Difficulties in management of vocal cord precancerous lesions

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Introduction

In the wide and varied spectrum of hyperplastic changes in the laryngeal mucosa, the conception of precancerosis has not yet been exactly determined. There is a lot of controversy about the histological features of precancerosis, its role in the process of malignancy and its aetiology and therapy. Clinicians and histologists do not always agree upon the clinical and histological appearance of hyperplastic aberrations in the laryngeal epithelium, typical of precancerosis. Because of the different evaluation of hyperplastic aberrations and an inadequate use of the conception of premalignant lesions, their prognosis and therapy are also varied.

Some authors consider all hyperplastic aberrations as precanceroses—from simple hyperplasia or epithelial keratosis to carcinoma-*in-situ*. This attitude, however, leads to confusion and false interpretation of the term. The success of treatment with various methods cannot be objectively evaluated as long as some authors regard all hyperplastic aberrations of the laryngeal mucosa—with the exception of infiltrative carcinoma—as precanceroses, while others define the term exactly.

The precancerous stage is an established condition of the tissue from which, sooner or later, malignancy may develop. Therefore, the main questions in the problem of precancerous lesions are, under which conditions and when the pathologic aberrations of the tissue, the so-called precancerous stage, i.e. aberrations that do not show all histological, biological and clinical properties of cancer, become malign (Del Bo and Rossi, 1957; Kambić, 1965; Kambić, Lenart and Radšel, 1975).

As long as we do not come to an agreement as to what the histological appearance of precancerosis looks like, there will be differences in opinion among us, and any objective evaluation of the various therapies will remain impossible. It is only when the typical histological appearance of the precancerosis is determined that our points of view will be the same, we shall speak the same language and be able to evaluate our therapeutic results objectively.

Difficulties appear, however, already in the clinical terminology. Various authors describe identical clinical changes by different names, like keratosis, pachydermia, leucoplakia or hyperkeratosis and, even more frequently, a clinical term is used for histological conception and *vice versa*, which all leads to confusion.
The terms pachydermia and leucoplakia have no definite meaning at all. The term hyperkeratosis is completely inaccurate, for it is well known that a healthy laryngeal epithelium is not keratotic, therefore, we may only talk about a horny condition or about keratosis.

In the literature, 16 different classifications of hyperplasia have been found (Kambić, Lenart and Radšel, 1975). Many are almost similar, identical even, others differ considerably. All classifications of the laryngeal hyperplastic aberrations are based on the approach of the histological appearance of these changes to the histological features of cancer. The temporary histo-pathological appearance and biological features of hyperplastic aberrations do not always correlate. Therefore, a lot of difficulties arise, in particular when classifying the aberrations into the group of the so-called precancerous lesions.

Does the development of cancer regularly require a preparatory stage of precancerosis and, is it possible that it develops from healthy tissue, in this case, from the normal epithelium of the laryngeal mucosa? These are the questions we have to answer before we can discuss the conception of precancerosis objectively and its role in the development of cancer (Kambić, 1965; Lambić, Lenart and Radšel, 1975).

At this point we should ask ourselves whether, in our terminology, the term precancerosis is appropriate at all. Enough evidence has grown up to show that malignancy may develop from the clinically perfectly healthy epithelium and that this occurs even more frequently than from the condition of precancerosis. By contrast, the changes that are histologically diagnosed as precanceroses never turn malign. The term precancerosis, if adequate at all, is the empirical result and has been adopted through experience. It appears it would be better to introduce the term ‘risky epithelium’ instead of the term precancerosis which by itself definitely indicates cancer.

Our classification of precanceroses

On the basis of 2,700 biopsies of the pathologically changed laryngeal mucosa and an extensive follow-up, we have classified hyperplastic aberrations according to their histological features into four groups:

The epithelium is thicker, mainly on account of cells in the spinous layer. The basal layer is unchanged. In the subepithelial tissue, immunocompetent cells are very limited (Fig. 1).

The epithelium is thicker on account of ‘basalification’. Basal cells extend to the middle of the epithelium. Pathological mitoses and atypias are not seen.
The subepithelial space contains more immunocompetent cells (Fig. 2).
**FIG. 1**
Simple hyperplasia. (Haematoxylin-eosin, ×400.)

**FIG. 2**
Abnormal hyperplasia. (Haematoxylin-eosin, ×400.)
Both groups represent basically a hyperplastic process in the epithelium of the laryngeal mucosa which usually does not become malign and is explicitly reversible.

(3) Hyperplasia atypica—Atypical hyperplasia.
This group includes all changes, from atypias to carcinoma-in-situ. Cells of the entire hyperplastic epithelium have the shape of basal cells. Nuclei are hyperchromatic and slightly polymorphic. Here and there, mitoses appear that are partly atypical. The subepithelial space is full of immunocompetent cells, which is particularly characteristic for this aberration (Fig. 3).

