Chronic Prostatitis

Clinical, Microbiological, Cytological and Immunological Aspects of Inflammation

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Proteinases and Proteinase Inhibitors in Ejaculates of Men with Adnex Affections

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Introduction

Proteinases of the male genital tract are important primarily for the fertilization process. They are taking part also in coagulation and liquefaction of ejaculate as well as in stimulation of sperm migration within the female genital secretions. Moreover, proteinases are involved as mediators of the inflammatory response in the male genital tract aggravating the clinical symptoms (Schill, 1975; Hafez, 1976; Havemann and Janoff, 1978).

These proteinases are either sperm specific enzymes (acrosin), secretory products of the accessory sexual glands (seminin, BAEE-splitting enzyme, urokinase, tissue kallikrein) or they are liberated in the adnexal region during degranulation of leukocytes (elastase).

In the male genital tract proteolytic activity of the proteinases are kept under control by potent antagonists, the high molecular weight plasma proteinase inhibitors α_1-proteinase inhibitor (formally α_1-antitrypsin) and α_1-antichymotrypsin as well as the low molecular weight, acid-stable secretory products leukostatin (HUSI-I) and acrostatin (HUSI-II) (Schiessler et al., 1976; Schill, 1976; Schiessler and Schill, 1977; Schill and Schiessler, 1977).

We were interested, therefore, to see whether in chronic adnex affections alterations in the proteinase/proteinase inhibitor system of the ejaculate are measurable, probably qualified as diagnostic criteria.

Material and methods

Ejaculates were withdrawn from patients undergoing standard diagnostics such as 3-tube test and analysis of the urethral smear, prostatic fluid and urine. Diagnosis of chronic adnexitis was confirmed by the following criteria: significantly high numbers of gram-negative bacteria, enterococci, mycoplasmas, Ureaplasma urealyticum and Chlamydia trachomatis, leukocytes more than 20 per visual field; evidence of complement factor 3c and coeruloplasmin in seminal plasma. Ejaculates from 40 patients with adnex affections were examinated; 14 patients showed vegetative urogenital syndrome (VUG) and anogenital symptomcomplex (AGS), 24 patients suffered from chronic and 2 from acute adnexitis. Within the group of chronic adnexitis patients were further differenciated according to the concentration of the complement factor 3c as follows: patients with C3c values lower ($n = 14$) or higher ($n = 10$) than 1.2 mg%, respectively. Activities of seminin, urokinase, and the BAEE-splitting enzyme in seminal plasma were determined using known methods (FRITZ, 1972; SCHILL, 1973). Tissue kallikrein was quantified by a specific radioimmunoassay (FINK and GÜTTL, 1978). The immunological concentrations of α_1-proteinase inhibitor, α_1-antichymotrypsin, acrostatin and leukostatin were measured by radial immunodiffusion ("Mancini-technique"). The concentration of liberated granulocytic elastase bound to α_1-proteinase inhibitor (E-α_1PI) was estimated by a newly developed enzyme-linked immunoassay (NEUMANN et al., 1983). Statistical evaluation was performed by the independent Student-t-test.

Results and discussion

Significance and physiological function of the BAEE-splitting enzyme from prostatic secretions is rather unknown. So far, only during viscosity disturbances of seminal plasma, a clearly lowered enzyme activity could be proven (SCHILL, personal communication). Seminin, originating also from prostata, is involved in clotting and liquefaction of sperm. Moreover, it may facilitate penetration of spermatozoa into cervix mucus. In contrast to normal ejaculates, both enzymes showed a significant decrease during chronic adnexitis as well in VUG as in AGS. This might be caused probably by massage of prostata before ejaculation. With acute adnexitis, a clear increase in enzyme-concentrations was measurable in accordance with a commonly observed enhancement of organ function and synthesis during acute inflammatory reactions (Fig. 1).

