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Severe Infections Caused by *Propionibacterium acnes*: An Underestimated Pathogen in Late Postoperative Infections

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Propionibacterium acnes belongs to the cutaneous flora of humans and is rarely considered a pathogen in human diseases. It is a frequent contaminant in blood cultures; however, in some patients it has been identified as the causative agent of life-threatening infections. Within the last years we have observed an abrupt increase in severe *P. acnes* infections which prompted us to study in detail the clinical and microbiological features, risk factors, and outcomes of these cases.

In a retrospective review of microbiological records of 905 *Propionibacterium* isolates from a five-year period (1990-95), 70 were identified from 20 patients with clinical and microbiological evidence of a *P. acnes* infection. The clinical syndromes included endocarditis (7 patients), post-craniotomy infections (6 patients), arthritis and spondylodiscitis (4 patients), endophthalmitis (2 patients) and pansinusitis (1 patient). The predominant predisposing conditions were previous surgery preceding the infection from 2 weeks to 4 years and implantation of foreign bodies such as prosthetic heart valves, intraocular lenses and ventriculo-peritoneal shunts. Therapy consisted of intravenous antibiotics in all cases and surgical procedures to remove infected tissue in eighteen patients. The outcome was favorable in sixteen patients (80 percent) who had a complete recovery.

These data confirm the pathogenic potential of *P. acnes* in late post-surgical infections, in particular after implantation of a foreign body, and suggest a combined therapeutic approach with intravenous antibiotics and surgical removal of the infected tissue.

INTRODUCTION

Propionibacterium acnes is a Gram-positive anaerobic or aerotolerant rod and a member of the resident cutaneous and conjunctival flora of humans [1, 2]. Although its association with acne vulgaris is widely accepted, it is generally believed to have a low pathogenic potential and is mostly considered a contaminant in cultures that have been obtained by percutaneous punctures or biopsies [3]. Numerous anecdotal reports indicate, however, that *P. acnes* may cause severe infections at various body sites including endocarditis and other intravascular infections [4-6], central nervous system infections [7, 8], endophthalmitis [9], and, rarely, arthritis [10, 11] or dental infections [12]. Within the last two years, we have observed a sharp rise in cases with severe and life-threatening *P. acnes* infections prompting us to search systematically for such illnesses. We identified twenty patients within the last five years whose clinical features, risk factors, treatment and outcomes are presented.

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[e] *Abbreviations:* CSF, cerebral spinal fluid; CNS, central nervous system; VP, ventriculo-peritoneal.

PATIENTS AND METHODS

Selection of patients:

From 1 January 1990 to 31 August 1995, 905 isolates of *Propionibacterium* spp. were registered at the Department of Medical Microbiology of the University Zurich. By review of the microbiological and clinical records, 20 patients were identified who fulfilled clinical and microbiological criteria to convincingly make the diagnosis of a *P. acnes* infection. The clinical diagnosis was based on the presence of systemic signs of infection (fever, leucocytosis, elevated C-reactive protein, and/or erythrocyte sedimentation rate) and/or signs of a localized infection. Microbiological criteria included either i) two positive blood cultures with *P. acnes*, or ii) one positive culture from a heart valve, from the vitreous or aqueous eye chamber, or iii) repeated cultures from deep wounds, cerebrospinal fluids, or joints.

Microbiological techniques:

Aerobic and anaerobic blood cultures (Septi-Chek; Roche Diagnostics, Basel Switzerland or BacT/Alert Organon Teknika, Turnhout, Belgium) were incubated at 37°C for at least 6 days. In case of growth, they were subcultured aerobically at 37°C with 5 percent CO_2 on Columbia agar with 5 percent sheep blood and anaerobically on *Brucella* agar with 5 percent sheep blood (Becton Dickinson Microbiology Systems, Basel, Switzerland). Excised heart valves were processed under the laminar flow unit. As much fibrous tissue as possible was removed for cultures. One-half was directly cultured in brain-heart infusion (Difco, Detroit, Michigan) for 14 days, the other half was ground and processed as described before [5]. Tissue not grindable was cultered in brain-heart infusion. *P. acnes* was differentiated from other catalase-producing Gram-positive rods by its production of abundant propionic acid and indole. Minimum inhibitory concentrations were determined by the E-test (AB Biodisk, Solna, Sweden) on *Brucella* agar (BBL) with 5 percent sheep blood which has been shown to correlate well with the methods of the National Committee for Clinical Laboratory Standards [13].

