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Noninflammatory Chronic Pelvic Pain Syndrome: Immunological Study in Blood, Ejaculate and Prostate Tissue[1]

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Key Words

Chronic prostatitis · Chronic pelvin pain syndrome · Immunopathology · Interleukins · Complement

Abstract

Objectives: The aim of this prospective study was to observe immunophenotypic patterns in patients with noninflammatory chronic pelvic pain syndrome (Cat IIIB CPPS) for further description and as possible surrogate markers for diagnosis and treatment.

Methods: Eighty-eight patients with a referral diagnosis of chronic prostatitis underwent fractionated urinary cultures including expressed prostate secretion (EPS) and ejaculate analysis twice on two occasions. Monthly serum analyses included C3c, C4, IL-1α, sIL-2R, and IL-6. One hundred samples from healthy individuals were used as the control group for serum analysis. Monthly ejaculate testing was done for IgG, IgA, IgM, IL-1α, sIL-2R, and IL-6. The control group for ejaculate analysis was composed of 96 normal ejaculates (according to the WHO criteria). Immunohistochemical detection of CD3 cells (T lymphocytes) and CD20 cells (B lymphocytes) was performed in 71 biopsy cylinders of Cat IIIB CPPS patients and in 25 prostate biopsy cylinders of men without symptoms or obstruction.

Results: Complete sampling of urinary, serum and ejaculate specimens was achieved in 50/88 (57%) patients. Cat IIIB CPPS was observed in 44/50 (88%) patients. Intra-acinar T-lymphocytic infiltrates were dominated by T cytotoxic cells ($p = 0.05$). Immunohistochemical studies showed inflammatory expression in serum complement, serum interleukin, and ejaculate interleukin concentrations in relation to the presence of large numbers of T cells (all p values ≤ 0.01). No difference was found in the proportion of B lymphocytes in patients with Cat IIIB CPPS compared to the control group. Serum and ejaculate IL-6 and ejaculate IgA increased significantly and dropped again, correlating with a release of clinical symptoms.

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Conclusions: Interleukin, complement and immunoglobulin determinations in serum and ejaculate reveal an inflammatory process even in Cat IIIB CPPS. The findings of intra-acinar T-cell-rich infiltrates and the associated inflammatory reaction may be a significant advance in defining Cat IIIB CPPS caused by a possible autoimmune component. Serum and ejaculate IL-6 and ejaculate IgA are possible surrogate markers for the diagnosis and treatment of Cat IIIB CPPS.

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Introduction

Chronic prostatitis is one of the most common situations that the practicing urologist is confronted with [1, 2]. It is classified based on the presence of leukocytes and bacteria in the expressed prostate fraction [3, 4]. As pelvic pain is the leading symptom of patients with chronic prostatitis, in 1995 the American National Institute of Diabetes and Digestive and Kidney Diseases Working Group on Prostatitis proposed the name 'chronic pelvic pain syndrome' (CPPS) [5]. Researchers and clinicians agreed on a new classification system to aid diagnosis and management: I = acute bacterial prostatitis; II = chronic bacterial prostatitis; IIIA = inflammatory chronic pelvic pain syndrome; IIIB = noninflammatory chronic pelvic pain syndrome, and IV = chronic asymptomatic prostatitis. Bacterial infection of the prostate is the cause in only 5–10% of patients with chronic prostatitis [6, 7]. Noninflammatory CPPS (Cat IIIB CPPS according to the definitions of the National Institutes of Health) is characterized in patients with a painful syndrome of the small pelvis with no evidence of inflammation in prostatic secretions and seminal fluid [2]. The patients usually present with protracted pelvic pain, perineal miscomfort and significant lower urinary tract symptoms. They usually report a history of multiple courses of antibiotic treatment with no improvement and, as a result, they frequently have serious psychological disturbances [8]. The etiology of Cat IIIB CPPS is unknown and the disease is poorly understood. In the absence of any demonstrable infectious agent, we postulated that other mechanisms might be present and observable. We set out to determine whether any characteristic immunophenotypic pattern was present in patients with Cat IIIB CPPS, possibly leading to a better understanding of this condition and identification of possible surrogate markers for treatment. To our knowledge the immunological findings in prostate tissue, blood and ejaculate in Cat IIIB CPPS patients have not been systematically analyzed.

