LYMPHO-EPITHELIOMA OF THE PAROTID GLAND

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It has long been recognized that the region of the parotid gland is the site of a great variety of tumors of complex structure containing, for example, glands of various types lined with squamous, cylindrical, or flattened epithelium, large areas of small undifferentiated cells, which in general are considered to be remnants of aberrant parotid tissue, cartilage, and even, as Prudden has reported, striated muscle. The proportion of the solid and glandular structures varies greatly in different tumors. Some are composed almost wholly of glands lined with high cylindrical epithelium secreting mucus, the so-called cylindromata. In others the glands are lined with a flattened or indifferent epithelium, apparently not secreting much material. In this latter group may be placed the rare lympho-angiomas of the parotid. Another group is composed of the so-called adenolymphomas, containing cysts lined with high columnar epithelium and surrounded by lymphoid tissue (Fig. 1). True sarcomata, both of the lymphoid and spindle-cell type, are seen, and finally carcinomata may occur. Most of the latter are of the squamous-cell variety; some are adenocarcinomas with much mucus both in the primary growth and in metastases; others may repeat the undifferentiated type of cell which so often composes the ordinary mixed or complex tumors of the salivary gland.

The present paper is not concerned with any of the above groups, but with a variety to which attention was originally called in 1912 by Regaud, who later presented at the French Oto-Laryngological Congress a description of a tumor, which he had found to be highly radiosensitive, having a histological structure that he believed had previously been overlooked. "In this growth," he asserted, "there is a close and constant association between epithelial and lymphoid elements. This neoplasm might suitably be named lympho-epithelioma, which would remind us that it appears to arise from normal lympho-epithelial tissue."

The tumor described by Regaud had appeared in the hypopharynx. Shortly after his report, others, including Schmincke, described similar growths in the thymus and nasopharynx. In 1926 Jovin collected 8 examples which had been found in the cavities of the nose, mouth, and pharynx. All these tumors originated in what Jolly had designated as "lympho-epithelial organs," that is, structures in which there is a very close association between the cells of the epithelial investment and the lymphoid cells, as in the digestive canal, the thymus, and elsewhere. These cells "condense at certain points to form definite organic structures, as the tonsils or Peyer's patches; in fact, form a complete ring of small nodules covering the base of the tongue and the walls
of the pharynx. What characterizes these organs and distinguishes them from the purely lymphoid, such as the nodes and the spleen, is the participation of the epithelial investment in their formation."

It is through the elaborate studies of Jolly on the origin and growth of lympho-epithelial tissue that the general knowledge of those anatomic formations has been greatly widened, the histological structure of which is distinguished by this exceptionally close relation between epithelial and lymphoid cellular tissue. Regarding their histogenesis he writes:

"There first appears a more or less voluminous epithelial bud. This becomes the point of departure for a lymphoid infiltration of the adjacent tissues by elements of mesenchymatous origin, which are formed on the spot by the transformation of embryonic connective-tissue cells. The lymphoid elements thus produced break down the outer covering of epithelium and penetrate it. Thus is formed, in human beings, the palatine tonsil, which arises at the evagination of a branchial pouch, situated between the second and third branchial arches. This fact should be borne in mind, as it offers an explanation of the origin of lympho-epithelial tumors, of probably branchial derivation, in a region where there is normally no lympho-epithelial tissue.

These observations led Jolly to conclude that all the organs arising in this way present characteristics in common and that in the tonsils, the lingual follicles, adenoids, Peyer's patches, and the thymus gland, we have examples, growing progressively more complicated, of a symbiosis of lymphocytes and epithelial tissue which justifies their being called lympho-epithelial organs.

Building upon the histologic foundation which Jolly had provided, Jovin set out to examine a series of reported cases, with a view to establishing the prevalence of lympho-epithelioma among the relatively large number of new growths heretofore designated as carcinomas or sarcomas. Honsell, for example, among different varieties of epitheliomas had distinguished and discussed four cases diagnosed histologically as encephaloid carcinoma but from
the clinical point of view rather resembling sarcomas. These tumors showed cells with very large nuclei, collected in strands. Between the nuclei, which were exceptionally clear, connective-tissue elements were lodged. Tumors having these structural peculiarities regularly produced distant metastases, though not one of the other 60 carcinomas studied by Honsell metastasized at all.

