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Case series

Occupational exposures to formaldehyde and wood dust in nasopharyngeal carcinoma: A 10-year case series from Tunisia

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Abstract

Introduction: Nasopharyngeal cancer is a distinctive entity compared to other head and neck cancers. In Tunisia, it is ranked as the second most common head and neck cancer after laryngeal cancer. Although its pathophysiology is unclear, several genetic and infectious predisposing factors have been identified. However, there is limited data available on environmental and occupational factors.

Material and method: This is a retrospective descriptive survey of the records of subjects with nasopharyngeal cancer. These subjects consulted the occupational medicine department of the Farhat Hached University Hospital, Sousse, over a 10-year period from 1 January 2010 to 31 December 2019.

Results: A total of four cases were recorded, illustrating a variety of occupational exposures. All patients were males. Cervical adenopathy was the first symptom to appear. The diagnosis was confirmed by biopsy. Pathological examination revealed 3 undifferentiated nasopharyngeal carcinoma (UCNT) and one well-differentiated non-keratinizing squamous cell carcinoma. Two patients were welders; one was a qualified dairy production operator and the fourth was a worker in a car company. Three patients were exposed to formaldehyde and one to wood dust with an average seniority of 11.25 years. All four cases had their cancer recognized as an occupational disease according to table 28 or 54.

Conclusion: All cases of nasopharyngeal cancer should be considered work-related, to ensure recognition as an occupational disease and to safeguard patients' rights to treatment and compensation.

Key words: Cavum cancer, Nasopharyngeal cancer, Occupational exposure, Wood dusts, Formaldehyde

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1. Introduction

Cancers of the upper airways are common. They are the 4th most common cancers in men in France. Nasopharyngeal carcinomas are a specific entity, unlike other head and neck cancers[1]. Worldwide, almost 130,000 new cases of nasopharyngeal carcinoma are diagnosed annually[2]. In Tunisia, nasopharyngeal cancer is the second most common head and neck cancer after laryngeal cancer[1].These cancers have a very disparate geographical distribution, with a high endemicity in South-East Asia, where the incidence can reach 17.4 cases per year per 100,000 people, intermediate endemicity in the Maghreb and Mediterranean countries, and low endemicity in Western countries[3].

A number of factors are involved such as genetic, environmental, dietary, viral and occupational factors [4].In endemic regions, the majority of cases of cancer are mainly related to the Epstein-Barr virus (EBV) and smoking [5,6].

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Industrial progress has led to increased exposure of workers to harmful products. The upper airways, including the nasopharynx, are directly affected by these work-related exposures.

Occupational exposure to formaldehyde and wood dust has been classified by the International Agency for Research on Cancer (IARC) as having sufficient evidence to cause nasopharyngeal carcinoma in humans[7]. In addition, certain epidemiological studies have reported an excess of mortality due to these cancers in particular occupational categories [8].

This study aims to report on cases of nasopharyngeal carcinoma that consulted the occupational medicine department at the Farhat Hached University Hospital for professional investigation. We seek to determine the socio-professional characteristics of the affected subjects, to assess whether their condition is attributed to professional factors and explore their classification as occupational diseases according to Tunisian law.

2. Material and methods

This is a retrospective descriptive survey including patients with histologically documented nasopharyngeal cancer who consulted the occupational medicine department of the Farhat Hached University Hospital in Sousse, over a 10-year period from 1 January 2010 to 31 December 2019.

Data collection was based on medical records. The variables examined were socio-professional characteristics, clinical characteristics, occupational disease declarations and assessment of work ability. Data collection was based on medical records from the occupational medicine department of the Farhat Hached University Hospital in Sousse.

The parameters analyzed were as follows: Socio-professional characteristics (age, gender, marital status, education, sector of activity, workstation, seniority, duration of exposure, agent involved), clinical characteristics (clinical signs, treatment, histology and extension assessment data), declaration as an occupational disease, assessment of fitness for work. Observations of cases of nasopharyngeal cancer were reported, followed by a review of the literature concerning this topic.

3. Results

During the study period, four cases of nasopharyngeal cancer were reported.