Material and Methods

Clinics

From September 1996 until June 1997, 88 men, mean age 42 (range 28–61) years, with the clinical diagnosis of chronic prostatitis were consecutively enrolled in this prospective study. Evaulation of symptoms followed a standardized prostatitis questionnaire, including a visual analog pain scale, and score of quality of life. Complete history was recorded. The mean duration of prostatitis, by history, was 4 years and 2 months (range 3–360 months). The average number of previous consultations with other physicians (general physicians or urologists) was 3 (range 1–7). The patients had been treated with courses of antibiotic therapy over 3 (range 1–10) months prior to presentation at our prostatitis outpatient clinic at Zurich University Hospital.

All patients underwent fractionated urinary cultures including expressed prostate secretion (EPS) and ejaculate analysis twice. Serum, urine, and ejaculate studies were performed three times at monthly intervals. Further investigations such as urodynamics and anorectoscopies were performed when indicated.

Seventy-one biopsy cylinders from 15 Cat IIIB CPPS patients were collected as well as 25 biopsies from 5 men without lower urinary tract symptoms or obstruction. They where unpaid volunteers and agreed to prostate biopsy by informed consent in agreement with the specifications of the local ethics committee. In 4 volunteers, serum and ejaculate testing was performed equally as often to exclude a systemic inflammatory response to the biopsy cores taken. The mean age of the control group was 53 (30–66) years and did not differ significantly from the Cat IIIB CPPS group. Ultrasound-guided prostate biopsies were performed through a 7.5-MHz biplanar probe (Hitachi EUB-555®, Hitachi Med. Corp., Tokyo, Japan) and a spring-loaded biopsy device (Automatic Biopsy System®; Manan Med. Prod. Inc., Northbrook, Ill.) using a 18-gauge 'tru-cut' type biopsy needle. Whenever possible three biopsy specimens from each prostate side were obtained in every patient.

Bacteriology

First voided urine, midstream urine, EPS and voided urine after massage were cultured aerobically at 37 °C in a 5% CO_2-enriched atmosphere on Columbia agar with 5% sheep blood, on the same medium supplemented with colistin and nalidixic acid, on Thayer-Martin agar, on Vaginalis agar, and on MacConkey agar without CO_2 (all media from bioMérieux, Geneva, Switzerland). Prostatic swab and midstream urine were also tested for the presence of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* with the LCR assay (Abbott, Abbott Park, Ill.). The presence of *Mycoplasma hominis* and *Ureaplasma urealyticum* was examined with A7 mycoplasma agar and urea-arginine broth (bioMérieux), respectively. Cat IIIB CPPS was accepeted according the NIH criteria [2] when EPS microscopy in the high-power field (×1,000) showed <10 leukocytes, bacterial growth

Table 1. Serum immunology follow-up in patients with noninflammatory CPPS

Serum	Norm valuesa	Month 0[b]	[n<norm]:[n<norm][c]	Month 1		[n<value 0]:[n<value 0][c] (cured/better/same)[d]		
		(n = 44)	(n = 44)	(n = 29)	p^1	(n = 29)	p^2	p^3
IL-1a, pg/ml	<3.9	0 (0–15.6)	41:3	0 (0–22.4)	n.s.	20 (3/9/2): 9 (4/5/0)	0.016	n.s.
IL-2 receptor, IU/ml	<477	465.8 (40–751)	23:21	365.2 (114.5–780)	n.s.	19 (4/10/1): 10 (3/4/1)	n.s.	n.s.
IL-6, pg/ml	<3.1	1.15 (0–9.0)	30:14	4.4 (0–61.5)	0.004	6 (2/1/0): 23 (5/13/2)	0.0002	n.s.
C3c, g/l	1.35 (0.9–1.8)	1.06 (0.8–1.7)	36:8	1.115 (0.83–1.66)	n.s.	16 (5/8/2): 13 (4/6/1)	0.028	n.s.
C4, g/l	0.25 (0.1–0.4)	0.22 (0.19–0.42)	28:16	0.225 (0.18–0.25)	n.s.	10 (1/7/2): 19 (81712)	0.028	n.s.

