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Cancer Chemotherapy-associated Pigmentation of the Oral Mucosa

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Abstract. *Background/Aim: Oral adverse events caused by anticancer drugs are diverse, but few reports have examined pigmentation of the oral mucosa. The aim of this study was to clarify the prevalence of oral mucosal pigmentation caused by anticancer drugs. Patients and Methods: This single-centre retrospective study investigated patients who underwent oral examination in our hospital during cancer chemotherapy for 3 years from April 1, 2019 to March 31, 2021. Inclusion criteria were patients who could be followed-up for ≥3 months after completing chemotherapy with drugs that caused pigmentation. The primary predictive variable was the cancer chemotherapeutic agent used. The primary outcome variable was pigmentation of the oral mucosa. Collected data were statistically analysed using the χ^2 test or Fisher's exact test, with the level of significance set at $p<0.05$. Results: A total of 388 patients were enrolled in the study. Eleven patients (2.8%) showed oral mucosal pigmentation. Drugs causing pigmentation [deposition rate (number of patients with deposits/users)] were TS-1 (combination of tegafur, gimeracil, and oteracil potassium) [12.2% (5/41)], paclitaxel [4.0% (2/50)], gemcitabine [5.0% (1/20)], cyclophosphamide [2.3% (1/42)], carboplatin [1.6% (1/64)], fluorouracil [2.3% (1/43)], and capecitabine [3.4% (1/29)]. Conclusion: Oral pigmentation due to cancer chemotherapy was found in 2.8% of patients. TS-1, carboplatin, cyclophosphamide, capecitabine, fluorouracil, gemcitabine, and paclitaxel caused pigmentation of the oral mucosa. Among these, TS-1 was the most likely to cause pigmentation, affecting 12.2% of users.*

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Recent advances in systemic anticancer therapeutics, such as cytotoxic chemotherapy, targeted therapy, and immunotherapy, have greatly contributed to improving survival rates in patients with many types of cancer (1-3). However, these drugs can cause a variety of systemic and localized adverse events, including in the oral cavity (4-6). Oral adverse events associated with systemic anticancer therapeutics are also diverse and include mucositis, xerostomia, dysgeusia, lichenoid reactions, pigmentation, dysesthesia, and osteonecrosis (5-8). Among these, the most typical oral adverse events are mucositis, xerostomia, and dysgeusia (7, 9, 10).

Pigmentation mainly affects the skin, nails, and mucous membranes, including the oral and genital mucosa (11). For the oral mucosa, pigmentation is a low-grade adverse event similar to that of the skin, and because of the small number of cases, few systematic investigations have been conducted (12). Although the number of cases of oral pigmentation caused by anticancer drugs is small, distinguishing pigmentation caused by anticancer drugs from that caused by other diseases (particularly oral mucosal melanoma) is important. From an aesthetic point of view, pigmentation, especially on the lips, can troublesome. Oral mucosal pigmentation can be caused by various types of anticancer drugs, and the number of patients receiving cancer chemotherapy is only expected to increase in the future (4, 6). An understanding of the prevalence of oral pigmentation caused by cancer chemotherapies is therefore desirable.

The Saitama Medical Center is a regional core hospital and a base hospital for the treatment for a wide range of cancer types. The oral surgery clinic also includes a

multidisciplinary treatment team for cancer patients and supports cancer patients from the perspective of oral healthcare. This provides a great opportunity to encounter oral adverse events, including oral mucosal pigmentation, caused by various anticancer drugs in many patients, and to conduct clinical research into oral adverse events.

The present study investigated pigmentation rates for each drug, total number of occurrences of pigmentation with all chemotherapy treatments, and possible differences in pigmentation rates between different cancer types encountered in our hospital. While this is a clinical report from a single institution, this study may clarify tendencies in oral mucosal pigmentation associated with current chemotherapies.