First patient

We report the case of Mr. B.H, a 42-year-old man, having no medical history. From 2003 to 2014, he worked as a laborer for a company specializing in recycling and repairing car steering wheels. His main task was removing defective polyurethane foam layers from steering wheels via high-temperature baths. These steering wheels, which have a metal skeleton, are wrapped in polyurethane foam. These defective flywheels were soaked in high-temperature baths before being 'peeled' to remove the defective layer of foam and reintroduce the metal skeleton into the manufacturing process. Immersing the steering wheels in hot baths releases vapor with an unpleasant odor. In November 2013, the patient presented with upper cervical adenopathy. A biopsy was conducted, showing the presence of an undifferentiated nasopharyngeal carcinoma (UCNT). The patient had a poor outcome and died. In this working process, the thermal degradation of polyurethanes, the main material used in the manufacture of steering wheels, releases fumes containing aldehydes, particularly formaldehyde, which is known to be a nasopharyngeal carcinogen. His illness was therefore justifiably reported as an occupational disease according to table 28.

Second patient

Mr. H.R. is 45 years old. He worked as a welder from 2004 to 2013. The patient reported exposure to iron and wood dust. Since 2013, he has held the position of maintenance assistant. He oversees moving workstations, installing, removing and repairing machines, which involve carrying heavy equipment and exposure to dust. After the appearance of cervical adenopathy, this patient was diagnosed with nasopharyngeal cancer in November 2010, treated with chemotherapy and radiotherapy, with complications including dental lesions, post-radiation bi-apical pulmonary fibrosis and a low thyroid function. The analysis revealed a differentiated non-keratinizing squamous cell carcinoma, infiltrating the right maxillary sinus and invading the floor of the orbit with involvement of the inferior rectus muscle, treated with chemotherapy and radiotherapy in 2017. The nasopharynx-geal cancer was reported as an occupational disease according to Table 54 (wood and cork), and the patient was advised to avoid exposure to dust, particularly wood dust.

Third patient

Mr. N.T., a 43-year-old man, a smoker with no notable pathological history, had been working since 2009 as a highly qualified dairy processing room operator exposed weekly to ANIOS R88 disinfectant (a disinfectant composed of formaldehyde and quaternary) during equipment sterilization. In February 2015, the patient had an accident at work due to acute exposure to ANIOS R88 vapor. He reported inhaling the fumes, due to the inefficiency of his respiratory mask. He was hospitalized for 11 days in the otorhinolaryngology department; he complained of episodes of epistaxis and swallowing problems during this episode associated with cervical adenopathy. A biopsy revealed an undifferentiated carcinoma of the nasopharynx (UCNT). The patient underwent a course of cervicofacial radiotherapy and concomitant chemotherapy. His illness was reported as an occupational disease according to Table 28, related to formaldehyde and polymers. He was advised to avoid work involving sustained physical effort, carrying loads, night work and exposure to aero-contaminants and respiratory irritants. He was assigned to an appropriate job.

Fourth patient

Mr. S.M, aged 44, with a medical history of appendectomy, a smoker and a former alcoholic. He has worked as a welder since 1985 in several construction companies, frequently molding resin sheets and handling plastics, urea-formaldehyde glues and formaldehyde releasers. In September 2013, the patient presented with adenopathy under the left mandible. A CT scan and biopsy of the nasopharynx were performed, concluding in a UCNT-type nasopharyngeal carcinoma. Although the list of occupations exposing workers to formaldehyde is restrictive in its section relating to nasopharyngeal cancer, the patient's frequent exposure to formaldehyde during the manufacture of resin plates warrants the declaration of his illness as an occupational disease under table 28 to enable him to make use of any rights he may have.

The main information gathered for the four observations is presented in Table 1.

