

# Chemotherapy-Associated Tongue Hyperpigmentation and Blue Lunula

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## ABSTRACT

Combination chemotherapy is associated with cutaneous and mucosal side effects. Antineoplastic agents have been associated with mucosal and nail pigmentation. We describe a 16-year-old Saudi Arabian girl with combination chemotherapy-associated black tongue hyperpigmentation and blue lunula. The diagnosis of drug-associated pigmentary changes is based on correlating the onset of the clinical observations with the temporal initiation of the patient's chemotherapy agents. Spontaneous fading of antineoplastic therapy-induced tongue or nail dyschromia may subsequently occur following discontinuation of the causative drug.

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## INTRODUCTION

Hyperpigmentation of the tongue has been associated with several medications. A hyperpigmented tongue may result from increased melanin within the lingual mucosa.<sup>1</sup> Blue lunula is most frequently caused by drug ingestion. We describe a 16-year-old Saudi Arabian girl who was receiving combination chemotherapy for spinal medulloblastoma and developed lingual hyperpigmentation and blue lunula.

## CASE REPORT

A 16-year-old Saudi Arabian girl presented with tongue and fingernail pigmentary changes for evaluation in July 2011. She was diagnosed with spinal medulloblastoma in November 2007. She was initially treated with surgery; surgical intervention was also performed for 2 additional recurrences. The third surgery was followed by radiation therapy and a course of vincristine.

A new chemotherapy regimen was started on April 25, 2010, which included a cycle of cisplatin at 20 mg/m<sup>2</sup>, ifosfamide at 1.5 mg/m<sup>2</sup>, temozolomide at 160 mg/m<sup>2</sup>, and vincristine at 1.5 mg/m<sup>2</sup> for 5 days. After 2 cycles, the patient was switched from ifosfamide to cyclophosphamide. In addition, after the second cycle, the patient received alternating treatments of vincristine, irinotecan, and temozolomide with cyclophosphamide, vincristine, and doxorubicin. Doxorubicin was subsequently discontinued because of pancytopenia, and the patient's therapy was switched to gemcitabine and docetaxel.

In May 2010, after receiving a cycle of combination chemotherapy, she noted dark spots on her tongue and changes in the color of her fingernails. Physical examination approximately 1 year after the patient's discovery of these mucosal and nail changes

showed multiple black macules on the distal dorsal tip of her tongue (Figure 1). The thumb and fingernails had Beau's lines, longitudinal dark brown bands, and diffuse hyperpigmentation. In addition, all fingernails had blue lunula (Figure 2).

The patient was seen at follow-up after 6 months, in November 2011. The brown macules on her tongue had begun to spontaneously fade but were still present. Her fingernails still appeared dark; however, the lunulae were no longer blue and had returned to their normal color.

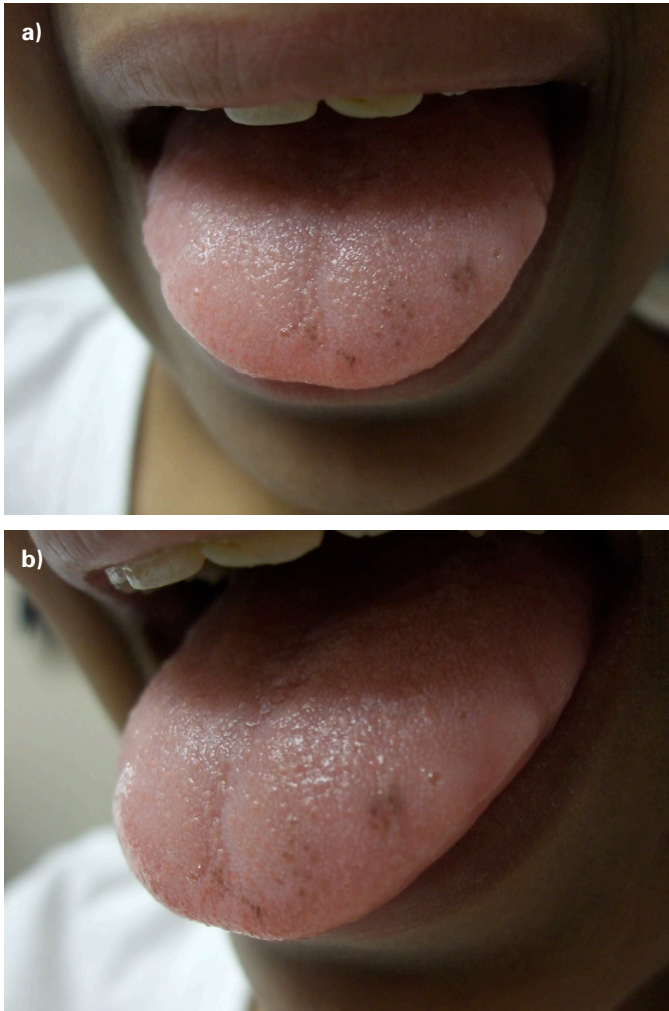
## DISCUSSION

Single-agent and combination-drug antineoplastic therapy can be associated with medication-induced side effects. These included dermatologic sequelae presenting as changes of the hair, skin, mucous membranes, and nails. Our patient developed coincident dyschromia of the tongue and lunula.