Patients and Methods

The study protocol was approved by the Ethics Committee at Saitama Medical Center, Saitama Medical University (Saitama, Japan) (approval no. 2022-030) and was conducted in accordance with the ethical standards of the Declaration of Helsinki (1964 and later amendments). This study was a single-centre retrospective study of patients who underwent oral examination in the Department of Oral and Maxillofacial Surgery at Saitama Medical Center, Saitama Medical University during cancer chemotherapy conducted within the 3-year period from April 1, 2019 to March 31, 2021. Inclusion criteria were patients who could be followed-up for ≥3 months after completion of chemotherapy with drugs that caused pigmentation. Exclusion criteria were patients with insufficient medical records.

Patients were treated with multiple anticancer drugs according to chemotherapy regimens. Drugs considered to cause pigmentation were determined with reference to a previous review (4). If two or more drugs were considered as causative drugs for pigmentation in a case, they could not be narrowed down to one drug, so both were listed together as causative drugs.

The primary outcome variable was pigmentation of the oral mucosa. In cases with pigmentation of the oral mucosa, the site of pigmentation, presence or absence of skin pigmentation, and state of pigmentation after 3 months and 9 months were investigated in possible cases. In most cases, precise determination of the interval from the start of anticancer drug administration to onset of oral mucosal pigmentation is difficult. Those items for which definitive information was obtained were therefore listed.

All statistical analyses were performed using js-STAR version 9 software. Collected data were analysed using the χ^2 test or Fisher's exact test. For all tests, values of $p<0.05$ were considered significant.

Results

A total of 388 patients (197 women, 191 men; mean age, 63.4±12.8 years; range=22-86 years) were enrolled in the study (Table I). More than 80 types of anticancer drugs were used for these 388 patients. The study included the following diagnoses, in order of decreasing frequency: blood cancers (n=67, 17.3%), breast cancers (n=67, 17.3%), colorectal cancers (n=60, 15.5%), bladder cancers (n=30, 7.8%), lung cancers (n=29, 7.5%), ovarian cancers (n=25, 6.4%), pancreatic cancers (n=22, 5.7%), uterine cancers (n=22, 5.7%), stomach cancers (n=19, 4.9%) and oesophageal cancers (12=5, 3.1%).

Table I. *General characteristics of the study population.*

	Number of patients (%)
Sex	
Male	191 (49.2)
Female	197 (50.8)
Age (years), mean±SD	63.4±12.8
Type of cancer	
Blood cancer	67 (17.3)
Breast cancer	67 (17.3)
Colorectal cancer	60 (15.5)
Bladder cancer	30 (7.8)
Lung cancer	29 (7.5)
Ovarian cancer	25 (6.4)
Pancreatic cancer	22 (5.7)
Uterine cancer	22 (5.7)
Stomach cancer	19 (4.9)
Esophageal cancer	12 (3.1)
Kidney cancer	9 (2.3)
Prostate cancer	8 (2.1)
Ureteral cancer	8 (2.1)
Peritoneal cancer	5 (1.3)
Duodenal cancer	4 (1.0)
Brain cancer	3 (0.8)
Liver cancer	2 (0.5)
Bile duct cancer	2 (0.5)
Others*	5 (1.3)
Pigmentation of oral mucosa	
Yes	11 (2.8)
No	377 (97.2)

SD: Standard deviation. *Others include 1 case of ileal cancer, malignant pleural mesothelioma, penile cancer, adrenal cancer, and tongue cancer, respectively.

