Case Report

Implantable Insulin Pumps: Infections Most Likely Due to Seeding From Skin Flora Determine Severe Outcomes of Pump-Pocket Seromas

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Summary - Complications at implantation site of implantable insulin pumps may lead to premature removal. To elucidate the origins and the outcomes of these local adverse events, we investigated seromas of the ‘pump-pocket’ that have been detected for an eight-month period during the follow-up of such-treated forty type 1 diabetic patients. At the start of study period, skin bacterial flora was sampled at umbilicus and groin, and isolated strains of Staphylococcus epidermidis were preserved in specific vials at -20°C. Each time a seroma was detected at transcutaneous 45 days-refill of pump reservoir, it was sampled for bacterial cultures. Isolated strains of S. epidermidis from seroma were genetically compared to preserved strains of corresponding patients using Pulsed-Field Gel Electrophoresis (PFGE) after genomic restriction by Smal.

Among the ten seromas that occurred after a mean time of 9.9 months since implantation, S. epidermidis were isolated in five cases. Genetic comparison of isolated strains could be performed in three cases. Compared strains showed identical (in 2 cases) or closely related (in one case) PFGE profiles. While the five aseptic seromas resolved with rest, four infected cases required explantations after one to nineteen months in spite of antibiotic therapy and the fifth one persisted without improvement under long-term antibiotics.

Our results suggest that seeding from the skin flora is a key-factor determining the severity of pump-pocket complications. We recommend that bacterial investigations of pump-pocket seromas should be systematically performed, while prophylactic measures might include antibiotic cover for each puncture of the pump-pocket.

Key-words: implantable insulin pumps, pump-pocket complications, Staphylococcus epidermidis, pulsed-field gel electrophoresis.

Résumé - Pompes à insuline implantables : les infections très vraisemblablement dues à un ensemencement à partir de la flore cutanée déterminent la sévérité du pronostic des épanchements séreux de la poche de pompe.

Les complications au site d’implantation des pompes à insuline implantables peuvent conduire à une explantation prématurée. Elucider l’origine et le pronostic de ces complications locales.

Nous avons exploré les épanchements séreux de la « poche de pompe » qui ont été détectés sur une période de huit mois au cours du suivi de quarante diabétiques de type 1 ainsi traités. Au début de l’étude, la flore bactérienne cutanée a été prélevée à l’ombilic et à l’aïne, et les souches isolées de Staphylococcus epidermidis ont été conservées dans des milieux appropriés à – 20 °C. À chaque fois qu’un épanchement était détecté lors du remplissage en insuline du réservoir de la pompe par voie transcutanée réalisé tous les 45 jours, un prélèvement était pratiqué pour mise en culture bacteriologique. Les souches de S. epidermidis isolées dans les épanchements ont été comparées génétiquement aux souche conservées des mêmes sujets par Electrophorèse en Champ Pulsé (ECP) après macrorestriction génomique par Smal.

Parmi les dix épanchements qui sont survenus 9,9 mois en moyenne après l’implantation, des S. epidermidis ont été isolés dans cinq cas. Une comparaison génomique des souches isolées a pu être réalisée dans trois cas. Les souches comparées de S. epidermidis montraient des profils d’ECP identiques (dans deux cas) ou étroitement liés (dans un cas).

Alors que les cinq épanchements aseptiques étaient résolus avec le repos, quatre cas infectés nécessitaient des explantations après un à dix-neuf mois malgré un traitement antibiotique et le cinquième cas a persisté sans aggravation sous antibiotiques au long cours.

Nos résultats suggèrent qu’un ensemencement à partir de la flore cutanée est un facteur-clé déterminant la sévérité des complications de la poche de pompe. Nous recommandons que des explorations bactériologiques des épanchements de la poche de pompe soient systématiquement réalisées, tandis que des mesures préventives pourraient comprendre une couverture antibiotique de chaque ponction de la poche de pompe.

