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REVIEW

Subcutaneous nodules: an important adverse event following immunization

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ABSTRACT

Introduction: Subcutaneous nodules are a rare adverse event following immunization (AEFI). Reported cases have frequently been associated with aluminum-containing vaccines. Despite the development of a consensus definition of a subcutaneous nodule from the Brighton Collaboration in 2004, there continues to be variation in definitions used in published literature.

Areas covered: We reviewed the literature regarding subcutaneous nodule etiology, definition, clinical features, management, and approach to future immunizations. Embase and MEDLINE databases were searched with relevant MeSH terms initially on 8 November 2016, the same searches were repeated on 9 September 2018 prior to finalizing this review. We reviewed published case reports and larger studies reporting subcutaneous nodules and also reviewed articles discussing broader use of aluminum in immunizations and AEFIs.

Expert commentary: Consensus from clinicians regarding the approach to management of subcutaneous nodules is vital. We believe that the safety concerns regarding aluminum causing subcutaneous nodules are far outweighed by the benefits of vaccines containing aluminum. Ultimately, supporting subsequent immunizations in individuals that develop nodules needs to be a priority.

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Adverse event following immunization; immunization; subcutaneous nodule; vaccine

1. Introduction

Subcutaneous nodules are a rare adverse event following immunization (AEFI). The definitions used for nodules have varied, though since 2004 a consensus definition from the Brighton Collaboration has existed [1]. Many nodules reported are associated with aluminum-containing vaccines, but there is also evidence supporting other factors such as the method of immunization as a factor associated with local AEFI development. Other common themes are diagnostic uncertainty and varied approach to nodule management and subsequent immunizations.

We consider 'subcutaneous nodule' and 'nodule' as equivalent terms throughout this manuscript and chosen to predominantly use 'subcutaneous nodule'. When we refer to a diagnosis of a nodule, it is implied to be a 'nodule at the injection site'; consistent with the Brighton Collaboration Case Definition used.

Our aim was to review the existing published research about subcutaneous nodules; highlighting the areas of contention and gaps for further research. Further, we aimed to develop an understanding of the typical clinical features, associated vaccines, possible contributing factors, definitions, management and approach to subsequent immunizations. We were particularly interested in nodules occurring in the context of childhood immunizations – as the majority of immunizations are given in early childhood, but not to the exclusion of nodules occurring in older individuals.

1.1. Method

We reviewed the current literature regarding children who developed subcutaneous nodules following immunization. We initially searched several databases on 8 November 2016 (MEDLINE and Embase) using MeSH terms that had been identified as relevant to the topic. A total of 885 papers were identified. We reviewed all papers available in English language, excluding papers where English versions were not available. We excluded some papers based on their abstracts. The remaining papers were reviewed in further depth and included or excluded based on their relevance, with a total of 38 remaining papers contributing to our literature review. Prior to finalizing the review, the identical searches were repeated on 9 September 2018 to ensure any recent relevant publications were included, with three additional papers included. MeSH terms used in the searches included 'vaccine', 'immunization', 'adverse event' and 'nodule'. The full details of the searches are in the attached supporting document. A small number of articles included were sourced from expert author recommendation or reference lists.

2. Subcutaneous nodules following immunization

2.1. Definitions

The World Health Organisation defines an adverse event following immunization (AEFI) as any untoward medical occurrence

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Article highlights

- Subcutaneous nodules are a rare adverse event following immunization (AEFI).
- Subcutaneous nodules have been frequently associated with aluminum-containing vaccines, along with variations in injection technique.
- Aluminum has been used as an adjuvant to increase vaccine response for many decades.
- Safety concerns regarding aluminum causing subcutaneous nodules are far outweighed by the benefits of vaccines containing aluminum.
- Clinical management of subcutaneous nodules is varied, but a priority should be ensuring subsequent immunizations are supported.

which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine [2]. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease [2]. Injection site reactions (ISR) are amongst the most common types of AEFI, second only to fever [3,4]. ISR are a broad group of reactions, commonly including swelling, induration, erythema, and less commonly subcutaneous nodules [4].

