

Non-Malignant Perineural Spread of Epithelial Tissue in the Orofacial Region

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Summary. A 48 year-old male had two operations because of severe neuralgic pains in the region of the right infraorbital nerve. The first operative specimen consisted of connective tissue, striated muscle fibers and two myelinated nerve bundles, surrounded by a ring of well differentiated squamous epithelium. Initially the lesion was assumed to show perineural spread of cancer in this region. As the pain was not alleviated, a second operation was performed. The framework of the second specimen also consisted of connective tissue and muscle. It contained in addition an atheromalike cyst and some nerve bundles, ensheathed by well differentiated epithelial cells partly in a ring-, partly in a horseshoe-like pattern. The perineural epithelial sheaths could be traced to a rupture of the cyst, and to benign proliferation of its epithelial lining in the connective tissue and along the nerve bundles. Following the second operation the patient was relieved of his complaints. During the last five years he had had repeated control examinations but no sign of malignant disease could be found; his state of health was perfect. Our finding of benign perineural spread of squamous epithelium has not been described previously. The nature of the so-called perineural lymph spaces is also discussed.

Key words: Perineural spread of cancerous and non-malignant epithelial tissue — Perineural lymphatics vs. perineural space.

Introduction

Among the histological criteria of malignancy cellular atypia and infiltrative-invasive growth are the most important features. Nonetheless, tumors are occasionally encountered with a marked cellular atypia which display a benign course clinically and biologically. The growth of tumor into adjacent tissues without biological malignancy is even a more unusual finding. A well-known example of infiltrative growth is the spread of tumors along the “perineural

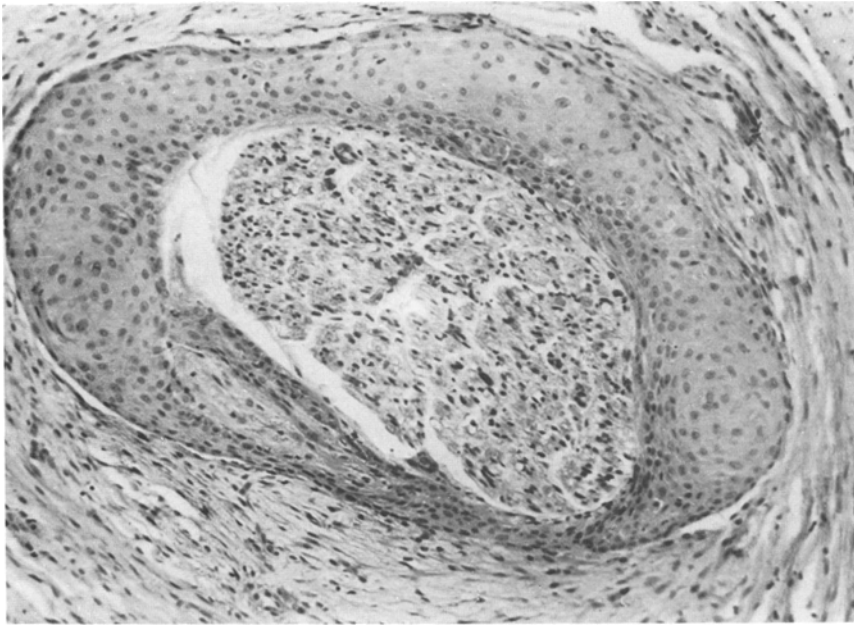


Fig. 1. Myelinated nerve bundle surrounded by a thick layer of squamous epithelium consisting of well differentiated cells

lymph spaces” first described by Ernst (1905). This often occurs in prostatic cancer and bronchogenic cancer of the hilar region, where the malignant character of the perineural spread is beyond question. There are, however, rare observations in which epithelial tissues spread perineurally in the form of small, compressed tubules. Perineural invasion was described in four instances of sclerosing adenosis among 316 breast biopsies by Davies (1972), and in two cases by Gould et al. (1975). These authors referred to analogous publications by Ackerman (1957) and Taylor et al (1967). In all these instances, follow up of patients with perineural spread of epithelial tissue in the female breast the lesion proved to be benign.

Case Report

A 48 y. old male was first admitted to the Dept. of Stomatology of our School in August 1971. He had had stinging, unbearable pains in the right upper half of the face for the last 6 weeks. From this quadrant several teeth were extracted without relieving his pain. On physical examination, a compact node of the size of a french-bean was palpated anteriorly to the infraorbital foramen. An upwardly convex shadow was seen at the base of the right maxillary sinus in an X-ray, this was presumed to be a tumor. To relieve his pain, the patient was given repeated bupivacain injections into the infraorbital canal without lasting improvement.

