

# Metallic cutaneous contaminant mimicking malignant melanoma<sup>1</sup>

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**A linear blue streak of the finger appearing as malignant melanoma is diagnosed with the analytical electron microscope as a cutaneous heavy metal contaminant having localized toxic effects ameliorated by the copresence of selenium.**

**Index terms:** Skin, metallic contaminant  
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Pigmented cutaneous bands or streaks are frequently a sign of malignant melanoma. Although biopsy is generally routine to establish a diagnosis, any unusual findings may necessitate specialized laboratory procedures. We describe one such lesion, which was attributed to a metalloid contaminant and diagnosed with the aid of an analytical electron microscope.

## Case report

A 31-year-old woman had been an apprentice jewelry maker for three years, but gave it up 10 years before noticing a progressively enlarging blue-black band in the lateral nail fold of her thumb. Biopsy was performed to rule out a malignant melanoma or benign pigmented nevus. There was no recent history of trauma.

Light microscopy failed to substantiate either malignant melanoma or an inflammatory disorder. Biopsy revealed refractile, fibrillar dermal structures surrounding a minute central area of sclerotic collagen. The fibers were amber-colored, anastomosing and bifurcating, and appeared to be colinear with the dermal collagen bundles (Fig. 1). These fibers were seen within the dermal connective tissue as well as within the adventitial dermis surrounding the blood vessels and sweat glands, and at high resolution were found to

contain fine opaque particles suggesting a nonbiological foreign material (Fig. 2). These inclusions did not appear to have elicited any inflammatory or giant-cell reaction.

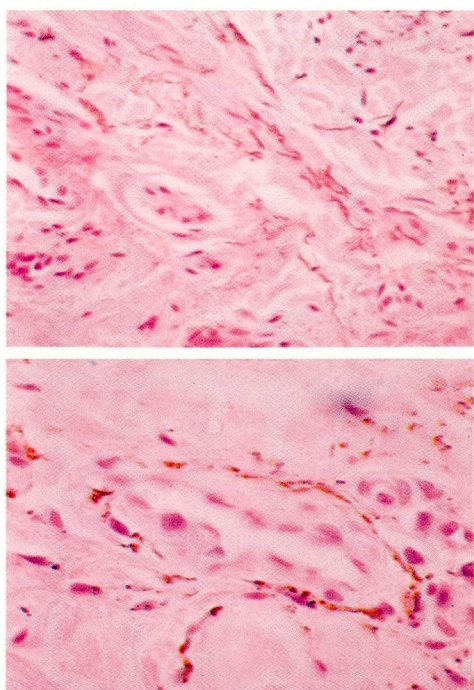
Due to the negative response of the fibers and particles to routine histologic stains, further characterization of the inclusions necessitated the use of a transmission analytical electron microscope. These studies revealed two distinct dermal inclusions. Elastic fibers containing small globular particles measuring 80-100 nm (Figs. 3-5) were found intertwined among the collagen bundles. The particles were located almost exclusively within the microfibrils forming the structural component of the elastic fibers (Figs. 4 and 5) and had a spatial distribution corresponding to the finely particulate amber fibers seen on light microscopy. X-ray analysis of these particles revealed the presence of silver, sulfur, and selenium (Fig. 6). A second set of dermal inclusions, appearing as sharply angulated crystals, was found between the individual fibrils composing collagen bundles and also within cellular structures, including dermal fibroblasts, endothelial cell nuclei, cell membranes, and mitochondria (Fig. 7). X-ray microanalysis of these crystals demonstrated calcium phosphate (Fig. 8).

## Discussion

Pigmented cutaneous linear streaks or bands are commonly attributed to melanocytic lesions or post-traumatic hemorrhage. However, finely particulate metalloid dermal contaminant may mimic such conditions by producing Tyndall diffraction or small particle aggregate coloration. This case not only demonstrated pigmentation by small particles and the need for clinical awareness of unusual causes of skin discoloration, but also provided an opportunity for studying cellular responses to localized metal intoxication.

Heavy metals are potentially toxic and could produce such metabolic disturbances as hemochromatosis (iron), Wilson's disease (copper), renal tubular necrosis (mercury), Fanconi's syn-

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**Figure 1.** Dermal segment of the skin demonstrates amber-colored filaments intertwined with collagen bundles (hematoxylin and eosin,  $\times 430$ ).

