
Vaccination-induced cutaneous pseudolymphoma

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Background: Although mild early cutaneous transient reactions to vaccinations are common, late-onset chronic lesions have been scarcely reported. We report herein a series of 9 patients presenting with cutaneous and subcutaneous pseudolymphoma.

Observations: Nine patients presenting with late-onset, chronic skin lesions occurring at the site of antihepatitis B (8 cases) and antihepatitis A (one case) vaccination were reported. Histopathologic and immunohistochemic studies, and molecular analysis of clonality of skin biopsy specimens, were performed. Furthermore, the presence of vaccine products was investigated in skin lesions by using histochemical, microanalytic, and electronic microscopy techniques.

Results: Histopathologic studies showed dermal and hypodermal lymphocytic follicular infiltrates with germinal center formation. The center of follicles was mostly composed of B cells without atypia, whereas CD4⁺ T cells were predominant at the periphery. Molecular analysis of clonality revealed a polyclonal pattern of B-cell and T-cell subsets. Aluminium deposits were evidenced in all cases by using histochemical staining in all cases, and by microanalysis and ultrastructural studies in one case. Associated manifestations were vitiligo (one case) and chronic fatigue with myalgia (two cases).

Conclusion: Cutaneous lymphoid hyperplasia is a potential adverse effect of vaccinations including aluminium hydroxide as an adjuvant. Further prospective studies are warranted to evaluate the incidence of this complication in the immunized population. (J Am Acad Dermatol 2005;52:623-9.)

In recent years, the wide development of vaccines has raised the benefits of a prophylactic policy. Adverse effects are usually benign, mostly consisting of mild transient reactions occurring at the site of injection.¹ On another hand, locoregional reactions after a chronic, persisting course over several

months or even years have also been described after immunization with aluminium-adsorbed vaccines or hyposensitization solutions.²⁻⁶ In these cases, histopathologic studies of skin lesions revealed either a histiocytic foreign body reaction, mostly in early lesions,^{7,8} or a lymphoid infiltration showing a granulomatous reaction with or without necrosis, sometimes with the presence of eosinophilic crystalline material.^{2,6,9,10} Cutaneous lymphocytomas, also called cutaneous lymphoid hyperplasia (CLH), are benign cutaneous infiltrates predominantly composed of B cells showing a follicular architecture.¹¹ They belong to the spectrum of cutaneous pseudolymphomas, defined as B and/or T lymphocytic infiltrates of the skin exhibiting clinical and/or histopathologic features that mimic those of cutaneous lymphomas, but differing from this latter entity by their benign course.^{12,13} Although cases of cutaneous pseudolymphomas have been related to well-identified causal factors such as *Borrelia burgdorferi*¹⁴ or viral infections,^{15,16} drugs,^{17,18} or tattoos,¹⁹ causal factors remain unknown in many cases.¹² So far, cutaneous lymphocytomas after vaccination have been scarcely reported, consisting of 3 cases of

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late-onset nodular lesions occurring in children after immunization with aluminium-adsorbed vaccines. However, these latter publications did not provide evidence for the presence of vaccine components among skin lesions, which hampers the ascertainment of the causal role of vaccination and the elucidation of the pathogenic mechanisms of these cutaneous reactions.²⁰⁻²²

In this study, we report the main clinical, histopathologic, and immunopathologic characteristics of 9 patients showing persistent CLH occurring at the site of antihepatitis virus vaccination. We identified aluminium hydroxide among the skin infiltrate in all cases.

METHODS

Patients

Between 1993 and 2003, 9 patients presenting with persisting cutaneous lesions involving the site of a previous vaccine injection were collected. We investigated the following parameters: age and sex; type of vaccination, which had to be ascertained by vaccination certificate; number of vaccine injections; delay between vaccination and onset of skin symptoms and the duration of lesions at the time of diagnosis; anatomic site and semiologic presentation of cutaneous lesions; and presence of associated general symptoms. All patients had a complete physical examination, a chest radiograph examination, a serologic detection of *Borrelia* infection, an analysis of blood cell counts, and a dosage of lactate dehydrogenase in the serum. The course of lesions after therapy was also evaluated.