Mots-clés : pompes à insuline implantables, complications de la poche de pompe, Staphylococcus epidermidis, électrophorèse en champ pulsé.
Implantable insulin pumps (IIP) may represent a key element of an implantable artificial pancreas for the treatment of diabetes [1]. The feasibility of long-term clinical use of IIP in diabetic patients has been demonstrated but some issues require further investigations [1]. Beside recurrent incidents of underdelivery that may be reduced by recent improvements of insulin stability [2], complications at implantation site (‘pump-pocket’) have been mentioned as an eventual cause of premature pump removal [1]. After we published a first series of 7 severe pump-pocket complications among 40 patients, reaching an incidence of 24 events per 100 patient-years [3], other authors reported in larger series lower incidences of 5.3 to 8.6 local adverse events per 100 patient-years [4, 5]. The spectrum of local complications extended from mild skin inflammation and transient seroma or hematoma to skin atrophy or erosion, persistent pain, chronically-infected seroma or pump subcutaneous migration [3-5]. Outcomes also varied from spontaneous resolution or improvement with rest and medical treatment to requirements of surgical repositioning, skin graft or explantation [3-5]. Determining mechanisms remained elusive in most cases, although we found intense physical activity to be a risk factor [3]. Identification of coagulase-negative Staphylococci in some seromas suggested possible seeding of the pump-pocket during surgical procedures or pump refills via transcutaneous puncture, as already described with other prosthetic devices [6].

MATERIAL AND METHODS

In order to elucidate the contribution of infections to pump-pocket complications, as well as their origin and their influence on outcome, we investigated seromas surrounding IIP that have been detected at pump refills for an eight-month period during the follow-up of 40 type 1 diabetic patients treated by model 2001 MiniMed Implantable Pumps (MiniMed Technologies, Sylmar, CA) in our unit.

Patients – Studied patients were 19 males and 21 females, aged 44 ± 10 years, with a diabetes history of 25 ± 8 years, to whom an IIP was implanted between April 1994 and April 1997. All had been recruited in a clinical trial testing the feasibility of long-term insulin delivery from IIP after approval of an ethics committee. Refills of pump reservoirs were performed every 45 days by transcutaneous puncture, in a specific ward, under surgical aseptic conditions, after skin disinfection by iodized polyvinylpyrrolidone, by 4 trained physicians.

Methods – At the start of study period, the skin flora of the patients, taken at umbilicus and groin, could be sampled with sterile swabsticks and bacteriologically investigated. Staphylococcus epidermidis isolates were preserved in specific vials at -20°C. Each time a pump-pocket seroma was detected during the study period, it was sampled under sterile conditions for bacterial cultures. If S. epidermidis was isolated in pure culture, preserved isolates from the corresponding patient were defrosted and genetically compared to the seroma isolate. Among genotyping methods, Pulsed-Field Gel Electrophoresis (PFGE) analysis of bacterial chromosomal DNA after restriction with the rarely cutting enzyme Smal I was used since it has been shown to be the most discriminatory for coagulase-negative Staphylococci [7, 8]. Genomic DNAs were prepared from identified S. epidermidis as previously described [8]. PFGE was then performed at 8°C with a CHEF-DR III apparatus (Bio-Rad Laboratories, Hercules, CA). The running parameters were as follows: initial pulse, 20 sec; final pulse, 5 sec for 20 h; voltage, 6 V/cm. A lambda ladder (successively larger concatemer of 48.5 kb DNA fragments) was used as a molecular size marker. The gels were stained with ethidium bromide, washed with distilled water and photographed under UV light. DNA banding patterns were compared by visual inspection and interpreted according to Tenover et al. [9]. According to the number of DNA fragments that differ between pulsotypes patterns, strains were considered to be indistinguishable (no difference), closely related (2 to 3 DNA fragments of difference) or possibly related (4 to 6 bands of difference). If more than 6 differences in DNA restriction fragment migration were observed, isolates were considered to be unrelated.

RESULTS

During the study period, pump-pocket seromas were found in 10 patients after a mean time of 9.9 months (range: 1-22) since implantation. Bacterial cultures remained negative after at least 72h incubation in 5 cases. In the five other cases, S. epidermidis was isolated in pure culture. In 3 out of these latter 5 cases, preserved skin samples were cultured and obtained bacterial strains were identified. In these 3 patients named P1, P2 and P3, skin and seroma S. epidermidis strains were found to be identical or closely related after PFGE (Fig. 1). In the two remaining cases with infected seromas (P4, P5), a comparison between seroma strain and preserved skin strains could not be performed because cultures could not be obtained from the latter ones.

