Subcutaneous nodule after vaccination with an aluminum-containing vaccine

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SUMMARY

Persistent subcutaneous nodules may arise after vaccination or allergen desensitization. The swelling might appear as a result of a specific histiocytic reaction to aluminum, which is used in many preparations to hasten immune response. A wide range of such vaccines are used in national childhood vaccination programs. Such nodules are frequently itchy or painful with local skin alterations. The condition tends to resolve spontaneously, although long-term observation is recommended. We describe the clinical history of a 10-year-old girl who presented with an itchy subcutaneous nodule that appeared five months after her second DiTe revaccination.

KEY WORDS

aluminum, nodules, persistent, subcutaneous, vaccination

Introduction

Persistent subcutaneous nodules develop frequently in infants and children. Differential diagnosis includes a wide spectrum of reactive conditions, such as non-specific inflammations, infections, and granulomatous reactions to insect bites, as well as a variety of cutaneous neoplastic disorders (1, 2).

In some cases the development of subcutaneous nodules may represent a specific histiocytic reaction to the aluminum used as an adjuvant in vaccines and hyposensitizing agents (1, 3, 4). The condition is frequently misdiagnosed either due to the rarity of persistent swellings at the injection sites or the long interval that may occur between vaccination and the presentation of the swelling (2, 3). Last, but not least, the lack of familiarity with this condition among pathologists may reflect a paucity of histopathologic description in the literature (3).

Aluminum granuloma may be associated with pain, itching and local skin alterations, such as hypertrichosis, eczema, excoriation, and hyperpigmentation, and systemic symptoms, such as low-grade fever, sleep disturbances, and irritability (1, 5, 6). These symptoms may deteriorate during upper respiratory tract infections (2). Nodules usually persist for several months or years, but a decrease in associated symptoms and spontaneous regression of the lesion are noted in all cases (2, 5).

Case history

A 10-year-old otherwise healthy girl was admitted to the University Department of Pediatrics with a his-

tory of subcutaneous swelling on the outer side of the left upper arm. The swelling was of 8 months duration. The swelling was itchy and became erythematous after being scratched. An insect bite in the same region had been recorded a few months earlier. The patient was vaccinated according to the national childhood vaccination program and had no history of allergic reactions. The second Di Te revaccination had been carried out 13 months prior to admission to the hospital. The vaccine (*Td pur, Chiron)*, serial number 023042A, included aluminum hydroxide as an adjuvant.

At admission, a firm, non-tender subcutaneous nodule on the outer side of the left upper arm was observed, measuring 3.5 × 3 cm at its greatest diameters. The nodule was movable, and was covered with slightly bluish skin. The regional lymph nodes were not enlarged.

A fine needle aspiration biopsy (FNAB) of the nodule was performed, but the results of the cytological examination were inconclusive. An excision biopsy followed.

Pathological findings

Three histopathological patterns of aluminum granuloma have been described: 1) loose subcutaneous collections of histiocytes; 2) prominent subcutaneous mononuclear inflammatory cell infiltrates with eosinophils and germinal center formation; and 3) deep granuloma annulare-like infiltrates with dense collections of macrophages surrounding the necrobiotic area.

In our case, histopathology revealed predominantly the first of the above histopathological patterns. This included a normal epidermis with mild perivascular and periadnexal inflammatory infiltrates in the upper dermis composed of lymphocytes and histiocytes. In the subcutaneous tissue, areas of hyalinized fat necroses, a few lymph follicles with reactive germinal centers and perifollicular areas, and a predominantly mononuclear inflammatory infiltrate were found. Inflammatory cells consisting of lymphocytes, histiocytes, plasma cells, and a few eosinophils were observed involving septa and lobules of subcutis. Focal accumulation of histiocytes was identified in Giemsa stained sections with abundant basophilic granular cytoplasm. These were PAS-positive and diastase-resistant. Figure 1.

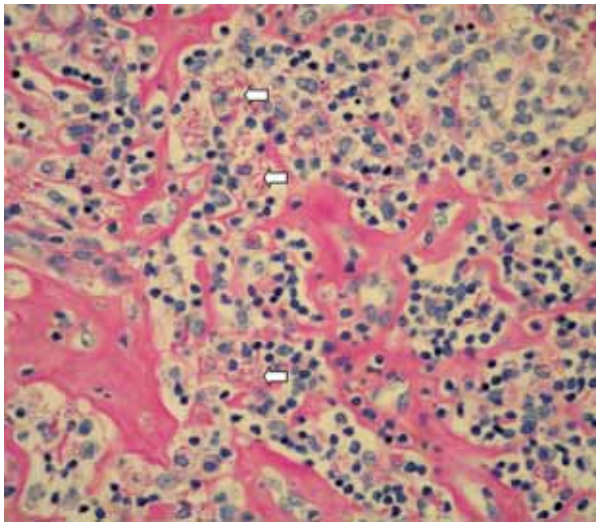

Figure 1. Focal accumulation of histiocytes with granular, PAS-positive cytoplasm (arrows).

The lesion was diagnosed as postvaccinal aluminum granuloma; that is, a histiocytic reaction to the aluminum commonly used as an adjuvant in many vaccines.

Discussion

Numerous preparations, including a wide range of vaccines used in national childhood vaccination programs, employ aluminum salt as an adjuvant because of its ability to increase and prolong the immune response to the antigen (1, 4, 7). Development of transient palpable nodules at the injection site following vaccination or upon hyposensitization with allergens containing aluminum salt is known. This is attributed to the immunologic interaction with the administered antigen and a foreign body reaction to the aluminum salt (1, 8).

In rare cases, the development of persistent itchy subcutaneous nodules at the injection site is observed (4, 5, 8), usually several weeks or months (minimum 1 month, maximum 2 years) after vaccination or desensitization with an allergen (2, 3, 5, 7, 8).

Based on histopathological features, the appearance of persistent subcutaneous nodules may be a result of two different mechanisms: (1) a non-allergic, possibly direct toxic effect from aluminum, and (2) a delayed hypersensitive reaction to aluminum. Note that the histopathology may demonstrate an overlap of patterns (4); however, various histopathological patterns of the lesion commonly share a similar clinical picture and outcome (1, 4, 8).

It has been suggested that the injection site and the technique used might also be involved in appearance of the nodule. Comparing subcutaneous and intramuscular injections, Frederiksen et al. considered subcutaneous application more likely to be associated with the development of a subcutaneous nodule resulting from the presence of Langerhans' cells in the epidermis. However, Bergfors et al. did not find any association between the type of injection and frequency of development of the nodules (6, 7). Some studies reveal a high percentage (up to 77 percent) of positive patch tests to aluminum, even in symptomless vaccinated siblings in control study groups; others have not found evidence of delayed hypersensitivity to aluminum of control group members with otherwise comparable clinical histories (2, 5, 7).

Despite the tendency for spontaneous regression, long-term follow up has been recommended (2). Delayed hypersensitivity to aluminum at the injection site, with a persistent antigenic stimulation causing a chronic immune response, could eventually evolve into a lymphoid malignancy (8).

In accordance with the clinical presentation and the histopathological finding, we diagnosed our clinical case as a specific histiocytic reaction to the aluminum, which was most probably initiated by a DiTe vaccine thirteen months previously to admission to our department. The girl was the first patient in our pediatric population with histologically proven diagnosis of postvaccinal aluminum granuloma mimicking lupus profundus, which is considered its rarest morphological variant.

Follow up

9 months after excision of the nodule, the patient is symptomless and enjoys good health. She merely has a hyperpigmented scar at the site of the biopsy, which was treated topically with antihistamines.

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