4. Discussion

Nasopharyngeal cancers represent a specific entity, unlike the head and neck cancers [1]. Their pathogenesis is still unclear and involves diverse risk factors: genetic, environmental, dietary, viral and even occupational. Today, the North African region has become highly endemic [9]. In Algeria, the annual incidence of this cancer is 5.5/105 males and 3/105 females [9]. Men are more frequently affected than women are (sex ratio: 2.5-3). In fact, all our patients are

Table 1. Summarizing the main data collected for the 4 observations

Case	Gender	Age	Life habits	Job	Suspected exposure	Seniority	Initial symptoms	Histological type	Outcome
1	Male	42 years	No significant history	Worker in an automotive company	Formaldehydes	11 years	Upper cervical adenopathy	UCNT	Death
2	Male	45 years	No significant history	Welder	Wood dust	9 years	Cervical adenopathy	Differentiated non-keratinizing squamous cell carcinoma	Undergoing treatment
3	Male	34 years	Smoker	Qualified butter room operator	Formaldehydes	7 years	Epistaxis, swallowing difficulties and cervical adenopathy	UCNT	Undergoing treatment
4	Male	44 years	Smoker Former alcoholic	Welder	Formaldehydes	18 years	Submandibular adenopathy and dysphagia	UCNT	Undergoing treatment

male. This cancer affects the 40-50 age group. The mean age of our patients was 43.5 years.

The symptoms were diverse. Cervical adenopathy was the most frequent complaint in our series, occurring in all patients, associated in one case with epistaxis and difficulty swallowing, and in another with headache and upper dysphagia. In fact, the diagnosis may be highlighted by otorhinological signs (tinnitus, otorrhea, hypoacusis, otalgia, rhinorrhea, epistaxis, nasal obstruction, etc.), or even neurological signs (secondary to damage to the cranial nerves resulting from the extension of the tumor process to the base of the skull: headaches, trismus, diplopia, etc.), neurological (secondary to damage to the cranial nerves resulting from the extension of the tumor process to the base of the skull: headaches, trismus, diplopia, dysphonia, dysphagia, etc.) and ophthalmic (exophthalmos) symptoms. But the most common sign is the cervical adenopathy [4,10].

After a full otorhinological examination, our patients underwent biopsy of the cervical ADP and nasopharynx, which revealed undifferentiated nasopharyngeal carcinoma of the nasopharynx (UCNT) in three cases and differentiated non-keratinizing squamous cell carcinoma in one case. According to previous studies, on pathological analysis, three histological types can be identified: keratinizing squamous cell carcinomas, non-keratinizing squamous cell carcinomas and undifferentiated carcinomas known as UCNT [3].

The predominant histological type in North Africa is undifferentiated carcinoma (UCNT), as was the case in our series [4]. This cancer was metastatic from the outset in the first case. Actually, diagnosis remains late, with advanced forms even metastatic at the time of diagnosis in almost 5% of cases [11].

Several risk factors have been involved in the genesis of nasopharyngeal cancer. The main risk factors are tobacco and alcohol consumption in genetically susceptible individuals. Other infectious or environmental factors, particularly nutritional and occupational, are also implicated. Initially, the particular ethnic differences in the genesis of nasopharyngeal cancers suggest a major influence of the genetic susceptibility behind this disease[12]. Indeed, host factors suspected of being linked to the risk of this cancer include specific human leukocyte antigens and the cytochrome P4502E1 (CYP2E1) [13]. In Morocco, Dardari et al., in 2009, also demonstrated that the HLA-B13 allele is associated with this cancer, as are the HLA-A10 and HLA-B18 alleles [14].

In addition, infection with the Epstein-Barr Virus has often been discussed in the pathogenesis of this cancer. Indeed, nasopharyngeal carcinoma is a unique cancer with strong etiological association with infection of the Epstein-Barr virus. It is the undifferentiated form of nasopharyngeal carcinoma (NPC) that shows the most consistent worldwide association with EBV [6]. Epstein-Barr virus (EBV) is endemic in North Africa, and its strong association with undifferentiated nasopharyngeal carcinoma (UCNT), as demonstrated by numerous studies, may explain the high prevalence of UCNT in this region [6]

Notably, epigenetic changes, such as DNA methylation abnormalities caused by EBV, are known to contribute significantly to EBV-associated cancers such as naso-pharyngeal cancer [15]. EBV-infected nasopharyngeal cells can secrete cytokines and exosomes containing viral products that can modulate the function of stromal cells in the tumor microenvironment, thereby facilitating disease progression and preventing host immune attacks[16].

