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PATHOLOGY OF MUCOUS AND SALIVARY GLAND TUMOURS IN THE LACRIMAL GLAND AND THE RELATION TO EXTRA-ORBITAL MUCOUS AND SALIVARY GLAND TUMOURS*†
(Studies on Orbital Tumours—3)

BY

ERIK GODTFREDSEN
COPENHAGEN

Introduction

Mixed tumours of the mucous and salivary gland types having recently been submitted to thorough revising investigations in Scandinavian literature (Therkelsen, 1934, Ahlbom, 1935, and Ringertz, 1938), the experiences from these investigations will be compared here with those gained from a series of cases of mixed tumours in the lacrimal gland. No studies of this kind are available, and histopathological parallelism does not a priori mean biological parallelism.

Previous investigations into lacrimal gland tumours

The lacrimal gland tumours constitute about one-fourth of the comparatively rare orbital tumours (Birch-Hirschfeld 30 per cent., Sattler 25 per cent., and Godtfredsen 20 per cent.). The experience gained by the individual observer is, therefore, limited. The literature is chiefly casuistic or compilatory. Thus Warthin collected 132 cases (the literature up to 1901) and Lane 112 cases (the literature up to 1922). Scandinavian communications are scarce (Ehlers and Okkels, 1931).

The value of these papers is reduced by the heterogeneity of the different writers' histopathological estimations based on different views, particularly concerning the histogenetic conditions (ectodermal, mesodermal, or "mixed" genesis). The same heterogeneity prevails in the text-book literature (Meisner and Birch-Hirschfeld in Schieck and Brückner's text-book, Seidel and Peters in Hencke and Lubarsch's text-book).

The histogenetic conditions will not be discussed in detail, only it should just be mentioned that, according to the modern, revised view the genesis of mixed tumours is now regarded as purely

* Read before the XI Scandinavian Congress for Ophthalmologists, Oslo, June, 1947. The work carried out with financial support from Landsforeningen til Kæmpelse.

† Received for publication: October 27, 1947.
ectodermal (or epithelial), (Ahlbom, Ewing, Kreyberg, Ringertz, Therkelsen). The apparently "mesenchymal" elements of the mixed tumours (fibrils, hyaline cartilage formation, etc.) are not mesodermal but ectodermal products of the epithelial cells which to a great extent undergo metaplasia, a.o. to squamous epithelium. The tumour-proliferating epithelium may, moreover, present all transitional forms from benign to malignant. These facts explain the great variations in the nomenclature (chondro-myxo-sarcoma, angio-reticulo-fibro-epithelioma, endothelioma, adenoid carcinoma, etc.). The term mixed tumour, now current in the literature and also used here, is thus actually inadequate, meaning strictly a tumour developed from different germ layers.

A clinically and histopathologically homogeneous impression from the literature is, therefore, out of the question. The frequency of malignant cases is difficult to estimate. Lane's report gives an approximative impression: Of 95 cases 12 died of the disease. There was recurrence in 20 per cent. and metastases occurred in 7 cases.

**Main features of biology of extra-orbital mucous and salivary gland tumours**

A number of biological main features, of importance for the present study, from the recent Scandinavian investigations into mucous and salivary gland tumours will be briefly summed up. The mucous and salivary gland tumours belong to the comparatively rare forms. They occur most often in the large salivary glands (parotid and submaxillary), where most of both Ahlbom's 254 cases and Therkelsen's 74 cases were localized. Each of these two series—collected over 24 and 20 years respectively—contained only one case of tumour in the lacrimal gland. Mucous and salivary gland tumours, developed from the glandular elements of the mucous membranes in the nose and paranasal sinuses, constituted 10 per cent. of Ringertz's 352 malignant cases. Localisation in the nasopharynx is rarer, constituting only about 1 per cent. of the malignant tumours here (5 of Godtfredsen's 432 verified cases, 1944). Confusion with parotid tumours is possible in these cases (Godtfredsen, 1947).

Mucous and salivary gland tumours may occur at any age, and there is no significant difference in sex. The past histories extend on an average over 2 years.

