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# The color of skin: blue diseases of the skin, nails, and mucosa

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**Abstract** Diseases of the skin, hair, nails and mucosa can appear as flesh-colored lesions or may present as any of the colors of the visual spectrum. Diseases associated with blue (or shades of blue) discoloration represent a unique group of conditions that occur de novo or as a reaction to either a topical or a systemic agent to which the individual has been exposed. Blue diseases can affect the skin, the nails or the mucosal membranes of the mouth (buccal mucosa, gingiva, lips, palate or tongue) or eyes (sclera). In addition to appearing blue, they can also appear as blue-black, blue-brown, blue-gray, blue-green, blue-purple, blue-red, and blue-silver. The conditions range from those secondary to exogenous agents (systemic or tattoo or topical) to syndromes to systemic diseases to tumors (adnexal, melanocytic, vascular, or miscellaneous). A comprehensive attempt to include all conditions that have been described as blue (or a shade of blue) has been performed by evaluating the following terms using the medical search engine PubMed: blue and either gingiva, lips, lunula, mucosa, nails, oral, palate, sclera, skin, or tongue. Subsequently, the conditions were organized by color (blue and shades of blue) and within each color by location (skin, nails, oral mucosa and sclera). The results are presented in organized tables; in addition, there is discussion of some of the conditions that are unique to one or more specific locations. In conclusion, 'preserve and cherish the pale blue dot' and remember that a big red rock eater with chrysiasis is the answer to the riddle, "What is big and blue and eats rocks?"


## Introduction

Blue diseases of the skin, nails, and mucosa represent a unique group of conditions that occur de novo or as a reaction to either a topical or a systemic agent to which the individual has been exposed.[1–237] Although Dr Carl Sagan (1934-1996) was referring to the Earth as a "pale blue dot," many of the mucocutaneous blue diseases present as pale blue dots.[238,239] And, taking the liberty to incorporate humor with science, a riddle may be used to aid in the conceptualization of an acquired blue condition.[240]

## Preserve and cherish that pale blue dot

On February 14,1990, the Voyager 1 space probe took pictures of Earth; the planet appeared as a pale blue dot secondary to polarization and scattering of the light that was reflected from the Earth. Dr Sagan (an astronomer and astrophysicist) lectured at Cornell University on October 13,1994; during his speech, he included the pale blue dot.[238] He also referred to it in the title of his book that was published that same year, *Pale Blue Dot: A Vision of the Human Future in Space*.[239]

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## What is big and blue and eats rocks?

As a child (and still as an adult), my favorite riddle was on the first page of Bennett Cerf's *Book of Riddles*: "What is big and red and eats rocks? The answer: a big red rock eater."[240] Now, influenced by Mr. Cerf, I have created a riddle: "What is big and blue and eats rocks? The answer: a big red rock eater with chrysiasis."

## Approach to selection of blue diseases

The purpose of this contribution is to summarize diseases of the skin, nails, and mucosa that appear blue or a shade of blue. To accomplish this task, I have conscientiously attempted to include all of the conditions that were obtained when the following terms were listed in the medical search engine PubMed: blue and either gingiva, lips, lunula, mucosa, nails, oral, palate, sclera, skin, or tongue. The conditions are organized by color (blue and shades of blue) and within each color by location (skin, nails, oral mucosa, and sclera). Subsequently, some of the conditions that are unique to one or more specific locations are discussed.

## Discussion

Diseases associated with blue (or shades of blue) discoloration are listed in Tables 1 to 8. The conditions are grouped under the following categories: exogenous agents (systemic, tattoo, and topical), syndromes, systemic diseases, and tumors (adnexal, melanocytic, miscellaneous, and vascular). The specific location of the discoloration on the oral mucosa is summarized in Table 9. The numbers in the Tables represent the references cited in the reference section.

## Blue diseases

Blue diseases are listed in Table 1. Methemoglobinemia may have congenital causes; however, it also can be induced by toxic agents such as chloroquine,[136] dapsone,[155] indoxacarb,[185] and nail polish remover.[138] Regardless of the causative agent, a blue cyanotic appearance is typically present not only on the skin (eg, of the finger tips) but also on nails (and nail beds) and oral mucous membranes such as the lips, oral cavity, and tongue.

The administration of systemic chemotherapy can also result in patients who appear blue. Phase I trials of ametantrone acetate, an intensely blue anthracenedione, in patients with various solid organ tumors demonstrated that all individuals who received three or more courses of therapy developed a blue discoloration of their skin; after cessation of therapy, the blue discoloration was slowly reversible.[64,66]

Mitoxantrone, another anthracenedione antineoplastic agent, also caused blue discoloration at the sites of a skin prick test that persisted for nearly 2 weeks in a 44-year-old woman whose multiple sclerosis had been treated with combination therapy (baclofen, piracetam, and mitoxantrone) that resulted in a drug rash with eosinophilia and systemic signs syndrome.[30]

US Federal Food, Drug, and Cosmetic Act blue dye No. 1 has been added to total parenteral nutrition that critically ill patients are receiving either by a nasogastric tube[225,226] or percutaneous gastrojejunal tube[150] to determine if there is aspiration of gastric contents. A 79-year-old woman developed blue nail discoloration of her fingers and toes within 2½ weeks after starting the dye; the dye was discontinued, and the blue nail discoloration slowly moved distally in her nails during the next 4 weeks and finally disappeared before expiring 4 weeks later.[150] A 12-month-old boy developed not only blue skin but also blue serum and urine 1 day after the dye was added to his enteral feedings; he died that day.[225]

Factitial dermatitis can also result in blue skin. A 29-year-old beautician with insulin-dependent diabetes and a psychiatrist-diagnosed dissociative disorder, whose husband had recently died of cancer and was having problems in her relationship with her new partner, presented with a 20- × 8-cm blue patch that had appeared overnight on her left forearm 4 months earlier. Clinically, the clear-blue discoloration had the appearance of an artificial dye. A biopsy showed many dark-colored particles in the dermis and fat, predominantly ingested by histiocytes. The blue discoloration had faded on follow-up examination 1 year later; although denied by the patient, her doctors suspected that she had injected herself with one of the commercially available ink-containing syringes used to refill printer cartridges.[70]

Hydroxychloroquine can also result in blue discoloration of the skin. A 66-year-old woman with systemic lupus erythematosus had been receiving a daily dose of 400 mg of hydroxychloroquine for more than 30 years. During a previous visit to the emergency room, the drug-induced blue discoloration on her chest (Figure 1) had been misinterpreted by her physician as being trauma-induced. This resulted in Adult Protective Services being notified by the hospital and her family being investigated for suspected elder abuse.[78]

## Color variations of blue diseases

The appearance of the disease on skin, nails, or mucous membranes was not always pure blue. Shades of blue include combination with either black, brown, gray, green, purple, red, and silver. Indeed, some conditions more commonly present as a shade of blue, such as the blue-gray[12,115] or blue-brown[113] of erythema dyschromicum perstans or the blue-gray[17,18,32,37,39,58,74,131] of argyria.

