

Sinonasal cancer in a worker exposed to chromium in an unusual industrial sector

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SUMMARY

Background: Occupational exposure to chromium is carcinogenic for human respiratory system. Due to the low incidence of sinonasal malignancies, there is still a paucity of evidence to confirm that chromium^(VI) exposure is a cause of nasal cancer. **Objectives:** To report on a sinonasal cancer (SNC) of rare occupational origin, increasing the awareness on epidemiological knowledge of occupational exposures to chromium compounds. **Methods:** We describe a case of a 64-year-old chrome plater who worked in the galvanic industry in the early 1970s. After a latency period of 39 years, he was diagnosed with sinonasal undifferentiated carcinoma (SNUC). A brief review of the literature was conducted. **Results:** A thorough occupational history revealed a 4-year-long occupational exposure to chromium^(VI) during a magnesium cylinder plating process involved in computer production. The patient underwent endoscopic endonasal removal of the SNUC. He is alive with no evidence of disease at 40-month follow-up. Our literature review identified 8 papers concerning 40 cases of chrome-induced sinonasal tumors. The maximum relative risk of SNC developing in chromium-exposed workers was 15.4. **Conclusions:** When dealing with patients diagnosed with SNC, the possibility of an underlying occupational risk is worth further investigation. Because chromium exposure is rare, and the incidence of SNUC is low, any information emerging on clinical and exposure-related aspects of SNCs in chrome plating workers can contribute to adding evidence on the possible causal relationship between chromium and sinonasal malignancies.

RIASSUNTO

«**Carcinoma nasosinusale da esposizione a cromo in un settore industriale inconsueto**». **Introduzione:** L'esposizione professionale a cromo è cancerogena per l'apparato respiratorio. Data la bassa incidenza dei tumori nasosinusalali (TuNS), le evidenze scientifiche a supporto di un nesso di causalità tra cromo e tumori nasali sono piuttosto scarse. **Obiettivi:** Presentare un caso di TuNS in un paziente con una rara esposizione professionale a cromo, al fine di aumentare le conoscenze epidemiologiche sul tema ed evidenziare l'importanza di una approfondita anamnesi professionale. **Metodi:** Viene descritto il caso di un paziente di 64 anni che ha lavorato come addetto al trattamento galvanico di cilindri di magnesio nella produzione di matrici per computer nei primi anni '70. Dopo una latenza di 39 anni, è stata posta diagnosi di carcinoma nasosinusale indifferenziato. È stata inoltre condotta una breve analisi della letteratura. **Risultati:** L'anamnesi lavorativa ha rivelato un'esposizione professionale della durata di 4 anni a

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*cromo esavalente. Il paziente è stato sottoposto ad intervento chirurgico di exeresi tumorale per via endoscopica; a 40 mesi di follow-up si presenta libero da malattia. L'analisi della letteratura ha identificato 8 articoli comprendenti un totale di 40 casi di TuNS da esposizione a cromo. Il rischio relativo massimo riportato è 15.4. **Conclusioni:** È doveroso indagare l'esposizione professionale nei casi di TuNS, tumori ad alta frazione eziologica. Data la rarità dell'esposizione a cromo e la scarsa incidenza dei TuNS, ogni contributo volto a descrivere la correlazione clinica e professionale in tale ambito può corroborare l'evidenza di associazione tra cromo e TuNS.*

INTRODUCTION

Nasal disease in chrome workers has been described since 1890, reporting on a Scottish chrome pigment worker diagnosed with nasal adenocarcinoma. Since then, several studies have correlated chromium^(VI) compounds with airway diseases, such as lung cancer, nasal mucosa inflammation, nasal ulcerations, and septal perforations (5, 8). A few anecdotal cases of sinonasal cancer (SNC) in chromium-exposed workers have been reported, but most of the studies focused primarily on lung cancer (4, 10). Details on patients' occupational history have rarely been provided. The present paper describes the clinical case of a patient treated for SNC with a history of occupational exposure to chromium^(VI) many years earlier.

METHODS

The medical record of a chromium-exposed patient with sinonasal undifferentiated carcinoma (SNUC) was retrospectively reviewed. Data concerning his presenting symptoms, treatment, follow-up and occupational history were collected. A brief review of the literature on sinonasal malignancies in chrome platers was conducted in PubMed, matching the search terms "chromium" or "chromium plating", and "nasal cancer" or "sinonasal malignancy". Reference lists of retrieved articles were further screened for additional relevant publications. Anecdotal reports of single cases were excluded, as well as papers reporting multiple exposures to metals (e.g. nickel and chrome compounds).

