# Necrotizing infundibular crystalline folliculitis: a clinicopathological study

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Abstract: Background: Necrotizinig infundibular crystalline folliculitis (NICF) is a folliculocentric disorder associated with filamentous crystalline deposits, enclosed by parakeratotic columns within the partly necrotic follicle ostium and infundibulum. There are only very few data published about this disorder of unknown etiology.

Objective: To determine the clinico-pathological features and pathogenetic aspects of NICF.

Methods: Clinico-pathological characterization of nine patients with NICF and a second group of seven cases with coincidental findings of NICF in the vicinity of epithelial skin neoplasms.

Results: Clinically NICF is characterized by multiple waxy papules with predilection for the forehead (56%), neck and back. Birefringent crystalline deposits were present in the follicle ostia and enclosed by parakeratotic columns in all cases. The necrosis of follicle epithelium was found in 89% and perifollicular neutrophilic infiltrate in 22% of the biopsies. Both yeasts and gram-positive bacteria were identified within the affected follicles in 56% in the first group and in the second group in 86%.

Limitation: Single center retrospective study.

Conclusions: NICF is both a distinct entity and an epiphenomenon in the context of other disorders. In regard to the common association with yeast and gram-positive bacteria in the affected follicles, we hypothesize that NCIF is pathogenetically linked to these organisms which is supported by resolution after topical or systemic antimycotic treatment.

Dear Dr. Shea

We are submitting the enclosed revised manuscript "necrotizing infundibular crystalline folliculitis" (JAAD-D-10_01308 R1) as an original article to the Journal. We are very grateful for the comments of the reviewers. Enclosed please find the point-by-point answers to their comments. The corresponding changes in the manuscript has been highlighted by red.

Point-by-point answers to the reviewer's comments

(1) According to the comment of reviewer #1, we have now added an investigation of 9 cases of ostiofolliculitis. This investigation was mentioned in the lines 12 to 13. The results have been added in the revised manuscript in the lines 35 ff. "… and 9 cases with ostiofolliculitis were collected"; and in the lines 74 to 76: "Only few yeast spores were found in 2 cases (2 of 9; 22%) and bacteria in 4 cases (4 of 9; 44%) of ostiofolliculitis. Neither crystalline deposits nor necrosis of follicle epithelium were observed in any of theses cases".

(2) Following reviewer #2, we have added the reference by Cribier et al. to the revised manuscript on line 88 "…and in 2003 by Cribier et al. [10] as a further case report." The reference has been added to the references: Cribier BJ, Boehm N, Heid E, Grosshans E. Pathogenesis: Crystals in association with degenerated corneocytes in plugs of infundibula induce a distinctive papular eruption on the face. Dermatopathology: Practical and Conceptual 2003; 9 (2); published online at http://www.derm101.com.

(3) The finding of similar findings has been added and discussed in the revised manuscript in lines 137 to 139 with “Additionally the crystalline birefringent structures observed also in 3,5 % of 200 epidermal cysts were supposed by Cribier et al. to be keratinous fundamentally [10].”

(4) As proposed by the reviewer, we have added a photomicrograph as a figure 4 depicting coincidental NICF changes in close vicinity to an actinic keratosis.

We hope that the revised manuscripts fulfills the requirements and high standard for publication in the Journal. We very much appreciate your evaluation of our manuscript.

Yours sincerely,

Werner Kempf

# Necrotizing infundibular crystalline folliculitis: A clinical-pathological study

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- Necrotizinig infundibular crystalline folliculitis is characterized by waxy lesions and histologically by folliculocentric filamentous negative birefringent crystalline deposits.
- The median age of patients was 51 years and more commonly forehead, neck and back involvement.
- Yeast and gram-positive bacteria were identified in the majority of cases.
- Topical or systemisc antimycotics may be usefull in the treatment of this disorder.