Since the 1960s, there have been increasing numbers of subcutaneous nodule cases reported in the literature [5], the definitions attributed to these diagnoses have varied. The Brighton Collaboration is a vaccine safety research network that has developed a range of case definitions for common AEFI. In 2004, the Brighton Collaboration case definition (BCCD) was published for subcutaneous nodule or nodule at the injection site (see Figure 1), based upon clinical findings [1]. The definition was designed primarily for research use, though relies on clinical features making it applicable in clinical assessment. The guidelines were consensus based, as published data regarding onset, duration, and size of nodules was limited at the time of the development. The BCCD does not contain specific time and size limits regarding these aspects of nodules, making the diagnostic criteria easier to fulfill. Within the BCCD there is acknowledgment that nodules may occur in the same patient, overlapping with other common AEFI including acute induration and swelling at injection site. They suggest nodules may spontaneously resolve, persist (depending on the timeframe of follow-up) or progress to development of sterile abscess.

Despite the development of the BCCD criteria in 2004 for subcutaneous nodules, we were unable to identify published cases that subsequently clearly used this case definition. In a review of the applicability, reliability, sensitivity, and specificity of the BCCD including for nodules, there was evidence that it was a difficult AEFI to define, with low sensitivity and inter-rater reliability [6]. In part, this is attributed to the definition including the absence of abscess formation and erythema, where medical records often do not record what is absent, or negative findings. Also, despite pruritus often being a dominant feature in many of the nodules reported, it is a minor component of the case definition [7].

2.2. Incidence

Although there are limited estimates of the incidence of subcutaneous nodules, they are accepted as an uncommon AEFI [8]. Several studies in Sweden relating to aluminum-containing vaccines have estimated incidence between 0.03% (3–6 per 10,000) and higher rates of 0.83% (38/4,558 cases), from a cohort study investigating nodule development [9,10]. Outside of the Scandinavian region incidence rates have not been reported. Incidence estimates for subcutaneous nodules may be difficult to report accurately. AEFIs are passively reported in most countries and calculating the baseline population and number of vaccine time-points is variable. Other factors that may contribute are the ongoing variation in definitions used for nodules, despite the presence of standard case definition from the Brighton Collaboration [1,10]. Also, passive vaccine surveillance systems may be less likely to report milder cases, because of fewer symptoms and spontaneous resolution. This was demonstrated in a prospective cohort study that showed active case finding highlighted milder cases of subcutaneous nodules [10].

2.3. Possible antecedent factors

The etiology of subcutaneous nodule development is not well understood. There is evidence that multiple factors may

A nodule (also referred to as subcutaneous nodule, antigen cyst or granuloma) is defined by:

THE PRESENCE OF
- Discrete or well demarcated soft tissue mass or lump

THAT IS
- Firm AND
- At the injection site

There may be additional less discrete, soft swelling surrounding the nodule at the injection site, especially early in its development. There may also be tenderness and pruritus.

IN THE ABSENCE OF
- Abscess formation AND
- Erythema AND
- Warmth

(Level 2 and 3 of diagnostic certainty are not relevant)

Figure 1. Brighton criteria case definition for nodule at the injection site as an adverse event following immunization (level 1 of diagnostic certainty) [1].

contribute to the development of subcutaneous nodules, including how the immunization is administered, vaccine factors including aluminum content and patient predisposition [8]. It is likely that the normal immune system response to immunization also contributes to the reaction [11].

2.3.1. Route of administration (subcutaneous versus intramuscular) and needle length

The route of administration (eg. subcutaneous versus intramuscular) is important in the reactogenicity of the vaccine and consequential rate of AEFI [8]. This was demonstrated in 2003 when a high incidence of subcutaneous nodules was reported following a period of subcutaneous administration of a particular vaccine, these nodules did not occur subsequent to the correct intramuscular administration of the same vaccine [8,12].

Studies that directly evaluated the length of needle used for immunizations showed that those vaccines given with longer needles were less reactogenic [13,14]. With deeper injections less likely to cause local AEFI, this has been suggested that they were more likely to be given into the intramuscular rather than subcutaneous space. These studies primarily examined the outcomes of redness and swelling, rather than a subcutaneous nodule. It is likely that the route of administration plays a similar role for all these local AEFIs. The suggested underlying physiology was poor blood flow within the subcutaneous space, leading to injected material remaining in the subcutaneous tissue longer, compared to intramuscular route [13]. Further, Langerhans cells within the epidermal region may also contribute to the inflammatory reaction [7].

