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Plasma fibronectin concentrations in patients with human immunodeficiency virus infection

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Abstract

Plasma fibronectin (PFN) concentrations were assessed in 21 patients with AIDS, in seven with AIDS-related complex (ARC), in 17 asymptomatic seropositive patients, and in 36 age and sex matched healthy control subjects. A single radial immunodiffusion technique was used to determine PFN concentration. A significant decrease in PFN concentrations was observed in patients with ARC and AIDS (especially in those patients with *Pneumocystis carinii* pneumonitis). On the other hand, normal PFN concentrations were observed in asymptomatic seropositive patients. The determination of PFN concentration in patients with AIDS and ARC may contribute to the diagnosis of such patients.

Fibronectin is a large glycoprotein of 450 found as a soluble dimer in plasma and as insoluble multimer in the basement membrane and intercellular matrix.[1 2] Fibronectin is known to be an adherent and opsonic glycoprotein.[3] It may enhance cell adherence and chemotaxis of phagocytes[4 5] and it helps to maintain the oxidative bactericidal capacity of macrophages. Fibronectin is also found in areas of fibrosis and inflammation.[3] Kuusela[6] showed that fibronectin binds to *Staphylococcus aureus* group, A, C, and G, streptococci as well as to *Streptococcus sanguis* and *Streptococcus pneumoniae*.[7 8] Patients with AIDS may also experience persistent or recurrent staphylococcal infections limited to the skin.[9] Fibronectin has also been shown to bind to *Candida albicans*,[10] to protozoan pathogens such as *Trypanosoma cruzi* and Leishmania,[11] and to the envelope glycoprotein of viruses.[12] Fibronectin is also included in the immune complexes found in patients with some bacterial and rheumatic diseases.[13 14] This protein may also increase the size of the immune complexes, facilitating their clearance. Most infections that occur in patients with AIDS are caused by a relatively small number of opportunistic organisms. Infection with bacterial pathogens, particularly with *S aureus*, *S pneumoniae*, and *Haemophilus influenzae* may also occur.[15 16] It has been shown that in patients with AIDS and lymphadenopathy syndrome chemotaxis is defective.[17] Several monocyte functional abnormalities have also been reported in AIDS, including defective chemotaxis and phagocytosis.[18 19] The activity of plasma fibronectin in patients with HIV infection is interesting because fibronectin has been found to interact with phagocytes at several stages in the phagocytic process.[20] Recently, Ogden *et al* showed normal plasma fibronectin concentrations in patients with AIDS or ARC. This study was undertaken to determine the plasma concentration of fibronectin in HIV antibody positive patients.

Methods

Twenty one patients with AIDS (mean (SD) age 29·9 (8·1) years), seven with ARC (mean (SD) age 27·2 (4·3) years), and 17 asymptomatic but seropositive to HIV patients (mean age (SD) 26·6 (6·8) years) were studied. All patients included in this study fulfilled the criteria for the diagnosis of AIDS established by the Centers for Disease Control, Atlanta. All patients were intravenous drug users except for three with AIDS who were homosexual. One homosexual patient had Kaposi's sarcoma. Thirty six healthy subjects (mean (SD) age 28·7 (4·4) years) acted as controls. Plasma specimens were prepared from EDTA and immediately frozen at −20°C.

Plasma fibronectin was determined in all patients by the single radial immunodiffusion technique using a monospecific antiserum against human plasma fibronectin (Medic Pathology, Milan, Italy). The assay requires a 20 μl plasma sample. The plates were left at 25°C for 48 hours and the diameter of the resulting precipitation rings was measured.

Significance was determined with the Student's *t* test for unpaired samples. All data were expressed as mean (SD). P values of < 0.05 were regarded as significant.

Results

Table 1 shows the plasma fibronectin concentrations in patients infected with HIV. Normal concentrations were observed in asymptomatic seropositive patients. On the other hand, patients with ARC and AIDS showed a significant and noticeable diminution of plasma fibronectin concentrations ($p < 0.01$). Patients with *Pneumocystis carinii* pneumonitis also had very low plasma fibronectin concentrations.