## Introduction

The microscopical findings of necrotizing infundibular crystalline folliculitis (NICF) were first described by Lucke[1] and coworkers in 1999 as transepidermal elimination of urate-like crystals followed by the case report by Kossard[2] et al. in 2001 under the term of NICF.

This disorder is characterized clinically by sharply demarcated waxy papules and histologically by distinctive filamentous material within the partly necrotic hair follicle ostium and infundibulum. In the cases described by Lucke and coworkers negative birefringent needle-shaped crystals within the filamentous material were identified. Various hypotheses for the development of NICF have been proposed[1][2]. The pathogenesis and the clinicopathological features including its course remain to be elucidated. We therefore studied 9 patients with histologically proven NICF, a series of biopsies, in which similar histological findings were observed coincidentally with other skin disorders and a series of biopsies with ostiofolliculitis.

## Materials and Methods

All lesions diagnosed as NICF between 2006 and 2010 were retrieved from the files of our dermatopathology laboratory. A total of 9 cases with the diagnosis of NICF were identified. Data from these cases were compiled and analyzed for age of the patient at diagnosis, gender, localization and clinical as well as histological features of the lesions. Data on therapy and its outcome were obtained from the treating dermatologists. In addition to the 9 patients with NICF, 7 cases with coincidental findings of NICF associated with different epithelial skin neoplasms and 9 cases with ostiofolliculitis were collected.

All biopsies were formalin-fixed paraffin-embedded. The cases were routinely stained for hematoxylin and eosin, periodic-acid-Schiff and Brown-Brenn-Gram to identify fungi and bacteria, respectively. In addition, all biopsies were analyzed by polarizing light microscopy.

## Results

Results are summarized in Table 1. There were 4 male and 5 female patients, aged between 20 and 72 years (median age = 51 years). All but three lesions developed on the forehead (5 out of 9, 56%) (Fig. 1), followed by back (2 out of 9; 22%), neck and nose in equal proportions (1 out of 9; 11%). Lesions generally consisted clinically of waxy erythematous papules.

All cases of NICF showed birefringent crystalline deposits within the follicle ostia enclosed by parakeratotic columns (Fig. 2). The necrosis of follicle epithelium was found in 8 out of 9 cases (89%). Perifollicular neutrophil granulocytes infiltrate was present in 2 out of 9 cases (22%). In all cases (9 out of 9; 100%) the filamentous material contained birefringent urate-like crystal sturctures revealed by polarizing light (Fig. 3). Yeasts and gram-positive bacteria were detected within the affected follicles in equal proportions in 5 cases (56%).

The constant finding in all cases with coincidental findings of NICF was crystalline deposits within the follicle ostium enclosed by parakeratotic columns (Fig. 4). Neither the necrosis of follicle epithelium nor perifollicular neutrophils could be detected in any of these cases.

Yeasts and gram-positive bacteria were present within the affected follicles in equal proportions in the majority of cases with coincidental findings of NICF (n=6, 86%).

Only few yeast spores were found in 2 cases (2 of 9; 22%) and bacteria in 4 cases (4 of 9; 44%) of ostiofolliculitis. Neither crystalline deposits nor necrosis of follicle epithelium were observed in any of theses cases.

## Discussion

The designation of NICF was introduced by Kossard et al in 2001[2] to describe a folliculocentric umbilicated crater filled mostly by filamentous material surrounded by a parakeratotic rim and lined by partly necrotic hair follicle epithelium. Similar histological findings with birefringent crystalline urate-like structures within the filamentous material had been described before by Lucke et al[1] as transepidermal elimination of urate-like crystals and in 2003 by Cribier et al. [10] as a further case report.

Our study is the first analyzing a series of patients with NICF. In our series, both genders are equally affected by NICF. Most patients are in the 5th decade with a broad range of age at diagnosis. The head and neck area, particularly the forehead, is the predilection site involved in 78% of the patients, followed by the back. NICF shares therefore the predilection sites of acne. The clinical manifestation of NICF with waxy papules, however, is different from acne.

