Reactogenicity to a live attenuated varicella vaccine in Canadian children

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OBJECTIVE: To assess the reactogenicity and safety of a thermostable, high titre, varicella vaccine in healthy infants and children.
DESIGN: Open study of 505 children monitored for 42 days after vaccination.
SETTING: Three urban Canadian centres (Halifax, Ottawa and Vancouver).
PARTICIPANTS: 505 healthy children one to 12 years of age were enrolled and 504 completed the study. All were susceptible to varicella by history.
INTERVENTIONS: All participants received one dose of live attenuated varicella vaccine ($1\times10^{4.5}$ plaque forming units/dose) subcutaneously.
MAIN OUTCOME MEASURES: The children were monitored from the day of vaccine administration (day 0) until day 42. All local and general symptoms and signs were recorded on diary cards by the patients' parents, who were encouraged to fill in the cards on days 2 to 3 and 18 to 24 via telephone calls from study personnel.
RESULTS: Most of the symptoms noted after vaccine administration were mild and transient, and all resolved within the respective follow-up periods. Injection site symptoms included pain (17.5%, 13.9% and 30.4% in centres 1, 2 and 3 respectively), redness (21.1%, 32.1% and 48.8%) and swelling (7%, 10.3% and 29.2%). The general symptoms reported were fever 37.5°C or higher (3.5%, 4.8% and 3.0%) and varicella-like rashes (6.4%, 2.4% and 0%). Two subjects had severe symptoms (one with cervical lymphadenopathy, and one with a fever higher than 39°C) probably related to vaccine administration. No serious adverse events were reported during the entire study.
CONCLUSION: The vaccine was well tolerated.

Key Words: *Chickenpox; Reactogenicity; Varicella vaccine*

Réaction à un vaccin vivant atténué contre la varicelle chez des enfants canadiens

OBJECTIF : Évaluer la réactivité et l'innocuité d'un vaccin thermostable de haut titre contre la varicelle chez des nourrissons et des enfants en bonne santé.
MODÈLE : Étude ouverte regroupant 505 enfants sous surveillance pendant 42 jours après la vaccination.
CONTEXTE : Trois centres canadiens urbains (Halifax, Ottawa et Vancouver).
PARTICIPANTS : Cinq cent cinq enfants en bonne santé âgés de 1 à 12 ans ont été inscrits et 504 ont mené l'étude à terme. De par leurs antécédents, ils étaient tous sujets à la varicelle.
INTERVENTIONS : Tous les participants ont reçu une dose d'un vaccin vivant atténué contre la varicelle ($1\times10^{4,5}$ unités formant des plages par dose), par voie sous-cutanée.
PRINCIPALES MESURES PARAMÉTRIQUES : Les enfants ont été surveillés à compter du jour de la vaccination (jour 0) et jusqu'au jour 42. Tous les signes et symptômes localisés et généralisés ont été consignés sur des carnets par les pa-

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rents des patients qui ont été encouragés à les remplir aux jours 2 et 3, puis 18 à 24, au moyen d'appels téléphoniques effectués par le personnel de l'étude.
RÉSULTATS : La plupart des symptômes notés après l'administration du vaccin étaient légers et transitoires et sont tous rentrés dans l'ordre à l'intérieur des périodes de suivi respectives. Les symptômes au point d'injection étaient notamment la douleur (17,5 %, 13,9 % et 30,4 % dans les centres 1, 2 et 3 respectivement), rougeurs (21,1 %, 32,1 % et 48,8 %) et enflure (7 %, 10,3 % et 29,2 %). Les symptômes généraux signalés ont été la fièvre à 37,5 °C ou plus (3,5 %, 4,8 % et 3,0 %) et des éruptions cutanées varicelliformes (6,4 %, 2,4 % et 0 %). Deux sujets ont présenté des symptômes graves (l'un, une lymphadénopathie cervicale et l'autre, une fièvre à plus de 39° C) probablement associés à l'administration du vaccin. Aucune réaction indésirable dangereuse n'a été signalée durant la durée entière de l'étude.
CONCLUSION : Le vaccin a été bien toléré.

