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SHORT COMMUNICATION

Eccrine Squamous Syringometaplasia of Underlying Syringoma Associated with Tegafur/Gimeracil/Oteracil (TS-1)

Jihee Kim[1], Su Hee Kim[2], Min-Geol Lee[1], Kee Yang Chung[1] and Dae Suk Kim[1]*

*[1]Department of Dermatology & Cutaneous Biology Research Institute and, [2]Department of Pathology, Yonsei University College of Medicine, Yonsei University College of Medicine, Severance Hospital, Yonseiro 50, Seodaemun-gu, Seoul, 120-752, Korea. *E-mail: DSKIN@yuhs.ac*

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Eccrine squamous syringometaplasia (ESS) is defined as metaplasia of the eccrine ductal epithelium into squamous epithelial cells. It has been reported in patients with malignancy receiving chemotherapeutic agents. Histologically, the lesions exhibit transformation of normal cuboidal epithelial cells into 2 or more layers of squamous epithelial cells (1). Tegafur/Gimeracil/Oteracil (Teysuno, TS-1; Jeil Pharmaceutical Co. Ltd, Seoul, South Korea) is a combined oral chemotherapeutic agent indicated for advanced gastric cancer, and its use has been expanded to colorectal, lung, laryngeal, pancreatic, and biliary cancers.

CASE REPORT

A 68-year-old woman presented with several match head-sized papules with surrounding erythema and central confluence along the periorbital area (Fig. 1). The skin lesion was mildly pruritic and lasted for 10 days. She had a history of advanced gastric cancer (stage II2a) and had previously undergone subtotal gastrectomy. The patient was started on adjuvant chemotherapy with TS-1 with 3 capsules at a time, twice daily, for 28 days (Tegafur 20 mg/Gimerasil 5.8 mg/Oteracil 19.6 mg),and 2 weeks thereafter, the skin eruption had appeared. She had no other remarkable medical history. Skin biopsy revealed metaplastic eccrine ducts in the dermis with intercellular bridge formation (Fig. 2A). On high power view, eccrine ductal epithelia showed mitotic figures and necrotic duct cells. Other parts of the specimen demonstrated transformation of cuboidal epithelium into 2 or more layers of squamous cells with intraductal keratinisation (Fig. 2B–D). Considering the patient's history of internal malignancy and histological features, the final diagnosis was ESS.

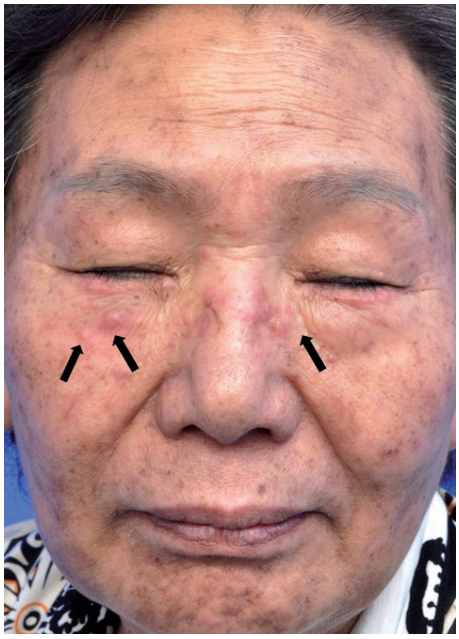

Fig. 1. Several match head-sized erythematous papules and nodules along the periorbital area. A written permission is given to publish this figure.

DISCUSSION

Chemotherapy-associated eccrine reactions usually arise 2 to 30 days after the agent's administration. They may present as non-specific features, ranging from erythematous papules on the periorbital area to diffuse patches on the intertriginous areas (2). The lesions usually spontaneously resolve within 15 days with mild desquamation and postinflammatory hyperpigmentation. There have been reports of successful treatment with topical and systemic steroids. ESS has been reported with chemotherapeutic agents including bleomycin, cytarabine, cisplatin, and tyrosine kinase inhibitors (3). Recently, there have been reports of ESS in patients with metastatic melanoma receiving vemurafenib and dabrafenib (4). However, it does not seem to have a strong association with any particular chemotherapeutic agent or malignancy, and some cases are associated with infection or inflammatory conditions.