RESULTS

A 64-year-old man with a 1-year history of right-side nasal obstruction and rhinorrhea referred to our

Department of Otorhinolaryngology. He was a non-smoker and his medical history was negative except for a mild form of hypothyroidism. Nasal endoscopic examination revealed a vascularized vegetating mass in the right nasal fossa that extended to the posterior ethmoidal cells and nasopharynx. The posterior third of the nasal septum was identified as the site of origin. Head and neck computed tomography (CT) and contrast-enhanced magnetic resonance imaging detected osteolytic bone erosion of the anterior wall of the ipsilateral sphenoid sinus. A biopsy performed under local anesthesia revealed a highly-proliferative epithelial neoplasm. Total body positron emission tomography (PET) - CT ruled out any regional or distant metastases. The patient underwent endonasal endoscopic resection of the tumor with free surgical margins and was discharged on the third postoperative day. No intra- or postoperative complication occurred. Postoperative histological examination was consistent with a T4aN0M0 SNUC with a proliferative index (MIB-1) of 60% and angio-lymphatic invasion. Given the histological findings, the case was discussed by a multidisciplinary team, after which the patient was administered adjuvant concurrent chemoradiation. This treatment consisted of cisplatin and 64.4 Gy of intensity-modulated radiation therapy fractionated over 28 days and extended bilaterally to the neck. The patient was routinely followed-up according to the National Comprehensive Cancer Network (NCCN) Guidelines for the head and neck. No evidence of recurrence was present at a 40-month follow-up.

The patient was referred to an occupational physician to ascertain the possibility of an occupational etiology. Given the peculiarity of the patient's occupation, his working history was collected with the help of a senior industrial hygienist.

The patient started working at the age of 22 (from 1970 to 1974) at the galvanic center of a

multinational technology company. His task consisted in the chrome plating of magnesium cylinders that were used to obtain the punched cards for computer data processing in early seventies. He had never been exposed to chromium or other carcinogenic compounds after that time, having worked as a computer technician until retirement. The latency period between his chromium exposure and the diagnosis of SNUC was 39 years.

Preliminary steps of the computer cards manufacturing process consisted in manual drawings of the magnesium cylinders on boards, which were then transferred onto photographic plates. The magnesium cylinders (about 15 cm long and 7 cm in diameter) were etched to obtain the required pattern for the punched cards. The average life of cylinders allowed for punching of about one million cards, but chrome-plating the cylinders extended their working life to about 10 million cards.

The patient itself completed the whole chrome plating process. His task consisted in soaking the magnesium cylinders into tanks containing various solutions. The phases of this process included: i) washing the tanks with water; ii) adding potassium cyanide (KCN) to an alkaline medium; iii) re-washing the tanks with water; iv) preparing chrome plating baths containing a potassium dichromate solution; v) re-washing the tanks with water. Each electrolytic plating cycle lasted about 30 minutes. The cylinders were submerged manually in the serial baths. All the baths were heated to a temperature of 50-60 degree Celsius, which led to the production of vapors. Each of the tanks had a small, fixed extractor of square cross-section located on one side, placed about 30 cm above the surface of the solution. The cylinders were left in contact with the solution for approximately 5-6 minutes in each bath.

The patient never used gloves or masks for airway protection. He managed two sets of baths simultaneously (12 baths in all). Being expert with chemicals, he also prepared and monitored the chemical solutions for the baths, manually weighing the reagents, diluting them with water and finally draining them out of the tanks.

Given this exposure, a first certificate of occupational disease was issued and the disease was reported to the Italian National Institute for Insur-

ance against Accidents at Work (INAIL) also for epidemiological purposes (Legislative Decree, June 10th 2014).

DISCUSSION

SNCs are highly related to occupational exposure, in particular to wood and leather dusts (2, 13). Emanuelli et al. recently reported that SNC risk was significantly higher for patients exposed to mastic/solvent and leather dust (6). SNCs were also associated to occupational contact to formaldehyde, textile fibers, farming, construction, nickel and chromium compounds (1).

Ulcerations of the nasal mucosa and nasal septum perforations were commonly observed among hexavalent chromium ($\text{Cr}^{(\text{VI})}$) exposed workers in chromate production and chrome plating (5, 10, 17). Moreover, it is well known that $\text{Cr}^{(\text{VI})}$ has carcinogenic effects (11). Even if the precise mechanism is still unknown, *in vitro* studies have revealed mutagenic and cytogenic effects of chromium compounds, determining chromosome aberrations, sister chromatid exchanges, DNA strand breakage, DNA-DNA and DNA-protein cross-links, and nucleotide modifications (8). *In vivo* studies have shown an increased tumor growth after the administration of $\text{Cr}^{(\text{VI})}$ compounds on rats and mice (10).

The International Agency for Research on Cancer (IARC) evaluated chromium exposure as carcinogenic to humans, based on a sufficient evidence for lung cancer but limited for sinonasal cancer (11). Among chromium workers, occupational exposures may occur during the production, use and chrome plating of chromium-containing metals and alloys (e.g. stainless-steels), in electroplating, or during the production and use of chromium-containing compounds (e.g. pigments), catalysts, chromic acid, tanning agents and pesticides. In particular, high levels of $\text{Cr}^{(\text{VI})}$ ($>1 \text{ mg/m}^3$) are found in chrome plating processes (9).

