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Skin and Oral Mucosal Pigmentation as an Early Cutaneous Marker of Vincristine-Based Chemotherapy Toxicity

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ABSTRACT

Background: Vincristine is a core component of chemotherapy regimens for acute lymphoblastic leukemia, lymphoma, rhabdomyosarcoma, and other malignancies, and its dose-limiting toxicity is classically peripheral neuropathy rather than a dermatologic effect. However, scattered case reports and broader drug-induced pigmentation reviews have repeatedly described skin, nail, and oral mucosal pigmentary change in patients receiving vincristine-containing regimens. Objective: To synthesize the published evidence on cutaneous, ungual, and oral mucosal pigmentation associated with vincristine-based chemotherapy and to evaluate its potential clinical utility as an early, non-invasive marker of treatment effect. Methods: A narrative review was conducted of case reports, case series, and systematic reviews addressing chemotherapy-induced mucocutaneous pigmentation, with particular attention to reports arising in vincristine-containing regimens (vincristine-actinomycin, vincristine-adriamycin-dexamethasone, hyper-CVAD, R-CHOP, and pediatric leukemia consolidation protocols) and comparator data from other cytotoxic and targeted agents. Findings: Vincristine-containing regimens have been associated with serpentine supravenous hyperpigmentation, transverse melanonychia and chromonychia, diffuse melanoderma, reticulate truncal hypermelanosis, and pigmentation of the nail bed and tongue, with onset typically within one to several treatment cycles and gradual resolution over months after discontinuation. Because vincristine is administered almost exclusively in combination regimens, single-agent causal attribution is frequently uncertain, and several reports assign greater causal weight to co-administered alkylating agents or anthracyclines. Comparator literature indicates that antineoplastic agents broadly account for roughly a third of drug-induced hyperpigmentation cases, and that oral mucosal pigmentation, though less frequently documented specifically with vincristine, is a recognized, agent-dependent, and readily inspected finding across cytotoxic regimens. Conclusions: Skin, nail, and oral mucosal pigmentation is a recurrent, generally benign, and clinically accessible cutaneous accompaniment of vincristine-based chemotherapy that clinicians can incorporate into routine bedside monitoring, while recognizing that firm attribution to vincristine alone, as distinct from its regimen partners, remains an area requiring further dedicated case-level documentation.

Keywords: *vincristine toxicity; chemotherapy-induced hyperpigmentation; oral mucosal pigmentation; melanonychia; serpentine supravenous hyperpigmentation*

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Introduction

Vincristine is among the most widely used vinca alkaloids in modern oncology, forming a backbone component of regimens for acute lymphoblastic leukemia, Hodgkin and non-Hodgkin lymphoma, rhabdomyosarcoma, Wilms tumor, and a range of other pediatric and adult malignancies, most often in combination with alkylating agents, anthracyclines, corticosteroids, and antimetabolites [1]. Its dose-limiting toxicity is classically peripheral sensorimotor neuropathy, and clinical attention to vincristine's adverse-effect profile has accordingly centered on the neurologic and gastrointestinal domains rather than the skin. Yet a body of case reports, small case series, and broader drug-induced pigmentation reviews has repeatedly documented cutaneous, nail, and oral mucosal pigmentary change in patients receiving vincristine-containing regimens, ranging from serpentine streaking along the infused vein to diffuse melanoderma, transverse melanonychia, and lingual or gingival darkening [2,3,4]. Because these changes are visible, frequently appear within the first one to several cycles of

treatment, and can precede or accompany more classically monitored toxicities, they have been proposed as an accessible, non-invasive cutaneous signal that a treatment course is producing a measurable biological effect on pigment-forming and pigment-transferring cells, one that clinicians and patients alike can observe at the bedside without laboratory testing [5].

