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LETTER TO THE EDITOR

Transient perforating folliculitis induced by sorafenib.

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Dear Editor,

Sorafenib is an oral multikinase inhibitor originally developed as a Raf-1 kinase inhibiting agent, but has been demonstrated to inhibit other kinases such as vascular endothelial growth factor receptor-2, vascular endothelial growth factor receptor-3, platelet-derived growth factor receptor-β, and FLT3. Cutaneous side effects are frequently associated with sorafenib, which include hand-foot syndrome, facial erythema, alopecia, xerosis, pruritus, and subungual splinter hemorrhages[1]. Rarely the drug induses perforating folliculitis (PF)[2], keratosis pilaris-like eruption[3] and follicular hyperplasia[4]. We report a case of PF associated with sorafenib. To the best of our knowledge, this is the first report of sorafenib-associated PF in Japan.

A 77-year-old Japanese man was treated with sorafenib 400mg twice daily for metastatic renal cell carcinoma. Two weeks after the initiation of the therapy, he noticed hair loss, which was followed by typical hand-foot syndrome with symmetric red area on palms and soles and patchy hyperkeratosis on plantar pressure areas. Sorafenib was continued without lowering the dose and seven weeks after the initiation of the therapy, asymptomatic, up to 6mm-sized, solitary dark red papules surrounded by erythema developed on the extensor aspect of the lower extremities, buttocks and lumbar area (Fig.1). Each papule contained a central cone-shaped keratotic plugging. Histopathological examination disclosed prominent keratotic plugging, and dilated follicular infundibulum filled with compact parakeratotic cornified cells (Fig 2a). Neutrophils were infiltrated into the cornified cells. Upper follicular epithelial cells showed marked vacuolization (Fig 2b) and

dyskeratosis. Perifolliclar infiltration of lymphocytes and vascular proliferation were also noted.

The patient was diagnosed as PF associated with sorafenib. Although topical corticosteroid therapy was not effective, the central debris was spontaneously shed out and the skin lesions disappeared with residual pigmentation despite the continuous use of sorafenib within 8 months.

Sorafenib has been used for advanced inoperable cases of renal cell carcinoma in Japan. 93% of patients with renal cell carcinoma receiving soraenib (400 mg twice daily) had dermatologic symptoms, including rash/desquamation (66%) and hand-foot syndrome (62%), and dermatologic related symptoms, such as alopecia (53%)[1].

Wolber et al[2] reported PF, which was also associated with

anigioedema and hand-foot syndrome in a patient treated with sorafenib. They suggested that sorafenib-induced xerosis plays a pathogenic role, as itch-induced traumatic scratching could elicit PF. Combined treatment with tretinoin, mometasone furoate, calcipotriol and minocycline for 8 weeks was unsuccessful. Isotretinoin therapy reduced the hyperkeratosis and flattened the papules. 5 months after the start of retinoid therapy the lesions had largely regressed despite continuation of sorafenib therapy. Kong et al[3] reported another case of sorafenib-associated keratosis pilaris-like eruption. He stated sorafenib was successfully reinitiated at reduced doses after temporary rest periods despite keratosis pilaris-like eruptions in some patients. They hypothesized that sorafenib altered keratinocyte differentiation/ proliferation pathways. Lopez et al [4] reported a case of facial follicular hyperplasia induced by sorafenib. Complete regression was obtained after

switching to Fotemustine. Althogh the dose of sorafenib was not reduced in our case, the lesions were regressed after 8 months the initiation of sorafenib. We also believe that PF based on sorafenib are likely to regress spontaneously as our case.

Although the pathogenesis of sorafenib-induced PF remains unknown, the distribution of the eruption suggests that abnormal keratinization at the hair follicle triggered by chronic friction might have lead to the peculiar transient PF-type eruption in our case.