Our series show all histological hallmarks in accordance with the three prior reports. The pathognomic filamentous material containing birefringent urate-like crystals in all cases, however, was located mostly in the ostia in the hair follicles and rarely in the infundibular region (1out of 9 cases; 11%). Thus we propose to modify the term necrotizing infundibular crystalline folliculitis to necrotizing ostial crystalline folliculitis. Focal necrosis of the hair follicle epithelium was found in about 90% of the biopsies and column-like hyperparakeratosis surrounding the filamentous material was observed in all biopsies rendering these features to pathognomic findings. An inflammatory infiltrate was present in more than half of the biopsies, but neutrophils admixed to the infiltrate were not a consisting feature as they were found in only 22% of the biopsies.

Remarkably, yeasts (with the morphology Malassezia) as well as gram-positive bacteria (corresponding to Propionibacterium acnes) were detectable in approximately in 56 % of cases with the NICF and in 86 % of the biopsies, in which NICF was a coincidental finding

accompanying other disorders. Similar clinical picture with small whitish follicular papules associated with Malassecia spp. had been referred as Pityriasis versicolor papulosa by Male in 1978[9]. Unlike NICF only few yeast spores were found in 22 % and bacteria in 44% of ostiofolliculitis cases.

Two principal pathways for the etiopathogenesis of NICF have been proposed. Kossard and coworkers hypothesized that either physical or chemical injury or bacteria and Malassezia yeasts in the infundibulum of follicles may induce the crystalline structures[2]. Montagna[4] reported in 1963 about polarizable crystals of sebaceous lipids and recognized them as esters of cholesterol. These crystals resist HE-related solvents in histological preparations and water-based potassium hydroxide solution in their fresh preparations[5]. These features rule out that the crystals in NICF consist only of pure cholesterol and urate crystals.

Different cell types of the epidermis with the enzymatic potential for cholesterol esterification were established by Freinkel and Aso[6]. Gonzalez-Serva et al.[5] 2004 demonstrated polarizable crystals in vast majority of closed acne comedones in their study. The authors suggested that crystallization of sebum is a common event during comedogenesis and crystal formation increase the cohesion of filamentous material within the comedo. Increased steryl ester levels were found in lipids extracted from comedones, compared to lipids from skin surface wipings, probably because of concentrated bacterial proliferation and cholesterol esterification within the comedones [7]. Puhvel[8] demonstrated that Propionibacteria are also able to esterify cholesterol. Furthermore the lipases of Propionibacteria hydrolyze di- and triglycerides to free fatty acids and glycerol. The esterification of cholesterol is often increased by Propionobacterium acnes within the comedones. Malassezia spp. are lipid dependent yeasts and require an external source of lipid e. g. free fatty acids and triglycerides produced by sebaceous glands. Malassezia species produce an enzyme with lipoxygenase activity, as demonstrated by its ability to oxidize free and esterified unsaturated fatty acids, squalene and cholesterol derived in part from the decomposition of corneocytes[9].

Catterall et al. 1978 referred previously accumulation of amorphous material between the squamae as a result of destruction of tonofilaments of corneocytes by Malassezia spp. penetrating Str. corneum. Kossard et al. 2001[2] detected disrupted tonofilaments within the amorphous material of NICF by electron microscopy. Additionally the crystalline birefringent structures observed also in 3,5 % of 200 epidermal cysts were supposed by Cribier et al. to be keratinous fundamentally [10].