Morphologic studies

A skin biopsy was performed in all cases. Histopathologic analyses were carried out with light microscopy on paraffin-embedded sections stained with hematoxylin-eosin-safron. Immunohistochemical staining of skin biopsy specimens was performed on formalin-fixed specimens with a standard avidin-biotin immunoperoxidase procedure. Monoclonal antibodies used for this study were anti-CD1a, -CD3, -CD10, -CD20, -CD68, -Bcl2, and -Bcl6 (Dako, Trappes, France).

Molecular analysis of clonality

Polymerase chain reaction (PCR) amplifications of IgH/TCR γ V(D)J junctions were performed in 5 cases on DNA from fresh or snap-frozen biopsy specimens using consensus primers as previously described.^{23,24} Briefly, for IgH genes, VH-JH rearrangements were amplified by two sets of PCR reactions, using a mixture of 7 oligonucleotides directed against conserved sequences of the FR1 region of each VH family and

one consensus JH primer and the second using a consensus FR3 primer and a consensus JH primer. For TCR γ (TCR γ) genes, the procedure included 3 reactions with 3 different mixtures of primers (VGI-cons-JG2S2; VGI-cons-JGP-JGP1,2; and VG9-VG10-VG11-JG2S2-JGP-JGP1,2). PCR products were analyzed by polyacrylamide gel electrophoresis, with revelation by ethidium bromide staining.

Detection of aluminium hydroxide in skin lesions

A search for inorganic deposits (aluminium) was performed in skin biopsy specimens by using Morin technique as previously described.²⁵ Briefly, sections were subjected to staining with Morin reagent (penta-hydroxyflavone) after pretreatment with hydrochloric acid allowing dissolution of calcium salts, and examined using fluorescence microscopy at 515 to 545 nm. Ionic microanalysis and electron probe microanalysis were performed to assess the distribution of elements in the tissues and the chemical composition of intracellular inclusions, as described previously.²⁶ Briefly, on unstained sections, images of the distribution of aluminium in a field of 250 μ m in diameter were obtained by microanalysis with an ion microscope (SMI 300 CAMECA) as previously described and electron probe microanalysis was conducted on an electron microscope (Philips; the Netherlands, EM300) equipped with a radiographic spectrometer (CAMECA MBX; Courbevoie, France), as previously described.

Patch tests

Patch tests were performed with 2% aluminium chloride hexahydrate in petrolatum, with thimerosal, and with the whole vaccine preparation. Results were analyzed 48 hours and 96 hours later.

RESULTS

Epidemiologic and clinical features

As shown in Table I, 8 female patients and one male patient were included, their age ranging from 13 to 54 years (median: 21 years). They were free of any history of skin disease and of drug hypersensitivity. Anamnesis revealed no evidence of drug intake before skin lesions, and no history of tick bite could be assessed. The injected vaccines at the site of skin lesions were aluminium hydroxide-adsorbed vaccines in all cases, consisting of antihepatitis B in 8 cases, and antihepatitis A in one case. The delay between the last vaccine injection and the onset of lesions was less than 12 months in most cases, ranging from 1 month to 5 years (median: 3 months). In all cases, skin lesions appeared after a recall injection. The duration of skin lesions at the time of inclusion ranged from 7 to 38 months (median: 18 months). The lesions involved the site of vaccination

Table I. Characteristics of patients with cutaneous lymphoid hyperplasia related to vaccination

