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SHORT COMMUNICATION

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Panmucositis and chemosensitisation associated with betel quid chewing during dose-dense adjuvant breast cancer chemotherapy

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Abstract *Purpose*: The severity of chemotherapy-induced oral mucositis has previously been reported to be greater in patients who chew betel quid (areca), an addictive habit shared by hundreds of millions of individuals worldwide. Here, we report a case of fulminant panmucositis complicating dose-dense adjuvant breast cancer treatment in a betel-chewing patient without evidence of other risk factors. *Methods*: Grade IV mucositis was triggered by the initial use of standard-dose anthracycline chemotherapy, and involved not only the mouth but also the genital and anal mucosa, as well as other severe non-mucosal toxicities. *Results*: Despite subsequent treatment with dose-reduced CMF and docetaxel regimens—which are seldom associated with mucosal toxicity at these dose intensities in the absence of neutropenia—high-grade oral mucositis continued to complicate the therapeutic course. *Conclusion*: These observations suggest that the potentiation of chemotherapy-induced mucositis by quid chewing may not be mediated solely by local effects on the oral epithelium, but also involves the systemic absorption of toxic chemosensitising molecules.

Keywords Cytotoxic drug treatment · Iatrogenic toxicity · Areca

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Introduction

Between 10 and 20% of the world's population chew betel (areca) nut—an ancient masticatory that is especially popular with Asian females, who typically combine it with betel leaf, lime paste, and leaf tobacco to form betel quid [1]. Like cigarette smoking, which is relatively more prevalent among Asian males, quid chewing is an addictive stimulant [2] that reduces the appetite for food [3]. The psychoactive constituents of betel nut include the neuroalkaloids arecoline and guavacoline, which block the inhibitory synaptic transmitter gamma-aminobutyric acid (GABA), whereas the aromatic phenols of Piper betel leaf trigger catecholamine release and thus cause tachycardia and arousal [4].

The detrimental effects of continued smoking on cancer outcomes after chemotherapy and radiotherapy have been well documented [5, 6] but little has been reported as to the therapeutic effects of concurrent betel quid chewing. Here, we describe a case in which adjuvant breast cancer chemotherapy in a betel quid-chewing patient was complicated by the development of panmucositis and other systemic toxicities necessitating hospitalization, opiate analgesia, and treatment of multi-organ damage.

A 55-year-old Indian female underwent right lumpectomy and axillary dissection for a node-positive 4-cm grade 3 invasive ductal carcinoma. The clinical history was notable only for habitual betel quid chewing, and the family history was unremarkable. Physical examination was normal apart from moderate obesity, xanthelasma, and hypertension; there was no trismus or other evidence of oral fibrosis. The only abnormalities on pretreatment blood testing were mild hypercholesterolemia and hypertriglyceridemia; random blood glucose was within the normal range. Routine adjuvant chemotherapy was planned using four cycles of dose-dense (G-CSF-accelerated) doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 (AC) every 2 weeks, followed by four cycles of paclitaxel 175 mg/m^2. For the first cycle, a cautionary 10% body surface area reduction

was made to simulate ideal body weight. Five days following initial administration of AC, the patient required urgent admission due to subacute onset of abdominal and oral pain due to mucositis (severe enough to preclude eating) in addition to vaginal and perianal mucositis. There was no fever, but the neutrophil count was reduced to 0.040×10^9 per litre. Intravenous fluids and antibiotics, continuation of filgrastim support, and symptomatic measures (including opiate analgesia) were instituted; blood and urine cultures proved negative. Following a 6-day hospital stay and recovery of the neutrophil count, the patient was discharged and strongly advised to discontinue betel quid chewing.

The patient returned for the second cycle of chemotherapy a week behind schedule due to convalescence, but declined further AC chemotherapy. She was, therefore, treated for the next three cycles with intravenous CMF as calculated using a 20% further reduction of body surface area. Direct questioning about the status of her betel quid chewing at this time indicated that she had managed to "cut down", but not eliminate, the habit. Four days following the first cycle of intravenous CMF, she presented again with vaginal mucositis, dysuria, mouth pain, and furunculosis. There was no fever, and the neutrophil count, and serum glucose remained normal; the episode was managed on an outpatient basis using symptomatic measures, but initiation of the next chemotherapy cycle was delayed by 10 days. Additional 20% (5-fluorouracil and methotrexate) and 33% dose reductions (intravenous cyclophosphamide) were made for the following two cycles, both of which were accompanied by moderate oral mucositis. The adjuvant regimen was then changed as planned to docetaxel, using an initial 45% reduction of the 80 mg/m^2 dose usually used in our Center for non-Caucasian patients. Four days after treatment, the patient again presented with severe oral and throat pain related to mucositis, requiring opiate analgesia. One week following the second cycle of docetaxel, the patient developed grade 3 oral mucositis associated with bilateral ankle edema; serum NT pro-BNP was elevated, consistent with cardiac failure. The final two cycles of dose-reduced docetaxel were completed with the aid of diuretics, intensive mouth care, and scheduling delays to permit symptom tolerance. One month after completion of therapy, the patient's quality of life had returned to normal.

