Mumps vaccine associated orchitis: Evidence supporting a potential immune-mediated mechanism

Vanessa Clifford\textsuperscript{a}, Jane Wadsley\textsuperscript{b}, Bernard Jenner\textsuperscript{c}, Jim P. Buttery\textsuperscript{a, d, *}

\textsuperscript{a} Infectious Diseases Unit, Department of General Medicine & Murdoch Childrens Research Institute, Royal Children's Hospital Melbourne, Parkville, Victoria 3052, Australia
\textsuperscript{b} Occupational Physician, Brigade Medical Officer, Public Health Management, St Kilda Road Medical Centre, 391 St Kilda Road, Melbourne, Victoria 3004, Australia
\textsuperscript{c} Department of Paediatrics, Barwon Health, Geelong, Victoria 3220, Australia
\textsuperscript{d} Infectious Diseases Unit, Monash Children's Hospital, Dept of Paediatrics, Monash University, 264, Clayton Rd, Clayton, Melbourne, Victoria 3168, Australia

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\textbf{A B S T R A C T}

We report 3 cases of orchitis following vaccination with mumps–measles–rubella (MMR) vaccine, two with an onset within 3 days following vaccination. Orchitis is a common complication of mumps infection, particularly in post-pubertal males, and is also recognized as a very rare complication of mumps vaccination. These cases, discussed together with a comprehensive review of the existing literature regarding post-vaccine orchitis, highlight uncertainty regarding the pathogenesis of post-vaccine orchitis.

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1. Introduction

Orchitis is a common complication of mumps infection, particularly in post-pubertal males, and is also recognized as a very rare complication of mumps vaccination. We report three new cases of orchitis following mumps vaccination, reported through the state Surveillance of Adverse Events Following Vaccination In the Community (SAEFVIC) registry.

Two of these cases are unusual because of the brief time period elapsed between vaccination and the development of orchitis, highlighting uncertainty about the pathogenesis of post-vaccine orchitis.

2. Case report

2.1. Case 1

A 37-year old, otherwise healthy, male health care worker, was immunized with mumps–measles–rubella (MMR) vaccine (Priorix\textsuperscript{TM}, GSK Biologicals, mumps strain RIT 4385 derived from the Jeryl Lynn strain). He gave a history of a single measles vaccination in childhood. He also had a history of possible childhood wild type mumps infection, with bilateral parotid swelling. He did not develop clinical orchitis at the time of his initial infection.

This patient felt unwell immediately post-vaccine and developed bilateral testicular discomfort and swelling 3 days after receiving the vaccine. Examination revealed tender inguinal lymphadenopathy and bilateral submandibular (but not parotid) gland swelling. Ultra-sonography confirmed orchitis, with an inflammatory type pattern. There was no ultrasonographic evidence of torsion as a cause of testicular swelling and he had no other signs to suggest infectious epididymo-orchitis. He did not undergo any diagnostic biopsy or aspirate. His testicular swelling was managed conservatively and persisted for 5 weeks before settling spontaneously. There were no ongoing sequelae.

2.2. Case 2

A 36-year-old male health care worker received a 2nd dose of MMR vaccine (Priorix\textsuperscript{TM}, mumps strain RIT 4385) to complete his immunisation course, having received a 1st dose of MMR vaccine in 1991 in the United Kingdom. He was otherwise healthy and had a history of possible measles infection as a child.

He felt unwell with a high fever 48 h post-vaccine, with associated pharyngitis and cervical lymphadenopathy. He subsequently developed unilateral testicular discomfort and swelling the next day. Ultrasound demonstrated non-specific inflammation consis-
tent with orchitis with no ultrasonographic evidence to suggest torsion. There was no clinical evidence to suggest infectious epididymo-orchitis. He did not undergo any diagnostic biopsy or aspirate. His orchitis was managed conservatively and the swelling resolved after 7 days, without ongoing sequelae.