(4) Carcinoma.
(a) Carcinoma-in-situ—Pre-invasive cancer.
Basal membrane is apparently preserved. All signs of cell and nuclear atypias, macronucleoses, anisonucleoses, cellular atypia, pathological mitoses, appear in the surface of the epithelium. Signs of cell dissociation are seen and an intense reaction of the mesenchyme (Figs. 4 and 5).

(b) Carcinoma invasivum—Invasive cancer.
Among the precancerous lesions of the larynx we count solely the third group. The percentage of malignant alterations is relatively high among the changes classified in this group.

Keratinization has not been considered in our classification, since our experiences show that it is not particularly significant for the process of malignancy. The same can be said for histochemical aberrations; cellular metabolism changes with every moment while the shape of cells is more constant. The shape of papillae has also been neglected. We have used the principle that the process of cancerization results from two events, namely:

(1) changes in the epithelium; reproduction and maturation of cells, and,

(2) reaction of the mesenchyme which reflects the common reactions of the organism.

Until 1969, 1,500 biopsies of hyperplastic aberrations in the laryngeal mucosa were performed. Among them, 81 were classified as atypical hyperplasias; 72 patients were treated medically and among them, 16 developed malignancy within one to three years after the biopsy, i.e. 22 per cent. In the period from 1969 to 1975, 1,200 biopsies were carried out. The precancerosis, i.e. the third group in our classification was seen in 52 patients; however, malignancy did not develop because radical therapy was used for all the patients, namely, stripping of the vocal cord.

**Therapy**

Therapy for the precancerosis is rather controversial. Opinions about the effectiveness of the various methods of treatment differ considerably,
FIG. 3
Atypical hyperplasia. (Haematoxylin-eosin, ×400.)

FIG. 4
Intraepithelial cancer. (Haematoxylin-eosin, ×400.)
Scheme of our classification of hyperplastic aberrations on laryngeal epithelium: 0—Normal epithelium, 1—H. Simplex, 2—H. abnormalis, 3—H. atypica (premalignant lesion), 4a—Ca. in situ, 4b—Ca. invasive.
which is the result of different interpretations of the term. Most of the authors (Eggemann, 1973; Münzel, 1973; Kleinsasser, 1962 and 1964; Miller and Fischer, 1971 and Miller, 1974; Dalby, 1974; Som, 1974; Strong, 1974; Macbeth, 1970; Lederman, 1963), who reported on the success or failure of particular therapeutic methods, had not treated solely the precancerosis, in its real definition of the term, but also other hyperplastic aberrations in the laryngeal epithelium, from simple hyperplasia to carcinoma-in-situ.

The precanceroses are managed by medical treatment, surgery, actinotherapy, cryotherapy, radiotherapy and laser. None of the therapies is causal, they are all directed to treat the effect and not the cause, which remains unknown. For treatment, however, a therapy should be used which is considered the most effective, the simplest, and which causes the least impairment to the function of the organ. On the grounds of our experiences, we have concluded that the treatment of choice for vocal cord precancerous lesions is stripping (de-epithelialization).

Material and results

In the period of 1960 to 1975, 133 precanceroses of the vocal cord were diagnosed on the basis of our classification of hyperplastic aberrations. Until 1969, 72 patients received medical treatment (vitamins; inhalations; change of occupation, if necessary; avoidance of vocal abuse, alcohol and tobacco; balneotherapy; etc.) and 9 patients were treated by surgery (stripping). None of the patients treated medically showed significant improvement; on the contrary, 16 developed malignancy. In contrast, surgery was proven successful in all the patients. For this reason, since 1969, all the patients in whom the diagnosis of precancerosis of the vocal cord was proven by histology (52) and the 9 patients who were previously unsuccessfully treated medically (until 1969) have been managed by stripping. De-epithelialization has been performed in 61 patients. In the patients with limited precancerous changes which did not involve more than half of the vocal cord, de-epithelialization has been carried out by microlaryngoscopy. On the other hand, complete stripping has been done by thyrotomy following a prior tracheotomy.

Before excision of the mucous membrane, physiological solution is injected submucosally into the vocal cord so that the mucous membrane in lifted and stripping easily carried out. Bleeding is minimal. If thyrotomy is performed, a tracheal cannula is inserted but only for a few days. If the process involves both vocal cords and complete de-epithelialization has to be done, it is carried out in two sessions to avoid stenosis.

In most of our patients the vocal cord was re-epithelialized within three weeks and its function has been completely regained. The excised mucous membrane was sent for serial histological examination. Histology revealed that the atypical hyperplasia (= precancerosis) accompanied intraepithelial cancer in 3 patients and was associated with infiltrating cancer in 2 of them.
In the case where intraepithelial cancer had been proven, no additional treatment was instituted. When the infiltrating cancer had been diagnosed, cordectomy was additionally performed. The patients were followed up at intervals of two weeks initially, later at longer intervals. Very good therapeutic results were obtained, 47 patients were cured, the mucosa looked smooth and pale. Functional results were excellent. In 9 patients, however, residual disease occurred. The same therapy was repeated and proven successful in all patients.

