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Serum Sialyltransferase and Fucosyltransferase Activities in Patients with Multiple Myeloma*

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Abstract—*A significant elevation of serum sialyltransferase and fucosyltransferase mean activities was observed in* 19 *untreated patients with multiple myeloma. However, sialyltransferase mean activity was significantly lower in* 13 *other patients treated for* 1-30 months *with alkylating drugs and prednisolone. Such a definite decrease in serum enzyme activity on treatment was not recorded for fucosyltransferase. Instead, this activity was significantly increased in treated patients as compared to controls. The presenting clinical features of the* 32 *patients with multiple myeloma were the basis for a clinical staging system with regard to myeloma cell burden according to established criteria. In untreated patients (as opposed to treated ones), a significantly higher serum sialyltransferase (but not fucosyltransferase) activity was obtained among those* 11 *belonging to stage III than among the other eight with stages I and II, suggesting a link between tumour burden and enzyme activity. This assumption was further strengthened in those six patients followed lengthwise with regard to serum sialyltransferase activity. Concomitantly with objective evidence of change in tumour burden they showed corresponding alterations in sialyltransferase activity. The determination of sialyltransferase and fucosyltransferase activity in serum may be an additional contribution to refine initial assessment and follow-up of individual patients with multiple myeloma.*

INTRODUCTION

HUMAN carcinomas contain elevated levels of cell membrane glycoproteins and glycosyltransferases [1-4]. In particular, sialic acid, a sugar terminally located on the side chains of membrane glycoproteins, and its attaching enzyme, sialyltransferase, may have a role in tumour cell growth [5, 6]. Acute-phase reactants containing glycoproteins especially rich in sialic acid have been described as tumour markers [7].

Although an increase in serum glycosyltransferases has been reported in individuals with various malignant diseases [8-12], glycosyltransferases may also be elevated in other disease processes [13, 14]. This lack of specificity has generally discouraged extensive investigation of the role of glycosyltransferases as tumour markers. However, the absence of any clinically valid tumour-specific marker, and the limitations of other available clinical, radiologic and laboratory methods in diagnosing early neoplastic processes, or in determining the precise extent of disease, is well recognized. These limitations necessitate the continued search for specific and sensitive methods that allow early diagnosis as well as accurate assessment of tumour extension.

Neoplasms derived from plasma cells arise when a cell of the B-lymphocyte lineage undergoes malignant transformation and begins to proliferate in an uncontrolled manner to form a clone of abnormal cells. Although malignant diseases of this type can generally be recognized by routine laboratory methods there is still a need to find more specific markers of the disease and of the tumour burden.

In the present study serum levels of both sialyltransferase and fucosyltransferase were studied prior to any treatment in 19 patients with newly discovered multiple myeloma and in 13 patients subjected to alkylating chemotherapy. A

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few patients were additionally followed lengthwise during therapy with regard to these two transferases in serum.

MATERIALS AND METHODS

Patients and clinical data

Thirty-two patients were studied, 19 before and 13 already on treatment for multiple myeloma, diagnosed and subgrouped according to Durie and Salmon [15]. Seven of the untreated patients were followed longitudinally for up to 20 months on treatment. For details see Table 1.

Blood sampling and enzyme analysis

Blood samples were drawn at the time of inclusion in the study and every sixth week from those patients followed lengthwise. For comparison, samples were also drawn from 24 healthy volunteers.

Sialyltransferase and fucosyltransferase activities in serum were determined by the use of an affinity adsorbent technique and activities were expressed as previously described [12].

RESULTS

The staging of the 19 untreated and 13 treated patients in regard to tumour burden [15] is given in Table 1.

The relationship of sialyl- and fucosyltransferase activities to tumour burden in multiple myeloma patients' sera is presented in Table 2. Serum sialyltransferase mean activity in untreated patients was significanly higher ($P < 0.01$) among patients belonging to stage III than among those belonging to stages I and II (the only patient in stage II was included in stage I). A rather slight increase in stage III compared to the other stages was also obvious for fucosyltransferase, but this difference was not significant (Table 2). Nor were there any significant intergroup differences in sialyl- and fucosyltransferase activities in treated patients (data not shown).

