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Case Report

Pathology Section

Extensive Eccrine Squamous Syringometaplasia Mimicking Squamous Cell Carcinoma on Histopathology

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ABSTRACT

Eccrine Squamous Syringometaplasia (ESSM) is a histologically distinctive skin eruption occurring predominantly in acral or intertriginous areas presenting as erythematous macules, papules or patches. It is a response of eccrine ducts and glands to any injury or inflammation. The cuboidal epithelium of eccrine ducts and glands undergoes metaplasia and transforms to keratinised squamous epithelium in ESSM. Other types of metaplastic changes encountered are squamous, mucinous and adenomatous. In squamous syringometaplasia, the metaplastic squamous cells form lobules and florid types can pose a diagnostic dilemma, which if not well understood may lead to an erroneous diagnosis of neoplasia. Literature suggests ESSM as a condition associated with another pathogenic stimuli or therapy; however florid ESSM is very rare. Hereby, the authors present a case report of a 43-year-old male who presented florid ESSM mimicking well-differentiated Squamous Cell Carcinoma (SCC). The present case presented with a non healing elevated lesion on anterior aspect of right leg with itching. Similar lesions were not present in any other part of the body. The patient did not have history of any systemic disease or drug intake. The lesion was excised and sent for histopathology. On gross examination the skin showed irregular thickening and foci of erosion. Microscopy showed acanthotic, hyperkeratotic epidermis and dermal ESSM. There were irregular clusters of metaplastic squamous cell in dermis, resembling invasive islands of SCC. Meticulous examination revealed lobulated architecture of ESSM, lack of individual cell keratinisation/significant atypia or mitosis. The present report highlights the significance of histopathological diagnosis of benign squamous proliferations which can mimic malignancy and cause undue stress to the patient.

Keywords: Eccrine ducts, Metaplasia, Squamous metaplasia

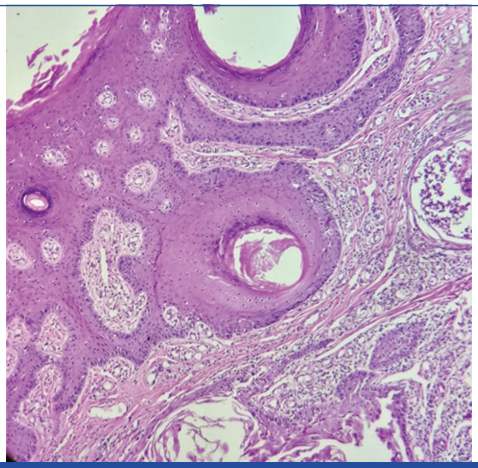
CASE REPORT

A 43-year-old male presented with an elevated skin lesion on the anterior surface of right leg, accompanied by itching for six months. The patient had been using some topical creams by self-medication, about which, details were not available. On examination, the lesion measured 1.6×0.7 cm and appeared to involve both the cutaneous and subcutaneous planes. Wide local excision of the lesion was done, and the sample was sent to laboratory for histopathological examination.

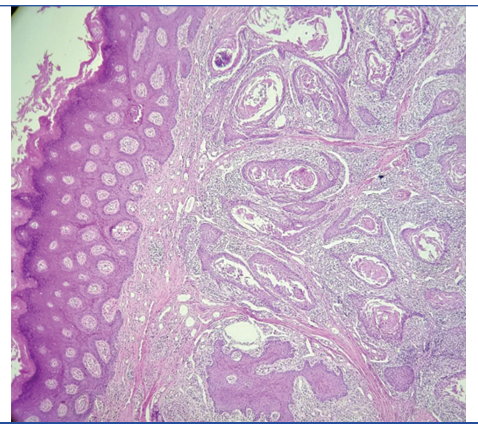
Gross examination revealed a skin-covered tissue bit measuring 2.4×1.8×1 cm. The skin showed focal erosions however well-defined ulceration was not seen. Cut section appeared greyish-white. Sections were taken from the margins and central part of the lesion, and the tissue was processed entirely. Slides were stained with Haematoxylin and Eosin (H&E).

Microscopic examination showed hyperkeratotic, acanthotic epidermis with focal erosions. The dermis exhibited irregular sheets and clusters of squamous cells, surrounded by a dense inflammatory cell infiltrate predominantly composed of lymphocytes. Numerous proliferating capillaries were also noted. Whorling by these squamous cells were noted [Table/Fig-1-3]. Individual cells had polygonal shape with ample amounts of eosinophilic cytoplasm. Intercellular bridges were noted at few places. The nuclei were ovoid to mildly pleomorphic, with vesicular chromatin and prominent nucleoli. Mitotic activity was not increased [Table/Fig-4]. Well-formed eccrine glands were not observed, although occasional lumen-like structures was noted [Table/Fig-5]. The sections from the surgical resection margin did not show the lesion, with the closest radial margin being 0.5 cm.