Infection by varicella zoster virus (VZV) usually results in benign disease in children. However, complications such as pneumonia, encephalitis and bacterial superinfection of the skin lesions (1,2) occur in some patients, mainly in adolescents and adults, and in immunocompromised children (1,2). In addition, children born to nonimmune mothers who contract varicella during pregnancy can develop congenital varicella syndrome (1,3), with limb hypoplasia and central nervous system damage.

A live varicella vaccine was developed in Japan in 1974 (4) using the OKA strain of the virus. The original wild type virus was isolated from a boy with natural varicella, and then attenuated by passages through human and guinea pig embryonic cells, and two human diploid cell lines, WI-38 and MRC-5 (4,5). The vaccine strain obtained after this treatment has different thermosensitivity and host range spectrum than the wild type virus (6). Additionally, it can be easily differentiated from wild type strains currently circulating in North America by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) testing (6,7).

All OKA varicella vaccine production lots are derived directly from a working seed lot (8), following the World Health Organization guidelines (9). Many clinical trials have demonstrated that this strain is safe and immunogenic (2,5,10,11). The vaccine produced by SmithKline Beecham Biologicals (Rixensart, Belgium), VARILRIX, was first licensed in Europe in 1984 (10,11). An OKA-strain varicella vaccine, Oka/Biken (Biken, Osaka, Japan), has been licensed in Japan since 1987 (5). Vaccines using the same strain, were licensed in the United States in 1995 (Oka/Merck or VARIVAX, Merck and Company Inc, Whitehouse Station, New Jersey [12]) and in France in 1997 (Pasteur Merieux, Lyon, France).

SmithKline Beecham Biologicals introduced recently a reformulation of the vaccine to increase its stability at 2 to 8°C and, therefore, facilitate its use for general vaccination (10). The vaccine will retain a titre of $1\times10^{3.3}$ plaque forming units (PFU) or more/dose after two years at 2 to 8°C. The safety and immunogenicity of this vaccine have been extensively tested (10,11).

We conducted a multicentre study to assess the reactogenicity and safety of two lots of the reformulated varicella zoster vaccine produced by SmithKline Beecham Biologicals in children from one to 12 years of age. This vaccine has a higher titre (approximately $1\times10^{4.5}$ PFU per dose) of virus at release and is more thermostable than the vaccine presently licensed in Canada. The purpose of the study was to obtain daily information on local and general reactogenicity to the vaccine. Such information is required by licensing agencies before a vaccine is made available to the public.

PATIENTS AND METHODS

Study design: The live attenuated OKA strain varicella vaccine used for these studies was manufactured by SmithKline Beecham Biologicals. Two consecutive lots of the vaccine were used: lot VA 125A42M for subjects 1 to 485 and lot VA 125A42B for subjects 486 to 505; each lot had a mean virus titre of $10^{4.5}$ PFU per dose, determined at the time of the release of the vaccine. The vaccine was supplied at –20°C, in monodose vials containing a freeze-dried pellet to be reconstituted before use with sterile water. One 0.5 mL dose was administered subcutaneously in the upper left arm of each child. Previous studies done in Belgium corroborated that the vaccine used in this study is thermostable and can be stored at regular refrigerator temperatures (53°C) for periods of up to 24 months with a drop in titre of about 0.5 log PFU/dose (10). In this study, the vials were kept at –20°C to avoid any loss of titre.

