Case report

Adverse reactions to FMD vaccine

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Abstract A case of adverse post-vaccination allergic reactions, which occurred in a dairy cattle herd 8 days after the annual foot-and-mouth disease (FMD) vaccination, is described. The dermatologic lesions observed in these cattle included: urticaria, exudative and necrotic dermatitis, along with oedema and vesicles on the teats. These reactions occurred in 11.3% of the heifers, in 10% of the first-lactating cows and in 14.6% of the adult cows. The average loss of milk production for an affected cow on this farm was 21.5% per day, for seven consecutive days. The extent of the lesions was apparently related to concurrent diseases such as bovine virus diarrhea – mucosal disease complex (BVD–MD) and Johne’s disease and, to a lesser degree, correlated with the age or breed.

Keywords adverse reactions, BVD–MD, foot-and-mouth disease, Johne’s disease.

INTRODUCTION

Foot-and-mouth disease (FMD) is an economically important disease of cloven-hoofed farm animals and is probably the most contagious disease known.1 FMD is still a major problem and one of the most difficult to control in the Middle East.

Intensive annual vaccination campaigns contribute to controlling the disease, reducing the number of outbreaks, and preventing the spread of FMD within the country and to neighbouring countries. The vaccine antigen is produced in suspension cell cultures of a baby hamster kidney cell line (BHK). The virus is inactivated and mixed with adjuvant.2

Antigens produced in BHK cells have been suspected of causing allergic reactions in cattle.3,4,5,6,7,8,9 The present communication describes adverse reactions apparently due to an FMD vaccine and the subsequent economic losses in a dairy cattle herd.

MATERIALS AND METHODS

A dairy cattle herd (Israeli-Holstein breed), comprised of 195 lactating cows and 220 heifers, was kept in a loose-housing system in large, completely covered open sheds. The herd was managed under a zero-grazing system (where cows are fed total mixed ration brought to them), and was kept in accordance with adequate standards of basic hygiene and mastitis control. The lactating cows were divided into two groups: first-lactating cows, and adult cows. Dry cows and three groups of replacement heifers, divided according to age, were kept in separate sheds. No change in feeding practices was performed. This herd is permanently infected with BVD–MD and Johne’s disease. Serological survey by ELISA test showed a prevalence of 94% and 12% for BVD–MD and Johne’s disease, respectively.

All the clinical, milk production, reproduction and management data were recorded by the Afimilk system (computerized dairy management system, Kibbutz Afikim, Israel). The dairy herd was maintained under an intensive management system and had a mean herd milk yield of 10 800 kg year⁻¹. During the vaccination campaign in autumn 1997, all animals greater than 3 month of age were vaccinated.

The inactivated FMD vaccine used (Aftovax; Merial, France) contains several serotypes: Type O, Type A₂2 and Asia1.3,4,5.6,7,8,9 The FMD vaccine is produced in suspension cell cultures of BHK cells (BHK-21). The adjuvants are aluminium hydroxide (AL(OH)₃) gel and saponin.

Two millilitres of vaccine were administered subcutaneously in the neck. The vaccinated herd was monitored for clinical signs every two days, for eight weeks.

The lesions of the post-vaccination reactions were very similar to FMD lesions; therefore the epidermal vesicles from the affected teats were collected for virus isolation in buffer glycerin. The epithelial tissue samples for virus isolation were rinsed three times in PBS, homogenized 1:10 with Earle medium and chloroform, and centrifuged. Supernatant was used for inoculation of eight suckling mice and 12 wells containing a monolayer of pig kidney cells (PKC). The mice were observed for
eight days and the inoculated PKCs for three consecutive days. In the case of negative results, three blind passages were followed. The presence of viral-type-specific FMD antigen was examined by capture ELISA, according to the Manual of Standards for Diagnostic Tests and Vaccines, chapter 2.1.1., Foot and Mouth Disease. The biopsy specimens were taken from the skin lesions for histopathological examination. The biopsy specimens were fixed in 10% neutral buffered formaldehyde and after dehydration and embedding in paraffin wax, 4–5 μm thick sections were cut and stained with haematoxylin and eosin.