In the final evaluation of our results, we did not consider 5 patients because serial histological diagnosis revealed infiltrating carcinoma in 2 and intraepithelial cancer in 3 of them (Table I).

Discussion

Assessment of the therapeutic results of de-epithelialization in precanceroses has been limited to the patients in whom the diagnosis of premalignant lesions was determined. All other benign or malignant forms of hyperplastic aberrations have not been considered.

Therapy for precancerosis is rather controversial because the term is not defined. Medical therapy is practically useless for atypical hyperplasia (= precancerosis). Preference is given to irradiation and surgery. Surgery, however, has many advantages because the diagnosis of precancerosis can only be determined exactly if the clinically changed mucosa has been completely removed from the vocal cord; otherwise the diagnosis may be premature, since it is known that the changes, evaluated as precanceroses, are frequently associated with intraepithelial or infiltrating carcinoma.

After stripping, functional results are always satisfactory if we pay attention to the muscles and ligaments. After irradiation, however, the laryngeal function does not always remain perfect because, if we choose irradiation at all, a curative dose, as for a malignancy, has to be applied. It is known that differentiated cells are very resistant to irradiation therapy (Lederman, 1963), therefore, the success of irradiation remains doubtful. Münzel (1973) reports that irradiation eliminates the submucous inflammatory infiltration. The question is, however, whether this infiltration represents the cause or the result of the changes in the epithelium. If the submucous inflammatory infiltration is the result of the epithelial changes, which it probably is, we have not gained anything by irradiation.

Follow-up and surveillance are much easier after surgery than after irradiation, since it is known that, in some patients, radiomucositis lasts for a long time.

Besides, there is also the problem of induction of cancer by irradiation (Włodyka, 1962, Kambić and Ravnihar, 1967); therefore, irradiation of benign processes in young people should be avoided.

In our opinion, functional results are of secondary importance for precanceroses. It is particularly important to remove premalignant
<table>
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<th>Therapy</th>
<th>Number of Patients</th>
<th>Turned Malign</th>
<th>Cured</th>
<th>Improved</th>
<th>Unchanged</th>
<th>Recurrences of residuals</th>
<th>Lost from follow-up</th>
<th>Died</th>
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<td></td>
<td></td>
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<td>(Vitamins, inhalations, avoidance of vocal abuse, smoking, alcohol, etc.)</td>
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<td>16</td>
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* Three cases of carcinoma in situ and two cases of infiltrating carcinoma were not considered here; they were diagnosed on serial histologic examination of the changed mucosa after stripping.
aberrations and to prevent malignant change in the tissue, and this, on the basis of our experiences, is achieved by de-epithelialization.

In future, hormonal therapy should also be considered, i.e. therapy with androgens, as reported by Loewit et al. (1977). On the basis of our experimental work we have also concluded that androgenous hormones play a very important role in the occurrence of hyperplastic aberrations in the laryngeal mucosa (Loewit et al., 1977; Kambic and Lenart, 1968; Kambic and Lenart, 1971).

In an experiment on animals, conducted in 1968, testosterone-propionate was injected into 10 castrated male and female dogs. Catarrhal laryngitis with keratotic aberrations in the vocal cord were observed. Histological examination revealed hyperplasia of the epithelium which matched the second group of our classification.

During the second part of the experiment, it was observed that these changes were irreversible. On the other hand, our opinion was confirmed by the fact that, in the patients that we had treated, there were no women at all in the precancerous group, although they had been subjected to the same macro- and micro-conditions.

Considering our results of the treatment and comparing them with those reported by the others, it appears that stripping (de-epithelialization) is the method of choice for the treatment of precancerosis of the vocal cord.

Abstract

Hyperplastic aberrations are differently classified and the term of precancerosis diversely interpreted; therefore, it is extremely difficult to evaluate the effectiveness of particular therapeutic methods.

A standardized classification would enable an objective assessment of the treatment for precanceroses.

Our own conception of the histologic patterns in precanceroses is presented.

In the period 1960–1975, a total of 2,700 biopsies were performed in patients with hyperplastic aberrations in the vocal cord mucosa. In 133 patients, histology revealed precancerosis. In the patients who had received medical therapy, no improvement was obtained; on the contrary, in 16 patients the process became malignant. Among the patients who had undergone de-epithelialization (61), 44 were cured. After the de-epithelialization, no precancerous case turned malignant.

De-epithelialization has been shown to be the procedure of choice for the treatment of precanceroses of the vocal cord.

REFERENCES

VOCAL CORD PRECANCEROUS LESIONS

Kleinsasser, O. (1962) Fortschritte der Medizin, 80, 903.

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