The histopathological main feature is the arrangement of the epithelium in alveolar groups, cords, or islands with an often considerable production of mucus extending partly into a central lumen in the alveolus and partly intracellularly and centrifugally,
thus causing bursting of the cell groups—and myxomatous degeneration. In addition to mucus the epithelial cells produce fibrils and hyaline substance, and different stages of hyaline cartilage formation may occur.

There are two histopathological main types: the fibro-myxo-epithelioma and the basalioma, which may both be either benign or malignant. Often there occur transitional forms, and even different phases within one tumour, so that the differential diagnosis may be difficult or impossible to make. The benign fibro-myxo-epitheliomas are characterized by copious mucus formation and an intact capsule (Fig. 1), whereas the malignant form presents a greater abundance of cells, polymorphism, numerous mitoses and metaplasia, as well as penetration through the capsule.

The basaliomas, whose name is due to the histopathological resemblance to the basal cell cancer of the skin, differ biologically very much from the torpid skin cancer by being highly malignant.

**Fig. 1.**

Fibro-myxo-epithelioma of benign type from the lacrimal gland of a man, aged 25 years (case 98), where the general picture (to the left) shows the heterogeneous structure with alveolar epithelial cell groups and fibrillar tracts, while the increased magnification (to the right) reveals intracellular myxoma formation and myxomatous degeneration.
The basaliomas have a cystic and a solid form, which may both be benign as well as malignant. The cystic forms, called also cylindromas, present well-pronounced, mucus-filled cavities surrounded by from 1 to 5 layers of cubic cells (Fig. 2). The solid forms are richer in cells and the cavity formation minimal or absent. The cylindromas are highly malignant despite inconsiderable nuclear atypia and polymorphism. The same has been observed, though rarely indeed, in other tumour forms (chondromas, plasmocytomas, etc.).

Fibro-myxo-epitheliomas occur more frequently (Ringertz 62 per cent., Ahlbom 73 per cent.) than basaliomas (Ringertz 33 per cent., Ahlbom 17 per cent.). Malignant cases are more frequent than benign. Infiltrative growth and metastases were observed more often by Ahlbom (33 per cent.) than by Ringertz (16 per cent.). The incidence of recurrence was found to be 40 per cent. (Ringertz).
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The principles of treatment consisted mainly in operation and irradiation, either separately or combined. The results were best in the cases of nasal and paranasal tumours, where Ringertz found a 5-year-cure-rate in 50 per cent., while Ahlbom found a 5-year-cure-rate in 25 per cent. of his cases of tumour in the large salivary glands. The radio-sensitivity corresponded to that of squamous cell carcinomas of low differentiation. In particular the cylindrmas were radiosensitive.

Own investigations

The present investigation was based on cases of mixed tumours in the lacrimal gland observed in the Eye Department of Karolinska Sjukhuset, Stockholm, within the 15-year-period 1932-46. 78 cases of orbital tumour were admitted within this period, of which 52 were verified as proper tumours, while 5 histologically were pseudotumours, and 21 not verified. Of the 52 proper orbital tumours 36 were primarily orbital with the following points of origin: most often the lacrimal gland (18 cases, of which 10 mixed tumours and 8 lymphomatosis cases); next followed the nerves—including the optic nerve (8 cases), the skeletal parts (6 cases); more rarely vascular elements (3 cases) and dermoid cyst (1 case). (For further particulars concerning this series vide Godtfredsen, 1947.)

The data of the 10 cases of mixed lacrimal gland tumour appear from Table I, on which no detailed comments will be made. Only it should just be mentioned that exophthalmos (6 cases) predominated among the initial symptoms, while visual impairment (2 cases), ptosis, and metastatic cervical glands (1 case each) were rarer. On admission there was in each case found a from pea- to almond-sized palpable tumour in the lacrimal gland of a semi-solid or hard consistence with varying nodular surface. The exophthalmos ranged from 2 to 13 mm. (Hertel). The visual impairment (in 7 patients) was often considerable, without or with attending ophthalmoscopically ascertained choked disc (2 cases) or stasis of retinal veins (1 case). X-ray-verified bone destruction was ascertained in only one of 7 examined cases (localized in the orbital apex). Metastatic lymphatic glands were found in 3 cases, partly preauricularly (1 case) and partly in homolateral cervical glands (2 cases).

