Case Report

Generalized Argyria
-A Case Report

Chin-Ya Yang   Yi-Ju Chen   Jui-Lung Shen

Generalized argyria is a rare disease caused by deposition of silver in the skin, nails, mucous membranes, and internal organs. It is characterized by a diffuse slate-blue discoloration in sun-exposed areas. Here, we report a case of 38-year-old woman with generalized argyria. Pathologically, there were numerous minute fine brownish-black pigments fairly uniform in size, which were observed in the dermal interstitium, around the hair follicles, sebaceous glands, eccrine glands and the walls of capillaries. Darkfield microscopy showed refractile white particles. In this report we also review the literature about this rare disease. (Dermatol Sinica 26: 75-79, 2008)

Key words: Argyria, Silver

INTRODUCTION

Generalized argyria is a rare disease caused by deposition of silver granules in the skin, nails, mucous membranes, and internal organs. A distinctive slate-blue pigmentation, most apparent in sun-exposed areas, is the main clinical presentation of this otherwise asymptomatic disease. Generalized argyria is now rarely reported because of the cessation of silver usage in oral medications and decreased occupational exposure.

CASE REPORT

A 38-year-old otherwise healthy woman presented with a 5-year history of slate-blue pigmentation. She first noticed the bluish skin color change in her face which subsequently also involved her forearms and nails. She denied having had any exposure to heavy metals or having taken any systemic medications or alternative health treatments. But she stated she had taken the breath freshener “Jintan (仁丹) silver pills” daily for the past 2 to 3 decades.

Physical examination revealed diffuse slate-blue cutaneous pigmentation, most strikingly on the sun-exposed areas of her eyebrows, nose, cheeks, neck, forearms and dorsal hands. (Fig. 1, 2) A subtle bluish discoloration was present in the lanulae of the fingernails. (Fig. 3) Her toenails, sclerae and oral mucosa appeared normal. Incisional biopsy of the left side of the nose was performed under the suspicion of argyria.

Histologically, there were numerous minute fine brownish-black extracellular pigments fairly uniform in size, which were observed in the dermal interstitium (Fig. 4), around the...
hair follicles (Fig. 5), sebaceous glands, eccrine glands (Fig. 6) and the walls of capillaries. Darkfield microscopy revealed brilliantly refractile white particles around eccrine glands, blood vessels and were interspersed in the dermis.

Generalized argyria was diagnosed based on clinical and pathological findings. However, the patient refused to undergo further examinations. Sun protection and opaque cosmetics were suggested to prevent further pigmentary change and to mask discoloration.

**DISCUSSION**

Argyria was recorded in ancient times. Bluish discoloration of the eyes caused by silver ingestion was first described in the 8th century. Argyria was common in the 19th century as a result of silver usage in treating mental illness, epilepsy, nicotine addiction, gastroenteritis, syphilis, and gonorrhea. Occupational exposure to silver contributed to the development of argyria in silversmiths, miners and photographers. However, since the cessation of medicinal use of silver and initiation of standards for occupational exposure, reported cases of argyria have been rare.

Argyria can be classified into localized and generalized forms. Localized argyria may appear as slate-blue macules. It is occasionally caused by silver earrings, acupuncture needles and topical application of silver-containing products for wounds. In contrast, generalized argyria is characterized by a slate-blue discoloration of the entire skin surface, which is most pronounced in the sun-exposed areas such as face, neck, “V” area of the chest, forearms and dorsum of the hands. The nails and mucous membranes may also be involved. Silver may also be detected in internal organs. However, there have only been a few case reports of neurologic, renal and hepatic problems associated with argyria. Nowadays, generalized argyria is associated with colloidal silver solution, nose drops as a vasoconstrictor, and silver-
coated sugar particles. The smallest amount of silver reported to cause generalized argyria ranges from 4 to 5g. In Japan, cases of generalized argyria due to the breath freshener “Jintan silver pills”, as in our patient, have been reported.

Skin biopsy is important to differentiate argyria from other causes of hyperpigmentation. Typical histologic findings include extracellular brownish-black fine granules deposited primarily in the dermis but especially concentrated in the basement membrane zone surrounding the eccrine glands and connective tissue sheaths around pilosebaceous structures.

Although histopathology is sufficient to make the diagnosis of argyria, there are other methods to confirm it. Dark-field microscopy displays numerous brilliantly refractile granules mostly around the eccrine glands. Scanning electron microscopy demonstrates silver granules as electron-dense clumps of particles, distributed along the basement membranes of dermo-epidermal junction, eccrine, sebaceous glands and elastic microfibrils. Scanning electron energy dispersion x-ray microanalysis can be used to confirm the presence of silver.

The deposition of silver in the skin is uniform. However, the slate-blue discoloration is most prominent in sun-exposed areas. This occurs because the discoloration is not caused by the deposited silver compounds themselves. Instead, the discoloration is caused by the combined effect of reduction of silver compounds and an increase in melanin production. The colorless silver is reduced by sunlight to brownish-black silver sulphides and selenide within tissues. The deposited silver also stimulates tyrosinase activity of melanocytes to produce more melanin.

The differential diagnosis for generalized argyria includes endogenous causes such as central cyanosis, methemoglobinemia, Addison’s disease, hemochromatosis, disseminated melanoma and uremia as well as exogenous causes such as ingestion of certain compounds.
(antimalarials, minocycline, amiodarone, chlorpromazine) or other metals (gold, mercury, and bismuth).10,11

Silver deposition and the discoloration of the skin in argyria are usually permanent and primarily of cosmetic significance.1,11 Depigmenting creams,19 hydroquinone, dermabrasion2 and chelating agents such as British anti-Lewisite, D-penicillamine and 2,3-dimercaptopropane-1-sulphonate are not effective.1,18,20 Sun protection and opaque cosmetics may help to prevent further pigmentary darkening and mask discoloration.

Thus, we report a rare case of generalized argyria associated with breath freshener “Jintan silver pills”. Argyria should be considered in the differential diagnosis of patients with hyperpigmentation.

REFERENCES
全身性銀質沈著症
-病例報告

楊智雅 陳怡如 沈瑞隆
台中榮民總醫院皮膚科

全身性銀質沈著症是由於銀沈積在皮膚、指甲、黏膜和內臟器官所造成的少見疾病。臨床上可在日曬處皮膚看到灰藍色的變化。本文報告一例發生在38歲女性的全身性銀質沈著症，病理可見在真皮間質、毛囊、皮脂腺、汗腺和微血管壁周圍有許多細小的棕黑色色素，暗視野顯微鏡下見到白色小點。在本文中，我們同時回顧和此病相關的文獻。（中華皮誌：26: 75-79, 2008）