The broader literature on chemotherapy-induced pigmentation situates vincristine within a well-characterized family of pigmentary reactions attributable to cytotoxic agents generally. Pooled and systematic analyses estimate that antineoplastic drugs are implicated in roughly a third of all cases of drug-induced hyperpigmentation captured in aggregated cohorts, a burden on par with or exceeding that of antimalarials, minocycline, and amiodarone [6]. Within this category, vincristine is almost never reported as a sole causative agent; rather, it appears repeatedly as one component of combination regimens—vincristine plus actinomycin D, vincristine-adriamycin-dexamethasone (VAD), hyper-CVAD, R-CHOP, and multiagent pediatric leukemia and sarcoma protocols—in which the pigmentary pattern is attributed to the regimen as a whole or to a co-administered alkylating agent or anthracycline, with vincristine's contribution inferred from its consistent presence rather than demonstrated in isolation [2,4,7]. This attribution problem recurs throughout the literature synthesized here: the case for vincristine as a pigmentation-inducing agent rests on convergent, repeated observation across regimens rather than on single-agent pharmacovigilance data.

This narrative review synthesizes published case reports, case series, and broader chemotherapy-induced pigmentation literature bearing on vincristine-containing regimens, organized across five domains: the proposed mechanisms by which vincristine and its regimen partners might induce melanogenesis and vascular pigmentary change; the case-level evidence for cutaneous and nail pigmentation specifically arising in vincristine-treated patients; the evidence bearing on oral mucosal pigmentation as an early, accessible marker of treatment effect; the comparative landscape of pigmentary reactions across other cytotoxic agents, which contextualizes vincristine-associated findings; and the diagnostic and management approach appropriate to a patient who develops new pigmentation during vincristine-based therapy. The aim is not to overstate vincristine's independent causal role but to characterize, as precisely as the evidence permits, the recurring patterns that have led investigators to implicate it, and to translate that evidence into practical guidance for clinicians.

Mechanisms of Vincristine-Associated Melanogenesis and Vascular Pigmentary Change

Vincristine exerts its principal antineoplastic effect by binding tubulin and inhibiting microtubule polymerization, arresting dividing cells in mitosis; this disruption of microtubule-dependent processes is invoked as one plausible substrate for its dermatologic effects, since melanosome transport from melanocytes to keratinocytes is itself a microtubule- and motor-protein-dependent process that could be perturbed by a tubulin-targeting agent, altering melanin distribution and retention within the epidermis [5]. Beyond this drug-specific hypothesis, the broader mechanistic framework proposed for cytotoxic-agent hyperpigmentation applies directly to vincristine-containing regimens: direct cytotoxic injury to basal keratinocytes and melanocytes triggering a reactive, post-inflammatory-like increase in melanin synthesis and transfer; localized stimulation of melanocyte activity or tyrosinase upregulation; and dermal deposition of drug, metabolite, or melanin with associated melanophage uptake, a pattern documented histologically in several reviewed case reports [8,7].

A distinct mechanism operates in the serpentine supravenous hyperpigmentation reported with vincristine-actinomycin combinations, in which a linear or reticulate band of pigmentation develops directly over the superficial vein used for drug infusion [2]. Proposed explanations include a local irritant or subclinical toxic effect of the infused drug on the vessel wall and adjacent epidermis, localized post-inflammatory pigmentation following subclinical phlebitis, and vessel-wall permeability changes allowing diffusion of the cytotoxic agent into the perivascular dermis at a concentration sufficient to injure resident melanocytes without overt extravasation injury [9,10]. Systematic review data on this entity—most cases attributed to 5-fluorouracil but including reports implicating vincristine-containing regimens—describe vacuolar or lichenoid interface dermatitis in roughly half of biopsied cases, consistent with a low-grade cytotoxic injury pattern rather than simple reactive melanocyte stimulation [9].

