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Vibroacoustic Disease and Respiratory Pathology I - Tumors

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Abstract [636] **BACKGROUND.** Malignancy in vibroacoustic disease (VAD) patients has been under close surveillance since 1987. To date, in a universe of 945 individuals, there are 41 cases of malignancies, 9 are multiple. Low frequency noise (<500 Hz, including infrasound) (LFN) is a genotoxic agent, increasing the frequency of sister chromatid exchanges in LFN-exposed organisms. To date, all 10 cases of respiratory tract tumors in VAD patients are squamous cell carcinomas (SCC). This report focuses on the morphological features of these tumors. **METHODS.** Tumoural fragments were collected (endoscopic biopsy/ surgery) from 10 male VAD patients (ave. age: 50 +/- 5 years, 3 non-smokers): 2 in glottis and 8 in the lung. In 3 non-smokers, 2 had lung tumors and 1 had a glottis tumour. All were employed or retired in LFN-rich environments. Fragments were prepared for light and electron microscopy. Immunohistochemistry studies used chromagranine and synaptophysine staining. **RESULTS.** All lung tumors were in the upper right lobe bronchioles and, were histologically poorly differentiated SCC. Neuroendocrine markers were negative in all cases. Eight of the patients are deceased, including the 3 non-smokers. The 2 surviving patients are heavy smokers (more than 2 packs/day). **DISCUSSION.** SCC account for approximately 40% of all lung tumors in men. It is not surprising that military helicopter pilots are affected the earliest because this group of workers exhibited the highest values for the frequency of sister chromatid exchanges. Given the results herein, specifying the exact histological type of tumour in all statistical studies is of the utmost importance.

1 INTRODUCTION

Low frequency noise (<500 Hz, including infrasound) (LFN) is a genotoxic agent of disease. This has been demonstrated in both LFN-exposed workers (1,2) and animals (3). LFN-induced pathology has been under study in Portugal since 1980, and has led to the definition of vibroacoustic disease (VAD), a systemic pathology caused by long-term (years) exposure to LFN (4-6). VAD is characterized by the abnormal growth of the extra-cellular matrices (7-16). The hallmark of VAD is pericardial thickening, in the absence of an inflammatory process, and with no diastolic dysfunction (17). Pericardial thickening can be assessed through echocardiography (18-20).
Malignancy became the object of interest when, in a 1987 autopsy of a deceased VAD patient, two tumors were identified: a renal cell carcinoma and a cerebral glioma. The cause of death was myocardial infarct, and no suspicion of malignancy was ever documented (21). Until 1996, in a universe of 945 individuals, there were 41 known cases of malignancies, of which nine were

multiple. They occurred in hollow organs or cavities, such as bladder, intestine, kidney, and lung. In the CNS, all were malignant gliomas, where it is speculated that the skull functions as yet another cavity (6).
The respiratory pathology seen in aircraft technicians prompted, in 1992, the usage of LFN-exposed Wistar rats that disclosed dispalstic and metaplastic appearances of the tracheal epithelia (13,15). No tumors were ever identified among LFN-exposed rodents, most probably because rat life span is too short for tumoral development. Other studies support the concept that acoustical phenomena impinge on the respiratory tract (22-25).
To date, 10 cases of respiratory tract tumors have been documented in VAD patients. This report describes the histological similarities of these tumors.

2 METHODS

All subjects were employed or retired as aircraft technicians, military or airline pilots and, thus, were occupationally exposed to LFN. All exhibited the characteristic, VAD-specific pericardial thickening, as seen through echocardiography. Tumoral fragments, obtained through endoscopic biopsy or surgery, were collected from 10 male VAD patients (ave. age: 50 +/- 5 years): 2 from the glottis and 8 from the lung. Of the 3 non-smokers, 2 had lung tumors and 1 had a glottis tumor. Fragments were immediately fixed either for light or transmission electron microscopy (TEM). Immunohistochemistry studies used chromagranine and synaptophysine staining.