It was the opinion of Dietrich that many of the sarcomas previously diagnosed as alveolar sarcoma were actually unrecognized lympho-epithelioma, and as such he classified the four growths described by Honsell. These observations convinced Jovin that growths found in the upper respiratory tract, in the intestine, and in the thymus gland were all of the same nature as those which had been previously designated as "mixed" tumors. The eight cases of lympho-epithelioma which he collected conformed to the description of lympho-epithelial growths given by Regaud, and were histologically identical with many of the new growths of the buccal cavity which had previously been designated as malignant mixed tumors. He thus eliminated "the idea that the growths arose because of a purely local relation between the lymphocytes on the one hand and ordinary epithelial structures on the other. On the contrary, it is impossible to escape the conclusion that special epithelial tissue, constituting a true histopathologic entity, takes its rise from the epithelial elements which are incorporated in normal lympho-epithelial tissue."

The eight cases which were studied by Jovin were all of tumors located in the pharynx, the tonsil, or the nasal cavity. Summing up their common histological characteristics, Jovin says:

"These growths are carcinoma composed of epidermal cells collected into strands, these cellular elements often showing little or no differentiation or evidence of being in the course of epidermoid evolution. The epithelial strands or cords are surrounded by leukocytes, which have reached the interior by passage through the surrounding stroma, and will be found ranged with considerable regularity between the ranks of the epithelial cells."

Elsewhere Jovin says:

"These trabeculae are always composed of two kinds of cells in association; one sort distinctly epithelial; the others having the characteristics of lymphocytes. The epithelial cell elements are more voluminous, their protoplasm is not sharply delimited, so that they frequently form a syncytium. The nuclei are clear, poor in chromatin, their contours very distinctly lobulated and marked off. They always contain one or two large nucleoli. Mitotic figures are frequent.

"Side by side with these epithelial cells, the second element—the lymphocyte—is constantly found. These can be clearly distinguished, even under low magnification, by nuclei rich in chromatin which occupy practically all of the cell. These cellular elements are very irregularly distributed in the interior of the epithelial trabeculae. The number of lymphocytes, in proportion to the epithelial element, is extremely variable. There are scattered areas where the lymphoid elements predominate (although these are relatively rare), so there is but a vague trace of the epithelial structures. Other areas are almost denuded of lymphocytes, and it is in these that one has an opportunity to examine the epithelial structural framework. Often the lymphocytes will form little nests consisting of four or five elements—veritable intra-epithelial globes. The lymphocytes may also be observed in the process of transition and migration, elongated and more or less detached. In general, the proportion is of one lymphocyte to two epithelial nuclei.

"In addition to small lymphocytes, there may sometimes be encountered, embedded in the interior of the trabeculae, polynuclear eosinophiles and very exceptionally, plasma cells as well."
"The connective-tissue stroma which separates the layers of epithelium is rich in cellular elements, some of which are fixed connective-tissue cells, while others are mobile—lymphocytes, polymuclear neutrophiles, eosinophiles, plasmocytes and sometimes, mastocytes. In this varied infiltration of the stroma there is one constant element which always predominates—the lymphocyte. The boundaries between the epithelial strata and the connective tissue are not always clearly defined; yet there is no interlacing of the connective-tissue elements and the epithelium, for the cords are always recognizable even under very low power, even though they are not always separated by any membrane or other limitation.

"At the periphery of the trabeculae, in the zone of extension, invasion takes place by infiltration; there one occasionally encounters connective fibers and fibroblasts between the epithelial cells. Usually there will be no trace of vessels nor of connective fibers in the interior of the trabeculae.

"This close and constant association between two diverse elements, one epithelial and the other lymphoid... does not constitute a complex epithelio-sarcomatous neoplasm, but rather a pure carcinoma, having as a special characteristic, a peculiar attraction for lymphocytes. This affinity becomes evident in those growths where the inter-trabecular stroma contains polymorphous and leukocytic elements. It can be noted then that lymphocytes alone—or at least a vast preponderance of these cells—penetrate the epithelial structures...