**Figure 2.** High-resolution micrograph of perivascular fibers with opaque granular inclusions. Fibers and granules did not respond to von Kossa calcium, iron, and Fontana-Masson melanin stains. Verhoeff-van Gieson stain for elastica served only to obscure localization of fibers and granules (hematoxylin and eosin,  $\times 1400$ ).

drome (lead), osteomalacia (cadmium), or cardiomyopathy (cobalt). The tendency of bivalent heavy metals to form complexes with sulfhydryl-based proteins makes such metals potent intoxicants and almost every protein in the body a potential target of heavy metal binding.<sup>1,2</sup> Normally, however, the body depends on serum proteins such as albumin, alpha-2-macroglobulin, and metallothionein<sup>3-6</sup> to bond to heavy metals, thereby diverting them from critical cellular targets. In our patient, silver was a contaminating intoxicant and produced degenerative changes, as evidenced by abnormal calcification within dermal cellular components. The association of selenium with the silver particles may represent a biological reaction resulting in amelioration of the toxic effects of the silver.

Working as an apprentice jewelry maker over a three-year period, this woman had been involved in daily lapping and polishing of silver

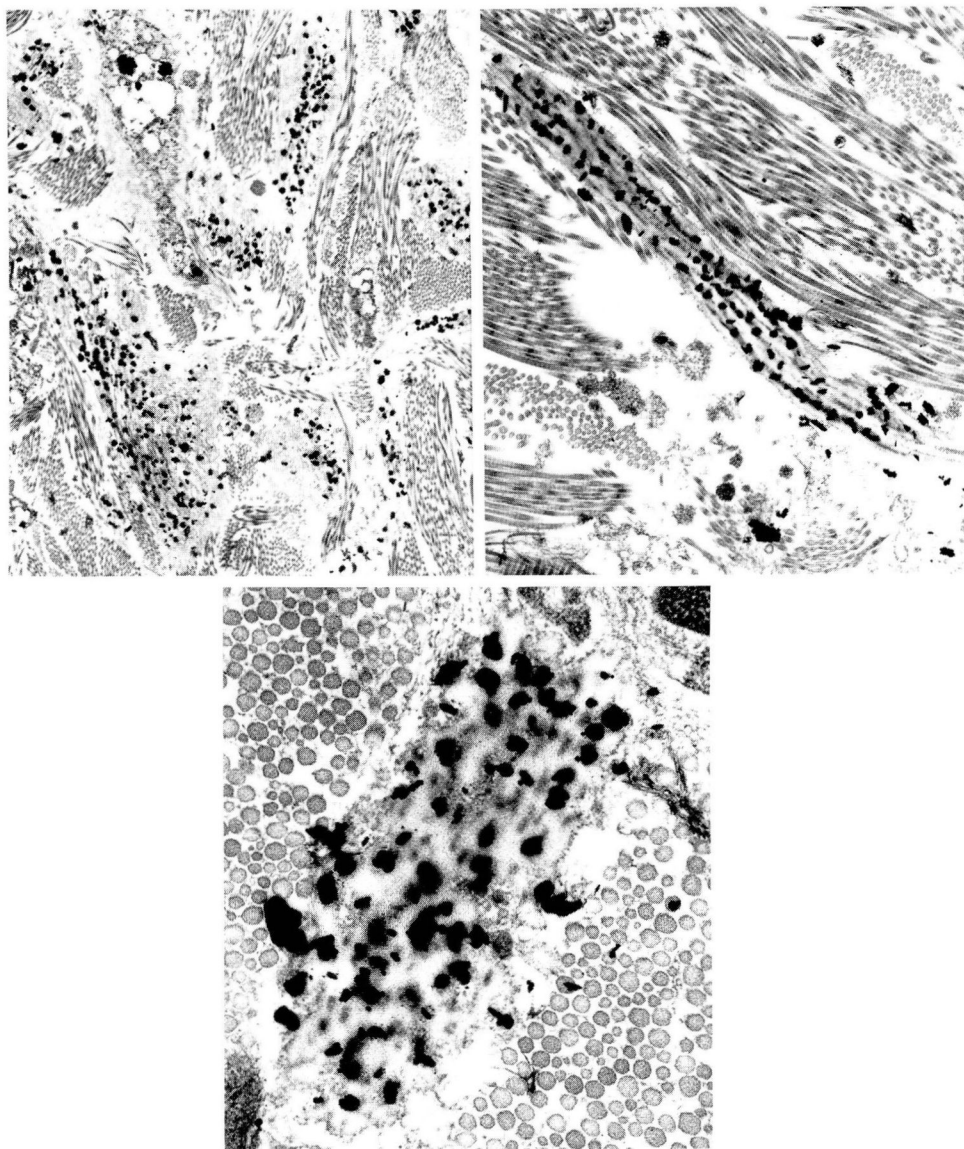
with abrasive compounds. As a result, small particles of silver may have entered abraded areas of the skin on the fingers and collected in the cutaneous tissues. Mobilization of these particles over the following 10-year period, although the patient was no longer involved in silversmithing, resulted in the concentration of microscopic silver particles within the microfibrillar component of the elastic fibers. The long hiatus between exposure to silver and the discovery of an expanding pigmented lesion may indicate slow turnover of the elastic microfibrils as well as their chemical affinity for silver.

