Keratin Granulomas in Irradiated Squamous Cell Carcinoma of Various Sites

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Summary
An extensive foreign-body giant cell reaction around necrotic or degenerating keratinized tumor was observed in 20 instances of human squamous cell carcinoma of various sites and following external X-ray or radium therapy. The data presented suggest that radiation injury in squamous cell carcinoma may be manifested by marked hyperkeratinization of tumor cells. The keratin compounds which are liberated from injured tumor cells induce a severe foreign-body giant cell reaction as well as a mixed leukocytic reaction. In this material, the development of keratogenesis and keratin granulomas did not seem to have influenced the malignant potential of irradiated squamous cell carcinoma.

Introduction
Giant cells of stromal origin have long been observed in various malignant tumors (1). More specifically, multinucleated foreign-body giant cells have been repeatedly described in association with well-differentiated squamous cell carcinoma of the uterine cervix by Cullen in 1900 (3). Ewing offers in his “Human Neoplasms” an excellent illustration of a foreign-body giant cell phagocytozing an epithelial pearl in a case of squamous cell carcinoma of the skin (5). Hall and Friedman also described the histologic changes in squamous cell carcinoma of the oral cavity produced by external radiotherapy noting in particular the presence of foreign-body giant cells around keratin debris (10).

The aim of this study is to report on the extensive foreign-body granulomatous reaction induced by radiotherapy in squamous cell carcinoma of various sites and to discuss the possible pathogenesis and significance of these lesions.

Materials and Methods
The material consisted of sections of 115 autopsies and 168 surgically excised specimens of patients with irradiated squamous cell carcinoma of various sites. All patients were treated with radiotherapy with or without subsequent surgical procedures. Irradiation consisted of fractionated external roentgen therapy usually by means of a 250-kv or 2-million-volt machine or by means of a cobalt-60 machine. In the case of carcinoma of the cervix, treatment consisted of radium needle implantation according to Corscaden’s technic with or without external radiotherapy.

In 20 instances, the irradiated primary or metastatic lesions showed an extensive foreign-body granulomatous reaction around necrotic or degenerating keratinized tumor tissue. These 20 cases constitute the core of this study.

Although there were no serial biopsies done before and after radiotherapy, in each instance except for Case 18 one or several biopsies preceding external radiotherapy or radium therapy were available for comparison with postirradiation biopsy or autopsy slides. For the few autopsy cases in which distant metastases were found, these were compared with lesions located in the field of irradiation. The interval between the last day of radiotherapy and the time at which subsequent biopsy specimens first showed keratin granulomas was also estimated in all instances.

Pertinent clinical, histologic, and radiotherapeutic data on the 20 selected cases of irradiated squamous cell carcinoma are listed in Table 1. It must be emphasized that this selection was primarily guided by the availability of fully documented cases. Primary lesions that were not satisfactorily documented before irradiation, as in most cases of carcinoma of the lung, were considered unsuitable for this study.

Results
In our surveyed material of 115 autopsies and 168 surgically excised specimens of irradiated squamous cell carcinoma of various sites, 3 main histologic patterns seem to emerge: (a) massive tumor necrosis usually with extensive irradiation changes in the stroma of the tumor and its surrounding tissues; (b) viable tumor tissue with frequent bizarre or giant tumor cells and some focal tumor necrosis; (c) apparent “maturation” of the tumor as evidenced by extensive and marked keratogenesis characterized by abundant central masses of hyperkeratotic tissue and many pearls of cornification. Although foreign-body giant cells were occasionally observed in all 3 types of irradiated tumors, the extensive keratin granulomas were always located in the midst of fields exhibiting marked keratogenesis. It must be emphasized that not infrequently the 3 patterns of radiation response were noted within the same tumor and in adjacent fields.

As shown in Table 1, among the 20 patients with postradiation keratin granulomas, 9 had their primary lesions located in the oral cavity and oropharynx, 1 in the larynx, 5 in the uterine cervix, 4 in the esophagus, and 1 in the urinary bladder. There was no unusual sex or age distribution except that anticipated for these types of tumor. In 10 cases the postradiation biopsies showed a well-differentiated squamous cell carcinoma. In 7 cases the tumors were moderately differentiated and in 2 instances,
**TABLE 1**