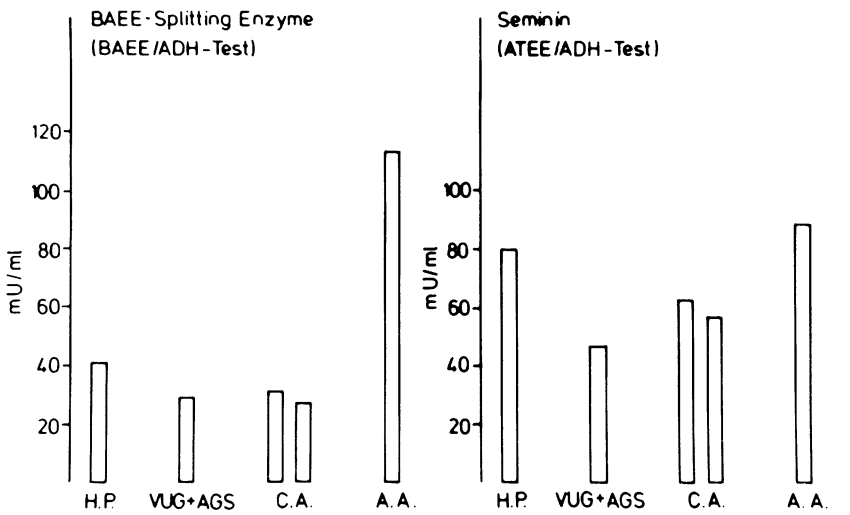

Fig. 1. Activity of BAEE-splitting enzyme and seminin in ejaculates of men with adnex affections (H.P. = healthy persons; VUG = vegetative urogenital syndrome; AGS = anogenital symptom complex; C.A. = chronic adnexitis with complement factor C3 < 1.2 mg% or > 1.2 mg%, respectively; A.A. = acute adnexitis).

Urokinase and tissue kallikrein were also demonstrable in prostatic secretion; their physiological relevance, however, ist still unknown. Probably, tissue kallikrein takes part in stimulation and maintenance of spermatozoon motility via liberation of pharmacologically highly active kinins from sperm plasma kininogen. In comparison to healthy persons, both enzymes showed a slight, though statistically not significant reduction in patients with chronic adnexitis and VUG; again, in acute adnexitis an expected increase of the enzymes' concentrations was measurable (Fig. 2).

The high molecular weight plasma proteinase inhibitors α_1-proteinase inhibitor and α_1-antichymotrypsin, transudated from serum into seminal plasma, showed no significant alterations during VUG, AGS or chronic adnexitis, respectively. However, throughout acute adnexitis the well-known dramatic increase of the inhibitors' concentrations was demonstrable in seminal plasma. This enhancement may be due not only to a considerably increased synthesis of the inhibitors as acute phase proteins during the acute inflammatory response but also to a lowered blood-seminal plasma-barrier (Fig. 3).

The acid-stable, low molecular weight proteinase inhibitor leukostatin synthesized in the vesicular glands is supposed to be the natural antagonist of leukocyte proteinases. It did not exhibit significant alterations. The same holds true for acrostatin (Fig. 4), the highly potent inhibitor of the penetration enzyme acrosin which is localized in the acrosome of the spermatozoon. The low

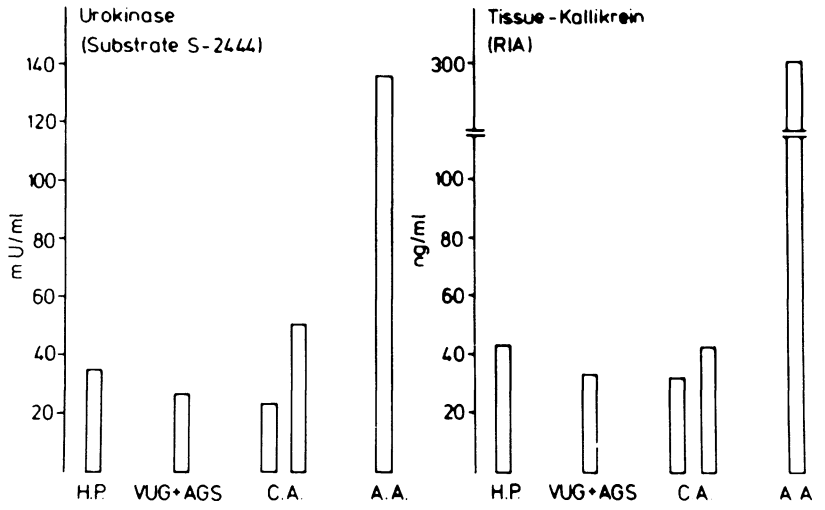

Fig. 2. Activity of urokinase and concentration of tissue kallikrein in ejaculates of men with adnex affections.

