

# Association of chromium exposure with multiple primary cancers in the nasal cavity

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## Abstract

A 56-year-old man who had worked at a chromate factory for 13 years developed squamous cell carcinoma of the left nasal cavity 11 years after retirement. He received intra-arterial chemotherapy, followed by surgery. Two years later, an adenocarcinoma was identified in the same nasal cavity just above the previous surgical region. He underwent medial maxillectomy in combination with postoperative irradiation. He has been disease free for 5 years after the second surgery. Microsatellite markers were examined in the second tumor specimen as a possible factor for carcinogenesis; however, replication errors were not observed in any of four loci (D2S123, D3S1067, TP53, D18S474) tested. The present case seems to have resulted from long-term exposure to chromium and, to our knowledge, is the first reported case with multiple primary cancers in the nasal cavity associated with chromium exposure.

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**Keywords:** Nasal cavity; Chromium exposure; Multiple primary cancers; Microsatellite marker

## 1. Introduction

At low concentrations, chromium is an essential micronutrient. Chromium deficiency in humans presents as impaired glucose tolerance, glycosuria and elevations in serum insulin, cholesterol and total triglycerides [1]. However, at higher concentrations, chromium is toxic to many organs and has been shown to be carcinogenic. Cases of occupational lung and nasal cancers after chromium exposure have been well documented [2–5]. Chromium compounds are potent inducers of tumors in experimental animals and active agents in causing various types of DNA damage, such as DNA strand breakage, DNA–DNA and DNA–protein cross-links and modified nucleotides [1,6,7]. Although the precise carcinogenic mechanisms are unknown, various types of

cancer may be associated with chromium exposure [8]. In terms of lung cancer, squamous cell carcinoma is reported to occur most frequently, followed by undifferentiated carcinoma, small cell carcinoma and adenocarcinoma [9–11]. In contrast, most reported cases of chromium-induced nasal cancer, which is less common than chromium-induced lung cancer, are squamous cell carcinomas [2,4,10,12]. Herein we report the case of a 56-year-old man with multiple primary cancers in the same nasal cavity associated with chromium exposure; the first tumor was squamous cell carcinoma and the second tumor was adenocarcinoma. Possible pathogenetic mechanisms of this rare case are discussed.

## 2. Case report

A 56-year-old patient who had worked at a chromate factory for 13 years visited our clinic complaining of left nasal obstruction. Eleven years has passed since his

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retirement. Rhinoscopic examination revealed that the tumor originated from the left inferior turbinate. Axial and coronal computed tomography (CT) scans showed a soft tissue density mass in the left nasal cavity without bony destruction (Fig. 1). Biopsy specimens of the tumor in the left nose revealed squamous cell carcinoma (Fig. 2). He received two courses of intra-arterial chemotherapy via the superficial temporal artery with carboplatin and fluorouracil (carboplatinum 100 mg, 2 days; fluorouracil 250 mg, 6 days) which resulted in marked tumor regression, followed by inferior medial maxillectomy through a sublabial approach.

Two years later, a tumor was identified in the same nasal cavity just above the previous surgical region. Biopsy specimens of the tumor revealed adenocarcinoma. Axial and coronal CT scans showed a soft tissue density mass in the left nasal cavity extending from the middle turbinate to the maxillary and ethmoid sinuses (Fig. 3). He underwent medial maxillectomy, followed by postoperative irradiation (40 Gy/20 fr.). During surgery, fresh-frozen tissues were preserved for examination of microsatellite instability. Histopathological examination showed typical adenocarcinoma, as seen in biopsy specimens (Fig. 4). Considering the possibility of recurrence of adenosquamous carcinoma, a periodic acid-Schiff (PAS) stain was carried out on the first (squamous cell carcinoma) and second (adenocarcinoma) tumor specimens. The first tumor was negative on PAS stain in any of serial sections, whereas the second tumor was positive in the lumina. From these results, we diagnosed this case as a multiple primary cancer in the nasal cavity. Currently, the patient has been free of disease for 5 years.