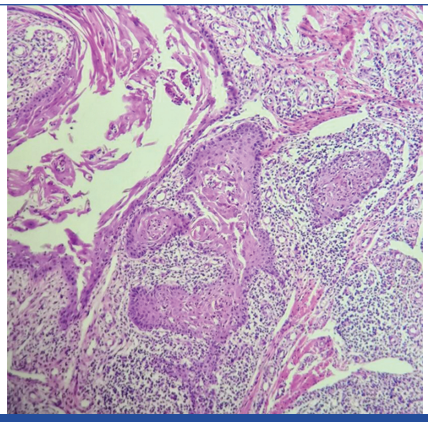
Based on the microscopic features, differential diagnoses of proliferative squamous lesions were considered. Benign lesions like pseudoepitheliomatous hyperplasia, infundibulocystic hyperplasia, and inverted follicular keratosis were ruled out on the basis of



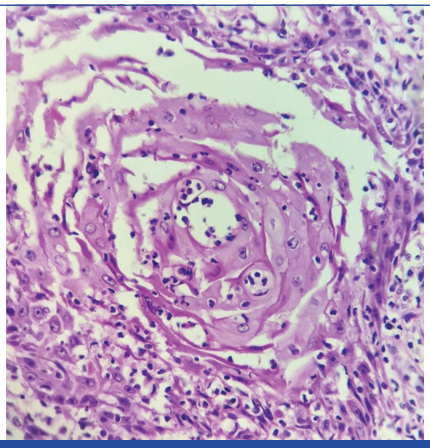
[Table/Fig-1]: Pseudoepitheliomatous Hyperplasia, eccrine ducts with squamous metaplasia (H&E stain; X100).



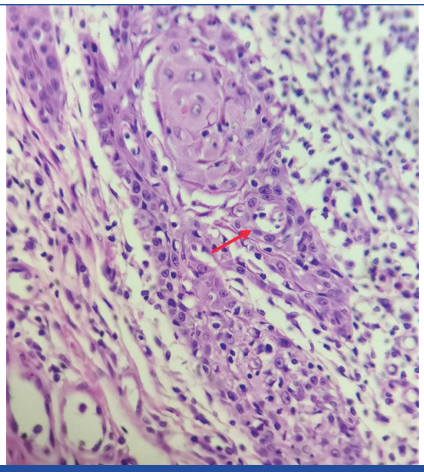
[Table/Fig-2]: Acanthotic epidermis and dermal eccrine squamous syringometaplasia (H&E stain; X100).



[Table/Fig-3]: Florid Eccrine Squamous Syringometaplasia (ESSM), metaplastic squamous lobules with irregular shape and dense inflammation; mimicking invasion (H&E stain; X100).



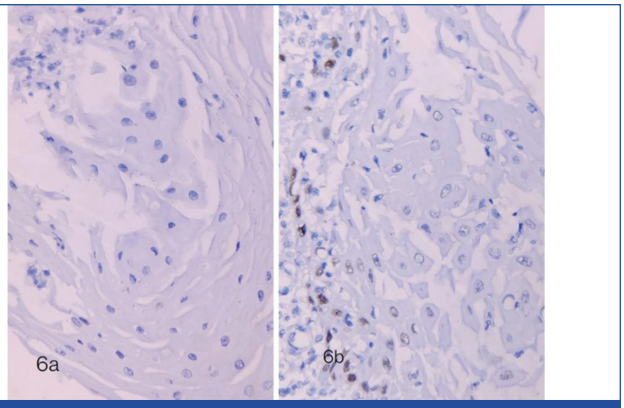
[Table/Fig-4]: Metaplastic squamous cells mimicking invasion (H&E stain; X400).



[Table/Fig-5]: Metaplastic squamous cell cluster with lumen-like structure marked by red arrow (H&E stain; X400).

epidermal findings. Among malignant lesions, SCC was considered but ruled out due to the absence of nuclear pleomorphism, individual cell keratinisation, keratin pearls, perineural invasion, lymphovascular invasion and mitotic activity. The presence of dermal nodules with a bland appearance and occasional lumina favoured the diagnosis of ESSM.

Immunohistochemical stains CAM 5.2 and p40 were performed, showing negativity in the metaplastic nodules [Table/Fig-6]. The diagnosis was primarily based on H&E morphological features and supported by Immunohistochemistry (IHC). As one can observe that there was marked acanthosis, hyperkeratosis, and dense mixed dermal inflammation, which were discussed with the clinician. However, the clinician attributed these findings as non specific dermatitis. Authors have been regularly following up with the case, and the lesion completely healed after a few months. It has not recurred after one year.



[Table/Fig-6]: 6a) Absence of cytokeratin CAM 5.2 staining; 6b) Absence of p40 staining in metaplastic squamous cells (immunohistochemistry, CAM 5.2 and p40 stain; X400).