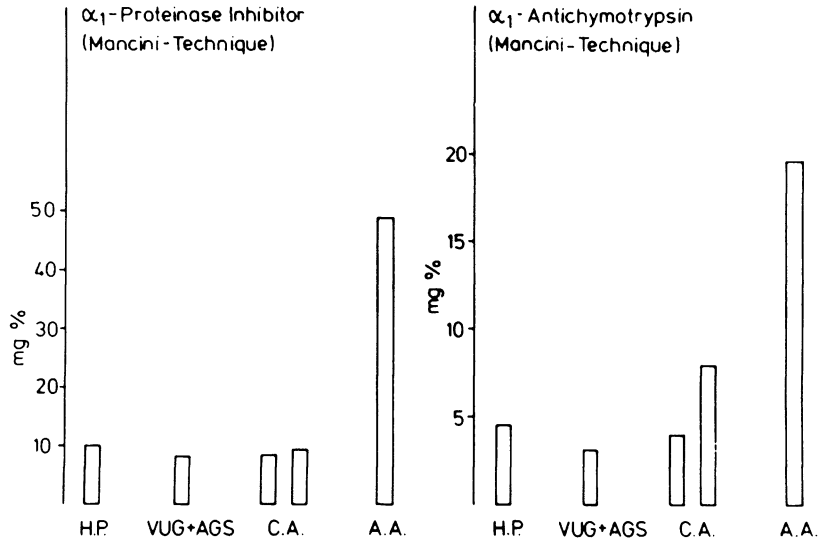

Fig. 3. Concentrations of α_1-proteinase inhibitor and a_1-antichymotrypsin in ejaculates of men with adnex affections.

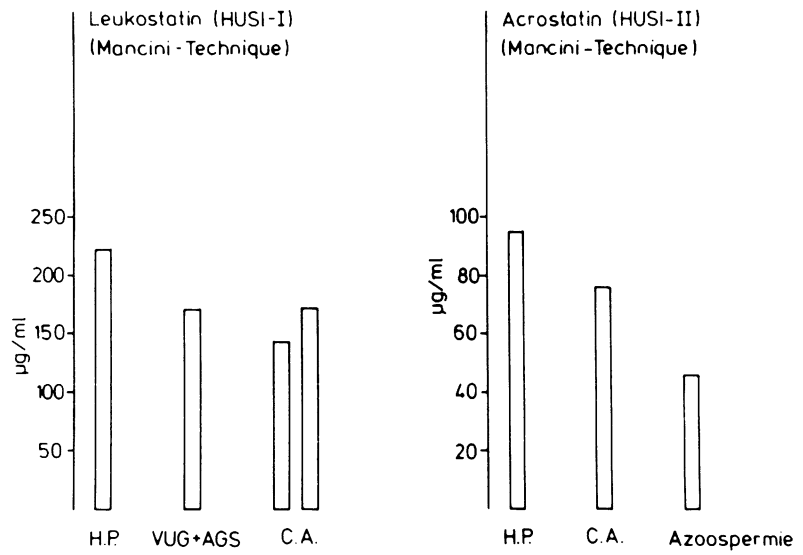

Fig. 1. Concentrations of leukostatin and acrostatin in ejaculates of men with adnex affections.

molecular weight, acid-stable acrostatin – synthesized in vesicular glands and epididymis – showed a clear reduction of the inhibitor concentration only in man with occlusive azoospermia (SCHILL and SCHIESSLER, 1977).