A conspicuous difference ($P < 0.01$) in serum sialyltransferase activities was also apparent when the mean value of untreated patients was compared with that of treated ones (Table 3). Again, the decrease in the corresponding value of fucosyltransferase activity was less pronounced and not significant. The normalization of serum sialyltransferase mean activity upon treatment was evident on comparison with control values. On the contrary, the mean value of untreated patients was pathologically elevated ($P < 0.001$) (Table 3). A similar pattern was also present for fucosyltransferase in serum with a pathological increase ($P < 0.001$) of this activity among untreated patients (Table 3). Also, treated patients

Table 1. Features of patients (19 untreated and 13 treated) at diagnosis with multiple myeloma divided into subgroups by classification in stages according to Durie and Salmon [15]

	n	Stage	Sex (M/F)	Age (yr)	Mean treatment time (months)	Type of monoclonal protein. No Bence-Jones proteinuria			IgG or IgA-type of monoclonal protein with Bence-Jones proteinuria	Only Bence-Jones proteinuria
						IgG	IgA	IgM		
Untreated patients	7	I	4/3	67.6	—	6	1			
	1	II	1/0	80	—	1				
	11	III	7/4	66.1	—	2	4	1	3	1
Treated patients†	3	I	1/2	65.3	14.3	2			1	
	1	II	0/1	68.0	10.0					
	9	III	2/7	68.1	10.2	5			2	2

†Treatment consisted of a standard dose of melphalan and prednisolone every 6 weeks. Some of the patients also had high voltage therapy on localized bone lesions.

Table 2. Serum sialyltransferase and fucosyltransferase activities in 19 untreated patients with multiple myeloma subdivided into different stages

Stages	*n*	Sialyltransferase (cpm)	Fucosyltransferase (cpm)
I + II*	8	782 ± 109	680 ± 285
		$P < 0.01$	N.S.
III	11	1442 ± 471	820 ± 321

*The only patient belonging to stage II was included in stage I.

Table 3. Serum sialyltransferase and fucosyltransferase activities as well as sedimentation rate (SR) in 19 untreated and 13 treated patients with multiple myeloma and in 24 healthy controls

	n	Sialyltransferase (cpm)	Fucosyltransferase (cpm)	SR (mm/hr)
Untreated patients	19	1670 ± 1380	1268 ± 757	125 ± 8*
		$P < 0.01$	N.S.	$P < 0.01$
Treated patients	13	591 ± 296	956 ± 552	75 ± 13†
		$P < 0.001$	$P < 0.001$	
		N.S.	$P < 0.01$	
Controls	24	546 ± 116	561 ± 211	< 15

*†Those patients with exclusive Bence-Jones proteinuria have been excluded; *n = 18; †n = 10.

displayed elevated fucosyltransferase activities compared to controls ($P < 0.01$).

The diminishing effect by treatment on serum sialyltransferase activity was also emphasized by following seven patients repeatedly with serum analyses from diagnosis and for up to 20 months (Fig. 1). The calculated regression of paraprotein concentration (per cent of initial value before treatment) correlated to the corresponding per cent decrease of sialyltransferase activity ($r = 0.82$; Fig. 2).

About half of the patients had succumbed to their disease 24 months after diagnosis and all except two belonged to stage III. Those patients displayed high sialyl- and fucosyltransferase mean activities at diagnosis which were 65.5 and 33.3% respectively above the corresponding initial values of patients still alive at 24 months, of which 6/10 belonged to stage I.

