

Aluminium and injection site reactions

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Abstract

Aims—To alert pathologists to the spectrum of histological appearances that may be seen in injection site reactions related to aluminium.

Methods—Four cases of injection site reaction were examined microscopically using routine staining with haematoxylin and eosin, electron microscopy and by electron probe microanalysis.

Results—As in previous reports, all four cases included collections of histiocytes which contained faint granular brownish refractile material within their cytoplasm; ultrastructural examination showed this to be aluminium. Two cases showed a prominent inflammatory reaction with numerous lymphoid follicles and a notable eosinophilic infiltrate. Two cases showed unusual features not described previously. In one, there was a sclerosing lipogranuloma-like reaction with unlined cystic spaces containing crystalline material. The other case presented as a large symptomatic subcutaneous swelling which microscopically showed diffuse and widespread involvement of the subcutis by a lymphoid infiltrate with prominent lymphoid follicles.

Conclusions—This report highlights the changes encountered in aluminium injection site reactions and emphasises that the lesions have a wider range of histological appearances than described previously.

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As a result of its ability to heighten the immune response,¹ aluminium hydroxide is used as an adjuvant in a wide range of vaccines, including those for diphtheria, tetanus, pertussis, hepatitis A, and hepatitis B. However, hypersensitivity reactions to aluminium compounds are well known and include allergic contact sensitivity developing after desensitisation of hay fever with aluminium precipitated allergens,² reactions to antiperspirant sticks,³ and reactions to the empty Finn chamber aluminium discs used for patch testing of potential allergens. Factory workers using recycled aluminium have developed a pruritic dermatitis from dust composed of a mixture of aluminium and possibly other metals⁴ and eczematous lesions have developed in aircraft workers exposed to aluminium filings.⁵ Transient inflammatory reactions causing little discomfort but lasting for up to a few weeks occasionally complicate vaccination^{2,6} and, rarely, painful subcutaneous nodules develop at vaccination sites up to two years

after injection of aluminium adsorbed vaccines^{2,7-11}. Most of the reported cases have occurred in children under three years of age, but reactions have been seen in adults up to 51 years old.¹²

Histologically, the classic appearance of these injection site reactions consists of a nodular inflammatory infiltrate with lymphoid follicles within the deep dermis and subcutaneous tissue.^{10, 11} Large collections of macrophages are seen and an eosinophil polymorph infiltrate is usual. In some cases scattered giant cells and areas of eosinophilic necrosis are present. Finely granular refractile material can usually be found within macrophages and the diagnosis can be confirmed using electron probe microanalysis.

We searched our files over the past five years for patients who developed subcutaneous nodules following vaccination and describe a variety of histological appearances, two of which are outside the range of patterns described previously. In addition, one case had an unusual clinical presentation and course.

Case histories

CASE 1

A two year old boy developed a tender subcutaneous lump on the right buttock, which had increased in size over six months and measured 10 mm in diameter at excision. He had received diphtheria, tetanus and pertussis vaccination at this site when he was one year old. This lesion was excised and did not recur.

CASE 2

A 48 year old woman developed a diffuse 70 mm diameter subcutaneous swelling over the left deltoid and upper arm, which was itchy and tender. The patient believed this to be related to an insect bite and the initial histopathological opinion supported this. She was treated with topical steroids, antifungal agents and antibiotics but with no improvement. The correct nature of the reaction became apparent at a clinicopathological review meeting some months later. She had received tetanus vaccination at that site three months prior to the development of symptoms and she was subsequently shown to have a positive reaction to empty aluminium Finn chambers used for patch testing. She underwent a total of three excisions over a two year period in an attempt to alleviate symptoms. Although there is no current visible swelling or induration the patient still complains of itching along and around the scar.

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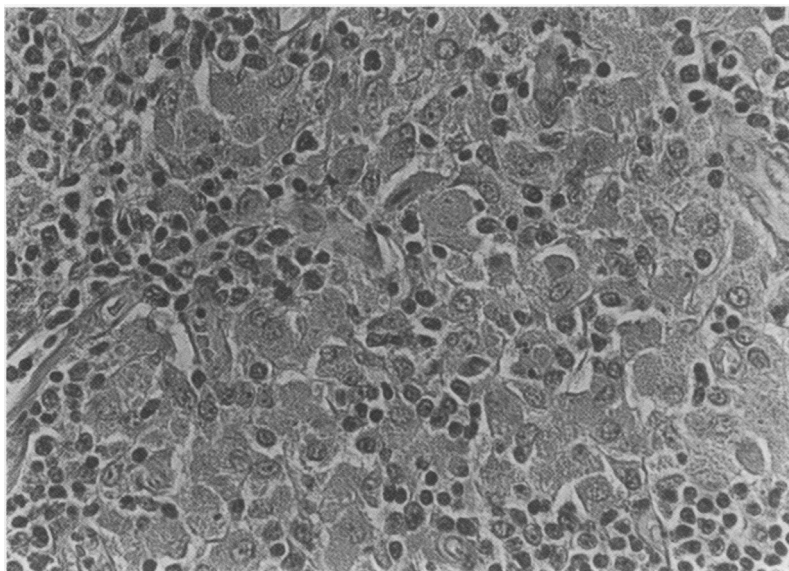


Figure 1 Macrophages containing cytoplasmic refractile granular material.