### Blue-black

Blue-black diseases are listed in Table 2. Often this discoloration of the skin occurs secondary to either systemic or topical exposure to an exogenous agent. A 47-year-old tanker driver spilled 90% phenol on his left foot and shoe; he continued to drive for another 4½ hours before he contacted emergency medical assistance. There was blue-black discoloration

**Table 1** Blue diseases

| Condition | Skin | Nail | Oral mucosa | Sclera |
|---|---|---|---|---|
| **Exogenous agents** | | | | |
| **Systemic** | | | | |
| Ametantrone acetate | 64,66 | | | |
| Amodiaquine | | 158 | | |
| Antimalarials | | 126 | | |
| Chemotherapy (combination) [a] | | 82,107,108 | | |
| Corticosteroids (long term use) | | | | 207,215,220 |
| Docetaxel | | 22 | | |
| FD&C blue dye No. 1 | 225,226 | 150 | | |
| 5-Fluorouracil | | 160 | | |
| Haloperidol | | | 177 | |
| Hyaluronic acid gel | 25 | | | |
| Hydroxychloroquine | 78 | | | |
| Hydroxyurea | | 83,119,120, 126 | | |
| Imatinib | | | 196 | |
| Methylene blue dye | 24 | | | |
| Metoclopramide [b] | | | 178,206 | |
| Minocycline | 11,213,231 | 11,109,126 | 11,231 | 11,213,207 |
| Mitoxantrone | 30 | | | 219 |
| Oxalic acid | | 157 | | |
| Patent blue dye | 9 | | | |
| Phenolphthalein | | 110 | | |
| Phenothiazines | | 161 | | |
| Quinacrine | | 159 | | |
| Resperidone [c] | | | 177 | |
| Retigabine (ezogabine) | | | 4,130 | |
| Textile dye | 31 | | | |
| Zidovudine | | 112 | | |
| **Tattoo** | | | | |
| Amalgam | | | 88,190,201, 232 | |
| Black and blue dye | | | 191 | |
| Ethnobotanical [d] | | | 187 | |
| India ink | 88 | | | |
| Radiation | 88 | | | |
| Traumatic (road rash) [e] | 6,88 | | | |
| **Topical** | | | | |
| Artificial dye (ink) | 70 | | | |
| Metal cleaners | | 157 | | |
| Paint remover | | 157 | | |
| **Syndromes** | | | | |
| Blue rubber bleb nevus syndrome | 203,204,205 | | 203,205 | |
| Blue toe syndrome | 15,42,133 | | | |
| Bony deformity and verrucae | | 92 | | |
| Caplan syndrome | | | | 222 |
| Carney complex [f] | 227 | | | |
| Ehlers Danlos syndrome - type VII | | | | 40 |
| Hallermann-Strieff syndrome | | | | 207 |
| Hereditary acrolabial telangiectasias | 96 | 96 | 96 | |
| Kabuki syndrome | | | | 207 |
| Laron syndrome | | | | 207 |
| Loeys-Dietz type 1 syndrome | | | | 207 |
| Marshall-Smith syndrome | | | | 207 |
| Normal variant [g] | | 20,105 | | |
| Other blue sclera syndromes [h] | | | | 207 |

**Table 1** (*continued*)

| Condition | Skin | Nail | Oral mucosa | Sclera |
|---|---|---|---|---|
| POEMS syndrome [i] | 35 | | | 211 |
| **Systemic diseases** | | | | |
| Acrocyanosis | 10,19,27 | | | |
| Acrodermatitis chronica atrophicans | 60 | | | |
| Argyria | | 160,134,144 | | |
| Chrysiasis [j] | 54,76 | | | 54 |
| Cyanosis (central or peripheral) | | | 182 | |
| HIV infection | | 156,166 | | 223 |
| Hyperhomocysteinemia [k] | | | | 210 |
| Iron deficiency | | | | 168,209,212 |
| Livido reticularis | 48 | | | |
| Methemoglobinemia | 136, 138,155 | 136,185 | 136,185 | |
| Myasthenia gravis | | | | 221 |
| Necrotizing fasciitis | 69 | | | |
| Ochronosis (alkaptonuria) | 7,16 | | 16 | 7 |
| Osteogenesis imperfecta | | | | 170,208 |
| Pernicious anemia | | 171 | | |
| Physiologic (in newborns) | | | | 215 |
| Postmortem (hypostasis) | | 140 | | |
| Vitamin B12 deficiency | | 122,123 | | |
| Wilson disease [l] | | 103,173,174 | | |
| **Tumors** | | | | |
| **Adnexal** | | | | |
| Eccrine angiomatous hamartoma | 116 | | | |
| Hidrocystoma [m] | 8,80,87,117 | | | |
| Pilomatricoma | 3,46 | | | |
| **Melanocytic** | | | | |
| Blue nevus [n] | 8,50,55,57,65 | 77,142,145, 149 | 1,198,199 | |
| Junctional nevus | | | 1 | |
| Melanoma [o] | 8,88,216 | | 1 | 216 |
| Mongolian spot | 90 | | | |
| Nevus of Ota | 41,65,93,224 | | 41,224 | 41,224 |
| Pigmented Spitz (Reed) nevus | 88 | | | |
| **Miscellaneous** | | | | |
| Adenoid cystic carcinoma (primary cutaneous of the scalp) | 85 | | | |
| Dermatofibroma (hemosiderotic) | 88 | | | |
| Dermatofibrosarcoma protuberans | 114 | | | |
| Glomangioma | 99,102 | 118 | | |
| Glomus tumor (subungual) | | 137,141,162. 167 | | |
| Intravascular lymphoma | 106 | | | |
| Maculae ceruleae | 236 | | | |
| Mucinous carcinoma | 89 | | | |
| Mucocele (oral) | | | 179 | |
| Myxoid cyst (subungual) | | 121 | | |
| Phylloides tumor of breast | 13,91 | | | |
| Seborrheic keratosis [p] | 88 | | | |
| Umbilical endometriosis | 86 | | | |
| **Vascular** | | | | |
| Angiokeratoma | 97,230,234 | | | |
| Angioleiomyoma (of the tongue) | | | 180,181 | |
| Hemangioma | 88 | | 176 | |
| Hematoma | | | 1 | |
| Intravascular papillary endothelial hyperplasia (mouth) | | | 184 | |
| Kaposi sarcoma | 88 | | | |
| Varicosities | | | 1 | |
| Venous aneurysm | 237 | | | |
| Zosteriform venous malformation | 98 | | | |

(*continued on next page*)

**Table 1** (*continued*)

[a] Combination chemotherapy regimens resulting in blue lunula include (1) bleomycin, dactinomycin, and vinblastine[107]; (2) cisplatin, ifosfamide, temozolomide, and vincristine[82]; (3) cyclophosphamide, dacarbazine, doxorubicin, and vincristine[108]; and 5-fluorouracil, cyclophosphamide, and doxorubicin.[108]

[b] The metoclopramide was concurrently being administered with prochlorperazine.

[c] The risperidone was augmented with amisulpride.

[d] An ethnobotanical tattoo was performed on the gingiva using *Datura stramonium* combined with lantern soot.

[e] Road rash includes traumatic implantation of dirt, glass, asphalt, metal, and gravel.

[f] Carney complex includes pigmented lesions of the skin and mucosa, cardiac, cutaneous, and other myxomatous tumors, and multiple endocrine and nonendocrine neoplasms. Other previously described syndromes are probably more appropriately classified as Carney complex; these include: LAMB, for lentigines, atrial myxomas, mucocutaneous myxomas, and blue nevi and NAME, for nevi, atrial myxoma, myxoid neurofibromas, and ephilides.