p^1 = Difference between median values compared to preceding serum sampling (Mann-Wilcoxon Whitney test).
p^2 = Groupwise difference between number of lower and higher values compared to the preceding blood sampling (χ^2 test).
p^3 = Groupwise difference between number patients with (cured/better/same) follow-up compared to the preceding blood sampling (χ^2 test).
[a] Median norm values with range (minimum–maximum) corresponding to the standards in routine serum-immunology.
[b] Median values with range (minimum–maximum) at time of noninflammatory CPPS diagnosis (0): and 1 and 2 months later.
[c] Number of values lower and higher than the preceding analysis/norm values.
[d] Number of patients with cured, better or unchanged clinical course.

Table 2. Ejaculate immunology follow-up in patients with noninflammatory CPPS

Serum	Control group[a]	Month 0[b]	p^1	[n<control]:[n>control][c]	Month 1	p^1	[n<value 0]: [n<value 0][c] (cured/better/same)[d]	p^2	p^3
	(n = 96)	(n = 35)		(n = 35)	(n = 23)		(n = 23)		
IL-1a, pg/ml	28.7 (0.9–562)	25.0 (0.9–517)	n.s.	20:15	26.3 (1.6–102.8)	n.s.	19 (2/9/3) : 4 (1/2/0)	n.s.	n.s.
IL-2 receptor, IU/l	2.4 (0–225)	3.5 (0–652)	n.s.	15:20	0.75 (0–541)	n.s.	18 (4/11/1): 6 (1/3/2)	0.03	n.s.
IL-6, pg/ml	7.5 (0.4–441)	12.2 (0–1713)	n.s.	7:28	43.2 (1.9–733)	0.01	8 (0/6/2) :15 (8/4/3)	n.s.	0.03
IgA, g/l	0.020 (0–0.3)	0.025 (0–0.30)	n.s.	13:22	0.020 (0–0.52)	n.s.	17 (4/12/0): 6 (1/1/3)	0.02	0.003
IgG, g/l	0.176 (0–0.98)	0.216 (0–0.34)	n.s.	12:23	0.195 (0–0.34)	n.s.	13 (3/8/1) :10 (2/5/2)		n.s.
IgM	not found	not found			not found				

p^1 = Difference between median values compared to preceding ejaculate sampling (Mann-Wilcoxon Whitney test).
p^2 = Groupwise difference between number of lower and higher values compared to the preceding ejaculate sampling (χ^2 test).
p^3 = Groupwise difference between number patients with (cured/better/same) follow-up compared to the preceding ejaculate sampling (χ^2 test).
[a] Median norm values with range (minimum–maximum) corresponding to the standard in routine serum-immunology.
[b] Median values with range (minimum–maximum) at time of noninflammatory CPPS diagnosis (0): and 2 months later.
[c] Number of values lower and higher than the preceding analysis/norm values.
[d] Number of patients with cured, better or unchanged clinical course.

was $<10^4$/ml EPS, and seminal fluid was devoid of significant bacterial growth and leukocyte counts [9].

