LEUKOPLAKIA OF THE ESOPHAGUS

GEORGE S. SHARP

Fellow in Cancer Research, Memorial Hospital, New York City

Leukoplakia of the esophagus rarely receives clinical recognition, although many excellent studies (most recently that of Schaeer) have shown this process to be commonly found at autopsy. There is, however, little in the literature concerning its significance. It is our hope that with the increasing application of esophagoscopy, clinical observation, and biopsy, material may be accumulated to show that leukoplakia of the esophagus is a process similar to leukoplakia involving other mucous membranes of the body and that for the same reasons it constitutes a precancerous lesion.

Leukoplakia has been known under various names since 1818, when it was first described by Alibert (1) in a case report of general ichthyosis which involved extensively the cutaneous surfaces of the body and the oral mucosa. It was not until the latter part of the nineteenth century, however, that leukoplakia of the esophagus was first described by Bucher (3) and Rothmann (10), who recognized it as a process similar to that found on the mucous membranes of the mouth. Since that time work has been confined to the pathologic histology of leukoplakia and except for its recognition as a clinical entity by Jackson and others, there are no clinical data on this subject.

ETIOLOGY OF LEUKOPLAKIA

The esophagus is the narrowest and at the same time one of the most muscular of the alimentary tubes. Much the same irritants that are present in the oral cavity are active in the esophagus. Being extremely narrow, however, not only is it subject to friction, but it is also in close contact with liquid and solid foods. This is particularly true of the lower end, where liquids are momentarily arrested for the first time during digestion.

The more important factors mentioned in the literature as
causing esophageal leukoplakia are hot liquids, hot foods, and alcoholic drinks. The significance of hot liquids cannot be overestimated. The more recent case histories, where this question has been carefully studied, support this opinion. The patient may state not only that he liked hot tea and coffee but even that he was accustomed to drink them hotter than did other members of the family. Fischer (5) has emphasized tea and coffee drinking above all other possible causes. Smoking and alcoholism are also believed to be important causative agents. A statistical study of the sex incidence for leukoplakia of the esophagus might offer supportive evidence, but this is not yet available.

Among local factors, probably the most important rôle is played by sepsis in the oral cavity. We have observed that intraoral leukoplakia is invariably associated with pyorrhea, infected tooth sockets, stumps, diseased tonsils, and ulcerating intraoral cancer. It seems that the toxic products from such lesions are equally active on the esophageal mucosa. Our case histories and examinations in general support this opinion.

The available evidence at hand, therefore, favors the hypothesis that chronic irritation in its various forms is the most important of the known causative agents for leukoplakia, both oral and esophageal. The same factors are believed to be significant in the etiology of cancer of the esophagus. This seems logical when one finds the two conditions associated, especially when leukoplakia is the antecedent lesion.

Lindemann (8) observed that there were two local conditions frequently associated with leukoplakia. The more common one was a chronic superficial esophagitis, but it was noted that esophagitis was frequently observed in the absence of leukoplakia. The second lesion was the esophageal varix. Other writers have suggested the importance of syphilitic and tuberculous ulcers. Ulcerations and scars from caustics and poisons have also been mentioned.

Certain constitutional factors seem important. Age is undoubtedly significant, but in a symptomless and hidden condition this question will remain chiefly a speculative one. Lindemann observed cirrhosis of the liver with esophageal varices in many cases of leukoplakia. He also mentioned the frequent association with gastric ulcer and other gastric disorders which cause regurgitation. A history of gastric disease is rarely found in our case reports.
The problem, therefore, is still inductive. There remains an unknown factor which calls forth such an abnormal response of the mucous membrane as to bring about leukoplakia in certain individuals and not in others.

Leukoplakia in the esophagus is symptomless in itself, unless it causes partial or complete obstruction, as in the three cases reported by Starr (12).

**Pathology**

Leukoplakia of the esophagus was early recognized as analogous to leukoplakia in the oral cavity by Rothmann and Bucher. These authors described it as consisting of raised whitish plaques, round, oval or elongated in shape, with regular or irregular borders. The surfaces appeared rough or smooth, and the plaques had an appearance not unlike Peyer’s patches in typhoid fever. The plaques show no orderly arrangement except in the case of the papillary millet-seed type which Bucher noted as occurring in longitudinal striations. He stated that this striated appearance and the characteristic formations were due to the arrangement of the corium papillae. Lindemann considered the origin to be purely one of mechanical effect and a result of the forces of digestion.