2.3. Case 3

A healthy 12-month-old child received his 1st dose of MMR vaccine (Priorix™, mumps strain RT 4385), according to the Australian National Immunisation Program schedule. Approximately 2 weeks after vaccination he developed unilateral scrotal and testicular swelling, confirmed upon examination by his family physician. He did not have further diagnostic investigation and the swelling resolved over several days. He subsequently presented 6 weeks after vaccination with bruising and mucosal bleeding and was found to be thrombocytopenic. Chronic idiopathic thrombocytopenia persisted for approximately 4 months before resolving spontaneously.

3. Discussion

Orchitis is a relatively common complication of wild type mumps infection, particularly in post-pubertal males, occurring in up to 30% of males with mumps infection [1]. It has rarely been reported as a complication of mumps vaccination. Our review of the literature identified only six reports, comprising a total of 10 patients, with post-vaccine orchitis reported as an adverse event following immunisation (AEFI). These are summarized in Table 1 [2–7], together with our three new cases.

Current Australian (and many international) guidelines recommend MMR vaccination for all high risk workers (health care workers and those who work with children) who are not immune or who have received only one dose of MMR [8] in addition to the routine vaccination of children. Increased awareness of potential adverse events associated with MMR in adulthood is therefore extremely important.

It should be noted that in all rare AEFIs, it is difficult to ascertain a causal relationship between vaccine administration and the event, rather than a temporal relationship alone. It is very difficult to firmly exclude the possibility that orchitis might be due to other causes (for example, circulating wild type mumps virus). In 2008 there were 286 notified cases of mumps infection in Australia (an average notification rate of 0.6 per 100 000), of which over half were in persons over 20 years of age [9] Orchitis is not reportable in Australia.

Establishing a causal link between MMR vaccination and orchitis is further complicated by the absence of a consensus case definition for post-vaccine orchitis. None of the previous published case reports of post-vaccine orchitis have specified a case definition. A reasonable definition may include the following components: a self-resolving inflammatory orchitis; ultrasonographic or histologic confirmation; occurring up to 28 days after vaccination and other causes of inflammatory orchitis excluded clinically.

The cases we report raise interesting questions about the likely pathogenesis of vaccine related orchitis. Orchitis typically follows 1–2 weeks after wild type mumps infection. It is thought to be due to direct invasion of testicular cells by the virus; isolation of replicating mumps virus from the testis or semen in mumps-related orchitis has supported this hypothesis [10].

The mechanism of post-vaccine orchitis is less clear. In some reported cases (including our 3rd case), orchitis occurred between 7 and 14 days following vaccination, as would be expected if it were due to direct invasion of the testis by mumps vaccine strain, with subsequent replication. Horiguchi and Uchida [3] reported symptoms of orchitis 2 weeks following administration of monovalent live attenuated virus and 1 week after development of parotid swelling. Suzuki et al. also reported orchitis following vaccination by more than 2 weeks [5]. Bakker’s [6] report of mumps vaccine associated orchitis in 5 prepubertal children following a vaccine campaign in Suriname, Indonesia, reported a typical delay of 7–14 days post-vaccine. They hypothesized that the reaction was probably due to inadequate vaccine attenuation, since a much larger number of children also reported a typical history of mumps infection (tender parotid swelling). The possibility of inadequate vaccine attenuation in our 3 cases is unlikely, since each was documented to receive vaccine from different batches. In addition, in two of our cases, both adults, the time elapsed between vaccination and development of orchitis was far shorter than would be expected with direct invasion of the testis by mumps virus. This suggests the possibility of an immune-mediated phenomenon in vaccinees previously exposed to mumps virus.

Unfortunately none of our cases underwent semen analysis or diagnostic biopsy to determine by molecular methods whether there was replicating virus present (in any case it is unlikely that vaccine virus would have been detected since it is usually present in extremely low titres in other tissues samples). Due to the passive surveillance mechanism of gathering information about AEFIs (in our case, the SAEFVIC registry), the time elapsed between the case occurrence and event reporting meant that it was too late to obtain appropriate pathological specimens.