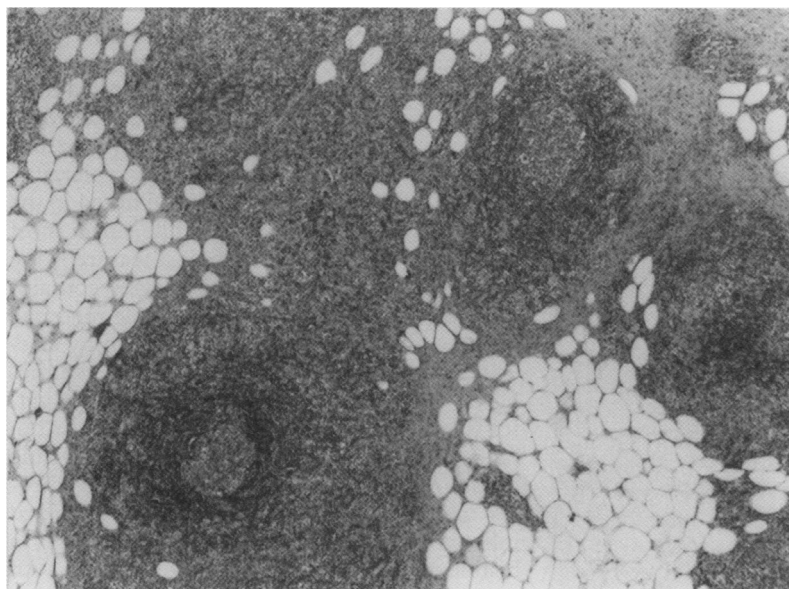


Figure 2 Case 2. Lymphoid follicles, sheets of macrophages and occasional fibrous tissue strands can be seen diffusely extending through the subcutaneous fat.

CASE 3

A three year old boy developed a tender subcutaneous lump in the left thigh which had been enlarging over the previous six months. He had received diphtheria, tetanus and pertussis vaccination at this site one year previously. On excision, the mass was a firm 10 mm nodule containing cystic spaces. There was no recurrence after excision.

CASE 4

A 26 year old woman presented with a painful subcutaneous nodule on the right upper arm which had developed gradually over six months following tetanus vaccination. There was no recurrence after excision.

Methods

Tissue from all patients was examined microscopically after routine staining with haematoxylin and eosin, by electron microscopy and by electron probe microanalysis. Tissue submitted for the latter was sent as 1 mm thick

slices fixed in 3% cacodylate buffered glutaraldehyde. Each slice was treated further with 2% cacodylate buffered osmium tetroxide and the block stained with 2% aqueous uranyl acetate. Tissue slices were then embedded in Spurr's epoxy resin.

Semi-thin 0.5 μm sections were cut and stained with toluidine blue for light microscopy, from which suitable areas for the preparation of ultra-thin 100 nanometre sections were selected. These sections were mounted on formvar coated grids. Tissue was then examined by transmission electron microscopy and an x ray spectrum was acquired over a period of 100 seconds at 60 KV using a Hitachi H7000 electron microscope equipped with a link PXA1 x ray analysis system.

Results

LIGHT MICROSCOPY

Case 1

This lesion consisted of a fibrous nodule within which were lymphoid follicles and sheets of macrophages containing granular slightly refractile brownish material (fig 1). Numerous eosinophils were seen. There was no evidence of necrosis and giant cells were not present. The vessels around the edge of the lesion showed a perivascular lymphocytic infiltrate.

Case 2

This case showed a more diffuse histological picture extending into subcutaneous fat. The infiltrate consisted of lymphoid follicles and sheets of histiocytes, some containing faint granular material. An abundance of eosinophils was present, but only occasional strands of fibrous tissue extended through the lesion (fig 2). A subsequent biopsy specimen taken from the edge of the lesion showed only a perivascular lymphocytic and eosinophilic infiltrate. The most recent excision biopsy specimen showed similar features to the first one.

