

Argyria an unrecognized cause of cutaneous pigmentation in Indian patients: A case series and review of the literature

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ABSTRACT

Argyria is an uncommon grey-blue pigmentation of skin and mucous membranes caused by prolonged silver exposure. The impetus behind this review is our experience with cases of generalized argyria resulting from a uniquely Indian socio-cultural practice and belief that it is under reported. Our objective is to increase the awareness for this esoteric entity through a review of the pertinent literature and to highlight clinical and histological features using our four well worked-up cases as examples.

Key words: Argyria, cutaneous pigmentation, Indian, silver

INTRODUCTION

Silver-the metal

Silver is a naturally occurring metallic element that has no known physiological or biological function in the human body. It is present widely in the human environment; henceforth, low concentrations are also present in the human body. Normal healthy people have silver levels of <3 µg/L.^[1]

Toxicity and metabolism of silver

The ability of a metal to produce toxic effects on body depends on the type of compound/form of the metal, the amount and mode of absorption, its metabolism in the body and the cellular vulnerability to toxic damage.^[1,2] Absorption of metallic silver is much less when compared with soluble silver compounds.^[2] Silver is absorbed into the body through inhalation, ingestion, intraparenteral through insertion of needles or implantation of medical devices or

accidental puncture wounds and through dermal or mucosal contact.^[1,2] The percutaneous absorption through intact skin is very low, however, in wounds and burns the absorption increases significantly.^[1,3] The metallic and inorganic silver compounds ionize to silver ion on exposure to body fluids, which after absorption in the systemic circulation by ion uptake binds to thiol and proteins ligands such as metallothioneins, albumins and macroglobulins and is metabolized.^[1,4]

The acute toxicity due to exposure to large doses of inorganic silver salts such as silver nitrate is similar to corrosive effects leading to irritation of the gastrointestinal tract (if ingested) manifested in the form of epigastric burning, vomiting and diarrhea or respiratory tract irritation (if inhaled), severe toxicity will cause decreased blood pressure and decreased respiration ultimately leading to convulsions and shock.^[2,3,5] Instillation of silver nitrate in the renal pelvis or urinary tract for chyluria have been reported to be associated with renal and hepatic failure, acute necrotizing ureteritis, obstructive nephropathy and papillary necrosis.^[1] The corrosive effects are likely to be due to the nitrate in the compound rather than by the silver itself.^[2] Organic silver compounds such as colloidal silver are less toxic however consumption of large doses of colloidal silver may lead to coma, pleural edema and hemolysis.^[5]

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The chronic toxicity occurs after prolonged exposure when the absorption of silver exceeds body metabolizing capacity leading to precipitation as inert silver sulfide and/or silver selenide in soft-tissues^[1] (with highest concentrations in skin, liver, spleen and adrenal glands).^[3] The chronic toxicity is not associated with an irreversible toxic damage to organs or carcinogenicity and the principal clinical manifestation is disfiguring cutaneous pigmentation called argyria or corneal/conjunctival pigmentation called argyrosis.^[1]

Several safe limits set up by different regulatory authorities exist for silver depending upon the form of silver and mode of exposure. For occupational exposure a recommended exposure limit of 0.01 mg/m³ in the air for both metallic and soluble compounds of silver and two separate exposure limits of 0.1 mg/m³ for metallic silver and 0.01 mg/m³ for soluble silver compounds are established by The National Institute for Occupational Safety and Health and The American Conference of Governmental Industrial Hygienists respectively.^[2] A chronic oral reference dose of 5 µg/kg/day is given by The environmental protection agency.^[3] World Health Organization limits are up to 0.1 mg/L for drinking water levels and total lifetime oral intake of 10 g for no observable adverse effect levels.^[1] However, it is difficult to determine the lowest dose of silver leading to argyria because various studies have not been able to establish a clear relationship between exposure to silver, blood silver levels or minimal body silver concentrations with early signs of the condition.^[1]

