Case and Review

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Multiple Basal Cell Carcinomas after Long-Term Exposure to Hydrazine: Case Report and Review of the Literature

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Key Words
Basal cell carcinoma · Hydrazine · Occupational exposure

Abstract
Hydrazine (N_2H_4) is a clear, inorganic colourless liquid. It is known to be a skin sensitizer, a corrosive agent and it causes dermatitis on contact. Hydrazine is employed in chemical plants, used as a corrosion inhibitor for feed waters and may be added to rocket fuels. The authors report the case of a 68-year-old man with multiple basal cell carcinomas (BCCs) covering his arms and face. The patient worked in a steam power plant with extensive exposure to hydrazine for a period of over 10 years. The present case report strongly suggests that there may be a correlation between the long-term exposure to hydrazine and an increased risk for multiple BCCs.

Introduction

Hydrazine (N_2H_4; fig. 1) is a clear, inorganic, colourless, oily fluid at ordinary temperature and pressure [1]. It is a highly reactive base and a strong reducing agent [1–3]. It was widely used as a rocket propellant in former times and is still employed for the current rocket fuel of the space shuttle programme [4–6]. Nowadays, hydrazine is mostly used as a raw material in the manufacture of agricultural chemicals and often applied as a corrosion inhibitor and oxygen scavenger for heating systems [1, 3, 7, 8]. Exposure of human beings to hydrazine might occur either during work or be caused by the intake of hydrazine-based drugs or tobacco smoke, with tobacco being the only natural source of hydrazine [9]. Hydrazine has been proven to elicit dermatitis on contact [10], and dermal sensitization [11, 12] has also been reported for gaseous exposure [13].

Interestingly, hydrazine preparations or derivates have been studied both as possible cancer-fighting drugs [14, 15] and cancer-causing agents. The mutagenicity of hydrazine has been proven, as this agent was found to cause thymidine mutation in mouse lymphoma cells [16]. In a number of studies it has been shown that hydrazine causes cancer in animals [17–22]. A possible correlation of the exposure to hydrazine and the occurrence of lung and colon tumours in humans has been discussed in previous reports [23–25]. Morgenstern and Ritz [23] also came to the conclusion that other types of cancer are likely to be induced by hydrazine.

Basal cell carcinomas (BCCs) are the most common skin tumours in humans. They metastasize rarely but can cause significant and extensive local destruction and disfigurement. BCCs seem to occur multifactorially by genetic and environmental factors. They are most often caused by long-term exposure to UV radiation and can occur after X-ray exposure, e.g. in a therapeutic setting. Chemicals like arsenic or immunosuppressant drugs have been proven to play an important role as cofactors. Genetic defects like in xeroderma pigmentosum or in Gorlin syndrome go along with multiple BCCs. To the best of our knowledge, this is the first case report suggesting a highly likely correlation of the occurrence of BCC to hydrazine exposure in humans.

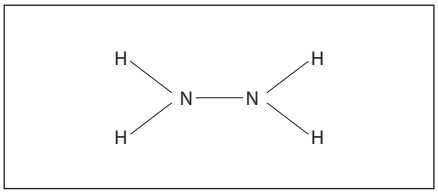

Fig. 1. Chemical structure of hydrazine.

Case Report

We report on a 68-year-old man with multiple BCC covering his arms and face, predominantly found on the bridge and

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Fig. 2. Solid BCC: erythematous solid tumour on the cheek with telangiectasias.

the alar wings of the nose. In addition, his earlobes, forehead, cheeks (fig. 2) and other regions of the face were affected. One further BCC could be identified on his shoulder.

The patient worked in a steam power station, near Munich, Germany, that used electricity-heat coupling, a process where diluted hydrazine solutions are used to deoxygenate water. He had been exposed to hydrazine at an unknown level for more than 10 years occupationally, working as a repair vender with his duties to repair broken engines or membranes, or to tighten gaskets once they were leaky. Wearing protective equipment was not a requirement for the personnel, i.e. for the patient. After 10 years of exposure to hydrazine-contaminated water steam, the carcinogenic property and therefore harmful effect were recognized, and the plant tried to minimize the exposure by changing piston pumps to diaphragm pumps, which was expected to protect the workers from further excessive hydrazine exposure.