Healthy children from 12 months to 12 years of age were enrolled. Children with a history of chickenpox, previous varicella vaccination or known exposure to chickenpox within the preceding four weeks were excluded. Other exclusion criteria were a history of allergic reactions to neomycin, a history of allergic or other adverse reactions to previous vaccinations, any acute febrile illness at the time of intended vaccination, and the administration of systemic corticosteroids, immunomodulating drugs or chemotherapy during the study period or within the preceding four weeks. Any patient with confirmed or suspected immunosuppressive condition, or family history of hereditary immunodeficiency was also excluded. To ensure a similar age distribution at each study centre and that the entire age range (12 months to 12 years) was appropriately covered, enrollments were stratified by age (patients one to 200 age younger than three years; patients 201 to 400 age three years to younger than seven years; patients 401 to 505 age seven to 12 years). The ethics review committees of each institution approved the study, and written informed consent was obtained from the children's parents before enrollment in the study.

Subjects were seen on two occasions. At the first visit, informed consent, a medical history and physical examination were obtained. One blood sample was collected for determination of pre-existing varicella antibodies, and the reconstituted contents of one vaccine vial were administered subcutaneously. Children were observed for 15 mins after vaccination. Diary cards for recording symptoms following the administra-

TABLE 1
Rates of solicited symptoms after vaccination including local (day 0 to 7), fever (day 0 to 3) and varicella-like rashes (day 0 to 42)

Symptoms	Centre 1 (N=171) n (%)*	Centre 2 (N=165) n (%)*	Centre 3 (N=168) n (%)*	ALL (N=504) n (%)*
Local symptoms				
Pain				
Total	30 (17.5)	23 (13.9)	51 (30.4)	104 (20.6)
Severe	0	0	0	0
Redness				
Total	36 (21.1)	53 (32.1)	82 (48.8)	171 (33.9)
Greater than 20 mm	6 (3.5)	17 (10.3)	32 (19.0)	55 (10.9)
Swelling				
Total	12 (7.0)	17 (10.3)	49 (29.2)	78 (15.5)
Greater than 20 mm	0	1 (0.6)	16 (9.5)	17 (3.4)
General symptoms				
Fever				
37.5°C or higher	6 (3.5)	8 (4.8)	5 (3.0)	19 (3.8)
Higher than 39.0°C	0	1 (1.6)	0	1 (0.2)
Rashes				
Total	30 (17.5)	33 (20.0)	14 (8.3)	77 (15.3)
Varicella-like†	11 (6.4)	4 (2.4)	0	15 (3.0)

**Percentage of subjects with symptoms reported over the number of subjects with returned symptom sheets; †Papulovesicular or vesicular rash. N Number of subjects with symptom sheet returned or with symptoms collected by the study personnel (see text); n Number of subjects with at least one symptom. The Fisher exact test shows that there is a statistical significant difference in the incidence of solicited local symptoms between study centres (P=0.006 for pain at injection site, P<0.0001 for redness and P<0.0001 for swelling)*

tion of the vaccine were provided to parents along with reaction measurement gauges and a digital thermometer to record daily body temperatures from day 0 to day 3 postvaccination and, in subsequent days, if the child appeared ill or had a rash. Local solicited adverse experiences (pain, swelling, redness) were recorded from day 0 to day 6. Any rashes, unsolicited signs and symptoms, and medications given were recorded from day 0 to day 42. When varicella-like rashes (papular or vesicular rash) occurred during the study period, parents were asked to visit the investigator as soon as possible for assessment and collection of vesicular fluid for varicella virus identification. Parents were telephoned by study staff on days 2-3 and 18-24 following vaccination to encourage completion of the diary cards and inquire about any adverse experience. At visit 2 on day 42 14, a second physical examination was completed, and the diary cards were collected and reviewed with the parents.

The intensity of local pain and unsolicited symptoms was classified by parents as either absent, mild, moderate or severe, according to whether the adverse experience was easily tolerated, sufficiently discomforting to interfere with daily activity or could prevent normal everyday activity, respectively. The largest size of redness or swelling was scored as: 1 less than or equal to 5 mm, 2 from 5 to 20 mm, 3 larger than 20 mm. Axillary temperatures were scored as 37.5 to 38.9°C equal to a score of 1, 38.1 to 39.0°C equal to 2 and above 39°C equal to 3. The parents or guardians were instructed to contact the investigator immediately if any serious adverse event occurred. A serious adverse event was defined as any experience that suggested a significant hazard to the vaccinee's health. The relationship of adverse events to the vaccination was assessed by the investigators according to the following categories: probable, suspected, unlikely or not related.

