

# Sinonasal Intestinal-type Adenocarcinoma in a Shoe Master: A Case Report with Immunohistochemical and Molecular Genetic Analysis and Review of the Literature

Zühal Özcan, Fügen Vardar Aker

## ABSTRACT

**Background:** Sinonasal intestinal-type adenocarcinoma (ITAC) is a rare tumour of the sinonasal tract with morphologic and immunophenotypic similarities to intestinal adenocarcinomas and increases significantly in wood and leatherworkers.

**Methods:** Here, we present a shoe master with a 50-year history of working. The patient was diagnosed with ITAC, colonic type, based on the histopathology, immunohistochemistry and genetic analysis. We discussed our findings and results related to the literature.

**Results and Conclusion:** ITACs are rare local aggressive neoplasms, and metastatic adenocarcinomas from the gastrointestinal tract must be excluded with systemic and clinical examination. Patients presenting with a sinonasal mass should be queried for any occupational exposure.

**Keywords:** Genetic, Sinonasal adenocarcinoma, Intestinal-type, Leather, Shoe worker

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## INTRODUCTION

Sinonasal intestinal-type adenocarcinoma (ITAC) is a primary adenocarcinoma of the sinonasal tract with morphologic and/or immunophenotypic similarity to adenocarcinomas of the intestines. ITACs are uncommon, with an overall incidence of <1 case per 1 million person-years (0.44 per million) and typically develop in the nasal cavity and sinuses<sup>1-2</sup>.

The entity is more common in men and usually occurs in the fifth to seventh decades of life. Occupational wood dust exposure is strongly associated with ITACs, and its incidence has been shown to be increased 500 times among people who work prolonged periods in the wood and leatherworking industries<sup>3</sup>. Patients typically present with nasal obstruction, epistaxis and rhinorrhoea.

The colonic type is the most frequent subtype and resembles conventional colorectal adenocarcinoma. The immunohistochemical profile for ITACs show positivity for CK20, CDX2, villin and MUC2, with variability for CK7. Variable rates of KRAS, BRAF, EGFR and TP53 mutations, as well as P16 alterations, have been reported in the literature<sup>4-8</sup>. ITAC is a locally aggressive tumour, and overall survival rates vary depending on grade. Treatment includes surgical excision, which may be combined with radiotherapy or chemotherapy.

## CASE REPORT

A 71-year-old man presented with nasal obstruction. Computed tomography (CT) of the maxillofacial region and magnetic resonance imaging (MRI) of the face showed a mass filling the entire left nasal cavity (Figure 1). Histopathologic examination

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revealed variable-sized glandular structures in a fibrotic stroma, which were lined by neoplastic columnar epithelial cells with palisaded hyperchromatic nuclei and a few goblet cells (Figure 2). Mitotic figures were frequent and necrosis was present.

Neoplastic cells showed diffuse and strong expression of CK20, CDX2 and CEA, as well as focal expression of CK7 (Figure 3). The tumour did not stain with P63, P40, chromogranin, CERN-B2 and MUC2 compared with the external controls. The Ki67 proliferation index was 10%, and p53 overexpression was detected.

A systemic examination suggested a distinction between “primary ITAC, colonic variant” and “metastatic colorectal adenocarcinoma”. The CEA value was within normal limits; colonoscopy

and biopsies taken from the colon were normal. Positron emission tomography (PET)/CT scanning demonstrated a soft tissue mass filling the entire left nasal cavity with nasopharyngeal extension with increased FDG uptake (SUDmax: 11.7) and hypermetabolic cervical and mediastinal lymph nodes (SUDmax: 6.4 and 13.7). Endobronchial ultrasound (EBUS) biopsy of a mediastinal lymph node revealed only reactive lymphoid tissue with anthracotic pigmentation. We learned that patient was a shoe master and worked in the leather shoe industry for 50 years.

Genomic DNA was extracted from FFPE specimen blocks using the AmoyDx FFPE DNA Kit containing nucleic acid purification spin columns (Amoy Diagnostics, Xiamen, China). Allpurified DNA samples were quantified by a Merinton SMA4000 spectrophotometer (MerintonInc., Beijing). Tissue PCR Mutation Assays. Mutations were analyzed for KRAS in exon 2, 3 and 4 (19 mutations in codons 12, 13, 59, 61, 117 and 146), NRAS in exon 2,3, and 4 (16 mutations in codons 12, 13, 59, 61, 117 and 146), EGFR in exon 18, 19, 20,21 (29 mutations) and BRAF in exon 15 (6 V600 mutation) genes by RT-

PCR mutation detection was performed by using the commercially available AmoyDx. KRAS, EGFR, NRAS and BRAF were negative.