Case 3

In this case, the subcutaneous fat contained a well circumscribed inflammatory mass with a sclerosing lipogranuloma-like appearance with surrounding fibrosis (figs 3 and 4). The inflammatory infiltrate consisted of lymphocytes and histiocytes containing granular material, shown to be aluminium on electron probe microanalysis. In addition, occasional crystalline deposits were seen within the walls of pseudocystic spaces with an associated foreign body giant cell reaction. These crystals did not stain with solochrome-azurin (for aluminium). Foci of dystrophic calcification were also present. Neither lymphoid follicles nor an eosinophil infiltrate was present in this case.

Case 4

This specimen consisted of subcutaneous fat containing a nodular collection of chronic inflammatory cells and sheets of histiocytes with faint granular cytoplasmic material. Very little fibrous tissue was present within or

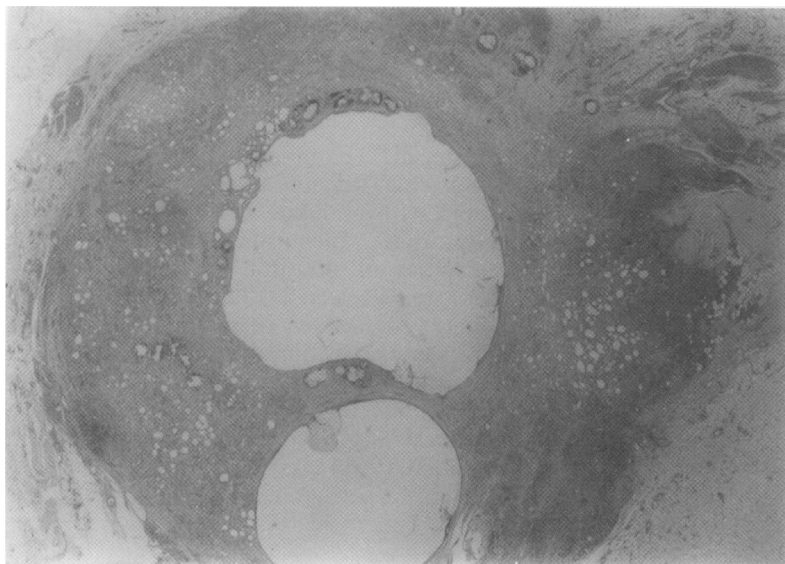


Figure 3 Case 3. A well circumscribed nodule of inflammatory tissue with associated fibrosis. Occasional deposits of crystalline substance within the lumen and walls of cystic spaces can be seen.

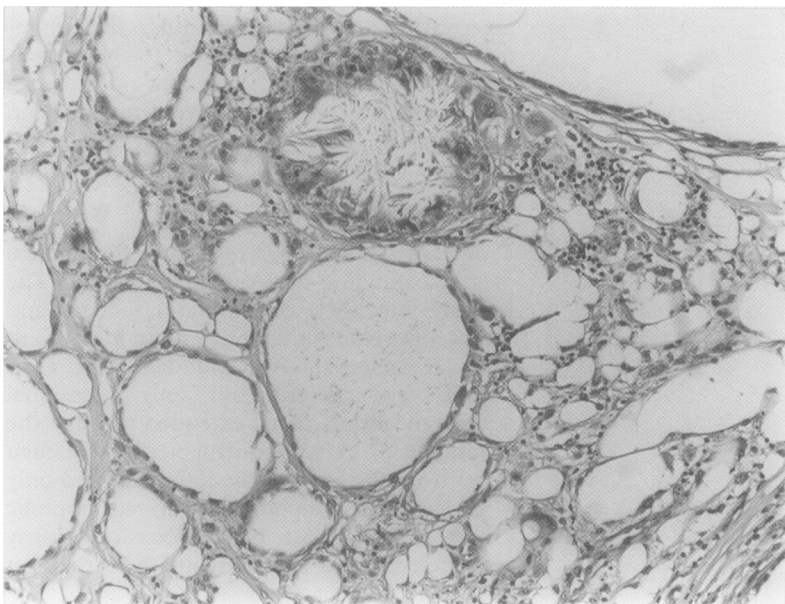


Figure 4 Case 3. Sclerosing lipogranuloma-like areas are present.