| Case no. | Age, y/sex | Vaccine type (no. of injections) | Delay between last vaccination and skin lesions, mo | Duration of skin lesions, mo* | Clinical presentation |
|----------|------------|-------------------------------------|---|----------------------------------|---|
| 1 | 54/F | Havrix (2) | 1.5 | 12 | Subcutaneous nodules, plaques |
| 2 | 18/F | Engerix B (3) | 1 | 30 | Subcutaneous nodule, vitiligo |
| 3 | 19/F | GenHevac B (2) | 2 | 36 | Two subcutaneous nodules |
| 4 | 21/F | GenHevac B (3) | 1 | 38 | Two subcutaneous nodules |
| 5 | 13/M | GenHevac B (3) | 4 | 7 | Subcutaneous nodules, papulonodule |
| 6 | 24/F | GenHevac B (4) | 3 | 36 | Subcutaneous nodules, papulonodule |
| 7 | 36/F | Engerix B (3) | 60 | 12 | Subcutaneous nodule, chronic fatigue, myalgias |
| 8 | 15/F | Engerix B (3) | 6 | 18 | Subcutaneous nodule |
| 9 | 40/F | GenHevac B (3) Engerix B (1) | 18 | 4 | Subcutaneous nodule, chronic fatigue, myalgias |

F, Female; M, male.

*At time of diagnosis.

in all cases of the study, including arm (9/9) and shoulder (1/9). Patients presented with a solitary lesion in 4 cases, and with multiple lesions in 5 cases. Cutaneous lesions consisted of subcutaneous nodules in all cases, associated with papulonodules in two cases (Fig 1). Of note, one patient developed a histologically proven vitiligo lesion surrounding the cutaneous postvaccinal lesion and a depigmentation of the eyelids (Fig 1). Five patients had mild pruritus at the site of skin lesions, and two patients presented with chronic fatigue with myalgia after a progressively worsening course (cases 7 and 9). Extracutaneous clinical examination did not reveal weight loss, fever, lymphadenopathy, or hepatosplenomegaly.

Biologic investigations

Blood leukocyte counts were within normal range in all cases, without atypical circulating cells by cytologic examination. The dosage of lactate dehydrogenase in the serum yielded normal levels in all patients. Serologic tests for *Borrelia* were negative in all patients. The serologic detection of antihepatitis B virus antibodies was available in cases 3, 7, and 8. In these 3 cases, anti-HBs antibodies were detected at a protective titer, without evidence of anti-HBc antibodies. The search for HBs Ag was negative in these patients.

Histologic and immunohistologic studies, and molecular analysis of clonality

Histologic evaluation revealed a pandermal dense lymphocytic infiltrate also involving subcutis. Infiltrates showed a nodular pattern in 5 cases whereas a diffuse and nodular architecture was observed in 4 cases. No evidence of cytonuclear atypia could be observed. In all cases there were germinal centers accompanied by variable interfollicular fibrosis with

a smattering of other inflammatory elements including eosinophils, plasma cells, and histiocytes. The cells in the histiocytic cell population were disposed singly or in a clustered array, manifesting rather abundant granular eosinophilic to basophilic cytoplasm. Phenotypic studies revealed that the germinal centerlike foci were indeed of follicular center origin as revealed by CD20, CD10, and bcl-6 positivity with no expression of bcl-2 (Fig 2, A). The lymphoid population peripheral to the germinal centers was composed of a mixture of CD3⁺ CD4⁺ T cells with CD68⁺ histiocytes (Fig 2, B to F).

Studies of the clonality status of skin lesions by PCR-based analysis of frozen skin biopsy specimens revealed polyclonal patterns of VH-JH and V γ -J γ loci in all 5 analyzed cases (cases 1, 3, 4, 6, 7).

Patients 7 and 9 underwent a deltoid muscle biopsy, respectively, 1 year and 6 years after the onset of skin lesions. In patient 7, histologic examination of muscle showed focal lymphocytic microvasculitis infiltrate, even though the architecture of muscle remains normal. In patient 9, a lymphoid hyperplasia similar to that evidenced by previous skin biopsy specimen was observed in perimuscular fat tissue. Immunostaining analysis using monoclonal antibodies antimajor histocompatibility complex class I and major histocompatibility complex class II antigens showed foci of HLA class I—expressing myofibers that were predominantly observed in perifascicular areas.

Electronic microscopy and microanalysis, and immunohistochemical studies, reveal the presence of aluminium hydroxide within skin infiltrates

In all cases, Morin staining disclosed fluorescence suggestive of aluminium deposits in large



Fig 1. Hyperpigmentation at site of underlying nodular subcutaneous lesion involving arm for patient 3 (*left*). In patient 2, hypopigmented macular lesion developed over subcutaneous nodule (*middle*), with further onset of vitiligo lesions on upper eyelids (*right*).