The testis is known to be an immunologically privileged site [11], with some protection against autoimmune attack. Neverthe-

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Table 1

<table>
<thead>
<tr>
<th>Author/date/year</th>
<th>Number of patients</th>
<th>Age (years)</th>
<th>Mumps vaccine strain</th>
<th>Time post-vaccine</th>
<th>Associated phenomena</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clifford et al.</td>
<td>1</td>
<td>37</td>
<td>Jeryl Lynn</td>
<td>3 days</td>
<td>Inguinal and submandibular lymphadenopathy</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Clifford et al.</td>
<td>1</td>
<td>36</td>
<td>Jeryl Lynn</td>
<td>2 days</td>
<td>Pharyngitis</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Clifford et al.</td>
<td>1</td>
<td>1</td>
<td>Jeryl Lynn</td>
<td>2 weeks</td>
<td>Cervical lymphadenopathy</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Hrynnash et al.</td>
<td>1</td>
<td>15</td>
<td>Leningrad 3</td>
<td>1 week</td>
<td>Thrombocytopenia</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Abdelbaky et al.</td>
<td>1</td>
<td>18</td>
<td>Jeryl Lynn</td>
<td>12 days</td>
<td>Fever</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Horiguchi and Uchida [3] (2002)</td>
<td>1</td>
<td>26</td>
<td>Hoshino</td>
<td>2 weeks</td>
<td>Thrombocytopenia</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Suzuki et al. [5] (2002)</td>
<td>1</td>
<td>16</td>
<td>-</td>
<td>16 days</td>
<td>None reported</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Kuczyk et al. [4] (1994)</td>
<td>1</td>
<td>30</td>
<td>Urabe Am 9</td>
<td>3 weeks</td>
<td>Tendonitis Viral arthritis</td>
<td>Full recovery</td>
</tr>
</tbody>
</table>
less, adoptive transfer of specific T lymphocytes has been shown to produce an autoimmune orchitis in experimental animals [11,12], suggesting that immune mediated events within the testis are possible.

One hypothesis to explain early post-vaccine orchitis would be an immune mediated adverse reaction with pre-existing specific lymphocytes (or preformed antibody) to vaccine antigen or wild type mumps virus in the testis, which reacted immediately once the vaccine antigen reached the testis. Both men had a history of possible (case 1) or confirmed (case 2) prior mumps exposure (the first with a history of wild type mumps infection and the second through previous vaccination), which may have led to a more rapid immune mediated reaction with a second exposure.

There have been previous reports of possible immune-mediated phenomena following MMR vaccine. Following a mass immunisation campaign in Australia in 1998, there were several reports of early onset parotitis following MMR vaccine [13]. Three cases developed parotitis relatively rapidly following vaccination (at 2 h, 24 h and 8 days). Again, these reactions raise the possibility of an immune-mediated phenomenon following prior sensitization, since the time course for the first two was too short for direct viral invasion and replication.

Several of the cases included in this review had a reported association of post-vaccine orchitis with other immune related phenomena. Horiguchi and Uchida [3] reported a case of post-vaccine orchitis with associated thrombocytopenia, which is thought to be immune mediated and can occur as early as 3–4 days post-vaccine. One of our cases also developed thrombocytopenia in association with orchitis. Kuczky et al. [4] also reported two probably immune-mediated phenomena (tendonitis and reactive arthritis) accompanying orchitis.

Clearly it is not possible to establish causality, as defined by the Bradford Hill criteria [14], on the basis of two unusual cases of post-MMR vaccine orchitis. Semen analysis for the presence of mumps virus (either wild type or vaccine strain) by molecular methods would have been useful in the first two cases to establish the biological basis of the swelling, as has been performed previously to establish the presence of virus in mumps orchitis. Nevertheless, an immune-mediated phenomenon is a biologically plausible explanation for the development of orchitis following MMR vaccination.

4. Conclusion

Orchitis is a rarely reported event following MMR vaccination and, as with all rare vaccine related adverse events, establishment of a causal relationship is difficult. The lack of a consensus case definition for post-vaccine orchitis further complicates the issue. We propose a reasonable definition might include the following components: a self-resolving inflammatory orchitis; ultrasonographic or histologic confirmation; occurring up to 28 days after vaccination; and other causes of inflammatory orchitis excluded clinically.

The short time course to development of orchitis following vaccination in two of our cases suggests the possibility of an immune-mediated phenomenon, rather than direct viral invasion and replication, although this cannot be firmly established in the absence of biological evidence.

References