Immunology

The C3-c and C4 levels in serum were analyzed by automated laser nephelometry (BNA Analyzer II, Behring Werke, Marburg, Germany). Analysis of the IL-1α, sIL-2R and IL-6 concentrations in serum and ejaculate was performed by an enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (human IL-1α and IL-6, RD Research and Diagnostics System, Minneapolis, Minn.; Cell-Free human ELISA sIL-2R, Endogen, Auburn, Mass.). Serum samples from 100 healthy individuals were collected and run in these assays (table 1). The control group for semen analysis consisted of 96 normal ejaculates according to the WHO criteria (table 2). These men had normal urogenital tracts without evidence of inflammatory prostatitis. The IgG, IgA and IgM levels in the ejaculate were measured by the radial immunodiffusion technique by LC-Partigen IgG, LC-Partigen IgA and LC-Partigen IgM plates (Behring Werke, Marburg, Germany).

Light Microscopy and Immunohistochemistry

The biopsy probes were immediately fixed in 4% formalin and routinely paraffin-embedded. Serial sections of 2-μm thickness were investigated by conventional light microscopy (hematoxylin and eosin stain). Additionally, they were stained with Giemsa, Gram and the periodic acid-Schiff reaction for evaluation of microbial colonization. In the immunohistochemical methods the tissue sections were incubated with monoclonal antibodies against the T-lymphocyte marker CD3 (Novocastra, Newcastle-upon-Tyne, UK; NCL-CD3-PS1; dilution 1:40) and the B-lymphocyte marker CD20 (DAKO, Copenhagen, Denmark; M755; 1:800). T lymphocytes were then differentiated into the T-helper or T-cytotoxic subtype, using antibodies against CD4 (Novocastra; NCL-CD4-1F6; 1:20) and CD8 (DAKO; M7103; 1:40), respectively. Visualization of these primary antibodies

Month 2		[n<value I:n>value I][c] (cured/better/same)[d]		
(n = 11)	p[1]	(n = 11)	p[2]	p[3]
0 (0–0.1)	n.s.	8 (3/2/0):3 (1/0/1)	n.s.	n.s.
492.6 (110.2–999.8)	n.s.	5 (2/1/0):6 (2/1/2)	n.s.	n.s.
2.9 (0–11.6)	n.s.	7 (6/1/0):4 (0/1/2)	0.027	0.02
1.235 (1.06–1.18)	n.s.	6 (3/2/0):5 (2/1/1)	n.s.	n.s.
0.205 (0.18–0.2)	n.s.	5 (3/1/0):6 (1/1/2)	n.s.	n.s.

was performed using rabbit anti-mouse antibodies (DAKO; Z259) and the alkaline phosphatase anti-alkaline phosphatase method (CD3, CD4 and CD8). With CD20, the peroxidase-labeled avidin-biotin technique was used (DAB Detection Kit; Ventana, Tucson, Ariz.). All histological slides were reviewed by 2 pathologists (A.B., S.H.) to minimize intraobserver bias. A four-tier grading system of the lymphomonocytic infiltrate (discrete, slight, moderate, and severe) was defined prior to the study. A discrete infiltration was considered a physiologic finding, and inflammation was only diagnosed when the infiltrate was increased with regard to this background. The localization of the inflammatory response was differentiated into: (1) intra-acinar (intraepithelial), i.e. within the basement membrane of the prostatic glands, and (2) stromal (interglandular) when the inflammatory cells were not directly connected to prostatic glands.

Only patients with complete samplings of urine, EPS, serum and ejaculate were accepted for further consideration. Data were processed by StatView 4.02® software (Abacus Concepts Inc., Berkeley, Calif.). Statistical analysis was based on χ^2, Mann-Whitney, and linear regression tests with $p < 0.05$ being the accepted significance level.

Results

Complete sampling of urinary, serum, and ejaculate specimens was achieved in 50/88 (57%) patients. In 38/88 (43%) patients prostatic secretion could not be obtained (n = 29), or urodynamic abnormalities such as detrusor-sphincter dyssynergy (n = 5) or anosphincteric pathology (n = 4) explained the pain syndrome. These patients were excluded from analysis.

