Three decades of gastroenterology in Soweto South Africa: from descriptive to scientific observations

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Citation for published version (APA):
Segal, I. (2002). Three decades of gastroenterology in Soweto South Africa: from descriptive to scientific observations.
Chapter 12

Pathological Effects of Pellagra on the Esophagus

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Nutr Cancer 1990; 14:233-238
**Introduction**

The significance of the esophagitis caused by pellagra is the relationship between vitamin deficiencies and esophageal cancer. This cancer is overall one of the most common cancers in the world (1). In South Africa, where it is the most common cancer in black men, the disease occurs primarily among maize eaters and is associated with a diet low in micronutrients such as niacin, riboflavin, zinc, and magnesium (2-5). This study determined the pathological effects on the esophagus of niacin/tryptophan deficiency and the response to treatment.

**Materials and Methods**

This study involved nine patients with severe clinical pellagra which was manifested by the characteristic skin changes and glossitis. All patients had odynophagia. Details of sex, age, and clinical manifestations were recorded. All patients underwent endoscopies with biopsies of the esophagus. Repeat endoscopies and esophageal biopsies six to seven days after the first biopsy, were carried out on the patients to assess progress. Esophageal biopsies of normal (nonpellagrin) controls, age and sex matched, were histologically assessed. Three additional controls for every female pellagra patient and five additional controls for every male pellagrin were studied (a total of 31 controls). The controls were patients who were undergoing diagnostic endoscopy for foregut symptoms. No esophageal symptoms were present. They formed part of a study undertaken to attempt to identify early esophageal cancer in patients with macroscopically normal esophageal.

**Treatment**

All Patients were hospitalized for at least 10 days. Patients were not permitted to smoke or drink alcohol, they ate a hospital diet that consisted of 53.5% carbohydrates (354.7 g), 17.2% protein (114 g), and 27.1% fat (79.9g). The total fat comprised 42.3 g saturated fat, 14.2g monounsaturated fat, and 15.8g polyunsaturated fat. The energy intake of this diet is 11,127.8 kj. The vitamin content was as follows: thiamine, 1.6 mg; riboflavin, 2.14 mg; nicotinic acid, 17.4 mg; vitamin B6, 1.71 mg; folic acid, 223.9 mg; vitamin B12, 6.91 mg, vitamin A, 39,729.6 IU; and vitamin D, 7.19 μg.

**Vitamin Therapy**

Treatment administered was oral nicotinamide, 100 mg, three times a day, and daily intramuscular injections of 2 ml vitamin B complex (thiamine hydrochloride, 20 mg;
riboflavin, 4 mg; nicotinamide, 200 mg; pyridoxine HCl, 10 mg, and d-panthenol, 10 mg). There was no difference between those patients who responded to treatment and those who did not with regard to smoking, drinking, and dietary habits during the treatment period.

Results
The Patients included seven women and two men. The mean age was 39.5 years. The mean daily consumption of alcohol (mainly home brews) was 88g daily. Smoking habits were not ascertained.

Endoscopic Findings
The grading of esophagitis was according to that of Blackstone (6) as follows: mild esophagitis: capillary dilatation, erythema, and friability; moderate: definite erosions; severe: ulceration and/or pseudomembranes.
At endoscopy, esophagitis was observed in all the patients: three had severe, two had moderate, and four had mild esophagitis.

Histopathology
All patients showed varying degrees of esophagitis as reflected by the presence of inflammatory cells and increased height and numbers of vascular papillae within the mucosa (Table 1). Four cases had mild active esophagitis, one had moderate esophagitis, and three had severe esophagitis, with one showing frank ulceration.
Histopathology of the repeat biopsies, following vitamin therapy, showed improvement in five cases; there was no improvement in four cases. Histopathology of normal controls showed no evidence of inflammatory infiltration within the epithelium, alteration of the vascular papillae, or basal cell hyperplasia.

Discussion
Pellagra is a multiple deficiency syndrome caused by a lack of niacin and the essential amino acid tryptophan, together with an imbalance of dietary amino acids (7). It results in dermatitis, as well as central nervous system and gastrointestinal manifestations. Some patients also exhibit the associated clinical signs of riboflavin and thiamine deficiencies. Glossitis and stomatitis are conspicuous early signs and are common findings. Glossitis may be a more sensitive gauge of the disease than are skin lesions. Other gastrointestinal manifestations include nausea, vomiting, abdominal pain, achlorhydria, steatorrhea, and diarrhea (8).
Maize is the staple food of the South African black population and contains the bound form of niacin that is not nutritionally available (7). It is not surprising, therefore, that in South Africa pellagra is associated with a high intake of maize. Communities who consume mainly a monocereal diet such as maize or wheat have been found to be at a high risk for developing esophageal cancer (1). In fact, deficiencies or imbalance of niacin, riboflavin, zinc, and magnesium provide a unifying explanation for the epidemiology of esophageal cancer (5). Other risk factors identified as agents in the etiology of the disease are tobacco and alcohol abuse (1). Tobacco smoked either in pipes or in hand-rolled cigarettes was found to be the principal carcinogenic stimulus in black South African populations that have been studied. Moreover, consumption of traditional beer made from maize was found to be a major risk factor (9). This accords with the finding by Cook (4) of an association in Africa with the use of maize for beer making. Previously, sorghum was a major ingredient of traditional brews, but in recent times it has been largely replaced by maize. The use of maize instead of sorghum grain has resulted in a decrease in the thiamine, niacin, and riboflavin content of traditional brews. This would have dramatic effects on the vitamin B status of people such as the esophageal cancer patients who consume large quantities of beer and whose low socio-economic status will result in a generally poor diet that is also largely composed of maize. These findings thus support the hypothesis that the consumption of beer made from maize is a factor in the development of esophageal cancer in Africa (9). The present study indicates that all the patients with gross niacin deficiency manifesting as pellagra had acute esophagitis. It has been suggested that chronic esophagitis is a precancerous lesion for esophageal cancer (10). However, it is not known whether acute esophagitis can develop into chronic

