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A BRIEF REVIEW ON ARGYRIA

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ABSTRACT
Argyria is a dermatologic condition that is caused by exposure to or ingestion of silver, and it presents with the insidious onset of grey or blue mucocutaneous discoloration. The condition can occur after a large-dose exposure or prolonged exposure to small amounts of silver. Argyria is an extremely rare condition first described by Hill and Pillsbury in 1939. Argyria is rare not life-threatening but it can have a serious impact on your life. The main objective of this review is to study in detail about argyria like its pathophysiology, subtypes, symptoms, causes, diagnosis, and treatment and so on.

KEYWORDS: argyria, silver, discoloration, laser therapy, etc.

INTRODUCTION

Argyria is a dermatologic condition that is caused by exposure to or ingestion of silver, and it presents with the insidious onset of grey or blue mucocutaneous discoloration. The word argyria is derived from the ancient Greek word for silver, argyros. Argyria is an extremely rare condition first detailed by Hill and Pillsbury in 1939. Argyria can cause localized or generalized skin pigmentation, depending on the form of silver exposure. Local argyria affects in limited regions of the body, such as patches of skin, parts of the mucous membrane or the conjunctiva and generalized argyria affects large areas over much of the visible surface of the body. It can turn your skin, eyes, internal organs, nails, and gums a blue-grey color, especially in areas of your body exposed to sunlight. That change in your skin color is permanent. Silver isn't necessarily a bad thing, and has some medical uses. For example, it's been used in bandages, salves, and medications like eye drops.[1,2,3]

Clinically, argyria characteristically presents with a blue or blue-grey uniform pigmentation of the skin (Intensity depend upon sunlight), mucous membranes, and nails. From nail, lunula is affected, and the hair take on a metallic look. The gums take a blue coloration. The conjunctival pigmentation is bluish grey or dark brown. It can also affect eyelids, lacrimal caruncle, semilunar fold, cornea, lens, vitreous humor, retina, and optic disc. Argyria is rare and not life-threatening, but it can have a serious impact on your life.[4,5]

Mechanism

When you swallow silver, it corrodes in your stomach acid and turns into silver salt, which can travel through your bloodstream and end up in your skin. When exposed to sunlight, the silver salt turns back to silver and colors your skin blue.[6]

Subtypes of Argyria

There are 3 subtypes of argyria are as follows:[7]

1. Generalized Argyria (GA)
2. Localized Argyria (LA)
3. Argyrosis

1. Generalized Argyria (GA)

Generalized argyria emerges following silver systemic exposure and its uptake by the dermis this leads to a grey/blue saltish or metallic diffuse skin pigmentation, which becomes evident predominantly in sun-exposed areas. Patients were most commonly present with gradually aggravating face and neck discoloration with a history of oral but also occupational aerosolized exposure to silver-containing products.[8,9,10,11]

Fig 1 shows characteristic bluish-greyish signs of generalized argyria. Fig 1(A) describe patient with discoloration of face caused by use of oral silver to treat his arthritis, a remedy he was introduced to through the Internet.[12] Fig 1 (B) describe a patient with disseminated dermatosis affecting head, neck and chest in sun-exposed region, nails at lunula and the proximal half of the nail bed, consisting uniform blue-grey pigmentation.[4] Fig 1 (C) describe a patient (Paul Karason's) whose skin turned blue after he used colloidal

silver to treat a skin condition.[13] Fig 1 (D) describe a patient with grey discoloration of her face and neck because she had ingested an ionic silver solution (1 mg/mL), which she purchased from a naturopathic practitioner, every two to three months for the previous 15 years as a remedy for various ailments.[14] Fig 1 (E) describe a patient (Ms. Jacob) with grey discoloration of her face and neck caused by nose drops which contains silver in them.[15] Fig 1 (F) describe a patient with blue-grey discoloration of entire caused by use of Coldargan.[16]

Fig 1: Characteristic bluish-greyish signs of generalized argyria.