Among the 388 patients, only 11 patients (2.8%) showed oral mucosal pigmentation (Table II). Of these, 3 patients (27.3%) had breast cancer, 3 patients (27.3%) had colorectal cancer (27.3%), and 1 patient had pancreatic, ovarian, lung, prostate, or tongue cancer (9.1%), respectively (Table II). Treatment comprised one or two (Patient 8 only) anticancer drugs among the following: TS-1 (combination of three active drugs, tegafur, gimeracil, and oteracil potassium), paclitaxel, gemcitabine, cyclophosphamide, fluorouracil, capecitabine, and carboplatin (Table II). Five patients (Patients 1, 2, 6, 7, and 9) were administered TS-1, and paclitaxel was used in 2 patients (Patients 8 and 11). Gemcitabine, cyclophosphamide, carboplatin, fluorouracil and capecitabine were used by only one patient each (Table II). The incidence of oral pigmentation was highest in the buccal mucosa (9 of 11 cases), followed by the tongue (6 of 11 cases), lower lip (4 of 11 cases), palate (4 of 11 cases),

Table II. *Details of patients with oral mucosal pigmentation.*

Patient	1	2	3	4	5	6	7	8	9	1x	11
Age (years)	75	74	74	54	32	74	76	64	77	68	59
Sex	M	M	M	F	F	F	F	F	M	F	F
Type of cancer											
Breast cancer				x	x						x
Colorectal cancer							x		x	x	
Lung cancer		x									
Ovarian cancer								x			
Pancreatic cancer	x										
Prostate cancer			x								
Tongue cancer						x					
Causative drug											
TS-1	x	x				x	x		x		
Fluorouracil										x	
Paclitaxel								x			x
Cyclophosphamide				x							
Carboplatin								x			
Gemcitabine			x								
Capecitabine					x						
Site of oral pigmentation											
Lower lip	x	x		x						x	
Buccal mucosa	x	x	x	x		x	x	x	x		x
Tongue	x	x			x		x		x		x
Gingiva	x										
Palate				x		x		x	x		
Concomitant skin pigmentation	x	x	x	x	x	x	x	x	x	x	x
Timing of oral mucosal pigmentation											
Unknown	x	x	x	x	x		x		x	x	x
After skin pigmentation						x*		x*			
State of pigmentation after 3 months											
No change	x	x	x	x	x	x	x	x	x	x	x
Unknown											
Improved											
State of pigmentation after 9 months											
No change	x							x		x	x
Unknown		x	x		x		x		x		
Improved				x		x**					

TS-1: Combination of tegafur, gimeracil, and oteracil potassium. *Pigmentation of the oral cavity re-confirmed at next examination (4 weeks later) after initial confirmation of skin pigmentation. **Vitamin C administration.

and gingiva (1 of 11 cases) (Table II). All 11 patients with pigmentation of the oral mucosa showed accompanying skin pigmentation (Table II). In two patients (Patients 6 and 8) for whom the timing of pigmentation was documented, oral pigmentation appeared after skin pigmentation (Table II). Follow-up study after 3 months showed no change in pigmentation of the oral mucosa (Table II). Of the 6 cases where follow-up was possible even after 9 months, 4 showed no change and 2 showed improvement. One of the two improved patients received vitamin C.

Table III. *Incidence of oral mucosal pigmentation after treatment with anticancer drugs.*

Causative drug	Number of patients	Number of patients with oral mucosal pigmentation (%)
TS-1	41	5 (12.2)
Fluorouracil	43	1 (2.3)
Paclitaxel	50	2 (4.0)
Cyclophosphamide	42	1 (2.3)
Carboplatin	64	1 (1.6)
Gemcitabine	20	1 (5.0)
Capecitabine	29	1 (3.4)

TS-1: Combination of tegafur, gimeracil, and oteracil potassium.

Table III shows the incidence of oral mucosal pigmentation by different types of anticancer drugs. Treatment with TS-1 induced the highest incidence (12.2%, 5/41), followed by gemcitabine (5.0%, 1/20), paclitaxel (4.0%, 2/50), capecitabine (3.4%, 1/29), cyclophosphamide (2.3%, 1/42), fluorouracil (2.3%, 1/43) and carboplatin (1.6%, 1/64).