Summarizing the given data, the proteinases and proteinase inhibitors described above did not turn out to be significant diagnostic parameters in chronic adnexitis, VUG and AGS, respectively. This is, however, different with leukocytic proteinases during these inflammatory processes.

The biological function of leukocytic proteinases is the intracellular protein catabolism of wasted endogenous substances and the degradation of phagocytized invasive organisms. If released extracellularly due to degranulation or disintegration of leukocytes, these proteinases may enhance tissue damage and activation of the inflammatory response. Of the leukocytic proteinases known so far, the neutral proteinase elastase from polymorphonuclear granulocytes deserves special interest because of its high amount within the granules as well as its nearly unlimited cleavage specificity. However, due to a relatively rapid reaction with α_1-proteinase inhibitor, the most important inhibitor of this enzyme, granulocytic elastase liberated extracellularly is found nearly exclusively in an already inactivated form.

With a highly sensitive enzyme-linked immunoassay about 180 ng complexed elastase (E-α_1-PI) per ml were found in ejaculates of 10 healthy persons. Patients with VUG and AGS showed a highly significant elevation up to x =

1100 ng/ml. In chronic adnexitis a similar increase (x = 1200 ng/ml) could be shown in seminal plasma containing C3c concentrations below 1.2 mg%, whereas C3 amounts above 1.2 mg% were combined with a further dramatic increase of complexed elastase up to 4500 ng/ml. Moreover, in acute adnexitis elastase levels far more than 10,000 ng/ml were measured (Fig. 5).

From these preliminary results of 40 ejaculates, which of course will be confirmed with a more extended patient collective, we draw the following conclusions:

1. The levels of complexed granulocytic elastase proved to be a highly sensitive and qualified parameter of inflammatory processes in adnex affections.
2. Most of the biochemical parameters determined so far in ejaculates of patients with adnex affections are only an indirect criterion of an impaired blood-seminal plasma-barrier during the inflammatory process. Levels of complexed granulocytic elastase, however, represent a direct quantification of an inflammatory mediator in the adnexial region.
3. Quantification of complexed elastase might become a reliable biochemical parameter additional to diagnostic criteria used now in adnex affections. This new parameter seems to reflect activity and severity of an inflammatory process more specifically and offers, therefore, new aspects for controlling the course of the disease as well as the therapy.

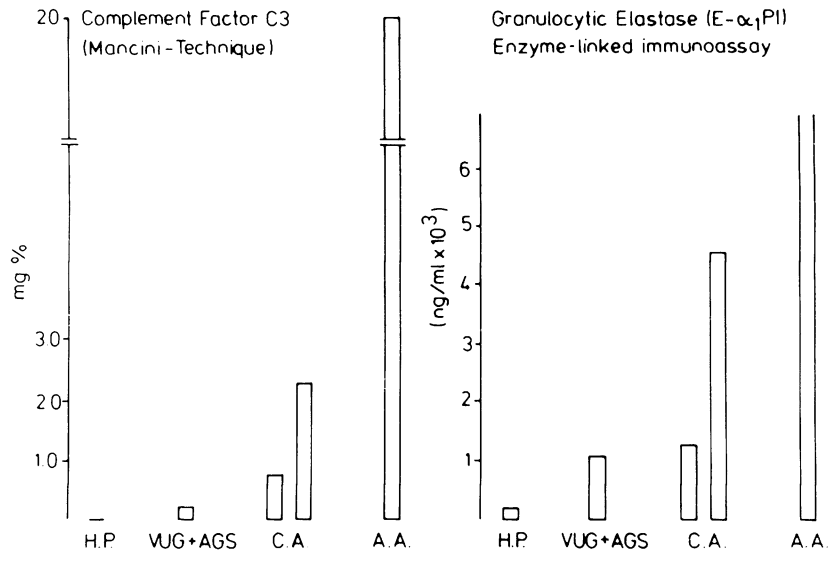

Fig. 5. Concentrations of complement factor 3c and granulocytic elastase in complex with α_1-proteinase inhibitor (E-α_1PI) in ejaculates of men with adnex affections.

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