Azure lunula is a bluish discoloration of the fingernails, more precisely of the lunula but with the possible extent to the proximal half of the fingernail that was frequently accompanying generalized argyria.[17, 18, 19, 20, 21]

Fig 2 shows characteristic bluish-grey discoloration of the nails (azure lunula). Fig 2 (A) describe patient with longitudinal ridging and non-blanching, bluish-grey pigmentation of the proximal nail bed following the shape of the lunula caused by the OTC drugs contains silver in them.[22] Fig 2 (B) describe patient with thumbnails showing blue discolouration of lunulae and the reason for this the she had been drinking one 250-mL glass of water that contained colloidal silver daily at her workplace for the past 2 years.[23] Fig 2 (C) describe patient with blue discoloration of nails caused by silver-containing cream which he had been applying on his ulcers over years.[24]

Fig 2: Characteristic bluish-grey discoloration of the nails (azure lunula).

2. Localized Argyria (LA)

Localized argyria is less commonly seen, being caused by local silver deposition following skin incisions or percutaneous absorption via sweat gland pores. This results in macular lesions or spots-clusters, confined to where the silver impregnation occurred and with coherent morphology, whose color, compared to GA's, tends to be darker, sometimes almost black. Patients most commonly present with complaints of asymptomatic lesions in a site of previous trauma, cautery with silver devices, or prolonged contact with silver-containing objects, creams, or solutions, as it occurs in the hands and forearms of silver-handling workers.[25, 26, 27, 28, 29, 30]

Fig 3 shows a characteristic dark-bluish-greyish macules of localized argyria. In Fig 3 (A) describe a patient with dark-bluish-greyish macules on nose due to nose piercing by silver jewellery.[31] Fig 3 (B) describe a patient with dark-bluish-greyish macules caused by acupuncture treatment.[32] Fig 3 (C) describe a patient with dark-bluish-greyish macules on index finger due to silver jewellery in the index finger.[33] Fig 3 (D) described a patient with Discoloration of the leg over a silver-coated megaprosthesis used for distal femoral osteosarcoma.[34]

Fig 3: Characteristic dark-bluish-greyish macules and discoloration of leg in localized argyria.

Amalgam tattoo is probably the most common form of LA. It is a common and easily recognizable entity that results from the impregnation of silver-contained dental amalgam into oral mucosa following tooth restoration procedures.[35, 36, 37, 38]

Fig 4 (A & B) described a patient with Amalgam tattoo characterized by the dark-blue macule on the buccal mucosa near a restored tooth.[39]

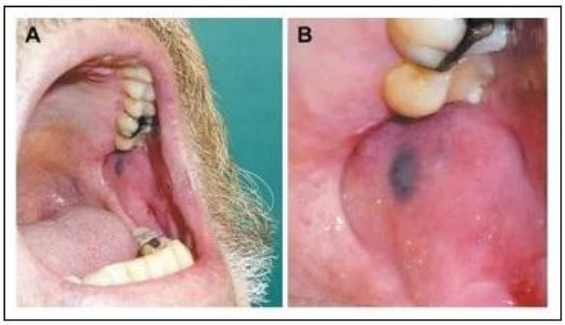

Fig 4: Amalgam tattoo characterized by the dark-blue macule on the buccal mucosa near a restored tooth.

3. Argyrosis

Argyrosis is a particular argyric manifestation evidenced by the ocular silver deposition that can occur in GA but also as a LA form. It is mostly detected in the cornea, bulbar and palpebral conjunctivae, and lacrimal caruncle. Its appearance ranges from small, darker lesions to a more disperse tinge, somewhat parallel to LA and GA and with greater heterogeneity concerning coloration, as greenish and brownish tones might be displayed other than the typical grey/blue.[40, 41, 42, 43, 44, 45]

Fig 5 shows ocular argyrosis characterized by intense dark pigmentation of the palpebral conjunctiva, with a more discrete bluish hue of the bulbar conjunctive.[46]