Discussion

This study reported the prevalence of anticancer drug-induced oral mucosal pigmentation among 388 patients in our hospital. The pigmentation rate was 2.8% (11 of 388 subjects), representing a low value compared to mucositis (20-40%) caused anticancer drugs (13). To date, few systematic reports have clarified the frequency of oral mucosa pigmentation as an adverse event of anticancer drugs (12). Anticancer drug-induced skin pigmentation is caused by stimulation of melanocytes, due to damage to the basal layer of the epidermis and the possible increase in melanin production (11) or impaired excretion. Pigmentation of the oral mucosa is also considered to be induced by similar mechanisms (8).

We observed pigmentation of the oral mucosa in 11 patients. Seven anticancer drugs (TS-1, paclitaxel, carboplatin, cyclophosphamide, capecitabine, fluorouracil, and gemcitabine) were identified as inducing agents, confirming previous reports (12, 14-17). Among these 7 compounds, TS-1 showed the highest incidence (12.2%), followed by gemcitabine (5.0%) and others (Table III). All drugs that caused oral mucosa in the present report were cytotoxic chemotherapy drugs (4). TS-1 is a combination formulation classified as oral fluoropyrimidine anticancer

agents, comprising tegafur with gimeracil and oteracil potassium as biochemical modulators, mainly used in Asian countries (18). In Japan, TS-1 has been approved for the treatment of a wide array of solid malignancies (gastric, colorectal, head and neck, non-small-cell lung, inoperable or relapsed breast, pancreatic, and biliary cancers) (18). Regional differences in pigmentation of the oral mucosa may be relevant. Of the seven pigmentation-causing drugs in this report, only TS-1 has received a detailed investigation regarding skin pigmentation, with event rates of 7.4-32% (19). The rate of oral mucosal pigmentation in the present study (12.2%) falls within this range, but may represent an underestimation compared to skin pigmentation.

Among targeted therapies, the tyrosine kinase inhibitor imatinib, used to treat chronic myelogenous leukaemia and acute lymphoblastic leukaemia, has been reported to cause pigmentation of the palatal mucosa (20). However, none of the patients included in the present study were administered imatinib.

Oral pigmentation is, of course, attributed to the anticancer drug used rather than the type of cancer. However, oral pigmentation potential according to cancer type may be helpful in explaining common adverse events to patients. In this study, patients with colorectal and breast cancer tended to experience pigmentation most frequently.

Whether oral mucosal pigmentation and skin pigmentation are observed concurrently is of interest (21). In this report, detailed data on skin pigmentation were often not included in the medical records, and patient memories regarding the appearance of pigmentation, including the oral mucosa, was extremely vague. Obtaining detailed data on all skin and oral pigmentations was thus difficult. Although few reports have described oral and skin pigmentation simultaneously, some reports have described oral pigmentation occurring without skin pigmentation (15, 22, 23). However, all 11 patients in this study showed skin pigmentation. From the present study, skin pigmentation should be suspected when pigmentation is observed in the oral mucosa. Information on the timing of pigmentation in the oral mucosa was described in only 2 cases. In both cases, oral mucosal pigmentation appeared after the detection of skin pigmentation. Pigmentation of the oral mucosa may occur later than that of the skin.

Treatment for pigmentation includes waiting for spontaneous resolution. Pigmentation of the skin and oral mucosa is generally considered likely to improve within a few months after discontinuation of the causative agent (11, 15, 22-24). However, a case with improvement, but not resolution, of pigmentation in the oral mucosa after 18 months of follow-up has been reported (25). In the present report, no significant change was observed in any of the 11 cases after 3 months of follow-up. Six patients were followed-up for more than 9 months. Of these, 4 showed no significant change and 2 showed improvement. The possibility of long-term pigmentation of the oral mucosa was also suggested, but the number of cases was too small to draw any definitive conclusions from the present study. One case in which improvement was seen had received treatment with vitamin C. Vitamin C administration has been used to reduce skin pigmentation (26). Vitamin C may be promising to prevent or cure pigmentation of the oral mucosa, but further research is necessary to clarify this issue (26).

