COMMUNICATIONS

TWO UNUSUAL SCLERO-CORNEAL NEOPLASMS*

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True tumours of the sclera (if they in fact exist) are rare. Doubt has been cast by later investigators on most published cases.

Ginsberg, in his critical review of 1928, declared for instance that their existence must be regarded as unproven.

Fibromata are scarcely distinguishable in many cases from chronically inflamed tissue, in particular from keloidal scarring. The diagnosis of a true blastoma is also very difficult. If we except limbal melanomata and growths arising from corneal epithelium, the same is true of the cornea. Limbal swellings as a rule are neoplastic.

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In general, a neoplasm composed of cells of a mature type is regarded as less malignant than a tumour with little connective tissue, and densely packed nuclei varying in size and shape, and with many mitoses.

Experience shows that the clinical course is not always correctly prophesied by the findings of biopsy. Modern cancer research has provided new facts whose clinical bearing cannot be disregarded, although divergent conclusions have been based upon them.

Cancer is a biological problem, and a purely histological investigation may be regarded as inadequate in the days to come. It is possible we have overlooked a rare opportunity in the two following cases:-

**Case I**

Geoffrey H., aged 15 years—A tumour resembling a phlycten was observed on the right limbus at 11 o'clock. It increased rapidly in size over two weeks.

The growth (Fig. 1a and 1b) was yellowish, painless, hard, and restricted to the quadrant shown. The overlying conjunctiva contained dilated vessels, and was freely movable.

The vision and the eye otherwise was absolutely normal. General examination, the Wassermann and Mantoux reactions, were negative.

As the swelling doubled in size in five weeks it was removed locally and sectioned. Biopsy, July 4, 1946—The tumour 3·5 mm in diameter was fixed in formalin and embedded in paraffin. The tumour mass of tissue is partly covered by normal epithelium, the basal line of which is infiltrated with polymorphs, lymphocytes,
and many plasma cells. The major part of the tissue consists of spindle cells whose fibres cross each other and enclose a considerable number of blood vessels (Fig. 2).

The nuclei being oblong are distributed unevenly. The densest area is central, the nuclei being more sparse in the periphery. The nuclei show very few mitoses, but are variable in size and shape. There is no pigment. Certain clear spots may correspond to myxomatous and others to fatty changes. At the edge of the sections fatty tissue is actually present. Leucocytes are seen around vessels in places in considerable numbers.

We concluded from this that the tumour was a spindle sarcoma of low or moderate malignancy, though the unequal density of the tissue was rather striking.

After local excision the remaining tumour tissue continued to increase in size, contrary to the prognosis given above, and the eye was therefore excised ten weeks after the original biopsy, and fixed in formol-saline.

The Excised Eye

The eye was sectioned equatorially and the ciliary surface of the tumour area examined by the slit-lamp (Fig. 3).

The entire retinal periphery within 6mm. of the ora serrata displayed a continuous wavy bluish white appearance. No nodules were visible. This colour change was most marked at the ora serrata underlying the tumour area, where the crests of the arcades are intensely whitish and convoluted, and can be traced over the surface of the ciliary body as far as the ciliary processes.
There is little doubt that this is a continuation of the whitish layer on the peripheral retina.

Among the large portion of conjunctiva deliberately excised with the eye, can be seen a normal palpebral lacrimal gland with one duct. The vessels are congested, and there is diffuse plasmocellular infiltration.

This swollen infiltrated conjunctiva has grown over the peripheral cornea, and overlaps the un-infiltrated part of the cornea (Fig. 4).

There is no definite boundary between the inflamed tissue, and the tumour infiltrating the outer third of the cornea and sclera.
FIG. 3.
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The tumour infiltration extends about 1.4 mm. from the limbus into the cornea, and remains localised to the outer lamellae. The limit of the tumour on the sclera is ill defined. It is impossible to define where the new growth in the sclera ends, and inflammatory tissue reaction starts.

The nature of the tumour coincides with the biopsy specimen, though the crisscross pattern of the spindle cells is less regular, and there are no more lymphocytes round the vessels. Pyknosis is frequent.

**Fig. 5.**
Medium power (appr. 150X) from Fig. 4X.

**Fig. 6a.**
Thionin staining at iris root. 1000X approx. Mast cells and free mast cell granules.
Giemsa staining — Mast-cell granules and mast cells in the outskirts of the tumour. (300 × approx.)

The fibres of the spindle cells are a greyish pink, and the intact scleral fibres with which they interlace eosin red. The photomicro does not show this colour contrast vividly in the specimen. Here and there are syncytial aggregations of ten and more nuclei, strongly suggestive of giant cells. They are located around small vessels at the edge of the growth.

Few pigment granules are seen in the trabeculae of Schlemm’s canal. There is a slight eversion of the pigment epithelium, and no inflammation of the iris. The retina is, especially in its anterior part, covered by an attenuated, much convoluted layer, containing fibrils, red blood corpuscles, and fine pigment granules. It corresponds with the curled threads (Fig. 3), and is unconnected with clearly seen glassy zonula fibres.