**Clinical and Histologic Data on Patients with Irradiated Squamous Cell Carcinoma**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age</th>
<th>Primary site</th>
<th>Tumor differentiation before irradiation</th>
<th>Radiotherapy (total tumor dose and duration)</th>
<th>Site of keratin granulomas and time when noted</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>c</td>
<td>43</td>
<td>Tonsillar area, extensive</td>
<td>Well differentiated</td>
<td>6000 r/6 wk</td>
<td>Soft tissues neck (O), 8 days</td>
<td>At autopsy, cervical node metastasis</td>
</tr>
<tr>
<td>2</td>
<td>♂</td>
<td>57</td>
<td>Base of tongue</td>
<td>Moderately differentiated</td>
<td>6180 r/5 wk</td>
<td>Cervical nodes (O), 20 mo</td>
<td>Living with cervical node metastasis</td>
</tr>
<tr>
<td>3</td>
<td>♂</td>
<td>63</td>
<td>Cervix, Stage III</td>
<td>Poorly differentiated</td>
<td>Radium point A 8000 r/1 wk Radium parametria 4000 r/1 wk Radium vagina 4000 r/1 day 3000 r/3 wk</td>
<td>Cervix (B), 24 mo</td>
<td>Died at home—no autopsy</td>
</tr>
<tr>
<td>4</td>
<td>♂</td>
<td>52</td>
<td>Esophagus</td>
<td>Well differentiated</td>
<td>5000 r/5 wk</td>
<td>Esophagus (A), 7 wk</td>
<td>At autopsy, widespread metastases in lymph nodes and viscera</td>
</tr>
<tr>
<td>5</td>
<td>♂</td>
<td>50</td>
<td>Cervix, Stage III–IV</td>
<td>Moderately differentiated</td>
<td>4000 r/4 wk</td>
<td>Uterus, pelvis (A), 3 mo</td>
<td>At autopsy, extension to vagina, uterus, pelvic wall</td>
</tr>
<tr>
<td>6</td>
<td>♂</td>
<td>62</td>
<td>Tonsillar area</td>
<td>Moderately differentiated</td>
<td>6000 r/7 wk</td>
<td>Soft tissues neck (O), 24 mo</td>
<td>Living with cervical node metastasis</td>
</tr>
<tr>
<td>7</td>
<td>♂</td>
<td>75</td>
<td>Floor of mouth</td>
<td>Moderately differentiated</td>
<td>Radium 4000 mg/hr 3000 r/2 wk 3000 r/3 wk</td>
<td>Soft tissues neck (O), 2 wk</td>
<td>Died at home—no autopsy</td>
</tr>
<tr>
<td>8</td>
<td>♂</td>
<td>68</td>
<td>Tongue</td>
<td>Well differentiated</td>
<td>5870 r/9 wk</td>
<td>Tongue (O), 7 3 wk</td>
<td>Died in another hospital—no autopsy</td>
</tr>
<tr>
<td>9</td>
<td>♂</td>
<td>55</td>
<td>Esophagus</td>
<td>Poorly differentiated</td>
<td>5600 r/4 wk</td>
<td>Esophagus (A), 4 mo</td>
<td>At autopsy, tumor in trachea, bronchus, mediastinal nodes</td>
</tr>
<tr>
<td>10</td>
<td>♂</td>
<td>64</td>
<td>Epiglottis and pyriform fossa</td>
<td>Well differentiated</td>
<td>6000 r larynx/7 wk 1000 r left neck/4 days 2400 r tongue/2 wk 4200 r left nodes/4 wk 2000 r right nodes/1 wk</td>
<td>Cervical nodes (O), 6 mo</td>
<td>Living with cervical node metastasis</td>
</tr>
<tr>
<td>11</td>
<td>♂</td>
<td>52</td>
<td>Vocal cord, extensive</td>
<td>Moderately differentiated</td>
<td>5870 r/9 wk</td>
<td>Tongue and cervical nodes (O), 6 mo</td>
<td>At autopsy, tumor in tongue and mediastinal nodes</td>
</tr>
<tr>
<td>12</td>
<td>♂</td>
<td>61</td>
<td>Cervix, Stage III</td>
<td>Well differentiated</td>
<td>4000 r/5 wk</td>
<td>Parametria (O), 2 mo</td>
<td>Living with no evidence of metastasis</td>
</tr>
<tr>
<td>13</td>
<td>♂</td>
<td>43</td>
<td>Cervix, Stage III–IV</td>
<td>Well differentiated</td>
<td>Radium 2500 mg/hr 4990 r/5 wk</td>
<td>Cervix (B), 9 days</td>
<td>Died at home—no autopsy</td>
</tr>
<tr>
<td>14</td>
<td>♂</td>
<td>69</td>
<td>Soft palate</td>
<td>Moderately differentiated</td>
<td>5000 r/6 wk</td>
<td>Cervical nodes (O), 4 wk</td>
<td>Living with cervical node metastasis</td>
</tr>
<tr>
<td>15</td>
<td>♂</td>
<td>64</td>
<td>Esophagus</td>
<td>Moderately differentiated</td>
<td>6000 r/6 wk</td>
<td>Esophagus (B), 3 wk</td>
<td>At autopsy, metastases in heart, pericardium, liver, lung</td>
</tr>
<tr>
<td>16</td>
<td>♂</td>
<td>61</td>
<td>Urinary bladder</td>
<td>Well differentiated</td>
<td>3000 r/4 wk</td>
<td>Bladder (O), 5 wk</td>
<td>At autopsy, metastases in prostate, peritoneum, liver, pancreas</td>
</tr>
<tr>
<td>17</td>
<td>♂</td>
<td>46</td>
<td>Base of tongue</td>
<td>Well differentiated</td>
<td>6000 r/3 wk</td>
<td>Muscle neck, cervical nodes (O), 7 wk</td>
<td>Living with cervical node metastasis</td>
</tr>
<tr>
<td>18</td>
<td>♂</td>
<td>70</td>
<td>Esophagus</td>
<td>No biopsy before irradiation</td>
<td>3000 r/3 wk</td>
<td>Esophagus (A), 4 wk</td>
<td>At autopsy, no gross tumor or metastasis found</td>
</tr>
<tr>
<td>19</td>
<td>♂</td>
<td>52</td>
<td>Tongue</td>
<td>Well differentiated</td>
<td>5300 r/8 wk</td>
<td>Cervical nodes (O), 8 wk</td>
<td>Living with cervical node metastasis</td>
</tr>
<tr>
<td>20</td>
<td>♂</td>
<td>50</td>
<td>Cervix, Stage II–III</td>
<td>Well differentiated</td>
<td>Radium 3600 mg/hr Radium 7800 mg/hr 9200 r/4½ wk</td>
<td>Appendix, pelvic nodes, (O) 7 wk</td>
<td>Died—no autopsy</td>
</tr>
</tbody>
</table>

