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Radioiodinated Fibrinogen in the Evaluation of Patients with Osteosarcoma

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Abstract—*Usefulness of radioiodinated fibrinogen in tumour localization and control of coagulation process in patients with osteosarcoma was evaluated. Tumour external detection demonstrated positive localization in all cases of osteosarcoma before any treatment and in 2 cases of relapse of the disease 4–6 months after the radiation therapy. Patients with osteosarcoma showed fibrinogen half-life, survival and turnover significantly faster than control subjects. FDP levels were correlated to half-life lowering. Heparin therapy corrected into normal range fibrinogen half-life in 3 patients treated. These results suggest that the alteration of fibrinogen metabolism depends on the presence of osteosarcoma and on the concentration of this agent in cancer tissues and propose radioiodinated fibrinogen as a diagnostic agent in clinical staging and follow-up of the patients suffering from osteosarcoma.*

INTRODUCTION

IN THE last decade survival of the patients with osteosarcoma has improved as a result of new therapeutic regimens [1, 2] and as a result of increased accuracy in clinical staging of disease. Nuclear medicine diagnostic techniques can play an important role in the clinical staging and follow-up of patients, suffering from osteosarcoma. In patients with lower limb osteosarcomas, bone scanning can present false positive uptake in distal areas below the primitive tumour, and tumour seeking agents, such as 67Ga citrate or radiobleomycin are more specific and manageable for defining the extent of disease [3].

Abnormal coagulation parameters are frequently present in patients with neoplastic disease [4, 5], moreover, alteration in fibrinogen kinetics have been demonstrated in cancer patients even when plasma fibrinogen levels were normal [6, 7]. Radiofibrinogen has been shown to localize in cancer tissues [8] and was proposed in tumour scintigraphic detection [9].

We used radioiodinated fibrinogen in the study of patients with osteosarcoma, in the monitoring of the coagulation process and tumour imaging.

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MATERIALS AND METHODS

Studies were performed in 7 patients with osteosarcoma during clinical staging before any treatment and in 10 healthy subjects.

For fibrinogen kinetics the radioactivity injected i.v. was 50–100 μCi of ^{125}I in 1 mg of iodinated fibrinogen (Sorin Radiochemical Center). Blood samples were withdrawn in EDTA 10 min after injection and twice daily for 6–7 days. Only the second exponential of the disappearance curve was considered for $t/2$ calculation. Fibrinogen survival was determined from the half-life divided by the natural logarithm of 2. Fibrinogen turnover was calculated from the fibrinogen concentration divided by the survival time. Platelet counts, fibrinogen concentration, FDP concentration, Quick and Howell time were calculated with standard techniques and considered in a coagulative parameter table. Student's t-test was used to determine significant difference from control.

For tumour detection, 200–300 μCi of ^{131}I fibrinogen and 1.5 mCi of ^{57}Co bleomycin were used. For both agents scintigraphic re-

gistrations were performed 6, 24 and 48 hr after injection on a dual 5-in. linear scanner assisted by a data processing device (WBS and VDP2 Elscint).

Thyroid uptake was blocked by daily administration of potassium iodide.

RESULTS

Table 1 shows some coagulation parameters in patients with osteosarcoma. Half-life and survival of fibrinogen were significantly lower in comparison to control, however fibrinogen concentration was normal and platelet count was minimally decreased. Fibrinogen turnover and FDP in patients with osteosarcoma were significantly increased in comparison to control.

Heparin therapy improved into normal range fibrinogen metabolism parameters in 3 cases treated.

The scintigraphic detection of osteosarcoma with radioiodinated fibrinogen demonstrated positive localization in all cases studied. Table 2 shows the scintigraphic results obtained by ^{131}I fibrinogen in comparison to ^{57}Co bleomycin. No significant difference in tumour uptake was observed (Fig. 1) even if the results obtained with radiobleomycin were altogether more homogeneous.

The tumour scan with radioiodinated fibrinogen, performed in 4 patients after radiochemotherapy, demonstrated marked diminution in uptake of tracer and in 3 of these patients the fibrinogen metabolism parameters resulted in normal range during follow-up after radiochemotherapy.

In 2 cases the increase of uptake during the tumour scintigraphic detection 4–6 months after the radiation therapy confirmed the relapse of the disease.

DISCUSSION

Many studies demonstrated the usefulness of radiofibrinogen for the *in vivo* study of fibrinogen metabolism [10–12]. Early reports demonstrated that labeling does not alter the clotting mechanism or biological behavior of fibrinogen [13]. The present data, in agreement with preceding studies, show increased fibrinogen consumption in patients suffering from osteosarcoma, even with normal plasma fibrinogen concentration. This can represent a low-grade consumption of clotting factors. Moreover, scintigraphic results demonstrated elevated localization of radiofibrinogen in osteosarcoma. This can be observed before any treatment and in relapse of the disease.

