THE RELATIONSHIP OF CELLULAR DIFFERENTIATION, FIBROSIS, HYALINIZATION, AND LYMPHOCYTIC INFILTRATION TO POSTOPERATIVE LONGEVITY OF PATIENTS WITH SQUAMOUS-CELL EPITHELIOMA OF THE SKIN AND LIP

LESTER D. POWELL

Mayo Foundation, Rochester, Minnesota

Received for publication February 16, 1923

The 98 cases of squamous-cell epithelioma of the skin and lip under discussion have been previously studied and graded by Broders. They represent all of the patients treated surgically at the Mayo Clinic for squamous-cell epithelioma of the skin and lip between November 1, 1904, and July 22, 1915, who died from recurrence of the lesion, or from metastasis.

The study of cellular differentiation, fibrosis, hyalinization, and lymphocytic infiltration was undertaken in an endeavor to determine the histologic factors causing the great variations in postoperative longevity (2, 3, 4, 5). Microscopic study of sections taken from many epitheliomas which were operable, and from others that were inoperable has revealed the presence of malignant cells taking on forms which closely resemble normal squamous-cell epithelium. They are well differentiated, as shown by the presence of pearly bodies. This phenomenon is termed cellular differentiation (fig. 1). In a great many of the cases the fibrous connective-tissue cells are seen working into and around the malignant tumor and apparently forming a barrier; this condition is known as fibrosis (fig. 2). Another phenomenon commonly seen is the presence of lymphocytes.

Abstract of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery, October, 1922. From the section on Surgical Pathology.
scattered intimately around the tumor cells, in some instances in such abundance that it is difficult to find the malignant cells. The abnormal presence of lymphocytes around a tumor is believed to be lymphocytic infiltration (fig. 3). A condition less

![Cellular Differentiation in a Case of Epithelioma of the Skin.](image1)

**Fig. 1. Cellular Differentiation in a Case of Epithelioma of the Skin.**

*× 100*

Two pearly bodies stand out prominently

![Areas of Malignant Cells Completely Surrounded by Dense Fibrous Connective Tissue Cells.](image2)

**Fig. 2. Areas of Malignant Cells Completely Surrounded by Dense Fibrous Connective Tissue Cells.**

*× 100*

commonly present is that of hyalinization (fig. 4) shown by a translucent or homogeneous condition of the connective tissue in and around the tumors.
Of the 32 patients with squamous-cell epithelioma of the skin treated surgically at the Clinic between November 1, 1904, and July 22, 1915, who are known to have died from recurrence of the lesion or from metastasis, complete data were obtained from 29. The tumors were sectioned and studied microscopically
without reference to clinical data; comparisons were drawn and deductions made as follows:

The average length of postoperative life was 444.6 days. The frequency of cellular differentiation was 65.5 per cent; of lymphocytic infiltration, 65.5 per cent; of fibrosis, 41.3 per cent; of hyalinization, 31 per cent; of cellular differentiation and lymphocytic differentiation combined, 37.9 per cent; of cellular differentiation and fibrosis combined, 27.5 per cent; of cellular differentiation and hyalinization combined, 17.2 per cent; of lymphocytic infiltration and fibrosis combined, 24.1 per cent; of lymphocytic infiltration and hyalinization combined, 20.6 per cent; and of fibrosis and hyalinization combined, 27.5 per cent.

The average length of postoperative life with cellular differentiation was 534.1 days; without cellular differentiation, 274.7 days (fig. 5); with lymphocytic infiltration, 496.2 days; without lymphocytic infiltration, 346.6 days; with fibrosis, 655.7 days; without fibrosis, 295.6 days; with hyalinization, 449.6 days; without hyalinization, 437.9 days; with cellular differentiation and lymphocytic infiltration, 644.5 days; without cellular differentiation and lymphocytic infiltration, 204 days; with cellular differentiation and fibrosis, 808.3 days; without cellular differentiation and fibrosis, 257.5 days; with cellular differentiation and hyalinization, 587 days; without cellular differentiation and hyalinization, 257.5 days; with lymphocytic infiltration and fibrosis, 739.8 days; without lymphocytic infiltration and fibrosis, 155.2 days; with lymphocytic infiltration and hyalinization, 404 days; without lymphocytic infiltration and hyalinization, 255.5 days; with fibrosis and hyalinization, 453.8 days; without fibrosis and hyalinization, 282.5 days; with cellular differentiation, lymphocytic infiltration, fibrosis and hyalinization, 444.6 days, and without cellular differentiation, lymphocytic infiltration, fibrosis and hyalinization, 54 days.