In 1970 Albert and Fleischer<sup>7</sup> described a silver stain with a specific affinity for elastic tissues and suggested that it could be used as a marker for electron microscopy. However, the silver was conjugated to tetraphenylporphine sulfonate (TPPS), which has been shown to be specific for elastic and eosinophils, but only when injected *in vivo*.<sup>8</sup> The mechanism of *in vivo* TPPS staining was hypothesized<sup>8</sup> to involve salt-type linkages between sulfonate and basic amino acids in the elastica, although it was unclear why other acidophilic histologic groups failed to take up the stain. In the present case, an *in vivo* accumulation of metal particles with an x-ray spectroscopic sulfur component was found to have a specific affinity for elastic fibers to the exclusion of all other dermal structures.

Precursors of elastic fibers appear to be synthesized by fibroblasts and smooth-muscle cells<sup>9-12</sup> and degraded by specific elastases synthesized in the pancreas<sup>13</sup> and white blood cells.<sup>14-16</sup> In contrast to the amorphous component, the microfibrillar protein is relatively rich in cystine and histidine,<sup>10,17,18</sup> both of which are subject to nucleophilic attack by electrophilic metal ions. Since turnover of elastic fibers is thought to be slow,<sup>17</sup> the addition of metal ions to the sulfhydryl groups of half cystine and the imidazole group of histidine may take place gradually over a period of many years, eventually producing a pigmented lesion. Since the microfibrillar protein is also thought to be a glycoprotein,<sup>19</sup> metal ions may also be attracted to the negatively charged sugar moieties. Thus any discoloration of the fingers or thumbs in our patient may have gone unnoticed until enough particles accumulated to produce a composite density or Tyndall diffraction.

The establishment of selenium as a cofocal component of the microfibrillar inclusions may indicate that certain naturally occurring reactions





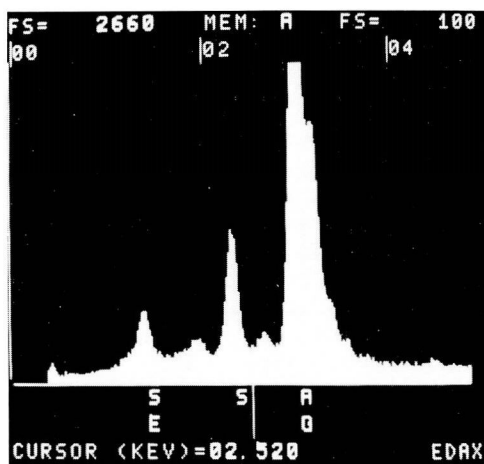
**Figure 3.** Electron microscopic survey of the dermis. Small electron-opaque particles are found exclusively within the elastic fibers and associated peripheral microfibrillar component (uranyl acetate/lead citrate,  $\times 4600$ ).

**Figure 4.** Electron micrograph of a longitudinal strap of elastia coursing parallel to the collagen bundles. The opaque particles have a linear deposition within the microfibrillar component of the elastic fiber. The amorphous component appears to be unaffected (uranyl acetate/lead citrate,  $\times 10,000$ ).