### 3. Replication error test at microsatellite loci

Microsatellite instability was examined using four different (CA)<sub>n</sub> repeats: D2S123, D3S1067, TP53 and D18S474 (Otsuka Assay). We compared amplified DNA

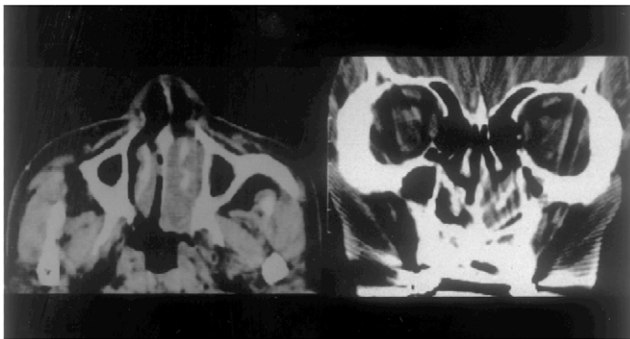
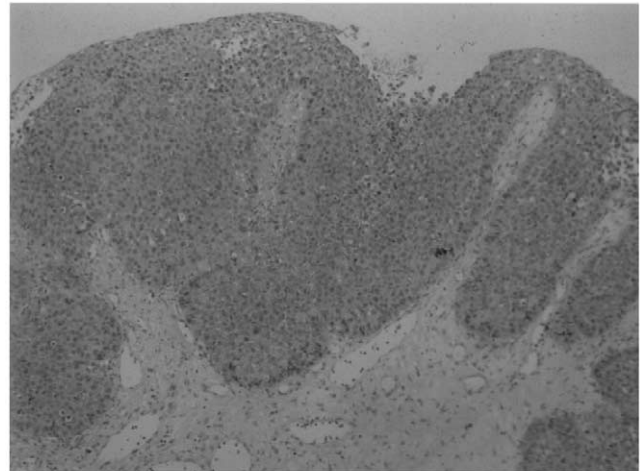
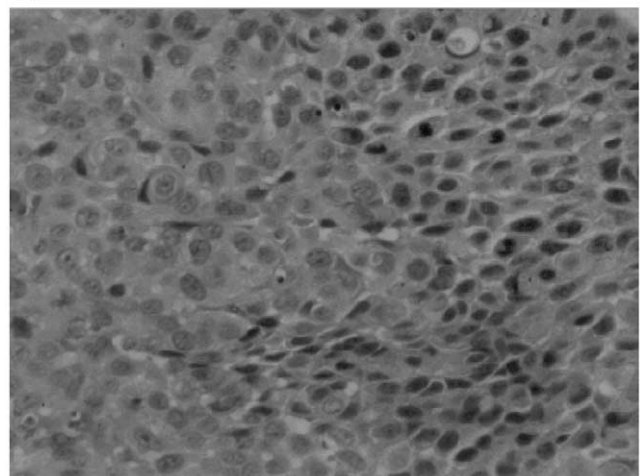


Fig. 1. Axial (left) and coronal (right) computed tomography scans showing a tumor in the left nasal cavity around the inferior turbinate without bony destruction.



(a)



(b)

Fig. 2. Microscopic features of the first cancer showing typical squamous cell carcinoma. Hematoxylin and eosin stain (a)  $\times 40$  and (b)  $\times 200$ .