Bacteriology

Cat IIIB CPPS was observed in 44/50 (88%) patients. No patient from this group had inflammation in the repeated analyses. Nonbacterial chronic prostatitis (Cat IIIA CPPS) was found in 1 case (2%), and chronic bacterial prostatitis (Cat II CPPS) in 5 cases (10%). *Corynebacterium glucuronolyticum* and *Enteroccoccus sp.* were present in 2 cases each, and *Staphylococcus sp.* in another case. *C. trachomatis*, *N. gonorrhoeae*, *M. hominis* and *U. urealyticum* were not encountered.

Serum Immunology

Initially (month 0), these 44 patients with Cat IIIB CPPS exhibited median serum complement factors C3c and C4 in the low normal range (table 1). They increased after 1 month, with individual C3c and C4 values higher compared to the initial sampling (p = 0.028). No statistically significant difference could be demonstrated in the further follow-up after 2 months. IL-6 increased significantly after 1 month from 1.15 to 4.4 pg/ml (p = 0.004), while IL-1α and serum sIL-2R values remained within the normal range over 2 months. Groupwise analysis after 1 month showed a significant increase compared to time 0 for IL-1α (p = 0.016) and IL-6 (p = 0.0002), but IL-6 decreased again (p = 0.027) after 2 months. No correlation could be demonstrated between cure rate (cured/better/same) and serum interleukins or complement factors during the observation period.

Ejaculate Immunology

Ejaculate IL-1α did not differ from the control group (table 2). sIL-2R was decreased after 1 month (p = 0.03) compared to the baseline value, while the mean sIL-2R concentration remained in the normal range. The mean ejaculate IL-6 concentration significantly increased after 1 month from initial 12.2 to 43.2 pg/ml (p = 0.01). Ejaculate IgA and IgG were moderately increased initially. The mean IgA dropped after 1 month (p = 0.02) and the cure rate increased within this interval (p = 0.003).

Immunohistochemistry (table 3)

B-lymphocytes (CD20) were equally distributed in the prostatic glands and stroma of patients with Cat IIIB CPPS compared to the control group. T lymphocytes (CD3) were significantly more often present within acini (p = 0.05) and were clearly dominated (p = 0.001) by the T suppressor/cytotoxic subclass (CD8). No evidence of intraprostatic bacterial colonization was found in the Giemsa-, Gram- and periodic acid-Schiff-stained slides. Interleukin values were opposed to intra-acinar T-lymphocytic distribution. IL-1α, IL-2R, and IL-6 in serum and ejaculate correlated with the increased numbers of intra-acinar T lymphocytes.

Table 3. Prostatic intra-acinar and stromal of T lymphocytes (CD3), B lymphocytes (CD20), T-helper/inducer lymphocytes (CD4) and T-supressor/cytotoxic lymphocytes (CD8) in patients with noninflammatory chronic pelvic pain syndrome (71 cylinders) compared to the control group of patients without lower urinary tract symptoms or obstruction (25 cylinders)

Cell type	Noninflammatory CPPS				Control group				p value
	+	++	+++	++++	+	++	+++	++++	
CD3 intra-acinar	41	14	12	4	16	3	4	2	0.05
CD4/CD8	33/9	12/22	17/28	4/7					0.002
CD3 stromal	41	6	17	7	14	4	4	3	0.65
CD20 intra-acinar	68	1	2	0	24	0	0	1	0.27
CD20 stromal	33	18	15	5	10	7	5	3	0.78

Applied grading: +-discrete; ++-slight; +++-moderate; ++++-severe.