In conclusion, our study demonstrates that NICF represents a distinct nosologic entity with characteristic clinical and histological features. Similar findings, however, may be observed as an incidental histologic finding in the context of other skin disorders, particularly in close vicinity to epithelial skin neoplasms. The latter phenomenon could be termed secondary NICF. We hypothesize that either sebum cumulate and crystallize thereby serving as nutrient medium for yeast and bacteria, or alternatively Propionibacteria and Malassezia spp. destruct tonofilaments and degrade lipids which results in accumulation of filamentous material with birefringent crystals within the hair follicle ostia and infundibula. The increasing amount of the filamentous material results in rupture of the follicular epithelium with subsequent inflammatory reaction. The clinical response of NICF to topical or systemic antimycotic treatment underlines the pathogenetic role of microorganisms in NICF.

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Abbreviations used:

NICF: Necrotizing infundibular crystalline folliculitis

**Table 1** Table I. Clinical and histological summary of patients with NICF

| Case | Age and gender | Clinical information | Location | Malassezia | Bacteria | Necrosis | Parakeratosis | Neutrophils | Birefringence |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 51 m | Waxy papules, lichenoid exanthema, Amyloid | Forehead | No | No | Yes | Yes | No | Yes |
| 2 | 72 w | Atopic dermatitis, photoallergic reaction | Scapula | Yes | No | Yes | Yes | No | Yes |
| 3 | 57 m | Follicular hyperkeratosis, spicules like at multiple myeloma | Forehead | n/a | n/a | Yes | Yes | No | Yes |
| 4 | 34 w | Pusteles, atopic dermatitis, dd pityrosporum, impetigo, Darier | Neck | Yes | No | n/a | Yes | No | Yes |
| 5 | 20 w | Folliculitis, dense keratotic papules, partly molluscoid | Back | Yes | Yes | Yes | Yes | Yes | Yes |
| 6 | 58 m | rosacea, molluscoid papules | Forehead | Yes | No | Yes | Yes | No | Yes |
| 7 | 64 w | folliculitis | Forehead | Yes | Yes | Yes | Yes | No | Yes |
| 8 | 40 m | Rosacea, dd lupus erythematosus | Nose | Yes | Yes | Yes | Yes | Yes | Yes |
| 9 | 48 w | Acne, rosacea, folliculitis, lupus | Forehead | No | Yes | Yes | Yes | No | Yes |

n/a, not applicable

**Table 2** Table II. Clinical and histological summary of patients with coincidentally findings of NICF

| Case | Age and gender | Clinical information | Location | Malassezia | Bacteria | Necrosis | Parakeratosis | Neutrophils | Birefringence |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 73 w | Actinic keratosis | Nose | Yes | Yes | No | Yes | No | Yes |
| 2 | 46 m | Precancerosis, basal cell carcinoma | Nose | Yes | Yes | n/a | Yes | No | Yes |
| 3 | 53 m | Seborrhoic keratosis, squamous cell cacinoma | Chin | Yes | Yes | No | Yes | No | Yes |
| 4 | 70 m | Basal cell carcinoma | Forehead | No | Yes | No | Yes | No | Yes |
| 5 | 82 m | Basal cell carcinoma | Thorax | Yes | Yes | No | Yes | Yes | Yes |
| 6 | 66 m | Actinic keratosis | Temple | Yes | No | No | Yes | No | Yes |
| 7 | 73 m | Actinic keratosis | Forehead | Yes | Yes | No | Yes | No | Yes |