[g] Blue lunula have been observed as a normal variant.[105] However, pseudoblue lunula were observed in an infant; the nail changes spontaneously resolved.[20]

[h] A review of syndromes associated with blue sclera (with inclusion of malformation of the head and neck) have identified 60 genetic syndromes in which blue sclera may be present. They include: Aarskog, Alazami, alkaptonuria, Alport, atelosteogenesis type 2, auriculoosteodysplasia, Baller-Gerold, brittle cornea type 1 and type 2, chromosome 4 q31,1-q32.1 deletion, chromosome 16 p13.3 duplication, cleidocranial dysplasia, Cole-Carpenter, Cornelia de Lange, Costello, Crouzon, cutis laxa type 1A, type 2B, and type 3A, Dubowitz, dysosteosclerosis, Ehlers-Danlos type 1, focal dermal hypoplasia, Goldenberg-Shprintzen, Grange, Grant, Hallermann-Streiff, hypophosphatasia (childhood), incontinentia pigmenti, insulin-like growth factor 1 resistance, Kabuki, keratoconus, Laron, Loeys-Dietz type 1, Marfan, Marshall-Smith, Marshall-Stickler, Melnick-Needles, mental retardation with *UBE2A* gene deficiency, mevalonic aciduria, nevus depigmentosus, osteogenesis imperfecta type 1, osteoporosis-pseudoglioma, pelvic hypoplasia with lower-limb arthrogryposis, phakomatosis pigmentovascularis, phosphatidylinositol glycan anchor biosynthesis class O protein, primary congenital glaucoma, proteus, pseudoxanthoma elasticum, pyenodysostosis, Roberts, Sanjad-Sakati, Silver-Russell, spondyloepimetaphyseal dysplasia with joint laxity, trisomy 18, Turner, unnamed syndrome #1-#9, and velocardiofacial.[207]

[i] POEMS syndrome is a multisystem disorder characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; the latter include hemangioma, hyperpigmentation, hypertrichosis, nail changes (clubbing and white), sclerodemoid changes, and vascular skin changes (acrocyanosis, hyperemia/erythema, Raynaud phenomenon, or rubor).

[j] Chrysiasis include the idiopathic[54] and Q-switch laser-associated[76] variants.

[k] The patient also had ectopic lentis.

[l] Wilson disease (hepatolenticular degeneration) is associated with a mutation in the *ATP7B* gene; patients may develop blue lunula, hyperpigmentation, palmar erythema, pruritus, telangiectasias, and yellowish skin.

[m] Hydrocystoma are either apocrine[8,87,117] or eccrine[80] and either nonpigmented[8] or pigmented.[80,87,117]

[n] Blue nevus includes common,[8,145] combined,[142] cellular,[8,50] plaque type,[55,57] epithelioid,[199] and malignant cellular[65] variants.

[o] Melanoma includes primary[8,88] and metastatic[216] tumors.

[p] The seborrheic keratosis was located on the hairline of the scalp; the area had previously been treated with hair dye.

of his swollen distal left leg, ankle, and foot. At 4-month follow-up, the blue-black discoloration was still present.[49]

Oral antimicobials[125,147] or antineoplastic agents[139] can result in blue-black discoloration of the nails. Sparfloxacin, typically at a daily dose of 200 mg, resulted in diffuse blue-black discoloration of multiple nails; interestingly, the patients often noticed the nail discoloration approximately 2 weeks after completing 7 to 15 days of antimicrobial therapy.[125,147] The discoloration slowly faded over the next 6 months[125,147]; however, repeat systemic challenge with the drug resulted in recurrence of the nail dyschromia.[125]

A 57-year-old woman with locally advanced lung cancer was being treated with gefitinib 250 mg once daily. After 3 weeks of treatment, blue-black discoloration appeared on not only the distal nail plates of her thumbs, but also on all of her fingernails. There was no associated nail dystrophy, and the discoloration could not be removed with solvents, such as alcohol.[139]

### Blue-brown

Blue-brown diseases are listed in Table 3. Erythema dyschromicum perstans (originally described as dermatosis cenicienta) presents as oval or circular blue-brown[113] to blue-gray[115] to gray macules and patches. They are typically symmetrically located on the back, upper portion of the chest, abdomen, extremities, neck, and face. It may be more common in individuals from Central America or of Latin American descent. In addition to ultraviolet light, numerous systemic and topical therapies have been used for treatment—with variable and often unsuccessful results.

A 15-year-old Brazilian girl presented with a pruritic and slowly enlarging pigmented lesion of 1-year duration on her left arm: an 8-mm blue-brown macule, with black-brown dots on the periphery. Melanoma was suspected, and an excisional biopsy was performed. The pathology showed a common blue nevus with satellitosis.[72]

### Blue-gray

Blue-gray diseases are listed in Table 4. Argyria results from cutaneous or mucosal exposure to silver substrate or silver salt. Systemic exposure to silver can occur by ingestion[17,18,32,131] or topical application to either wounds (in the form of wound dressings),[37] the nasal mucosa (in the form of nose drops),[39] or the tongue.[58] A diffuse blue-gray[17,18,32,37,39,58,74,131] or blue-black[37,74] or blue-green[43] discoloration of the skin occurs; although this typically affects sun-exposed areas, it can also occur on covered sites. In addition, this discoloration can occur on the nails,[18,32,131] oral mucosa,[32,39,58] and sclera.[32,58] A localized cutaneous presentation of argyria may occur on the ears, where silver earrings have pierced the skin; the dyschromia may appear blue-gray or blue-black (Figure 2).[43,74]

Parenteral gold had been used for the treatment of systemic conditions such as tuberculosis, systemic lupus erythematosus,

**Table 2** Blue-black diseases

| Condition | Skin | Nail | Oral mucosa | Sclera |
|---|---|---|---|---|
| **Exogenous agents** | | | | |
| **Systemic** | | | | |
| Antimalarials | 154 | | | |
| Chlorpromazine | | | 1 | |
| Clofazimine | | | 1 | |
| Gefitinib | | 139 | | |
| Heavy metals [a] | | | 1 | |
| Imatinib | | 124 | 124 | |
| Ketoconazole | | | 1 | |
| Minocycline | 12 | | 1 | |
| Oral contraceptives | | | 1 | |
| Quinadine | | | 1 | |
| Spanfloxacin | | 125,147 | | |
| Tetracycline | | | 1 | |
| Zidovudine | | 128 | 1 | |
| **Topical** | | | | |
| Phenol | 49 | | | |
| **Syndromes** | | | | |
| Peutz-Jeghers syndrome | 104 | | 104 | |
| **Systemic diseases** | | | | |
| Argyria [b] | 37,74 | | | |
| Flash pump dye laser (post treatment) | 52,56 | | | |
| Ochronosis (alkaptonuria) | 7,59 | 7 | | 59 |
| Selenium deficiency [c] | | 135 | | |
| Systemic lupus erythematosus [d] | | 169 | | |
| Vitamin $B_{12}$ deficiency | | 122 | | |
| **Tumors** | | | | |
| **Melanocytic** | | | | |
| Blue nevus [e] | 101 | 101,143,145, 148,164 | | |
| Melanocytic neuroectodermal tumor of infancy | | | 194,195 | |
| Melanoma [f] | 73 | | | |
| Melanotic macule | | | 183 | |
| Nevus of Ota | 214 | | | 214 |
| **Vascular** | | | | |
| Intravascular papillary endothelial hyperplasia | 81 | | | |

[a] The heavy metals include arsenic, bismuth, gold, lead, mercury and silver.
[b] Argyria resulted from either topical[37] or localized cutaneous[74] exposure to silver.
[c] Low selenium levels were observed in patients with HIV infection or AIDS.
[d] Blue-black nails were observed in black patients with systemic lupus erythematosus.
[e] Blue nevus includes cellular[101] variants.
[f] Melanoma includes a primary acral tumors.