Pathogenesis of argyria

The photocatalyzed reaction analogous to developing a photographic film is the underlying mechanism behind the discoloration of argyria seen preferentially in sun exposed areas.^[2] Recently, Liu *et al.* have proposed a conceptual model for pathogenesis of argyria. Sunlight catalyzes the silver complexes in the skin to elemental silver, which spontaneously forms the immobile silver nanoparticles. This is followed by transformations of silver nanoparticles into sulfides and further into selenides or Se/S mixed phases through exchange reactions.^[4] In addition, silver also stimulates melanin production thus adding to the discoloration.^[2]

CASE REPORT

A total of 4 patients, of these 1 were male and 3 were female presented with insidious onset

grey-blue macular shiny pigmentation involving predominantly sun exposed areas [Figures 1 and 2]. Nail involvement (azure lunulae) was observed in two patients [Figure 3] while discoloration of the oral mucosa was present in one patient. The cause of argyria was elucidated to be long-term ingestion of silver coated cardamoms in two and silver coated betel nut in other two [Table 1].



Figure 1: (a) Diffuse slate-grey pigmentation with accentuation along nasolabial folds and forehead. (b) Pigmentation of pinna and neck



Figure 2: Shiny diffuse ash-blue pigmentation



Figure 3: Azure lunulae (nail pigmentation)

Histopathological examination showed similar features in all patients. The distinctive feature observed was deposition of fine black granules in the basement membrane of eccrine secretory coils [Figure 4], blood vessels wall, around pilosebaceous units and along the elastic fibers of the papillary dermis [Figure 5]. The granules were refractile under dark field

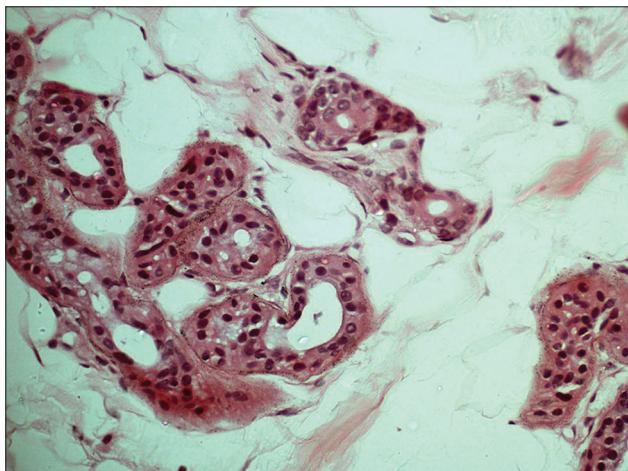


Figure 4: Fine black granules of silver in eccrine gland basal lamina (H and E, $\times 400$)

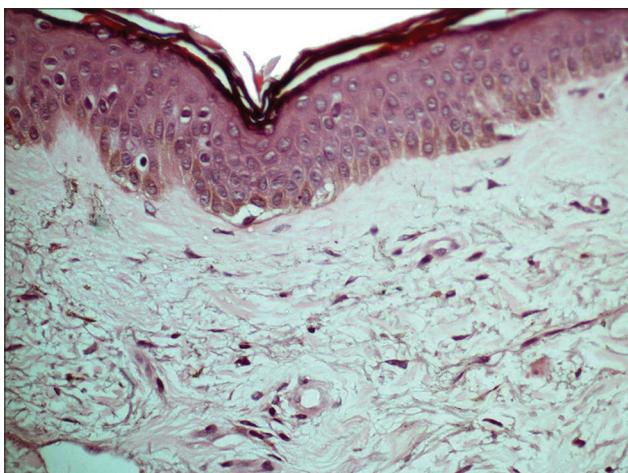


Figure 5: Fine black granules of silver along the elastic fibers in papillary dermis (H and E, $\times 400$)

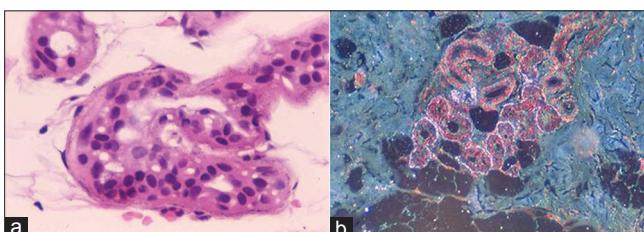


Figure 6: (a) Silver granules along eccrine glands not prominent under light microscopy, (H and E, $\times 400$). (b) Brightly refractive silver granules under dark field microscopy (H and E, $\times 400$)

microscopy [Figure 6]. Masson-Fontana and Perl's stain were performed to exclude melanin and hemosiderin granules respectively.