The main challenge of investigating occupational exposure to chromium is the frequent overlap with nickel exposure among the same workers population. Hernberg was the only author who separately reported odds ratio results for nickel and chromium (9). Other studies did not show any risk increase

among chromate workers (3, 12), probably because of the inclusion of workers employed in the stainless-steel welding or in the chromate spray painting, where levels of exposure are generally low.

From a brief review of the English literature, 8 articles met the eligibility criteria for the study (table 1), namely three cohort studies, three case-control studies, and two case series. Forty cases of SNC in chromium-exposed workers from Europe (Great Britain, Germany, Scandinavia), America (USA) and Asia (Japan) were reported (3, 4, 9, 10, 12, 14-16). The maximum relative risk calculated for exposed patients was 15.4 (4). The first noteworthy issue that emerged from literature analysis was a lack of clinical data concerning patients' symptoms, histological features or/and site of origin of chromium-induced SNC. Bloody sputum, a hard palate mass, nasal obstruction and unilateral rhinorrhea were the signs and symptoms described for only 3 patients

(15). When definite tumor histology was reported, the most frequent diagnoses included squamous cell carcinoma, adenocarcinoma and SNUC. The maxillary sinus and the lateral wall of the nasal cavities were identified as the site of origin of the neoplasia in 4 and 3 cases, respectively. In the series reported by Satoh (15), one patient suffered from squamous cell carcinoma of the nasopharynx, which appears as a very rare anatomical localization. In fact, there has been only one report of SNUC arising from the nasopharynx in a chromium-exposed worker (7). To the best of our knowledge, the tumor origin site presented in this case (the posterior third of the nasal septum) has never been previously reported in a chromium-exposed patient.

Another relevant finding from literature investigation was the paucity of quantitative data on the duration of patients' exposure to chromium, as well as on the latency period between their first exposure

Table 1 - Chromium exposure in sinonasal cancer from the literature

Author, year	Study design	Number of cases	Exposure/agent	RR	Site (n)	Histology (n)	Mean latency (y)
Hueper ¹⁰ , 1966	Case Report	6	-	-	Maxillary sinus (1) Turbinates (1) Unknown (4)	ADC (1) Unknown (5)	-
Hernberg ⁹ , 1983	Case-control	2	Spray painting (1) Steel worker (1)	2.7	-	-	-
Brinton ³ , 1984	Case-control	5	-	1.5	-	-	-
Davies ⁴ , 1991	Cohort	4	-	15.4	Maxillary antrum (1) Unknown (3)	SNUC (1) Unknown (3)	38.25
Luce ¹² , 1993	Case-control	12	-	0.7 0.4 2.4	-	SCC (4) ADC (3) other (5)	-
Satoh ¹⁵ , 1994	Case Report	4	Chromate plant	-	Middle turbinate (2) Nasal floor (1) Nasopharynx (1)	SCC (4)	39
Rosenman ¹⁴ , 1996	Cohort	6	-	6.85	Maxillary sinus (2) Nasal cavity (2) Unknown (2)	-	-
Sorahan ¹⁶ , 2000	Cohort	1	-	6.87	-	-	-
Present case	Case Report	1	Electroplating / Cr ^(VI)	-	Posterior septum	SNUC	39

RR=relative risk; y=years; Cr^(VI)=hexavalent chrome; ADC=adenocarcinoma; SCC=squamous cell carcinoma; SNUC=sinonasal undifferentiated carcinoma; -=not reported

to chromium and the diagnosis of SNC. These have rarely been investigated in chrome workers: only Satoh et al. and Davies et al. calculated a mean 26 years and 32.5 years of exposure among 4 workers, respectively, reporting mean latency periods of 38.25 years and 39 years (4, 15).

The reported working tasks of SNC patients who had been exposed to Cr^(VI) were chrome smelting, spray painting, leaching, working on kilns and chrome plating, involving exposure to Cr^(VI) in the form of chromic acid mist (4, 9, 16).

In conclusion, when dealing with SNC patients, a possible occupational etiology should always be considered and an accurate investigation on working history is of utmost importance. As testified by the lack of published literature on the topic, the occupational exposure described in the reported case was extremely unusual, so that the additional help of a senior hygienist was needed to thoroughly investigate the specific working tasks.

An occupational history to chromate compounds exposure associated to persistent sinonasal symptoms should be investigated in a multidisciplinary context with Otorhinolaryngologists, as an early SNC diagnosis is prognostically significant.

NO POTENTIAL CONFLICT OF INTEREST RELEVANT TO THIS ARTICLE WAS REPORTED BY THE AUTHORS

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