Laboratory analysis: Serum samples were collected on day 0 and stored at –20°C until analyzed. All tests were completed at the manufacturer's laboratory in Rixensart. Antibodies to varicella zoster were analyzed by indirect immunofluorescence using a commercial kit (Virgo VZV/IgG, Pharmacia, Peapack, New Jersey). Samples that showed no fluorescence or barely visible fluorescence at the starting dilution of 1:4 were considered as seronegative. Varicella titres were expressed as the reciprocal of the highest positive tested dilution. If a child was diagnosed as having varicella during the study period, a blood sample was collected two to four weeks after the acute visit and analyzed as above.

Vesicle fluid was collected from patients with varicella-like vesicles and stored in phosphate-buffered saline (PBS) at –20°C until it was sent to the manufacturer's laboratory. Samples were then denatured in a boiling water bath and amplified by polymerase chain reaction (PCR) in a DNA thermocycler as described (7). After digestion with *Bgl*I or *Pst*I, the PCR products were electrophoresed in ethydium bromide to identify the characteristic restriction enzyme length polymorphism (6,7).

RESULTS

A total of 505 children from three urban centres (Ottawa, centre 1, 171 children; Halifax, centre 2, 165 children; Vancouver, centre 3, 169 children) were enrolled in the study. The study cohort consisted of 267 (52.8%) females and 238 (47.2%) males stratified into three age groups: 200 younger than three years (39.6%); 200 three years to younger than seven years (39.6%); and 105 seven to 12 years of age (20.8%). There were no differences in age or sex distribution among the three centres.

Prevaccination blood samples were available for 469 (92.8%) children: 455 (97%) were seronegative for varicella

and 14 (3%) were seropositive. Diary cards were returned by 485 subjects (96%). Of the 20 subjects who did not return their diary cards, information concerning local and/or general symptoms was collected during the follow-up visit (n=15) or by telephone interview (n=4). Only one subject was excluded due to incomplete safety data. There were no patient withdrawals due to serious adverse events.

Local reactions: No severe cases of pain were reported at any of the study centres, although some pain at the vaccination site was reported by 20.6% of the participants (Table 1). Redness or swelling were reported by 33.9% and 15.5% participants respectively; redness or swelling greater than 20 mm in diameter were reported by 10.9% and 3.4%, respectively (Table 1). All local symptoms resolved within seven days, but most resolved within 48 h (not shown). The incidence of local symptoms between the study centres was significantly different (Table 1, $P=0.006$ for pain at injection site, $P<0.0001$ for redness and $P<0.0001$ for swelling). A teleconference was held by the study coordinators to look for factors that could explain the variability. Differences were detected in the needle size (centre 1: 27 gauge, 1/2 inch; centres 2 and 3: 25 gauge, 5/8 inch) and temperature of diluent (centre 1 room temperature; in centres 2 and 3 the diluent remained on ice with the vaccine, approximately 2°C). Some differences were found in the injection technique: in centre 3, an air bubble was drawn into the syringe but not injected, to allow for injection of the volume of the needle hub (about 0.02 mL); in centres 1 and 2 this was not done. Additionally, some patients used acetaminophen before or immediately after vaccination (38 in centre 1, 26 in centre 2 and nine in centre 3). Most of the children in centre 1, 29 of 38 children (76%), used the drug as a prophylactic measure, which may have decreased the number of local reactions in this centre. The other nine children (24%) were given acetaminophen to manage fever or pain. Only four of 26 and two of nine subjects used prophylactic acetaminophen in centres 2 and 3, respectively. No significant age related differences were observed in the incidence of local reactions in the three centres (not shown).

