

Adenocarcinoma of ethmoid sinus: an occupational disease

Adenocarcinoma dei seni paranasali: una malattia professionale

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Summary

Sinonasal tumours, particularly those of ethmoidal origin, are rare neoplasms, of which adenocarcinoma is the most frequent histotype in Europe. The association between sinonasal malignancies and exposure to wood or leather dusts has been widely documented, however, the precise tumour site and histology has seldom been reported. In the present study, exposure to wood or leather dusts was investigated in 499 patients diagnosed with sinonasal tumours, who were treated at the Head and Neck Surgery Department of the National Cancer Institute of Milan, Italy, between 1987 and 2001. The original tumour site and histology were carefully assessed. Of the 499 patients evaluated, 249 had ethmoidal tumours; 124 of which adenocarcinomas, affecting 115 males; 9 females. Of the males with adenocarcinoma, 90.4% had been exposed to wood or leather dusts; 16.3% of these had only been exposed for a short time and long before onset of the disease (median exposure 11 years; median latency 31 years). Of the remaining 125 patients with ethmoidal tumours other than adenocarcinomas, only 2 (1.6%) had ever been exposed to these dusts. Non-ethmoidal sinonasal tumours were seen in 250 cases; 17 of these (6.8%) were adenocarcinomas; no exposure to wood or leather dusts was reported in any of these patients. Ethmoid proved to be the sinonasal site affected by adenocarcinomas induced by exposure to wood or leather dusts. Even brief exposure, which may have occurred a very long time before onset of the disease, seems to be sufficient to increase the incidence of this tumour type. No significant correlation was observed between exposure and either non-ethmoidal sinonasal neoplasms or ethmoidal tumours other than adenocarcinomas.

Riassunto

I tumori nasosinusalni sono neoplasie rare ed in particolare quelle di origine etmoidale, fra queste ultime gli adenocarcinomi rappresentano in Europa l'istotipo più frequente. La loro associazione con l'esposizione a polveri di legno e cuoio è stata ampiamente documentata ma non sempre è riportata la precisa sede di origine e l'istologia della neoplasia. Abbiamo indagato l'esposizione a polveri di legno o cuoio in 499 pazienti con neoplasie nasosinusalni trattati dal 1987 al 2001, presso il Dipartimento di Chirurgia Cervico Facciale dell'Istituto per lo Studio e la Cura dei Tumori di Milano. È stata attentamente valutata la sede di origine e l'istotipo del tumore. Dei 499 pazienti da noi trattati, 249 presentavano neoplasie ad insorgenza etmoidale di cui 124 erano adenocarcinomi in 115 maschi e 9 femmine. Fra i maschi portatori di adenocarcinoma, il 90,4% erano risultati precedentemente esposti a polveri di legno o cuoio; il 16,3% di questi pazienti avevano presentato un'esposizione di breve durata e molto antecedente all'insorgenza della neoplasia (esposizione media: 11 anni; latenza media: 31 anni). Fra i rimanenti 125 pazienti con tumori etmoidali diversi dall'adenocarcinoma, solo 2 (1,6%) risultavano essere stati esposti alle polveri suddette. I tumori sinusalni non etmoidali da noi osservati erano 250, 17 di questi (6,8%) erano adenocarcinomi ed in nessuno di questi casi è stata documentata precedente esposizione a polveri di legno o cuoio. Dalla nostra casistica emerge che l'etmoide è l'unica sede sinusalna interessata dall'adenocarcinoma indotto dalla esposizione a polveri di legno e cuoio e sarebbe sufficiente anche un'esposizione di breve durata e molto antecedente all'insorgenza del tumore per indurre questa neoplasia. Non è emersa invece alcuna correlazione significativa fra l'esposizione e l'insorgenza di neoplasie nasosinusalni a partenza non etmoidale o neoplasie etmoidali diverse dall'adenocarcinoma.