"But when one comes to attempt to explain the affinity which these lymphocytes have for epithelial tissue, as a sort of tropism which the epithelial elements exercise upon the lymphocyte, it is even more difficult to establish in the case of neoplastic growths than it is when considering normal tissues. We can only assert that we have found—in certain special types of carcinomas—the same phenomenon we have previously seen in new growths located elsewhere—the persistence of a property characteristically peculiar to the tissue of origin. In the growth we are now discussing this property consists in symbiosis with lymphocytes."

In a later survey, F. Skorpil reported three examples of lympho-epithelioma of the tonsil; he regarded one of Jovin's cases as belonging to this group and mentioned a similar tumor described by Egli in an Inaugural Dissertation from Basle in 1930. He thinks that Case 2 in the paper of F. Stöhr and E. Risak should be classified with the lympho-epitheliomas of the tonsil, and not as a lymphadenoma, as Stöhr and Risak designated it. This brings the number of reported examples of this tumor of the tonsil to six. Skorpil also saw in the collection of Professor Konschegg of Graz an unpublished case. A case of lympho-epithelioma of the parotid gland is reported here.

Case Report

The patient was a white woman, aged twenty-eight, who for the past five years had had enlargements of both parotid glands. These were rather nodular to the touch and diminished in size from time to time.

The patient's past history is of little significance, except that she recalled as a child having had acute pain in both parotid glands after drinking pineapple juice. At eleven years of age she had mumps and a complicating left mastoiditis which was operated upon. She made an uneventful recovery and no enlargement of the parotid glands was observed until September, 1934. The swellings of the glands at this time were attributed to a "cold" and subsided in a few days. The patient stated that subsequently enlargement of the parotids occurred and subsided frequently. In the fall of 1935 she was observed for several weeks, x-ray studies were made, and she was told that there were small stones in both glands. No biopsy was done at that time.

In April 1938, both parotid glands were moderately swollen, and there was also an enlargement of both submaxillary glands. On the right side was a cervical lymph node which was hard and about the size of a small egg. The tonsils were enlarged and congested. The patient was given some short-wave treatments which decreased the swelling of both parotids. Shortly after one of the treatments there was a profuse drainage from the right parotid with
relief of the pain and a decrease of the swelling. The tonsils were removed, and the pathologic report was chronic hypertrophic tonsillitis with an acute lacunar process. At the same time a biopsy was taken of the enlarged cervical lymph node. No other lymph nodes could be palpated, and the spleen was not enlarged. The lacrimal glands were not enlarged.

Radiation therapy was instituted, and at the time of this report both parotids are normal in size, and the cervical lymph nodes are reduced in size.

Small pieces of tissue which were taken from the lower pole of the parotid gland present a finely granular, pinkish surface with several cysts in the peripheral portions which contain serous fluid. Microscopic examination shows a growth composed of syncytial masses of large polyhedral cells with large nuclei that are hyperchromatic and show a few mitoses (Fig. 2). These neoplastic cells are embedded in lymphoid tissue surrounding the acini and ducts (Fig. 3). The ducts are probably the remnants of the original parotid tissue left in situ. Neisse has found in the fetus that areas of lymphoid tissue are present in the parotid region which contain well marked ducts. Large cystic spaces are present, and these are walled-off by the tumor cells. There is a lymphocytic infiltration throughout.

**Summary**

To the small group of lympho-epithelial tumors another example has been added. These tumors are of great interest because in many instances they are radio-sensitive, as was first pointed out by Regaud. There is no question, however, that they vary greatly in their malignancy. The case recorded here is
FIG. 3. LYMPHOID STRUCTURES WITH PAROTID TUBULES AND AN AREA OF TUMOR. X 300

FIG. 4. SYNCYTIAL MASS UNDER HIGH MAGNIFICATION, SHOWING LYMPHOCYTIC INFILTRATION BETWEEN LARGE POLYHEDRAL CELLS
probably one of the more or less benign forms. Skorpil believes that one case of Jovin's and two of his own belonged in the malignant group, and that the rest are of a very slow-growing type and may be cured by relatively small doses of x-ray.

References