2.3.2. Aluminum

Aluminum salts were first used as a vaccine adjuvant in 1926 and have since become commonly used to enhance the immune reaction to specific antigens [15,16]. Aluminum is used as aluminum sulfate and aluminum hydroxide, the latter seems to have greater immunogenic properties. Several types of local reactions, such as erythema and induration have commonly also been reported following aluminum containing vaccinations [16,17]. Despite these cases, the addition of aluminum to vaccinations is widely accepted as safe [11,15,18,19]. Nonetheless, there also remains a level of ongoing concern about aluminum use [20,21], though it is largely peripheral to this discussion as the concerns focus on possible neurotoxicity and the quality of the evidence supporting this ranges from debatable to seriously flawed [21].

Subcutaneous nodules have been frequently associated with aluminum-containing vaccinations, with many reports focusing on aluminum as the triggering agent in nodule development [7,12,17,22–26], including some with biopsy specimens that identified aluminum. This is not unexpected as aluminum is present in the majority of immunizations. For example, in the 2018 Australian National Immunization Program, 69% or 9/13 injected immunizations contain aluminum (from birth to 4 years of age) [27]. Also, similar nodules have been documented to occur following vaccination for allergen immunotherapy, in these cases described the allergen extracts also included aluminum [28,29].

It should be stated that identifying aluminum on histology, does not confirm causality. Interestingly though, in animal model, Japanese investigators have reported aluminum containing vaccinations and development of subcutaneous nodules in mice [30], with biopsies between cohorts of aluminum and non-aluminum immunizations demonstrating nodule development only in those exposed to aluminum. Unfortunately, we do not have similar levels of evidence regarding the link of aluminum exposure and nodule development in humans.

2.3.3. Patient predisposition: role for allergy/delayed hypersensitivity

The role of aluminum allergy continues to be implicated in subcutaneous nodule development [25,26]. Administration of aluminum containing vaccinations is considered to be a sensitizing event, as is similar in aluminum-containing antiperspirants [17]. The reaction pattern is then thought to be either a nodule or eczema at the injection site. Delayed (type IV) hypersensitivity to aluminum (contact allergy) has been demonstrated by positive skin tests in a high proportion of patients with subcutaneous nodules following aluminum-containing vaccinations [10]. There has also been an association between multiple aluminum-containing vaccines, increasing the risk of developing subcutaneous nodule [10]. In cases with demonstrated aluminum allergy, this has been demonstrated to resolve in later stages of childhood [31].

In contrast, in a series of 54 subcutaneous nodules after DTPa vaccinations (aluminum-containing vaccine), skin patch testing was universally negative for aluminum allergy [9]. A systematic review of adverse events following aluminum containing DTPa vaccinations found some variation in the frequency of reported AEFI compared to non-aluminum containing vaccines, but no evidence of serious or long-lasting adverse events [16]. Specific analysis of nodule cases was not reviewed, likely related to the rarity of their occurrence. The review identified in young children (up to 18 months), vaccines with aluminum hydroxide caused significantly more erythema and induration, but significantly fewer reactions of all types. In older children (10–16 years) they found no association between vaccines with aluminum and the onset of local site reaction (induration and swelling).

There remains a degree of uncertainty regarding the role of aluminum, including aluminum allergy or hypersensitivity in the pathogenesis subcutaneous nodules. Despite this, there remains some persistent concern within the literature regarding the safety of aluminum use [20]. In cases of subcutaneous nodules with demonstrated aluminum hypersensitivity, it is commonly recommended to continue receiving subsequent aluminum containing vaccinations [24], as the risk of avoiding vaccination is greater than further exposure to aluminum.