Table 2 shows the plasma fibronectin concentrations in seven patients with *P carinii* pneumonitis who were receiving treatment with co-trimoxazole. A significant increase in plasma fibronectin concentrations was noted

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Table 1 Plasma fibronectin concentrations in different groups of patients with HIV infection

Patients		*Plasma fibronectin concentration (μg/ml)*
Controls	(n 36)	382·7 (78·7)
Asymptomatic seropositives	(n 17)	395·1 (79·9)
ARC	(n 7)	161·8 (58·0)*
AIDS	(n 21)	143·9 (67·4)*
with *P carinii* pneumonitis	(n 11)	122·9 (37·7)*

*p < 0·01 when compared with values of control group.

Table 2 Plasma fibronectin concentrations in seven AIDS patients with P carinii pneumonitis after 10 and 20 days days of treatment with co-trimoxazole

Case no	*Age (years)*	*Plasma fibronectin concentration (μg/ml)**		
		0	*10*	*20 days*
1	25	31	59	196
2	28	98	225	270
3	27	119	141	400
4	27	22	22	98
5	29	98	69	69
6	25	49	69	196
7	24	49	109	141
Mean (SD) values		66·5 (37·8)	99·1 (67·1)	195·7 (112·4)†

*Plasma fibronectin concentrations were determined by the single radial immunodiffusion technique.
†p < 0·05 when compared with initial plasma fibronectin concentrations.

after 20 days of treatment (p < 0·05). Oral or oesophageal candidiasis, or both, were also observed in such patients. Plasma fibronectin concentrations after 10 days of treatment were increased, but not significantly so, compared with the values at 0 days.

On admission, all patients had severe respiratory distress, with severe and diffuse interstitial pneumonitis evident on *x* ray picture. After 20 days of treatment all patients showed clinical and radiological improvement, together with a progressive increase in plasma fibronectin concentrations.

Discussion

This study shows that low plasma fibronectin concentrations are present in patients with ARC and AIDS (especially in those with *P carinii* pneumonitis). Fibronectin increases the phagocytic capacity of macrophages and neutrophils by increasing chemotaxis, phagocyte adherence, and phagocytosis.[20] In *P carinii* pneumonitis the alveolar lumens are filled with large numbers of organisms and macrophages. Such organisms may become coated with soluble fibronectin (and consequent depletion of plasma fibronectin), allowing alveolar macrophages to phagocytose *P carinii* coated with fibronectin. The progressive increase in plasma fibronectin concentration in patients with *P carinii* pneumonitis may indicate initial clearance of the organism due to antibiotic treatment. A good improvement in clinical and radiological signs but not a complete resolution of pneumonitis was observed in our patients after 20 days of treatment. In fact, relapses of *P carinii* pneumonitis are frequently seen in patients with AIDS as a complete and prolonged eradication of the organism is difficult to achieve. Leishmania and *Trypanosoma cruzi* bind host fibronectin to their surfaces, and that fibronectin then serves as a bridge in the binding of the organisms to host monocytes and macrophages.[22] Ogden *et al* observed that patients with ARC and AIDS showed no significant difference in their contractions of plasma fibronectin compared with those in the control group.[22] One possibility that might explain this difference between the results of Ogden's study and ours is the method used to assess plasma fibronectin concentrations. Determination of plasma fibronectin concentrations in Ogden's study was performed by an immunoturbidimetric assay. The difference of the assay, and in particular, of the antiserum to human fibronectin used may explain our conflicting data. Another possibility might be that drug users, and in particular those with HIV infection, are more susceptible to overt or occult bacterial infections than other HIV antibody positive patients such as homosexuals. Most of the patients in Ogden's study had Kaposi's sarcoma and only 10 out of 24 patients had opportunistic infections. On the other hand, in our study only one homosexual AIDS patient had Kaposi's sarcoma. Recently, Janier *et al* showed increased plasma fibronectin concentrations in patients with AIDS and Kaposi's sarcoma and in those with classic Kaposi's sarcoma. (Abstract presented at Fifth International Conference on AIDS, June 1989, Montreal; No C726.) These authors suggested that the increased plasma fibronectin concentrations observed in AIDS patients with Kaposi's sarcoma may be related to damage and active proliferation of endothelial cells as such cells produce discrete amounts of fibronectin.

In conclusion, the decreased plasma fibronectin concentrations seen in patients with ARC and AIDS may be related to the ability of fibronectin to bind to several opportunistic pathogens to limit infection and to promote healing.

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