BENIGN CALCIFYING EPITHELIOMA*

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A BENIGN calcifying epithelioma is a subcutaneous tumour, first described by Malherbe and Chenantais (1880), who called it *l'épithéliome calcifié des glandes sébacées*. Malherbe (1881, 1905) added more details, but only four examples of such tumours have been reported in the ophthalmic literature (Ashton, 1951; Kornblueth and Liban, 1955). Histological examination of material from the Radcliffe Infirmary, Oxford and from the Oxford Eye Hospital makes it seem probable that these benign tumours are more prevalent than the published reports would lead one to suppose. The present report is of 35 examples of such tumours, thirteen having been near the eye.

Many of the earlier papers on the subject came from German and French authors; the first extensive review in English was that of Ch'in (1933), who quoted 116 examples from the literature and added ten of his own. Côté (1936) later reported on a further twelve cases. Muehlton (1942) reviewed 85 cases. More recently, Lever and Griesemer (1949) described fifteen of their own cases and fully discussed the differential diagnosis, histology, and possible histogenesis. The findings of these authors are summarized in Table I, where enough information was available. It will be seen that more tumours occur in the younger age groups and that they are commoner in females than in males. In some cases multiple tumours have been

SITE, AGE, AND SEX DISTRIBUTION

Author	Date	No. of Patients	No. of Tumours	Sex			Age				
				Male	Female	Not Stated	0-5	6-10	11-20	21-30	31-40
Ch'in (survey of literature)	1933	116	116	12	23	81	← 7 →		7	← 8	
Ch'in (own cases)	1933	10	10	5	5	—	—		5	4	—
Côté	1936	12	13*	7	4	1	—	2	3	3	1
Sutton and Sutton	1935	1	1	—	1	—	—	—	—	1	—
Turhan and Krainer	1942	5	5	—	—	5	—	—	—	—	—
Higham and Ogden	1944	11	12*	7	4	—	1	1	2	1	—
King	1947	8	8	—	—	8	—	—	—	—	—
Lever and Griesemer	1949	15	15	5	10	—	← 9 →			← 4	
Ashton	1951	3	3	—	3	—	—	—	2	1	—
Kornblueth and Liban	1955	1	1	—	1	—	—	—	—	1	—
Total		182	184	36	51	95	39			25	

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found (Perthes, 1894; Naulleau and Ardouin, 1932; Bellanger, 1935; Côté, 1936; Highman and Ogden, 1944), but not all these were confirmed histologically. No cause has been found.

The commonest site seems to have been the head and neck, a large proportion lying near to the eye. In many cases the exact site was not specified, so these figures are only approximate. Occasional recurrence after removal has been recorded (Reverdin, 1901; Malherbe, 1905; Frey, 1921; Côté, 1936), and Gromiko (1927) noted a malignant recurrence. A possible familial trait was noted by Eve (1882); the patient concerned had a brother, father, and aunt, all of whom had similar nodules; unfortunately, the nodules were not examined histologically.

Material for the present report consists of tumours from 38 patients, diagnosed histologically at the Radcliffe Infirmary, Oxford, and at the Oxford Eye Hospital in the years 1942 to 1955 inclusive, during which time some 84,000 histological specimens were examined. Of these 38 cases, seven were subsequently rejected, since there was insufficient evidence to support the diagnosis. There were then 35 tumours from 31 patients available for study. A follow-up questionnaire was sent to each patient and in some cases a patient was also examined clinically.

Clinical Description and Results

Clinically, benign calcifying epitheliomata appear as hard subcutaneous nodules which may or may not be attached to overlying skin, and are usually mobile on deeper structures. They commonly grow slowly and have often been present for

