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Low grade intravascular coagulation in rhabdomyosarcoma

(A fibrinogen kinetic study in vivo)

By

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Chronic disseminated intravascular coagulation associated with embryonal botryoid rhabdomyosarcoma has been observed in an 8-year old child. The coagulation disorder has been diagnosed by in vivo fibrinogen kinetic test by means of ^{131}I labelled fibrinogen.

Rhabdomyosarcoma constitutes about 5% of childhood malignancies. Histologically, three forms can be differentiated, an alveolar, an embryonic and a botryoid form [10]. The alveolar form is the most frequent in juveniles [5]. Its prognosis is poor, death occurs in 79% within one year after onset of the first symptoms [6]. The tumour invades its surroundings and metastasis formation occurs by blood and lymph transfer. Haemorrhages are most uncommon [4, 11, 14]. Eldor et al [4] reported on a patient displaying haemorrhages due to consumption coagulopathy subsequent to subacute disseminated intravascular coagulation (DIC).

The present paper reports on a child with embryonic botryoid rhabdomyosarcoma. In spite of the absence of haemorrhages, chronic DIC was suggested by the laboratory findings. Fibrinogen kinetic studies have been performed to clear the problem.

REPORT OF A CASE

The patient was a well developed 8-year-old boy. A few days before admission a swelling had developed on the right side of his neck. He had been referred to the Department with a diagnosis of peritonsillar infiltration on the right side with bilateral lymphadenitis. Physical examination revealed behind the right mandibular angle a nut-sized, painless, solid swelling adhering to its surroundings, and a protrusion of the right pharyngeal arch and the tonsil. Laboratory findings were RBC, 4.2×10^{12}/l; haemoglobin, 7.0 mmol/l; WBC, 11×10^{9}/l; with 4% band cells, 68% granulocytes, 2% monocytes and 26% lymphocytes; ESR, 6 mm/h. An inflammatory origin was supposed and antibiotic treatment was started. As it had no effect, tonsillectomy and adenotomy were performed. Histological examination of the specimens

revealed embryonic botryoid rhabdomyosarcoma.

X-rays performed at that time showed an arcuate protrusion of the ramus upwards from the mandibular angle on the right side, blurred bone structure of the articular process and of the angle behind the last molar. The structure of soft tissue intensity at that site had constricted and dislocated the entire pharynx to the left. The posterior part of the maxilla and the basis of the skull showed destruction.

Then, surgical removal of the tumour was attempted, but radical removal was unsuccessful due to the unfavourable localization. During the postoperative phase the tumour reached and even exceeded its preoperative size. Because of dyspnoea induced by the pharyngeal compression, tracheotomy had to be performed.

The child was readmitted for cytostatic treatment two weeks later. By then, the right side of the face was enlarged and protruding, the skin was livid, occasionally excoriated. Nut-sized lymph nodes were palpated in the right submandibular region and an apple-sized one behind the sternocleidomastoid muscle. The tumour invaded almost the entire oral cavity, the pharyngeal structures could not be visualized. The liver surpassed the costal arch by about 1 cm, the spleen was not palpable. Laboratory findings were haemoglobin, 8.5 mmol/l; WBC, 9.2×10^9/l; thrombocytes, 190×10^9/l; 76% granulocytes; 24% lymphocytes. Total serum protein, 70 g/l; normal distribution of protein fractions; serum bilirubin, 10.2 μmol/l; SGOT, 16 U; thymol under 1 U; BUN, 4.68 mmol/l; serum Ca, 2.4 mmol/l; serum P, 1.4 mmol/l.

Treatment was started with intravenous adriablastin 50 mg/m² body-surface (bs), cyclophosphamide, at the beginning 400, then 600 mg/m² bs, vincristin, 1.5 mg/m² bs once a week. After a transitional improvement during treatment for several months, progression was observed. Therefore, the treatment was supplemented by actinomycin C in doses of 5×400 mg. Since no favourable action was observed, the therapy was discontinued, and symptomatic treatment alone was prescribed.

During the entire illness there was no sign of a haemorrhage. The platelet count varied between 140 and $240 \times \times 10^9$/l. Some weeks after the cytostatic treatment had been discontinued, a subcutaneous bleeding developed near the tumour (Fig. 1). Results of coagulation studies are summarized in Table I. The slight elongation of PTT, the low prothrombin activity and the elevated fibrin/ogen degradation products (FDP) raised the possibility of a subacute DIC. Since its presence cannot be determined by classical coagulation tests, kinetic studies with ^{131}I-labelled fibrinogen were carried out by methods described earlier [8, 9]. Results are presented in Table II.