The first BCC occurred 4 years after the initial contact with hydrazine. Till today the patient has had more than 25 BCCs removed. Every skin tumour has been excised resulting in the histopathological diagnosis of a solid BCC in the majority of cases.

Microscopic examination showed proliferation from basaloid cells with a thin pale cytoplasm and hyperchromatic nuclei with a rough chromatin pattern. A multitude of mitotic cells and the typical histological pattern of islands of cells with peripheral palisading could be observed. In addition, the authors tried to verify the patient's statement that multiple BCCs also occurred in more than half of his fellow workers (n = 3). Unfortunately up to now we have only been able to get access to one more coworker, who has had multiple BCCs without a positive family history. In addition, in the patient's history there was no extensive long-term exposure to UV radiation nor were there memorable sunburns. Neither a thorough personal nor family history revealed any skin or other tumour. The patient was otherwise in good health with no other medical history. Accordingly he did not take any medication.

At the latest follow-up examination in May 2010, the patient showed another clinically eye-catching area on his nose, a shiny pink lesion with rolled edges and small blood vessels at the maxilla, which has been excised with the histological diagnosis of another BCC. That is the 28th BCC in this patient.

Discussion

To the best of our knowledge, we present the first case of a highly likely correlation of exposure to hydrazine and the occurrence of BCC in humans. Given the patient's history without a positive family history, and the coinciding occurrence of BCC in at least one of his former colleagues, we hypothesize that the BCCs are most likely a consequence of long-term exposure to hydrazine.

In 1978 Back et al. [26] were the first to assume that hydrazine may have tumorigenic potential as well as chronic systemic effects. Hydrazine's toxicity was recognized because of acute effects after inhalation or ingestion [27]. In 1971 Sotaniemi et al. [28] reported about a fatal case of a person who had been exposed to hydrazine at unknown levels once per week for 6 months and who died 3 weeks after the last exposure to the agent. In 1984 workers in a thermo-electric power plant who had had contact with hydrazine and other chemicals were compared to the cancer register data from a near province, and a higher mortality rate of cancer could be observed for those who had been employed over a period of 10 or more years [29]. In 1999 Ritz et al. [24] suggested that employees, who had been exposed to hydrazine, were at higher risk for lung cancer mortality. In 2006 the same authors confirmed their previously published results that the exposure to hydrazine increases the risk of lung cancer, and they even observed an increased risk for colon cancer [25]. Moreover, Ritz et al. [25] could observe an increased rectum cancer incidence and a possible evidence for a dose-response association with pancreatic cancer. Hydrazine has been proven to cause cancer after cutaneous exposure in animals, as there were angiosarcomas induced in mice [30, 31], and in 2004 a report emerged about a case of an epithelioid sarcoma as a possible consequence of cutaneous exposure to hydrazine in humans [6]. Albert and Puliafito [32] observed a choroidal melanoma after a 6-year exposure to hydrazine in one of their patients. Although hydrazine is known to cause dermatitis by contact [27, 33], ranging from erythema to necrosis, there has been no report describing cancer development after cutaneous exposure to the substance in humans till today.

Nevertheless our patient had to work sporadically as a welder in the plant too. In so doing, he did always wear a protecting helmet. Single cases of the development of non-melanoma skin cancers in welders have been described in the literature. However, in major studies an increased incidence of BCC in welders could not be revealed [34–37].

Various factors (the amount of exposure, time period of exposure, route of exposure and individual characteristics like the state of health) determine whether a substance might cause harmful effects or not. Evaluating all the findings concern-

ing hydrazine, it can be regarded as of little hazard at normal levels for the general population. However, at the workplace and in the case of accidentally high dose exposure or intake levels it can be a significant health hazard.

We believe that our findings call for greater vigilance in the examination of further possible cutaneous manifestations related to long-term exposures to hydrazine. Moreover, we recommend careful monitoring of the skin in those who have been exposed to hydrazine. Last but not least, our finding justifies the need for further epidemiological investigations of a potential correlation of hydrazine with BCC.

Disclosure Statement

The authors declare no conflict of interest.

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