Leukoplakia was early demonstrated to occur most frequently in the lower third of the esophagus. Where it covered the entire mucosa, it appeared to be in a more advanced stage in the lower portion. Bucher also observed that cancer was more common in the lower third. This has led to much speculation as to the relation existing between the two conditions.

Knaut (7) was probably the first to give a detailed histological description of leukoplakia. He observed that the tunica propria was thickened and elongated. This caused thickening of the epithelium, to from five to ten times the normal, coincident with an increase in the number of cells. Lindemann demonstrated that the thickening of the epithelium was not as important as the increase in the number of cells. He compared true leukoplakia with the epithelium in chronic esophagitis and found them to be equally thickened. However, in the latter condition he found that the thickening was due to edema of the epithelial cells rather than to an actual increase in cell number. He also observed that post-mortem changes in the normal esophageal mucosa were characterized chiefly by an edema of the cells and intercellular
spaces. In this connection Aschoff (2) has shown that post-mortem changes do not simulate leukoplakia in any respect and that the leukoplakic plaques are more resistant to these changes than normal mucosa.

Fischer emphasized the cellular increase in the epithelium. He found an average of from twenty to twenty-four cell layers in the normal epithelium and twice or more than twice that number in the leukoplakic areas. He stressed the subepithelial infiltration of lymphocytes, eosinophiles, and leukocytes. He also observed that giant cells were common immediately beneath the plaques. Schaer has recently shown, however, that giant cells are frequently found in the subepithelial layer under normal conditions.

Fischer reported that Lubarsch found an increased glycogen content in leukoplakia and that he also demonstrated an increased cornification, by Gram staining. The latter characteristic is more prominent in the superficial layers of the epithelium in the advanced types of leukoplakia. The cornification is associated with an increased compactness of the cells and a gradual loss of nuclei.

**Degrees of Leukoplakia:** Leukoplakia is the same pathological process whether it appears as a diffuse film or as multiple elevated plaques. The degree of advancement appears to be dependent on its duration. Schaer has written the most complete survey on the histopathology. His analysis is based on 237 routine autopsies, in two-thirds of which he observed leukoplakia. Although we are not entirely in accord with Schaer’s attempt to grade leukoplakia, we wish to consider his grouping as explanatory of the successive degrees of the process.

Leukoplakia of the esophagus is divided into three grades. Grade I is by far the most common. It is characterized by a diffuse, patchy, opaque film with the simplest histologic changes, namely, a thickening of the epithelial layer and an increase in the number of the epithelial cells without changes in the basal layer. This type is most commonly observed over the lower half of the mucosa, but it may cover the full length, as in the first case in the present series.

Grade II includes the flat mucosal warts or plaques which show greater epithelial activity, with many mitotic figures, an elongation of the corium papillae, and an increase in the subepithelial infiltration. This grade is more frequently found in the lower third of the esophagus. When it is limited to that portion,
the filmy leukoplakia of Grade I ordinarily covers the remaining mucosa.

Grade III is characterized by elevated, opaque, whitish plaques of irregular size and shape, with a varying degree of induration. Histologically there is a further proliferation of the epithelium in both directions, toward the surface in pile-like formation and toward the deeper tissue layers by an extension downward of the tunica propria, which frequently invades the muscularis. The subepithelial infiltration is more marked, and mild inflammatory changes may be seen.

All degrees may be observed through the esophagoscope, although there may be some difficulty in recognizing the opaque, filmy type under artificial illumination. The advanced variety is readily demonstrated, as shown in the illustrations of Case 3. The esophagus normally is collapsed, and the lumen appears through the esophagoscope to be obliterated. In advanced leukoplakia, however, the lumen appears partially or completely patent. This decreased pliability of the walls is due to the thickening of the epithelium, with cornification, and the infiltration of the submucosa. A complete gross description of leukoplakia may be obtained by esophagoscopy and its relation to cancer noted, when the two are coexistent.