Evaluation of risk factors, therapy and outcome:

Analysis of the medical charts focussed on underlying medical conditions, immunosuppressive drugs, previous surgery and implantation of foreign bodies, choice and duration of antibiotics and surgical procedures to treat *P. acnes* and outcome at the discharge from the hospital.

RESULTS

Overall, we identified 20 patients (17 males, 3 females; ages 17 to 80 years, average age 54.3 years) with severe *P. acnes* infections including endocarditis (7 patients), postcraniotomy infections (6 patients), joint and spine infections (4 patients), endophthalmitis (2 patients), and pansinusitis (1 patient). Four of these infections occurred within the years of 1990-93, 16 in the last twenty months (1994-95/8). The clinical and microbiological data are summarized in Table 1.

Clinical presentations:

Six patients presented with the typical clinical laboratory signs of endocarditis including fever, loss of weight, leucocytosis and elevated C-reactive protein (No.1-6, Table 1). Two of these suffered from embolic events to the lower extremity and to the brain, respectively. Echocardiography revealed vegetations (2 cases), paravalvular abscesses (2 cases) and no abnormalities which would suggest the presence of endocarditis (3 cases). In patient 7, the diagnosis of endocarditis was unexpected at the time he underwent aortic

valve replacement for an incompetent bicuspidal aortic valve. Cultures of the resected valve and a blood culture taken after surgery grew *P. acnes*.

Table 1. *P. acnes* infections: Clinical and microbiological data

Case No.	Yr	Age/Sex	Site of infection	Predisposing conditions	Material cultured	Cultures pos/total	Gram+ rods** (microscopy)	Surgical therapy	IV Antibiotics (in weeks)
1.	95	43/m	endocarditis	homograft AVR* 4 years ago	septic embolus aortic valve	1/2 2/2	+++ +++	AVR (mechanical)	6
2.	95	63/m	endocarditis (abscess)	mechanical AVR 10 months ago	blood aortic valve	0/4 2/2	 +	AVR (homograft)	6.5
3.	94	47/m	endocarditis (abscess)	mechanical AVR 18 months ago	blood aortic valve	6/15 0/1	 +++	AVR (homograft)	10.5
4.	94	50/m	endocarditis	reconstruction aortic valve 12 months ago	blood aortic valve	9/12 0/2	 +++	AVR (homograft)	6
5.	94	68/m	endocarditis	mechanical MVR* 2 years ago	blood mitral valve	3/3 0/1	 +	MVR (mechanical)	11
6.	92	72/m	endocarditis (abscess)	mechanical AVR 7 weeks ago	blood aortic valve	4/8 1/1	 +++	AVR (homograft)	6
7.	94	59/m	endocarditis	bicuspid aortic valve	blood aortic valve	1/4 1/1	 nd	AVR (mechanical)	6
8.	95	23/m	VP-shunt infection	shunt insertion 9 months ago	CSF shunt	1/3 1/1	+ nd	shunt removal	1.5
9.	94	40/m	VP-shunt infection	shunt insertion 3 months ago	CSF shunt	1/1 2/2	++ nd	shunt replacement	4
10.	92	17/f	VP-shunt infection	shunt insertion 2 weeks ago	CSF shunt	3/3 0/1	+++ nd	shunt replacement	2
11.	94	34/m	craniotomy wound infection	amygdal-hippocampectomy 3 weeks ago	aspirate	3/4	+	removal of infected bone and tissue	8
12	91	44/f	osteomyelitis of the skull	brain tumor operation 6 weeks ago	bone	3/3	+++	removal of infected skull and tissue	3
13.	94	64/m	brain abscess	evac. intracerebral hematoma 5 wks ago	aspirate	4/5	+++	drainage abscess	6
14.	95	60/m	spondylodiscitis	-	blood vertebral body	3/3 5/7	 +	debridment	6.5
15.	94	64/m	spondylodiscitis	lumbar diskectomy 3 weeks ago	blood vertebral body	2/10 0/1	 -	debridment	6
16.	94	60/m	spondylodiscitis	lumbar diskectomy 9 weeks ago	blood vertebral body	3/3 1/1	 +	debridment	6
17.	91	68/f	arthritis (knee)	prosthesis implant 4 years ago	blood joint aspirate	0/3 2/13	 +++	none	3
18.	95	72/m	endophthalmitis	lens implant, 12 months ago	rinse fluid intraoperatively	1/1	-	vitrectomy, capsulectomy	2
19.	94	80/m	endophthalmitis	lens removal 5 months ago	smear of lens capsule	1/1	+++	vitrectomy, removal lens capsule	2
20.	94	58/m	pansinusitis	-	aspirate	4/4	+++	sinus drainage	1.5