**Table 3** Blue-brown diseases

| Condition | Skin | Nail | Oral mucosa | Sclera |
|---|---|---|---|---|
| **Exogenous agents** | | | | |
| **Systemic** | | | | |
| Imatinib | | | 124 | |
| **Systemic diseases** | | | | |
| Erythema dyschromicum perstans | 113 | | | |
| **Tumors** | | | | |
| **Melanocytic** | | | | |
| Blue nevus [a] | 72 | | | |
| **Miscellaneous** | | | | |
| Glomus tumor (subungual) | | 143 | | |

[a] Blue nevus includes the common variant with satellitosis.

**Table 4** Blue-gray diseases

| Condition | Skin | Nail | Oral mucosa | Sclera |
|---|---|---|---|---|
| **Exogenous agents** | | | | |
| **Systemic** | | | | |
| Amiodarone | 12,18,23,28, 33,38,132 | | 38 | |
| Antimalarials | | | 1 | |
| Chlorpromazine | 5 | | 1 | 5 [a] |
| Clofazamine | | | 1 | |
| Desipramine | 152 | | | |
| Imatinib | 124,196 | 124 | 124,196 | |
| Imipramine | 29,151 | | | |
| Ketoconazole | | | 1 | |
| Minocycline | 12,132,163, 165,228 | 165 | 1,163,165 | 1,132,163,165 |
| Oral contraceptives | | | 1 | |
| Quinacrine | 153 | 153 | 153 | |
| Quinadine | | | 1 | |
| Retigabine (ezogabine) | 4,132 | 4,132 | 4,132 | 4,132 [b] |
| Tetracycline | | | 1 | |
| Vandetanib | 127 | | | |
| Zidovudine | | | 1 | |
| **Tattoo** | | | | |
| Amalgam | | | 1,186,192 | |
| Ethnobotanical [c] | | | 188 | |
| Exogenous pigmentation | | | 194 | |
| **Syndromes** | | | | |
| Ehlers-Danlos syndrome - type VIIC | | | | 40 |
| **Systemic diseases** | | | | |
| Argyria [d] | 17,18,32,37, 39,74,131, 229,233 | 18,32,131 | 32,39,58 | 32,58 |
| Chrysiasis [e] | 54,67,53 | | 54 | 54 |
| Erythema dyschromicus perstans | 115 | | | |
| Necrotizing fasciitis | 51 | | | |
| Ochronosis (alkaptonuria) | 7 | 16 | | 7 |
| Osteogenesis imperfecta | | | | 217 |
| **Tumors** | | | | |
| **Melanocytic** | | | | |
| Blue nevus [f] | 62 | 34,142 | | |
| Dermal melanosis [g] | 21,68,189 | | 189 | 189 |
| Diffuse melanosis cutis [h] | 2,14,47,61 | | 14 | |
| Melanoma [i] | 12 | | | |
| Mongolian spot | 95 | | | |
| Nevus of Ota | 93,218 | | | 218 |
| **Miscellaneous** | | | | |
| Chloroma (granulocytic sarcoma) | 235 | | | |
| Condyloma accuminata | 71 | | | |
| Maculae ceruleae | 236 | | | |
| **Vascular** | | | | |
| Hemangioma | | | 200 | |

[a] The pigmentation was on the cornea and lens.

[b] There is black pigment deposits on the palpebral conjunctiva, lower fornices, and sclera.

[c] An ethnobotanical tattooing was performed on the gingiva using seeds and herbs that were burned and mixed with soot from a lamp. This was applied to the gingiva; then, the gingiva was pierced with thorns to make it bleed.

[d] Argyria resulted from either systemic[17,18,32,39,58,131,233] or topical[37,74] exposure to silver. Pigment was noted on the conjunctiva[32] and sclera.[58]

[e] Chrysiasis include the idiopathic[54,67] and Q-switch laser-associated[53] variants.

[f] Blue nevus includes cellular[62] variants.

[g] This includes dermal hypermelanosis[21] and acquired generalized dermal melanosis.[68,189]

[h] The diffuse melanosis cutis was observed in patients with metastatic melanoma.

[i] Melanoma includes metastatic tumors.

**Table 5** Blue-green diseases

| Condition | Skin | Nail | Oral mucosa | Sclera |
|---|---|---|---|---|
| **Exogenous agents** | | | | |
| **Systemic** | | | | |
| Copper [a] | 36 | 36 | | |
| FD&C blue dye No. 1 | 45 | | | |
| **Systemic diseases** | | | | |
| Argyria [b] | 43 | | | |
| Chrysiasis [c] | 54 | | | |

FD&C, US Federal Food, Drug, and Cosmetic Act.

[a] Exogenous copper can cause blue-green discoloration of hair, skin, and nails. A man developed blue-green discoloration of multiple seborrheic keratoses on his chest and back after swimming in a pool; the level of copper in the water of the swimming pool was more than double the recommended maximum set forth by the US Environmental Protection Agency. The discoloration of the seborrheic keratoses rapidly disappeared after he discontinued swimming in the pool.

[b] Argyria resulted from localized cutaneous exposure to silver.

[c] Chrysiasis include the idiopathic variant.

rheumatoid arthritis, and psoriasis or psoriatic arthritis. Chrysiasis is a blue-gray[53,54,67] or blue[54,76] discoloration of skin in patients who had received intravenous gold salts[54,67]; it usually affected sun-exposed areas. Rarely, the buccal mucosa or sclera were affected[54]; however, a localized cutaneous form of chrysiasis has also been described in patients who had previously received either intramuscular[53,76] or oral[76] gold and were subsequently treated with a Q-switched laser; the sites of treatment would develop discoloration (Figure 3).

### Blue-green

Blue-green diseases are listed in Table 5. An 11-year-old girl with cerebral palsy was hospitalized for pneumonia and dehydration; she was treated with intravenous antibiotics and fluids. The evening of hospital day 3, she started enteral nutrition (which contained the coloring agent US Federal Food, Drug, and Cosmetic Act blue No. 1 dye) via a feeding tube; the following morning she appeared cyanotic—her hands, face, and feet had a blue-green tone. In addition, her urine, stool, and serum were the same blue-green color. A new bag of enteral nutrition—without the blue food coloring—was started; within 24 hours, her skin color had almost returned to baseline.[45]

A man developed blue-green discoloration of the seborrheic keratoses on his chest and back after swimming in a pool for rehabilitation of a back injury. The discoloration of his "cupric keratosis" rapidly disappeared after he stopped his water exercises in the swimming pool. Evaluation of the water from the swimming pool demonstrated a copper level that was more than double the recommended maximum set forth by the US Environmental Protection Agency.[36]

### Blue-purple

Blue-purple diseases are listed in Table 6. Hemoglobin M disease is a congenital disorder. In addition to a brown hemoglobin M band on electrophoresis, patients with this disease

**Table 6** Blue-purple diseases

| Condition | Skin | Nail | Oral mucosa | Sclera |
|---|---|---|---|---|
| **Exogenous agents** | | | | |
| **Systemic** | | | | |
| Retigabine (ezogabine) | 130 | 130 | 130 | 130 [a] |
| **Syndromes** | | | | |
| Blue toe syndrome | 15 | | | |
| **Systemic diseases** | | | | |
| Acrodermatitis chronica atrophicans | 60 | | | |
| Asphyxia (traumatic) | 44 | | | |
| Hemoglobin M disease | 94 | 94 | 94 | |
| Lead poisoning [b] | | | 193 | |
| Ovarian cancer [c] | | | 175 | |
| Thrombocytosis [c] | | | 175 | |
| **Tumors** | | | | |
| **Adnexal** | | | | |
| Eccrine angiomatous hamartoma | 111 | | | |
| **Miscellaneous** | | | | |
| Glomus tumor (subungual) | | 129 | | |
| **Vascular** | | | | |
| Kaposi sarcoma | | | 197 | |
| Thrombus | | | 1 | |

[a] Pigmentation was noted on the retina.