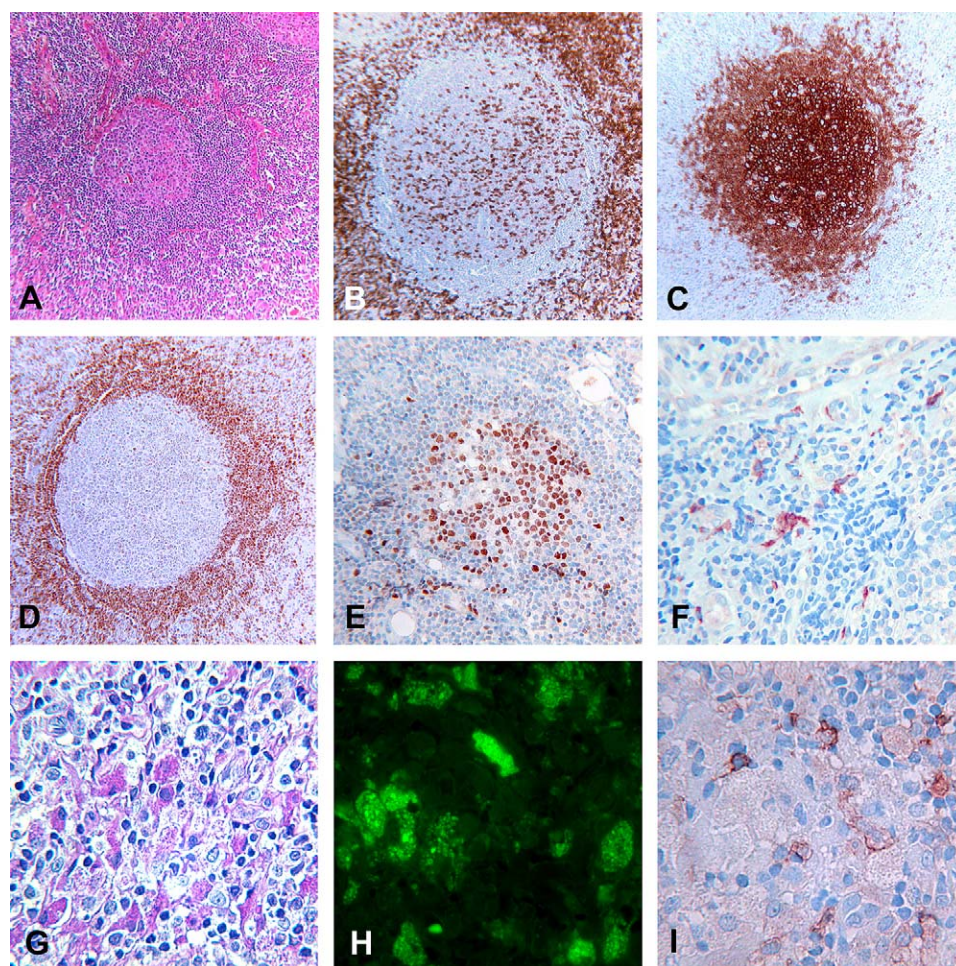


Fig 2. Histologic sections of paraffin-embedded skin biopsy specimens for patients with vaccine-induced cutaneous lymphoid hyperplasia. Hematoxylin-eosin stain reveals architecture typical of lymphoid follicle with germinal center formation (**A**). Immunoperoxidase stainings for CD3 (**B**), CD20 (**C**), Bcl-2 (**D**), Bcl-6 (**E**), and CD1a (**F, I**) show predominance of B lymphocytes within follicles, whereas T lymphocytes are detected in periphery of follicles and in interfollicular areas. Periodic acid–Schiff (PAS) staining allows detection of PAS-positive large macrophages (**G**). **H**, Results from Morin staining, showing granular cytoplasmic fluorescence of aluminium deposits in interfollicular macrophages.

mononuclear cells, presumably histiocytes, mainly located in interfollicular areas (Fig 2, *H*). Fluorescence was cytoplasmic with granular pattern, suggesting intralysosomal accumulation.