A third mechanistic thread concerns the reticulate, lacy pigmentary pattern described in patients receiving vincristine as part of multiagent leukemia consolidation therapy, in which net-like brown-to-black macular hyperpigmentation develops over the trunk within weeks of treatment initiation and fades over subsequent months [11]. This pattern has been described across several unrelated cytotoxic regimens and is generally interpreted as a shared cutaneous hypersensitivity-like or irritant reaction rather than a mechanism specific to any single drug, complicating efforts to isolate a vincristine-specific pathway [12,11]. Finally, the transverse melanonychia and chromonychia reported with vincristine-containing multiple myeloma and leukemia regimens are thought to reflect transient toxic injury to nail matrix melanocytes at the time of drug administration, producing a band of pigment that grows out distally over subsequent months, timed to individual cycles in some reports [3,4,13]. Across these threads, vincristine, whether acting alone or synergistically with regimen partners, appears to lower the threshold for melanocyte activation, melanosome mishandling, and dermal melanin deposition at cutaneous, ungual, and mucosal sites subjected to direct drug exposure or vascular transit.

Cutaneous and Nail Pigmentation in Vincristine-Containing Regimens: The Case-Report Evidence

The most detailed report linking vincristine to a specific pigmentary pattern is the description of persistent serpentine supravenous hyperpigmented eruption following combination chemotherapy with actinomycin D and vincristine, in which a linear, reticulate band of pigmentation developed along the previously infused vein and did not fade over extended follow-up, establishing vincristine-containing regimens within the serpentine supravenous hyperpigmentation literature that is more commonly associated with 5-fluorouracil [2]. This early report is frequently cited in later systematic reviews of the entity as one of the few non-fluorouracil regimens documented to produce this pattern [9,10].

Nail and periungual pigmentation findings are similarly prominent among vincristine-containing regimens, most

extensively documented in the setting of multiple myeloma and leukemia protocols that pair vincristine with an anthracycline and corticosteroid. A widely cited case report described a patient treated with vincristine, adriamycin, and dexamethasone (VAD) for multiple myeloma who developed three distinct nail alterations—transverse pigmented bands alternating with pale bands, transverse grooves, and diffuse white banding—together with diffuse skin hyperpigmentation of the forearms and palmar creases, all of which resolved within four months of treatment discontinuation, supporting a drug-induced rather than incidental etiology [3]. A comparable pattern was subsequently reported in a patient receiving the hyper-CVAD protocol (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine) for acute lymphoblastic leukemia, who developed transverse brown-gray hyperpigmentation of the proximal nail plate across all fingers with a sharp demarcation from unaffected distal nail, although the authors in that report attributed the finding primarily to doxorubicin and cyclophosphamide rather than to vincristine [4]. A broader review of chemotherapy-induced nail changes explicitly lists vincristine among the agents implicated in chromonychia and transverse nail banding, situating it alongside hydroxyurea, etoposide, daunorubicin, bleomycin, cyclophosphamide, and 5-fluorouracil as part of a recognized, if incompletely differentiated, group of nail-pigmenting cytotoxic drugs [13].

Representative published reports of skin, nail, or mucosal pigmentation arising in patients treated with vincristine-containing chemotherapy regimens.