[b] The blue-purplish line on the gums seen in lead poisoning is referred to as Burton line.

[c] In an evaluation of 82 Chinese women with epithelial ovarian cancer, a bluish-purple tongue was not only associated with increased platelet counts but also closely correlated with the recurrence of epithelial ovarian cancer.

**Table 7** Blue-red diseases

| Condition | Skin | Nail | Oral mucosa | Sclera |
|---|---|---|---|---|
| **Systemic diseases** | | | | |
| Majocchi granuloma[a] | 146 | | | |
| Postmortem (hypostasis) | | 140 | | |
| SELSTOC[b] | 26 | | | |
| **Tumors** | | | | |
| **Melanocytic** | | | | |
| Melanocytic matricoma[c] | 75 | | | |
| **Miscellaneous** | | | | |
| Merkel cell carcinoma | 84 | | | |
| Mucoepidermal carcinoma | | | 202 | |
| **Vascular** | | | | |
| Angioleiomyoma | | | 181 | |
| Angiosarcoma (breast) | 63 | | | |
| Kaposi sarcoma | 79,88 | | | |

SELSTOC, self-limiting sternal tumors of childhood.

[a] The fungal culture grew *Trichophyton rubrum*.

[b] A sternal tumor presented as a rapidly growing mass in 14 children (median age = 16 mo; range = 7-50 mo). In six of the children, the overlying skin had a blue-red appearance. Microbiology cultures were negative in all of the children and the tumor decreased in size within 1 mo (in both patients with or without antibiotics) and disappeared within 6 mo.

[c] The discoloration was pink to blue.

**Table 8** Blue-silver diseases

| Condition | Skin | Nail | Oral mucosa | Sclera |
|---|---|---|---|---|
| **Systemic diseases** | | | | |
| Argyria | | 172 | | |

have cyanosis with an absence of clubbing and blue-lavender discoloration of their skin and mucosal membranes.[94]

Blue toe syndrome presents as blue or purple toes; in addition, the digits can be cold, numb, or painful, and there may be superficial necrosis of the skin or even gangrene.[15,42,133] It occurs secondary to acute ischemia of the toe and is often a result of cholesterol emboli[42]; however, it has rarely been due to extrinsic compression by the extensor hallucis brevis tendon, resulting in significant stenosis of the dorsalis pedis artery.[15]

Eccrine angiomatous hamartoma is a rare condition that often occurs on the lower extremity and is present at birth. Lesional hyperhidrosis and pain may also be present. The benign tumor can present as a blue-purple[111] or flesh-colored nodule with blue papules.[116] Microscopic examination shows increased numbers of eccrine structures and numerous capillary channels. Excision alleviates painful tumors; however, asymptomatic lesions do not require aggressive treatment.[111,116]

### Blue-red

Blue-red diseases are listed in Table 7. Several cutaneous tumors may present as red nodules: angiosarcoma,[63] Kaposi sarcoma,[79,88] Merkel cell carcinoma,[84] and metastatic matricoma.[75] In addition, benign (angioleiomyoma) and malignant (mucoepidermoid carcinoma) tumors can present a red lesion of the oral mucosa: angioleiomyoma on the lips, palate, and tongue[181] or mucoepidermoid carcinoma on the palate.[202]

Self-limiting sternal tumors of childhood is characterized by a sternal tumor occurring in young children (7-50 months of age) that has no infectious or neoplastic origin. The pathology is nonspecific, and the lesions spontaneous regress (with or without antibiotic therapy) within 6 months. The skin overlying the sternal mass had a blue-red appearance in six of the 14 children with self-limiting sternal tumors of childhood.[26]

*Trichophyton rubrum*–associated Majocchi granuloma presented as painful blue-red papules and nodules of 1-month duration on the dorsal feet and toes (with dystrophic toenails) of a 68-year-old man who was receiving daily tacrolimus, mycophenolate mofetil, and prednisone after kidney transplant 6 months ago. Biopsy showed periodic acid–Schiff positive hyphae and spores within dermal abscess; culture grew *Trichophyton rubrum.* The lesions and his dystrophic toenails resolved after oral terbinafine and topical ciclopirox.[146]

### Blue-silver

Blue-silver diseases are listed in Table 8. A man developed blue-silver discoloration of all fingernails; the dyschromia was more prominent over the lunula. In addition, his cheeks and sclerae had a barely perceptible grayish discoloration. His argyria was secondary to uncontrolled ingestion of a silver-containing granular powder.[172]

## Location of blue diseases

Blue disease can be restricted to either the skin, the nails, or the mucosa of the mouth or the eyes (sclera); however, often more than one site is affected.

### Skin

Isolated blue (or shades of blue) conditions of the skin occur. A 66-year-old heterosexual man (with two partners during the prior 6 months) developed an asymptomatic, 8- × 10-mm, blue-gray plaque (arising within an erythematous background plaque) on his glans penis of 6 months' duration. A biopsy showed a condyloma accuminata; polymerase chain reaction of the specimen was positive for human papillomavirus type 6.[71]

Ochronosis presents with blue[7,16] blue-black[7,59] or blue-gray[7,16] discoloration of the skin; sites of involvement typically include sun-exposed areas, regions with a high density of sweat glands, and cartilaginous structures (such as those of the external ear). In addition, ochronosis can affect the nails,[7,16] the gingiva,[16] and the sclera.[7,59] The condition is inherited in an autosomal recessive manner and results from a deficiency of homogentisic acid oxygenase. Alkaptonuria refers to the systemic manifestations of this condition and can affect the skeletal, cardiovascular, genitourinary, and respiratory systems, in addition to the condition's ocular and cutaneous involvement.[7,16,59]