These animals, and the food products associated with these animals, were restricted according to FMD-suspect farm guidelines set forth in Israel.

RESULTS

The cattle in this dairy herd exhibited three types of skin lesions: pruriginous urticaria; numerous wheals (3–20 mm in diameter, covering most of the body) and exudative (Fig. 1) and necrotic dermatitis. The affected areas exhibited multifocal hairloss and the papules exuded serum and scabbed over. In addition, leg oedema and vesicles on the teats occurred (Fig. 2). The lesions appeared eight to twelve days post-vaccination, and persisted for three to five weeks. Wasting (4.2% mean loss of body weight) and lymphadenopathy were observed. Pyrexia and other clinical signs characteristic of FMD were not observed. These reactions occurred in 11.3% of the heifers, 10% of the first-lactating cows and 14.6% of the adult cows (Table 1). The most severe reactions occurred in the high-yielding cows (14 out of 80 cows).

The reacting animals became depressed and exhibited moderate pruritus. A drop in milk yield was noted beginning on day eight post-vaccination and persisting for seven days (Fig. 3). The average loss in milk production was 21.5% per day for a reacting lactating cow.

In various areas in the epidermis, marked hyperkeratosis and areas of necrosis of the squamous epithelium

Figure 1. Areas of weeping skin lesions with necrotizing dermatitis caused by FMD vaccination.

Figure 2. Vesicles on the teats.
were seen. In the superficial and deep dermis, severe infiltrations of inflammatory cells, neutrophils, histiocytes and eosinophils were seen. In the affected areas, some of the adnexa were also infiltrated by the same inflammatory cells; in other areas thrombosed blood vessels and necrotic collagen fibres could also be seen (Fig. 4).

Attempts to isolate the FMD virus from materials collected from animals with FMD-like lesions were unsuccessful.

**DISCUSSION**

Delayed skin reactions (type III hypersensitivity) to the annual vaccination of dairy cattle with the FMD vaccine have been reported previously.\(^\text{4,11–14}\) The skin lesions occurred eight to twelve days post-injection, as reported elsewhere.\(^\text{15}\) Reaction rates have ranged from 0.27% in Russia\(^\text{16}\) to less than 0.1% in Germany,\(^\text{12}\) and in 0.28% of the vaccinated animals in dairy cattle herds in Israel (Yeruham, unpublished data, 1978–97, Israel).

In the herd described in the present report, the average reaction rate reached 12.5%. There are various factors which may be involved in the adverse reactions of cattle to FMD vaccine.\(^\text{15}\) Possible factors which have apparently predisposed the animals and caused the relatively high rate of severe reactions include concurrent infections such as BVD–MD and Johne’s disease, and, to a lesser degree, the age and breed of the cattle.

All reacting animals had been vaccinated against FMD at least once prior to the present observations. One of the factors which has been reported to be responsible for sensitization as well as for the allergic reactions appears to be the BHK cell deriva.\(^\text{14,17}\) This might account for the delayed reactions occurring in cattle after repeated FMD vaccinations.\(^\text{11,14}\)

Since saponin is a natural product and there is considerable variation in quality,\(^\text{19}\) this would also account for the variation in incidence of adverse reactions between vaccine batches.

Black postulated that allergic reactions in the field may be initiated by the accidental administration of small quantities of vaccine by the intradermal instead of the subcutaneous route.\(^\text{2}\) In the past, when cattle were vaccinated with a vaccine produced by the Frenkel method, i.e. in cultures of surviving bovine tongue epithelium, no adverse reactions were observed.\(^\text{11}\)

Areas of weeping skin lesions with skin necrosis may be caused by delayed vaccine hypersensitivity reactions, with deposition of antigen–antibody complexes on intima of arterioles, thereby interfering with the local blood supply.\(^\text{20,21}\) Different skin lesions caused by FMD vaccine were reported by Dubarry et al.\(^\text{22}\) This may be due to the fact that a different type of vaccine was used (oil-based).