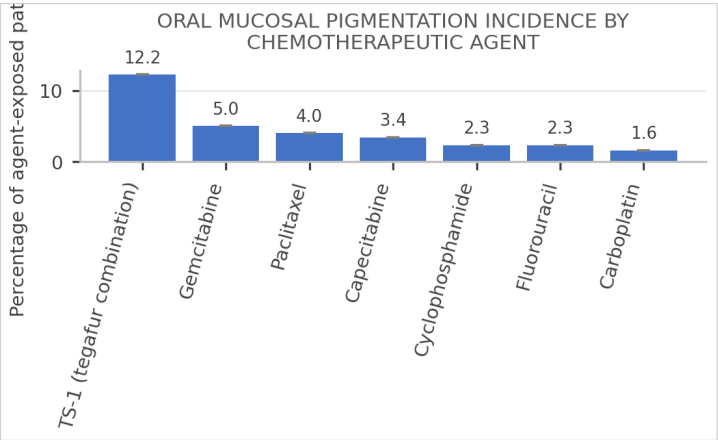
Report	Regimen (vincristine plus)	Indication	Pigmentary pattern / site	Outcome
Marcoux et al. 2000	Actinomycin D	Not specified (pediatric oncology)	Serpentine supravenous streaking over infused vein	Persisted at extended follow-up
Dasanu et al. 2006	Adriamycin, dexamethasone (VAD)	Multiple myeloma	Chromonychia, Beau's lines, diffuse forearm/palmar-crease melanoderma	Resolved within 4 months of discontinuation
Lopes et al. 2013	Cyclophosphamide, doxorubicin, dexamethasone (hyper-CVAD)	Acute lymphoblastic leukemia	Transverse proximal nail-plate hyperpigmentation, all fingers	Attributed chiefly to doxorubicin/cyclophosphamide
Yamamoto et al. 2024	Rituximab, cyclophosphamide, hydroxydaunorubicin, prednisolone (R-CHOP)	Lymphoma	Lower-leg, nail-bed, and tongue pigmented macules	Attributed chiefly to cyclophosphamide
Kumar et al. 2021	Methotrexate, cyclophosphamide, cytarabine, asparaginase	T-cell acute lymphoblastic leukemia (pediatric)	Reticulate, net-like truncal/gluteal hyperpigmentation	Resolved ~3 months after treatment completion

Diffuse cutaneous hyperpigmentation involving the lower extremities, nail beds, and tongue has also been documented in a patient receiving R-CHOP therapy—rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone—for lymphoma, in which xerotic, brownish, scaly plaques developed on both lower legs together with pigmented macules of the nail beds and tongue; histopathology demonstrated increased basal and stratum corneum melanin with melanin incontinence in the papillary dermis, and the authors implicated cyclophosphamide as the most probable causative agent while noting vincristine as a co-administered drug that could not be excluded [7]. Finally, a pediatric case of net-like reticulate truncal and gluteal hyperpigmentation developing one month into consolidation chemotherapy with methotrexate, cyclophosphamide, cytarabine, vincristine, and asparaginase for T-cell acute lymphoblastic leukemia, resolving approximately three months after treatment completion, extends the vincristine-associated pigmentary spectrum into the reticulate hypermelanosis category and is notable for occurring in a child, the population in which vincristine-based regimens are most heavily used [11]. Taken together, these reports consistently place vincristine within multidrug regimens associated with cutaneous and nail pigmentation, with authors variably assigning primary causal weight to vincristine or to its regimen partners, underscoring that firm single-agent attribution remains elusive despite the reproducible overall pattern.

Oral Mucosal Pigmentation as an Early Cutaneous Marker

Oral mucosal pigmentation is a less frequently reported but potentially more accessible manifestation of chemotherapy-associated pigmentary change, since the oral cavity is readily inspected at each treatment visit without requiring the patient to disrobe. The largest dedicated dataset, a retrospective study of 388 patients receiving cytotoxic chemotherapy over two years, identified oral mucosal pigmentation in 2.8 percent overall (11 of 388), with marked variation by agent: tegafur-uracil combination chemotherapy (TS-1) carried the highest rate at 12.2 percent, followed by gemcitabine (5.0 percent), paclitaxel (4.0 percent), capecitabine (3.4 percent), and cyclophosphamide and fluorouracil (2.3 percent each); vincristine was not separately analyzed in this adult solid-tumor cohort, but the study establishes oral pigmentation as a recognized, quantifiable, agent-dependent phenomenon across the wider cytotoxic drug class to which vincristine belongs [14]. Notably, in every documented case, oral pigmentation appeared concurrently with or after cutaneous pigmentation had already developed, which bears directly on how "early" a marker oral pigmentation can practically serve as [14].

Proportion of chemotherapy-treated patients developing oral mucosal pigmentation, by causative agent, in a retrospective cohort of 388 patients (Yamada et al., 2023); vincristine was not separately analyzed in this adult solid-tumor cohort but the agent-dependent pattern establishes oral pigmentation as a quantifiable marker across the wider cytotoxic drug class to which vincristine belongs.



