

Progressive circumscribed sclerosis – a novel side-effect of immunotherapy with aluminium-adsorbed allergen extracts

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A 47-year-old woman developed progressive, diffuse hardening of the left upper arm and left shoulder. The extent of induration was seen more clearly when she lifted her left arm (Fig. 1). The surface of her skin showed formation of dells, discrete erythema and hyperpigmentation. Six years before presenting with this induration, the patient had undergone immunotherapy for house dust mite (ALK - Abello, Hørsholm, Denmark). She had received repeated injections, nearly all in the upper left arm, because she had been an ambitious right-handed tennis player at the time.

In the susceptible patient aluminum may trigger an autoimmune reaction with progressive sclerosis as the key clinical feature.



Figure 1. Scleredema-like sclerosis of the upper arm with erythema, hyperpigmentation and dell formation when lifting the arm.

During the treatment itself, she had observed small indurated nodules at the injection sites, as well as experienced pruritus and erythema. Patch testing and a prick test for aluminium hydroxide-containing bee venom were negative. With intradermal application of aluminium hydroxide, however, the patient developed erythema and an infiltrate.

Antinuclear antibodies and antibodies to *Borrelia burgdorferi* were negative. She had elevated IgE (138 kU/l; normal range 0–100 kU/l) and elevated specific antibodies to house dust mite (0.41 kU/l; normal range: 0–0.35 kU/l).

Two biopsies from the left shoulder showed haphazardly oriented, thickened and hyalinized collagen bundles, reminiscent of Buschke's scleredema (Fig. 2A). A deep biopsy from the left upper arm finally revealed granulomas within the subcutaneous septae (Fig. 2B). Repeated Fite stains and PAS stains excluded an infectious aetiology. With high magnification and scanning electron microscopy, a finely, granular, basophilic material within histiocytes < 1 µm was seen.

With energy-dispersive X-ray spectrometry, we could prove that

the particles within the granulomas were aluminium oxide or at least partially oxidized aluminium particles, possibly also aluminium hydroxide particles.

Aluminium salts are used as an adsorbent and immunostimulant in vaccines and immunotherapy extracts because they stimulate and enhance the immune response to the antigen. Aluminium hydroxide may lead to a delayed hypersensitivity reaction, evidenced as itching, eczema and granuloma formation (1–4). When aluminium is injected intramuscularly without an adsorbed antigen or allergen, it may only elicit granulomas (5). These 'nonimmunological' granulomas contain phagocytosing macrophages with little evidence of fibroblast activation (6). The development of a lymphoid tissue response with abundant eosinophils is linked with the presence of an adsorbed vaccination antigen or allergen (4, 5). These 'immunological' granulomas may also contain epithelioid cells and be accompanied by fibrosis (6).

Well known side-effects of aluminium-containing vaccinations are necrotizing and non-necrotizing

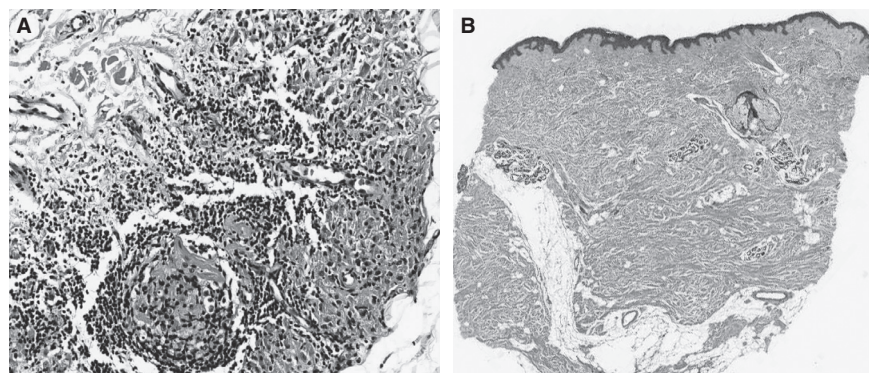


Figure 2. (A) Low magnification (40-fold, haematoxylin- and eosin-stained section) reveals haphazardly oriented, thickened and hyalinized collagen bundles within the mid and deep reticular dermis. Inlet: Note the thickened collagen bundles. (B) High power magnification (200-fold, haematoxylin- and eosin-stained section) shows small granulomas with an admixed lymphoid infiltrate. Discrete, finely granular material is visible within histiocytes.

granulomas, cutaneous pseudolymphomas, focal fibrosis, panniculitis, keloid scars or macrophagic myofasciitis (4, 7–9). The latter is a recently recognized entity associated with chronic fatigue, widespread muscle weakness and pain after intramuscular injections of aluminium hydroxide-containing vaccines.

The case reported here is unique because it was marked by diffuse and progressive circumscribed sclerosis beyond the vaccination sites rather than localized subcutaneous nodules. Repeated biopsies were needed to demonstrate the likely relationship between immunotherapy and fibrosis. Although the patch test to aluminium may be positive, this was not the case in our patient (10, 11). Intradermal application of aluminium was needed to demonstrate infiltration and erythema.

In macrophagic myofasciitis, aluminium-containing macrophages were described at the site of previous intramuscular injections (12). Our patient should have received subcutaneous injections. However, we have reason to assume that the injections were administered at least partly by the intramuscular or intradermal route. The working hypothesis is that the ability to clear aluminium from muscle and also from the dermis is impaired in predisposed individuals because aluminium was observed in nodules after inaccurate intradermal application of immunotherapy (2). As no muscle biopsy was performed in our patient, we do not know whether aluminium was also phagocytosed in intramuscular macrophages (12).

The mechanism of circumscribed progressive sclerosis may be similar to that underlying silica-induced scleroderma (13). Crystalline particles of silica < 5 µ may be phagocytosed by macrophages and release lymphokines and monokines, which activate fibroblasts and enhance their collagen and glycosaminoglycan synthesis (14).

In the susceptible patient, aluminium may trigger an autoimmune reaction, which subsequently leads to sclerosis. Although aluminium granulomas recede over time, the further prognosis in our patient remains unknown. Using a substance different from aluminium as adjuvant should be considered in the future for several reasons. One of these is the unwanted Th2 cell immune response in allergic diseases and the second, its considerable toxicity (15).

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