

Raynaud's of the tongue following chemoradiation for squamous cell carcinoma of the oropharynx

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Abstract. Raynaud's of the tongue following radiation alone or chemoradiotherapy (CRT) is a rare occurrence. The present study reports a case where typical symptoms and signs of Raynaud's phenomenon involving the tongue occurred ~18 months following CRT treatment in a 53-year-old female, who was a smoker prior to CRT with stage T₂N₂cM0 local-regional advanced stage IV oropharyngeal cancer. The patient was treated using cisplatin chemotherapy and intensity-modulated radiation with a dose of 70 Gray (Gy). The intermittent episodes of painful discoloration of the tongue were exacerbated due to the cold and emotional stress. No definite clinical or laboratory evidence of connective tissue disorder was identified. To the best of our knowledge, this is the first reported case of Raynaud's of the tongue following CRT without primary Raynaud's of the digits. The possible pathogenesis involving vascular and neural mechanism is discussed in the case report.

Case report

A 54-year-old female with a 20 pack-year smoking history, idiopathic peripheral neuropathy, hypercholesterolemia and polymyalgia was treated with concomitant cisplatin administered at 100 mg/m² every 3 weeks for 3 cycles and prescribed doses of 70 Gray (Gy) radiation at 2 Gy per fraction/5 days a week for 7 weeks chemoradiotherapy (CRT) for a T₂N₂cM0 [according to the tumor-lymph nodes-metastasis (TNM) staging system], p16-negative squamous cell cancer of the base of the tongue. At ~18 months following CRT, the patient experienced tingling of the tongue, numbness with white discoloration of the tongue, and difficulty in speaking (Fig.1A). Following these symptoms, the tongue turned bright

red, concomitantly with the onset of severe pain. Shortly afterwards, the pain subsided and the tongue returned to its normal color. The entire episode lasted 90-120 sec (Fig. 1B). Laboratory testing revealed that the patient's complete blood count (CBC), numbers of platelets, electrolytes, rheumatoid factor, 24-h urine cortisol, cyclic citrullinated peptide immunoglobulin G (IgG), thyroid function test and erythrocyte sedimentation rate (ESR) were within the normal limits. The patient was positive for antinuclear antibody (ANA), although ANA-8 proved to be negative. C-reactive protein was increased to a level of 8.9 mg/dl. During the two most recent years, intermittent episodes of painful discoloration have persisted, particularly during cold weather and in times of emotional stress; otherwise, the patient is well. The rheumatology department of Northwestern University was consulted and, due to characteristic symptoms and discoloration, a diagnosis of Raynaud's of the tongue was made. The patient has no history of Raynaud's affecting her digits, and she refused to take steroids, vasodilators or calcium-channel blockers.

Discussion

Raynaud's disease is a disorder of blood flow. Due to vasoconstriction, when exposed to cold or emotionally stressful situations, the affected area turns white or blue, followed by tingling and throbbing pain, with color returning to normal after the blood flow has returned. The pathophysiology of primary Raynaud's has yet to be fully elucidated (1), although secondary Raynaud's is known to be caused by underlying connective tissue disease, injury or medication. Herrick *et al* (2) have described the pathogenesis according to three categories of abnormality: Vascular, neural and intravascular.

Raynaud's phenomenon of the tongue is a rare condition, although it has been shown to occur in patients with a prior history of primary Raynaud's of the extremities, with or without connective tissue disorders (3-5). An association among radiation, chemotherapy and Raynaud's has been reported. In patients with pre-existing primary Raynaud's of the digits, developing Raynaud's of the tongue and lips following radiation alone for oropharyngeal and lip cancer was first reported by Westbury *et al* (6). This group hypothesized that radiation-induced Raynaud's is most likely due to late injury caused to the capillaries and vasculature, with the primary target being endothelium. Additionally, radiation-induced

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Figure 1. Appearance of the tongue during and after Raynaud's episode. (A) White discoloration of the tongue during an acute phase of Raynaud's phenomenon. (B) Normal coloration following the end of Raynaud's episode.

damage to vascular media and adventitia results in fibrosis. The end result is the structural and functional alteration of blood vessels, impairment of chemical mediators such as nitric oxide, hypoxia, and altered vascular response to cold stimuli.

Cisplatin alone or in combination with other chemotherapeutic agents has been shown to induce Raynaud's phenomenon. Mohokum *et al* (7) performed a meta-analysis of 24 studies published between 1981 and 2010, and concluded that, despite the heterogeneity among the studies, patients who received cisplatin-based chemotherapy had a greater incidence of Raynaud's. The exact mechanism of this association has yet to be fully elucidated. It is possibly associated with cisplatin-induced hypomagnesemia, given the important roles mediated by magnesium in maintenance of vascular smooth muscle tone (8), vascular ischemia (9) and the autonomic nervous system (10).

In our patient, the symptoms of Raynaud's were likely to have been due to vascular and neural toxicity from CRT. The symptoms appeared ~18 months following the completion of CRT. At two years following the first appearance of symptoms, the patient is doing well, despite intermittent episodes of Raynaud's of the tongue. To the best of our knowledge, Raynaud's of the tongue following CRT without primary Raynaud's of the digits has not previously been reported. That the occurrence of this phenomenon is so rare may result in delayed diagnosis and intervention.

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