A Rare Case of Liver Granulomatous Disease Secondary to Argyria

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Abstract:

This case report discusses a rare occurrence of liver granulomatous disease secondary to Argyria, a skin disorder resulting from silver exposure. A 61-year-old male presented with fatigue, weakness, and bluish skin discoloration. A diagnostic workup revealed liver granulomas and silver deposits on pathology. History was significant for prolonged ingestion of silver tablets which prompted treatment cessation, antibiotic therapy, and a tapering course of Prednisone. Argyria's association with liver granulomatous disease emphasizes the need for awareness and comprehensive diagnostic evaluation in such cases.

Introduction:

Argyria is a rare skin disorder that can be acquired through ingestion or overexposure to silver. The excess can deposit on the skin and stain the mucous membranes, causing them to turn a bluish-slate gray color [1–3]. It can be classified into three subtypes. Generalized argyria occurs due to extensive exposure to silver, leading to its absorption by the dermis and resulting in a grayish-blue or metallic appearance of the skin. Localized argyria, alternatively, occurs when silver is deposited in specific areas of the skin, typically through incisions or absorption via sweat gland pores lastly, argyrosis refers to the accumulation of silver in the eye [1].

Argyria can also lead to the development of liver granulomas, a disorder that can also be commonly manifested in sarcoid disease. The granulomatous disease is characterized by the growth of tiny collections of inflammatory cells in any part of the body. It can also affect various other organs such as the lungs, lymph nodes, eyes, skin, and heart [4,5]. Although the exact cause of this disorder is unknown, some theories suggest an autoimmune association secondary to an abnormal immune response to bacteria, viruses, dust, or chemicals. In response to these associated factors, the body triggers an immune response, which leads to a collection of inflammatory cells called a granuloma [6,7]. Awareness should be noted of Argyria’s rare association with granulomatous disease.

Clinical Course:

A 61-year-old Caucasian male with a past medical history of type 2 diabetes mellitus, depression, and reflux disease presented to the emergency room exhibiting fatigue, weakness, and bluish discoloration of the upper extremities and face. Laboratory results revealed elevated creatinine levels at 5.39 mg/dL (baseline 1.04 mg/dL), sodium levels of 128 mmol/L, and calcium levels of 16.3 mg/dL (corrected calcium 12.3 mg/dL). Parathyroid hormone was low at 3.6 pg/mL, while PTH-related peptide was < 2.0 ng/mL. The ferritin and iron panel were within normal limits. However, calcitriol levels were high at 140 ng/ml, alongside an elevated alkaline phosphatase

level of 711 U/L and a normal ACE level of 80 mcg/L. The remainder of liver enzymes were within normal limits. Abdominal ultrasound indicated right renal cortical thinning, while a chest x-ray showed patchy nodular infiltrates in both lungs. CT scans of the abdomen/pelvis revealed a possible non-obstructing right renal stone and significant heterogeneous attenuation of liver parenchyma with multiple abdominal and retroperitoneal lymph nodes. A positron emission tomography/computed tomography scan demonstrated patchy areas of increased metabolic activity throughout the liver and a reticulonodular pattern in the lungs. A non-targeted liver biopsy revealed granulomatous inflammation, portal fibrosis with focal areas suggestive of micronodule formation, and significant silver deposits with moderate fibrosis stage on trichrome stain. Pulmonology consultation was sought for possible sarcoidosis, but no bronchoscopy or lung biopsy was recommended. Blood cultures, Streptococcus pneumonia, Legionella, and COVID-19 tests yielded unremarkable results. Further infectious workup for hepatic granuloma, including tests for Histoplasmosis, Coccidioidomycosis, Toxoplasmosis, Candidiasis, Coxiella burnetii, Brucellosis, Mycobacterium tuberculosis, HIV, Hepatitis B and C, Epstein Barr virus, Cytomegalovirus, Schistosomiasis, Enterobius vermicularis, and Strongyloides, were all negative. Malignancy workup, including tests for CA 19-9, carcinoembryonic antigen (CEA), and alpha-fetoprotein (AFP), also yielded negative results. Autoimmune causes were explored, with negative findings for antimitochondrial antibodies and primary biliary cirrhosis. Liver biopsy excluded PBC diagnosis. IgE, IgG, and IgA levels were all unremarkable. The patient later on reported a history of oral silver tablets ingestion, consuming 32 oz daily for over 20. Following treatment with IV Ceftriaxone and Doxycycline for pneumonia, the patient was recommended to discontinue the silver tablet supplementation and was initiated on a long-term tapering dose of Prednisone: 20mg for 21 days, 15mg for 21 days, and 10mg for 21 days. His condition improved, and he was discharged with a follow-up scheduled in Hepatology for further evaluation.