The patient was operated upon on August 17th. Having removed the facial bony wall of the sinus, a mucocoele was seen at its base. At the same time, an attempt was made to remove the previously described node lying anterior to the infraorbital foramen. Biopsies were taken (1) from the mucocoele of the sinus; (2) from the mucosa of its lateral wall; and (3) from the vicinity of the right infraorbital foramen.

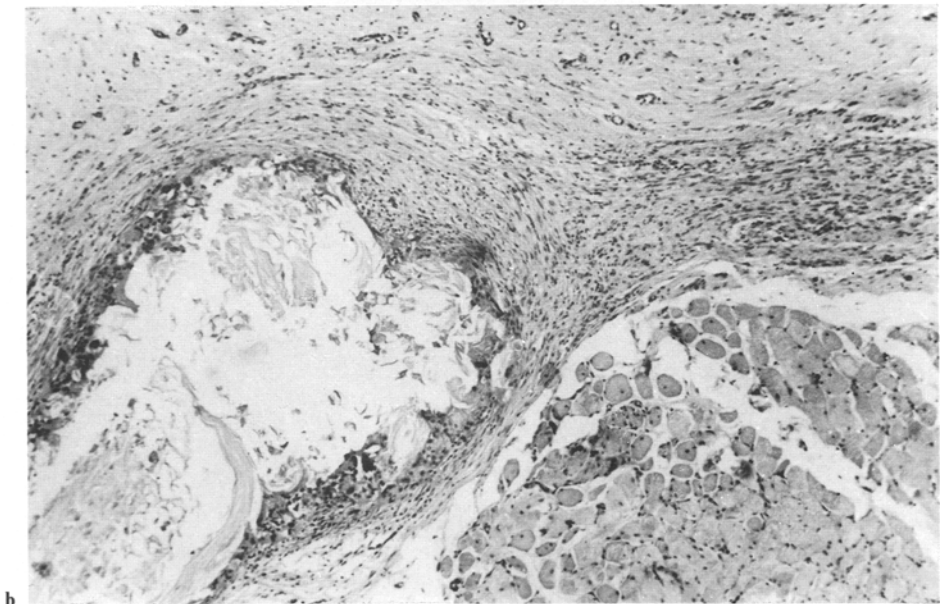
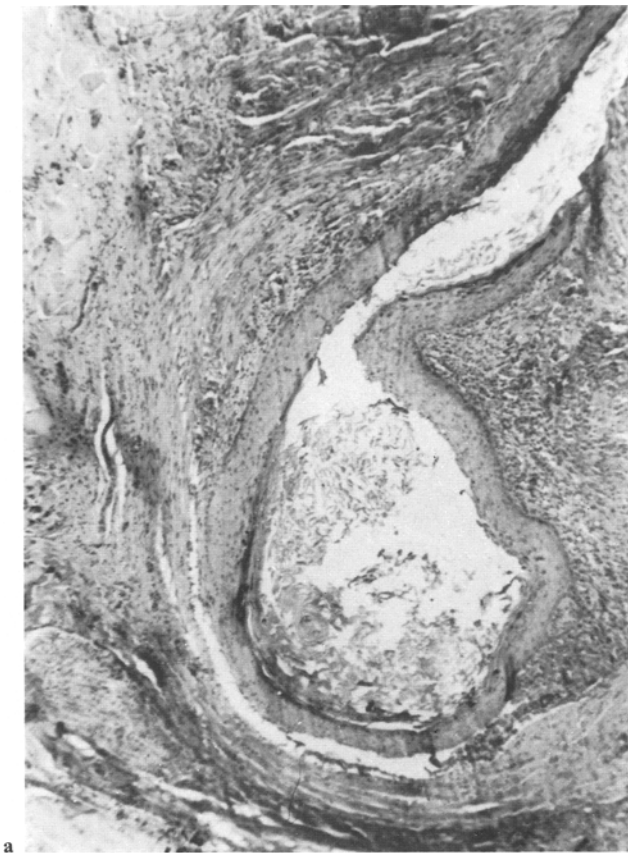