Histopathological diagnoses were made partly on biopsy samples, and partly on totally excised tumours, and special staining was carried out to the necessary extent. All the preparations were revised. Histopathological distribution, fate of patients, results of treatment, etc., will be discussed below.
<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age</th>
<th>Symptoms, nature, durat. (mths.)</th>
<th>Ophth. find.</th>
<th>Histopath. diagnosis's</th>
<th>Treatment</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Exophthalmos in mm.</td>
<td>Vision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>51</td>
<td>Exophthal. (36) Loss of vis. (3-4)</td>
<td>10</td>
<td>0'4</td>
<td>Fibro-myoepithelioma (benign) do.</td>
<td>Krönlein</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>54</td>
<td>Exophthal. (24)</td>
<td>10</td>
<td>0'1</td>
<td>do.</td>
<td>Krönlein + radium</td>
</tr>
<tr>
<td>98</td>
<td>M</td>
<td>25</td>
<td>Ptosis (18) Exophthal. (4)</td>
<td>3</td>
<td>1'0</td>
<td>do.</td>
<td>Excision + X-rays</td>
</tr>
<tr>
<td>66</td>
<td>M</td>
<td>23</td>
<td>Cerv. gl. (48) Exophthal. (8)</td>
<td>9</td>
<td>0'4</td>
<td>Fibro-myoepithelioma (malignant) Basaloma cystic</td>
<td>X-rays</td>
</tr>
<tr>
<td>26</td>
<td>F</td>
<td>58</td>
<td>Exophthal. (36) preauric. gl. (1)</td>
<td>6</td>
<td>0'2</td>
<td>1/ X-rays 2/ Evisc</td>
<td></td>
</tr>
<tr>
<td>105</td>
<td>F</td>
<td>38</td>
<td>Exophthal. (3)</td>
<td>8</td>
<td>0'5</td>
<td>do.</td>
<td>X-rays + evisc.</td>
</tr>
<tr>
<td>106</td>
<td>M</td>
<td>36</td>
<td>Loss of vis. (12) Exophthal. (1)</td>
<td>7</td>
<td>0'1</td>
<td>do.</td>
<td>do.</td>
</tr>
<tr>
<td>89</td>
<td>M</td>
<td>74</td>
<td>Loss of vis. (?) Cerv. gl.</td>
<td>12</td>
<td>perc. of light</td>
<td>Solid basalioma 1/ X-rays 2/ Evisc</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>72</td>
<td>Exophthal. (11)</td>
<td>7</td>
<td>1'0</td>
<td>Basalioma? Sarcoma? Evisc. + radium</td>
<td></td>
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</table>
Discussion

Although the present series of mixed lacrimal gland tumours is fairly small it possesses certain advantages over those collected by Warthin, Lanè, a.o., the present series being homogeneous with regard to revising histopathological estimation and principles of treatment. The patients were furthermore followed up in accordance with the follow-up system of Radiumhemmet. The histopathological estimation was made on modern principles indicated by Therkelsen, Ahlbom, and Ringertz. Accordingly a comparison with the experiences of these writers concerning extra-orbital mixed tumours is very perspicuous.

Of the orbital tumours, constituting about 1 per cent. of the cases admitted to eye departments of any size, only one-eighth are mixed tumours in the lacrimal gland (10 out of 78 cases in the present investigation). These latter tumours constitute an even smaller proportion of the entire number of mixed tumours ( 1/8 to 1 per cent. according to Therkelsen and Ahlbom).

Histopathologically my own 10 lacrimal gland tumours were distributed like the extra-orbital mixed tumours (Ahlbom, Ringertz), 5 being fibro-myo-epitheliomas, one of which was malignant, and 4 (perhaps 5) basaliomas, of which 3 were cylindromas and all were malignant. In one case the differential diagnosis between basalioma and sarcoma of low differentiation was uncertain.