2.4. Clinical signs and symptoms

Clinical signs and symptoms of a subcutaneous nodule may occur in overlap with the common injection site reactions. As swelling, induration and erythema resolve from the injection site, a firm lump becomes evident, with associated pruritus [32]. Subcutaneous nodules may be identified shortly after

vaccination (eg. days to weeks) [33]. There may also be a significant time (months to years) between vaccine administration and lump or mass noted at the same physical site [7]. This latency may contribute to uncertainty and anxiety from both clinicians and patients regarding diagnosis and the lesion being related to vaccination [34]. Subcutaneous nodules have been commonly reported to persist for many years, up to 8 years post-vaccination [7].

Subcutaneous nodules may be asymptomatic or be associated with pruritus, pain, overlying redness or erythema [29,35–37]. Skin changes are commonly associated with subcutaneous nodules [7,34]. Although these have been documented to occur, it is unclear if this is primarily related to the inflammatory response of the reaction or secondary to the itch-scratch cycle of chronic pruritus. Local changes in associated hypertrichosis and hypopigmentation or hyperpigmentation have been documented [22]. These localized symptoms can cause significant morbidity for young children and parents, in particular, chronic pruritus at night may cause sleep disturbance [7]. In addition, after the establishment of a subcutaneous nodule, intercurrent illness (e.g. upper respiratory tract infections or gastroenteritis) has been documented to exacerbate symptoms [7,24,34].

2.5. Histological findings

In concordance with surgical excision within the literature, there are many cases where a specific histological diagnosis is reached [5,29,38]. Chong *et al*. described a case series of 14 patients with varied histological diagnoses found in patients with subcutaneous nodules at the injection site [29]. The main pathological findings were panniculitis, pseudolymphoma, and granulomas. The majority of these cases (10/14 [71%]) were asymptomatic nodules. The wide variety of histopathological findings suggests that the cohort of patients with nodules may be a heterogeneous group of histological processes leading to a common clinical lesion.

2.6. Approach to management

Some reported cases describe a common approach to the treatment of subcutaneous nodules, with clinical monitoring and symptomatic management as an acceptable approach, given the majority of lesions are expected to spontaneously resolve [35]. In cases with typical eczematous changes of itch and erythema, topical steroids have been used successfully as treatment [39].

Surgical excision has historically been common practice for these lesions, primarily for diagnostic purposes [5,29,38]. Excision offers a panacea of diagnosis, treatment, and parental reassurance, ultimately giving histological diagnosis; but arguably is unnecessary if there is sufficient certainty of the clinical diagnosis of subcutaneous nodule. The consensus paper from the Brighton Collaboration concluded that 'biopsy of a nodule at the injection site is not routinely necessary or recommended' [1]. Logically if unnecessary procedures such as excisional biopsies can be avoided in children, this is of course always preferable. Management may also be driven by parental concern, particularly in the modern context of internet resources with varied scientific rigor, and concerned parents undertaking self-directed reading prompting a myriad of questions about vaccine and aluminum safety [40].

2.7. Bacilli Calmette-Guerin (BCG) vaccine reactions

BCG vaccine is known to trigger significant local reactions that can fit the clinical pattern of subcutaneous nodules [41,42]. These reactions can occur early following vaccinations (i.e. weeks to months), but have been documented to persist for decades [43]. It is hypothesized to be a reaction to a vaccine component and evidence of tuberculosis at the site is uncommon [41]. Histological findings in local reactions are commonly granulomatous [42]. The BCCD does not make a distinction in nodules triggered by BCG compared to other vaccines. This review does not attempt to review the literature of BCG local reactions, but to highlight their existence. Instead, we have focused on non-BCG site reactions and nodules.

2.8. Impact on subsequent immunizations

Subsequent immunizations have been delayed or declined in cases of children with subcutaneous nodules [7]. Subcutaneous nodules are not considered a contraindication to receipt of further vaccines, but some clinicians have raised concerns and sometimes suggest avoiding aluminum-containing vaccines in subsequent immunizations [44]. In children with subcutaneous nodules, ensuring subsequent immunizations are given via an intramuscular route seems to have prevented recurrence, even in cases with documented aluminum hypersensitivity [39]. Deep intramuscular (IM) immunization has been hypothesized to reduce the amount of inadvertent vaccine material in the subcutaneous tissue; this would, therefore, trigger the inflammatory response of a subcutaneous nodule [34]. Accordingly, to reduce the risk of recurrence with subsequent immunizations, deep IM is recommended.