Two lots of the vaccine were used for these studies: lot VA125A42M for subjects 1 to 485 and lot VA125A42B/1 for subjects 486 to 505. These last 29 children were all at study centre 3, and all were in the older than seven year age group. No significant differences in reactogenicity were detected between the two lots (not shown).

Systemic reactions: Nineteen episodes of fever (3.8%) were reported among the three centres within the three days follow-up period; 11 children were younger than three years old, six were three to younger than seven years old and two were older than seven years old. Sixteen episodes occurred within 48 h of vaccination, only one episode was considered severe (higher than 39.0°C, Table 1). All febrile episodes resolved within five days of the injection.

Rashes: There were 11 suspected cases of varicella clinically diagnosed by the investigator at study centre 1 (time of onset days 0 to 21) and four in centre 2 (onset days 4 to 13) (Table 1). Six children in centre 1 were younger than age three years; four children, two in centre 1 and two in centre 2, were in the three to younger than seven-year-old group; and five, three in centre 1 and two in centre 2, were older than age seven years. In all cases, the number of papules and/or vesicles was fewer than 30. Serological analysis was completed for nine patients (eight from centre 1 and one from centre 2), and three had rashes serologically confirmed as varicella, with titres of 2048, 2048 and 4096 (all from centre 1). The other six sera analyzed had titres of 16, 32, 64, 64, 64, and 128, and they were suspected to be vaccine related (10,11). PCR analysis of vesicular samples taken from the three seropositive subjects identified the DNA extracted as wild type varicella DNA. Four other samples from suspected cases were tested by PCR, and all were negative for viral DNA. All cases resolved within 18 days (two to 18 days). The three cases confirmed as varicella had durations of seven, 11 and 18 days. The onset of symptoms for these patients was four, seven and 19 days postvaccination, which suggests that two of them may have been infected by wild type varicella virus before or at the time of vaccination. Four varicella-like rashes were identified in centre 2. However, the lesions were too small to permit the collection of vesicular fluid for PCR analysis. All rashes resolved within seven days of onset. No vaccine strain was isolated from patients with a rash or from members of the same household.

Fourteen children (2.8%) – four from centre 1, seven from centre 2 and three from centre 3 – had VZV antibodies in the serum sample taken before vaccination (titres 16 to 1024), despite a negative history of varicella. One child was three years of age, three children were three to younger than seven years of age, and nine were older than seven years of age. Six of the children had no adverse experience after vaccination, seven had symptoms considered unrelated or unlikely to be related to the vaccination, and one presented with a rash at the injection site, suspected to be related to the vaccination.

DISCUSSION AND CONCLUSIONS

The safety and reactogenicity of a thermostable, high titre, OKA-strain varicella vaccine produced by SmithKline Beecham Biologicals' were assessed in 505 healthy children aged 12 months to 12 years. The vaccine was well tolerated, and no serious adverse events that required hospitalization were reported during the entire study. Most symptoms reported were at the injection site, and they were mild and of short duration.

A significant difference in the incidence of local symptoms was detected between the centres. The procedures for vaccine administration followed in each centre might explain some of the differences found in the rate of local reactions postvaccination. Although this study did not include a placebo arm, the same vaccine lot was used in most patients at the three centres, which suggests that technical differences in vaccine administration and not the vaccine were involved in the variability in local reactions. The frequency of pain or redness at the injection site published for the SmithKline varicella vaccine recipients is 8.2% (10), lower than the values reported in this study (15% to 30%). The main differences found between both studies were in the ages of the children, nine to 36 months in previous studies compared with two to 12 years in this study.

It is possible that the increased rates of local reactions observed in this study were due to these differences in age, with older children reporting events more often than their younger counterparts. Additionally, the diary cards used for this study emphasized the detection of symptoms and signs postvaccination, and probably recorded data that would have remained unnoticed.

