Abstract

Chemoradiation therapy used on pediatric oncology patients often causes dental developmental anomalies that affect future dental care. Defects noted include tooth and root agenesis, root thinning and shortening, and localized enamel defects. Histologically, these defects appear as osteoid-like niches in the developing dentin which alter the overlying enamel. Odontogenic cell sensitivity is dependent upon the position on the cell cycle and the mitotic activity at the time of chemoradiation therapy. Knowledge of the stage of dental development at the time of oncology treatment and the type of therapy allows the clinician to predict dental effects of the chemoradiation. Representative cases illustrate the clinical manifestations of chemoradiation on the developing dentition. (Pediatr Dent 15:6–12, 1993)

Chemoradiation therapy: effect on dental development

Curt Goho, DDS

Introduction

More than half of the 5000 children who develop cancer each year survive because of improved treatment methods.[1] As patient lifespans increase, dental effects of oncology treatment become clinically significant. Chemoradiation therapy is a major part of pediatric oncology treatment and is implicated in causing tooth agenesis, microdontia, root shortening, early apical closure, and coronal hypocalcification.[2, 3] Understanding the causes of these dental developmental changes is important for proper diagnosis, prognosis, and dental treatment of these patients. This article overviews chemoradiation therapy, its effects on dental development, and presents cases associating chemoradiation therapy with dental developmental anomalies.

Radiation Therapy

Radiation therapy attempts to destroy tumor cells with minimal damage to normal tissue. However, any cells in the path of an external radiation beam or near implanted radioisotopes may be affected. External radiation creates deep penetrating gamma and X-ray photons, and internal radioisotopes create gamma and X-ray photons and beta particles. These particles damage DNA and amino acids, either directly by ionizing critical structural molecules, or indirectly by first ionizing intracellular water.

Cell sensitivity to radiation depends upon its location in the cell cycle during irradiation. Cells are most susceptible to damage during increased mitotic activity in phase M, G_1 and G_2 (Fig 1). However, very high dose radiation affects even nonproliferating cells in phase G_0.[4]

Radiation effects are either lethal or sublethal, depending upon the cumulative and per dose amount of radiation. If the radiation dose exceeds a certain level, cells cannot repair the damage and the cell dies. Cells farther from the radiation target or protected by shielding receive less radiation and show only limited damage.

Dental Sequelae to Radiation Therapy

Amelogenesis and dentinogenesis are affected by radiation directed at or near the mouth. Teeth located along the edge of a radiation exposure field receive up to 45% of the administered dose.[5] Radiation directed at distant areas of the body has no effect on dental development. Some oncologists deliver bilateral radiation to equalize facial skeletal growth disturbances and prevent hemifacial hypoplasias. Radiation therapy effects may be noted bilaterally even if the tumor is unilateral.

Sufficiently high radiation doses cause ameloblast and odontoblast death regardless of their position in the cell cycle. Even nonproliferating odontogenic precursor cells

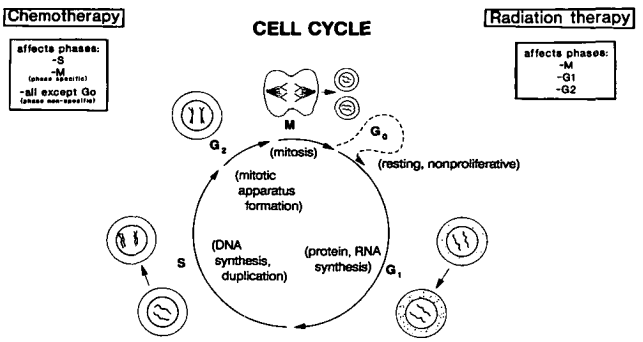

Fig 1. Cell cycle with radiation-specific and chemotherapy-specific sites of action.

(second and third molars in an infant) are destroyed, resulting in complete tooth agenesis. Partially formed teeth have remaining development halted, resulting in tooth and root agenesis.[6,7]

Lower radiation doses cause sublethal changes which vary with both radiation amount and cellular mitotic activity. Minimal doses causing localized dental defects in animal models range from 200 R[8] to 5000 R.[9] Human dental development shows localized damage at 400 R.[10] The radiation threshold at which odontogenic cell death instead of cell damage occurs is unknown.