3. Conclusion

Subcutaneous nodules are a benign, self-limiting AEFI, but their importance should not be discounted. In the context of a chronic nodule with pruritus and skin changes, they can lead to significant morbidity and the burden of these lesions in the young child should not be minimalized. Additionally, they are important as a reaction that may influence completion of scheduled vaccinations.

Factors involved in subcutaneous nodule development appear to be related to the correct administration of vaccinations, contents of the vaccination, with aluminum particularly associated with their development. There is possibly an underlying predisposition in the vaccinee, for example, in the occurrence of allergy.

There is a spectrum of the natural history, clinical features, and histological findings. Future research is required to gain a greater understanding of the natural history of subcutaneous nodules. Prompt recognition may prevent associated anxiety from the patient and family. Concern may be related to a lack of diagnosis, unnecessary investigation and intervention from health professionals. The difficulty of diagnosis and

anxiety may be compounded by the previously discussed delay between immunization and identification of subcutaneous nodules up to months to years. Previous case reports demonstrate there is often significant clinician concern regarding more serious lesions such as malignancy, heightening parental concern [10].

4. Expert opinion

Subcutaneous nodules are a rare and poorly understood AEFI and they are clearly important as they can cause chronic symptoms and can influence vaccine uptake. Particularly in the context that nodules are a rare AEFI, we believe that immunizations, including those with aluminum adjuvants, are safe and an important life-saving intervention for children and adults worldwide.

We are concerned about the association of vaccines containing aluminum with subcutaneous nodule development being presented by many authors as a causative link. Especially as there may be other factors, such as methods of vaccine delivery that contribute to nodule development. Causation is a complex process and although with future research this question may be definitively answered; we do not feel that there is sufficient information currently to draw these conclusions.

However, it is clear that there continues to be significant concern within the scientific community regarding the role of aluminum in vaccines and associated side effects. Accordingly, it is not surprising that vaccine-hesitant families will continue to raise concerns regarding aluminum-containing vaccines. It is important that we encourage discourse from all sides of the scientific community regarding the role of aluminum, but this needs to be with rigorous evidence. As clinicians, we feel strongly that the benefits of immunization are undisputed, and therefore the use of aluminum adjuvant is currently a necessary part of this. It is possible that an alternative adjuvant or newer delivery technology may ameliorate the need for aluminum adjuvant in the future. We believe the safety concerns regarding aluminum causing subcutaneous nodules are far outweighed by the benefits of vaccines containing aluminum and supporting subsequent immunizations following nodule development is paramount.

Consensus from clinicians regarding the approach to cases of subcutaneous nodules is vital. Greater knowledge of nodules as an AEFI will ensure early diagnosis, to minimize unnecessary concern and investigations. We propose that appropriate management for subcutaneous nodules should include timely clinical diagnosis, with assistance drawn from the BCCD guidelines, reassurance, and minimal intervention. Topical treatments such as corticosteroids should be considered, especially if pruritus is a dominant symptom. Careful and judicious use of investigations may be warranted when the diagnosis is unclear, but particularly the role for surgical excision remains unclear. Clearly, appropriate identification and follow-up for subcutaneous nodule cases is key to this process. This would ideally occur in the context of an established AEFI surveillance program, that offers follow-up of AEFI cases as a priority. We believe this can be best facilitated through specialized immunization services where available, to ensure a robust discussion of the risks and benefits of vaccination is available. In our opinion, subsequent vaccines delivered via deep intramuscular injection may prevent nodule recurrence and this is local practice in our clinical context, though this approach has not been supported by published evidence. Ensuring subsequent vaccinations are encouraged and ultimately completed is a major concern and priority.

Across the coming five years we advocate for greater awareness of subcutaneous nodules as a known AEFI, and consolidation of the clinical approach to definition, diagnosis, and management. This may include reviewing and refining the BCCD definition. As novel technologies for vaccine delivery develop, there is a possibility that we may see the incidence of nodules decrease. Evolving discussions about the role of aluminum in vaccine production and safety should be considered, carefully weighing up the associated risks and benefits.

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