Table 1. Coagulation parameters in patients with osteosarcoma and in control

	Platelet count	Fibrinogen concentration (mg %)	Fibrinogen half-life (hr)	Fibrinogen survival (hr)	Fibrinogen turnover (mg%/hr)	FDP (μg/ml)
Control	240,000	352	72	103	3.4	2.5
	180,000	340	88	126	2.6	1.25
	350,000	256	80	115	2.2	2.5
	400,000	376	72	103	3.6	2.5
	220,000	524	76	138	3.7	5.0
	180,000	340	76	109	3.1	1.25
	320,000	400	92	132	3.0	2.5
	415,000	256	88	126	2.0	2.5
	150,000	420	90	129	3.2	5.0
	280,000	280	70	101	2.7	2.5
Mean ± S.D.	273,000 ±94,000	354 ±82	82 ±9	118 ±13	2.9 ±0.5	2.7 ±1.3
Osteosarcoma	170,000	448	60	86	5.2	10
	220,000	360	60	86	4.1	5
	130,000	392	38	54	7.2	5
	300,000	360	54	77	4.6	5
	230,000	404	72	103	3.8	5
	30,000	416	40	57	7.2	5
	190,000	456	60	86	5.3	10
Mean ± S.D.	181,000 ±85,000	405 ±38	54* ±12	78* ±17	5.3* ±1.3	6.4* ±2.4

*Difference from control significant at $P<0.01$.

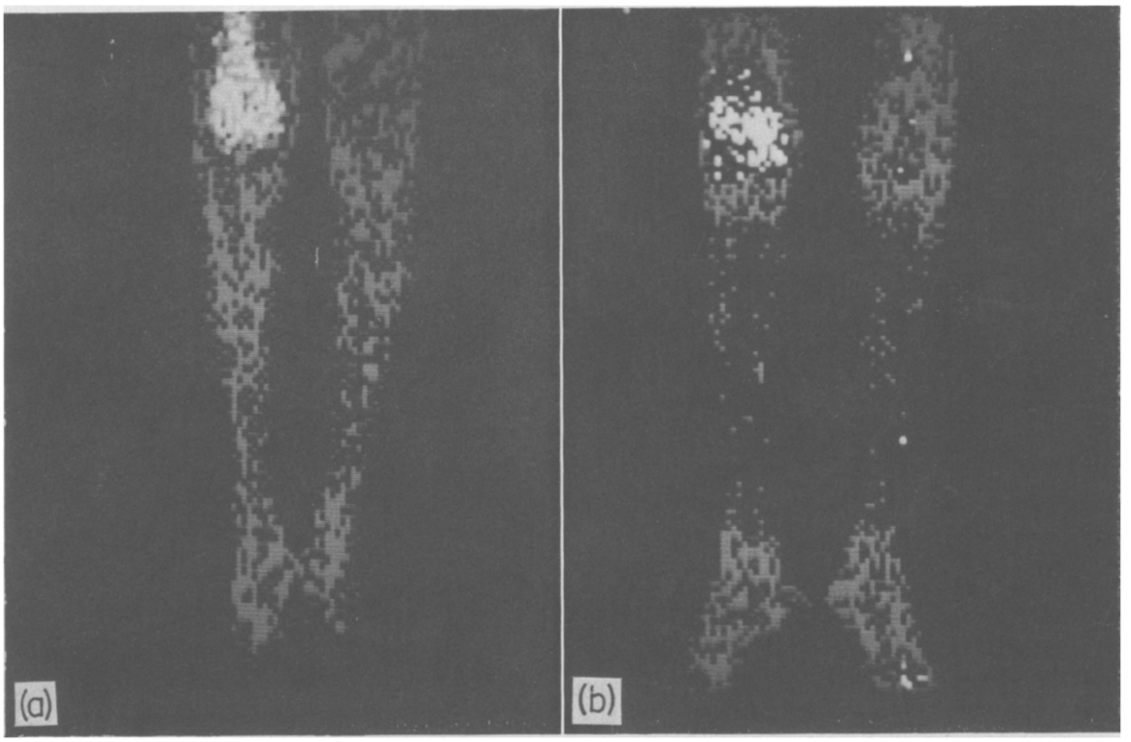

Fig. 1. ^{131}I *fibrinogen* (*a*) *and* ^{57}Co *bleomycin* (*b*) *images of patient with osteosarcoma of right femur.*

Table 2. Comparative scan results in osteosarcoma

	Tumour location	^{131}I fibrinogen	Co bleomycin
D.R.G.	Tibia	+ +	+ +
B.L.	Tibia	+ +	+ + +
R.L.	Femur	+	+ +
S.S.	Femur	+ + +	+ +
B.M.	Femur	+	+ +
R.G.	Femur	+ +	+
L.F.	Lumbar rachis	±	+

Radiochemotherapy regimen in patients with osteosarcoma can be followed by diminution in tumour uptake of radiofibrinogen and by normalization of fibrinogen metabolism parameters.

These results suggest that the alteration of fibrinogen metabolism depends on the presence of osteosarcoma and on the concentration of this agent in cancer tissues. For these characteristics radioiodinated fibrinogen can be proposed as a radiodiagnostic agent in clinical staging and follow-up of patients suffering from osteosarcoma.

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