More directly relevant to vincristine, the pediatric case of reticulate hyperpigmentation arising during a methotrexate-cyclo phosphamide-cytarabine-vincristine-asparaginase consolidation regimen for T-cell acute lymphoblastic leukemia developed within one month of treatment initiation, illustrating that vincristine-containing pediatric protocols can produce visible pigmentary change on a timescale compatible with early detection, even though that report centered on truncal rather than oral findings [11]. Broader reviews of drug-associated oral mucosal hyperpigmentation catalogue chemotherapy as one of several recognized causes of acquired oral pigmentation, alongside physiologic racial pigmentation, smoker's melanosis, Peutz-Jeghers and Laugier-Hunziker syndromes, Addison disease, and heavy-metal deposition, and emphasize that drug-induced pigmentation typically presents as diffuse or patchy brown-to-gray macular discoloration of the buccal mucosa, gingiva, hard palate, or dorsal tongue without the surface irregularity or ulceration that would raise concern for a neoplastic process [15,16]. A detailed case series of four patients reinforces that the buccal mucosa and attached gingiva are the most frequently affected intraoral sites and that lesions are typically asymptomatic, multifocal, and slow to resolve after the causative drug is withdrawn, consistent with what has been separately reported for chemotherapy-associated tongue and gingival pigmentation [15].

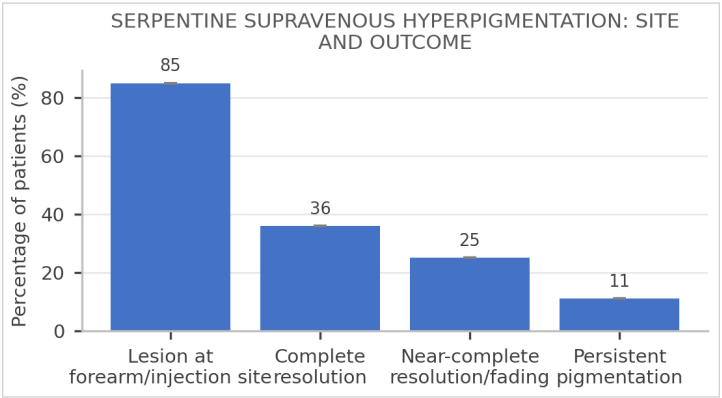
Because an estimated 10 to 20 percent of acquired oral pigmentation overall is attributable to medications, and because chemotherapeutic agents are one of the more frequently implicated drug classes within that group, clinicians managing patients on vincristine-containing regimens have a plausible basis for incorporating a brief oral mucosal examination into routine chemotherapy visits, both to document a benign, expected finding when it occurs and to exclude look-alike diagnoses of greater concern [16]. While the direct evidence specifically linking vincristine to oral pigmentation remains limited to reports in which vincristine is one of several co-administered agents, the convergence of a plausible mechanistic basis, a recognized broader chemotherapy-oral-pigmentation association, and at least one pediatric case demonstrating rapid-onset reticulate pigmentation during a vincristine-containing regimen supports continued clinical attention to this sign, particularly given how readily it can be assessed without additional cost or invasive testing.

Comparative Perspective: Pigmentary Patterns Across Cytotoxic and Targeted Agents

Interpreting vincristine-associated pigmentation requires situating it within the wider landscape of chemotherapy-induced pigmentary reactions, since many patterns attributed to vincristine-containing regimens overlap with those produced by other agents in the same or unrelated protocols. Serpentine supravenous hyperpigmentation, the pattern most specifically linked to a vincristine-actinomycin regimen in the case-report literature, is overwhelmingly attributed to 5-fluorouracil in systematic reviews: one identified 28 patients across 26 published reports, with 85 percent of lesions localized to the forearm near the infusion site, complete resolution in 36 percent, near-complete fading in 25 percent, and persistent pigmentation in 11 percent at last follow-up, figures drawn largely from fluorouracil-treated cohorts but directly comparable to the vincristine-actinomycin report above [9]. A second, independent systematic review of the same entity corroborates the forearm predominance and variable resolution pattern while extending the causative-agent list to additional taxane, platinum, and vinca-alkaloid-containing regimens, reinforcing that the pathophysiology is likely shared across drug classes rather than unique to any single mechanism [10].