A Precancerous Lesion

A large group of carcinomas develop from normal cells which have been altered by a series of changes induced by chronic irritation. The abnormal cells which demonstrate these preliminary cell changes are considered to be potentially malignant. Leukoplakia of the mucous membranes probably represents the largest group of precancerous lesions. Sufficient clinical and histologic evidence is available to support this sequence of events on the oral mucosa to make the leukoplakic origin of a certain percentage of intraoral carcinomas unquestionable.

Bucher first observed that leukoplakia of the esophagus was a common condition at autopsy. He concluded that, if leukoplakia were a precancerous lesion, leukoplakia and cancer should more frequently be found together. In other words, the incidence of carcinoma of the esophagus was low as compared with that of leukoplakia. We find this fact equally true in relation to intraoral leukoplakia and carcinoma. Schaer, on the other hand, has recently demonstrated a degree of leukoplakia in all of his cases
of carcinoma of the esophagus. In his twelve cases, however, he did not find Grade III leukoplakia associated with cancer in a single instance, while Grade II was found eight times and Grade I five times. This frequency is even greater than that of leukoplakia in association with intraoral cancer. Schaer concluded that leukoplakia coexistent with cancer showed epithelial changes which were absolutely benign and which in no way constituted a lesion which could develop carcinoma. However, he agreed that such formations might by further cellular changes produce cancer.

This lack of definite histologic evidence may be applied equally to intraoral cancer developing in association with leukoplakia; yet the clinical evidence supports the leukoplakia-cancer sequence in many cases. The only method whereby the intermediate stages may be observed in the esophagus is through the esophagoscope, as is shown in Case 3. Here a relatively early carcinoma was coexistent with a far advanced leukoplakia. The leukoplakia completely surrounded and partially covered the growth. It is hardly likely that leukoplakia could reach such an advanced stage of development during the clinical course of carcinoma of the esophagus without the initial stages being present before the origin of the carcinoma.

The independent development of leukoplakia and cancer in the same organ has not been considered. This is of frequent occurrence in the oral cavity, where cancer develops on one mucosal surface and a degree of leukoplakia is present elsewhere, but in no proximity to the growth. It might be argued that the cancer overshadowed a preexisting leukoplakic plaque, but this is unlikely. It is more reasonable to assume that the irritating factors brought about a leukoplakic response in one area and the same or additional factors caused cancer in another. This is likely to occur in the esophagus where the superficial leukoplakia is associated with cancer. However, where advanced leukoplakia and cancer are associated, we find the more advanced process surrounding the cancer (Cases 3 and 4).

There are numerous instances, in various organs, where it is universally recognized that certain pathological conditions are followed in a variable but high percentage of cases by carcinoma (Ewing, 4). Such a lesion does not have carcinoma in itself, but merely precedes and favors the development of carcinoma. In this group we believe leukoplakia of the esophagus should be included.
The following cases from our accumulating records on this subject are reported as illustrative of the clinical characteristics and significance of leukoplakia of the esophagus.

**Case Reports**

**Case 1: Superficial Leukoplakia of the Esophagus, A Common Condition at Autopsy:** W.D., male, aged fifty-two, was admitted to Memorial Hospital May 1, 1930. The history dated back three months to the occurrence of shooting pains to the left ear, which gradually increased in severity. Five days before admission there was a sudden hemorrhage from the mouth. For years the patient drank three cups of coffee and two cups of tea daily. He smoked a pipe almost constantly during his waking hours. No history was given of alcoholism or syphilitic infection. The examination showed a well developed and well nourished man with an ulcerated, indurated growth involving the floor of the mouth. The tongue was drawn to the left and motion was limited. Pyorrhea was marked, and teeth were carious. Leukoplakia was not evident on the oral mucosa. In the left neck there were multiple metastatic nodes.

A biopsy specimen from the primary lingual growth showed infiltrating squamous carcinoma, Grade II, relatively radiosensitive.

A program of external and interstitial irradiation was outlined according to the lethal tissue dosage for squamous carcinoma. Five days after the implantation of the radon seeds, it was necessary to remove a portion of the tongue to secure better drainage. This was
performed with the cautery under general anesthesia. A fatal postoperative lung abscess developed.