The diary cards were particulary sensitive for the detection of rashes of all types, including rashes not related to the varicella vaccine, such as diaper rashes, insect bites and drug or food sensitivity (Table 1). Fifteen varicella-like rashes occurred during the six-week follow-up period (an incidence rate of 3%, Table 1); 11 of these cases were reported in centre 1. All cases were mild (less than 30 vesicles) and of short duration. At the time of the study, there was an outbreak of varicella in centre one, which may explain the increase in the number of varicella-like rashes found in this centre. Breakthrough cases of varicella in vaccinees have been described previously (5,11, 13-15), and, in most cases, the infections by wild type virus were mild and of short duration. The frequency of breakthrough cases with the varicella vaccines available varies between 2% and 12.3% (5,11,13-15). For the vaccine currently licensed in Canada, Varivax (Merck Frosst Canada Inc, Kirkland, Quebec), it is 4.3% per year (13).

Unsolicited symptoms were reported in 18% of patients during the 42 days follow-up period and were considered probably related or suspected of being related to the vaccination. The most frequent were reactions at the injection site (5.6%), fatigue (1.0%), fever (1.8%), gastrointestinal symptoms (3.2%), nervousness (1.4%) and infections (1.4%). Most of the unsolicited local reactions (23 of 27) were due to bruises at the injection site that were not included as solicited local reactions. All the unsolicited symptoms resolved within 18 days of onset.

The OKA strain varicella vaccine has been extensively studied in Japan (OKA/Biken, [5]), Europe (VARILRIX, SmithKline, [10,11]) and in the United States (VARIVAX, Merck, [12, 13]) with similar results. After more than 20 years of use in some countries, the vaccine has been well tolerated and immunogenic in healthy as well as in immunocompromised children. The number and intensity of adverse reactions reported is low, and injection site reactions or fever are the most common side effects reported (2,5,10-13). There is no evidence of waning immunity 20 years after vaccination; moreover, mild or asymptomatic reinfections of vaccinees with wild type virus may contribute to the persistence of immunity (15). New formulations of the vaccine with high titres and increased stability of the virus, like the vaccine used for these studies, raise the response rate in the vaccinees without an increase in the number of serious adverse events (10,11). Additional concerns were raised by the persistence and reactivation of wild type VZV in elderly or immunodepressed patients (16,17). It has been shown that the OKA strain persists in vaccinees and that it can be reactivated in immunocompromised or healthy hosts; however, zoster rates were significantly lower and milder than in nonvaccinees (2).

The varicella vaccine may be used to protect susceptible adolescents, adults or children at high risk or as part of national programs of vaccination. Routine VZV immunization at the time of measles-mumps-rubella vaccine administration was recommended in 1995 by the American Academy of Pediatrics and the Advisory Committee on Immunization Practices in the United States (12,18). Cost-benefit analysis of routine children vaccination programs in the United States indicated that immunization costs are similar to the medical costs to treat the disease. However, when other socioeconomic costs are considered, such as the cost of lost work by the parents, immunization for varicella becomes cost beneficial for the community (19). A coverage of approximately 70% should be attained, however, before a vaccination program becomes cost and health effective (20). Partial coverage of susceptible populations may shift the epidemiology of the disease to older ages, with the consequent increase in the number of serious cases and of congenital varicella. According to the World Health Organization, "[r]outine childhood immunizations against varicella may be considered in countries where the disease is a relatively important public health and socioeconomic problem, where the vaccine is affordable, and where a high (85% to 90%) and sustained vaccine coverage can be achieved."(21)