Furthermore, a study conducted in North Africa showed that smoking was significantly associated with differentiated nasopharyngeal cancer but not with undifferentiated carcinoma (UCNT), which is the main histological type in these populations. Also, smoking marijuana significantly increased the risk of NPC[17]. It should be noted that one of our patients was a smoker and another patient started smoking a few months before the discovery of his disease. A case-control study carried out in Morocco on GSTM1 and GSTT1 polymorphisms and smoking as risk factors for nasopharyngeal carcinoma showed an increased risk of NPC with the GSTM1 genotype (OR=8; 95% CI [6.03-19.08]) and that low or even brief exposure to tobacco smoke generates significant expression of carcinogenic mutations [18]. The aforementioned studies have not established a link between alcohol consumption and nasopharyngeal cancer. This association remains controversial to this day.

In addition, eating habits may influence the risk of developing nasopharyngeal cancer[19]. In highly endemic regions, the consumption of salted fish and tinned food, particularly during childhood, has been blamed. These foods, which can contain high levels of nitrosamines, have been linked to this cancer in Asian regions [13]. Evidence concerning other dietary factors is still limited. A study by

Federica Turati et al. has shown that the Mediterranean diet, based on high consumption of vegetables, fruit and olive oil, moderate consumption of fish and wine, and low consumption of meat, may have a protective effect against these cancers [20]. A case-control study carried out in North America showed a significantly reduced risk of differentiated squamous cell carcinoma in people with vitamin C intakes above the lowest quartile. In the same study, the researchers discussed the role of smoking in the depletion of the plasma ascorbic acid pool. In smokers, free radical sequestration capacity may be limited and antioxidant status may be compromised [21].

Apart from the risk factors mentioned above, certain occupational risk factors were associated with an increased risk of developing nasopharyngeal cancer. Three of our patients were exposed to formaldehyde at work, and one patient was exposed to wood dust.

Occupational exposure as a potential risk factor for NPC has been examined in numerous epidemiological studies; however, the causal link is still unclear. An increased risk of death from NPC has been reported among servers in Hong Kong, China[22] . One of the explanations put forward was exposure to passive and active tobacco smoke, which has also been associated with these cancers.[2]. Carpèn et al. found that women in charge of laundry had a statistically higher risk of NPC than the general population. In dry cleaning, tetrachloroethylene is the main solvent used throughout the world and in the Nordic countries [2].

A large Chinese case-control study showed that participants exposed to dusts (OR, 1.45; 95% CI, 1.26-1.68), chemical vapors (OR, 1.37; 95% CI, 1.17-1.61), exhaust gases/fumes (OR, 1.42; 95% CI, 1.25-1.60), or acids/alkalis (OR, 1.56; 95% CI, 1.30-1.89) in the workplace presented an increased risk of nasopharyngeal cancer compared with unexposed individuals. After analysis of the occupational agents evaluated, the positive associations were mainly related to metal, textile, cement or coal dusts; organic solvents or dyes; exhaust gases or fumes from diesel, firewood, asphalt/tar, vehicles or welding; and sulfuric acid, hydrochloric acid, nitric acid, concentrated alkali, ammonia and formaldehyde vapors [23].

Formaldehyde is a chemical with several virtues, widely used in many industrial sectors, particularly in the manufacture of plastics, resins, textiles and paper, and in some woodworking and construction industries. In their case-control study conducted in the United States, Vaughan and his colleagues observed, after adjustment for smoking and race, a trend towards an increased risk of nasopharyngeal cancer in participants occupationally exposed to formaldehyde. This association appears to be specific to squamous cell carcinomas [24]. Formaldehyde (H-CH O) is an electrophilic substance, chemically extremely reactive: it has a strong affinity for compounds rich in nucleophilic sites, such as biological macromolecules (proteins, membrane phospholipids and nucleic acids). For this reason, it binds instantly and covalently with the constituents of superficial tissues: skin and mucous membrane of the upper airways. This binding explains the effects observed: local cytotoxicity through protein denaturation and the absence of significant systemic diffusion of the aldehyde. Nearly 98% of the inhaled dose is retained in the nasopharyngeal mucosa [25].