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* Irradiation by external X-ray therapy unless otherwise indicated.

† (O) indicates that tissue was removed during radical operation following irradiation; (B) represents a biopsy specimen; (A) finding at autopsy. The time at which keratin granulomas were first noted is estimated from the date of completion of course of radiotherapy.
poorly differentiated. In our experience, no keratin granulomas were encountered in irradiated adenocarcinomas or totally undifferentiated tumors although squamous metaplasia is not uncommon in irradiated glandular tumors or normal tissues. The modalities of radiotherapy varied considerably from case to case as to conform to local conditions. Except in 4 instances in which the tumor had obviously metastasized at the time of therapy to distant sites (Cases No. 1, 5, 11, 13), the type of radiotherapy administered was aimed at cure. In 9 out of 10 patients with tumors of the oral cavity or upper respiratory tract, there were persistent masses with keratin granulomas in the cervical lymph nodes or in the soft tissues of the neck. All 9 cases demonstrated clinically such a strong resistance to radiotherapy as to necessitate subsequently radical surgical procedures.

In all preirradiation biopsies, the lesions contained few or no tumor or stromal giant cells whereas postirradiation areas of tumor were characterized by extensive keratinization of tumor cells, tumor necrosis, abundant amounts of free keratin debris or degenerating keratinized cells frequently surrounded by multinucleated giant cells which were clearly nonmalignant and of the foreign-body type. Focal calcification within areas of necrotic keratinized tumor was frequently observed. In some areas, tumor necrosis and foreign-body giant cell reaction were so extensive as to simulate the caseation necrosis of tuberculosis. Examples of the evolution of a poorly or moderately cornified carcinoma to a markedly keratotic tumor with extensive keratinization are shown in 3 sets of illustrations of preirradiation and postirradiation tissue (Figs. 1–3).

The following comment is indicated for Case 18. This 70-year-old Japanese male presented himself with dysphagia of 3 months duration. X-ray study of the upper gastrointestinal tract after a barium swallow revealed a fungating lesion of the mid-esophagus which was considered typical for carcinoma (Fig. 4). Biopsy tissues obtained at esophagoscopy were considered inadequate for diagnosis; however, in view of the typical X-ray picture a full course of external X-ray therapy was delivered and the lesion receded rapidly leaving a shallow ulcer at its base. The patient died 4 weeks after the completion of radiotherapy with confluent bronchopneumonia. There was no gross tumor recognized at autopsy. Histologic sections of the base of the shallow esophageal ulcer revealed multiple granulomata within the esophageal wall surrounding free keratin and degenerating pearls of cornification (Fig. 5).