Odontoblasts are most susceptible to low-dose radiation just before initiating dentin matrix formation.[9–11] These presecretory odontoblasts are proliferating rapidly and have increased mitotic activity.[12] Mature secretory odontoblasts and ameloblasts are not affected by low-dose radiation. Histologically, irradiated presecretory odontoblasts change from columnar to cuboidal shape. Mitotic activity ceases, although the cells do not die. "Osteodentin" forms between the arrested odontoblasts and the pulp. The osteodentin is secreted by osteoblast-like cells originating from undifferentiated pulp mesenchyme. The pulp mesenchyme forms these cells either due to direct radiation damage, or due to induction by the damaged odontoblasts.[13] The osteodentin is visible microscopically as a "niche" in the dentin, or as a wavy, irregular dentinoenamel junction.[8] It is delineated from normal dentin both apically and incisally, indicating that only presecretory odontoblasts are damaged by low-dose radiation (Fig 2).

Osteodentin also differs chemically from normal dentin. In normal dentin, phosphorylated phosphoprotein (PP-H) is the predominant noncollagenous protein. PP-H initiates hydroxyapatite nucleation, an early step in dentinogenesis.[14] PP-H is reduced significantly in osteodentin, altering its ability to initiate dentinogenesis and resulting in shortened, thin, tapered roots.

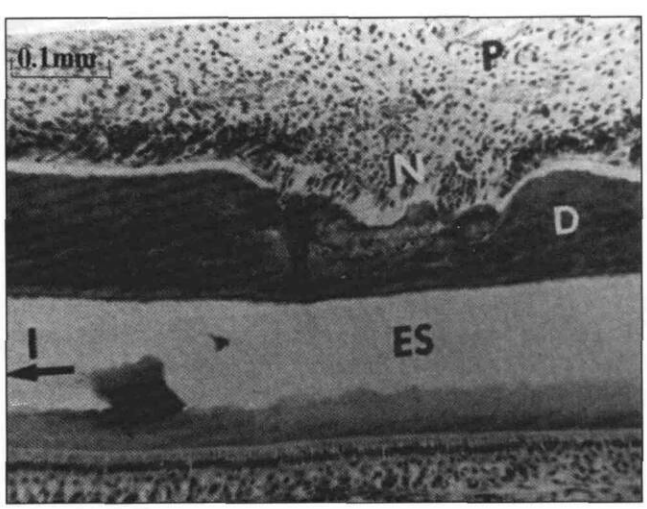

Fig 2. Radiation therapy-induced dentin niche. N = niche, D = dentin, ES = enamel space, P = pulp mesenchyme. Osteodentin visible in the niche defect (microphotograph couresy of Dr. Hanna S. Koppang, University of Oslo).

Low-dose radiation effects noted in enamel appear to be due to damage to the underlying dentin and not to direct ameloblast injury. Nucleation of enamel crystals requires a properly mineralized dentin substrate. Enamel crystals theoretically grow from existing dentin crystals at the dentinoenamel interface. Or, dentin crystals actually may grow into the enamel matrix to induce enamel crystal formation.[15–17] Abnormal osteodentin alters dentinogenesis, which alters the mineralization of enamel. Enamel hypoplasias over the defective dentin are the result.

Chemotherapy

Chemotherapy also attempts to destroy tumor cells, with minimal toxicity to normal cells. Chemotherapy is selectively toxic to actively proliferating cells by interfering with DNA synthesis and replication, RNA transcription, and cytoplasmic transport mechanisms. Since tumors consist primarily of rapidly proliferating cells, they are more susceptible to chemotherapy.

Chemotherapeutic agents are either cell cycle phase specific or cell cycle phase nonspecific (Table). Phase-specific agents interfere with DNA synthesis (S phase) or cell division (M phase). They include antimetabolites (methotrexate, mercaptopurine, thioguanine, cytarabine, azacytidine, fluorouracil, procarbazine, and hydroxyurea), vinca alkaloids (vincristine and vinblastine) podophyllotoxins (VP-16, VM-26), and asparaginase.

