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Is there an association with Wilson's disease and multiple tongue dysplasia lesions and in situ carcinoma? A case-report based literature review

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SUMMARY

Wilson's Disease (WD) is a rare autosomal recessive hereditary disease with copper accumulation in the body, particularly the liver, brain and cornea. WD is widely treated with chelation agents who enable the copper excretion. Since high concentrations of copper are toxic, WD is associated with hepatocellular carcinoma and cholangiocarcinoma, with low incidence of other types of cancer. We present a case of a 33 year old man who was treated in the Oral and Maxillofacial Surgery Department of the Aristotle University of Thessaloniki with multiple dysplasia lesions and an in situ carcinoma of the tongue, which is to our knowledge the first case report of oral lesions to a patient with WD. Literature is reviewed on copper levels on patients with head and neck cancer, and on chelation agents and their effect on cancer cells.

Key words: oral cancer, Wilson's disease, precancerous lesions, copper.

INTRODUCTION

Wilson's disease (WD) is a rare autosomal recessive disease. The affected chromosome is the 13q14.3-q21.1 that contains the ATP7B gene which translates a copper transport (1). This transport is required for the copper excretion. Without it, copper is accumulated in the liver, the eye cornea and brain resulting to permanent damage (2). This is also the reason why WD is also referred to as hepatolenticular degeneration. WD has a wide clinical presentation, with symptoms varying from mild hepatic failure up to severe neurological damage. The therapy for WD consists of copper excretory drugs, such as penicillamine, and zinc, which induces copper binding (3).

Copper accumulation has been associated with cancer formation, either directly, since copper is a toxic metal in high quantities, either indirectly, since copper accumulation in the liver causes chronic hepatic failure sub-sequencing in hepatocellular carcinoma. It is not well documented whether it is associated with other types of malignancies, since very few cases have been published (4).

The aim of this study is to report a case of a patient with WD who was treated in the Oral and Maxillofacial Surgery Department with multiple asynchronous precancerous lesions on the surface of his tongue.

CASE REPORT

A 33-year-old male patient was referred to the Oral and Maxillofacial Surgery Department by the Oral Pathology Department for a white lesion in the right ventral surface of the tongue, extended from the midway of the length of the tongue to the retromolar triangle. Biopsy was already taken from the lesion, which showed high grade dysplasia.

The patient states in his medical history that he has Wilson's disease (WD), currently regulated under medication (penicillamine, zinc, biperiden). Copper levels had been well regulated (copper 135 mcg/dl, ceruloplasmin 30 mg/dl). Clinically the patient has mild dysarthria without any other neurological defect. He did not have any other medical condition or a history of prior surgeries. He did not mention any family history of cancer in the first degree relatives. No tobacco or alcohol use was recorded.

The lesion was excised under general anesthesia. Postoperative course was uneventful and the

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patient was discharged. The pathology revealed a possible low grade dysplasia with inflammatory elements. A new leukoplakia-like lesion appeared three months after the initial excision and a new excisional biopsy was performed. The pathological examination revealed high grade dysplasia of the mucosa, without elements of malignancy. The patient was scheduled to timely follow-ups.

One year after the initial excision and with a new reappearance of the same lesion in a higher degree, a new biopsy was performed showing high dysplasia with in situ carcinoma. Preoperatively, a magnetic resonance scan was performed which did not describe the lesion or locoregional disease. The patient underwent a fusiform excision of the lesion on the right ventral surface of the tongue, with direct suturing of the defect and selective neck dissection of levels I, II and III of the neck ipsilaterally. The excision had disease free margins as revealed in the frozen sections intraoperatively. The final histopathology did not reveal any malignancy, but high dysplasia with hyperkeratosis, mild parakeratosis and spongiosis.

One year after the major excision, a new lesion at the same area appeared and a new local excision was performed. The pathology examination revealed again a high grade dysplasia.

The patient is still being routinely checked up at the outpatient clinic of our Department. Five years after the first lesion, he is at the time being without local recurrence.

DISCUSSION

The background of correlation between copper levels and cancer formation derives from the hypothesis that alterations in micronutrients seem to change the oxidative response of cells, and may be prone to malignant transformation. Increased copper levels are known to play a significant role in reactive oxygen species (ROS), and endothelial proliferation causing angiogenesis (5, 6). These two factors are well known prerequisites of cancer formation and proliferation, thus safely assuming that copper can play a central role in this process (7). A prospective study dating at 1989 proposes that increased copper serum levels advances the development of cancer in the next 4 years (8).