DISCUSSION

Silver deposition leading to pigmentation had been recorded as early as 8th century. The term "argyria" was coined by Fuchs in 1840.^[5] It was prevalent in 19th and early 20th century.^[6]

Argyria can be localized or generalized, depending upon the mode and amount of silver absorbed. Localized argyria is the pigmentation of skin or mucous membranes due to impregnation of silver confined to the site of direct contact.^[2] Besides the commonly characterized forms of localized argyria i.e., cutaneous, ocular (argyrosis) and oral cavity (amalgam tattoo), some unusual locations of localized argyria are nasal mucosa,^[7] trachea,^[8] urinary tract,^[9] vagina,^[10] and penis.^[11] In generalized argyria, the silver is systemically absorbed and is widely deposited in skin, eyes, mucous membranes and nails.^[2]

Etiological factors

Occupational

Silver, apart from its wide usage in jewelry and silverware, has extensive industrial applications including photography, soldering, in batteries, in mirrors to name a few.^[2] Silver exposure in miners and other occupations as the cause of argyria, especially generalized, has become less prevalent due to availability as well as enforcement of better protective measures at work place.^[2] However, isolated cases of occupational argyria mostly localized^[7,12-16] and rarely generalized^[17] continue to be recorded. Some interesting reports of occupation related argyria cited

Table 1: Clinical details of four cases

Case no.	Age/sex	Clinical features	Cause of silver exposure
1	55 years/ female	Blue grey discoloration of face, scalp, neck, forearm, dorsa of hands and nails	Intake of 10-15 silver coated cardamoms per day for 7-8 years
2	56 years/ male	Blue grey discoloration of the face, earlobes, nails and oral mucosa	Intake of silver coated betel nut with tobacco for 20 years
3	50 years/ female	Blue grey discoloration of face with predilection for nose, forehead and pinnae	Intake of silver coated betel nut for 8 years
4	46 years/ female	Blue-grey pigmentation on face involving perioral area, cheeks and temple	Intake of silver coated cardamoms for several years

in the literature include black tears as a result of occupational inhalation of silver,^[18] localized argyria in an antique restorer^[19] and localized cutaneous argyria in a dental surgeon called as cutaneous amalgam tattoo by the authors.^[20]

Medicinal and therapeutic

Silver has had medicinal uses since ancient times. Historically, silver nitrate was used for neurological disorders such as epilepsy and tabes dorsalis. In the late 19th and early 20th century, silver compounds and colloidal silver proteins for their antimicrobial, caustic, astringent and hemostatic properties had varied spectrum of usage. Silver compounds were used for treatment or prevention of infectious diseases like gonorrhea including Crede's method for ophthalmia neonatorum and syphilis, gastrointestinal disorders, oral ulcers, for removal of warts and for bladder irrigation. Silver was also used in allergy and cold remedies, eye drops, nasal sprays, lozenges and antismoking pills.^[2,3,5,9,21] Thus, the medical exposure was the most common source of argyria.^[2,3] With the development of antibiotic and better pharmaceutical agents the medicinal use of silver declined.^[2,5] In 1999, US Food and Drug Administration prohibited the sale of over the counter (OTC) medications containing silver.^[5]