Bleomycin remains the agent most classically associated with flagellate hyperpigmentation, a linear, whip-like streaking pattern generally attributed to post-inflammatory pigmentation following pruritus-induced scratching, a mechanism distinct from the direct cytotoxic and vascular explanations invoked for vincristine-associated patterns [12]. Reticulate hyperpigmentation, the pattern documented in the pediatric vincristine-containing regimen described above, has also been reported with paclitaxel, gemcitabine, and other cytotoxic agents, indicating that this morphology is a shared cutaneous response rather than a signature specific to any one drug class [12,11]. A large single-center case series of 54 patients with anti-tumor chemotherapy-associated hyperpigmentation across a range of regimens found cutaneous involvement in 83.3 percent, melanonychia in 18.5 percent, and a mean latency to onset of approximately six weeks, with a clear predominance among patients of darker constitutive skin phototypes, findings broadly consistent in timing and distribution with the vincristine-containing case reports reviewed here even though vincristine-specific regimens were not separately analyzed [17].

Site distribution and longitudinal outcome of chemotherapy-associated serpentine supravenous hyperpigmentation among 28 patients pooled across 26 published reports, the clinical entity most specifically documented with a vincristine-actinomycin regimen (Shan et al., 2024).



Broader reviews of cutaneous reactions to cytotoxic and targeted anticancer therapy catalogue pigmentary change as a recurring toxicity across taxanes, alkylating agents, antimetabolites, anthracyclines, and an expanding list of targeted agents including tyrosine kinase inhibitors, situating classical vinca-alkaloid- and anthracycline-associated hyperpigmentation within a landscape that continues to broaden [18,19,20]. A pooled meta-analysis across drug classes estimated antineoplastic-agent-associated hyperpigmentation at approximately 35.5 percent among treated patients, a figure that, while derived predominantly from non-vincristine-specific data, anchors counseling for patients on vincristine-containing regimens about the plausibility of developing some pigmentary change [6]. Comprehensive reviews of dermatologic adverse effects of cytotoxic chemotherapy reinforce that pigmentary reactions, while cosmetically and psychologically significant, are rarely dose-limiting and rarely mandate regimen discontinuation, a conclusion equally applicable to the vincristine-containing reports synthesized here [1].

Diagnostic Evaluation and Clinical Management

Evaluating a patient who develops new pigmentation during vincristine-based chemotherapy begins with establishing the temporal relationship between drug exposure and pigmentary onset and characterizing the precise pattern and distribution, since the literature reviewed here demonstrates that pattern recognition—serpentine supravenous streaking, reticulate truncal hypermelanosis, transverse melanonychia, or diffuse mucocutaneous darkening—often permits a confident clinical diagnosis without biopsy [5,8]. A comprehensive medication history covering the full current regimen, rather than vincristine in isolation, is essential given that every vincristine-associated pigmentary report reviewed here occurred within a multidrug protocol, and clinicians should resist attributing a finding to vincristine alone when a co-administered alkylating agent, anthracycline, or antimetabolite is an equally or more plausible cause [4,7].

Excluding alternative explanations remains essential, particularly for pigmentation that is asymmetric, indurated, ulcerated, or otherwise atypical for a benign drug reaction; relevant differential considerations include post-inflammatory hyperpigmentation from an unrelated dermatosis, endocrinologic causes such as primary adrenal insufficiency, physiologic or racial oral pigmentation, and, most importantly in an oncology population, cutaneous or mucosal metastasis or a second primary pigmented lesion, for which dermoscopy or biopsy should be pursued without hesitation when clinical suspicion exists [16,15]. Because oral mucosal pigmentation can be assessed at no additional cost during a scheduled infusion visit, incorporating a brief intraoral inspection into routine toxicity assessment for patients on vincristine-containing regimens is a reasonable, low-burden addition to standard monitoring, particularly in pediatric populations in which vincristine-based protocols are most extensively used [14,11].