The authors are well aware that occasional foreign-body giant cells are not infrequently observed in fields of degenerating or seemingly healthy nonirradiated squamous cell carcinoma. One rarely encounters, however, extensive keratin granulomas in the absence of irradiation. A striking example of keratin granulomas in a case of nonirradiated squamous cell carcinoma of the cervix is shown in Fig. 6. Furthermore, keratin granulomas are not confined to malignant epidermoid tumors. Such granulomas are well known to occur in the calcifying epithelioma of Malherbe or more typically in ruptured epidermal inclusion cysts (Fig. 7).

Among the autopsied cases, only 3 cases (Cases No. 4, 15, 16) showed distant metastases away from the field of irradiation. In Case No. 4, distant metastases in supraclavicular lymph nodes and adrenals, and in Case No. 15 a solitary nodule in the liver were all characterized by marked keratogenesis and formation of foreign-body giant cells around keratinized masses. In Case No. 16, distant metastases were, however, represented by undifferentiated nonkeratinized tissue. It is therefore not possible to draw any conclusion here on the interesting possibility of distant effect of irradiation. Keratogenesis in distant metastatic sites may simply represent an inherent histologic trait of the primary or metastatic tumor.

Discussion

The keratin granulomas of irradiated squamous cell carcinoma elicit the following questions: (a) Does radiotherapy induce or accelerate the histologic “maturation” of squamous cell carcinoma and lead to hyperkeratinization and subsequent formation of keratin granulomas? If so, how? (b) What is the basis for the inflammatory response and more specifically the foreign-body giant cell reaction to keratin or hyperkeratotic cells? (c) What is the prognostic significance of these keratin granulomas?

Glücksmann has concluded on the basis of extensive histologic studies of biopsy material from patients treated for carcinoma of the cervix that irradiation frequently promotes differentiation of squamous cell carcinomas and with it the sterilization of tumor cells and that radiocurability of uterine carcinoma is closely correlated with the degree of differentiation of tumor tissue brought about during therapy (6–8). Joles and Koller (12) considered that hyperkeratinization of tumor cords occurring in squamous cell carcinoma is a degenerative process and not as maintained by Glücksmann a form of radiation-induced differentiation. Hall and Friedman (10) studied 28 patients with squamous cell carcinoma of the mouth and oropharynx subjected to periodic biopsies during X-ray treatment. They noted that the destructive effect of irradiation on squamous cell carcinoma was achieved by acute cell death, progressive enlargement of surviving cells to giant-sized tumor cells and by acceleration of keratogenesis. In their experience, under-irradiation of a tumor, chiefly in the form of small daily doses, achieves some destruction of tumor cells but mainly provokes keratogenesis of the more radioresistant cells. In 11 of their 28 cases, multinucleated foreign-body giant cells were formed next to keratin masses. Crossland (2) also noted a gradual keratinization in basal cell carcinoma during the course of successful radiotherapy. In his experience, with higher doses death of tumor cells was manifested by phagocytic multinucleated giant cells. Our observations likewise strongly suggest that irradiation does accelerate keratogenesis in squamous cell carcinoma. It is doubtful, however, that this is an indication of true differentiation or maturation. Squamous metaplasia and keratinization of normal epithelial surfaces or glandular tissues are common reactions to injury of various types including ionic radiations and may represent a relatively primitive form of cell function. Keratinization of epithelial cells was shown to occur in vitro in a relatively simple and well-defined chemical medium (17). It is possible therefore that radiation keratogenesis is a form of survival of injured tumor cells at a low metabolic pace and under suboptimal nutritional conditions as is the situation in the hyperkeratosis and squamous metaplasia observed in chronic inflammation, chronic irritation, or avitaminosis A.