* AVR = aortic valve replacement; MVR = mitral valve replacement.

** = no bacteria; + = <500; ++ = 500-2500, +++ = >2500 bacteria/µl; nd = not done.

Six patients developed *P. acnes* infection after craniotomy. Three had a ventriculo-peritoneal (VP)[e] shunt infection and developed clinical signs of increased intracerebral pressure without fever (No. 8-10). Two patients developed local signs of infection in the area of a surgical craniotomy wound (No. 11, 12). One patient with a *P. acnes* brain abscess following evacuation of an intracerebral hemorrhage presented with headache and fever (No. 13). Three patients developed spondylodiscitis with increasing back pain as the leading symptom (No. 14-16); diagnosis was based on typical MRI signs of spondylodiscitis. Another patient with a prosthesis of the left knee acquired a *P. acnes* arthritis in that knee presenting with fever, night sweats and a painful local swelling (No.17). Two patients developed endophthalmitis after intraocular surgery (No. 18, 19). Both presented with impaired vision, ocular pain and conjunctival injection. One patient with sinusitis presented with high fever, facial pain and visual disturbances of his right eye (No. 20). Computed tomography revealed an extensive inflammation of the right paranasal sinuses with edema of the right orbit.

Predisposing conditions:

Previous surgery at the site of *P. acnes* infection was noted in 17 patients (85 percent) and included heart valve surgery, craniotomy, lumbar disk hernia operations, and eye surgery (Table 1). In 11 of these patients, foreign bodies had been implanted (65 percent) which included six prosthetic heart valves, three ventriculo-peritoneal (VP) shunts, one intraocular lens, and one joint prosthesis. One patient without previous surgery developed endocarditis on a bicuspid aortic valve (No. 7). In two patients, no local predispositions at the site of infection were found. One patient with spondylodiscitis had alcoholic liver cirrhosis (No. 14), while the patient with pansinusitis was completely healthy before he developed the infection (No. 20). The interval between surgery and clinical signs of infection lasted from two weeks to four years. In five patients, the interval was one year and longer, in the other patients it averaged 19 weeks. Three neurosurgical patients received corticosteroids while they developed *P. acnes* infection. One patient with endocarditis and two patients with spondylodiscitis had diabetes mellitus.

Microbiological findings:

From these 20 patients, a total of 70 *P. acnes* cultures were isolated. Sixty-two grew anaerobically and 26 aerobically on primary isolation. The mean time for isolation was 6.1 (range: 3-19) days for blood cultures, and 4.7 days (range: 2-14) for other specimens. Tissue (valve/anulus) from five patients with endocarditis were processed by the grinding technique allowing us to make the diagnosis of endocarditis by culture and microscopy [5]; in 4 of these the bacteria were not detectable by the conventional method. In 17 patients, *P. acnes* was identified in monoculture. In three patients, other microorganisms were identified including a coagulase-negative *Staphylococcus* in case 9 (CSF), *Peptostreptococcus micros* in case 17 (knee aspirate) and a mixed anaerobic flora in case 20 (sinus aspirate). In all three cases, however, *P. acnes* was the predominant microorganism. *P. acnes* was susceptible to penicillin (12/12), clindamycin (12/12), vancomycin (6/6) and rifampicin (3/3), and resistant to nitroimidazole (12/12).