Discussion:

Argyria is a Greek word derived from “Argyros” for silver. Silver exposure can be via inhalation, transdermal, or even oral into our respiratory and gastrointestinal tracts [3]. Silver is used in various medicines, such as antimicrobials, astringents, and caustic agents, resulting in systemic deposits in different body parts. The risk of exposure to silver exists in different occupations such as silver mining, metalwork, jewelry crafting, and the photographic field. Argyria may be present either in specific areas or across the entire body, depending upon the method and quantity of silver absorption [7,8].

Upon exposure, silver salt is catalyzed by light and goes through a reduction process leading to diverse pigments such as sulfides and chlorides. These pigments, characterized by their chemical stability and low solubility, gradually store in various body tissues. They notably affect skin melanocytes, increasing their activity and resulting in irreversible skin discoloration, particularly in regions exposed to sunlight. The body naturally keeps a small amount of silver, causing its cumulative presence to rise with age. This accumulated silver, bound to proteins, is spread throughout tissues. As silver levels increase, photoactivation and metal reduction contribute to the formation of a bluish-gray discoloration in areas exposed to light [8].

Argyria may slowly look like a gray or bluish tint on the skin, spreading gradually throughout the body. However, it is generally considered harmless and not associated with malignancies. The silver deposits can occur both locally and throughout the body. In the case of our patient, the cause was the ingestion of silver over a period exceeding 20 years which resulted in skin discoloration and liver granulomas [3,8].

The clinical evaluation to differentiate argyria from other conditions presenting with skin discoloration involves considering various possible causes. Generalized argyria can resemble metabolic pigmentation disorders, although these are rare. A comprehensive clinical evaluation is vital for accurately recognizing the underlying cause [7].

Despite argyria primarily impacting the skin and superficial tissues, there have been rare cases where silver deposition in the body has been linked to the development of liver granulomatous disease, causing challenges for diagnosis as it can mimic other prevalent conditions. Although silver deposition in the liver is not characteristically associated with liver damage, it has been noted in some cases to exacerbate existing liver conditions [7].

The skin signs in argyria may be similar to those of other conditions such as cardiac cyanosis, metastatic melanoma with melanuria, hemochromatosis, and methemoglobinemia. This similarity in presentation can carry challenges for healthcare providers, making the diagnosis of argyria a consideration in rare cases [3].

Skin biopsy was done to evaluate for silver deposition; under microscopic examination, the skin showed small granular black pigment deposits located within the basement membranes of the epidermis and sweat ducts. The pigment displayed bleaching when treated with a solution containing 1% potassium ferricyanide in 20% sodium thiosulfate, confirming the presence of silver ions within it [9].

Cessation exposure to silver and protecting the skin from sunlight with sunscreen can prevent further worsening of pigmentation. However, treatments like chelation therapy, hydroquinone application, and dermabrasion are ineffective in treating the condition [7].

Conclusion:

Argyria is a rare skin disorder from ingesting or exposure to silver which can cause liver granulomatous disease like sarcoidosis. Diagnosis can be challenging to ascertain in the presence of non-specific symptoms and treatment protocol includes discontinuation of silver ingestion and symptomatic treatment.

References:

1. Jerger SE, Parekh U. Argyria. [Updated 2023 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK563123/
2. Simon M, Buchanan JA: Argyria, an Unexpected Case of Skin Discoloration From Colloidal Silver Salt Ingestion. J Emerg Med. 2020, 59:e39–41. 10.1016/j.jemermed.2020.05.011
3. Prescott RJ, Wells S: Systemic argyria. J Clin Pathol. 1994, 47:556–7. 10.1136/jcp.47.6.556
4. Rosenman KD, Seixas N, Jacobs I: Potential nephrotoxic effects of exposure to silver. Br J Ind Med. 1987, 44:267–72. 10.1136/oem.44.4.267
5. White JML, Powell AM, Brady K, Russell-Jones R: Severe generalized argyria secondary to ingestion of colloidal silver protein. Clin Exp Dermatol. 2003, 28:254–6. 10.1046/j.1365-2230.2003.01214.x
6. Kwon HB, Lee JH, Lee SH, Lee AY, Choi JS, Ahn YS: A case of argyria following colloidal silver ingestion. Ann Dermatol. 2009, 21:308–10. 10.5021/ad.2009.21.3.308
7. 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, 79:805–11. 10.4103/0378-6323.120735
8. Wadhera A, Fung M: Systemic argyria associated with ingestion of colloidal silver. Dermatol Online J. 2005, 11:12.
9. Prescott RJ, Wells S: Systemic argyria. J Clin Pathol. 1994, 47:556–7. 10.1136/jcp.47.6.556