The term keratin has been used throughout this text rather loosely. Actually, the keratins show great variations in molecular
structure. They are fibrous proteins composed of long polypeptide chains held together by disulfide cross-bridges. The keratins are further characterized by their great resistance to enzymatic digestion and their relative insolubility. The “soft” keratins have a fairly high lipid content. Phospholipids, cholesterol, and fatty acids are probably situated around or bonded to keratin fibrils (15, 18). Jarrett et al. have subjected normal and pathologic human epidermis to histochemical, fluorochrome, and enzymatic processes and observed abnormal keratinization in squamous cell carcinoma as well as in psoriasis and in warts (11). It is possible therefore that the keratin or keratins released by irradiated squamous cell carcinomas attract macrophages and other leukocytes by virtue of their characteristic chemical inertness, their association with lipids, and the chemotactic effect of disulfide groups. The spontaneous or X-ray-induced synthesis of abnormal and highly antigenic keratins in certain squamous cell carcinomas is also a distinct possibility.

There is considerable disagreement in the literature on the relation of histologic differentiation or grading of preirradiation and postirradiation tumor samples to radiation response and ultimate prognosis. Warren et al. (19) attempted to correlate the radiosensitivity of carcinoma of the cervix with histologic grading. Their data suggest that the survival of patients with Grade II (moderately differentiated) carcinoma was somewhat better than that with Grade III (poorly differentiated) tumors. Glücksman’s analysis of sequential biopsies during radiotherapy has been mentioned earlier. More recently, Loring (14) in a study of 44 patients with irradiated malignant tumors of the nasopharynx observed that the 5-year survival rate in patients with well-differentiated squamous cell carcinoma was lower than that of patients with undifferentiated carcinoma. On the other hand, Gricouroff (9), Kottmeier (13), and Novak (16) have all warned about the limitations of histologic findings in the prognosis of radiation-treated cancer and stressed the lack of uniform response to radiation. Davis has reviewed the problem of radiosensitivity and cervical cancer taking into consideration both tumor characteristics and host factors (4). In our material, it is difficult to assess the prognostic value of keratogenesis and keratin granulomas because of the limited number and the arbitrary selection of cases. As indicated earlier, there is a definite lack of uniformity in tumor response and furthermore these findings were noted in both radiosensitive cases as well as in rare situations in which the response to therapy was most favorable as in Case No. 18. Rather than attribute a prognostic value to keratin granulomas, we prefer to assume that radiation keratogenesis is both a manifestation of radiation injury and an attempt on the part of tumor cells to survive under adverse conditions.

Acknowledgments

The authors are indebted to many members of the Departments of Pathology and Radiotherapy at The Francis Delafield Hospital for their help and advice, and to Mr. Edward Hajjar for the photographs.

References

7. ———. Radiation Histology. II. The Response of Human Tissues to Radiation with Special Reference to Differentiation. Ibid., 25: 38—43, 1952.
Fig. 1. Case No. 7: 75-year-old male with squamous cell carcinoma of the floor of the mouth. A, Biopsy sample before irradiation showing a moderately differentiated squamous cell carcinoma. × 175. B, Cervical lymph nodes removed during radical dissection of the neck 2 weeks after radiotherapy. Keratin granuloma in a field of intense chronic inflammation. Note foreign-body giant cells next to dead or degenerating keratinized cells. × 175.
Fig. 2. Case No. 11: 52-year-old male with squamous cell carcinoma of the vocal cord. A, Preirradiation biopsy showing a well-differentiated carcinoma. X 350. B, Cervical lymph removed 6 months after irradiation showing keratin granulomas with giant cells around seemingly nonviable eosinophilic material and "ghost" tumor cells. X 190.
Fig. 3. Case No. 4: 52-year-old woman with squamous cell carcinoma of the esophagus. A, Preirradiation biopsy showing a well to moderately differentiated but poorly keratinized tumor. × 360. B, Esophagus at autopsy, 7 weeks postirradiation showing marked keratogenesis with degenerating pearls of cornification. Several foreign-body giant cells are also seen in this field. × 185.
Fig. 4 (left). Case No. 18: 70-year-old male with clinical diagnosis of carcinoma of the esophagus. X-ray picture of the upper gastrointestinal tract after ingestion of barium meal. Note the irregular filling defect in the midregion of the esophagus which is characteristic of a malignant tumor.

Fig. 5 (right). Case No. 18: section of the base of an esophageal ulcer obtained at autopsy 4 weeks after irradiation. No tumor was recognized grossly at autopsy. Note foreign-body giant cell reaction around “ghost” keratinized tumor cells and keratin debris. × 350.
Fig. 6 (upper). Well-differentiated squamous cell carcinoma of the cervix exhibiting marked keratogenesis with formation of foreign body giant cells. This lesion was not previously irradiated. X 185.

Fig. 7 (lower). Ruptured epidermal inclusion cyst showing active phagocytosis next to keratin debris. X 175.
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