The most critical steps in the production of the FMD vaccine are those of the inactivation process.\(^\text{21}\) In

### Table 1: Reaction rates and types of skin lesions

<table>
<thead>
<tr>
<th></th>
<th>Reactors/ nonreactors (%)</th>
<th>Vesicles on teats</th>
<th>Urticaria, exudative and necrotic dermatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heifers</td>
<td>25/220 (11.3)</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>First-lactating cows</td>
<td>8/80 (10)</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Adult cows</td>
<td>19/130 (14.6)</td>
<td>4</td>
<td>19</td>
</tr>
</tbody>
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Figure 3. Decrease in milk production in the reacting cows in comparison with nonreacting cows.
case of improper inactivation, and if safety tests fail to
detect low residual infectivity in the vaccine batch, the
vaccine may still contain some active virus particles. 
This does not appear to account for the FMD-like
lesions on the teats of six cows in the herd described here,
because the attempts to isolate the FMD virus failed.

The evidence presented in this paper, namely the severe
adverse clinical reactions in the FMD-vaccinated herd,
negative virological examination, the histopathological
findings and the circumstantial evidence of the vaccina-
tion campaign, lead to the conclusion that the FMD
vaccine was probably responsible for the described
delayed skin lesions and significant economic losses in
the reacting lactating cows. Research should be
continued, to improve these FMD vaccines.

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Résumé  Cet article décrit un cas de réaction secondaire allergique suite à une vaccination, qui est apparu dans
un troupeau laitier 8 jours après une vaccination annuelle contre la fièvre aphteuse. Les lésions dermatologiques
observées chez ces vaches étaient: urticaire, dermatite exsudative et nécrosante, ainsi qu’un œdème et des vésicules
sur les rayons. Ces réactions sont apparues chez 11.3% des génisses, 10% des vaches en première lactation
et 14.6% des vaches adultes. La perte laitière moyenne pour les vaches atteintes dans cette ferme était de 21.5% par
jour pendant sept jours consécutifs. L’étendue des lésions était apparemment liée à des maladies concomitantes,
comme la BVD – MD (bovine virus diarrhea – mucosal disease) et la maladie de Johne, et plus faiblement corrélée
avec l’âge et la race. [Yeruham, I., Yadin, H., Haymovich, M., Perl, S. Adverse reactions to FMD vaccine. (Réaction
secondaire au vaccin fièvre aphteuse.) Veterinary Dermatology 12: 197–201.]
Adverse reactions to FMD vaccine

Resumen Se describe un caso de reacciones alérgicas post-vacunación, ocurrido en un rebaño de vacas de leche, 8 días después de la vacunación anual de fiebre aftosa (FA). Las lesiones dermatológicas observadas en estos animales incluían: urticaria, dermatitis exudativa y necrotizante, junto con edema y vesículas en las ubres. Estas reacciones ocurrieron en un 11.3% de las terneras, en un 10% las vacas de primera lactación y en un 14.6% de las vacas adultas. La media de pérdida de leche para cada vaca afectada fue del 21.5% por día, durante siete días consecutivos. La extensión de las lesiones estaba aparentemente relacionada con las enfermedades concomitantes como la diarrea bovina vírica – complejo de enfermedad de las mucosas (BVD–MD) y paratuberculosis y, en menor grado, correlacionado con la edad o la raza. [Yeruham, I., Yadin, H., Haymovich, M., Perl, S. Adverse reactions to FMD vaccine. (Reacciones adversas a la vacuna de Fiebre Aftosa.) Veterinary Dermatology 12: 197 – 201.]