References

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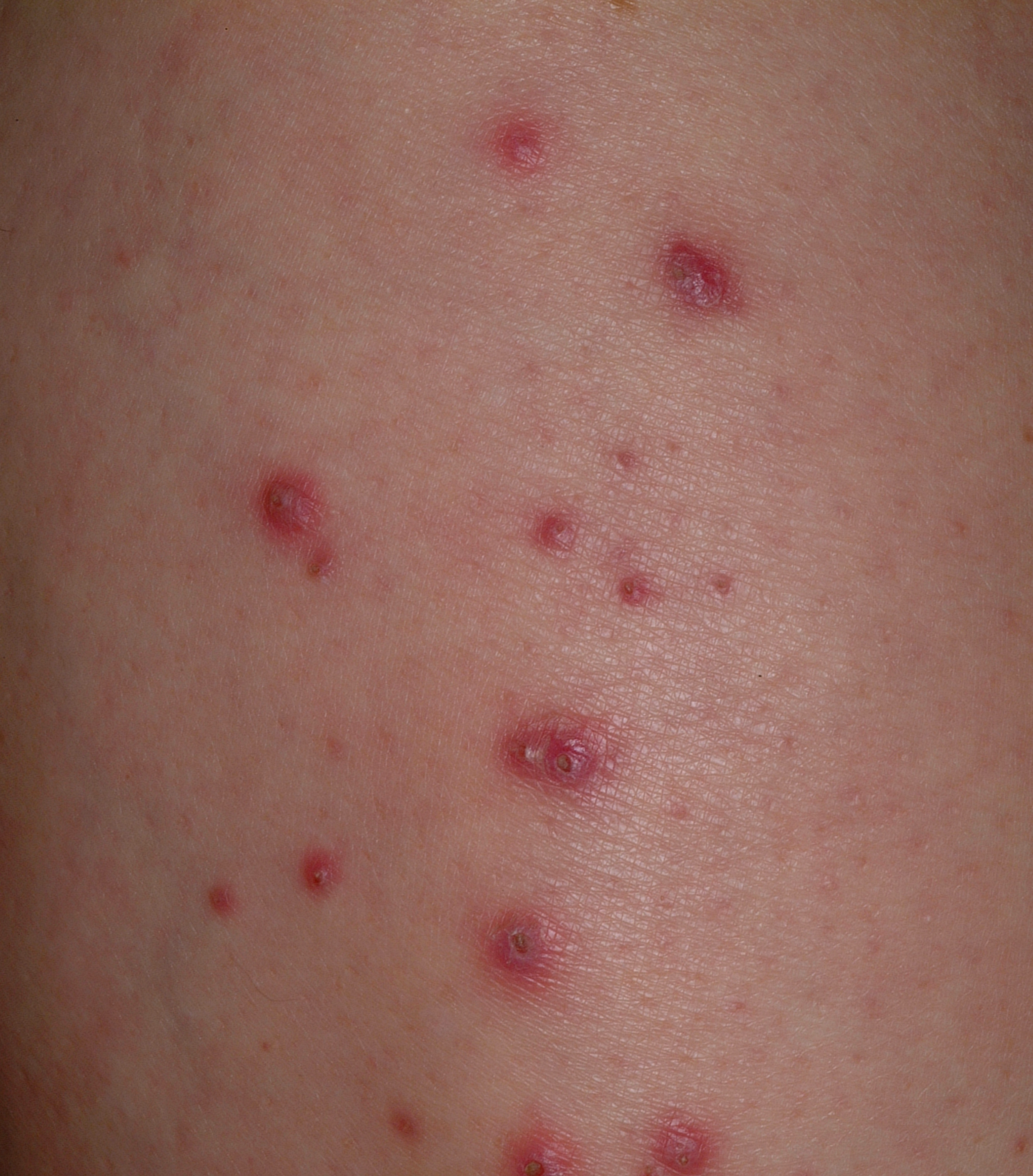
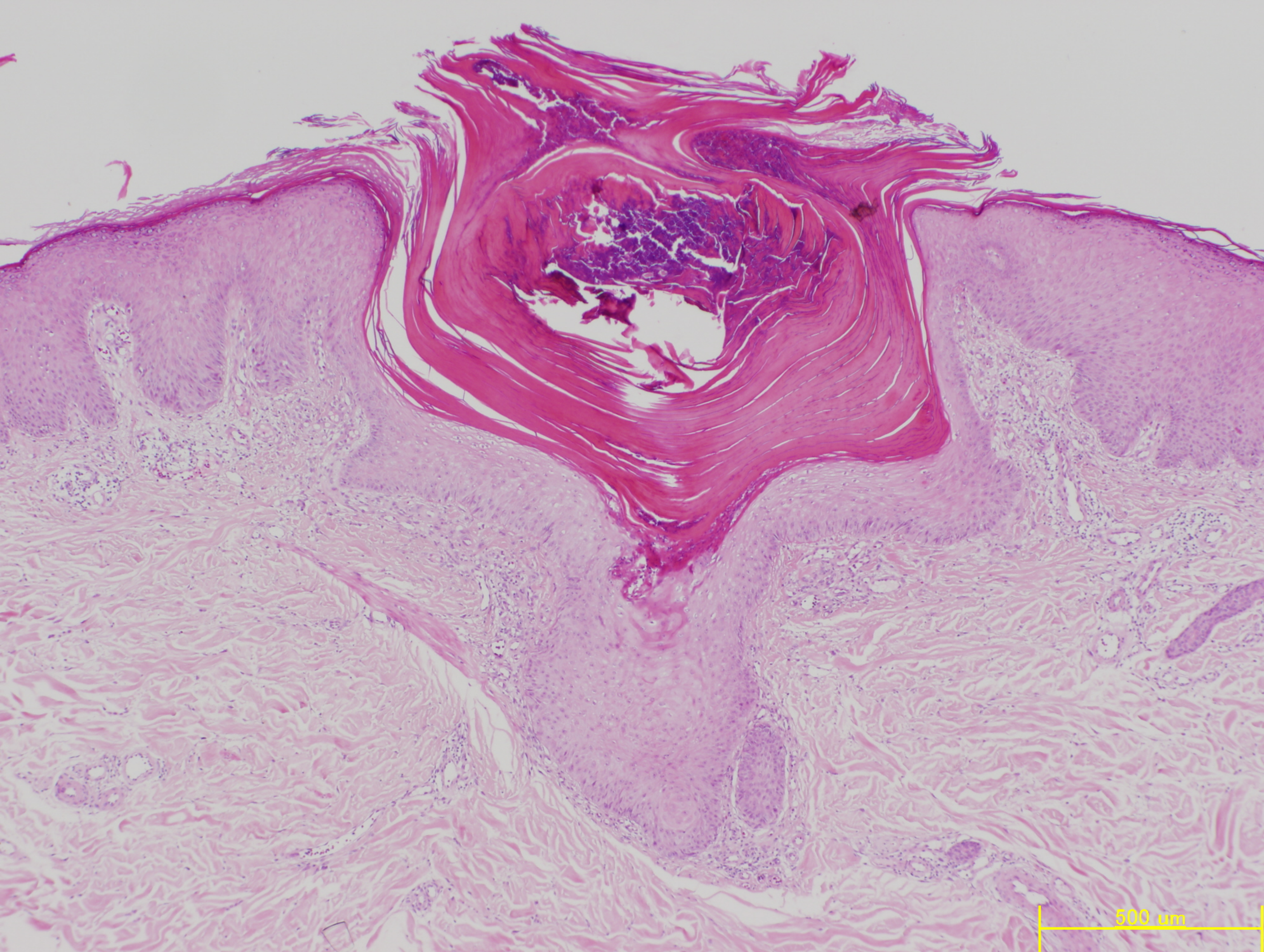
Figure legends