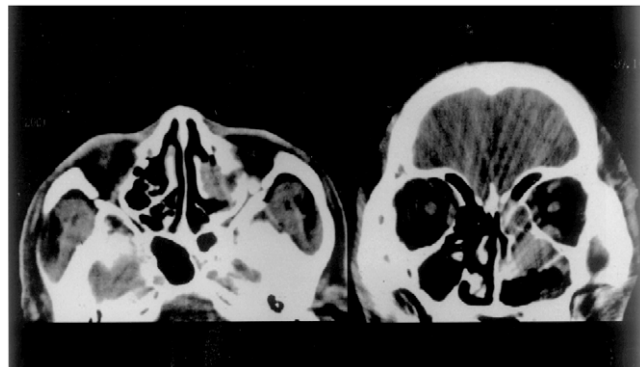


Fig. 3. Axial (left) and coronal (right) computed tomography scans showing a tumor in the left nasal cavity extending from middle turbinate to the maxillary and ethmoid sinuses.

samples from the second tumor specimen with normal constitutional DNA (normal nasal mucosa and peripheral blood lymphocytes) and could not detect micro-

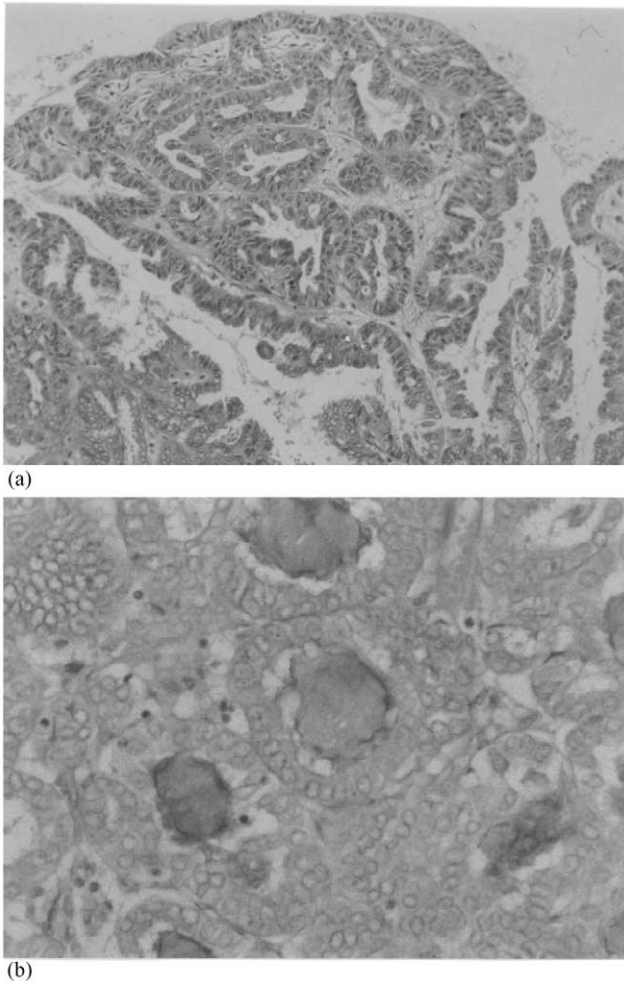


Fig. 4. Microscopic features of the second tumor showing typical adenocarcinoma with mucin production. Hematoxylin and eosin stain (a)  $\times 40$  and (b)  $\times 200$ .

satellite instability at any of the four loci tested. Loss of heterozygosity at 2p, 3p, 17p and 18q loci was not seen either (Fig. 5).

#### 4. Discussion

Numerous epidemiologic studies have established that chromium compounds are potent carcinogens [1,5] and the lung and nose are known to be major sites of chromium-induced cancers [2–4,10]. In addition, chromium exposure increases the incidence of a variety of cancers, including those of the ureter, urinary bladder, testes, kidney, prostate, brain and stomach [7]. Furthermore, malignant lymphoma including Hodgkin's disease, leukemia and bone cancer, also occur more frequently in workers with a higher exposure to hexavalent chromium compounds [8]. Although the precise mechanism of its carcinogenicity is unknown, chromium exposure has been reported to induce DNA damage,