The average age of the 29 patients was 60.7 years. The oldest was 77 years, the youngest, 42 years. There were 25 males and 4 females. The average duration of the preoperative lesion was 6.1 years.
The lesions were in the head and neck in 22 cases; in the buttocks and sacral region in 3, in the extremities in 3, and in the abdomen in 1.

Of the 66 patients operated on for squamous-cell epithelioma of the lip between November 1, 1904, and July 22, 1915, all are known to have died from recurrence of the disease, or from metastasis. Data were obtained from 63 of these:

The average length of post-operative life was 359.8 days. The frequency of cellular differentiation was 71.4 per cent; of lymphocytic infiltration, 92.1 per cent; of fibrosis, 6.3 per
cent; of hyalinization, 6.3 per cent; of cellular differentiation and lymphocytic infiltration, 66.6 per cent; of cellular differentiation and fibrosis, 6.3 per cent; of cellular differentiation and hyalinization, 4.7 per cent; of lymphocytic infiltration and fibrosis, 4.7 per cent; of lymphocytic infiltration and hyalinization, 4.7 per cent; of fibrosis and hyalinization, 4.7 per cent.

The average length of postoperative life with cellular differentiation was 388 days; without cellular differentiation, 290.4 days (fig. 6); with lymphocytic infiltration, 365.9 days; without lymphocytic infiltration, 293 days; with fibrosis, 186.7 days; without fibrosis, 371.8 days; with hyalinization, 293.7 days; without hyalinization, 364.7 days; with cellular differentiation and lymphocytic infiltration, 386.8 days; without cellular differentiation and lymphocytic infiltration, 116 days; with cellular
differentiation and fibrosis, 186.8 days; without cellular differentia-
tion and fibrosis, 290.4 days; with cellular differentiation and hyalinization, 207.6 days; without cellular differentiation and hyalinization, 275 days; with lymphocytic infiltration and fibrosis, 174.6 days; without lymphocytic infiltration and fibrosis, 310.5 days; with lymphocytic infiltration and hyalinization, 317.3 days; without lymphocytic infiltration and hyalinization, 310.5 days; with fibrosis and hyalinization, 207.6 days; without fibrosis and hyalinization, 367.1 days; with cellular differentia-
tion, fibrosis, hyalinization and lymphocytic infiltration, 200 days; and without cellular differentiation, fibrosis, hyalinization, and lymphocytic infiltration, 117 days.

The average age of the 63 patients was 59.2 years. The oldest was 97 years, the youngest, 25 years. There were 61 males and 2 females. The average duration of the preoperative lesion was 3.57 years.

CONCLUSIONS

The average length of postoperative life of patients with epithelioma of the skin is increased when the factors differentiation, lymphocytic infiltration, fibrosis, and hyalinization are present. Postoperative life is increased when any one of these factors or a combination of them is present in the skin (fig. 7). However, this is not true in cases of epithelioma of the lip in the series studied. In these cases, postoperative life was increased when the factors cellular differentiation or lymphocytic infiltration were present (fig. 8); but with the factors fibrosis or hyalinization singly or in combination, postoperative life was decreased. This discrepancy may be owing to the fact that in the series of cases of epithelioma of the lip there were only 4 of fibrosis and 4 of hyalinization. Three of the patients with fibrosis also had hyalinization. One patient was 76 years of age, one was 68, and the other was 48, but had had the lesion for 11 years previous to operation. One patient with fibrosis alone was 70 years of age. The 1 with hyalinization alone was 58 years of age and had had the lesion 9 years previous to operation. Of the 4 patients with fibrosis, 3 had lived an average lifetime and
the fourth, although but 48, had had the lesion for 11 years and, therefore, his resistance was diminished. Two of the patients with hyalinization had lived 76 and 68 years respectively. The other 2 had had lesions 11 and 9 years respectively, and the defense offered by hyalinization must have been exhausted.

Despite the fact that with fibrosis and hyalinization there was a decrease in postoperative life in the cases of epithelioma of the lip, the presence of all the factors checked against the absence of all the factors showed an increase of postoperative life.

A larger series of cases should be studied before deciding that cellular differentiation, lymphocytic infiltration, fibrosis, and hyalinization, when in association with malignancy, prolong postoperative life as an entity, but from the data obtained from these 92 cases it would seem that each of these factors should be considered as a defense in cases of malignancy.

REFERENCES