medical center.

**Exposures:** Evidence of ductal obstruction in each specimen was examined following staining with hematoxylin-eosin, periodic acid-Schiff, and Gram stain.

**Main Outcomes and Measures:** Comparison of biopsy specimens with control specimens and additional controls consisting of noninflamed skin.

**Results:** Using 36 biopsy specimens, this study confirmed the observations by Sulzberger et al on the blockage of sweat ducts in AD. Blocked acrosyringia were noted in each specimen on routine staining with hematoxylin-eosin. The study also confirmed the findings by earlier investigators about the blockage of sweat ducts in miliaria, showing eosinophilic material in the ducts that was positive for periodic acid-Schiff. Previous researchers also observed bacteria in the blockages, and this study demonstrated the same findings in AD, rather than miliaria.

**Conclusion and Relevance:** Subclinical miliaria may be the earliest change in AD and likely initiates the process that causes intense pruritus.

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**I**N 1947, SULZBERGER ET AL<sup>1</sup> published a micrograph of a blocked acrosyringium in a patient with atopic dermatitis (AD), believing that it had a large role in the disease process. They were unable to pursue this further because appropriate probes (eg, periodic acid-Schiff [PAS]) were not available at that time. However, they determined that the pH of the vesicle fluid was much more in keeping with secreted sweat than with edema from inflammation.

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Dobson and Lobitz<sup>2</sup> in 1957 and Hölzle and Kligman<sup>3</sup> in 1978 convincingly showed in miliaria rubra created by heat and skin occlusion (“true” miliaria) that the sweat ducts were blocked by PAS-positive material admixed with bacteria. Later, Mowad et al<sup>4</sup> demonstrated that the only bacteria they were able to culture that would induce anhidrosis (and be integral in producing miliaria) were “slime-

producing” *Staphylococcus epidermidis*. The slime represents a biofilm and is composed of an extracellular polysaccharide substance that is PAS positive. The biofilm itself is under genetic control and arises most frequently from the effect of an *ica* operon gene in response to the occlusion.<sup>5</sup> The *aap* gene and others may also be responsible for biofilm production in these organisms.<sup>6</sup>

We present evidence of blocked acrosyringia in AD that aligns with the description by Sulzberger et al.<sup>1</sup> The fact that these ducts are blocked with PAS-positive material and bacteria supports the findings by Dobson and Lobitz,<sup>2</sup> Hölzle and Kligman,<sup>3</sup> and Mowad et al<sup>4</sup> about miliaria except that these results were from AD, not miliaria.

## METHODS

We examined 36 pathologic specimens submitted with clinical diagnoses of various inflammatory diseases. Each submission had a secondary differential diagnosis of (atopic) eczema. The specimens underwent routine pro-

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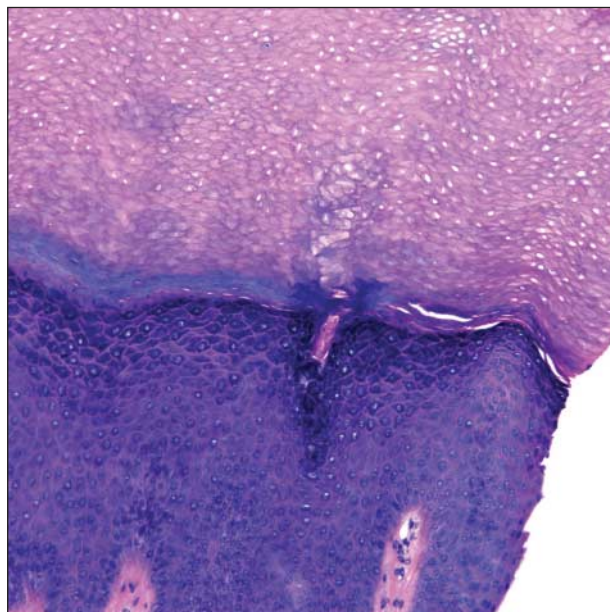


**Figure 1.** Atopic dermatitis. The acrosyringium is filled with eosinophilic material (original magnification  $\times 60$ ).

cessing with hematoxylin-eosin, and all were tested with PAS and Gram stain. Multiple sections ( $\leq 30$ ) of each specimen were studied to observe whether ductal obstruction was present. Observations were not performed in a blinded manner.

As controls for these specimens, we matched the leading clinical differential diagnoses with reference samples, including psoriasis, pityriasis rosea, tinea corporis, and contact dermatitis, among others. We examined those specimens with routine stains and with PAS. As in the lesional samples, multiple sections of each control specimen were studied to observe whether any ductal obstruction was present. We also matched the location of the disease processes as closely as possible, believing location to be a better control than other variables. Furthermore, we examined 12 cases of noninflamed skin (surgical tips from samples where no crusts were present) to observe whether ductal obstruction was present. This study was approved by the institutional review board of Drexel University College of Medicine. All patients gave informed consent for their biopsies.