IN CALCIFYING EPITHELIOMATA

		Site									
61-70 +	Not Stated	Head and Neck (Total)	Lids and Eye-brows	Face	Scalp, Fore-head and Temple	Neck	Around Ear	Un-specified Head and Neck	Trunk	Limbs	Not Stated
9 →	85	57	12	8	6	10	5	16	15	23	21
—	1	7	1	1	4	—	1	—	—	3	—
—	1	7	1	2	1	2	1	—	1	4	1
—	—	—	—	—	—	—	—	—	—	1	—
—	5	—	—	—	—	—	—	—	—	—	5
3 →	1	8	2	—	2	4	—	—	1	2	1
—	8	← not analysed →								8	8
2 →	—	6	—	—	—	1	—	5	1	8	—
—	—	3	3	—	—	—	—	—	—	—	—
—	—	1	1	—	—	—	—	—	—	—	—
17	101	89	20	11	13	17	7	21	18	41	36

months or years (in one instance 30 years) before the patient seeks advice. In some cases the overlying skin may be reddened and there may be tenderness and inflammation, with breakdown of the tumour and discharge of the contents to the surface.

A clinical diagnosis of benign calcifying epithelioma was made in only one case. In the other thirty cases the nodules were diagnosed as sebaceous cysts (16), neuromata (3), dermoid cysts (3), miscellaneous (9). The tumours occurred more often in women than in men (17:14), a fact noted by Malherbe (1881), Muehlton (1942), Lever and Griesemer (1949), and Ashton (1951). Benign calcifying epitheliomata occur more commonly in the younger groups, as will be seen in Table II.

Four patients had multiple tumours proven histologically, and in addition a further two cases had multiple tumours, all alike clinically, but in each patient only one was examined histologically.

Eve (1882) suggested the possibility of these tumours having a familial trait. In the present series there were two instances of tumours occurring in siblings (Cases 4 and 31; 23 and 24), all children. In one family they occurred as multiple and in the other as single swellings. There was no other history of similar tumours in these families.

No evidence of any associated disease was found. In three cases congenital anomalies were present. These were a blocked naso-lacrimal duct, a bilateral patent processus vaginalis, and a bilateral ptosis respectively.

TABLE III
SITE OF BENIGN CALCIFYING
EPITHELIOMATA

Site of Tumour	No. of Patients
Head and Neck (all parts)	28
Lids and Eyebrows ..	13
Face	1
Scalp, Forehead, and Temple	6
Adjacent to Ear ..	4
Neck	4
Trunk	3
Limbs	2
Unknown	2
Total	35

TABLE II
AGE DISTRIBUTION OF BENIGN
CALCIFYING EPITHELIOMATA

Age Group (yrs)	No. of Patients
0-5	3
6-10	8
11-20	4
21-30	5
31-40	3
41-50	1
51-60	4
61-70*	3
Total ..	31

* Including one tumour present for 30 years

The sites of the swellings were noted in 33 instances. The data available did not permit a more accurate analysis than that given in Table III.

No exciting cause was found. In only one case was trauma mentioned, and here it was probably coincidental, as the tumour was removed from the left supra-orbital margin only 2 weeks after a traumatic haematoma of the left upper lid.

Treatment was by surgical removal; often the details were not given.

A follow-up questionnaire was completed and returned by eighteen of the 31 patients, and of those replying five were also examined clinically. The follow-up covered a

period of from 4 months to 9 years, the average time being $2\frac{1}{2}$ years. In no case was a recurrence found.

Histological Examination

Histologically these tumours are quite characteristic. They are usually well localized and have a fibrous capsule, prolongations from which traverse and subdivide the tumour. Inside lie irregular clumps and bands of fairly large basal cells with large basophilic nuclei and well marked nucleoli. It is commonly found that the cells on one side of these clumps stain more deeply than on the other; on the latter side, the nuclei gradually become smaller, some fragmenting and becoming darker, but most losing their staining properties, leaving only the vague cell outlines, the characteristic "ghost" cells (Figs 1, 2, 3).

FIG. 1.—Low-power view, showing an irregular serpiginous band of basal cells. Above and to the right are ghost cells undergoing calcification; below and to the left the granulomatous reaction is seen. Haematoxylin and eosin. $\times 86$.

FIG. 2.—Transition of basal cells to ghost cells. $\times 250$.

FIG. 3.—Islands of ghost cells surrounded by a granulomatous reaction containing giant cells. $\times 190$.