Ultrastructural studies of a skin biopsy specimen from patient 6 revealed the presence of dense needle-shaped inclusions in histiocytes (Fig 3). Images of distribution of aluminium obtained by analytic ion

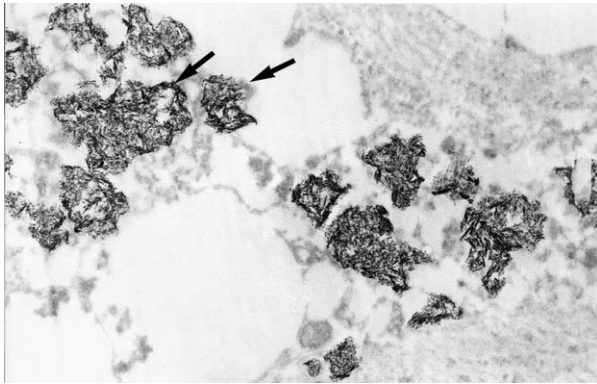


Fig 3. Electron probe microanalysis of lesional skin biopsy specimen in case 6. Intracellular, electron-dense crystal inclusions are observed in histiocytes (arrows).

microscopy showed that this element was concentrated in spots, in the cytoplasm of histiocytes (Fig 4). The electron dense particles observed in histiocytes were identified by electron probe microanalysis as aluminium crystals. No significant amounts of aluminium were demonstrated in the cytoplasm of lymphocytes. Although the presence of phosphorus and calcium traces was also evidenced, aluminium was the only inorganic element to be detected.

Patch tests with aluminium and vaccine preparation yielded negative results in two cases analyzed (patients 7 and 8).

Follow-up

Skin lesions followed a chronic course in all cases, with a mean follow-up of 24 months (range 0-60 months; median 18 months). The treatment consisted in surgical excision of lesions in 4 patients without further relapse (cases 6-9). Intralesional steroid injection was performed in cases 2 and 3, resulting in complete remission within 4 and 12 weeks, respectively. A clinical stability was observed for patient 1 who received topical dipropionate betamethasone. Patient 4 received hydroxychloroquine sulfate 400 mg/d without significant effect during an observation period of 4 months, and was further lost to follow-up. Study patients did not receive further injections of the responsive vaccine.

DISCUSSION

We report herein 9 patients presenting with persisting cutaneous lesions occurring at the site of previous antihepatitis B or antihepatitis A vaccine injections, showing morphologic features of CLH. The causal role of the vaccine injection in skin lesions was suggested on the basis of the chronology and of the topography of initial lesions, and was fully established by the positive detection of aluminium

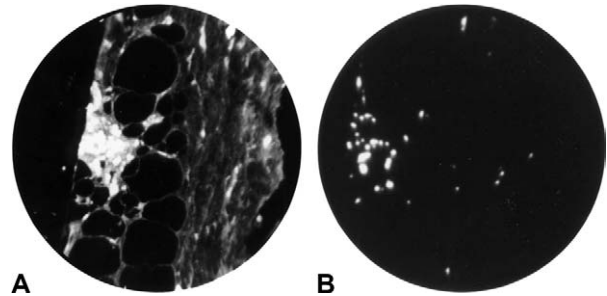


Fig 4. Results from ionic microanalysis of hypodermal tissue within skin biopsy specimen in patient 6. Images represent distribution of calcium (A) and aluminium (B). Calcium distribution allows localization of histiocytic infiltrate. Aluminium deposits are exclusively observed within macrophagic infiltrate.

hydroxide in lesional skin biopsy specimens from all cases, without evidence of other causal factor of CLH. To our knowledge, even though 3 cases of late-onset cutaneous lymphoid nodules after aluminium-adsorbed vaccination have been described previously,²⁰⁻²² the currently reported cases are the first demonstration of antihepatitis B and hepatitis A vaccination-derived aluminium deposits within lesions of CLH.