A final diagnosis of "ITAC, colonic type" was made, and the patient received radiation therapy totalling 33 sessions. But, he presented with asphyxiation 8 months after treatment, and histopathologic examination of the biopsies and excisions revealed the same residual tumour with added focal intraluminal papillary projections and squamous metaplastic areas (Figure 4). The last clinical and oncological control showed no recurrence or residual mass in the location at 3 months after the last resection.

**DISCUSSION**

Sinonasal ITAC is a rare entity and has diagnostic difficulties related to its histologic and immunohistochemical similarities with colorectal carcinomas. ITACs occur mostly in males, with a wide age range, and usually occurs in the fifth to seventh decades of life. ITAC most commonly involves the ethmoid sinus (40%), nasal cavity (25%) and maxillary antrum (20%). Patients mostly present with

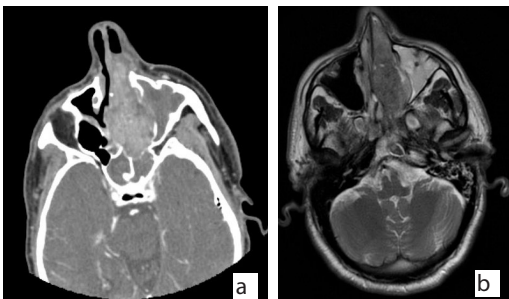


Figure 1. The mass filling the entire left nasal cavity (a. CT and b. MRI of face).

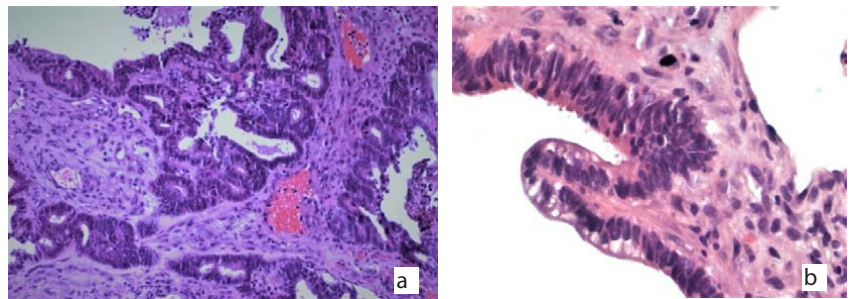


Figure 2. Variable-sized glandular structures lined by neoplastic columnar epithelial cells with palisaded hyperchromatic nuclei(a) and a few goblet cells (b). (H&E, a. X100, b. X200)

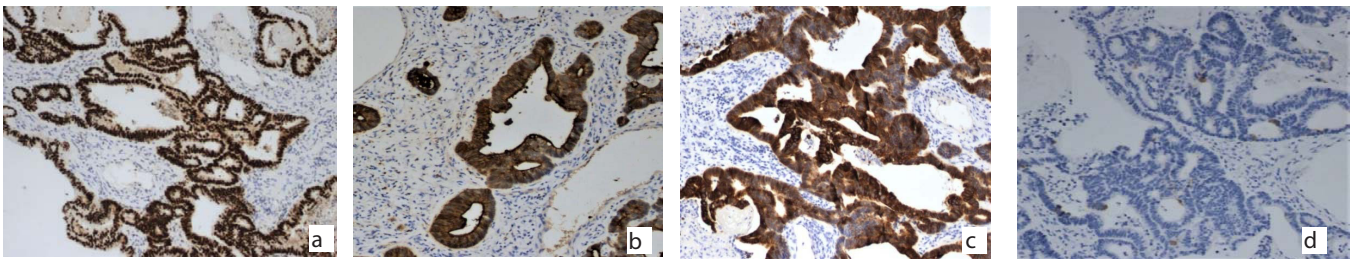


Figure 3. Diffuse positive staining with CDX2 (a), CEA (b) and CK20 (c), as well as focal positivity with CK7 (d). (a. and d. X40, b. and c. X200)