Case-control studies have shown an increased risk of NPC in workers occupationally exposed to formaldehyde. In a case-control study based on the cancer registry and death certificates of 173 cases of NPC in Connecticut, people who had been occupationally exposed to high concentrations of formaldehyde for more than 20 years had a 2.3-fold (95% CI: 0.9 to 6.0) increased risk compared with people who had never been exposed[8]. Based on a hospital-based case-control study of 108 cases of NPC in the Philippines, West et al. reported a 2.1-fold increase in the risk of NPC (95% CI: 0.7 to 6.2) in people considered to have been occupationally exposed to formaldehyde for more than 15 years [26]. In addition, a study of Chinese people living in Selangor and the Federal Territory in Malaysia found, after adjusting for the risk associated with diet and cigarette smoke, a statistically significant relationship between the risk of nasopharyngeal cancer and exposure to wood dust (OR = 2.36; 95% CI: 1.334.19) and industrial heat (OR = 2.21; 95% CI: 1.12-4.33) [27]. In a Nordic study, wood burning was found to be a potential risk factor for NPC and a potential exposure agent for these cooks. [2]. In a study concerning cancers of the nasopharynx, nasal cavities and sinus cavities, wood dusts were implicated in almost 90% of the cases for which a moderate or strong imputability was retained, mainly in the specialized construction or woodworking sector [28].

Data from a previous study of 27 cases of NPC in western Washington State showed a weak association with occupations involving exposure to wood dust (adjusted OR 1.2, 95% CI 0.2 to 4.6) [29]. Occupational factors seem to be involved in the development of nasopharyngeal cancers. Among these occupational risk factors, two: formaldehydes and wood dusts, had sufficient evidence of carcinogenicity to be classified by the IARC as certain human carcinogens for nasopharyngeal cancer [30].

In recent years, the treatment of these cancers has improved considerably, especially with new therapeutic protocols, notably concomitant radio-chemotherapy. Overall survival at 5 years, as reported by several randomized studies, ranges from 49.7% to 78.4% [31]. Nasopharyngeal cancer is highly radiosensitive, which allows a satisfactory rate of locoregional control via locoregional transcutaneous radiotherapy, improved by the association with initial or concomitant chemotherapy for lesions with extensive cervical lymph node involvement (N2-3) or large nasopharyngeal tumor volume [31]. The place of surgery is limited but can be discussed in a multidisciplinary consultation meeting when it is possible [32].

For a disease to be officially recognized as an occupational disease under Tunisian law, specific conditions must be fulfilled. The compensation system is based on a set of official tables that clearly outline the causal agents involved, the maximum allowable period for claim eligibility, the list of occupational activities concerned, often requiring a minimum duration of exposure and the necessity of diagnostic confirmation through additional medical examinations [33,34]. At present, under Tunisian legislation, two tables of occupational diseases provide compensation for the damage associated to nasopharyngeal cancers: Formaldehyde and its polymers, and Wood and cork. After checking the conditions from the tables, our patients had their cancers recognized as occupational

diseases: three patients under table number 28 and one patient under table number 54.

The Tunisian occupational disease compensation tables offer a clear legal framework that facilitates the recognition of certain work-related illnesses. By defining specific causal agents, exposure durations, and diagnostic criteria, they help standardize the compensation process and provide guidance for both medical professionals and claimants. However, the system has notable limitations. The list of recognized diseases is relatively narrow and may not reflect current scientific knowledge or emerging occupational risks. In addition, the rigid criteria can exclude legitimate cases that fall outside the defined parameters, particularly in situations involving multifactorial or low-level chronic exposures.

Our study has certain limitations. The retrospective nature of the survey increases the frequency of missing data. The small number of cases of nasopharyngeal carcinoma who consulted for professional expertise may be explained by the underestimation of the occupational origin. The potential influence of confounding factors (such as smoking) might not have completely controlled due to the limited sample size.

5. Conclusion

Nasopharyngeal cancers represent a public health problem due to their social cost, especially as they affect young working individuals. The concept of occupational cancer highlights the need to incorporate the occupational hazards and exposure situations into the diagnostic process and etiological analysis of nasopharyngeal cancer. This identification is important for implementing effective prevention strategies, which should include close and systematic screening of high-risk workers, even after retirement. Furthermore, establishing a causal link with occupational exposure will enable patients to initiate a possible claim for compensation for their condition.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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All authors contributed to the article and approved the submitted version.

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