In present day medicine, the use of silver is mainly confined to silver dressings for burns/wound management and in medical appliances.^[3,21] The silver dressings have come a long way from silver foils to popular silver sulfadiazine cream to present day nanocrystalline dressings.^[5,21] The spectrum of silver based medical appliances has also evolved from silver wire sutures to various other devices such as prosthetic implants, splints, catheters, heart valve, stents, bone cement, dental fillings.^[1,21] The incidence of argyria with these forms of applications is low, however, localized argyria has been reported with the use of silver dressings/cream^[10,11,22-24] and with the implantation of medical devices.^[8,25-27] Rarely generalized argyria has been documented either with prolonged use of silver dressings/cream or application over large body surface area such as in cases of burns, epidermolysis bullosa and venous leg ulcers.^[10,28-30]

Recently, there has been a resurgence in the unregulated use of silver in the form of dietary supplements and as a constituent of alternative medicine/home remedies.^[2,5] There are hundreds of websites proclaiming the benefits of silver compounds.^[2,5,31-33]

Most of the reported cases of generalized argyria in the 21st century have been associated with long-term and indiscriminate use of these preparations.^[5,6,31-52] It is worth mentioning herein, two reports of familial argyria in members of the same family due to prolonged use of silver containing formulations as a form of alternative medicine.^[53,54] Apart from this, localized cases of argyria have also been reported following acupuncture.^[55-57]

Personal and socio-cultural

Cases of argyria have been associated with certain personal and socio-cultural practices. Examples include argyria associated with the use of mouth fresheners^[55,58-60] and sugar coated particles.^[61] Silver earrings^[62,63] and eyelash dye^[64] have led to localized argyria. Generalized argyria cases have been reported in psychiatric illnesses, such as, schizophrenia,^[58] somatic delusions,^[31,51] schizoaffective disorder^[52] and due to chewing of photographic film.^[65]

Environmental and incidental

Localized argyria has occurred due to chemical explosion,^[66] and trauma.^[67,68] Contaminated water used in hemodialysis has led to generalized argyria.^[69]

Clinical features

In general, the macular pigmentation in argyria is slate – grey. It arises insidiously and is asymptomatic. The pigmentation is subtle and goes unrecognized for months and years.^[6,32,33,46] It is more pronounced on sun exposed areas including face, neck, [Figure 1] arms and dorsum of the hands.^[2] It is often viewed by the patient as persistent tan. However, the clinical morphology and anatomic pattern is sufficiently distinctive as exemplified by our four patients. The shiny quality of pigmentation [Figure 2] and the diffuse pattern is in contrast to brown-black patchy pigmentation of melasma. Mucosal/conjunctival involvement and azure lunulae (nails) [Figure 3] are characteristic attributes of argyria. In our opinion, with knowledge and awareness, argyria can be clinically recognized.

Clinical differential diagnosis of argyria includes other causes of cutaneous discoloration [Table 2]. Generalized argyria can closely mimic metabolic causes of pigmentation, which too are uncommon and only a thorough clinical work-up will allow the correct diagnosis to be arrived at. Generalized argyria has been mistaken for cyanosis in individuals of light skin.^[32,41,70] The localized argyria needs to be

distinguished from melanocytic lesions like blue nevi^[12,57,68] and malignant melanoma.^[12,16,56,71]

An exhaustive history is necessary for eliciting the mode and duration of silver exposure. At times, the exposure to silver may not be readily apparent as is evident from a reported case of generalized argyria caused by silver element in a tea kettle.^[70]

Histological features

Argyria appears as invisible dermatosis under scanning magnification. Diagnostic features seen on high power are characterized by the deposition of uniform fine brown black granules in the basal lamina of the secretory portion of eccrine glands [Figure 4], blood vessel walls and elastic fibers of the papillary dermis [Figure 5]. To a lesser extent deposits are also seen in connective tissue sheath surrounding pilosebaceous units, perineural tissues and arrector pili muscles.^[12,72] Dark field microscopy under which the granules are brightly retractile is particularly useful in suspected cases of argyria where the deposits are not evident under light microscopy [Figure 6]. In localized argyria an unusual histological finding of yellow brown collagen bundles similar to pseudo-ochronosis

has occasionally been described.^[12,56]