Betel/areca quid chewing is mutagenic, teratogenic, and carcinogenic [7, 8]. The oral mucosa is subjected to chronic oxidative stress by quid ingredients, leading to DNA double-strand breaks [9] and dose-dependent genetic instability [10]; oral tumors arising in the context of betel-chewing thus appear to have an inferior prognosis [11]. In addition to the genotoxic effects of arecoline, betel quid induces direct proliferative effects on the oral epithelium, the mechanism of which may relate either to thiol depletion [12] (which may impair repair of methylation damage, and thus simulate wounding) or else to the activation of pro-inflammatory signaling [13]. This combination of pro-mitogenic and DNA-damaging effects could, therefore, sensitise affected normal tissues to the cytotoxic effects of chemotherapy.

Consistent with this possibility, a longterm cytokine-dependent complication of quid chewing termed oral submucous fibrosis (OSF) [14, 15] has previously been implicated as a risk factor for chemotherapy-induced oral mucositis [16]. Isolated xerostomia—a common early symptom in betel chewers progressing to OSF [17]—is also predictive of oral mucositis in cancer patients receiving fluoropyrimidine chemotherapy [18]. Hence, all patients habituated to betel chewing may be at risk of mucositis, even if frank OSF has not yet developed. We recommend that oncologists heed this risk when prescribing cytotoxic drugs or radiotherapy for patients who are regular quid-chewers, and consider offering an initial test dose of any drug for which mucositis is a recognized toxicity.

The florid panmucositis that characterised the initial complication in the present case suggests the peripheral effects of an absorbed sensitiser (e.g., via saturation of a repair pathway such as O^6-methylguanine methyltransferase). Consistent with a systemic mechanism, smoking is associated with more severe skin reactions to radiotherapy [19], even though smoke-associated toxins do not directly contact the skin. Quid chewing is firmly associated with the circulation of mutagenic adducts [20], providing a plausible explanation for sensitising effects of DNA-damaging masticants on tissues distant from the oral cavity [21]. If chronic exposure to these circulating mutagens creates a 'memory' of low-level cytotoxic apoptosis in peripheral gut mucosa [22]—which, since mutation has been excluded by others [23], presumably occurs by clonal selection for epigenetic transcriptional repression of pro-apoptotic genes—the severe mucositis in our patient may be modeled as a recall reaction [24], similar to those triggered by anthracylines in previously irradiated patients [25] (Table 1).

A limitation of the present report is that it fails to satisfy Koch's postulates, leaving unresolved the issue as to whether cessation of quid chewing (which was not achieved in this case) improves chemotherapy tolerance—and if so, how quickly. Although the patient claimed to have reduced her exposure, the persistence of her apparent chemosensitisation raises the possibility that quid chewing may cause longer-term end-organ sensitivity to chemotherapeutic damage, rather than simply a transient pharmacodynamic interaction. Prospective studies involving both metabolic profiling and tissue-based analyses will be required to clarify this remaining uncertainty.

In conclusion, the case described here raises the possibility that chronic betel quid chewing may not only predispose oral mucositis, but may also act as a systemic chemosensitiser. It is not known whether retinoid treatment may have the same preventive effects on iatrogenic betel-chewing mucositis—whether oral or systemic—as it does on reverting betel-induced premalignant leukoplakia [26], nor whether purported oral mucositis preventives such as topical GM-CSF [27] or keratinocyte growth factor (KGF) [28] may prove useful. With an increasing

Table 1 Comparison of the features of mucositis associated with betel chewing, smoking, chemotherapy, radiation therapy, and radiation recall

	Betel quid chewing	Tobacco smoking	Cytotoxic chemotherapy	Radiotherapy	Radiation recall
Timing	Chronic	Chronic	Acute	Acute	Delayed
Severity	Usually mild	Usually mild	Moderate	May be severe	Moderate
Location	Mainly oral	Upper aerodigestive tract	Generalised	Localised	Localised
Mechanism	Inflammation, DNA damage	DNA damage	DNA damage	DNA damage, devascularisation	Repair gene methylation
Non-mucositis oral toxicity	Oral fibrosis	Leukoplakia	Herpes simplex, nausea	Dental, xerostomia, candidiasis	–
Neoplastic upper GI complications	Squamous cancers	Squamous cancers	–	Squamous esophageal cancers	–
Other cancers	–	Lung, aerodigestive, urothelial	Leukemias, carcinomas	Leukemias, sarcomas, carcinomas	–

number of oncology patients now hailing from developing societies where quid chewing is widespread, available evidence favors vigilance in the approach to chemotherapy and radiotherapy of such individuals who may be at risk of undertreatment due to dose-limiting toxicities and delays, while also perhaps being hypersusceptible to iatrogenic second malignancies.

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