Introduction

Malignant neoplasms of the ethmoid are rare tumours¹. It is very difficult to establish the exact incidence rate of this malignancy since cancer registers usually group tumours of the ethmoid together with other sino-nasal tumours.

In the largest available case records, the incidence of ethmoidal cancers accounts for 6% to 25% of all sinonasal tumours². In the Italian National Cancer Registry, the yearly incidence rate, among the adult population, is 0.33 per 100,000 for cancer of the paranasal sinuses and 0.44 per 100,000 for cancer of the nasal cavities. These data are identical to those in the adult

population of the United States (0.75/100,000 for both sites)³. However, it is very important to locate the primary site of these tumours, since both the histological and epidemiological aspects differ considerably between the various sino-nasal cancers. Whereas in the maxillary sinus, the most common histological type is squamous cell carcinoma (SCC), poorly differentiated carcinomas and, especially intestinal-type adenocarcinomas are more frequent in the ethmoid. This latter type is the most frequent in European series⁴⁻⁸, while in American series, SCC, more or less differentiated, is the most common type⁹⁻¹⁴.

The association of sino-nasal tumours, in particular ethmoidal adenocarcinomas, with exposure to wood or leather dust is widely documented¹⁵⁻²⁴. Most of these reports refer to epidemiological studies among wood and leather workers.

In the present study, however, a different approach was used to investigate this relationship. First, all those patients diagnosed with malignant tumours of the para-nasal sinuses, who underwent surgery in our Institute (Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy) were taken into consideration and then how many of these patients had actually been exposed to these well-known oncogenic agents was determined.

Patients and methods

Clinical records have been examined of all patients diagnosed with malignant tumours of the paranasal sinuses and nasal cavity, who underwent surgery, alone or combined with neoadjuvant or adjuvant radiotherapy or chemotherapy, between 1987 and 2001. Patients with either nasal vestibule tumours or cutaneous tumours involving the paranasal sinuses were excluded. The surgical treatment was proportional to the extension of the disease, since the aim was to achieve radical resection of the tumour and,

therefore, either partial, total or enlarged maxillectomies, or cranio-facial resections were performed. In most cases, the primary site of the tumour was assessed. For doubtful cases, the radiological images were re-examined and the primary site was identified as the most involved structure. The clinical records of the Institute usually list the patient's occupational history. When this information was lacking, either the patient or a relative were contacted by telephone and asked to provide the missing data. Those patients not carrying out any activity involving either wood or leather at the time of hospitalisation were explicitly asked whether they had ever engaged in such activities in the past, and, if so, for how long.

Results

Between 1987 and 2001, 249 patients (188 male, 61 female) with malignant ethmoidal neoplasms underwent surgery at the Department of Head and Neck Surgery at Istituto Nazionale per lo Studio e la Cura dei Tumori in Milan, Italy. In that same period, 250 patients (116 male, 134 female) presented with malignant tumours in the other sinonasal sites. Grouping of these tumours according to histological type is shown in Table I. Ethmoidal adenocarcinomas were identified in 124 patients (115 male, 9 female) (Table II). The mean age at onset of disease, for both male and female patients, was 60 years (range 30-80). For 107 (86.3%) of the 124 patients with ethmoidal adenocarcinomas, exposure to wood or leather dust was clearly documented: 69 patients had been exposed to wood dust and 38 to leather dust. The male/female ratio of patients exposed to dust was 104/3. In 17 patients (13.7%), no dust exposure was reported. As far as concerns male patients, of the 115 patients submitted to surgery, exposure was confirmed in 104 cases (90.4%): 69 patients reported exposure to wood dust and 35 to leather dust. Only 11 (9.6%) patients

Table I. Main patient characteristics according to histopathology and tumour site.

