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Study of Muc2 and Muc4 Mucins in Cancer of the Higher Aerodiversity.

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Abstract

Objective: To know the role played by the MUC2 and MUC4 mucins genes in cancers of the upper aero-digestive tract.

Material and methods: It was a cross-sectional retrospective study of 10 years (July 2004 - July 2013) carried out in the otolaryngology departments of the University Hospital Center of Brazzaville and general hospital Adolph Sicé (in Pointe-noire, Congo). All patients with upper aerodigestive tract cancers with histological evidence were included. For the study of mucins “MUC2 et MUC4” the molecular biology technique used was immunohistochemistry on pieces of laryngeal biopsies embedded in paraffin.

Results: A total of 85 cases of upper aerodigestive tract cancers were collected with a sample comprising the tumor and peri tumoral mucosa. The incidence was 8.5 cases of upper aero-digestive tract cancer per year and a ratio of 1.8 in favor of men. The main risk factor was smoking (94.2%) and all patients with squamous cell carcinoma found on the tumor lining. On immunohistochemistry, the mucins MUC2 and MUC4 were present in the normal mucosa of the upper aero-digestive tract and gradually lost their expression from the metaplastic mucosa to the tumor mucosa (P=0.03). These mucins “MUC2 and MUC4” were absent on tumor mucosa in both smoking and non-smoking patients with a statistically significant difference (P=0.01).

Conclusion: The loss of expression of the MUC2 and MUC4 genes within the tumor mucosa is a key mechanism in the carcinogenesis of the upper aero-digestive tract.

Keywords: Cancers, Upper aero-digestive tract, Mucins.

Introduction

Cancers of the upper aero-digestive tract poses a major public health problem not only because of their incidence which is increasing but also because of the diversity of risk factors (tobacco, alcohol, virus, etc.) making the mechanisms of carcinogenesis complex [1-4]. Some studies have shown the involvement of glycoproteins called "mucins" in the genesis of these cancers but their phenotypes are poorly understood [4-6]. Various authors believe that the MUC2 and MUC4 genes are responsible for invasion and tumor progression [7-9], but in Congo no study to date has mentioned the expression of these mucins within the airway mucosa. The aim of this work is to understand the expression of MUC2 and MUC4 mucins genes in order to understand their role in the carcinogenesis of the upper aero-digestive tract.

Materials and Methods

It was a cross-sectional retrospective study of 10 years (July 2004 - July 2013) carried out in the otolaryngology departments of the University Hospital Center of Brazzaville and general hospital Adolph Sicé (in Pointe-noire, Congo). All patients with upper aerodigestive tract cancers with

histological evidence were included. Patients not included in this study were those who had a benign tumor or lymphoma of the upper aerodigestive tract. All epidemiological, clinical and pathological data concerning the patients included in the study were provided by well-kept medical records. Then we recovered the laryngeal biopsy parts of all the patients from the anatomy pathology laboratory. These samples included in paraffin concerned the tumor and peri tumoral mucosa and then finally sent to France via air transport in order to study the expression of "MUC2 and MUC4" mucins. The molecular biology technique used was immunohistochemistry performed at the general hospital center of «Mantes La Jolie» in France. For identification reasons, the presence of mucin was marked by the «**+**» sign and its absence by the « – » sign. Thus, the parameters studied were epidemiological (frequency, age and sex), clinical (risk factors and tumor site) and biological (histopathological type, tumor invasion and expression of mucins). For data analysis, the X^2 test was used for the comparison and correlation of several observed distributions in order to define the independence of two qualitative variables. The comparison of the quantitative variables was made by the Student test. The significance threshold was set at $p < 0.05$.

Results

A total of 85 cases of upper aerodigestive tract cancers were collected, each with a sample comprising the tumor and peri tumoral mucosa. This corresponds to an annual incidence of 8.5 cases of cancers of the upper aero-digestive tract. The mean age was 60.94 years ± 10.63 (40 and 79 years) and a ratio of 1.8 in favor of men (Table 1). The main risk factor was tobacco found in 94.2% of patients. Glottal location came first (59%) followed by the oral cavity (23%) and hypopharynx (6%) (Table 2). Pathologically, in all cases, it was a squamous cell carcinoma (100%)

Sex	**Male**	**Feminine**	**Total**
Age	N (%)	N (%)	N (%)
40-49	5 (5,8)	10 (11,6)	15 (17,4)
50-59	15 (17,4)	0	15 (17,4)
60-69	25 (29,4)	10 (11,6)	35 (41)
≥ 70	10 (11,6)	10 (11,6)	20 (23,2)
Total	55 (64,2)	30 (34,8)	85 (100)
N : Number ; % : Percentage			

Table 1: Age and Sex of patients.

Seat		**Number**	**Percentage (%)**
Larynx	Glottis	50	59
	Sus-glottis	0	0
	Sub-glottis	5	6
Oral cavity	-	20	23
Hypophar-ynx	-	5	6
Ethmoid	-	5	6
Total	-	85	100

Table 2: Seat of the tumor.

Types of mucosa	**« MUC » profiles** **MUC2 MUC4**	**N (%)**	**P**
Normal	**+ +**	5 (5,8)	
Métaplastic	**– +**	80 (94,2)	0,03
Tumor	– –	85 (100)	
N: Number; %: Percentage; «**+**»: Présent; « – »: Absent			

Table 3: "MUC" profiles according to the types of mucosa.