**Table 9** Oral mucosa location of blue (and shades of blue) diseases

| Condition | Buccal | Gingiva | Lips | Palate | Tongue | NOS |
|---|---|---|---|---|---|---|
| **Exogenous agents** | | | | | | |
| **Systemic** | | | | | | |
| Amiodarone | | | 38 | | | |
| Antimalarials | | | | 1 | | |
| Chlorpromazine | | | | 1 | | |
| Clofazamine | | | | 1 | | |
| Desipramine | | | | | | |
| Haloperidol | | | | | 177 | |
| Heavy metal | | 1 | | | | 1 |
| Imatinib | | 196 | | 124,196 | | |
| Ketoconazole | | | | 1 | | |
| Metoclopramide [a] | | | | | 177,178,206 | |
| Minocycline | 11,163 | 11,163 | 163 | 1,165 | 1,163,231 | 11 |
| Oral contraceptives | | | | 1 | | |
| Quinacrine | | | | 153 | | |
| Quinidine | | | | 1 | | |
| Resperidone [b] | | | | | 177,206 | |
| Retigabine (ezogabine) | | 130 | 4,130, 132 | 4,130 | | |
| Tetracycline | | | | 1 | | |
| Zidovudine | | | | 1 | | |
| **Tattoo** | | | | | | |
| Amalgam [c] | 1,88,190,192,201 | 1,88,186, 190,192,201 | | 201 | 88,201 | |
| Black and blue dye | | 191 | | | | |
| Ethnobotanical [d] | | 187,188 | | | | |
| Exogenous pigmentation | | | | 194 | | |
| **Syndromes** | | | | | | |
| Blue rubber bleb nevus syndrome [e] | | | 205 | | 203,205 | |
| Hereditary acrolabial telangiectasias | | | 96 | | | |
| Peutz-Jeghers syndrome | 104 | 104 | 104 | 104 | | |
| **Systemic diseases** | | | | | | |
| Acrocyanosis | | | 10 | | | |
| Argyria [f] | | 32 | | | 32,58 | 32,58 |
| Chrysiasis [g] | 54 | | | | | |
| Cyanosis (central or peripheral) | | | | | 182 | |
| Hemoglobin M disease | | | | | | 94 |
| Lead poisoning | | 193 | | | | |
| Methemoglobinemia | 136 | | 136,155 | | 136 | 136 |
| Ochronosis (alkaptonuria) | | 16 | | | | |
| Thrombocytosis | | | | | 175 | |
| **Tumors** | | | | | | |
| **Melanocytic** | | | | | | |
| Blue nevus | 1 | | | 1,198, 199 | | 1 |
| Dermal melanocytosis | | 189 | 189 | | | |
| Diffuse melanosis cutis | | | | | | 1 |
| Junctional nevus [h] | 1 | | 1 | 1 | | 1 |
| Melanoma | 1 | | | 1 | | |
| Melanocytic macules | | | | | 183 | |
| Melanocytic neuroectodermal tumor of infancy | | | | | | 194, 195 |
| Nevus of Ota | | | | 41,224 | | |
| **Miscellaneous** | | | | | | |
| Mucoepidermoid carcinoma | | | | 202 | | |
| Mucocele (oral) | 179 | 179 | 179 | 179 | 179 | 179 |
| Ovarian cancer | | | | | 175 | |
| **Vascular** | | | | | | |
| Angioleiomyoma | | | 181 | 181 | 180,181 | |

(*continued on next page*)

**Table 9** (*continued*)

| Condition | Buccal | Gingiva | Lips | Palate | Tongue | NOS |
|---|---|---|---|---|---|---|
| Hemangioma | | | | 200 | 176 | |
| Hematoma | | | | | | 1 |
| Intravascular papillary endothelial hyperplasia | 184 | 184 | 184 | | 184 | |
| Kaposi sarcoma | | | | 197 | | |
| Thrombus | 1 | | 1 | | | |
| Varicosities | | | | | 1 | |

NOS, not otherwise specified.

[a] The metoclopramide was concurrently being administered with prochlorperazine.

[b] The risperidone was augmented with amisulpride.

[c] Pigment can also be present on the floor of the mouth.

[d] An ethnobotanical tattoo was performed on the gingiva using either *Datura stramonium* combined with lantern soot or burned seeds and herbs that were mixed with soot from a lamp.

[e] Lesion can also be present on the mucosa of the gastrointestinal tract.

[f] A 58-year-old woman had ingested 1 L of colloidal silver solution daily for approximately 16 mo as a traditional remedy; in addition to blue-gray discoloration of the skin (most prominent in sun-exposed areas such as her face and hands) she also had discoloration of her oral mucosa, gums, eye conjunctiva, ears, nail beds, and trunk.[32] A 33-year-old woman had a 10-y history of oral ulcers; 6 y before presentation, she had repeatedly painted her tongue with silver nitrate. Five years before presentation, she developed generalized slate gray discoloration of her skin (that was most pronounced on her face and neck); on examination, she also had blue-gray discoloration of her oral mucosa, tongue, sclera, and conjunctiva.[58]

[g] Chrysiasis includes the idiopathic variant.

[h] In addition to junctional nevi being present on the palate, intramucosal compound nevi can be present on the buccal mucosa and lips.

## Nails

Blue lunula have occasionally been observed in otherwise healthy black people and mestizos.[105] In addition, the fingernails of dead persons appear dark red to blue. The presence of deoxyhemoglobin accounts for the blue to bluish-red color of the typical postmortem hypostasis changes observed in the fingernails.[140]

Blue nail color changes were observed in a healthy 12-hour-old newborn; the child had no signs of cyanosis, and Apgar scores were 9 and 10 after delivery. The nail changes (blue color extending from the proximal nail bed to the midnail bed region) were still present at discharge from the hospital on day 7. Subsequently, the "pseudoblue lunula" spontaneously cleared by age 2 weeks.[20]

Blue lunula can be associated with individual medication, such as minocycline,[11,109,126] phenolphthalein,[110] and zidovudine.[112] It has also been associated with individual antineoplastic agents such as docetaxel[22] or hydroxyurea.[83,119,120,126] In addition, combination chemotherapy can result in blue lunula (Figure 4).[82,107,108]

Nutritional deficiency can be associated with blue fingernails. Specifically, bluish or blue-black pigmentation of the nails can be observed in patients with vitamin $B_{12}$ deficiency.[122,123] Also, blue toenails or fingernails were observed in two black men with pernicious anemia; their nails returned to their normal color after treatment with oral folic acid or cyanocobalamin injections.[171]

Wilson disease (also known as hepatolenticular degeneration) is an autosomal recessive disorder of copper metabolism. A mutation in the *ATP7B* gene (Wilson disease protein, located on chromosome 13), results not only in ceruloplasmin that does not link to copper and is therefore secreted in a form that lacks copper but also copper accumulation in the liver (and the brain and other organs). In addition to blue (azure) lunula, dermatologic manifestations of Wilson disease may include changes associated with cirrhosis (such as palmar erythema and telangiectasias), hyperpigmentation (or the lower extremities), pruritus, and yellowish skin.[103,173,174]

Subungual glomus tumors typically present with a triad of clinical manifestations: severe pain, point tenderness, and cold sensitivity; the tumor may appear as a subungual nodule beneath an intact nail, or there can be a deformity of the nail plate There is frequently a blue discoloration of the nail on the affected digit[137,141,162,167]; however, less commonly, the nails are either blue-purple[129] or blue-brown.[143]

## Oral mucosa

The oral mucosa includes the buccal mucosa, the gingiva, the lips, the palate, and the tongue. Blue disease and conditions presenting in shades of blue can affect only one site of multiple areas.