Phase nonspecific drugs are toxic to cells in all phases of the active cell cycle. The only cells not affected are nonproliferating cells (G_0 phase). These agents interfere with DNA replication by cross linking DNA bases.[18] Nonspecific agents include alkylators (nitrogen mustard, cyclophosphamide, chlorambucil, busulfan, melphalan), nitrosureas (BCNU, CCNU), antibiotics (actinomycin D, doxorubicin), DTIC, and cisplatin.[19]

Since tumor cells replicate asynchronously, they are not all in susceptible phases during the initial chemotherapy exposure. Chemotherapeutic agents are eliminated rapidly, and a single dose does not affect tumor cells entering a susceptible phase at a later time. Furthermore, chemotherapy works on first order kinetics, in which only a percentage of cells are killed with each dose, leaving some undamaged cells. Chemotherapeutic agents are therefore administered in multiple (fractionated) doses, so that tumor cells unaffected by the first dose are destroyed by following doses.

Dental Sequelae to Chemotherapy

Chemotherapy damage is related directly to the doses and repetition of the various agents. Odontoblasts and ameloblasts in susceptible phases of the cell cycle are damaged easily. Cells in nonproliferative, germinal stages (second or third permanent molars in the infant) are unaffected and should develop normally. This differs from high-dose radiation therapy, in which even non-proliferating dental cells may be destroyed. Furthermore, although radiation only affects cells in its path, chemotherapy is

Table. Chemotherapeutic agents

Cell Cycle Phase Specific	*Cell Cycle Phase Nonspecific*
Antimetabolites	Alkylators
ARA-C (Cytarabine)	Busulfan
5-Fluorouracil	Chlorambucil
6-Mercaptopurine	Cytoxan (Cyclophosphamide)
MTX (Methotrexate)	Nitrogen mustard
6-Thioguanine	Melphalan (LPAM)
Azactidine	DTIC (Dacarbazine)
Procarbazine	
Hydroxyurea	Nitrosureas
	BCNU (Carmustine)
Vinca alkaloids	CCNU (Lomustine)
Vincristine	
Vinblastine	Antibiotics
	Actinomycin D
Podophyllotoxins	Doxorubicin
VP-16 (Etoposide)	Daunorubicin
VM-26 (Teniposide)	
	Cisplatin
Antibiotics	
Bleomycin	
Enzymes	
Asparaginase	
Corticosteroids	
Prednisone	

systemic in its effect. Developing odontogenic cells far from a tumor are susceptible to chemotherapy damage. Dental defects attributed to chemotherapy include arrested root development, inhibition of dentin formation, and enamel defects.[1, 20, 21] Tooth eruption times appear unaffected by chemotherapy.[23]

Chemotherapy damages presecretory odontoblasts, creating dentin niches identical to those caused by radiation.[11] Incisally located odontoblasts, already in their secretory phase, have a lower mitotic index and are unaffected. Apically, odontoblasts show no effect, since at the time of chemotherapy these cells were undifferentiated pulpal mesenchyme which regenerated normal preodontoblastic cells.

Because of the short half-life of chemotherapeutic agents, dental defects are usually localized, resulting from transient changes in odontoblast function, instead of odontoblast death. Narrow pulp chambers and localized enamel defects may be noted at the level of the dentin niche.[24] Coronal size and shape are not affected, however, since crown morphology is determined before birth.[25] Niche formation at or below the level of the cementoenamel junction results in shortened, thin roots. Repetitive high doses of some agents (cyclophosphamide) may result in root agenesis. Intensive, repetitive chemotherapy at the time of initial hard tissue formation may cause tooth agenesis.

Some chemotherapeutic agents also affect mature secretory odontoblasts and ameloblasts. Vinblastine and vincristine disrupt cytoplasmic microtubules of the intracellular transport system.[26, 27] Interference with odontoblast microtubules disrupts collagen fibril formation and dentin matrix secretion,[28, 29] resulting in short, thin, tapered roots. Disruption of the ameloblast microtubule calcium transport mechanism[30] results in hypomineralized enamel defects. Ameloblast microtubules also form the ruffled border where absorption of organic material from the enamel matrix occurs.[31] Vinca alkaloids destroy the ruffled border and create smooth-ended ameloblasts which cannot remove organic proteins from enamel matrix. Hypomature enamel defects result.[32]

Multimodal Therapy

Many pediatric cancers are treated with a combination of radiation and multiagent chemotherapy to create synergistic and additive effects. Tumor cells not destroyed by one therapy may be destroyed by another while minimizing toxicity to normal cells. While this reduces a single agent's toxicity to odontoblasts and ameloblasts, it also increases the number of agents influencing them. Multiple agents make it difficult to attribute defects specifically in odontogenesis to any single agent or therapy.[33, 34]