DISCUSSION

Eccrine ducts and glands can undergo metaplastic changes due to various physiological and pathological stimuli [1]. Metaplasia is a benign adaptive cellular process where a different mature cell type replaces the original cell type [2]. The types of metaplasia noted in eccrine ducts are squamous, mucinous, and adenomatous [1-3]. Eccrine Squamous Syringometaplasia has been described in previous studies; however, florid ESSM is very rare [3]. In ESSM, the cuboidal lining of eccrine glands and ducts is replaced by keratinised squamous cells with moderate to abundant amounts of eosinophilic cytoplasm [1]. According to Gill P et al., the term "florid ESSM" should be used when both superficial and deep ducts/glands are involved, the glandular differentiation is minimal to absent, squamous metaplasia is present in more than 50% of the secretory coil, and keratinocyte clusters are forming nodules [3]. ESSM is one of the benign mimickers of SCC [4].

Eccrine Squamous Syringometaplasia is usually an incidental finding. Two types of ESSM have been described: the first type occurs in patients with a history of chemotherapeutic drug use or other therapeutic agents, and the second type occurs in patients without such a history [1]. Freeman RG has described ESSM as a type of pseudoepitheliomatous hyperplasia involving cutaneous appendages, while King DT and Barr RJ have considered them to be similar to salivary gland necrotizing sialometaplasia [5,6]. Patient did not have a history of drug use; he had a pruritic raised lesion over his right leg. As described in previous studies, extremities are the usual site for ESSM; however, involvement of the face, trunk, and external genitalia had also been noted [3,7].

The aetiopathogenesis of ESSM is controversial, and a few causes are noted in [Table/Fig-7]. Eccrine ductal epithelium can undergo reactive metaplastic changes in response to injury or inflammation [2]. Chemotherapeutic agents, other drugs, and certain inflammatory dermatoses can cause necrosis of ductal epithelium and induce

Non neoplastic	Neoplastic	Therapy-related
Ischaemia [1,3]	Syringoma [9]	Cisplatin [1]
Trauma, burns, radiation [1,3]	Chondroid syringoma [10]	Bleomycin [1]
Infectiouns e.g., Cytomegalovirus (CMV), Herpes Simplex Virus (HSV) [1]	Fibrous hamartoma of infancy SCC [1]	Cytarabine and other chemotherapy drugs* [1,3,7-9]
Inflammatory dermatosis e.g., Systemic Lupus Erythematosus (SLE), morphea, lobular panniculitis, pyoderma gangrenosum [1,3,7]	Keratinizing tumours like SCC, keratoacanthoma [1]	Tyrosine kinase inhibitors (imatinib, sunitinib), BRAF V600E inhibitor (vemurafenib) [1]
Graft versus host disease [1,3,7]	Syringotropic mycosis fungoides [1]	Non steroidal Anti-Inflammatory Drugs (NSAIDS) like pelubiprofen [8]

[Table/Fig-7]: Causes of Eccrine Squamous Syringometaplasia (ESSM).
*Carmustine, Cyclophosphamide, Daunorubicin, 5-fluorouracil, Doxorubicin, Etoposide, Methotrexate, Busulfan, Melphalan, Mitoxantrone, Suramin, Thiotepa, Tegafur

metaplasia [1,8,9]. Squamous proliferations are known to occur with the use of vemurafenib, and some drugs can indirectly activate the Mitogen-Activated Protein Kinase (MAPK) pathway and cause squamous proliferations [1,9].

Microscopically, florid involvement of eccrine glands by ESSM is rare, and in the presence of marked inflammation and reactive changes, it might be mistaken for SCC [3]. Tan KB et al., had described ESSM as one of the benign mimics of SCC on histology; however, the dermal squamous islands have a lobular configuration, connection to eccrine ducts, and bland nuclear features [4]. The present case showed a lobular configuration and proliferation in relation to eccrine ducts; however, mild nuclear atypia was present as a reaction to dense inflammation. According to Gill P et al., most clusters do not have paradoxical maturation; central polygonal eosinophilic cells are surrounded by basaloid cells, and SSCs have paradoxical maturation [3]. The presence of a lumen within the squamous islands also favours ESSM [1]; however, in present case, these features were relatively inconspicuous.

When eccrine ductal epithelium undergoes metaplasia, it loses immunohistochemical staining with CAM 5.2 [1]. The present case was also negative for CAM 5.2 staining. We also performed p40 staining (p40 is positive in SCCs), but the central cellular area with dermal squamous islands was negative for p40, while the cells in the peripheral part and basal layer of the epidermis showed positivity. This is likely explained by the metaplastic process involving these squamous cells rather than true neoplasia.

CONCLUSION(S)

Eccrine ducts and glands can undergo metaplastic changes in response to injury or therapy-related effects, which are increasingly common and reported more often due to recent drugs. On histology, florid ESSM can be mistaken for invasive SCC. The present case did not have a significant past history of medical or drug use. Such cases further increase the diagnostic dilemma if, the doctors involved in management are not well aware of this entity and its mimics. The present case highlights the significance of understanding the histopathological and cytological features of squamous proliferations and metaplastic changes.

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