Fig. 2. a Atheroma-like cyst in the connective tissue lined by squamous epithelium, containing a lamellar keratinous mass. At the base of the cyst a small nerve bundle with a hairpin bend can be seen. **b** In the lower right corner striated muscle tissue, in the middle part a bifurcating nerve bundle. In the bifurcation loose horny mass, surrounded by multinucleated foreign body giant cells

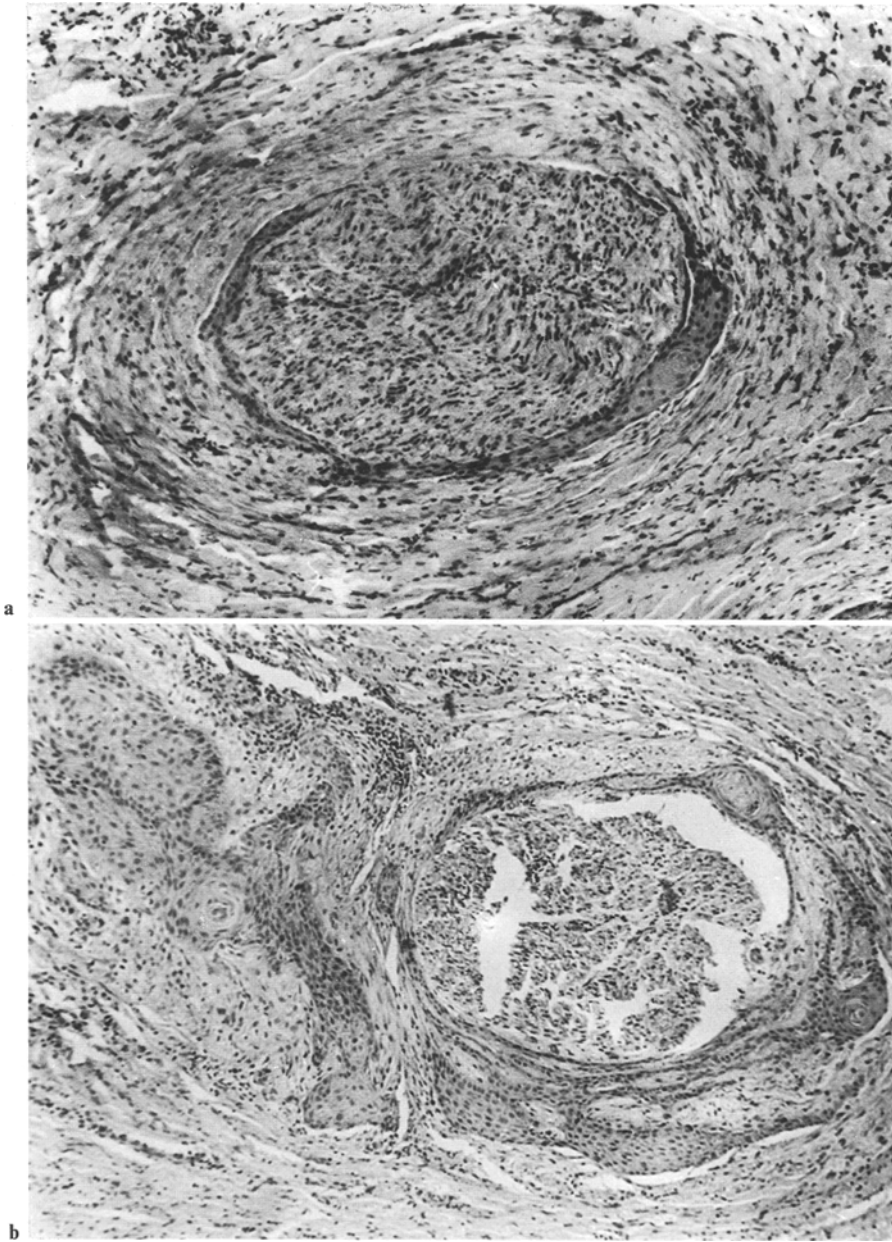


Fig. 3. a Small nerve bundle; only a part of its circumference is surrounded by a thin epithelial layer. **b** Irregular epithelial cell complex in the connective tissue, in direct contact with a nerve ensheathed by epithelium

Examined microscopically 1. and 2. consisted of edematous respiratory mucosa, with a mild degree of chronic inflammation in the submucosa, free from any sign of malignancy. Specimen Nr. 3. consisted of connective tissue with interspersed striated muscle bundles, cross sections of blood vessels and of bundles of myelinated nerve fibers. Two of these nerve bundles were surrounded, in a ring-like fashion, by a continuous layer of well differentiated stratified epithelium, the thickness of which varied between 2–3 to 12–16 cell layers (Fig. 1). In spite of the absence of cellular atypia, the pathologist on service, influenced by the frequency of perineural spread of carcinomas, suggested that the findings represented the spread of a primary cancer somewhere in this region. The absence of clinical signs of a tumor elsewhere in the body, and a more extensive study of the microscopic preparations lead us to change the first diagnosis and to declare that the findings represented the proliferation of benign epithelial tissue along nerve bundles.

