Accumulation of the Xanthophyll Lutein in Skin Amyloid Deposits of Systemic Amyloidosis (AL Type)

To the Editor

Tissue deposition of soluble autologous proteins as insoluble amyloid fibrils is associated with a range of serious diseases including Alzheimer's disease, the transmissible spongiform encephalopathies (prion diseases), and systemic amyloidosis (Glenner, 1980; Kisilevsky, 1998). Although yellow or brownish skin amyloid plaques have been described in several different types of systemic amyloidosis (Touart and Sau, 1998; Asl *et al*, 1999), the chromophore responsible for this yellowish hue has not been identified to date. We have used high-performance liquid chromatography (HPLC) to analyze for the first time such colored skin lesions *ex vivo*. We found a selective accumulation of the xanthophyll lutein in skin amyloid deposits of a patient with systemic amyloidosis suggesting the participation of a naturally occurring carotenoid in the pathogenesis of amyloidosis *in vivo*.

In our patient, an 86-y-old female, amyloidosis was associated with a clonal plasma cell dyscrasia caused by multiple myeloma (Touart *et al*, 1998). A defining characteristic of this serious and usually fatal type of systemic amyloidosis are amyloid proteins derived from immunoglobulin light chains (amyloid L, AL). Histologic examination of lesional skin specimens from our patient (**Fig 1*a***) revealed prominent amyloid deposits that displayed green birefringence with Congo red stain throughout the dermis (**Fig 1*b***). The ultrastructural appearance of these amyloid fibrils is demonstrated in **Fig 1(*c*)**.

For reversed-phase HPLC, tissue and plasma carotenes were extracted and separated as previously described (Wingerath *et al*, 1999). A selective 60-fold elevation in lutein concentration was detected in skin lesions of our patient (**Fig 1*d***). The mean lutein concentration was 6 nmol per g in lesional skin tissue and 0.1 nmol per g in nonlesional tissue. In contrast, plasma concentration of lutein was within normal limits (0.29 nmol per ml) indicating that the binding of lutein to skin amyloid deposits is specific.

Yellow color of the skin can be due to the presence of several physiologically occurring colored compounds such as bilirubin or carotenoids. In contrast to carotene icterus, a typical symptom after high dietary intake of β-carotene, lutein-caused coloration of the skin has not been described so far. Lutein is a micronutrient that is not formed in the metabolism of humans but can be found in dark green vegetables (e.g., kale, collards, mustard greens) and yellow or orange fruits. This carotenoid can inactivate electronically excited molecules and participate in free radical reactions (Schalch *et al*, 1999; Wingerath *et al*, 1999).

It has lately been shown that the macula lutea (Latin for yellow spot) acquires its color because the retina accumulates lutein and its structural isomer zeaxanthin from the diet via the plasma. Both carotenoids are radical scavengers and thought to protect primate retinas against damage by light and against risk of severe vision loss from age-related macular degeneration (Schalch *et al*, 1999).

Previously, we described the use of reversed-phase HPLC to separate and assign carotenol fatty acid esters in human skin (Wingerath *et al*, 1999). Here, we show the selective accumulation of the xanthophyll lutein, a major parent carotenol, in skin amyloid plaques of a patient with systemic amyloidosis. Emerging from our findings is the idea that amyloid fibrils avidly and selectively bind the naturally occurring carotenoid lutein *in vivo*, because we found extraordinarily high amounts of lutein in lesional skin only, but not in normal skin or in the blood. Our patient did not eat a special lutein-rich diet, indicating that the accumulation of lutein was not induced by an alimentary excess of the carotenoid. The abundance of lutein in amyloid deposits relative to its trace concentration in nonlesional skin tissue and in the plasma is remarkable and argues against a direct binding of lutein to the monoclonal immunoglobulins formed by the myeloma cells.

Our case thus clearly indicates a specific interaction of the naturally occurring carotenoid lutein with amyloid fibrils *in vivo*. There is considerable evidence that oxidative stress exerted by inappropriate deposition of amyloid fibrils can affect signal transduction pathways, and result in cytotoxicity (Kisilevsky,

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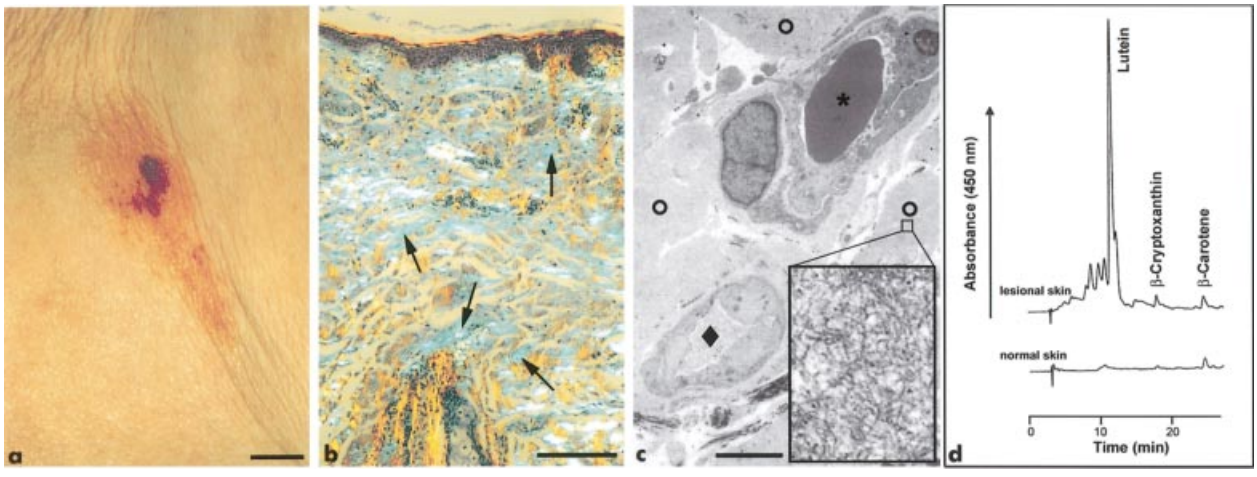

Figure 1. Accumulation of lutein in skin amyloid deposits. (*a*) A characteristic waxy yellow-orange amyloid plaque on the upper trunk of a patient with systemic amyloidosis. Purpura is a hallmark of plaque-associated amyloid angiopathy. (*b*) Micrograph of a skin amyloid plaque displaying green birefringence of Congo red-stained amyloid deposits (*arrows*) under polarized light. (*c*) Ultramicrographs of skin amyloid deposits (○) surrounding small lymphatic (◆) and blood (*) vessels (inset: fibrillary architecture of amyloid deposits). (*d*) HPLC separation of tissue carotenoids in our amyloidosis patient: significantly more lutein is present in lesional skin tissue (mean lutein concentration: 6 nmol per g, top) than in nonlesional tissue (0.1 nmol per g, bottom). Correspondingly low lutein levels were observed in normal skin of a control person (data not shown). *Scale bars*: (*a*) 1 cm; (*b*) 500 μm; (*c*) 5 μm.

1998). Consequently, an inescapable facet of linking the accumulation of lutein to amyloid pathology is the modulation of deleterious amyloid effects by the protective radical-scavenging potential of lutein. Further experimental elucidation of the role of lutein in amyloid deposits may provide new insight into amyloid-associated pathology with potentially important therapeutic implications.

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