In previously published reports, histopathologic features of subcutaneous nodules occurring in immunized patients were suggestive of a foreign body reaction, showing a predominant granulomatous pattern with giant cells and a central necrosis, with evidence of the presence of calcium phosphate in some cases.²⁻⁶ The current series differs from previously reported cases by the lack of any granulomatous feature and of giant cells in 8 cases, whereas the presence of granulomatous changes, mixed with follicular infiltrates, was observed in one case. In one previously reported case, early histologic findings consisted of a granulomatous pattern and inclusions with germinal centers were observed later on, suggesting that inorganic deposit-containing vaccines, such as aluminium hydroxide, could sequentially induce histiocytic foreign body reaction, granuloma mixed with follicular infiltrates, and, finally, follicular infiltration.²⁷ Indeed, the long delay between the causal vaccination and the date of skin biopsy in our cases (median time: 3 years) are consistent with this latter model, and it is noteworthy that the only case with granulomatous features was the one with the shortest time duration of skin lesions.

The series reported herein shows that aluminium hydroxide-containing vaccines are a potential causal factor of cutaneous pseudolymphoma. Indeed, vaccines causally involved in the current cases contained aluminium hydroxide. Morin staining evidenced

aluminium salts in interfollicular macrophages and macrophagic inclusions displayed a crystalline ultrastructure suggestive of hydroxide rather than aluminium phosphate. Positive detection of aluminium hydroxide within the macrophagic component of lesions of CLH support its imputability, which has been previously established in granulomatous lesions after subcutaneous injection of vaccines containing aluminium in animal models.^{5,6} Our observations also raise the issue of the mechanisms underlying this unusual adverse effect of vaccinations. CLH shows a follicular architecture with germinal center formation, suggestive of an antigenic stimulation. The follicles are mostly composed of large B cells in the center, with small B lymphocytes in close contact with T CD3 lymphocytes at the periphery, whereas interfollicular zones are mostly composed of T lymphocytes mixed with macrophages.^{28,29} Furthermore, the fact that different types of vaccinations, and different lots of the same vaccine, were involved rules out a contamination of vaccines by a common agent. The negativity of patch tests using aluminium hydroxide and/or vaccine in our patients is not surprising, because contact hypersensitivity to aluminium has been scarcely documented in granulomatous delayed lesions occurring in vaccinated patients, and the injection route is likely to be mandatory in these unusual reactions.^{15,16,18,21-25} The pathogenic role of aluminium hydroxide in our cases is reinforced by the presence of chronic fatigue with myalgia in two cases, raising the overlap of CLH with macrophagic myofasciitis (MMF), a recently recognized entity related to intramuscular injection of aluminium hydroxide-containing vaccines, with evidence of macrophagic aluminium inclusions in muscle biopsy specimens.^{30,31} Interestingly, lymphoid follicular features have been shown associated with a macrophagic infiltrate in 22% of muscle biopsy specimens in patients with MMF.³¹ Thus, a common pathogenic mechanism might underlie vaccination-induced CLH and MMF, and, accordingly, general and muscular symptoms should be systematically assessed in studies of patients with CLH related to vaccine injections.

Alternatively, aluminium hydroxide could participate in the pathogenic mechanisms by its stimulatory properties on the immune system, because aluminium has been shown to induce a Th2 response³² and to up-regulate accessory properties of human monocytes by an IL-4 dependent mechanism.³³ Following this second hypothesis, aluminium hydroxide would enhance an immune response to unidentified target antigens.

This reported set of cases warrants further prospective studies to evaluate the incidence and the

clinical course of CLH in the population receiving aluminium hydroxide-containing vaccinations. These cases and those of MMF also raise the interest of aluminium-free preparations in these patients. In the future, the production of vaccines that could be delivered through alternative routes such as mucosal and transcutaneous pathways could also be beneficial. Furthermore, the characterization of antigenic targets of skin-infiltrating lymphocytes should be a crucial step to recommend guidelines in forthcoming vaccinations.

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