Discussion

Prostatitis is the most common genitourinary disease in men between 18 and 50 years of age. In the United States, there are about 2 million estimated physician consultations per year for prostatitis [1]. Despite the frequency with which primary care physicians and urologists diagnose prostatitis, there are no proven efficacious therapeutic regimens for chronic prostatitis. Patients usually are treated by long, costly, and often unsuccessful antibiotic regimens which have attendant risks and side effects. These patients typically consult multiple physicians and urologists, and often experience psychologic problems including sexual dysfunction and impotence [8]. Chronic bacterial infection of the prostate gland occurs in only 5–10% [6, 7]. Standardized diagnostic procedures, including fractionated urinary cultures, microbiologic examination of the EPS and ejaculate, are prerequisites for a correct classification of chronic prostatitis syndromes, especially for nonbacterial prostatitis and Cat IIIB CPPS. Contaminations must be carefully excluded in all bacteriological cultures. Especially in the ejaculate, nonsignificant bacterial growth is frequent and may lead to false-positive cultural interpretation, thus inducing inappropriate antibiotic therapies [10, 11].

Some evidence of autoimmune etiology in Cat III CPPS has been demonstrated in animal models. Donadio and Depiante-Depaoli [12] studied the degree of lymphocytic infiltration alongside the phenotype of the infiltrating cells and major histocompatibility complex antigens during experimental autoimmune prostatitis in rats. Keetch et al. [13] injected prostate antigen into syngeneic mice. They observed a prostate-specific inflammation in recipient mice, which was shown to be of immune origin by adoptive transfer studies. They deducted that chronic nonbacterial prostatitis could be at least in part immune-mediated. Nevertheless, from these models we cannot define the possible immunological mechanisms in patients with Cat IIIB CPPS.

Table 4. Regression coefficients of serum and ejaculate interleukins correlated to discrete, slight, moderate and severe T-cell distribution in the intra-acinar prostate parechyma of patients with noniflammatory CPPS

Cell type (x)	Cytokine (y)	Regression	R^2	p value	n
Serum					
CD3	Serum IL-1α	y = –0.05+0.11x	0.93	<0.0001	14
CD3	Serum sIL-2R	y = 1.11+0.53x	0.50	0.003	15
CD3	Serum IL-6	y = 0.68+0.37x	0.48	0.01	12
Ejaculate					
CD3	Ejaculate IL-1α	y=–239.4+171.7x	0.87	<0.0001	17
CD3	Ejaculate sIL-2R	y=–253.7+202.3x	0.86	<0.0001	13
CD3	Ejaculate IL-6	y=–282.0+169.5x	0.60	0.001	14

Our objective was to look for an autoimmune component that might be involved in the etiology of Cat IIIB CPPS. To our knowledge our study is the first to systematically describe the inflammatory findings in the prostate, blood and ejaculate of patients who fulfill the NIH criteria of Cat IIIB CPPS. Our findings showed an intra-acinar T-cell increase with CD8 cell dominance in patients with Cat IIIB CPPS (table 3). Furthermore, CD3, CD4 and CD8 cell presence correlated with serum and ejaculate interleukin concentrations, as well as with serum complement component (table 1, 2, 4). T-cell HLA-Dr cell typing was not performed in this study.

Although there is no evidence of a bacterial or viral prostate gland infection in our Cat IIIB patients (i.e. negative urine, ejaculate and prostate expression cultures on 2 occasions; negative ligase chain reaction for *Chlamydia* and *Gonococcus*, negative cultures for *Ureaplasma* and *Mycoplasma*; and EPS with <10 Lc in higher power field), we observed inflammatory expressions in serum complement, serum interleukin, and ejaculate interleukin concentrations. This seems to correspond with the immunohistochemistry

Table 5. Immunopathological pathway in noninflammatory CPPS

Stimulus	Responding cells	Effector function	Differentiation response and function	Cytokine production	Effector function
Bacterium, virus fungus	Macrophages } cytokine T and B cells } production	Phagocytosis elimination of Ag Antigen presentation Production of auto antigen	T_{H1} cell+CD_4 T cells+CD4 T_{H2} cell+CD_4	χIF IL2, sIL2, Rec IL6 IL1α/β IL-4 IL-5 IL-6 sIL2 Rec	**A** Cellular immunity – Expansion of T-cytotoxic CD_8 cells – Activation of T-cytotoxic CD_8 cells – NK cell DTH **B** Humoral immunity – Polyclonal B-cell activation – B-cell differentiation – Immunoglobulin production (IgA) – Autoimmunity ADCC
⟶ Initial phase ⟶					⟶ Chronic phase ⟶