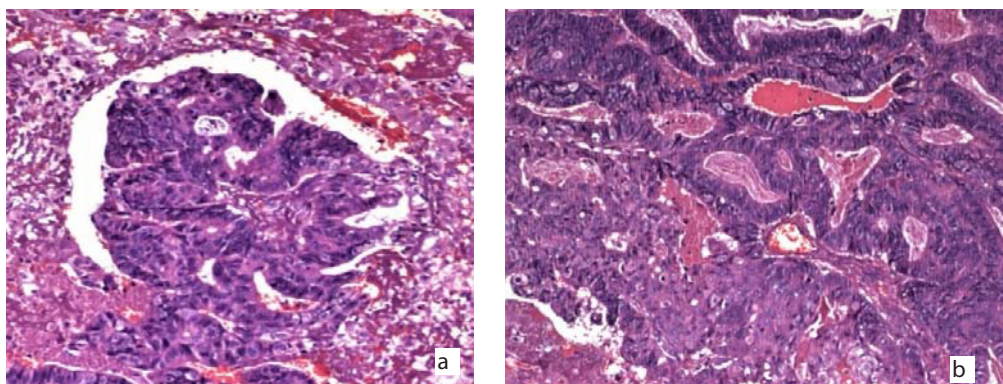


Figure 4. Histopathologic examination ofpost-therapeutic tumour excision with focal intraluminal papillary projections (a) and squamous metaplasticareas (b). arrows (H&E, X100)

nasal obstruction, epistaxis and rhinorrhoea and less commonly with pain, facial contour changes, diplopia, foul smelling discharge and growing soft tissue mass<sup>1,9,10</sup>. ITACs appear as soft tissue densities, with or without extension to the adjacent structures, including the orbit, pterygopalatine fossa, infratemporal fossa and cranial cavity, or with bone destruction on CT or MRI<sup>11</sup>. They are classified into a variety of subtypes (papillary, colonic, solid, mucinous and mixed), and the colonic type is the most common subtype (40%). It displays tubuloglandular architecture that resembles a conventional colorectal adenocarcinoma, which is lined by neoplastic columnar cells having stratification and hyperchromatic nuclei, and a few goblet cells may be seen.

ITACs are often associated with occupational exposures including wood and leather dust. The latter is probably associated with exposure to the dust of leather soles and heels that usually occur in the preparation, pressing and finishing rooms of factories making boots and shoes by the welted process<sup>12</sup>. Carcinogenesis is believed to be promoted by mutagenic and irritating inhalants, which cause malignant transformation of sinonasal mucosa. Also, toxic effects on the human nose has demonstrated that workers had significantly lower nasal mucociliary transport rates as compared to a group not exposed to dust, showing metaplastic squamous-cuboidal or columnar epithelium, goblet-cell hyperplasia and dysplasia<sup>13,14</sup>.

An intestinal-type tumour detected in the sinonasal tract needs a differential diagnosis with immunohistochemistry and systemic examination. Both ITACs and colorectal carcinomas express CK20, CDX-2, villin and MUC2, but the expression of CK7 in a tumour may be suggestive of ITAC [15]. Some authors decline to argue that CK20 is a more specific marker for ITAC and CDX2 is a marker for cellular phenotype<sup>16,17</sup>. Also, lacking strong CEA expression and displaying neuroendocrine differentiation is associated more with ITACs than with colonic adenocarcinomas<sup>18</sup>.

Surgical resection is the main treatment, with or without radiotherapy or chemotherapy. It is a locally aggressive tumour with local recurrences (>50%), while distant metastases are not frequent. The 5-year cumulative survival rate is about 40%; therefore, new therapeutic approaches have been discussed in the studies to improve the prognosis. Variable rates of KRAS, BRAF, EGFR and TP53 mutations, as well as p16 alterations, have been reported in the literature<sup>3-7</sup>. Also, KRAS mutations have been noted as predicting good prognosis in ITAC<sup>17</sup>. A significantly higher expression of EGFR and high prevalence of TP53 mutations in sinonasal tumours in wood workers have been found in studies<sup>19,20</sup>.

Our case was a 71-year-old man who had similar clinical, histopathological and immunohistochemical findings in concordance with the literature. In our case, there were not any dysplastic changes in the surface epithelium adjacent to the tumour. The patient was a worker in the leather shoe industry for 50 years, and it was a compatible information with the aetiology known as ITAC. KRAS, EGFR, NRAS and BRAF were negative in our case. The patient relapsed 8 months after the radiation therapy, and the mass was resected widely. The last control showed no recurrence or residual tumour at the location.

## CONCLUSION

ITACs are rare locally aggressive neoplasms, and metastatic adenocarcinomas from the gastrointestinal tract must be excluded with systemic and clinical examinations. An association with occupational exposure to leather dust is known, and our case had a 50-

year work history in the shoe industry. Local recurrence is frequent for this entity, and the patient relapsed after the radiation therapy, necessitating the performance of a wide resection.

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