Various chemotherapy agents cause tongue hyperpigmentation (Table 1). Single agents include adriamycin, capecitabine, cyclophosphamide, doxorubicin, and tegafur. None of these patients had nail changes.

Doxorubicin has also been shown to cause hyperpigmented tongue. After discontinuing the use of doxorubicin in a 41-year-old black woman who was being treated for breast cancer, the pigmentation faded; she was still receiving 5-fluorouracil and cyclophosphamide. It has been speculated that doxorubicin stimulates melanocyte-stimulating hormone (MSH).<sup>2</sup> MSH levels vary among individuals of different skin phototypes, which may explain why only certain patients develop hyperpigmenta-

**FIGURE 1.** Frontal **a)** and lateral **b)** views of the distal dorsal left side of the tongue of a 16-year-old Saudi Arabian girl with spinal medulloepithelioma who was treated with combination chemotherapy: cisplatin, ifosfamide, temozolomide, and vincristine. She developed multiple macular areas of black hyperpigmentation.

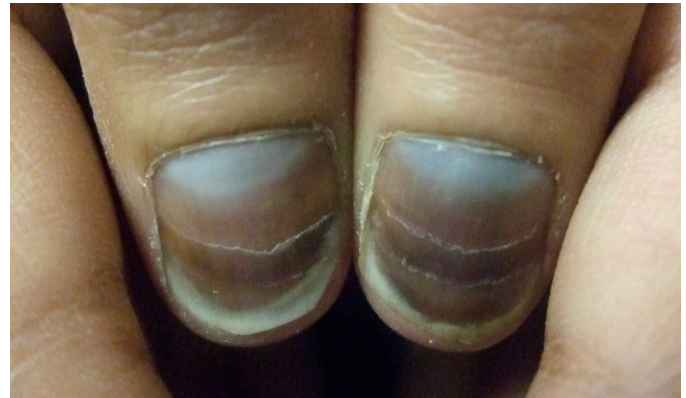


tion while on chemotherapy. MSH increases cyclic adenosine monophosphate and tyrosine within melanocytes; subsequently, these elevated levels of tyrosine may stimulate the increased production of melanin.<sup>3</sup>

Interferon- $\alpha$  is used in the treatment of chronic myelogenous leukemia. It is also used in the treatment of hepatitis C in combination with ribavirin. It has been postulated that it has the same mechanism of action as doxorubicin, increasing the expression of MSH. It cannot be excluded that ribavirin, which was concurrently used in the patients being treated for hepatitis C, contributed to the development of lingual hyperpigmentation.<sup>4</sup>

The lunula is the moon-shaped visible white portion of the distal nail matrix. Blue lunula is more readily observed on the digits of the hand and most readily observed on the thumbs.

**FIGURE 2.** Blue lunula are observed on the thumbnails of a 16-year-old Saudi Arabian with spinal medulloepithelioma after receiving cisplatin, ifosfamide, temozolomide, and vincristine. Diffuse brown hyperpigmentation and Beau's lines, appearing as horizontal ridges caused by chemotherapy, are also present.



**TABLE 1.**

**Chemotherapy-Associated Tongue Hyperpigmentation<sup>a</sup>**

Single Agents	Comments
Adriamycin	19 mo black girl with acute lymphoblastic leukemia <sup>7</sup> 9 y black woman with Wilms' tumor <sup>7</sup>
Capecitabine	58 y woman with metastatic breast cancer <sup>8</sup> 59 y man with adenocarcinoma of stomach <sup>9</sup>
Cyclophosphamide	10 women, (age range, 9-54 y); 8 women had breast carcinoma, and 2 had non-Hodgkin's lymphoma <sup>10</sup>
Doxorubicin	39 y man with HIV and Kaposi sarcoma <sup>11</sup> 41 y black woman with breast cancer <sup>2</sup>
Tegafur	58 y woman with colon adenocarcinoma <sup>12</sup>

**Combination Therapy**

Cisplatin, ifosfamide, temozolomide, vincristine	16 y Saudi Arabian girl with spinal medulloepithelioma [CR]
Interferon- $\alpha$ and ribavirin	7 white women and 1 black woman (age range, 33-66 y) with hepatitis C <sup>3,4,13-18</sup>

CR, current case report; HIV, human immunodeficiency virus; mo, months of age; y, years of age.

Blue lunula has been caused by congenital disorders, drugs, heavy metals, and as an idiopathic occurrence (Tables 2 and 3).

Drug-associated blue lunula has been observed not only after the administration of antineoplastic agents, but also after treatment with other medications such as minocycline, phenolphthalein, and zidovudine (Table 3). Similar to our patient, individual reports describe patients who developed blue lunula while receiving treatment with combination chemotherapy. To the best of our knowledge, none of these patients also had hyperpigmentation of the tongue.

TABLE 2.