## Buccal

Minocycline can result in blue (or shades of blue) discoloration of the skin, nails, oral mucosa, and sclera.[1,11,12,109,126,132,163,165,207,213] Several types of minocycline hyperpigmentation have been described; these include blue-black hyperpigmentation of prior scars (such as on the face), blue-gray hyperpigmentation on normal skin (such as the forearms and legs), and brown discoloration in sun-exposed areas.[12,213] In addition to the buccal mucosa[11,163] other sites of the oral mucosa can also be affected.[11,163,165]

Tumors, such as mucoceles and intravascular papillary endothelial hyperplasia, can also develop blue discoloration of the buccal mucosa.[179,184] Oral mucoceles are most common on the lower lip; however, less frequently, they present as firm or soft, colored (most frequently either blue, purple, or gray) lesions on other areas of the mouth.[179] Although the lower lip, followed by the tongue, and the upper lip are the most


**Fig. 1** Blue dyschromia associated with hydroxychloroquine. Distant frame *A* and closer frame *B* view of the hydroxychloroquine-associated blue discoloration on the upper right chest of a 66-year-old woman. She had systemic lupus erythematosus and had been receiving hydroxychloroquine for more than 30 years. The blue dyschromia (and drug-induced black hyperpigmentation on her forehead, face, neck, and upper central chest) had previously been misinterpreted to be secondary to trauma. The family was investigated by Adult Protective Services for elder abuse; the family was subsequently cleared of all suspicion of elder abuse. She is currently receiving plasmapheresis, via the infusion port on her left chest, for myasthenia gravis. (Published with permission from Cohen PR. Hydroxychloroquine-associated hyperpigmentation mimicking elder abuse. Dermatol Ther (Heidelb). 2013;3:203-210.)

commons sites of intravascular papillary endothelial hyperplasia of the mouth, the lesions may also present on the buccal mucosa and mandibular vestibule as bluish to reddish nodules.[184]

## Gingiva

Tattooing of exogenous agents can result in blue[187,193] or blue-gray[188] pigmentation of the gingiva. A 28-year-old Ethiopian woman was incidentally noted to have dark blue to gray coloration of her gingiva and interdental papilla; when she was 12-years-old, she had been taken by her mother to a neighbor's home to have a mixture of blue and black dye rubbed onto the gingiva followed by tattooing with numerous needle sticks.[191] Similarly, women from Ethiopia,[187] and from other African and Middle Eastern nations,[188] have had ethnobotanical tattooing of their gingiva using either *Datura stramonium* combined with lantern soot[187] or burned seeds and herbs that were mixed with soot from a lamp.[188]

Burton line refers to the blue-purplish line on the gums in persons with lead poisoning. Henry Burton (1749-1849) described this clinical sign in 1840 while studying the effects of "medicinal" lead in patients being treated for pulmonary and other disorders. He noted that the edges of the gums attached to the teeth were bordered by a narrow leaden-blue line, whereas the remainder of the gum retained its normal color.[193]

## Lips

Acrocyanosis is an uncommon condition; it refers to the blue or cyanotic discoloration of skin over the extremities due to decreased oxyhemoglobin. In addition to bluish discoloration of the fingers and toes (occasionally including the entire hands and feet and even the forearms), other peripheral parts of the body (such as the ears, nose, lips, and nipples) can also be affected. Marked clamminess and hyperhidrosis of the hands and feet occur in almost all patients. Acrocyanosis can be either primary (as a disease of young people diagnosed in their adolescence—between the ages of 10 and 30—and resolved in most individuals before reaching middle age with almost no patients with primary acrocyanosis after menopause) or secondary (to other causes such as autoimmune, infective,


**Fig. 2** Localized cutaneous argyria. There is blue-gray discoloration surrounding the sites of ear piercings on the anterior surface of the left earlobe of a 68-year-old woman; microscopic examination of a skin biopsy demonstrated yellowish-brown colored granular material adjacent to the elastic fibers in the dermis in frame *A*. The anterior frame *B* and posterior frame *C* views of the left ear show blue-black discoloration (arrows) at the site of piercing. (Published with permission from Beutler BD, Lee RA, Cohen PR. Localized cutaneous argyria: report of two patients and literature review. Dermatol Online J. 2016;22(11). pii: 13030/qt4wm1j7pt.)

metabolic, neurologic, and psychiatric); indeed, secondary acrocyanosis has been associated with not only involuntary starvation and anorexia nervosa but also up to nearly a quarter of cancer patients.[10,19,27]

Hereditary acrolabial telangiectasias is an unusual familial syndrome of suspected autosomal dominant inheritance, characterized by migraine headaches, varicosities of the distal part of the legs, telangiectasias (punctate and linear) of the chest, elbows, and dorsal surface of the hands, and diffuse blue discoloration of the lips, nipple areola, and nail (lunula and nail beds). A mother and her two daughters were described; the blueness of the lips and nail beds was noted in one daughter by age 3 months and in the mother and second daughter within the first year of life. The blue discoloration was intensified by emotional excitement, exercise, and exposure to cold temperatures.[96]

Peutz-Jeghers syndrome (also known as periorificial lentiginosis) is an autosomal dominant inherited condition associated with a mutation of the *STK11* gene. It is characterized by gastrointestinal hamartomas (such as polyps) and mucocutaneous hyperpigmentation (such as pigmented macules of not only the oral mucosa, but also the perianal and genital regions. The pigmented lesions on the skin and lips may fade after puberty; however, the blue-black oral lesions (on the buccal mucosa, gingiva and palate) are usually permanent.[104]

### Palate

An amalgam tattoo may occur secondary to the traumatic implantation of dental amalgam (which can consist of a mixture of copper, mercury, silver, tin, and zinc) into the soft tissue of the mouth.[88,186,190] Amalgam tattoos can present as a blue[88,190,201] or blue-gray[1,186,192] discoloration of the oral mucosa. In addition to the palate,[201] amalgam tattoos can appear on the buccal mucosa,[1,88,190,192,201] gingiva,[1,88,186,190,192,201] and tongue.[88,201]

Imatinib is a tyrosine-kinase inhibitor; it targets not only BCR-ABL protein but also c-Kit and platelet-derived growth

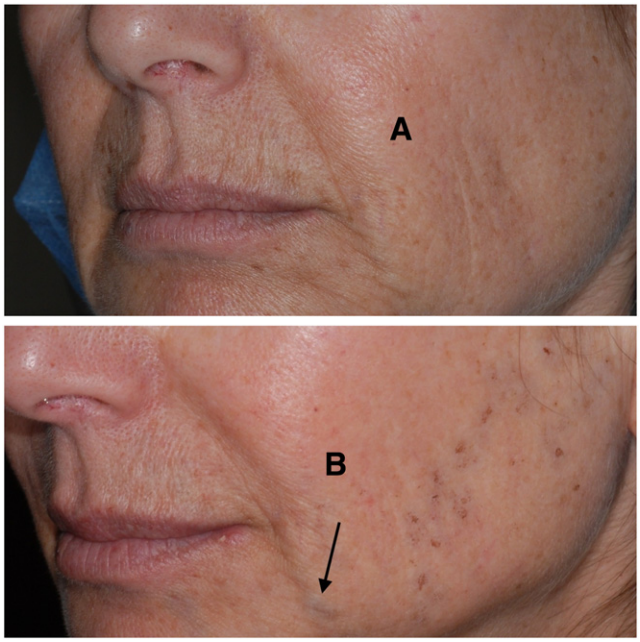


**Fig. 3** Q-switched alexandrite laser-induced chrysiasis. Before laser treatment, multiple brown macules can be seen on the left side of the face of a 60-year-old Caucasian woman in frame *A*. During the treatment session, several of the macules were treated with a 532-nm long-pulsed potassium-titanyl-phosphate laser; as expected, there was darkening of the pigmented lesions and mild perilesional erythema in frame *B*. However, when some of the low-contrast lighter lentigines were treated with a 755-nm Q-switched alexandrite laser, blue patches (arrow) surrounding the smaller lentigines appeared in frame *B*. Additional history revealed that her rheumatoid arthritis had been treated with intramuscular gold (sodium aurothioglucose) for several years; however, it had been more than 26 years since her last gold treatment. (Published with permission from Cohen PR, Ross EV. Q-switched alexandrite laser-induced chrysiasis. J Clin Aesthet Dermatol. 2015;8(9):48-53.)