Clinical Implications

Dental treatment affected by chemoradiation damage to developing teeth includes orthodontic tooth movement, prosthetic abutment considerations, periodontal health, space maintenance, requirements for home fluoride regimens to protect hypomineralized areas, restoration options for hypoplastic/hypomineralized teeth, and endodontic procedures. Dental anomalies and their effect on the dental care of pediatric cancer patients often can be predicted by correlating the type and amount of chemoradiation with dental development at the time of therapy.

Radiographs just prior to chemoradiation therapy indicate the stage of dental development, allowing the clinician to predict potential dental defect extent and locations for parents and medical staff. Thus, a panoramic radiograph may be indicated as a routine part of a child's

preoncology dental treatment care plan. If pretherapy radiographs are not available, the clinician must rely on estimates of dental development at the time of chemoradiation therapy from dental/chronological development charts. Postchemoradiation therapy radiographs indicate the severity of dental damage and provide retrospective clues as to the stage of dental development during chemoradiation therapy.

By correlating dental development at the time of therapy with the type of therapy, future dental developmental anomalies and treatment needs may be predicted. Since localized enamel defects may not be visible radiographically, a prognosis should include all defects that might occur.

The following case summaries demonstrate chemoradiation therapy effects on dental development.

Case Report 1

The patient was diagnosed at age 2 years with neuroblastoma, Stage III. Surgical resection of the tumor was followed by 10 monthly doses of vincristine, cisplatin, cyclophosphamide, DTIC, VP-16, and adriamycin. At age 3 years, the patient received an autologous bone marrow transplant, melphalan, cyclophosphamide, and 2000 R total body irradiation.

At age 5 the patient had a mixed dentition with normal primary dentition, and missing, developmentally arrested, and malformed permanent teeth (Fig 3).

Permanent first molars complete crown formation between age 2 to 2-1/2 years. Chemotherapy from age 2 to 3 altered odontoblastic activity during initial root formation, resulting in thin, tapered roots.

The second premolars and second molars are not visible. Premolar hard tissue formation begins just before age 2, and second molar hard tissue formation begins at age 2-1/2 to 3 years. The prolonged chemoradiation therapy destroyed second premolar and second molar precursor cells, disrupting initial dentin and enamel matrices, and caused agenesis.

The effect on the first and second permanent molars and second premolars demonstrates the severity of insult to any actively proliferating cells at age 2–3 years. Other probable but not radiographically visible defects include local enamel hypoplasias on the incisors, canines, and first premolars in areas forming at that time. Since development of these teeth continued after chemoradiation therapy, later developing root morphology should be normal.

The radiation dose did not cause root agenesis in teeth which already had initiated hard tissue formation. The continued development of the incisors, canines and first premolars suggests that the radiation was not sufficiently high to affect the germinal third molars, which should develop normally.

Case Report 2

The patient was diagnosed at age 4 years with parapharyngeal rhabdomyosarcoma, Stage III. Treatment

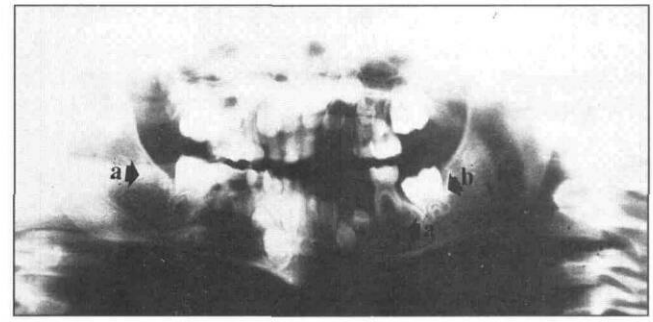

Fig 3. Age 5, following chemoradiation therapy at age 2. Second premolar and second molar agenesis (a), and first permanent molar thin, tapered roots (b).

at age 4 consisted of 5000 R head and neck irradiation, and chemotherapy with vincristine, actinomycin, cytoxan, methotrexate, hydrocortisone, and cytosine arabinoside. From age 4-1/2 to 6-1/2 years, maintenance chemotherapy was continued bimonthly with vincristine, actinomycin, and cytoxan.