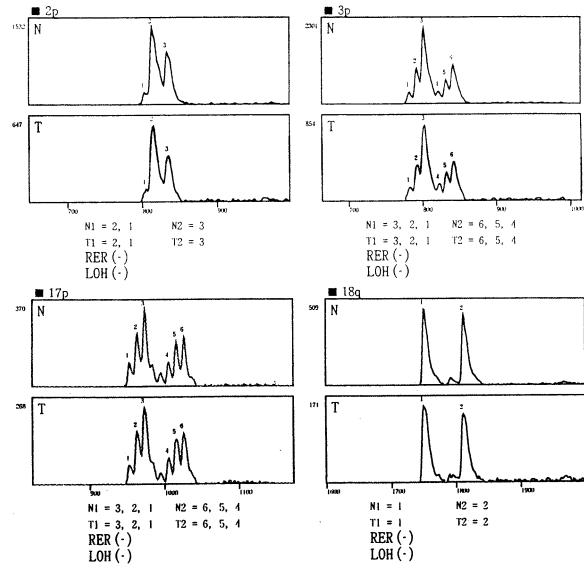


Fig. 5. Replications error test at D2S123, D3S1067, TP53, D18S474. Microsatellite instability was not observed at any of these loci.

such as DNA strand breakage, DNA–DNA cross-links, oxidative damage to DNA nucleobases and mitotic recombination [1,6,7,13,14]. These features seem to explain the development of a wide variety of cancers in various organs, and, at the same time, suggest a possible pathogenesis of the multiple primary cancers seen in this patient. In fact, an experimental animal study using rats revealed that intrapleurally implanted chromium induced multiple primary cancers in the same lung (squamous cell carcinoma, adenocarcinoma and sarcoma) [10].

Recurrence of adenosquamous carcinoma might be another possible explanation for the development of two different cancers in this case, as both tumors originated in the same nasal cavity and were close together. Adenosquamous carcinoma is defined as having histologic features of both adenocarcinoma and squamous cell carcinoma. They may be admixed or separate from one another. However, an adenocarcinoma component was not identified in the specimen of the first tumor despite the performance of PAS staining. In addition, a squamous cell carcinoma component was not observed in any histologic sections of the second tumor. Furthermore, both squamous cell carcinoma [2–4,10,12] and adenocarcinoma [15] have been reported to be chromium-induced nasal cancers. Therefore, the occurrence of two different tumors in this case seems to be the result of multiple primary cancers rather than recurrence of adenosquamous carcinoma.

Microsatellite instability has been reported to occur frequently in tumors from patients with hereditary nonpolyposis colorectal cancer (HNPCC) who often develop multiple cancers [16]. This genetic phenotype is

considered a direct outcome of alterations in the DNA mismatch repair system. Abnormalities in the mismatch repair system can often be monitored by examining genetic instability in the form of replication errors at microsatellite loci in cancer cells [16,17]. Microsatellite instability has also been reported to occur frequently in patients with multiple primary cancers other than HPNCC [18]. Based on these reports, we examined microsatellite instability to determine whether it had a clinicopathologic significance on this patient. Results showed negative findings for both microsatellite instability and loss of heterozygosity at the four tested loci. However, this finding does not necessarily imply that genetic instability is irrelevant to chromium-induced cancer as the tested loci were limited to four loci, which had been used for the screening of HNPCC until 1997. In fact, Hirose et al. [19] recently reported that the frequency of microsatellite instability at six loci (D3S647, D3S966, D3S1289, D5S346, D9S161, TP53) in the chromate lung cancer group was significantly higher than that in the nonchromate lung cancer group. They also reported that the frequency of loss of heterozygosity at 3p, 5q, 9p, and 17q loci in tumors with chromate exposure was not significantly different from that in tumors without chromate exposure, suggesting that microsatellite instability may play a role in chromium-induced carcinogenesis.

To the best of our knowledge, the present case represents the first report of multiple primary cancers in the nasal cavity associated with chromium exposure.

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