Management of confirmed vincristine-regimen-associated pigmentation is overwhelmingly conservative. The reports reviewed here consistently describe spontaneous fading over weeks to months after chemotherapy completion—three to four months in the VAD and pediatric leukemia reports specifically—although some patterns, particularly serpentine supravenous hyperpigmentation, can persist beyond a year in a meaningful minority of cases [3,11,9]. Sun protection of affected skin is commonly recommended on the basis that ultraviolet exposure can potentiate or prolong drug-induced pigmentation, and the largest case series reviewed here found that dermatologic intervention including photoprotection counseling was associated with cosmetic improvement in most patients followed longitudinally [17]. Because chemotherapy-induced pigmentation, including the patterns described here, is rarely dose-limiting and does not by itself indicate a dangerous drug reaction, most authors advise continuing the causative regimen when clinically indicated, reserving dermatologic referral for diagnostic uncertainty, marked cosmetic distress, or features suggestive of an alternative diagnosis [1]. Counseling patients and families before treatment initiation—that mild, self-limited skin, nail, or oral darkening is a recognized, generally reassuring accompaniment of vincristine-based therapy rather than a sign of disease progression—is a low-cost intervention that may meaningfully reduce anxiety when these changes appear.

Conclusion

Skin, nail, and oral mucosal pigmentation is a recurrent, if incompletely attributed, cutaneous accompaniment of vincristine-containing chemotherapy regimens, spanning serpentine supravenous streaking, diffuse melanoderma, transverse melanonychia and chromonychia, reticulate truncal hypermelanosis, and lingual or gingival darkening [2,3,11]. Because vincristine is administered almost exclusively within multidrug protocols, the case-level evidence synthesized here cannot establish it as an independent causative agent with the same confidence afforded to 5-fluorouracil for serpentine supravenous hyperpigmentation or bleomycin for flagellate pigmentation, and several of the reports reviewed explicitly assign greater causal weight to co-administered alkylating agents or anthracyclines [4,7]. Nonetheless, the consistency of the reported patterns across independent vincristine-containing regimens—pediatric leukemia consolidation, multiple myeloma VAD therapy, hyper-CVAD, and R-CHOP—together with a plausible mechanistic basis rooted in vincristine's disruption of microtubule-dependent melanosome handling, supports continued clinical attention to pigmentary change as an accessible bedside sign during vincristine-based treatment [5,14]. Given the low cost, non-invasiveness, and reassurance value of routine skin, nail, and oral mucosal inspection during chemotherapy visits, and the broader epidemiologic context establishing that a substantial minority of patients receiving cytotoxic chemotherapy of any kind develop some form of drug-induced hyperpigmentation, clinicians caring for patients on vincristine-containing regimens are well positioned to recognize, correctly attribute, and appropriately reassure patients about these findings without unnecessary additional workup [6,17]. Continued case-level documentation specifically isolating vincristine's contribution from that of its regimen partners remains a worthwhile direction for future clinical reporting.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Wozniak M conceived the review, conducted the literature search, and drafted the manuscript. Walsh C contributed oncologic and chemotherapy-regimen context, assisted with literature screening, and critically revised the manuscript for important intellectual content. Karagiannis S contributed expertise on oral and mucosal pigmentary findings, provided additional context on diagnostic evaluation, and approved the final version for submission.

Ethics Statement

Not applicable. This is a narrative review of previously published literature and did not involve new experimental data, human participants, or animal subjects.

Data Availability

No new data were generated or analyzed for this review. All sources synthesized are cited in the reference list and are available through their original publishers.

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