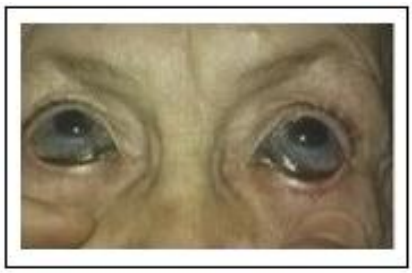

Fig 5: Ocular argyrosis characterized by intense dark pigmentation of the palpebral conjunctiva, with a more discrete bluish hue of the bulbar conjunctiva.

Symptoms

The symptoms of argyria includes:[6, 47]

1] Symptoms may start in your mouth, with your gums turning grey-brown.
2] Your skin may start to turn slate-grey, metallic, or blue-grey. This could happen after a few months or years, depending on how much silver you are exposed to. It may only affect one area of skin, or it could change the appearance of all your skin.
3] The discoloration may stand out most on your forehead, nose, hands, and other areas that are exposed to the sun and areas of the skin that are exposed to the sun may turn much darker than areas that are generally covered up.
4] The whites of your eyes and nail beds may also turn blue-grey.
5] Some people's internal organs in their abdomen such as the spleen, liver, and intestines take on a bluish color, but you wouldn't know this unless you had surgery.

Causes

Some causes of argyria are as follows:[6]

1] The most common causes of argyria are secondary to exposures in the workplace. Silver miners, silversmiths, and photograph developers are frequently exposed to compounds containing silver.

2] If you take medication that contains silver for a long time, it can cause argyria. The following uses of silver are among those that have been shown to cause argyria:

- Silver nitrate used to treat gum bleeding and varicose veins
- Silver sulfadiazine cream used to prevent infection in wounds and burns
- Silver acetate used in lozenges and other products to help quit smoking
- Colloidal silver protein used in eyedrops.

3] You might get argyria if you take dietary supplements that contain silver.

- **Colloidal silver:** This dietary supplement can cause argyria. It consists of tiny silver particles in a liquid. Makers of these products may claim they boost your immune system and can treat cancer, HIV and AIDS, shingles, herpes, and eye problems, but scientific research doesn't support that. The FDA says over-the-counter drugs and supplements containing colloidal silver or silver salts aren't safe and effective. Silver has no known benefits when swallowed and isn't essential to the human body.

Diagnosis

The diagnosis can be done by following ways:[48, 49, 50]

1] Argyria is considered a diagnosis of exclusion, and most cases are diagnosed after a thorough history and physical exam. The gold standard for diagnosis is a skin biopsy of the affected region of the body. This procedure involves the removal of a small piece of skin for analysis under the microscope. The appearance of brown-black granules within the sample indicates the presence of silver.

2] A doctor may request blood, urine, and stool samples from a person with suspected argyria. These will help them determine whether a person has come into contact with silver in the last week.

3] The doctor will also need to rule out other conditions that can cause blue-gray skin discoloration. These include:

- **Exogenous ochronosis:** Skin discoloration that usually results from the prolonged use of skin-lightening creams, such as hydroquinone.
- **Chrysiasis:** Skin discoloration due to the long-term use of gold salts to treat rheumatoid arthritis.
- **Hemochromatosis or iron overload:** A condition in which the body absorbs too much iron. It can be fatal without treatment.