Epidemiological and anatopathological characteristics	**« MUC » profiles** MUC2 MUC4	**N (%)**	**P**
Risc factors			
tabacco	– –	5 (5,8)	
none	– –	80 (94,2)	0,03
Tumor invasion			
invasive tumor	– –	10 (11,8)	
non-invasive tumor	– –	75 (88,2)	0,03
N : Number; %: Percentage; « – »: Absent			

Table 4. "MUC" profile association on tumor mucosa with epidemiological and anatomopathological characteristics.

found on the tumor mucosa. The tumor was invasive in 75 cases (88.2%) and non-invasive in 10 cases (11.8%). Within the peri-tumor tissues the mucosa was normal (5 cells, in 5.8%) and metaplastic (80 cells, 94.2%). The search for mucins by the immunohistochemistry technique made it possible to highlight three profiles according to the expression of the mucins "MUC2 and MUC4" in different mucous membranes: normal mucosa=(MUC2 +, MUC4 +), metaplastic mucosa=(MUC2–, MUC4 +) and tumor mucosa=(MUC2–, MUC4–) as presented in Table 3. The mucins MUC2 and MUC4 were present in the normal mucosa of the upper aero-digestive

tract and gradually lost their expression from the metaplastic mucosa to the tumor mucosa (P=0.03). Whether the tumor was invasive or non-invasive these mucins were absent and so was the tobacco poisoning. The loss of the expression of the mucins "MUC2 and MUC4" was observed on the tumor mucosa in both smoking and non-smoking patients with a statistically significant difference (P = 0.01). Table 4 shows the “MUC” profiles on tumor mucosa with the epidemiological and anatomopathological characteristics.

Discussion

The incidence of cancers of the upper aero-digestive tract varies from country to country. While in Cameroon, NJIFOU report an annual incidence of 22 cases, is more than twice that of ours, AMANA in Togo on the other hand report an incidence of 9 cases per year, close to our results [1,5]. However, the ratio remains in favor of men as reported by most authors from Africa and elsewhere [3-6]. The mucins “MUC2 and MUC4” are epithelial surface glycoproteins present on the normal mucosa of the upper aerodigestive tract [10]. Their expression can be disrupted by inflammatory or tumor mucosal lesions, making these mucins true protective factors for surface epithelia [10,11]. In the present study by comparing the phenotypic profiles on different mucosa, there is a progressive loss of MUC2 and MUC4 genes expression from the normal mucosa to the tumor mucosa (P=0.03), but the loss of MUC2 gene expression begins earlier than that of the MUC4 gene. This lesion continuum seems to confirm the role of mucins "MUC2" and "MUC4" as suppressor genes for cancers of the upper aero-digestive tract. Some studies also performed on biopsy specimens of laryngeal mucosa confirm our results, this is the case of JEANNON who reports that the loss of MUC2 gene expression from the normal mucosa to the tumor mucosa in patients with laryngeal cancer [12]. As a result, alteration of “MUC2” expression would be an important factor in carcinogenesis of the laryngeal mucosa or even of the entire upper aerodigestive tract. Other authors report that inhibition of “MUC2” gene expression during cell differentiation is an important factor in epithelial carcinogenesis [13-15], therefore the MUC2 gene could be considered as a suppressor gene for epithelial tumors, and could be used as a biomarker diagnosis [16,17]. The same observation is made for the “MUC4” gene, which seems to be also decisive in the carcinogenesis of the upper aerodigestive tract. Unlike the “MUC2” gene, the “MUC4” gene loses its expression only in the tumor mucosa while it is still present in the normal and metaplastic mucosa. This suggests that the loss of the "MUC4" gene corresponds to the stage of invasive carcinoma while that of the "MUC2" gene can occur on both metaplastic and tumor mucosa. At this time, the “MUC4” gene could be considered as a prognostic biomarker for monitoring patients with carcinoma of the upper aerodigestive tract. Although tobacco intoxication is the main risk factor for upper aerodigestive tract carcinomas [2,3], it does not influence the expression of the “MUC2 and MUC4” genes. In fact, the simultaneous loss of these two genes was observed on the tumor mucosa in both smoking and non-smoking patients (P = 0.01). Likewise, at the end of the carcinogenesis process, the loss of the “MUC2 and MUC4” genes remains the common element in cases of invasive and non-invasive carcinomas (P=0.03).Thus the phenotype (MUC2–, MUC4–) can be considered as the specific expression of the biological diagnosis of invasive carcinomas of the upper aerodigestive tract. Our results are close to those reported by Van Der Sluis and De Fraipont [18,19] who attribute to the mucins “MUC2 and MUC4” the role of protective genes of the laryngeal mucosa. Under normal conditions they are found in the mucosa and in laryngeal secretions, however they both lose their expression in pathological conditions such as dysplasia and carcinoma of the laryngeal mucosa [20].

Conclusion

The loss of expression of the MUC2 and MUC4 genes within the tumor mucosa is a key mechanism for the carcinogenesis of the upper aerodigestive tract. Whether the patient is a smoker or not, the “MUC2–, MUC4–” phenotypic profile appears to be specific to the biological diagnosis of upper aerodigestive tract cancers.

Conflicts of Interest: The authors do not declare any conflict of interest in this work.

Contribution of Authors

- Otouana Dzon HB, Ngouoni GC, Diembi S: design, documentary excavation, writing
- Ondzotto GW, Tsierie-Tsoba A: writing of the discussion
- Itiere Odzili FA, Ondzotto G: critical reading

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