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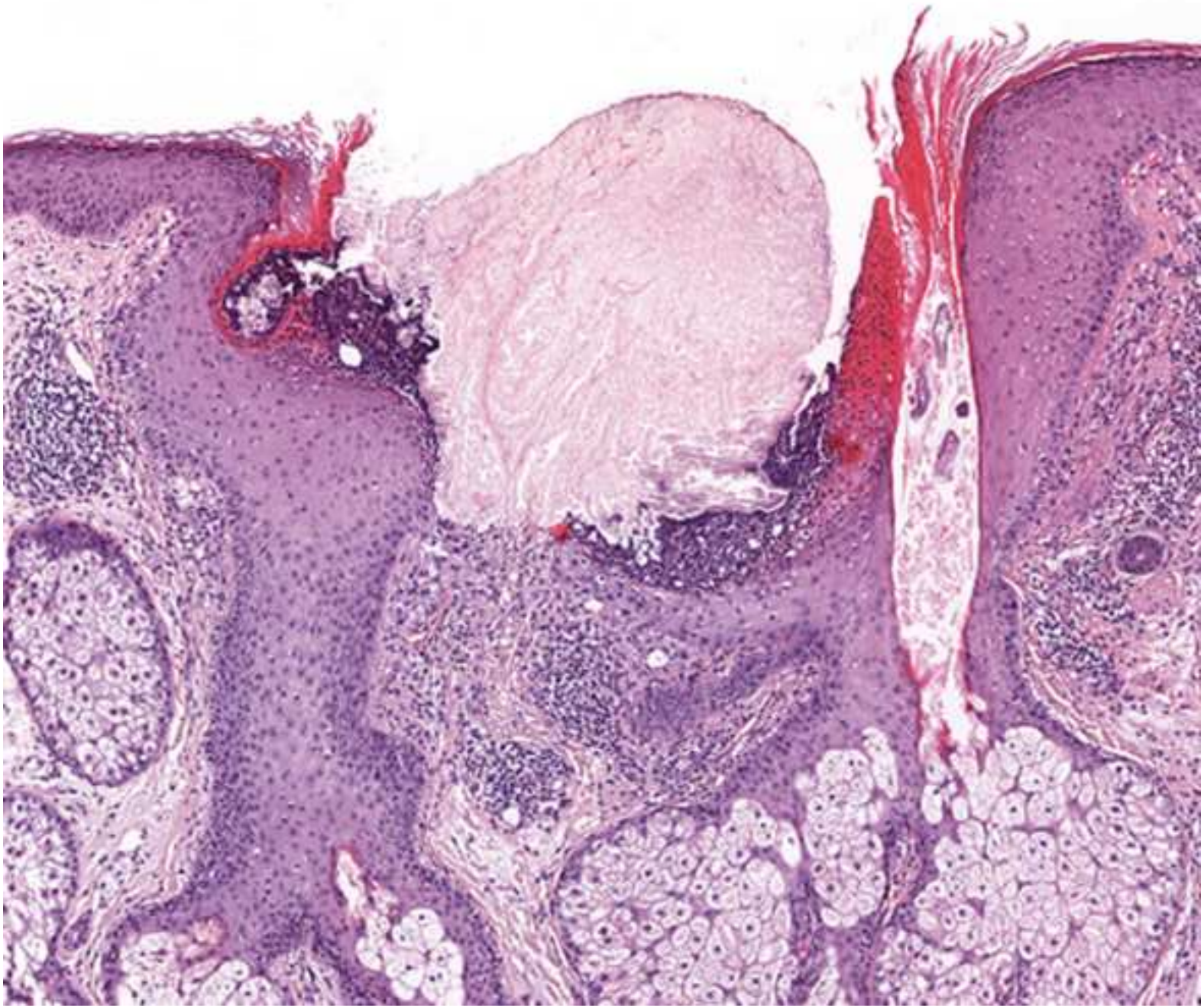