There are an unusual number of mast cells in the iris and ciliary body, and underlying the tumour area, less frequent in the choroid. Their granules are metachromatic, and well marked with Giemsa, Leishmann, methylene-blue, but are also recognisable with Van Gieson, haematoxylin-eosin, Mallory and Masson. In contrast to the usual lobate or kidney-shaped nucleus the nuclei are here round or oval, and the cell diameter 10-14 μm, against the usual average of 8-10 μm. (Whitby & Britton, 1946).

Typical fibroblasts are visible in the growth packed with small metachroic granules.

Discussion (Case I)

The growth consisted of mature cells. The concentration of the nuclei was unusually variable, being diffuse in the periphery and concentrated in the centre.
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The tumour infiltrates the sclera, and has no clear line of demarcation, so that even at the centre of the growth area the tumour cells are seen in the interstices of normal scleral fibres, an unusual appearance in typical malignant new growths of this area. The nuclei at the periphery of the growth assume groupings, suggesting giant cells in many places.

Masses of mast cells spread into the uvea from the tumour area.

If we add to these findings, the clinical facts that the growth was hard in consistency, painless, and rapid growing, it is not easy to classify it as a common mesodermal malignant blastoma, and casts doubt on our original diagnosis, which led to excision of a functioning eye.

It is true that the clinical appearance primarily led to this decision, but even after careful histological investigation it is difficult to "type" this growth with certainty.

Obviously it is not an infectious granuloma, nor a keloidal formation; certainly it is not a scleritis.

Our impression is of a tissue reaction to an agent, which unlike most pathogenic organisms does not produce cellular destruction but cellular division (Borrel).

Rous, in 1910, was the first to describe a tumour which was a transmissible and filterable sarcoma of chickens, followed by Fujinami and Unamoto in 1911, with their myxosarcoma. No tumours of this type have been described as yet in man.

Assumption of a virus aetiology would explain why the mode of

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**Fig. 7a.**

Rous's sarcoma. H.E. 60X. Strands of tumour tissue growing between healthy muscle tissue.
growth in our case differed from the picture we are used to find in a true blastoma of this region.

On studying the slides of two virus tumours, a Rous sarcoma and a Fujinami tumour, by the kindness of Dr. Peacock, I (A.L.) was amazed by the mode of infiltration of the new growth which splits normal muscular tissue by many tumour strands. We have found no mast cells in Giemsa stained slides—but have no information about the occurrence and behaviour of this cell form in birds.

Proof of the assumption of a virus aetiology of this new growth is a difficult matter, as a routine microscopic investigations will not at present render a virus visible unless it forms inclusion bodies. Future investigation with the electron microscope promises to show the filter passing virus particles directly.

Injection of tumour material into the anterior chamber of an animal was considered too late to apply it, and the best animal species for this purpose has yet to be established.

Virus tumours grow best in traumatized tissue especially young fibroblastic tissue according to Oberling.

No precedent trauma was observed in this case. It was pointed out, however, by Dr. Peacock (a pioneer in experimental cancer research) that a small skin dose of X-rays (600 r) might produce a local fibroblastic reaction from the virus if it was still in the circulation. As the boy had been irradiated post-operatively, we enquired but were assured by the Radiologist that no reaction of this type had been detected in or around the orbit from the first small doses used to estimate the amount of irradiation that could be safely given.
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This negative finding will not, however, exclude a virus as cause, as by this time the virus might have left the circulation if in fact it had ever entered it.

The assumption of a virus aetiology for this limbal tumour, therefore, remains guesswork only.

Case II

Annie S., aged 65 years.—Little history could be obtained in this case. The patient stated that the left eye had always had good sight with glasses (+3·0), and that the right had been blind about fifteen years, while during the last five a growth had appeared on the eye. She denied any form of ocular injury.

On examination the lower two-thirds of the right cornea displayed a whitish cauliflower-like growth of firm consistency, elevated about 2mm. above the surface at its highest point. All investigations including the Wassermann and Mantoux reactions were negative.

The condition was obviously neoblastic, and the eye blind. Excision was performed on January 9, 1947, and the eye preserved in formol-saline.

Histology. The lower two-thirds of the cornea are covered by a fungus-like growth about 1·25 mm. thick (Fig. 8). An irregular epithelium two to five rows in thickness invades the growth to a depth of 3-500 μm thus dividing it into segments (Fig. 9). The epithelial covering is complete except for a central area of about 0·3 mm.

The cornea underlying the growth has a more or less well preserved Bowman's membrane, but no epithelial covering. The tumour itself is composed of fibrous strands of varying diameter, some containing metachromic granules. The external fibres are
Corneal fibroma. H.E. 120 X appr. Epithelial outgrowth divides the tumour in its outer rim. The deeper layers of the tumour are vascularized.

parallel, with a few interstitial nuclei. The deeper fibres are arranged in a crisscross manner, and are more vascular. Small areas without nuclei or fibres suggest myxomatous degeneration. An irregular line of calcareous tissue runs obliquely through the growth.