The incidence of malignant cases on the basis of histopathological criteria (6 out of 10 cases) corresponds to that indicated by Ahlbom (60 per cent.) and Ringertz (72 per cent.), but does not accord with the biological malignancy. From a biological point of view nearly all lacrimal gland tumours are malignant, since the tumour proliferation or the resulting exophthalmos has a deleterious effect on the optic nerve and/or retinal vessels. The vision was unaffected in 3 cases only. Recurrence despite histological benignity occurred in two cases (2 and 36 months respectively after the treatment).

A comparison between the clinical data of the present 10 cases of mixed lacrimal gland tumours and the symptomatology of the extra-orbital mixed tumours shows a rather close accordance with regard to length of past history, age incidence, regional lymphatic gland metastases, and frequency of recurrence.

Although the lacrimal gland tumours are rather superficial and fairly easy of access for both surgical and radiological treatment, the results of treatment are poor. Despite tumour excision with or without irradiation, only 5 of the present 10 patients were found alive, one with recently ascertained recurrence, and the others after
fairly short periods of observation (4 to 24 months). Two of these 5 cases were histo-pathologically malignant.

The tendency of the tumours to spread appears from the fact that distant metastases were observed in two of the deceased, malignant cases (brain and lungs).

Three of the deceased, malignant cases showed that malignant tumours may be radiosensitive, since irradiation brought about freedom from symptoms for from 14 to 36 months.

In point of prognosis the lacrimal gland tumours resemble the large salivary gland tumours (notably the parotid tumours), where the prognosis is worse than for tumours proceeding from glandular elements in the mucous membranes of the nose and paranasal sinuses (5-year-cure-rate for 25 per cent. and 50 per cent. respectively). That the lacrimal gland and the parotid gland as the only purely serous tubulo-alveolar glands of the body also present pathological points of resemblance is perhaps due to the parallelism in anatomical structure.

Conclusion

The mixed lacrimal gland tumours were previously regarded as histologically and biologically very polymorphous tumour forms. However, the present investigation, based on modern histological criteria, shows that the morphology is simple and that the lacrimal gland tumours resemble, histologically as well as biologically, mucous and salivary gland tumours in other regions, both those in the large solitary salivary glands and those proceeding from mucous membrane elements (Therkelsen, Ahlbom, and Ringertz).

After a clinical diagnosis of lacrimal gland tumour, the symptomatology of which is often simple, it is necessary to have the nature of the tumour ascertained as soon as possible by histological examination of a biopsy specimen, the result of which is decisive for the principles of treatment. If microscopy shows the tumour to be a basalioma it is practically always malignant, whereas the fibro-myxo-epithelioma is most often benign. Biopsy should be omitted only in obviously malignant cases (metastases, bone destruction).

The principles of treatment, settled in concert with Radiumhemmet, are as follows: for benign tumours excision either by Kroenlein's operation or by anterior orbitotomy, and for malignant tumours pre-operative X-ray treatment (4-5,000 r.), and 1 month later evisceration of the orbit. Evisceration should not be omitted even if the tumour responds favourably to irradiation (as in 2 of the present cases), because the chance of recurrence is great. Both of the above cases relapsed promptly.
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Despite the poor results of treatment in the present series it must be emphasized that more exact diagnosis (biopsy of all suspicious tumours) as well as intensified and earlier instituted treatment would no doubt improve the chances for these patients. The histopathological and biological parallelism demonstrated here between mixed tumours in and outside the lacrimal gland suggests that it should be possible to bring the results of treatment to the same level.

Summary

The literature on lacrimal gland tumours (most of it casuistic or compilations) is not up to date regarding modern histological classification. The biology and modern histological aspects of extra-orbital mucous and salivary gland tumours are briefly summed up. Next a comparison is made between these tumour forms and the lacrimal gland tumours of mixed type. (Own investigations from 10 cases histologically revised and followed-up.) It appears that there is a pronounced parallelism both histopathologically and biologically.

REFERENCES


