Malignant melanomas of the nasal cavity after occupational exposure to formaldehyde

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Abstract

Formaldehyde is a well known nasal carcinogen in rodents, but so far there has been no convincing evidence that workers occupationally exposed to formaldehyde have an increased risk of nasal cancer. In this study three cases of malignant melanoma of the nasal mucosa in persons occupationally exposed to formaldehyde for a long time are presented. The occurrence of such a rare tumour in patients with significant exposure to a known carcinogen warrants further investigation.

Nasal cancer is an infrequent disease despite the nose being a contact organ for all inhaled substances. Nasal cancer in man has been linked with exposure to wood dust, nickel, and leather dust.¹⁻³

Formaldehyde has been considered for the past few years as a risk factor for nasal cancer since it was shown that it is a potent carcinogen in rats exposed long term to high doses.⁴ Formaldehyde is a very reactive substance, causing single strand breaks with DNA and DNA protein cross links,⁵ and mutations in human cells in vitro.⁶

It is highly irritant to the upper respiratory tract in man and nasal symptoms are common in occupationally exposed workers, as are physiological disturbances of olfaction and nasomucociliary clearance.⁷ In workers occupationally exposed to formaldehyde, histological changes in nasal mucosa such as loss of cilia and metaplasia, have been reported⁸; in one study dysplasia was also noted.⁹ No convincing evidence has accrued to show that formaldehyde is carcinogenic in man, however, despite several epidemiological studies. Two studies reported a correlation between formaldehyde and the occurrence of nasal cancer,^{10,11} but others, in particular the mortality study of Blair *et al* on more than 26 000 workers exposed to formaldehyde, did not.¹² In the study of Walrath and Fraumeni on embalmers,

persons with probably the highest occupational exposure, no correlation between formaldehyde exposure and nasal cancer was found, although mortality was significantly raised for cancer of the colon and of the skin (eight cases of skin cancer (four malignant melanomas) were found *v* 3.6 expected).¹³ Correlations between dermal malignant melanomas and extrinsic factors such as ultraviolet irradiation,¹⁴ polyvinyl chloride,¹⁵ polychlorinated biphenyls,¹⁶ and L-dopa¹⁷ have been reported.

In this study we describe three cases of malignant mucosal melanoma of the nasal cavity in patients who have been occupationally exposed to formaldehyde.

Case reports

CASE 1

A 58 year old woman presented with a large mass in the anterior left nasal cavity invading the vestibulum nasi and the soft tissue of the nasolabial fold. It was removed by a lateral rhinotomy approach. Histological examination showed invasive malignant melanoma (figure).

History of exposure

She had worked on a family chicken farm for five years between the ages of 18 and 23 and for the past five years, cleaning the broiler cabins. Thus she experienced a total of 10 years of exposure. The cabin cleaning was performed in the same way throughout

Photomicrograph of malignant melanoma taken from patient 1 showing collection of pigment. H and E $\times$ 500. (By kind permission of Professor L Michaels.)

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with a formaldehyde spray from a hand pump carried on her back. The cleaning, which occupied a full time week, took place at nine week intervals. Exposure to formaldehyde during the intervals was minimal. No protection was used when handling the formaldehyde. She was not exposed to other known carcinogens.

The patient complained of mild upper respiratory tract symptoms during exposure to formaldehyde, but she experienced no dermal symptoms or headache. Between 23 and 52 years of age she was a housewife and for seven years she worked as a domestic cleaner. During this time she also occasionally helped with cleaning the broiler cabins.

CASE 2

A 59 year old man was referred with a blockage of the right nostril from which a red fleshy polypoidal mass was subsequently removed by a lateral rhinotomy approach. Histological examination showed an amelanotic melanoma.

History of exposure

This patient was employed for 12 years as a pathology assistant in a histology department, making museum preparations and thus having daily exposure to formaldehyde. He was subsequently employed for seven years as a laboratory assistant in the chemical industry where he was exposed to formaldehyde, chloroform, benzene, and mercuric chloride. He then returned to the post of pathology technician and has remained there since (18 years) with daily exposure to formaldehyde. The department also had constant ventilation problems with an air recirculation and filtration system.

In total he has been occupationally exposed to formaldehyde for 37 years. During exposure he experienced epiphora or smarting of the eyes and nasal obstruction and during peaks of exposure he also complained of nasal discharge. Neither headache nor dermal problems were reported.

CASE 3

A 67 year old man was referred after a right side nasal polypectomy. Histological examination had suggested an anaplastic carcinoma for which an initial course of radiotherapy had been given. A lateral rhinotomy, later extended to a craniofacial resection was performed and histological examination showed a non-pigmented malignant melanoma. This was compatible with the material obtained from the original polypectomy.

History of exposure

After nine years in the army, this patient worked for 40 years in building construction. His job was mainly to fill cavities in houses with an insulation material containing urea formaldehyde, which was pumped

into the walls. This was carried out both indoors and outside. During exposure to formaldehyde his eyes were irritated and he experienced a sore throat and pricking and itching of the skin. No nasal problems were reported.

Discussion

As the nose comes into contact with all inhaled substances, it is probable that local defence mechanisms are responsible for the rarity of nasal cancer compared with malignancy in the rest of the respiratory tract. From animal studies it is known that formaldehyde causes ciliastasis in the anterior part of the nose¹⁸ and loss of cilia and metaplasia in this region if exposure is continued.¹⁹ This deterioration in mucociliary function is probably an important factor in carcinogenesis. After long term and high dose exposure (15 ppm) to formaldehyde cancer occurs in 50% of exposed rats.⁴ In man a dose dependent deterioration in mucociliary function due to exposure to formaldehyde has been shown by Andersen and Mølhave²⁰ and a significant reduction in mucociliary clearance time has been found in workers occupationally exposed to formaldehyde.⁷

It has been estimated that exposure to doses of formaldehyde under 1 ppm is not associated with cancer risk in man²¹ and currently mean exposure values above this concentration are rare in industrialised countries.²²

In this report three cases of malignant melanoma of the nasal mucosa are described. This is a rare tumour²² that has not, to our knowledge, been reported before in workers exposed to formaldehyde, although Walrath and Fraumeni described an increased incidence of cutaneous melanomas in their study of embalmers.¹³

It has not been possible to measure the concentrations of formaldehyde, or other chemicals exposed to, for any of the cases presented but the histories suggest that all three had experienced high peak concentrations of formaldehyde and a long exposure.

Risk factors due to exposures to other chemicals were apparently not present. Also, the families had no histories of melanomas, a factor that has been reported to be significant.²³ No other manifestations of cutaneous or mucosal malignant melanomas were found.

Discussion concerning the aetiology of malignant melanomas has mainly centred on the effect of sunshine, but several reports exist of increased incidence of malignant melanomas in occupational groups such as workers in the telecommunications industry²⁴ and in various chemical industries.²⁵⁻²⁸ Certain chemicals have been linked to the induction of melanomas—for example, 7, 12-dimethyl benzanthracene in tests on Syrian golden hamsters²⁹ and PCB¹⁶ and L-dopa¹⁷ in epidemiological studies.

The epidemiological link between formaldehyde and nasal cancer is not yet proved but when considering such a rare disease in patients with significant exposure to a known carcinogen, the apparent association warrants documentation and further investigation.

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