Table 1: Histological diagnosis in pellagrins: before and after treatment*

<table>
<thead>
<tr>
<th>No.</th>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Before Treatment</th>
<th>After Treatment</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BM</td>
<td>42</td>
<td>F</td>
<td>Mild esophagitis</td>
<td>Mild esophagitis</td>
<td>No significant change</td>
</tr>
<tr>
<td>2</td>
<td>RM</td>
<td>44</td>
<td>F</td>
<td>Mild esophagitis</td>
<td>Mild esophagitis</td>
<td>No significant change</td>
</tr>
<tr>
<td>3</td>
<td>BM</td>
<td>38</td>
<td>M</td>
<td>Severe ulcerated esophagitis</td>
<td>Severe ulcerated esophagitis</td>
<td>No significant change</td>
</tr>
<tr>
<td>4</td>
<td>PN</td>
<td>51</td>
<td>F</td>
<td>Moderate esophagitis</td>
<td>Mild esophagitis</td>
<td>Improvement</td>
</tr>
<tr>
<td>5</td>
<td>JM</td>
<td>43</td>
<td>F</td>
<td>Mild esophagitis</td>
<td>Normal</td>
<td>Improvement</td>
</tr>
<tr>
<td>6</td>
<td>EP</td>
<td>37</td>
<td>M</td>
<td>Severe esophagitis</td>
<td>Mild esophagitis</td>
<td>Marked improvement</td>
</tr>
<tr>
<td>7</td>
<td>EM</td>
<td>38</td>
<td>F</td>
<td>Severe esophagitis</td>
<td>Mild esophagitis</td>
<td>Marked improvement</td>
</tr>
<tr>
<td>8</td>
<td>MN</td>
<td>30</td>
<td>F</td>
<td>Moderate esophagitis</td>
<td>Mild esophagitis</td>
<td>Improvement</td>
</tr>
<tr>
<td>9</td>
<td>CD</td>
<td>42</td>
<td>F</td>
<td>Mild esophagitis</td>
<td>Mild esophagitis</td>
<td>No significant change</td>
</tr>
</tbody>
</table>

* After treatment, there was improvement in 5 patients but no improvement in 4 patients.
esophagitis. It would be interesting to determine whether pellagra and esophageal cancer are independent events or are related. There are common factors in both diseases, which may indicate an association. Pellagra is not only due to deficient intake of niacin but is in fact a multiple vitamin deficiency. Moreover, the adequate production of endogenous niacin from tryptophan is decreased by insufficiency or imbalance of other B vitamins. Thiamine, riboflavin, and pyridoxine are all important in the metabolism of tryptophan to nicotinic acid (11).

In a similar vein, there is an overall poor nutritional status among esophageal cancer patients, with increased risks related to a low intake of most vitamins. This effect is clear for vitamin C, riboflavin, nicotinamide, and vitamin E (12). Dietary, clinical, and biochemical studies have been carried out in all endemic areas (13). In the Transkei, a low status for nicotinic acid, riboflavin, vitamin C, zinc, calcium, and magnesium was confirmed. Low intakes of vitamin A, vitamin C, and riboflavin were identified in Iran, and in China it is likely that there is general deficiency in nutrients, particularly riboflavin, vitamins A and C, and zinc. Experimental studies on baboons fed on a diet completely lacking in riboflavin showed marked macroscopic and microscopic architectural disorganization of the skin, mouth, and esophagus (14). The esophageal lesions were particularly striking and appeared to resemble similar pathological lesions in humans. Control animals given riboflavin did not show these abnormalities. It is thought that riboflavin is an essential factor in the maintenance of the integrity of the stratified squamous epithelium, especially in the esophagus, which is continuously exposed to environmental insults (14).

A corollary to nutritional deficiency and esophageal cancer is that vitamins have a protective effect on the esophagus. Tuyns and co-workers (12) showed this with regard to fresh vegetables and fruit. Recently, Thurnham and colleagues (15) reported on results of supplementation of the usual diet of 610 Chinese farmers with riboflavin, retinol and zinc. They found that an improvement in blood retinol is associated with a lower prevalence of esophageal lesions. It was also reported that a reduced prevalence of micronucleated esophageal cells occurred in diets supplemented with riboflavin, retinol, and zinc compared with placebo (16).

Thus, it would seem that the two diseases have common etiologic factors, but there is among other things, a difference in severity and degree. Pellagra is due to a gross vitamin deficiency manifesting as an acute clinical syndrome, whereas in esophageal cancer a state of predisposition probably arises from lifelong mild deficiency usually subclinical of several micronutrients (13). A high risk is always associated with a diet based on maize or wheat.
whereas old traditional staples such as sorghum, millet, cassava, and peanuts are always associated with a low risk (13). It is important to establish whether pellagra patients eventually develop esophageal cancer. However, we know of no long-term follow-up studies that have been done on pellagra.

The evidence that micronutrient deficiencies are important in the etiology of esophageal cancer, and the amelioration of the esophagitis in pellagrins following a short course of vitamin therapy, may have important implications in the prevention of cancer. This study shows that an improvement in acute esophagitis occurs in some pellagrins following a short course of vitamin therapy. This factor, plus the additional evidence that micronutrient deficiencies are important in the etiology of esophageal cancer suggest it would be prudent to provide nutrient enrichment to commercially available cereals in countries with a high incidence of squamous esophageal cancer.

References