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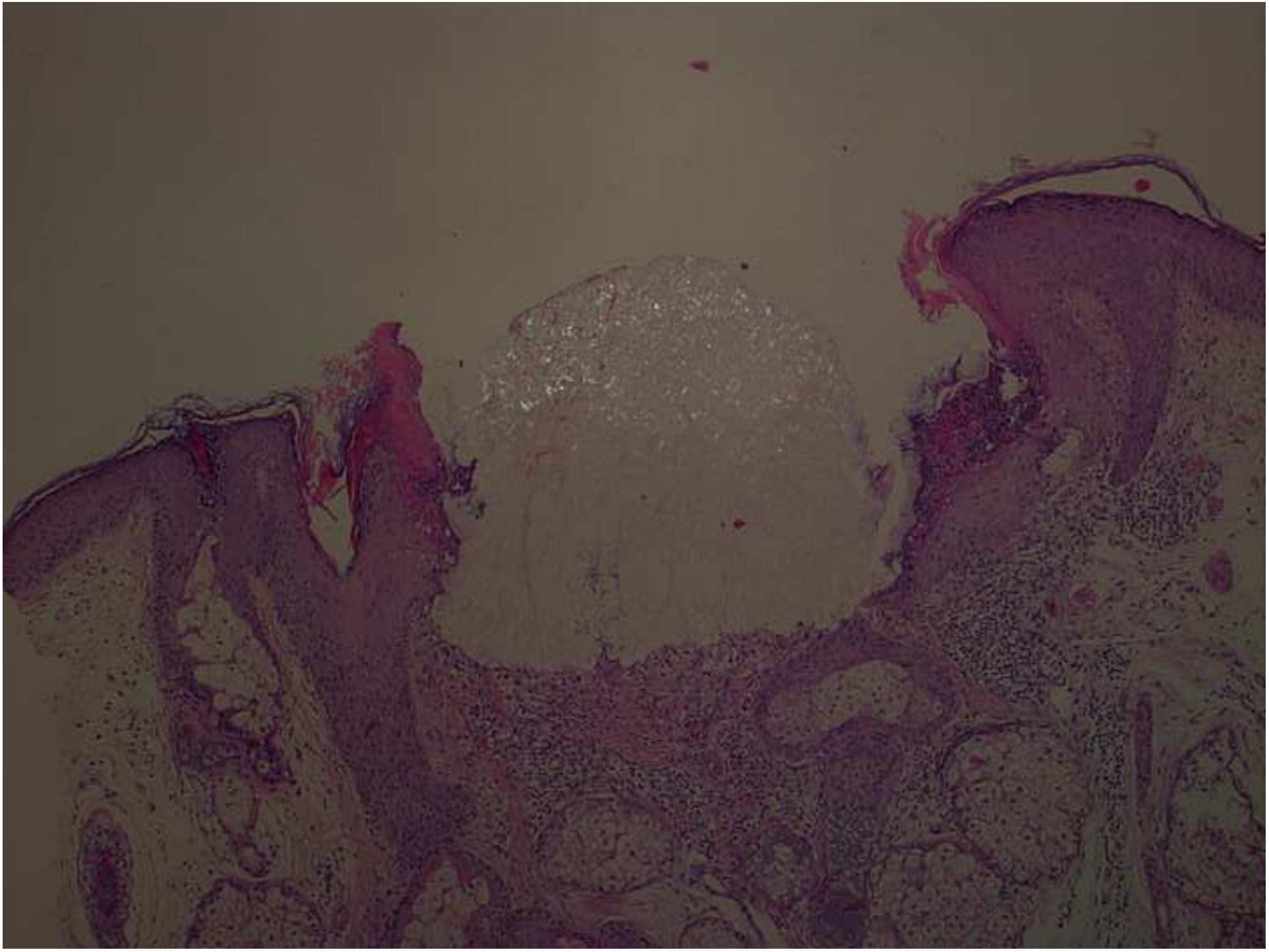