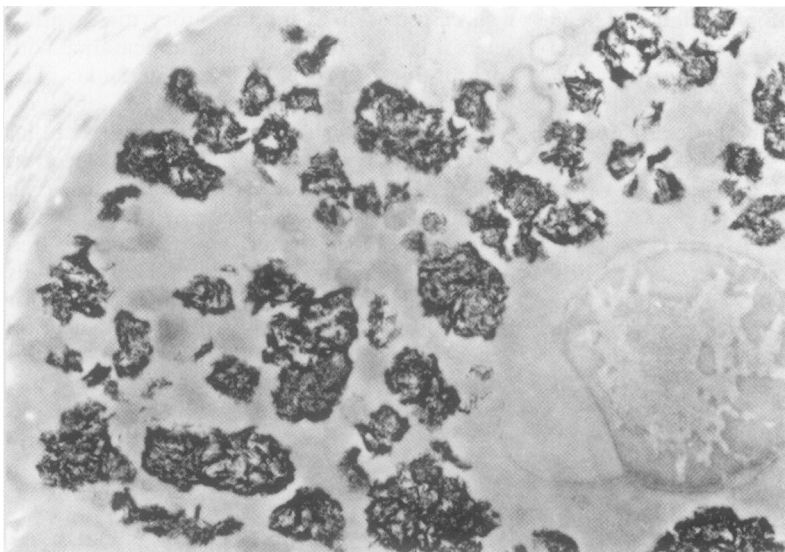


Figure 5 Macrophage containing granular aluminium deposits (original magnification $\times 8000$).

around the lesion. There were no giant cells, lymphoid follicles nor an eosinophil infiltrate.

ELECTRON MICROSCOPY AND ELECTRON PROBE MICROANALYSIS

All four cases showed characteristic granular electron dense deposits within histiocytes (fig 5), and these were confirmed as aluminium on electron probe microanalysis.

The crystalline deposits in the third case dissolved on tissue processing for electron microscopy and it was not possible to assess their nature by electron probe microanalysis.

Discussion

The clinical site and the knowledge of a recent vaccination may alert the clinician to the correct diagnosis of an injection site reaction to aluminium. However, if the reaction develops some time after the vaccination, then the patient and the clinician may attribute the lesion to another cause. To make a correct diagnosis, the histopathologist should be aware of the range of appearances of this condition, otherwise the histological picture may be easily mistaken for those of a non-specific inflammatory reaction, infection or an insect bite. Most cases present as a tender or itchy subcutaneous nodule which may be gradually enlarging; eczema and hypertrichosis may be noted in the skin overlying the lesions.^{10 13} The single most important diagnostic histological feature is the presence of collections of histiocytes containing faint granular brownish refractile material, which can be shown to be aluminium by electron probe microanalysis. Previous studies have highlighted two common histological patterns seen in addition to the histiocyte sheets in biopsy specimens.¹¹ There may be a necrotising granulomatous reaction with associated fibrosis and chronic inflammation or a mixed inflammatory reaction with fibrosis and a histiocytic or lymphocytic proliferation. An eosinophil polymorph infiltrate is also commonly present.

Our cases show a wider variation in appearances than other reports, with two of the cases showing features not described previously.

In one (case 3) there was a sclerosing lipogranuloma-like reaction with pseudocystic spaces within dense fibrous tissue, some containing crystalline aggregates with an associated foreign body giant cell reaction. Attempts at identifying the nature of this substance failed, but they may have represented deposits of crystallised vaccination material. What induced this lipogranulomatous reaction is unclear. We are not aware of an 'oily' base in current vaccines used routinely, and this has been confirmed on personal enquiry to the manufacturers.

Case 2 was unusual both clinically and histologically. Not only was the lesion considerably larger and more diffuse than in previously described cases but the patient suffered severe symptoms. Histologically, the lesion involved the subcutaneous fat and consisted predominantly of lymphoid follicles and the characteristic histiocyte sheets with a prominent eosinophil infiltrate. Attempts to excise

the area completely for symptom relief have not been fully successful. The patient remains symptomatic and the histological inflammatory changes have extended to the margins of the final wide excision. Injection site reactions typically present as a relatively localised mass, whereas this patient had very widespread and diffuse changes, far outside the area of vaccination. The patient was sensitive to aluminium on patch testing, and her severe symptoms and diffuse and widespread inflammatory response presumably relate to this.

The combination of a prominent eosinophil infiltrate in the background of lymphoid follicles has provoked some discussion about the relation between such reactions and angiolymphoid hyperplasia with eosinophilia. Occasional irregularly shaped capillaries with conspicuous endothelial cells were present in our cases, but they were not a prominent feature. Although the aetiology and pathogenesis of angiolymphoid hyperplasia are not known, it typically presents as multiple cutaneous nodules on the head and neck region of young adults.¹⁴ The striking lymphoid and eosinophil reaction in both settings presumably reflects continued antigenic stimulation. Cases which have been diagnosed as angiolymphoid hyperplasia and which were associated with previous vaccinations should be examined carefully for the presence of the typical granular histiocytes which should permit confident distinction between the two conditions. A diagnosis of angiolymphoid hyperplasia should only be made if the typical capillaries with conspicuous endothelial cells are a prominent

feature and no aluminium laden histiocytes are found.

In summary, we report these cases to alert histopathologists to the changes encountered in aluminium injection site reactions and to emphasise that the lesions have a wider range of histological appearances than hitherto described.

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