## RESULTS

Each of the 36 specimens showed spongiosis, variable lymphocytic exocytosis, and mild dermal lymphohistiocytosis. Eosinophils were variably present in the dermis. Given the differential diagnoses, which included eczema, these specimens were diagnosed as spongiotic dermatitis compatible with eczema. All had blocked acrosyringia on routine staining with hematoxylin-eosin (**Figure 1**), and all these blockages contained PAS-positive material (**Figure 2**). Gram stain of these sections showed gram-positive organisms in the ducts as well, but not in every sample. The gram-positive organisms were noted in 14 (40%) of our samples. In the eczema cases, no neutrophilic microabscesses were noted, and no fungal organisms were seen on PAS. No extravasated red blood cells, interface changes, or vasculopathy was present. All control specimens showed patent sweat ducts, and neither PAS-positive material nor gram-positive organisms were noted in those ducts. Expected findings of

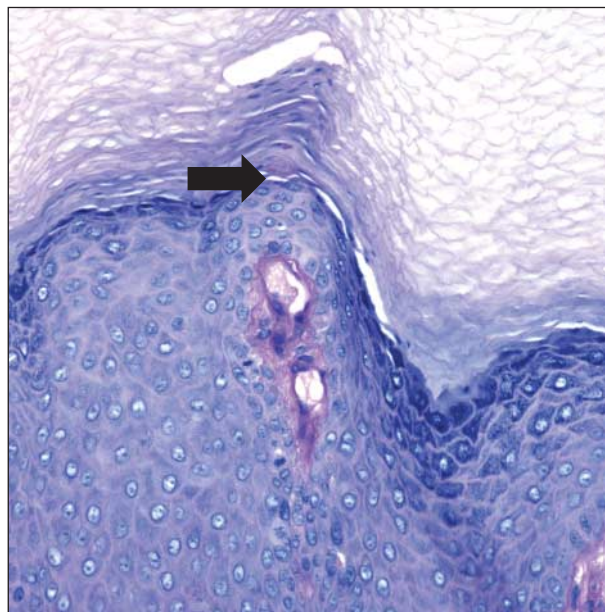


**Figure 2.** Atopic dermatitis. Material positive for periodic acid-Schiff (PAS) is present in the acrosyringium (above and below arrow); mild spongiosis is present (original magnification  $\times 60$ ). Some shrinkage of PAS-positive material has occurred with processing.

the other diseases (eg, neutrophilic microabscesses in psoriasis) were present in those controls. All the noninflamed skin controls had patent eccrine ducts.

## COMMENT

We believe that our specimens with the findings of spongiotic dermatitis and occluded acrosyringia were similar to those presented more than 6 decades ago by Sulzberger et al.<sup>1</sup> We also theorize that our specimens showing PAS-positive material and gram-positive organisms in the acrosyringia are similar to those outlined by Dobson and Lobitz,<sup>2</sup> Hölzle and Kligman,<sup>3</sup> and Mowad et al<sup>4</sup> in true miliaria. By combining these two observations, we postulate that AD may be incited by a form of subclinical miliaria. Furthermore, because miliaria rubra is pruritic, we believe that the subclinical miliaria may have itching that begets scratching and results in the clinical lesions of AD. The mediators of the inflammatory response to the ductal occlusion may be related to Toll-like 2 receptors that respond to gram-positive organisms and biofilms from gram-positive organisms; further research into that possibility is needed.

In support of the concept that subclinical miliaria has an important role in AD, Eishi et al<sup>7</sup> demonstrated that inducible sweat production was decreased 5-fold in lesional skin of patients with AD; this compares exactly with the 80% reduction in patent eccrine ostia in miliaria noted by Hölzle and Kligman.<sup>3</sup> In further support of this concept, evidence shows that *S epidermidis* biofilms are present on the lesions of AD and that pure cultures of *S epidermidis* and other staphylococci are also found on these lesions.<sup>7</sup> Using XTT protocols (a water-soluble tetrazolium colorimetric assay that changes color when staphylococcal biofilms are present), we determined that these staphylococcal organisms were capable of creat-

ing biofilms, and all were multidrug resistant.<sup>8</sup> These findings (the cultures of staphylococci, the capability of the organisms to make biofilms, and the presence of the biofilms) support the notion, at least circumstantially, that the sweat ducts are blocked by the organisms and their biofilms. The biofilms are produced under the direction of an *ica* operon and perhaps *aap* or other genes, and we are investigating whether these genes are present in our cultured samples of the various staphylococci.

It also seems likely that the atopic lesion arises from a “double-hit” phenomenon.<sup>9</sup> The genetic hit is filaggrin deficiency (present in >50% of patients with AD)<sup>10</sup> or some other genetic or environmental defect in the stratum corneum. The environmental hit is the presence of staphylococci and their biofilms. Without the biofilm, these staphylococci would assume their role as “normal flora” and would not have any pathologic effect. Even with the biofilm, if the genetic component is absent, AD would not be present; in this case, true miliaria would arise if the said biofilm occluded a sweat duct.

Our findings are discordant with other light microscopic and ultrastructural reviews,<sup>11,12</sup> and the discrepancies cannot be easily explained. Those researchers found no blockage of sweat ducts in dyshidrosis. Possible explanations of their findings compared with ours are (1) the timing of biopsies (ie, earlier may be better than later for finding blocked ducts) and (2) the need to examine multiple sections to find the occluded ducts. This may also explain our not finding bacteria in all the specimens. Also, even in true miliaria, not every duct is occluded. Hölzle and Kligman<sup>3</sup> showed approximately 80% occlusion, which conforms to the observations by Eishi et al,<sup>7</sup> who demonstrated a 5-fold reduction of sweat production in lesional skin among patients with AD. In the ultrastructural data, the sample size by necessity must be limited, so the number of ducts examined in this instance may not have been optimal.

We believe that this study helps elucidate further the origin and pathogenesis of AD. Furthermore, this work should increase the ability to diagnose AD using the findings of blocked acrosyringia and PAS-positive material within those ducts that we found in all our pathologic specimens.

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