DISCUSSION

In previous studies elevated levels of serum glycosyltransferases were associated with neoplasia [11, 12, 16], perhaps as a result of shedding of cell membrane components containing membrane-bound enzymes into the serum. Our results indicate a general elevation of both sialyltransferase and fucosyltransferase activities in

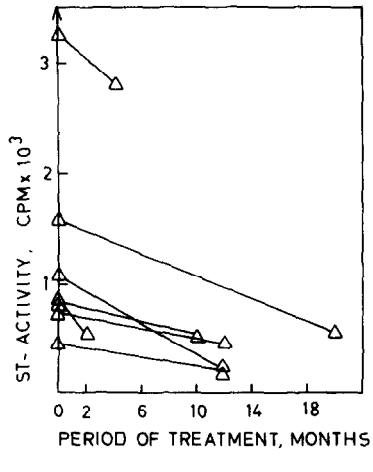

Fig. 1. Effect of treatment on serum sialyltransferase (ST) activity in seven patients with multiple myeloma.

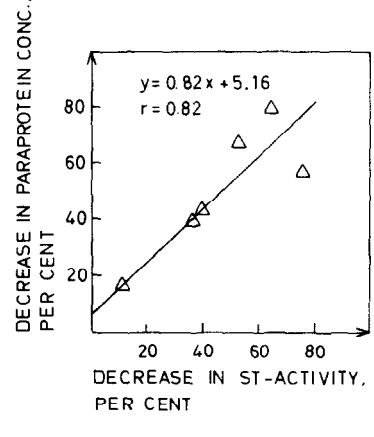

Fig. 2. Relationship between degree of reduction of paraprotein concentration (ordinate) and of serum sialyltransferase (ST) activity (abscissa) on treatment.

serum of patients with untreated multiple myeloma. Those patients having stage III disease showed the highest pretreatment values, especially for sialyltransferase activity. This indicates a correlation between this enzyme activity in serum and tumour burden. An objective response to therapy (reduced paraprotein production) was also followed by a decreased sialyltransferase activity. This observation, together with the correlation that failed to appear between serum creatinine concentration and sialyltransferase activity ($r = -0.03$), is contradictory to a possible relationship between increased sialyltransferase activity in serum and decreased renal function. The simplest explanation is therefore that there may exist a reciprocal relationship between tumour burden and enzyme activity. Such a relationship is concordant with the studies on patients with malignant melanoma by Silver *et al.* [17]. The metabolic turnover of sialic acid on the tumour cell surface also seems to be important for other cancer cell characteristics. Hence the ability of some tumour cells to metastasize spontaneously is somehow connected to total sialic acid content, the degree to which the sialic acid is exposed on the tumour cell surface and, most strongly, with the degree of sialylation of galactosyl and *N*-acetylgalactosaminyl residues in cell surface glycoconjugates [18, 19]. Since sialyltransferase is intimately linked to these metabolic events in the surface membrane [20], studies of this enzyme activity in serum in patients with a neoplastic disease may help to increase the information about that type of disease.

In contrast to sialyltransferase, the serum levels of fucosyltransferase were elevated in the patients with multiple myeloma, whether untreated or undergoing drug therapy. This enzyme utilizes glycoprotein acceptors with terminal *N*-acetylglucoseamine residues [21, 22], but its role in the biology of the cell is unknown. However, somewhat similar to our findings, Khilanani *et al.* [23] observed markedly elevated plasma levels of this enzyme in patients with acute myelogenous leukemia during drug-induced remissions. Also, both cell surface electronegativity and incorporation of radioactive fucose into membrane glycoproteins were markedly increased in murine leukemia cells exposed to the anthracycline antitumour drug adriamycin, while cell surface hydrophobicity and incorporation of thymidine into DNA decreased [24]. We have only examined the endogenous serum acceptors of the glycosyltransferases in the present study. However, glycosyltransferase activities have been measured with and without exogenous acceptor in serum of patients with neoplastic diseases and found to be rather similar [25, 26]. These observations [25, 26] indicate alterations in plasma glycoproteins accompanying the neoplastic process, and might explain the observation of Winzler [27], who found a high level of protein-fucose in patients with cancer.

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