At autopsy the esophageal wall was normally flaccid. The upper half of the mucosa was entirely covered by a diffuse, filmy leukoplakia. In the lower half it was patchy, although still quite diffuse. The plaques had smooth surfaces and irregular, indefinite borders. The levels of constriction did not alter the distribution or degree of leukoplakia.

Microscopic examination showed a moderately thickened epithelium with an average of thirty cell layers (Fig. 1). The basal cell layer was within normal limits and the subepithelial tissues were normal.

Comment: This case is one of several in the recent autopsy files which demonstrates the superficial type of leukoplakia. Schaer observed this grade in two thirds of his routine autopsies. The etiologic factors presented in the history were tea and coffee drinking and pipe smoking. Oral sepsis is the most important associated condition. It is demonstrated in this patient by poor oral hygiene, pyorrhea, carious teeth, and an ulcerating growth. The toxic products from widespread infection of this degree must be considered as active chronic irritants in the development of leukoplakia.

Case 2: Advanced Leukoplakia Involving the Mucous Membrane of the Oral Cavity, Hypopharynx, and Esophagus, with the Development of Carcinoma of the Base of the Tongue: C.S., male, aged fifty-five, was admitted to Memorial Hospital Feb. 18, 1930. The history started with a sore throat in July 1929. The tongue gradually became stiff and less mobile. The patient smoked two or three cigars and a half package of cigarettes daily. He drank an average of two cups of coffee daily. Alcohol was limited to an occasional cocktail. A history of syphilis was denied. The leukoplakia had first been noticed on the tongue about five years previously. It remained symptomless, unless the initial symptom of stiffness of the tongue could be attributed to it.

Examination showed a well developed and fairly well nourished man with difficulty in speaking and swallowing. The primary lesion was a papillary, ulcerated growth in the left base of the tongue. An advanced, pearly-white and indurated leukoplakia surrounded the lesion and covered the dorsum of the tongue. A lesser degree of leukoplakia covered the floor of the mouth, both cheeks, and hard palate. The left upper and lower cervical chain of lymph nodes contained multiple metastases.

The treatment outlined was external irradiation to each neck with radon implants into primary and metastatic lesions later. Two weeks after the last treatment the patient was admitted to the hospital for hemorrhage from the base of the tongue. A new metastatic lesion appeared in the right neck at this time. On Feb. 26 and March 4 the
FIG. 2. POST-MORTEM APPEARANCE OF LEUKOPLAKIA OF THE ESOPHAGUS OF THE ADVANCED TYPE, SHOWING THE GRADATIONS FROM THE FILMY, DIFFUSE TYPE IN THE UPPER THIRD TO THE ELEVATED LEUKOPLAKIC PLAQUES IN THE LOWER THIRD
left and right cervical nodes were exposed successively, and the involved areas were treated with radon in gold seeds. The primary growth showed a marked regression from the cross-radiation, and interstitial application was delayed pending an abeyance of the reaction. All went well until April 18, when the patient developed bronchopneumonia and cardiac decompensation. He died one week later.

The post-mortem examination of the leukoplakic involvement demonstrated an advanced type over the tongue, hypopharynx, and esophagus. The base of the tongue was covered by an indurated white sheet of leukoplakia which completely surrounded the carcinomatous crater. The process extended over onto the posterior wall of the hypopharynx in a lesser degree. It was continuous with a diffuse, filmy leukoplakia over the upper third of the esophageal mucosa (Fig. 2). It became patchy and indurated over the middle third. In the lower third the plaques appeared elevated, and the leukoplakia appeared grossly to be in the same degree of advancement as the process on the tongue.

As viewed microscopically, the leukoplakia in the lower third of the esophagus was characterized by an increase in the thickness and the cellular structure of the epithelium (Fig. 3), which had an average of forty-two cell layers. An increased cornification in the superficial layers was clearly demonstrated. The corium papillae were elongated and in the
submucosa there was a marked inflammatory reaction consisting chiefly of perivascular infiltration of lymphocytes. Leukoplakia was not present on the gastric mucosa.