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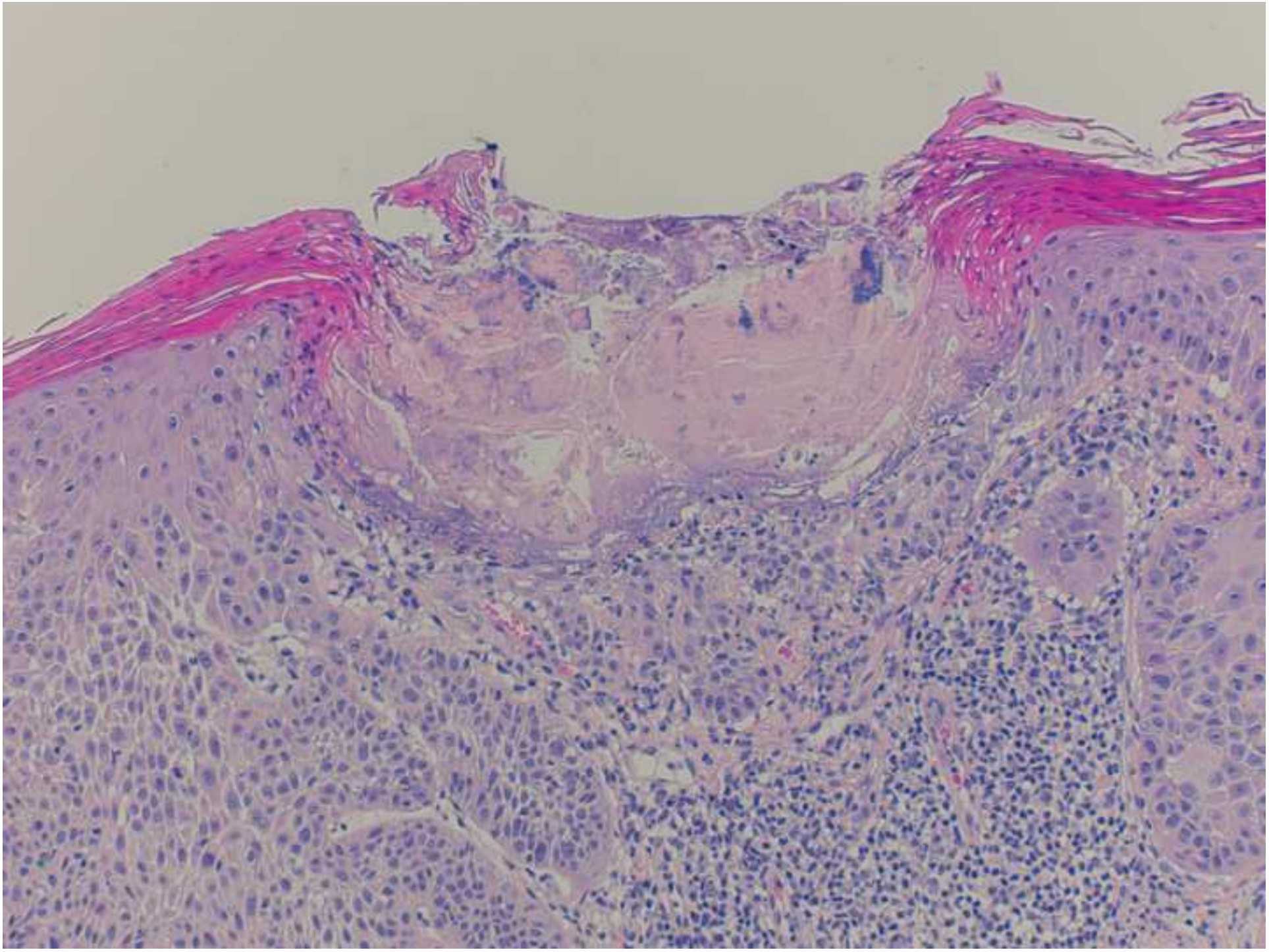

**Figure Legend 1**

1 Fig 1. Waxy erythematous papules on the forehead.

**Figure Legend 2**

Fig 2. Filamentous deposits, enclosed by parakeratotic columns within the partly necrotic follicle ostium (Hematoxylin-eosin stain; original magnification: x 10).

**Figure Legend 3**

Fig 3. Filamentous negative birefringent crystalline deposits within the follicle ostium (Hematoxylin-eosin stain; original magnification: x 4).

**Figure Legend 4**

Fig 4. Coincidental NICF changes in close vicinity to an actinic keratosis (Hematoxylin-eosin stain; original magnification: x 10).

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