For the diagnosis of ESS, histological examinations are important to exclude squamous cell carcinoma (SCC). Three distinguishable features suggestive of ESS include epidermal dystrophy, neutrophilic eccrine hidradenitis, and necrosis of eccrine ducts. Our patient had both early and well-established patterns of ESS, showing hyperplastic eccrine ducts with mitotic figures and intraductal keratinisation within the areas of squamous metaplasia.

The main component of TS-1, tegafur, is the prodrug of the active substance fluoruracil (5-FU), and other components are for reducing gastrointestinal toxicity. In addition to its use in gastric cancer, TS-1 recently showed successful outcomes in head and neck SCC. Therefore, it would seem paradoxical for such a drug to cause squamous transformation in the eccrine duct lumen. However, *in vitro* data have demonstrated that

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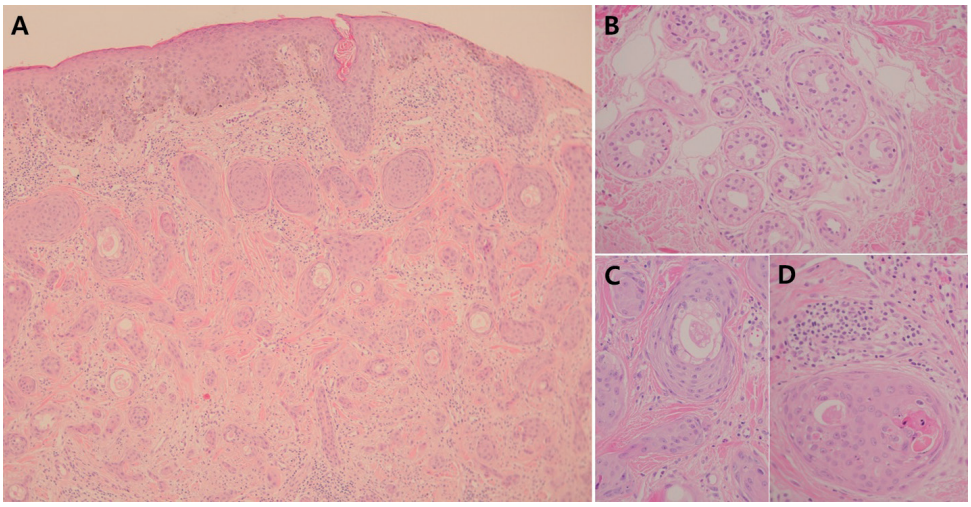

Fig. 2. Histopathologic features of the patient. A) A biopsy specimen shows metaplastic eccrine ducts in the dermis with intercellular bridges. B) Hyperplastic eccrine ducts with mitotic figures and necrotic duct cells. C) Transformation of eccrine cuboidal epithelium into 2 or more layers of squamous cells. D) Metaplastic eccrine duct with intraductal keratinisation (Haematoxylin-eosin stain, A, × 100, B, C, D, × 400).

TS-1 inhibits expression of Akt/ NFkB pathways, which may lead to the activation of the MAPK pathway, leading to squamous cell proliferation (5, 6).

Currently, the underlying pathomechanism of ESS is yet to be elucidated. Direct toxic effects of the chemotherapeutic drug on the eccrine gland may be responsible for the secondary changes. Considering the paucicellular inflammatory cell inflammation surrounding the eccrine duct, ductal necrosis due to high concentrations of the drug within glandular structures may induce squamous metaplasia. Indeed, there have been reports of systemically administrated 5-FU causing squamous metaplasia of the lacrimal gland which eventually cause canaliculus obstruction (7).

To our knowledge, this is the first case of ESS reported as a result of treatment with TS-1.

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