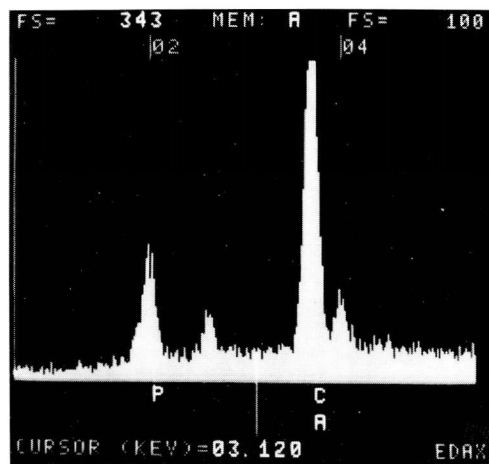
**Figure 5.** Electron micrograph of a cross section of elastic fiber. Opaque particles are found exclusively within the microfibrillar component (uranyl acetate/lead citrate,  $\times 28,000$ ).

mitigate the effects of silver toxicity. Selenium is a trace element, which is incorporated into the body as selenate through the ingestion of plants. Following metabolism of selenate to selenite and its reaction with reduced glutathione, the glutathione reductase system begins a series of reactions that ends in formation of selenoproteins

and transport of selenium throughout the body.<sup>2</sup> At tissue sites, selenium may act as an effective agent for detoxification of various metallic ions through the formation of metalloselenium protein complexes.<sup>2,20,21</sup> Experiments involving administration of equimolar heavy metal salts and selenium as selenite in animals have resulted in

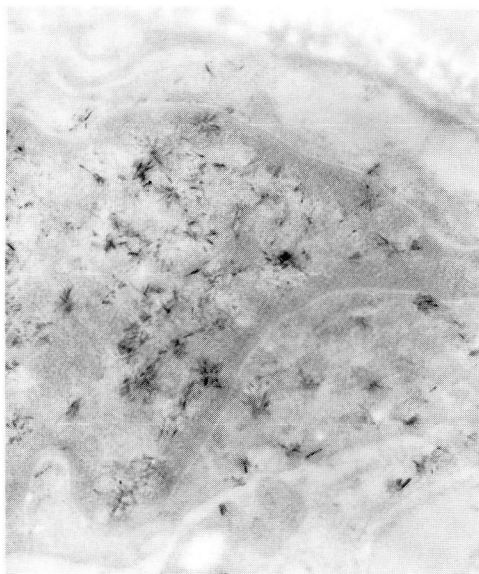


**Figure 6.** X-ray fluorescence spectroscopy of opaque particles within the microfibrillar component of the elastic fiber: silver  $L\alpha$  (2.98 keV), silver  $L\beta_1$  and  $L\beta_2$  (3.15 and 3.35 keV), sulfur  $K\alpha$  (2.31 keV), and selenium  $L\alpha$  (1.39 keV).



**Figure 8.** X-ray fluorescence spectroscopy of the angulated crystals: calcium  $K\alpha$  (3.69 keV), calcium  $K\beta$  (4.01 keV) and phosphorus  $K\alpha$  (2.02 keV).

diminished or absent signs of metal intoxication, demonstrating the effectiveness of selenium in providing protection against acute metal toxicity.<sup>2,20-25</sup> Alleviation of silver toxicity by increasing the amount of selenium in the diet has been demonstrated in laboratory animals that previously showed profound reduction in the activity of certain tissue enzymes.<sup>25</sup> Although ingestion of selenium may cause accumulation of silver-selenium complexes in tissue, diversion of silver to biologically inactive forms may reduce its tox-



**Figure 7.** Electron micrograph of an unstained section of the dermal endothelium, with angulated crystals scattered in the nucleus and cytoplasm ( $\times 17,000$ ).

icity. In humans, selenium has been implicated in the sequestration of mercury compounds in the proximal tubules in patients with mercury-associated nephrotic syndrome,<sup>26</sup> within the lysosomes of the neurons and astrocytes in patients with Minamata disease,<sup>27</sup> and within the macrophagic lysosomes of patients with industrial mercury pigmentation.<sup>28</sup> Thus the presence of selenium and silver within the dermis of our patient may be indicative of a natural amelioration process of local metallic intoxication.

Although the mechanism of silver binding to elastic fibers remains unknown, the analytical electron microscope has proved to be a valuable tool in the differential diagnosis. In the present case, the linear pigmented streak could not have been explained by light microscopy.

#### Acknowledgment

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