Pigmentation of the oral mucosa involves several problems that must be resolved. One is the differential diagnosis. For pigmentation due to anticancer drugs, a history of cancer chemotherapy is required. Skin pigmentation may be a clue. The clinical feature of cases of oral mucosal pigmentation caused by anticancer drugs including this report was presentation as localized to multiple and diffuse brown-bluish-black areas (27). Affected sites were the lips, buccal mucosa, tongue, gingiva, and palate (Table II). In the lip, the mucous membranes, vermilion border, and skin surfaces could be involved. The most important differential diagnosis is oral mucosal melanoma, which is clinically common among individuals in their 40s to 70s, consistent with the age at which cancer is most likely to occur (28, 29). The clinical features in early stages are presentation as mainly brown or black macules/patches or nodules. In the advanced stage, oral mucosal melanoma shows rapid enlargement with ulceration, swelling, and bleeding. The hard palate and alveolar gingiva are the most frequently affected sites (27, 30). However, no consensus has yet been reached on the clinical diagnosis of oral mucosal melanoma. Therefore, in cases of drug-induced pigmentation, including anticancer drugs, clinical monitoring is important and observation every 12 months and self-monitoring by the patient every 3-4 months are recommended (27).

Pigmentation of the oral mucosa may occur as a symptom of systemic diseases, including Peutz-Jeghers syndrome, McCune–Albright syndrome, neurofibromatosis, and adrenal gland diseases. A medical history is important, as these patients may already have a systemic diagnosis.

Drugs that induce oral pigmentation other than anticancer drugs include minocycline, antimalarial drugs (*e.g.*, hydroxychloroquine, mepacrine, and quinacrine), clofazimine (an anti-leprosy agent), zidovudine (an anti-retroviral), oral contraceptives, amiodarone (an antiarrhythmic) and phenothiazines (chlorpromazine) (8). To differentiate between drug-induced pigmentations, examination of the medical history and drugs used for treatment is necessary.

Another issue is that of aesthetics. This point was the impetus for the present research. Patients, regardless of sex, are showing more concern about pigmentation. Particularly when the lips are involved, pigmentation is conspicuous, and patients can feel acutely self-conscious about feeling the need to explain that pigmentation was due to cancer treatment. Ironically, wearing masks during the coronavirus

disease 2019 pandemic helped affected patients to hide their mouths. Pigmentation of the oral mucosa may be rare, but does occur. Patients should be informed in advance that pigmentation may occur as an adverse event and continue for a long time.

This research has some limitations. First, the types of cancer and drugs investigated in this study were limited by the nature of the study as an observation of a single institution. However, the main cancers and anticancer drugs used for them were included. The results may thus provide insights into tendencies for oral mucosal pigmentation. Second, skin pigmentation status was not clear from the medical records of patients. Deriving a detailed relationship between skin pigmentation and oral mucosa pigmentation was therefore not possible. Third, we were unable to observe how long pigmentation of the oral mucosa persisted. After completing a course of chemotherapy, many patients returned to the referring hospital in the area for follow-up.

In conclusion, oral mucosal pigmentation due to cancer chemotherapy was found in 2.8% of patients. TS-1, carboplatin, cyclophosphamide, capecitabine, fluorouracil, gemcitabine, and paclitaxel were identified as causes of pigmentation of the oral mucosa. Among these, TS-1 was the most common, affecting 12.2% of users. Further multicentre searches are needed to clarify general trends in anticancer drug-induced oral mucosal pigmentation.

Conflicts of Interest

The Authors wish to confirm that there are no known conflicts of interest associated with this publication. Furthermore, there has been no significant financial support for this work that could have influenced its outcome.

Authors' Contributions

MY and YI were involved with data interpretation and drafting of the manuscript. MS and SH were involved in data collection. NH assisted with the design of the work. MS, HS, and TK contributed to interpretation of the results and editing of the manuscript. All Authors read and approved the final version of the manuscript.

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