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CLINICAL VIGNETTE

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DIAGNOSIS

A computerized axial tomogram (CT) scan of the arm was obtained on the sixth day of hospitalization (Figure 1). It shows thickening of the subcutaneous tissue with an extensive multiloculated fluid collection extending from the level of the wrist to the elbow, anteriorly and posteriorly through the interosseous space. Adjacent muscles appeared swollen. The radiologist's interpretation was that it was markedly abnormal with changes "in keeping with diffuse cellulitis, abscess formation and possible myositis". An ultrasonographic examination revealed "a hypoechoic volar compartment with loss of normal muscle striation". The sonographically abnormal area was aspirated and a drain was inserted, releasing 40 mL of purulent material, which on Gram stain showed 4+ polymorphonuclear leukocytes and Gram-positive cocci in clusters. The aspirate yielded growth of *S aureus* with the same sensitivity pattern as the blood isolate. The patient was taken to the operating room where copious amounts of purulent material were drained and the forearm irrigated. All the muscles were intact, with no evidence of necrotizing fasciitis. A transthoracic echocardiogram showed no abnormalities. Postoperatively, the patient received a total of four weeks of intravenous and two weeks oral antimicrobial therapy, and made a slow but steady recovery. Six months after surgery, he had mild limitation of pronation and supination with reduced hand dexterity.

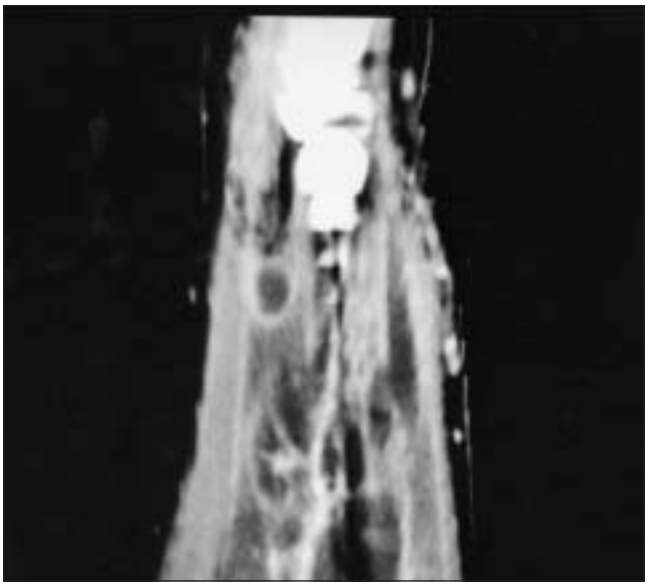

Figure 1) *Enhanced sagittal image of the right forearm, showing multiloculated low attenuation in the interosseous space (with peripheral enhancement), extending both dorsally and ventrally*

DISCUSSION

Despite advances in the diagnosis and therapy of bacterial disease, *S aureus* remains a major cause of soft tissue infection. These infections can be extremely serious, particularly if associated with bacteremia, where the overall mortality has remained unchanged at 11% to 43% over the past 15 years (1). Diabetic patients, both insulin and noninsulin dependent, appear to have a higher incidence of severe and unusual infections due to this organism (2), as is seen in the present case. Postulated mechanisms for the latter include increased colonization rates, abnormal polymorphonuclear leukocyte function due to hyperglycemia, complement dysfunction, and both macro- and microvascular changes (3).

This case also demonstrates the difficulty in classifying soft tissue infections because their extent may only be ascertained reliably by surgical exploration (4). Although our case clearly was a deep space infection, it is less clear whether it was a variant of pyomyositis or a non-necrotizing fasciitis. Walling and Kaelin (5) described 'non-tropical' pyomyositis occurring in temperate countries and with an apparent predilection for patients with diabetes mellitus, where 56% of the infections were caused by *S aureus*. The pathophysiology of this entity may involve the hematogenous seeding of a traumatic intramuscular hematoma (6), with initial pain and mild swelling followed by 'woody' induration of the area. A second phase with systemic symptoms occurs as isolated pockets of purulent material develop and a third, septic phase occurs when entire muscle groups are replaced by pus. This case may have been an early phase of pyomyositis or a noninvasive form of fasciitis with spread along fascial planes. In cases of deep space infections of the extremities where the exact location of the pathological process is unclear, a CT scan of the area may be a useful radiological modality. It may also aid in directing a surgical approach.

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