Comment: This patient demonstrates the advanced degree of leukoplakia on the oral and esophageal mucosa. Furthermore, this degree of leukoplakia is shown to be capable of malignant tendencies by the development of a carcinoma in the base of the tongue. Therefore, the clinical and histologic similarity of the process in the two locations supports the opinion that esophageal leukoplakia is likewise potentially malignant.

CASE 3: Advanced Leukoplakia and Carcinoma of the Esophagus as Demonstrated by Esophagoscopy: J.H. von G., male, aged fifty-three, was admitted to Memorial Hospital May 1, 1930. The history began in July 1929, with difficulty in swallowing solid food, which caused a sensation of sticking in the “throat.” For two months prior to admission there had been difficulty in swallowing semi-solid foods, and deglutition had become painful. There had been no difficulty with liquids. The patient had habitually smoked eight to twelve cigars daily and had used alcohol in moderation for years. He drank two cups of coffee daily. Spicy foods were never favored.

Examination showed a fairly well developed and poorly nourished man who had evidently lost weight. The oral cavity was free from gross infection. The oral mucosa was of good color and there was no leukoplakia.

The esophagoscopic examination was described by Dr. Quick as follows. The sphincter was easily passed. The lumen appeared patent, as though the walls were abnormally rigid (Fig. 4). The upper third of the mucosa was covered by a diffuse, opaque, slightly roughened leukoplakia. Midway down the leukoplakia became patchy and slightly elevated, and the surfaces were irregular. In the lower third the mucosa was entirely covered by leukoplakia of advanced degree. The walls were thickened and did not have the normal pliability. The lumen was diminished to half the normal width. In the extreme lower end there was a low papillomatous and ulcerated growth about 1.5 cm. in diameter, surrounded by indurated and dirty white leukoplakia. The growth seemed to spread out beneath the leukoplakia with a further constriction of the lumen. It was possible to pass the 50 cm. Jackson esophagoscope by the lesion, which extended 4.0 cm. down the anterior wall. The same degree of leukoplakia was observed around the lower border of the growth. A biopsy was taken near the periphery of the growth.

Microscopic examination showed an epidermoid carcinoma, largely squamous but with some radiosensitive anaplastic areas, Grade II, mostly radioresistant. An advanced degree of leukoplakia was shown to be closely related to the new growth (Fig. 5). The epithelium was
Fig. 4. *Intra-esophageal Pictures at Consecutive Levels from Above Downward*

Plates 1–4 demonstrate the gross characteristics of advanced leukoplakia from the upper sphincter to the level of the cancer. Note the patency of the lumen in Plate 1. Plates 2, 3, and 4 show the distribution and degree of advancement of the leukoplakia from above downward. Plate 5 illustrates the low papillary growth which is surrounded by the most advanced stage of leukoplakia. Plate 6 shows the extensive leukoplakia causing a narrowing of the lumen.
thickened, having an average of fifty-four cell layers. The corium papillae were elongated. The infiltration of the submucosa with lymphocytes was marked.

Treatment by external irradiation with the radium element pack was outlined. During the first three weeks the patient received 250,000 millicurie hours at 20 cm., divided equally between the anterior and posterior portals. Six weeks later the edema from the early radium reaction caused a temporary obstruction and it was necessary to perform a gastrostomy. Death occurred eighteen months after the onset of symptoms.

Comment: The illustrations obtained during the esophagoscopy examination of this patient demonstrate quite accurately the conditions found (Fig. 4). There was a progressive degree of leukoplakia from the opaque, superficial type in the upper third of the esophagus to the advanced and elevated lesion in the lower third. The greatest development of the leukoplakia was shown in the vicinity of the growth. This stage of advancement is supportive of the existence of the leukoplakia before the origin of the cancer.

Through the esophagoscope the esophageal walls appear to be
collapsed under normal conditions. In the presence of advanced leukoplakia the lumen frequently appears patent. This feature was particularly well demonstrated in the above patient. The diminished pliability is due in all probability to the added support given the walls by the leukoplakic process.

**CASE 4:** Advanced Leukoplakia and Carcinoma of the Esophagus as Demonstrated at Autopsy: G.D., male, aged sixty, was admitted to Memorial Hospital March 22, 1930. There was a history of hoarseness dating back four months. A cough developed and was accompanied by hemoptysis. For one month sharp pleuritic pains had occurred occasionally in the lower left chest. No symptoms referable to esophageal obstruction were noted. The patient had always been a heavy smoker, consuming a package of pipe tobacco daily, and had used alcohol excessively. There was a history of indigestion for twenty years, suggestive of peptic ulcer.