Early studies on this correlation indicated that copper, among other trace minerals, gradually increases in the serum of patients that have precancerous or cancerous oral lesions, recording a direct correlation between the copper levels and the transition from dysplasia to cancer (9). A more recent study compared the serum levels of trace elements in patients with head and neck cancer to a control group. They found an increase of copper, magnesium and manganium level in the serum of head and neck patients, but it was not significantly higher than in the control group (10). Similar results are published by Baharvand *et al.* (7), who indicate that the copper serum levels are statistically higher in patients with oral cancer. It is believed that copper plays a significant role in chronic inflammation through angiogenesis, but the exact mechanism is not well understood (11). It is also not known whether in these patients with head and neck cancer the copper levels were elevated due to increased production or decreased secretion. On the contrary, Ashkavandi *et al.* did not manage to prove a statistically significant increase in copper serum levels of patients with benign and malignant salivary gland tumors, but their study was highly heterogeneous (12).

Interestingly, there is a study agreeing with the previous mentioned, but also states that copper deficiency may also be increasing oral cancer risk (13). The proposed mechanism that consorts with this finding is that copper is significant in the formation of enzymes reducing ROS, and ROS accumulation promotes DNA fragments and epithelial cell mutations.

A study published by Ayinampudi and Narsimhan (14) suggests that the copper levels in the saliva of patients with oral premalignant and malignant lesions is significantly increased compared to a control group. Despite being presented as a promising predictive factor of oral lesions, their study group is small for such a conclusion, and a larger scale prospective study is needed to ascertain such possibility. Similar results with a higher number of patients were reported by Shetty *et al.* (15). In an analogous study, 94 patients with head and neck cancer (not only oral cancer), were examined for trace mineral concentrations in their hair, and it was concluded that the copper concentration, among other, is significantly higher in patients with head and neck cancer compared to a control group (16).

There is only one publication stating that copper levels in tissues of head and neck malignancies are increased compared to normal tissues, but only four patients in a total of 35 concern oral cancer, where the rest are cases of oropharyngeal and laryngeal cancer (17).

The knowledge of increased copper in cancer cells has led to the assumption that copper chelation agents could play an active role in anticancer therapies. Indeed, copper-based proteasome in-

hibitors, such as penicillamine, can reduce copper levels from cancer cells, and as a result reduce its angiogenetic effect on tumors. In addition, copper chelation agents are well tolerated with low toxic side effects, and could be beneficial as chemotherapy agents (18-20). A recent in vitro study shows that the copper chelator ammonium tetrathiomolybdate enhances the effect of cisplatine on head and neck squamous cancer cells, proving that ATP7B plays an active role on chemotherapy response (21). This could partly explain our patient's course of lesions, considering that there was a high drive of epithelial cells for mutation towards malignancy, but all lesions were dysplastic and an invasive carcinoma was never fully developed.

Very few cases have been published on patients with WD who developed malignant lesions besides hepatocellular carcinoma. Lee *et al.* speculate that that colon cancer may be associated to patients with WD who receive treatment, as they publish a case of a young male patient with adenocarcinoma of the colon who has been receiving treatment for WD (22). Li *et al.*, publish a case report of a female patient with WD who developed an invasive ductal carcinoma of the breast (23).

All current research is focused on the copper serum level of patients without any known copper excretion dysfunction (24). There is no known research on patients with WD studying the deregulated levels of copper and its possible correlation with the development of precancerous or malignant lesion in the oral cavity. It is still unclear to the authors of this report whether the susceptibility of our patient to oral dysplasia lesions was coincidental or not. WD has been only tightly linked to hepatocellular carcinoma, and other cases of other malignant development in patients with WD have been sporadic. This patient to our knowledge is the first reported with WD complicated with oral lesions.

In conclusion, copper deregulation plays a significant role in malignancy formation and proliferation. Patients with WD may be of higher risk of cancer development, but anti-copper drugs could be a strong inhibitor in this process. Further research is needed in assessing the risk of cancer formation in patients with WD.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

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