3 RESULTS

All lung tumors were located in the bronchi of the upper right lobe. Histology disclosed that all were poorly differentiated squamous cell carcinomas. The search with neuroendocrine markers was negative in all cases.
Vast areas of necrosis were observed in all tumors. In the edges of the tumor, apoptotic cell death was the most common feature. Ultrastructurally, small desmosomes were visible, some perpendicular to the membranes of adjacent cells. (Figure 1). Tonofilaments were scarce. No microvilli were identified in the intercellular processes, but microvillus-like structures (filopodia) were present (Figure 1). This cellular pattern is typical of poorly differentiated squamous cell carcinomas.

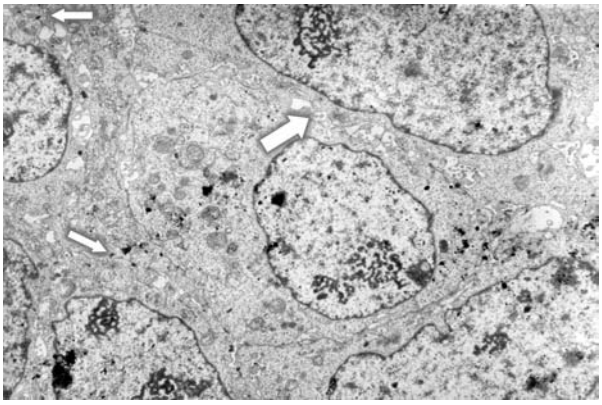

Figure 1: *Poorly differentiated squamous cell carcinoma. Small tumor cells with desmosomes perpendicular to the cell membrane (small arrows). Tonofilaments are absent; compact aggregates of narrow cellular processes (filopodia) are seen (large arrow). (TEM x5600)*

All helicopter pilot tumors (5 cases) occurred before the age of 50 (range 44-48 years). Eight of the patients are deceased, including the 3 non-smokers. The 2 surviving patients are heavy smokers

(more than 2 packs/day) and, since their surgery, have been retired and remove from occupational LFN-rich environments. One of the surviving patients, an airline pilot, received surgery 10 years ago, and remains under tight clinical surveillance, and still smoking.

4 DISCUSSION

Given the results herein, it would seem appropriate to suggest that lung cancer incidence studies begin specifying the histological types of tumors that are found. Squamous cell carcinomas seem to be associated with LFN exposure. This concept is corroborated by the fact that displasia and metaplasia were identified in the respiratory epithelia of LFN-exposed rats (13,15). Other agents of disease may also induce this type of carcinoma, which accounts for 40% of all lung cancer (26), however it would seem that LFN exposure specifically induces the development of squamous cell carcinomas.

The synergistic effect of LFN exposure plus whole-body vibration induces a higher frequency of sister chromatid exchanges in Wistar rats than LFN or vibration alone (3). Thus, it is not surprising that the earliest cases of lung cancer among LFN-exposed workers occur among military helicopter pilots. These pilots are exposed to larger vibrational compnents than aircraft technicians or airline pilots.

The fact that all lung tumors have developed in the upper right lobe might be associated with the relative position of the heart. The difference in the acoustical properties inherent to different organ geometry most probably plays an important role in the location of the development of lung tumors in VAD patients, and may partially explain the apparent increased susceptibility of the right lobe. These results are reminiscent of an experiment conducted by Ponomarkov *et al.* in 1969 (22). Here the authors expose dogs to wide-band noise at 105-155 dB, for 1.5-2 hours. Autopsies revealed 3mm diameter hemorrhages in the lungs of the animals exposed to about 126 dB, and which were located under the pleura. These hemorrhages were most commonly found in the costal surface of the upper lobe of the right lung.

5 SUMMARY

LFN-exposed individuals should be monitored for respiratory pathology, particularly the more susceptible workers. LFN seems to specifically induced squamous-cell carcinomas in the respiratory tract. This is corroborated by animal experiments. It is strongly suggested that cancer-related epidemiological studies take the histological tumor-type into account.

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