Histopathology	n	Ethmoid		Non-ethmoidal sinonasal site	
		n	%	n	%
Adenocarcinoma	124	115	49.7	17	6.8
Squamous cell ca.	26	26	10.4	86	34.4
Esthesioneurobl.	23	23	9.2	0	0
Adenoid cystic ca.	19	19	7.6	6	24.8
Anaplastic carcinoma	13	13	5.2	15	6
Malignant melanoma	9	9	3.6	9	3.6
Mucoepidermoid ca.	1	1	0.4	15	6
Other histology	34	34	13.1	46	18.4
Total	249	249	100	250	100

Table II. Adenocarcinoma of the ethmoid sinus and exposure to wood or leather dusts.

Patients		Total exposed	Early exposed	Unexposed
M	115	104/115 (90.4%)	17/104 (16.3%)	11/115 (9.6%)
F	9	3/9 (33%)	0/3 (0%)	6/9 (67%)
Total	124	107/124 (86.3%)	17/107 (15.9%)	17/124 (13.7%)

Table III. Cases of early exposure: duration of exposure and latency to presentation.

Patient number	Exposure type	Age at start (years)	Duration of exposure (years)	Latency (years)
1	wood	28	1	4
2	wood	18	9	23
3	leather	22	5	25
4	leather	19	6	2
5	wood	9	18	28
6	wood	10	10	29
7	wood	15	11	30
8	leather	10	1	30
9	leather	8	11	30
10	wood	8	5	30
11	wood	17	12	36
12	wood	14	10	36
13	leather	20	4	37
14	wood	15	9	37
15	wood	23	4	40
16	wood	17	9	44
17	wood	8	6	46

reported no exposure. In the female patients, on the other hand, only 3 (33%) out of 9 had been exposed to wood dust, while the remaining 6 (67%) had no history of dust exposure. As far as concerns age at diagnosis, 68 (65.4%) of the 104 male patients with previous dust exposure were <65 years and were still working when the disease became evident; 19 (18.3%) were >65 years, had been retired for 5-15 years and had been exposed to the oncogenic agents since they were young. These two groups of patients had been exposed for a minimum of 25 to a maximum of 55 years. A third group of 17 patients had experienced very early, limited, exposure, followed by a long interval between the end of exposure and onset of the disease (Table III). For 16 of these patients, the mean interval was 33 years (range 23-46), while the mean duration of exposure was 7.5 years (range 4-18). In one case, exposure did not exceed one year and the patient developed adenocarcinoma 4 years later. The mean age at onset of the disease, in this group of patients, was 56 years.

Of the 125 patients diagnosed with other kinds of ethmoidal neoplasms, only 2 (1.6%) had been exposed to wood dust (1/26 SCC and 1/13 undifferentiated carcinoma). None of the 250 patients with tumours originating in a non-ethmoidal sinonasal site, had been exposed to either wood or leather dust.

Discussion

As already pointed out, adenocarcinoma is the most frequent histotype among all ethmoid tumours in Europe^{4-7 19}. Data emerging from the largest series of case records of patients who underwent craniofacial resection, when the primary site of the tumour had been precisely established, showed that adenocarcinomas accounted for between 47%⁴ and 72%⁶ of cases. As far as concerns personal case records, adenocarcinomas comprised 49.7% of all malignant ethmoidal tumours (124 out of 249) (Table I). These data are not consistent with the North Ameri-

can case records, where the percentage of adenocarcinoma ranged from 3% to 14%⁹⁻¹⁴. In Australia, the percentage was 37%²⁵.

The numerous papers published in Europe, on this issue, confirm that adenocarcinoma is the most common histotype of ethmoid tumours, but this is not the case for tumours of other sinonasal sites.

In those case records in which all paranasal tumours are grouped together, the incidence of adenocarcinomas is very low being 9%, 14% and 7% according to Elwood²⁶, Battista et al.¹⁸ and Takasaka et al.²⁷, respectively. A possible explanation for this apparent discrepancy is that, in these series of case records, the percentage of ethmoidal tumours is much lower than the percentage of maxillary tumours.