Since the pains of the patient had not subsided and in order to look for a primary tumor a second operation was performed—with the removal of the palpable mass from the region of the right infraorbital foramen (in this instance via the skin). Macroscopically the subcutaneous mass looked like an atheroma, the contents of which were partly spilled during the surgery.

The cut surface of this material (20 × 15 × 15 mm) was brownish-red with a white center. The specimen was cut into three, and each was then examined histologically in incomplete sets of serial sections. The superficial layer consisted of adipous tissue, and the remainder mostly of striated muscle fibers. Besides an oval cavity was found lined by keratinized squamous epithelium containing loose keratinous material with a concentric structure. The lining epithelium was 8–16 cell layers thick with all of its typical strata. The borderline between epithelium and connective tissue was smooth; no papillary layer was present (Fig. 2a). Centrally, an area of cicatrizing connective tissue was seen with minimal chronic inflammation containing a few necrotic, calcified muscle fibers. In the preparations taken from the neighbourhood of this cyst, a horny mass of lamellar structure was found surrounded by multinucleated foreign body giant cells. This ovoid formation of microscopic size was contiguous with a bifurcating nerve bundle (Fig. 2b). At another site, in a rather circumscribed area two greater and two smaller nerve bundles were seen surrounded by squamous epithelium of varying width—partly in a ring-like fashion, partly in the form of open rings (Fig. 3a). These perineural epithelial sheaths consisted of highly differentiated cells with well discernible tonofibrils; a few abortive horny pearls were also seen. One of the epithelially ensheathed nerves was in direct contact with an irregular epithelial island situated in the connective tissue framework. This epithelial complex was built up of similarly well differentiated cells (Fig. 3b).

Discussion

Apart from the very rare occurrence of non-cancerous perineural invasion of the epithelium, the very nature of the so-called perineural lymph spaces requires clarification. In contrast to the generally accepted view of Ernst (1905), Ballantyne et al. (1963) considering cancers of the head and neck region displaying perineural spread, stated that these “lymph spaces” do not communicate with lymphatic vessels or with lymph nodes. No peri- or endoneural lymphatics could be demonstrated either in man or dog by Larson et al. (1966) in experimen-

tal and autopsy studies. The so-called perineural lymph sheaths should be correctly labelled "perineural spaces". The clinical importance of perineural tumor spread still remains, and it is well-known that malignancies may propagate along this route.

In our case the benign perineural epithelial proliferation may have started from the atheroma-like cyst. This, lined by squamous epithelium, might be due to a developmental anomaly, or less probably to an epithelial cell complex dislodged by one of the bupivacain injections. Two clinical points disprove the latter suggestion; viz. (1.) a nodule was palpated anterior to the infraorbital foramen before any injections were given, and (2.) the first injection given into the infraorbital canal preceded the first operation by only 5 days. During such a short interval neither an epithelial cyst nor an epithelial proliferation could have been formed.

If the first assumption is correct accidental disruption of the pre-existing cyst may have been due to a minor injury which escaped the patients notice. In this way, viable epithelial cells from the cyst's lining were pushed into the adjacent connective tissue, here they found a suitable ground for growth and later came into contact with the nerves of this region.

This explanation is supported by Figure 2b. It can be seen that a horny mass from the interior of the cyst getting into the adjacent connective tissue induced a foreign body giant cell reaction. The ousted horny mass is situated in the bifurcation of a nerve bundle. In Figure 3b, additionally, an irregularly shaped epithelial complex is clearly shown in the connective tissue, and its direct contact with a nerve bundle ensheathed by an epithelial ring is established. After making contact with the nerve the epithelium continued to grow along this route (Fig. 3a). The severe pains of the patient were probably due to the constriction of the nerves by the epithelial growth in the perineural spaces.

The benign character of the epithelial perineural proliferation is proved by the clinical course. In the five years since these operations the patient was kept under periodical clinical control; he remained free of subjective complaints and was able to do his physical work in good health.

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