Patient P1 presented the same strain in seroma and umbilicus (lanes 1 and 2). Two other strains also isolated in umbilicus were unrelated to the seroma isolate (lanes 3 and 4). In patient P2, the strain isolated from groin sample (lane 5) was closely related to the strain isolated in seroma (lane 6). Among other strains isolated from umbilicus (lane 8) and groin (lanes 7 and 9), two of them showed a similar PFGE.
Our data provide strong arguments for the seeding of pump-pocket from skin flora in three out of five cases of infected seroma. The five infected seromas were detected between 3 and 21 months after implantation. Since these seromas were not present at previous pump refills, their infectious origin is very likely and suspected seeding mode was the previous transcutaneous puncture required for reservoir access. In two cases (P1 and P3), PFGE patterns of *S. epidermidis* identified in skin flora exactly match with those of *S. epidermidis* infecting pump-pockets, indicating that strains were indistinguishable from each other. Close relationship between *S. epidermidis* in groin and in seroma in P2 corresponds to a difference due to a single random genetic event, such as a point mutation or an insertion or a deletion of DNA [9]. This scarce DNA variation can be observed even when the same strain is cultured repeatedly over time or isolated on multiple occasions from the same patient [9]. Interpretation of genetic similarities between identified strains from skin floras and from seromas as a most likely seeding from skin to seroma is coherent with the contrasting high diversity of *S. epidermidis* strains that is commonly present among various cutaneous sites in the same patient [10]. Thus, the likelihood that two strains of *S. epidermidis* with identical or closely related PFGE patterns are epidemiologically related is very high.

As already reported with other prosthetic devices [6], *S. epidermidis* infections of IIP could not be eradicated and resulted in persistent seroma leading to premature removal in most cases. Non-infected seromas occurred between 1 and 19 months after implantation and were absent at the next refill, 45 days later. A mechanical cause for these seromas was likely and rest allowed a favourable outcome.

The rather high incidence of seromas with a severe outcome in our series is understandable, since we demonstrate that the seeding of our IIP was strongly determined by the development of infections from skin flora. During the study period, twice more frequent punctures of pump-pocket for reservoir refill were necessary because of poor insulin stability in pumps [2]. The reduction of time intervals between refills from 90 to 45 days may have indirectly increased the risk of pump-pocket seeding through more frequent skin punctures. In spite of the systematic use of a bactericidal disinfectant before skin puncture, it has already been shown that deep colonization of skin reaching sudory glands and hair follicles prevents absolute efficacy of skin disinfectants [11]. Therefore, surgical anti-bioprophylaxy has been tested and shown to provide an additional benefit against bacterial contamination from skin flora in prosthesis surgery [12].

From our experience, bacterial investigations of all pump-pocket seromas should be recommended. Moreover, we suggest that prophylactic measures of severe local complications related to infections from skin flora might include antibiotic cover for each puncture of the pump-pocket in addition to usual skin disinfectants and aseptic conditions. This proposal seems to be supported by our ongoing use of anti-bioprophylaxy on each refill day since the present study, that dramatically reduced the occurrence of severe local adverse events in our patients.

## DISCUSSION

Our data provide strong arguments for the seeding of pump-pocket from skin flora in three out of five cases of infected seroma. The five infected seromas were detected between 3 and 21 months after implantation. Since these seromas were not present at previous pump refills, their infectious origin is very likely and suspected seeding mode was the previous transcutaneous puncture required for reservoir access. In two cases (P1 and P3), PFGE patterns of *S. epidermidis* identified in skin flora exactly match with those of *S. epidermidis* infecting pump-pockets, indicating that strains were indistinguishable from each other. Close relationship between *S. epidermidis* in groin and in seroma in P2 corresponds to a difference due to a single random genetic event, such as a point mutation or an insertion or a deletion of DNA [9]. This scarce DNA variation can be observed even when the same strain is cultured repeatedly over time or isolated on multiple occasions from the same patient [9]. Interpretation of genetic similarities between identified strains from skin floras and from seromas as a most likely seeding from skin to seroma is coherent with the contrasting high diversity of *S. epidermidis* strains that is commonly present among various cutaneous sites in the same patient [10]. Thus, the likelihood that two strains of *S. epidermidis* with identical or closely related PFGE patterns are epidemiologically related is very high.

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## REFERENCES