factor.[124,196] Imatinib therapy can result in blue,[196] blue-black,[124] blue-brown,[124] or blue-gray[124] discoloration of the palate[124,196] or gingiva[196] in patients being treated for chronic myelogenous leukemia, gastrointestinal stromal tumor, and pelvic fibromatosis.[124,196] In addition, some of patients may develop blue-gray discoloration of the skin[124,196] and the nails.[124]

## Tongue

The blue-tongue sign refers to the "strikingly blue" tongue observed in patients who have been treated with selective $D_2$ dopamine antagonists; however, it was initially noted in a patient who was receiving large doses of haloperidol (a butyrophenone agent).[178]

Subsequently, the same author and a colleague observed the blue-tongue sign in a 19-year-old healthy woman who had been treated with 12.5 mg of intramuscular prochlorperazine (a phenothiazine dopamine-receptor antagonist) followed in 12 hours by 30 mg—in divided doses—of intramuscular metoclopramide (a selective $D_2$ dopamine antagonist) for

**Fig. 4** Combination chemotherapy-associated blue lunula. A 16-year-old Saudi Arabian girl with spinal medulloepithelioma developed blue lunula on her thumb nails after receiving combination chemotherapy consisting of cisplatin, ifosamide, temozolomide, and vincristine. Beau lines (appearing as horizontal ridges caused by chemotherapy) and diffuse brown hyperpigmentation are also present. (Published with permission from Casamiquela KM, Cohen PR. Chemotherapy-associated tongue hyperpigmentation and blue lunula. J Drugs Dermatol. 2013;12:2230226.)

nausea and headache. Twenty-four hours after the first injection, she presented with a 12-hour history of progressive swelling of the tongue and partial upper airway obstruction; examination also revealed her tongue to be blue. Within 15 minutes after she received 2 mg of benztropine, her tongue size and respiratory distress disappeared; in addition, her tongue resumed its normal color.[178]

The blue-tongue sign was also observed in a 23-year-old man with schizophrenia who initially received 6 mg (that was increased to 8 mg) daily of risperidone (a selective $D_2$ dopamine antagonist). After 6 weeks of treatment, amisulpride (a dopamine $D_2$- and $D_3$-receptor antagonist) was added (initially at 200 mg daily which was increased to 600 mg daily after 1 week). He developed an abnormal tongue pigmentation at 3 weeks of discharge; his tongue spontaneously resumed it normal color without discontinuation of his antipsychotic medications or replacement with other neuroleptics.[177]

Central cyanosis typically is accompanied by arterial desaturation, clubbing, and a blue tongue; however, rarely, patients with peripheral cyanosis—which usually presents with blue discoloration in cool areas such as the nose, earlobes, cheeks, and nail beds—may also have a blue tongue. A cachectic 53-year-old woman with mild proptosis and progressive right-sided heart failure secondary to severe rheumatic tricuspid regurgitation, presented with normal oxygen saturation accompanied by a purple nose and cheeks, cyanotic lips and a blue tongue. Although her blue tongue suggested central cyanosis, she had typical signs of peripheral cyanosis; her physicians postulated that her increased right atrial pressure resulted in highly congested and dilated lingual veins that caused her tongue to appear blue.[182]

A bluish-purple tongue was not only associated with increased platelet counts but also closely correlated with the recurrence of epithelial ovarian cancer. Investigators evaluated

82 women with epithelial ovarian cancer. An increased platelet count significantly correlated with a bluish-purple tongue; in addition, both increased platelet count and the bluish-purple tongue were associated with recurrence of the epithelial ovarian cancer.[175]

### Sclera

Blue sclera was noted in 60 genetic syndromes, seven disorders, and three pharmacologically induced pigmentations in a comprehensive review by Brooks.[207] The six genetic syndromes with frequent expression of blue sclera are Hallermann-Streiff syndrome, Kabuki syndrome, Laron syndrome, Loeys-Dietz type 1 syndrome, Marshall-Smith syndrome, and osteogenesis imperfecta. The nongenetic etiologies reported with blue sclera include Caplan syndrome,[222] HIV infection,[223] hyperhomocysteinemia,[210] iron deficiency anemia,[168,209,212] myasthenia gravis,[221] nevus of Ota,[41,224] and POEMS (for polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) syndrome.[211] Medication-associated blue sclera have been observed in patients who received minocycline,[11,213] mitoxantrone,[219] and prednisone.[215,220]

Sclera have also been observed that have shades of blue: either blue-black or blue-gray. Syndromes and systemic conditions include argyria (blue-gray),[32,58] chrysiasis (blue-gray),[54] Ehlers-Danlos syndrome type VIIC (blue-gray),[40] ochronosis (blue-black[59] and blue-gray[7]), and osteogenesis imperfecta (blue-gray).[217] Pigmented lesions include acquired and generalized dermal melanosis (blue-gray)[189] and nevus of Ota (blue-black).[214] The medications include minocycline (blue-gray)[1,132,163,165] and retigabine (or ezogabine) (blue-gray).[4,132]

### Miscellaneous blue diseases

Retigabine (or ezogabine) is an antiepileptic medication that was approved by the US Food and Drug Administration for the treatment of partial seizures in adults in 2011.[4,132] Its mechanism of action involves activation of the neuronal potassium channels.[4,130,132] A blue[4,130] or blue-gray[4,132] or blue-purple[130] discoloration of the skin,[4,130,132] nails, oral mucosa (gingiva,[130] lips,[4,130,132] and palate[4,130]), and ocular mucosa (including the cornea,[4,132] conjunctiva,[132] lens,[4,132] retina,[130,132] and sclera[132]) has been observed in some patients who are being treated with retigabine.

## Conclusions

Blue (or shades of blue) discoloration may be a distinctive presentation of conditions that occur *de novo* or as a reaction to either a topical or a systemic agent to which the individual has been exposed. These conditions can affect not only the skin, but also the nails or the mucosal membranes (of the mouth or the eyes). In addition to blue diseases appearing blue, they can also appear as variations of blue: blue-black, blue-brown, blue-gray, blue-green, blue-purple, blue-red, and blue-silver. The mucocutaneous or nail discoloration can result from exposure to exogenous agents (systemic or tattoo or topical); also, the skin, nail or mucosal dyschromia may be a component of a syndromes or systemic diseases. Finally, several tumors (adnexal, melanocytic, vascular, or miscellaneous) may appear blue or a shade of blue. Conditions presenting as blue discoloration or shades of blue dyschromia are summarized in summarized in comprehensive tables; in addition, for each color, the location (skin, nails, oral mucosa, and sclera) of the pigmentary change is provided. A more detailed description is given for some of the conditions that are unique to one or more specific locations. “Preserve and cherish that pale blue dot...” and remember that a big red rock eater with chrysiasis is the answer to the riddle, “What is big and blue and eats rocks?”

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