Figure 1: Isolated dark red multiple papules surrounded by erythema, each containing a central cone-shaped keratotic plugging.

Figure2a: Keratotic plugging filled dilated follicular infundibulum. Note arrector pili muscle on the left.

Figure2b: Granular layer is absent and upper epithelial cells are vacuolated. A number of neutrophils are infiltrating in the cornified layer.

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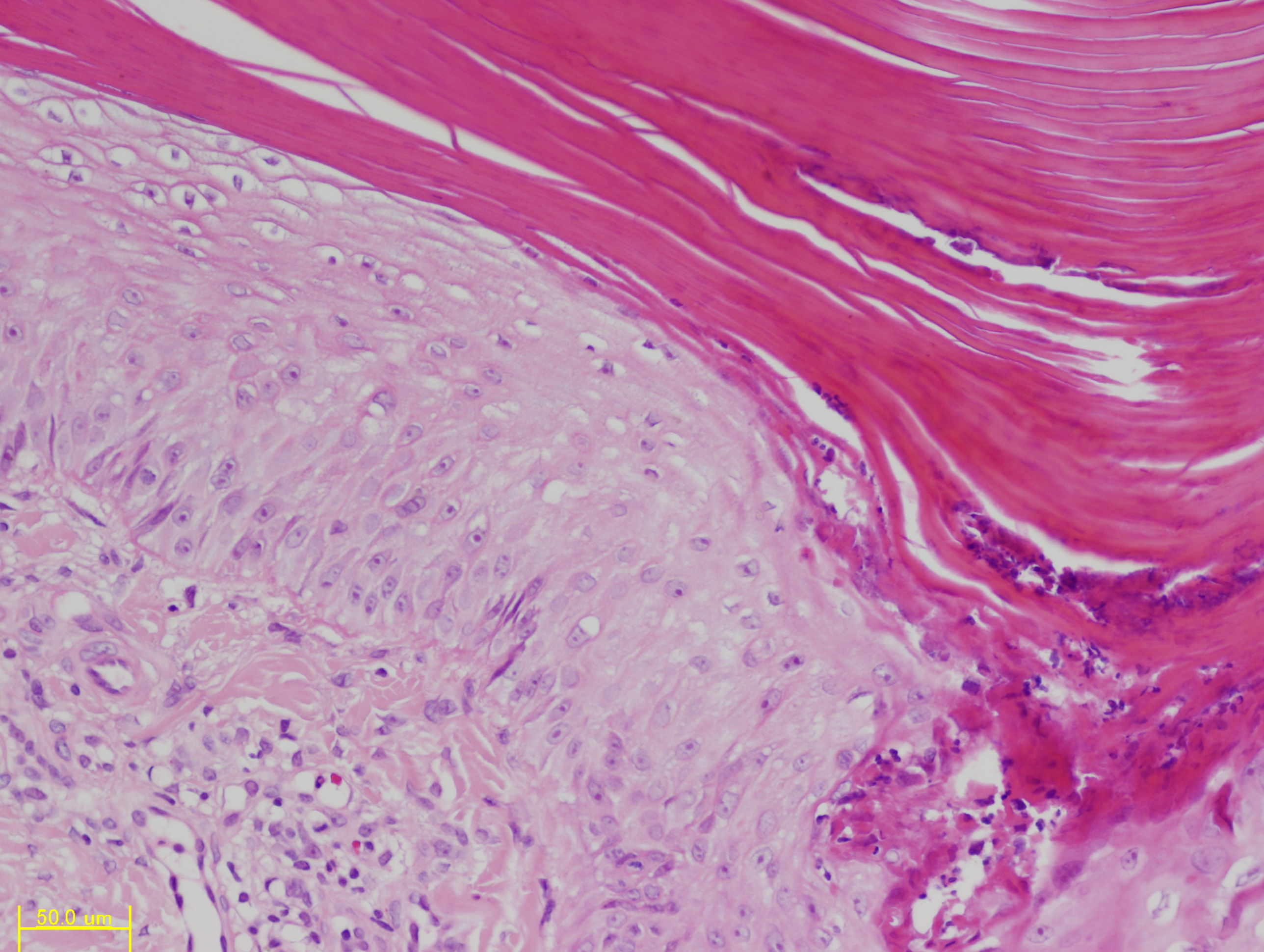
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