Treatment

Argyria is considered a permanent, irreversible skin condition. Many potential treatments have been attempted without success. Dermabrasion and hydroquinone have been trialed without notable results.[14]

For a long time, there has not been an effective and safe treatment method for argyria.[51, 52, 53] In the last few years, cases of successful skin pigmentation resolution with conventional tattoo-removal laser technique have been reported. The use of Q-switched 1064 nanometers neodymium-doped yttrium aluminum garnet (Q-S 1064 nm Nd: YAG) laser therapy and its utility in the removal of very dark pigmented tattoos. It was thought that this could be utilized in an attempt to reduce the gray and blue pigmentation in patients with argyria. However, the study found that the fluence of this particular laser therapy is too high for argyria, and it induced pinpoint bleeding and marked pain. However, when a low-fluence 1064-nm Q-switched Nd: YAG laser using a top-hat mode was utilized, there was documentation of successful resolution of discoloration of skin. Unfortunately, this resolution may be temporary, as there have been documented cases of argyria recurring approximately 1 year after Q-S 1064 nm Nd: YAG laser therapy was performed.[54, 55, 56]

These are some recommendations for limiting further skin discoloration include:[49]

- wearing sunscreen with a high sun protection factor
- limiting the amount of time in the sun
- wearing protective clothing and eyewear when working with silver
- avoiding medicines, supplements, and cosmetics containing silver

Complications

Argyria is the dermatological manifestation of chronic silver exposure toxicity. However, if a large quantity of silver-containing compounds is acutely ingested, silver toxicity can occur and may be fatal. The dose needed to be fatal is 50 mg or more of intravenous colloidal silver. This would lead to pulmonary oedema, haemorrhage, and necrosis of bone marrow, liver, and kidneys.[57]

CONCLUSION

From this review we concluded that, the argyria is nothing but an insidious onset of grey or blue mucocutaneous discoloration due to exposure to or ingestion of silver. It is a permanent, irreversible skin condition. Many potential treatments have been attempted without success and for a long time, there has not been an effective and safe treatment method for argyria. In the last few years, cases of successful skin pigmentation resolution with conventional tattoo-removal laser technique (Q-S 1064 nm Nd: YAG) have been reported but the resolution may be temporary and cases of argyria recurring approximately 1 year after laser therapy has been reported.