At age 12, the patient exhibited asymmetrical facies, atrophied oral musculature, and a complete, but damaged permanent dentition (Fig 4). The incisors, canines, and premolars exhibit short, thin, tapered roots. The level at which the root anomalies begin corresponds to the root development completed at age 4 years. The two years of maintenance chemotherapy continued to alter root development, precluding any repair of localized damage from the initial chemotherapy. Short tapered roots resulted.

Posteriorly, the first molars show arrested root development. The early apical closure corresponds with the level of root development in first molars at age 4 to 4-1/2 years. The second molars exhibit dramatic total root agenesis. The partial and complete root agenesis of the molars is attributed to radiation therapy. Chemotherapy is systemic in its effect, and if it were responsible for this root agenesis it also would be noted on the incisors, canines, and premolars.

Second molar crown formation was not complete at the time of the chemoradiation therapy and therefore, enamel defects in the cervical third of the crown are predicted. Crown form itself is unaffected however.

The first and second molar root agenesis suggests the agenesis of the third molars. Radiation doses sufficiently high to produce root agenesis also would destroy the third molar odontogenic precursor cells. As radiation damage increases, the closer the teeth are to the radiation target, third molars receive even higher radiation doses. Anterior teeth, and those further from the radiation beam, were unaffected.

Case Report 3

The patient was diagnosed at age 7 years with medulloblastoma. Treatment at age 7 consisted of surgical excision of the tumor, and 3750 R of spinal and cranial irradiation. Chemotherapy with CCNU and vincristine

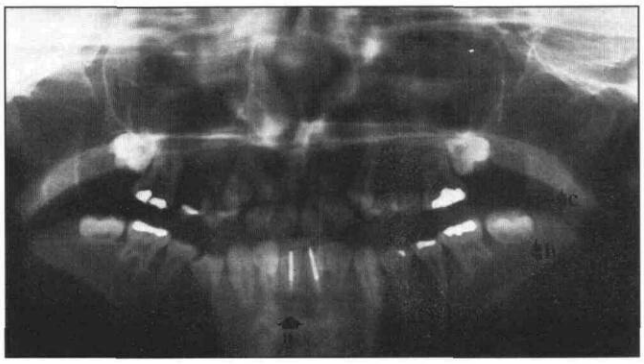

Fig 4. Age 12, following chemoradiation therapy at age 4. Incisors, cuspids, premolars have short, thin, tapered roots (a). First and second molar root agenesis (b) and third molar agenesis (c) noted.

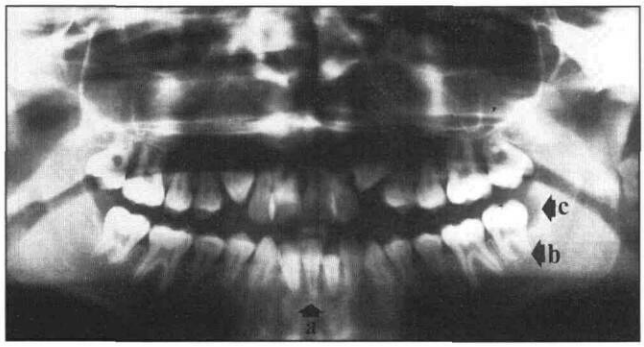

Fig 5. Age 16, following chemoradiation therapy at age 7. Incisors, cuspids, premolars, and first molars show minimal root shortening and tapering (a). Second molars show thinning and early apical closure (b). Agenesis of third molars noted (c).

was initiated and maintained for one year.

At age 16 the patient exhibited short stature, and complete, but damaged permanent dentition (Fig 5). All incisors, canines, and premolars exhibit minimal root shortening, tapering, and thinning. First molars show only minimal thinning in the apical quarter of the root. These effects were caused by the phase-specific chemotherapy (vincristine) and correspond with the level of root development expected at age 7.

Second molars exhibit moderate root shortening and early apical closure. Some of the increased damage is attributable to chemotherapy during the heightened odontoblastic activity in these teeth at age 7–8 years, when root formation is initiating. However, the root agenesis also is attributable to radiation effects due to second molar proximity to the radiation beam. This root agenesis shows the radiation dose was sufficiently high to irreparably damage odontogenic cells. Distal to the second molars are radiolucencies that may be associated with primordial cysts of the third molars. The radiation destroyed the odontogenic precursor cells, resulting in agenesis.