Histopathological examination is important to establish the definite diagnosis and to exclude other causes of pigmentation because these have significantly different implications from the management and prognostic point of view. The cutaneous deposits can be histochemically characterized as silver compounds by techniques such as transmission electron microscopy with electron loss spectroscopy or scanning electron microscopy with energy dispersive radiograph microanalysis.^[73] However, these techniques are not readily available, in this setting, the specific characteristics and the localization of the silver granules as observed under light microscopy with dark field microscopy can distinguish it from some of the other common heavy metal granules [Table 3].^[12,72,74]

Management

Cessation of silver exposure and sun-protection with sunscreen are useful for preventing further progression of pigmentation. Various treatment options such as chelation, hydroquinone and dermabrasion are not effective. Recently, Q-switched 1064-nm neodymium-doped yttrium aluminium garnet laser has been reported to be useful for resolving the skin discoloration in argyria.^[42,47,50,54]

Indian perspective

All the four cases of argyria, described in this article are due to intake of silver coated betel nut/cardamoms [Table 1]. An extensive literature search conducted

Table 2: Clinical differential diagnosis of argyria

Generalized argyria ^[6,41,46,60]	Localized argyria ^[12,16,56,57,68,71]
Metabolic	Melanocytic lesions
Addison's disease	Blue nevus
Hemochromatosis	Malignant melanoma
Wilson's disease	
Cyanosis	Tattoo
Methemoglobinemia	
Ochronosis	
Melanosis	
Erythema dyschromicum perstans/lichen planus pigmentosus	
Melanosis secondary to wide spread melanoma	
Drug deposition	
Chlorpromazine	
Amiodarone	
Minocycline	
Antimalarial	
Clofazimine	
Metals	
Gold	
Mercury	
Bismuth	
Arsenic	
Lead	

Table 3: Histopathological differentiating features of important heavy metal granules^[12,72,74]

Metal	Granule characteristics	Cutaneous localization
Silver (argyria)	Uniform, brown-black, minute <1 µm, retractile under dark field	Basement membrane of eccrine glands, blood vessel walls and elastic fibers of papillary dermis. To a lesser extent in the connective tissue sheaths of pilosebaceous units, perineural tissue and in arrector pili muscle
Gold (chrysiasis)	Larger, irregular in size, round or ovoid, refractile under dark field, orange red birefringence under polaroscopic examination	Macrophages around blood vessels in upper and mid dermis
Mercury	Large aggregates of up to 340 µm	Macrophages around blood vessels, along the elastic fibers and free among collagen bundles in upper dermis

with the purpose to identify the reports of argyria pertaining to related forms of exposure yielded five citations.^[55,58-61] Interestingly, of these, four are from Japan and one from Taiwan. In four of the citations the cause of argyria is ingestion of mouth freshener "Jintan,"^[55,58-60] while in one, argyria is attributed to consumption of silver coated sugar particles.^[61] This appears to be a unique cause of argyria due to cultural practice confined to the Asia.

The thin silver leaves called as "Warq" are quite commonly used to coat sweets, cardamoms and betel nut and mouth fresheners. Ash of silver is also widely used in Ayurveda one of the Indian traditional systems of medicine.^[75] Silver containing topical medicines are freely available as OTC drugs in India. To the best of our knowledge, this pattern of argyria has not been previously documented from India. Knowing how habit forming is the practice of chewing silver coated mouth fresheners and how widely it is prevalent in India, it comes as a surprise that there are not many more reported cases of argyria. We are tempted to speculate that argyria is under diagnosed because of lack of awareness and because of its insidious onset resulting in a "darkened skin" that is probably tolerated as a natural age or sun exposure related deterioration of the skin.

CONCLUSION

Argyria, particularly the generalized type, is worth remembering in the differential diagnosis of cutaneous pigmentation. The clinical picture and the natural course of the disease are sufficiently distinctive. The diagnosis is easily clinched by eliciting history of silver ingestion by asking leading questions (may require Sherlockian approach!) and by demonstrating silver deposition in the skin through appropriate histopathological evaluation. Failure to recognize argyria may result in prolonged psycho-social morbidity and unnecessary investigations and treatments.

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