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**Title: Seborrheic inclusion cyst with sebaceous gland involvement: what does it mean?**

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Seborrheic inclusion cyst is a rare variant of epidermoid cyst that is characterized by seborrheic keratosis-like lesion in the cyst wall [1-3]. However, the proposed viral involvement in its pathogenesis is still controversial [4, 5]. Herein we report a case of seborrheic inclusion cyst with focal sebaceous differentiation in relation to local trauma.

A 78-year-old Japanese man was referred to our clinic for evaluation of a cyst on his right lower leg. He had a definite past history of a nail stuck in his right lower leg 20 years ago. He noticed a slowly growing lesion just in the traumatized site. Physical examination showed an intradermal cyst, 25 × 18 mm in size, located on the right lower leg (*figure 1A*). The lesion was resected under local anesthesia. Histopathology revealed a cyst containing keratin materials without apparent connection to the overlying epidermis (*figure 1B*). The cyst wall was composed of keratinocytes and showed focal acanthosis containing some pseudohorn cysts and sebaceous glands (*figure 1C*). Both epidermoid and trichilemmal keratinization were seen (*figure 1D*). Sebaceous duct-like cuticular keratinization and sebaceous differentiation were also seen (*figure 1E*). There were no viral vacuolated cells in the wall. Immunohistochemically, some cells in the acanthotic area were positive for adipophilin (*figure 1F*) but were negative for pan human papilloma virus (HPV) (not shown). Based on these findings, a diagnosis of seborrheic inclusion cyst with focal sebaceous differentiation was made.

Seborrheic inclusion cyst is rare with an estimated incidence of only 0.5% about of all cases of seborrheic keratosis [6]. The overlying epidermis is grossly normal and has no relationship to the cyst. The etiology of seborrheic inclusion cyst remains to be elucidated. Chun and Im reported a case with numerous PAS-positive vacuolated cells and suggested the involvement of a nevoid change or mechanical factor in the pathogenesis [2]. Brown and Youngberg reported a case at the site of previous excision of seborrheic keratosis, suggesting a mechanical factor in the development of the cyst [3]. In contrast, Terada reported a case in which immunohistochemical examination showed HPV-positive cytoplasmic inclusion bodies in the cyst wall [4]. However, HPV was not detected with polymerase chain reaction by Fernandez-Flores [5].

It is thought that epidermoid cyst originates from the infundibular epithelial wall, whereas trichilemmal cyst originates from the isthmic epithelial wall [7]. Differential diagnosis includes hybrid cyst that shows both epidermoid and trichilemmal keratinization [8]. However, seborrheic keratosis-like lesion (pseudohorn cyst) is not seen in the hybrid cyst. In the present case, we clearly showed sebaceous gland involvement and focal sebaceous differentiation in the cyst wall after obvious trauma. Until now, no attention has been given to the sebaceous gland of seborrheic inclusion cyst. Based on our new findings, seborrheic inclusion cyst is most probably caused by overgrowth of the epithelial wall

between the infundibulum and the isthmus in the hair follicle, just around the opening of sebaceous duct, after a mechanical factor with or without viral involvement.

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## **Figure Legends**

**Figure 1. A)** Physical examination showed an intradermal cyst, 25 x 18 mm in size, located on the right lower leg.

**B)** Histopathology revealed a cyst containing keratin materials in the deep dermis without apparent connection to the overlying epidermis (black bar, 2.5mm).

**C)** The cyst wall was irregularly acanthotic and contained some pseudohorn cysts and sebaceous glands (black bar, 250µm).

**D)** Both epidermoid and trichilemmal keratinization were seen (black bar, 100µm).

**E)** Mature sebocytes were present in the cyst wall (black bar, 50µm).

**F)** Some cells in the cyst wall were positive for adipophilin (black bar, 50µm).