Examination showed a fairly well developed and cachectic man, appearing chronically ill. Pyorrhea, diseased tonsils, chronic glossitis, and caries of the remaining teeth indicated gross infection of the oral cavity. There were several retained roots. There was no leukoplakia on the oral mucosa.

On the basis of the history, a bronchoscopic examination was performed, disclosing a papillary, ulcerated growth in the left middle bronchus.

Esophagoscopic examination showed a patent lumen. The upper third of the mucosa was covered by a diffuse, opaque leukoplakia. This increased in degree and in the lower third appeared as an elevated, roughened layer over the mucosa. It completely surrounded a papillary ulcerated growth in this region. The lumen was not contracted and the growth caused little obstruction. The obturator could be easily passed beyond the growth. A biopsy was taken from the papillary area.

Microscopic examination showed a cellular carcinoma resembling the transitional-cell type, Grade III, radiosensitive.

The Wasserman reaction was four plus.

Palliative treatment was outlined: external irradiation with the radium element pack. During the first three weeks 160,000 millicurie hours were given at 15 cm. distance. This was divided equally between the anterior and posterior portals. The growth regressed remarkably, although it left an esophagobronchial fistula, which caused a fatal pneumonia.

At autopsy the cancer was shown to arise in the esophagus and to have invaded the bronchus secondarily. The primary growth involved the lower half of the esophagus and measured 9.0 cm. in length and 6.0 cm. in the widest diameter. It was ulcerated over the entire surface and was covered by a greenish slough. An opaque, rather superficial leukoplakia covered the mucosa of the upper third of the esophagus. However, in the vicinity of the growth it was elevated and the surface
was roughened, as seen in leukoplakia of advanced degree. Numerous superficial erosions were scattered through the leukoplakic area. The growth ulcerated into the primary bronchus, causing two adjacent fistulous openings. The bronchus was plugged with mucus and food particles. There were several focal pneumonic consolidations in the lower lobe.

The microscopic examination of the leukoplakia demonstrated the advanced degree (Fig. 6). The epithelium was thickened and contained an average of from fifty-six to sixty cell layers. The epithelial cells appeared more active and there was not as much cornification as observed in other advanced cases. The subepithelial infiltration was very prominent. It consisted chiefly of lymphocytes, although there were many eosinophiles and leukocytes.

Comment: Certain factors are presented for the etiology of leukoplakia in this patient. He was a heavy pipe smoker. The chronic alcoholism was a habit of many years' duration. The history of indigestion for the past twenty years was very suggestive of a gastric or duodenal ulcer. The autopsy findings, however,
were negative for ulcer and the indigestion was probably due to a chronic gastritis of alcoholic origin. Hot liquids and foods should not be overlooked in this connection as being important. The gross oral infection in this patient is probably the most important activating condition. In addition, there was the superficial esophagitis. The latter was probably present for a considerable period, as esophagitis is frequently observed in association with oral infection, as shown by Lindemann. Toxic products from such sources may reasonably be considered irritants, particularly to the esophageal mucosa, before they are altered by digestive agents.

Prognosis

Leukoplakia of the esophagus is recognized more frequently through the increasing use of esophagoscopy. Clinical judgment on the prognosis of this abnormal process has heretofore been entirely lacking. The similarity of leukoplakia in the esophagus and oral cavity is recognized on clinical and pathological study. The prognosis of intraoral leukoplakia is becoming increasingly more guarded, particularly for advanced lesions. The same prognosis is justified for esophageal leukoplakia.

Conclusions

1. Leukoplakia of the esophagus is a common pathological condition.

2. Carcinoma of the esophagus is frequently associated with leukoplakia in a greater or lesser degree.

3. Leukoplakia in the esophagus is a similar pathological process to leukoplakia in the oral cavity.

4. Esophagoscopy will permit earlier and more frequent recognition of leukoplakia.

5. Leukoplakia of the esophagus may be a precancerous lesion in the advanced stages.

Bibliography