REFERENCES

1. Brandt D, Park B, Hoang M, Jacobe HT. Argyria secondary to ingestion of homemade silver solution. J Am Acad Dermatol, 2005; 53: S105-7.
2. Arenas R. Argyria. Case report and review of the topic. Rev Mex Dermatol, 1986; 30: 24-35.
3. Chang AL, Khosravi V, Egbert B. A case of argyria after colloidal silver ingestion. J Cutan Pathol, 2006; 33: 809-11.
4. Molina-Hernandez, A.I.; Diaz-Gonzalez, J.M.; Saeb-Lima, M.; Dominguez-Cherit, J. Argyria after Silver Nitrate Intake: Case Report and Brief Review of Literature. Indian J. Dermatol, 2015; 60: 520.
5. Cho EA, Lee WS, Kim KM, Kim SY. Occupational generalized argyria after exposure to aerosolized silver. J Dermatol, 2008; 35: 759-60.
6. https://www.webmd.com/skin-problems-and-tratments/aryria-overview
7. Luis Mota, Ricardo Jorge Dinis-Oliveria. Clinical & forensic aspects of different subtypes of argyria. Journal of Clinical Medicine, 2021; 10(10): 2086.
8. Bingham E, Cohrssen B. Patty's Toxicology. 6th ed. USA(NJ):Wiley-Blackwell: Hoboken publishers, 2012.
9. Van de Voorde K, Nijsten T, Schelfhout K, Moorkens G. Lambert, J. Long-term use of silver containing nose-drops resulting in systemic argyria. Acta Clin. Belg, 2005; 60: 33-35.
10. Lansdown A.B. Silver in health care: Antimicrobial effects and safety in use. Curr. Probl. Dermatol, 2006; 33: 17-34.
11. Park SW, Shin HT, Lee KT, Lee DY. Medical concern for colloidal silver supplementation: Argyria of the nail and face. Ann. Dermatol, 2013; 25: 111-112.
12. Wadhera A, Fung M. Systemic argyria associated with ingestion of colloidal silver. Dermatol. Online J., 2005; 11: 12.
13. www.today.com
14. Bracey NA, Zipursky JS, Juurlink DN. Argyria caused by chronic ingestion of silver. Can. Med. Assoc. J., 2018; 190: E139.
15. Jacobs R. Argyria: My life story. Clin. Dermatol, 2006; 24: 66-69.
16. Tomi NS, Kranke B, Aberer W. A silver man. Lancet, 2004; 363: 532.
17. Burgert JM. Argyria resulting from chronic use of colloidal silver in a patient presenting for colonoscopy. A&A Pract, 2014; 3: 73-75.
18. Kim Y, Suh HS, Cha HJ, Kim SH, *et al*., A case of generalized argyria after ingestion of colloidal silver solution. Am. J. Ind. Med., 2009; 52: 246-250.
19. Kubba A, Kubba R, Batrani M, Pal T. Argyria an unrecognized cause of cutaneous pigmentation in Indian patients: A case series and review of the literature. Indian J. Dermatol. Venereol. Leprol, 2013; 79: 805-811.
20. Reddy SG, Martin JM, Kraus EW, Meffert JJ. Generalized blue-gray pigmentation—Quiz case. Arch. Dermatol, 2009; 145: 1053-1058.
21. Gottesman SP, Goldberg GN. Immediate successful treatment of argyria with a single pass of multiple Q-switched laser wavelengths. JAMA Dermatol, 2013; 149: 623–624.
22. Fox J.D, Baker J.A, Tosti A. Chromonychia in an Asymptomatic Vitamin Consumer. Ski. Appendage Disord, 2016; 1: 131-133.
23. Kalouche H, Watson A, Routley D. Blue lunulae: Argyria and hypercopprecaemia. Australas. J. Dermatol, 2007; 48: 182–184.
24. Rodriguez V, Romaguera RL, Heidecker B. Silver-Containing Wound Cream Leading to Argyria-Always Ask About Alternative Health Products. Am. J. Med, 2017; 130: e145–e146.
25. Sato S, Sueki H, Nishijima A. Two unusual cases of argyria: The application of an improved tissue processing method for X-ray microanalysis of selenium and sulphur in silver-laden granules. Br. J. Dermatol, 1999; 140: 158-163.
26. Williams N. Longitudinal medical surveillance showing lack of progression of argyrosis in a silver refiner. Occup. Med. (Lond.), 1999; 49: 397-399.
27. Ellison DW, Chant AD, Harrison TA, Theaker JM. Localized argyria: A complication of the repair of inguinal hernia with silver filigree. Br. J. Surg., 1993; 80: 1325.
28. Enei ML, Paschoal F.M, Valdes R. Argyria mimicking a blue nevis: Dermoscopy features. An. Bras. Dermatol, 2013; 88: 452-455.
29. Beutler BD, Lee RA, Cohen PR. Localized cutaneous argyria: Report of two patients and literature review. Dermatol. Online J., 2016; 22: 11.
30. Granstein RD, Sober AJ. Drug and heavy metal-induced hyperpigmentation. J. Am. Acad. Dermatol, 1981; 5: 1-18.
31. Al-Niaimi F. Localized argyria from silver nasal piercing unresponsive to Q-switched laser successfully treated with a 1064 picoseconds laser. J Cosmet. Dermatol, 2020; 19: 1535-1536.
32. Park MY, Lee JS, Jin HJ, You HS, Kim GW, *et al*. Localized argyria: Troublesome side-effect of acupuncture. J Eur Acad Dermatol Venereol JEADV, 2018; 32: e62-e65.
33. Garcias LJ, Hernandez BP, Torregrosa JL, Martínez-Aparicio. A Localized cutaneous argyria: A report of 2 cases. Actas Dermo. Sifiliogr, 2013; 04: 253-254.
34. Karakasli A, Hapa O, Akdeniz O, Havitcioglu H. Dermal argyria: Cutaneous manifestation of a megaprosthesis for distal femoral osteosarcoma. Indian J. Orthop, 2014; 48: 326-328.
35. Dummett CO. Systemic significance of oral pigmentation and discoloration. Postgrad. Med, 1971; 49: 78-82.
36. Buchner A. Amalgam tattoo (amalgam pigmentation) of the oral mucosa: Clinical manifestations, diagnosis and treatment. Refuat Hapeh Vehashinayim, 2004; 21: 2528.
37. Wu Q, Yang Z, Su L. Light microscope and energy dispersive X-ray analysis of amalgam