The tumour free area of the cornea is covered by a vascular degenerative pannus, which pierces Bowman's membrane here and there.

The corneal parenchyma is normal, except for some deep peripheral vessels.

Iris. There are broad root synechiae of the extremely atrophic iris, and extensive supra-intra-and pre-choroidal and pre-retinal haemorrhage.

Retina. The retina itself is degenerate with intra-retinal hyaline patches, which here and there penetrate the limiting membrane, and spread in a pre-retinal plane. This pre-retinal tissue contains many thin-walled vessels with a wide lumen. Giemsa staining shows many large mast-cells in the pannus, especially at the edge near the tumour. Fibroblasts within the tumour are full of metachromatic granules.

Discussion (Case II)

Such tumours of the cornea have been described by several authors. Ginsberg (1905) referring to a corneal tumour in a nine years old child, covering the whole and destroying a considerable part of the cornea, expressed his belief that these corneal tumours are inflammatory pseudo-tumours, although they have been described as fibromata, myxofibromata, or myxomata.
Ginsberg found many mast cells and mast cell granules within the outskirts of the tumour tissue. His mast cells were as a rule unusually large (like those described in our case).

The tumour of Case II is a relatively acellular, slow growing fibroma, with a sign of regressive change in the shape of calcareous and myxomatous degeneration.

The numerous mast cells in both pannus and the tumour outskirts, and the mast cell granules filling the fibroblasts of the tumour, are reminiscent of a chronic inflammation. The growth has originated in the pannus. An unusual stimulus is supposed to have caused this type of pannus newgrowth. The stimulus might have been of mechanical, chemical, or biological nature.

If a mechanical stimulus is present, e.g., by exposure to atmospheric influences, tyloma-like corneal thickening is observed frequently in such cases, e.g., Loewenstein has described cystic growth of corneal epithelium after a chemical stimulus with local burning with chloroform during general anaesthesia. Ichikawa (1913) has described a typical progressive Mooren's ulcer exactly at the place where seven years before the cornea was burned by chloroform.

Nothing in the history suggests that either of the first two possibilities played any part, though one cannot exclude them entirely.

On the other hand, a biological stimulus is a possibility.

In 1931 Shope described fibromata in wild rabbits due to a transmissible filterable virus, and in 1932 a warty like growth which when transferred to domestic rabbits might undergo malignant metaplasia.

Oberling quotes a most interesting experiment performed by Green, Goodlow, Evans, Peyton, and Titru, who transplanted a wart from the eyelid of a seventy-one year old man into the anterior chamber of three monkeys. In each case epithelial tumours developed in the anterior chamber of the monkey, and in the conjunctiva at the site where the needle penetrated.

Laryngeal papilloma, condyloma, and the common wart in man, are known to be of virus origin. We suggest, therefore, as a possibility that this conversion of pannus into tumour tissue may be due to a virus, and might be transmissible to animals. Unfortunately the idea of such an experiment came too late.

Summary

A description is given of two unusual pathological cases:

(a) A hard painless limbal growth of rapid growth infiltrating both cornea and sclera and with dilated vessels in the overlying conjunctiva. This was removed locally. Histologically this proved
to be a spindle cell sarcoma of a mature type, unequal cell distribution, markedly vascularised with giant cell formations in the vessel walls. A considerable number of large mast cells with a big round nucleus were present. Metachroic granules fill the plasm of certain fibroblasts and are also found free in the tissues.

As the clinical progress was more rapid than the histology would suggest, the eye was excised. A milky film was found at slit-lamp investigation covering the retinal periphery, and continued forward over the ciliary processes. There were no signs of uveitis.

It is possible that the tumour may belong to the group of neoplasms much studied in the last three decades by Rous (1910), Fujinami and Unamoto (1911), Shope (1932), and many other authors.

These authors have described transmissible tumour caused by a filterable virus in birds and wild rabbits. Angiosarcoma, myxosarcoma, and endotheliomata with a virus aetiology have been found in birds as well. Virus-caused tumours are known to exist in man, e.g., the common wart, condylomata, and laryngeal papilloma.

(b) In the second case a benign fibroma containing areas of calcareous and myxomatous degeneration is described arising from a degenerative pannus.

A large number of mast cells are found in both growth and surrounding pannus tissue, and mast cell granules fill the protoplasm of many fibroblasts.

It is suggested that the agent producing the metaplasia may be a virus similar to the Shope fibromatous type in wild rabbits. This suggestion is speculative, and without proof, as the idea of animal inoculation was a fruit of the histological investigation when it could no longer be carried out.

This must remain an unproved speculation, as the histological investigation which suggested it destroyed the material needed for the biological experiment which alone could have afforded proof.

Such cases should, therefore, in future be considered "ab initio" from the biological before the histological angle.

The amount of material required for injection into the anterior chamber of a rabbit (or better still a monkey) is so small that it need in no way prejudice the usual histological tests.

REFERENCES
5. Oberling.—Riddle of Cancer. Translated by Wogiom. Yale Univ. Press. 1944.