Therapy and outcome:

All patients received intravenous antibiotics. Patients with endocarditis, spondylodiscitis and brain abscess were treated for 6 to 11 weeks intravenously, in some patients followed by an oral regimen (Table 1). In the other patients, therapy ranged from 10 days to 4 weeks. Beta-lactams were used in fifteen cases. Other drugs used included vancomycin, clindamycin and rifampicin. Eighteen patients (90 percent) underwent surgical procedures to remove infected tissue including heart valve replacement, removal of VP

shunts, vitrectomy and drainage. The outcome was favorable in sixteen patients (80 percent) who recovered completely. One patient died because of intracerebral hemorrhage that appeared to be unrelated to *P. acnes* infection, and one patient had residues from an embolic stroke (endocarditis). The patient with sinusitis lost vision of his right eye. One patient was lost to follow-up.

DISCUSSION

The isolation of *P. acnes* challenges the clinician to decide whether he is dealing with a contaminant or whether he has to treat a true *P. acnes* infection [3, 14, 15]. As outlined in *Patients and Methods*, strict clinical and microbiological criteria were applied in this study. Most of the tissue and material that grew *P. acnes* was surgically removed which makes a contamination less likely. In the cases where *P. acnes* was isolated from body fluids obtained by percutaneous aspiration, *P. acnes* was cultured repeatedly and either in monoculture or as predominant microorganism confirmed by Gram stain. In our survey over five years, *P. acnes* proved to be a real pathogen in only 70 of 905 isolates (7.7 percent), however, these infections were serious and involved heart valves, the brain, spine, joints and the eye. A significant finding was the high association of *P. acnes* with postoperative infections at the site of previous surgery. Precedent surgical interventions were noted in most of the earlier reported cases [5, 6, 11, 16]; and in a study of *P. acnes* infections of the central nervous system, 9 out of 11 occured after neurosurgical procedures [8]. Since endocarditis and postcraniotomy infections represent 72 percent of the postoperative infections in our study, possible risk factors for the development of surgical wound infections due to *P. acnes* appear to be craniotomy and sternotomy. *P. acnes* is associated with sebaceous glands and hair follicles which are predominantly located in the scalp and the sternal region.

The interval between surgery and clinical signs of infection lasted from two weeks to four years (average 4-5 months) indicating that such infections occur late in the postoperative course. The question whether inoculation of *P. acnes* during surgery was responsible for the infections remains open. *P. acnes* has a high affinity for deep skin structures making it difficult to eradicate with commonly applied disinfectants [16]. High inocula during surgery may account for short incubation periods of approximately 2-6 weeks leading to acute postoperative infections. However, *P. acnes* may also reside intracellularly and remain in a dormant state for weeks resulting in long incubation periods, in particular when the surgical site is inoculated with only few bacteria [3]. Alternatively, inoculation may occur after surgery by intermittent *P. acnes* bacteremia. We found implanted foreign bodies in 65 percent of postoperative infections which might favor bacterial attachment at a site with impaired local defense mechanisms.

The identification of *P. acnes* in the microbiology laboratory requires some precautions [1]. Time for detection required 19 days in one case emphasizing the importance of incubating blood and tissue specimens longer than the usual 5-7 days, when *P. acnes* infection is suspected. A crucial step for the microbiological diagnosis of *P. acnes* endocarditis appears to be the grinding technique with heart tissue that has recently been described in detail [5]. The detection of *P. acnes* in five cases by this method confirmed that this technique is superior to the conventional procedures.

The management of *P. acnes* infections included a combination of intravenous antibiotics (β-lactams) and surgical procedures including drainage of the infected site or removal of the infected device. Sixteen patients recovered completely, and in the remaining four, only one complication was directly related to progressive infection. Based on this experience, we recommend the combined approach, although it remains unknown whether the removal of the device is required to control *P. acnes* infection [8].

Sixteen *P. acnes* infections in this study occurred in the last twenty months which accounts for an eight- to ten-fold higher rate than in the years before 1994. Since the end of this study (August 1995), six more cases of endocarditis and CNS infections have been diagnosed, suggesting that the trend continues. The reason for this high rate of *P. acnes* infections remains unclear. The strong association of *P. acnes* infections with implanted foreign bodies and the increased use of foreign body devices in cardiac, eye and orthopedic surgery may not fully explain the phenomenon. Also, until recently, "diphtheroid" bacteria have been widely considered as contaminants and were rarely of interest to the clinicians, possibly resulting in underreporting *P. acnes* infections. Our study here clearly documents the pathogenic potential of *P. acnes* and establishes a significant role of this microorganism in late postoperative infections.

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