**Blue Lunula: Associated Causes**

Congenital disorders	Bony deformity and verrucae associated <sup>a,19</sup> Hemoglobin M disease <sup>b,20</sup> Hereditary acrolabial telangiectasia <sup>c,21</sup>
Drug-associated	See Table 3
Heavy metals	Argyria <sup>d,22</sup>
Systemic diseases	Hepatolenticular degeneration (Wilson's disease) <sup>e,23</sup>
Idiopathic	Normal variant <sup>f,24</sup> Pseudo-blue lunula <sup>g,25</sup>

<sup>a</sup>A 10-year-old child with congenital bony deformity, verrucae, hypertrophied terminal pulps of the fingers, and blue lunula with no corresponding lung or heart disease.

<sup>b</sup>Patients with this disease have cyanosis, lavender-blue discoloration of the skin and mucosal membranes, absence of clubbing, and a brown hemoglobin M band on electrophoresis.

<sup>c</sup>A mother (age 56 years) and her 2 daughters (aged 24 and 26 years) were reported to have blue lips, blue nipples, blue areolae, and blue lunulae. All 3 patients also had telangiectasias of the elbows, chest, and dorsal portion of the hands. The mother and the 26-year-old daughter first noted the blue lunula after the first year of life. The blue lunula was first noted in the 26-year-old after 3 months of age. The blue color became more pronounced with time, cold exposure, and exercise.

<sup>d</sup>Silver poisoning causes blue discoloration of the lunula due to the disposition of silver in the lunula area. This case report describes the occupational exposure of silver nitrate in 15 patients, 7 of which developed generalized argyria and 6 developed localized argyria. Under light microscopy, brown-black granules with silver and sulfur surround the eccrine glands.

<sup>e</sup>This is an autosomal recessive systemic disorder of copper metabolism with slow production of ceruloplasmin and severe interference with biliary excretion of copper.

<sup>f</sup>Blue lunula occasionally has been observed to occur in otherwise healthy black people and mestizos. It has also been reported as an idiopathic occurrence in a 65-year-old retired grain weigher.

<sup>g</sup>A 12-hour-old infant had blue nails with no signs of cyanosis and a pulse oximeter reading of greater than 97%. He was full term and had an Apgar score of 9 out of 10. His complete blood cell count was within normal limits. Physical examination was unremarkable, and he had no heart murmur. The blue color of his lunula resolved spontaneously within 2 weeks.

**"Albeit uncommon, coincident dyschromia of the tongue and lunula of the nails may occur following multiagent cancer chemotherapy."**

A 60-year-old African American man receiving docetaxel for adenocarcinoma of the prostate developed blue lunula on his right and left thumb 3 months after starting docetaxel. Three months after discontinuing the docetaxel, his nail beds returned to their original color.<sup>5</sup>

Hydroxyurea has been used in the treatment of chronic myelogenous leukemia; however, a 45-year-old man with recalcitrant plaque psoriasis who took hydroxyurea 500 mg twice daily developed blue lunula 2 weeks after starting the drug.<sup>6</sup> Physical examination showed uniform blue pigmentation in all finger-nails in addition to psoriasis-associated nail changes of nail pitting and thickening. Three potential mechanisms to account

TABLE 3.

**Drug-Associated Blue Lunula**

Single agents	Docetaxel <sup>5</sup> Hydroxyurea <sup>6</sup>
Combination chemotherapy	Bleomycin, dactinomycin, vinblastine <sup>a,26</sup> Cisplatin, ifosfamide, temozolomide, vincristine [CR] Cyclophosphamide, dacarbazine, doxorubicin, vinicristine <sup>b,27</sup> 5-fluorouracil, cyclophosphamide, doxorubicin <sup>c,27</sup>
Other medications	Minocycline <sup>28</sup> Phenolphthalein <sup>29</sup> Zidovudine <sup>30</sup>

CR, current case report

<sup>a</sup>A 42-year-old man with metastatic testicular carcinoma developed blue lunula after starting this combination chemotherapy.

<sup>b</sup>A 26-year-old Arabic man with Ewing sarcoma developed pigmentation after the initial course of this combination chemotherapy.

<sup>c</sup>A 33-year-old black woman with breast cancer developed blue lunula after taking this combination chemotherapy.

for hydroxyurea-associated nail dyschromia have been postulated: (1) toxic effects to the distal nail matrix basal cells, (2) pigment deposition in the nail matrix, or (3) focal stimulation of melanocytes to produce melanin.<sup>6</sup>

**CONCLUSION**

Single-agent and combination-drug antineoplastic therapy can be associated with hair, mucocutaneous, and nail adverse sequelae. Our patient received cisplatin, ifosfamide, temozolomide, and vincristine; she subsequently developed not only macular black pigmentation on her tongue, but also blue lunula on the nails of her fingers and thumbs. The blue lunula resolved, and the tongue pigmentation was beginning to fade 18 months after the casual agents were discontinued. Albeit uncommon, coincident dyschromia of the tongue and lunula of the nails may occur following multiagent cancer chemotherapy.

**DISCLOSURES**

The authors have no relevant conflicts of interest to disclose.

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