DTH = Delayed-type hypersensitivity; ADCC = antibody-dependent cytotoxicity (T cells).

findings characterized by the presence of large numbers of T cells (table 4). Together with the absence of B cells, this implies that the inflammatory reaction in Cat IIIB CPPS is cell mediated (table 3, 4). We hypothesize that increased ejaculate and serum interleukins in patients with Cat IIIB CPPS originate from activated T cells.

In addition, other cell types like granulocytes or macrophages may participate in elaboration of the cytokines leading both to serum interleukin elevation and to increased T-cell trafficking to organ sites via chemokine upregulation. Similar findings to our study were recently found by Alexander et al. [14]. In a group of 18 patients with Cat IIIB CPPS they found elevated seminal levels of TNF-α and IL-1β, while there was no correlation between either TNF-α or IL-1β levels and the number of leukocytes in the high power field of the EPS. IL-1β was reported to be increased in infertile men without correlation to determined pathology [15]. However, extensive seminal cytokine studies in patients with Cat IIIB CPPS have not been performed before. In our study, within the 2-month observation period, the serum complement components decreased and the serum interleukins increased temporarily, suggesting an inflammatory, symptomatic phase (table 1). Serum IL-6 increased significantly, and ejaculate IL-6 concentrations clearly corresponded to intra-acinar T-lymphocyte distribution (table 1, 4). IL-6 in serum and ejaculate, and ejaculate IgA may represent surrogate markers in the diagnosis, treatment and clinical course. IL-6 acts on a variety of cells and exerts a number of activities. It is also involved in T-cell activation, growth and their differentiation. IL-6 induces IL-2 receptor expression in T cells and thymocytes and acts as a second signal for IL-2 receptors and IL-2 production in T cells. Furthermore IL-6 plays an important role in polyclonal B-cell abnormalities, for example autoimmune diabetes type I [16], autoimmune thyreoditis [17], and rheumatoid arthritis [18]. We suggest an autoimmune process as the possible etiology of CPPS. Recurrent irritative pain phases with the demonstrated cytokine alterations would correspond to active autoimmune cycles. Autoimmune etiology could be either the primary cause of symptoms or occur after a bacterial colonization of the prostate. On one hand, the activation of macrophages leads to phagocytosis and elimination of pathogens (bacteria, fungi, virus). On the other hand, the function as antigen-presenting cells (initial phase). As a consequence of the production of certain cytokines by leukocytes, CD4-positive lymphocytes will mature to CD4 T_{H1} or T_{H2} cells. Therefore depending on the production of the different cytokines, the immune reaction will be directed to either the cellular defense with the consequent activation of CD8 cytotoxic lymphocytes or a humoral reaction with polyclonal activation of B lymphocytes and production of antibodies of different classes. Within the activation of a polyclonal humoral reaction it is possible that also antibodies to self antigens can be triggered leading to autoimmunity. In the chronic phase these autoantibodies can lead to cell and tissue destruction through the 'antibody-dependent cellular cytotoxicity' as a pathophysiological mechanism (table 5). Immunosuppressive therapy and

intravenous application of immunoglobulins are not unlikely to be set up in a controlled group of Cat IIIB CPPS patients.

IL-6 in serum and ejaculate, and ejaculate IgA correlate with the clinical outcome and may serve as surrogate markers in the diagnosis and treatment.

Conclusions

In patients with 'noninflammatory' CPPS, inflammation is evident in serum complement, serum interleukin, and ejaculate interleukin concentrations. The findings of intraacinar T-cell-rich infiltrates and the associated inflammatory reaction may be a significant advance in defining Cat IIIB CPPS, caused by a possible autoimmune component.

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