Case Report 4

The patient was diagnosed at age 3–1/2 months with neuroblastoma, stage 4S. Chemotherapy with cytoxan was initiated upon diagnosis. At age 6 months, surgical excision of the neuroblastoma was followed by chemotherapy with cytoxan and adriamycin. From 6 to 24 months, cytoxan and adriamycin were repeated bimonthly.

Dental evaluation at age 4–1/2 years revealed a complete but damaged primary dentition (Fig 6). Central and lateral incisor roots exhibit early apical closure. Canines and primary molars show various degrees of root thinning, tapering, and shortening. The onset of this damage corresponds with the initiation of cytoxan and adriamycin chemotherapy, following the surgical excision of the neuroblastoma.

The permanent dentition shows no radiographic effect of this early chemotherapy. The short half-life of the chemotherapeutic agents and the reduced mitotic activity of the permanent tooth buds at the time of chemotherapy explain the lack of noticeable effect on the permanent dentition. The parent was informed that all permanent teeth should develop with normal gross crown and root morphology. However, the incisors and first permanent molars may show some localized enamel defects, since some enamel formation was occurring during the time of maintenance chemotherapy.

Case Report 5

The patient was diagnosed at age 18 months with neuroblastoma, stage 4. Initial treatment consisted of six, monthly doses of chemotherapy with vincristine, cytosine, DTIC, cisplatin, adriamycin, and DP-16. At age 24 months, the patient received 1200 rad total body irradiation and a bone marrow transplant. From age 24 months to 32 months the patient received eight doses of cytoxan and adriamycin.

Dental examination at age 4 revealed anomalies in both the primary and permanent dentitions (Fig 7). Root thinning and tapering on the primary molars are present, beginning at the level of the root forming at age 18 months. Permanent second premolars and second molars are absent. Both of these teeth initiate hard tissue formation at age 24–30 months. Chemoradiation therapy disrupted the initial hard tissue formation during this time, causing agenesis. Permanent first molars may exhibit root agenesis, although the full extent of damage is not predictable

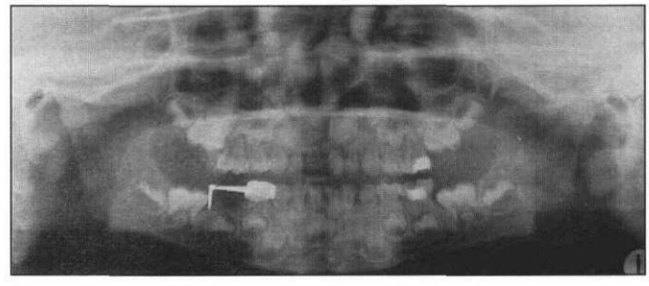

Fig 6. Age 4, following early chemotherapy only. Permanent dentition intact, with root shortening and thlnning noted in primary dentition.

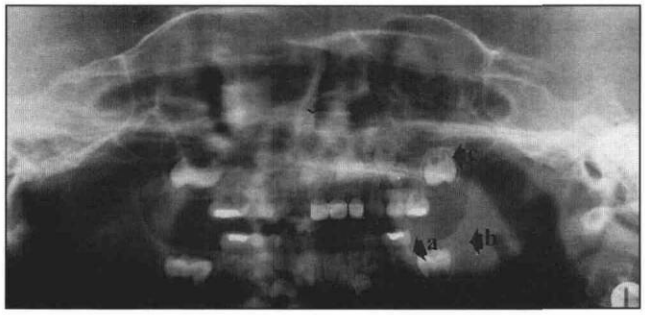

Fig 7. Age 4, following chemoradiation therapy age 2–3. Primary molars show root tapering (a). Permanent second premolars and second molars absent (b). Possible root agenesis of permanent first molars (c).

at this age. Radiographic examination in one year definitively will show root disturbances. However, since primary molar root development continued, it is possible that the doses were sufficiently low that permanent dentition root formation may continue, and third molars may form.

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Dr. Goho is presently Chief, Pediatric Dentistry, U.S. Army Dental Activity, Würzburg, Germany. Reprint requests should be sent to: Dr. Curtis Goho, DENTAC, Unit 26610, APO AE 09244.

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