In our patients' case records, we were able to assess the exact primary site of the tumours, as all patients underwent computed tomography scan and magnetic resonance imaging before treatment. The high percentage of ethmoidal tumours reported in our study is due to the fact that our Institute is currently a national specialised centre for cranio-facial resections of ethmoidal tumours.

Many Authors have already highlighted the increased odds ratios (ORs) for the development of sinonasal adenocarcinoma in those workers exposed to wood or leather dust^{19 20 22}.

In our study, a different approach has been used since an analysis has been made of all the patients treated for adenocarcinomas of the ethmoid, among whom we focused on those who had been exposed to wood or leather dust.

From a review of our data, we can confirm that most male patients (90.4%) with adenocarcinoma of the ethmoid were, indeed, found to have had previous exposure to wood or leather dust. This percentage is so high that we can consider this malignancy as an almost exclusively occupational disease. It is noteworthy, in fact, that only in two of the 125 patients with malignant ethmoidal cancers, other than adenocarcinomas, was exposure to the oncogenic agents demonstrated, while no exposure at all was reported for any of the 250 patients with malignant sinonasal neoplasms originating in sites other than the ethmoid. For female patients, only 3 out of 9 (33%) had been exposed to wood dust, and none had been exposed to leather dust. As 't Mannelje et al.²³ report, this outcome may be due to the fact that the number of women employed as wood workers is very small, compared to leather workers. The cases of exposure among the female population, as compared with the male population, were so few (9/115), that no significant statistical data can be derived.

The most remarkable finding emerging from the present study is the demonstration that the ethmoid is the only paranasal site affected by adenocarcinomas

induced by wood or leather dust exposure, since, although it is largely confirmed, by the medical literature, that a clear relationship exists between this histotype and occupational exposure, only in a few studies was the site of onset of the disease clearly determined¹⁹.

Among the male patients, 87 out of 104 had been exposed to wood or leather dust during their working life (25-55 years), while 17 had been exposed for just a short period. In the latter individuals, exposure occurred many years before onset of the disease (23-47 years); for 4 of them, exposure continued for <6 years and in one of them, exposure lasted only one year. This result was completely unexpected and should be further investigated and confirmed in larger series of case records. In fact, data already exist showing that the increase in risk of ethmoidal adenocarcinoma is proportional to the time of exposure to the oncogenic agents. According to Olsen and Asnaes²⁸, the OR increases from 16 to 30 for workers who have been exposed for >10 years. These data are confirmed both by Bolm-Audorff et al.²⁹, who report an increase of ORs from 3.8 to 7.8 in the case of exposure >5 years, and by the pooled data of Demers et al.³⁰ in 15 case-controlled studies. Our data suggest, by contrast, that even a few-years' exposure, sometimes followed by a very long latency period, may be sufficient for gene deregulation to occur, which leads to onset and development of the disease. In a previous study, we were able to demonstrate a high percentage of TP53 mutations and p14ARF and p16INK4a promoter methylation in exposed ethmoid adenocarcinomas, thus strongly supporting the epidemiological observation of a genotoxic origin of the tumour³¹.

Many Authors have confirmed that there is a very weak correlation between wood or leather dust exposure and the onset of a SCC of the ethmoid^{19 20 28}. Our survey would confirm this observation.

No significant relationship could be established between occupational dust exposure and the onset of ethmoidal neoplasms other than adenocarcinomas, or neoplasms originating from other sinonasal sites.

In the light of the above results, all available technology should be employed to remove wood and leather dust from work places and prevent workers from inhaling these oncogenic agents. It is also necessary for otorhinolaryngologists, who are usually the first specialists to see patients with nasal obstructions and/or nosebleeds, to establish whether the patient has ever been exposed to any oncogenic agent in the past. Whenever exposure is confirmed, ethmoidal adenocarcinoma should be suspected, and all appropriate diagnostic and therapeutic examinations and procedures should be planned accordingly.

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