The ghost cells form eosinophilic masses which may become calcified or even ossified. Some of the basal cells are a little reminiscent of those found in rodent ulcers. A considerable amount of granulation tissue with frequent giant cells, some containing ghost cell material, is found amongst the viable basal cells and the ghost cells.

The diagnostic criteria used in the present study were:

- (i) The presence of *basal cells* arranged in irregular clumps and bands;
- (ii) Eosinophilic masses of *ghost cells*.

Neither calcification, although it was present in some 25 cases, nor the granulomatous reaction with giant cells was regarded as an essential constituent.

Discussion

In view of the few cases of benign calcifying epithelioma reported in the ophthalmic literature, it is interesting to note that, of the 184 tumours from all parts of the body recorded in the literature (Table I), the area of the eye seems to be one of the commonest sites. Almost 50 per cent. of all tumours were in the head and neck, and of these about 25 per cent. were around the eye. The distribution in the present series is even more striking, 80 per cent. of tumours occurring in the head and neck, and nearly half of these near the eye (Table III). These specimens were selected from histological material of all types and do not represent only that coming from an eye hospital.

It was not possible to plot the exact position of all tumours, so no accurate correlation could be made with such features as developmental clefts, etc., but many occurred in sites where dermoid cysts are also found.

The clinical differential diagnosis obviously presents some difficulty for in only one case was it correct. Around the eye these tumours may be confused with meibomian, dermoid, or sebaceous cysts, neurofibromata, or more rarely with a foreign-body granuloma, a fibroma, or a carcinoma of the lacrimal gland (which has been reported in young people, Duke-Elder, 1952).

The occurrence of multiple tumours and their benign nature have been confirmed. There were no recurrences, though admittedly the follow-up was not as complete as one might have wished.

Whereas benign calcifying epitheliomata lack characteristic clinical features, histologically they seem to form a distinct pathological entity. The irregular clumps and sheets of basal cells, together with the formation of "ghost" cells, give a characteristic picture. The clumps of basal cells, if viewed in isolation, might well be mistaken for those seen in a basal cell carcinoma.

The granulomatous reaction was not regarded as a specific feature, but rather as a non-specific response to the ghost cell material, islands of which could be seen engulfed by giant cells. This reaction resembled that found where sebaceous cysts have burst into the surrounding tissues or in meibomian cysts or foreign-body granulomata.

The origin of benign calcifying epitheliomata is in dispute. Several theories have been put forward. Malherbe and Chenantais (1880) suggested that a papillomatous process occurred within a sebaceous cyst, whereas Linser (1901) suggested the same process within a dermoid cyst. In this series, two sebaceous cysts and one benign calcifying epithelioma (proven histologically) occurred in the same patient.

A familial incidence, as was suggested by Eve (1882), has also been found in the present series. The numbers available were insufficient to allow of a detailed analysis. It is interesting to note that sebaceous cysts have also been frequently reported as familial, a clinical feature likely to cause further confusion. On the other hand, the frequent occurrence of benign calcifying epitheliomata near the eye, on the temple, and adjacent to the ear, suggests a similarity with dermoid cysts, as does their common occurrence in young people.

As they are subcutaneous, it seemed likely that they might arise from a skin appendage. Turhan and Krainer (1942) suggested that these tumours arise from hair matrix cells, a view also held by Highman and Ogden (1944). This view received support from Lever and Griesemer (1949), who, in an extensive discussion of the histological features, differentiated benign calcifying epitheliomata from calcified epidermal cysts, and pointed out that the latter contained squamous cells, whereas the former had basal cells. They thought that both could have ghost cells and become calcified.

In the present series, there was no evidence to support or deny their origin from hair matrix cells and there was little to refute Côté's suggestion that this is a lesion *sui generis*.

Summary

35 examples of benign calcifying epithelioma are reported. Previous views on the age and sex distribution have been confirmed. No recurrences were noted in a follow-up which ranged from 4 months to 9 years.

The frequent occurrence of these tumours adjacent to the eye has been emphasized; some 80 per cent. of all the tumours occurred in the head and neck and of these nearly 50 per cent. were found near the eye.

In some cases these tumours occur in families.

The characteristic histological appearances are described and the aetiology discussed.

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