pigmentation. Zhonghua Kou Qiang Yi Xue Za Zhi, 1995; 30: 140-142.
38. Bell CD, Cooksey DE, Nickel WR. Amalgam tattoo (localized argyria). Arch. Derm, 1952; 66: 523-525.
39. Dubach P, Caversaccio M. Images in clinical medicine. Amalgam tattoo. N. Engl. J. Med, 2011; 364: e29.
40. Madi HA, Kotagiri AK. Multimodal imaging in a patient with ocular argyrosis complicated by diabetic retinopathy. Can. J. Ophthalmol, 2018; 53: e262-e266.
41. Jensen SF. Argyrosis of conjunctiva in studio photographer. Acta Ophthalmol. (Copenh.), 1962; 40: 544-54.
42. Hodson TJ, Gillies WE. Argyrol, argyrosis and the acquisition of art. Aust. N. Z. J. Ophthalmol, 1985; 13: 391-394.
43. Couto A, Molles S, Simionato R, Kamlot D. Eye's and excretory lacrimal apparatus' argyrosis: Case report. Arq. Bras. Oftalmol, 2009; 72: 836-838.
44. Weiler HH, Lemp MA, Zeavin BH, Suarez AF. Argyria of the cornea due to self-administration of eyelash dye. Ann. Ophthalmol, 1982; 14: 822-823.
45. Karcioglu ZA, Caldwell DR. Corneal argyrosis: Histologic, ultrastructural and microanalytic study. Can. J. Ophthalmol, 1985; 20: 257-260.
46. Bradely J, Mitchell K, Dominguez L, et al. List Eye Atlas Contributors, SOM Ophthalmology Eye Atlas: Conjunctiva. Texas Tech University Health Sciences Center, 2021.
47. https://www.healthline.com/health/argyria-cure
48. Lencastre A, Lobo M, Joao A. Argyria-case report. Anais brasileiros de dermatologia, 2013.
49. https://www.medicalnewstoday.com/articles/325581
50. https://www.statpearls.com/ArticleLibrary/viewarticle/17814
51. Bleehen SS, Gould DJ, Harrington CI, Durrant TE, *et al*. Occupational argyria; light and electron microscopic studies and X-ray microanalysis. Br. J. Dermatol, 1981; 104: 19-26.
52. Sue YM, Lee JY, Wang MC, Lin TK, *et al*. Generalized argyria in two chronic hemodialysis patients. Am. J. Kidney Dis., 2001; 37: 1048-1051.
53. Lee SM, Lee SH. Generalized argyria after habitual use of AgNO3. J. Dermatol, 1994; 21: 50-53.
54. Han TY, Chang HS, Lee HK, Son SJ. Successful treatment of argyria using a low-fluence Q-switched 1064-nm Nd:YAG laser. International journal of dermatology, 2011.
55. Krase JM, Gottesman SP, Goldberg GN. Recurrence of Argyria Post Q-Switched Laser Treatment. Dermatologic surgery: official publication for American Society for Dermatologic Surgery, 2017.
56. Griffith RD, Simmons BJ, Bray FN, Falto-Aizpurua LA, *et* al. 1064 nm Q-switched Nd: YAG laser for the treatment of Argyria: a systematic review. Journal of the European Academy of Dermatology and Venereology: JEADV, 2015.
57. Fisher NM, Marsh E, Lazova R. Scar-localized argyria secondary to silver sulfadiazine cream. Journal of the American Academy of Dermatology, 2003.