Fibrinogen life span was essentially shorter than normal despite the abnormally high plasma fibrinogen concentration (Fig. 2). Fibrinogen catabolism was increased as suggested

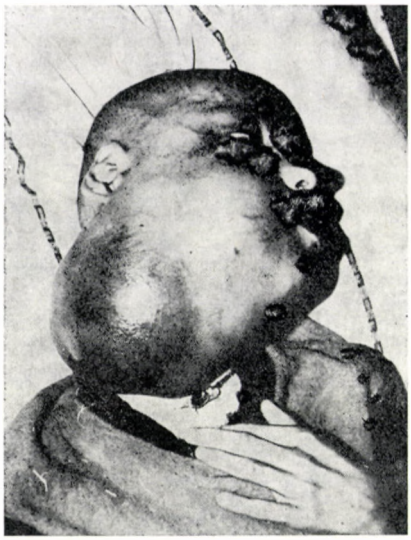

FIG. 1. Rhabdomyosarcoma patient

TABLE I

Blood coagulation data of patient

Test	Patient	Normal
Bleeding time (Ivy), min	2.5	2—8
Coagulation time (Lee-White), min	4.0	2—8
Thrombelastogram (Hartert)		
r value, min	7.0	6—11
k value, min	4.5	3—6
a_{max}, mm	58	46—60
Partial thromboplastin time		
(PTT, Langdell et al.), sec	55	30—50
Prothrombin activity (Quick), per cent	16	60—120
Thrombin time (Marbet-Winterstein), sec	25	23—27
Fibrinogen, g/l	5.0	2—4
Factor II (Schultze), per cent	20	65—120
Factor V (Schultze), per cent	40	65—120
Factor VII (Schultze), per cent	10	65—110
Factor VIII (Langdell et al.), per cent	90	60—160
Factor X (Hougie), per cent	85	70—120
Fibrinolysis (Marbet)	neg.	neg.—1+
Fibrin/ogen degradation products		
(FDP, Merskey et al.), mg/l	36	10
Ethanol gelation test (EGT)	neg.	neg.
Platelet count (Fleissly-Lüdin), x 10^9/l	180	150—400

TABLE II

Fibrinogen metabolism in patient

	Patient	Normal
Plasma volume, ml/kg	48	51 ± 18
Plasma fibrinogen, g/l	5.0	2.8 ± 0.8
C_1 value	0.42	0.62 ± 0.09
Plasma fibrinogen pool, mg/kg	230	118 ± 21
Half-life of fibrinogen, day	1.5	2.3 ± 0.43
Fractional catabolic rate constant	1.1	0.51 ± 0.14
Absolute catabolic rate, mg/kg/day	253	62 ± 32

by the fractional catabolic rate (FCR) being double the normal. The absolute catabolic rate (ACR) was four times the normal and suggested, together with the increased plasma fibrinogen level, a compensatory effort of the liver at enhanced fibrinogen production. On the basis of the results the

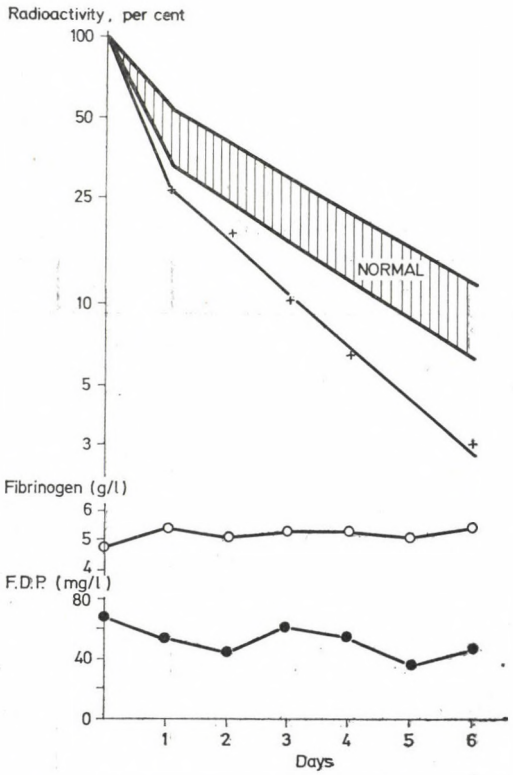

FIG. 2. Fibrinogen metabolism in the patient. Radioactivity of clottable protein, fibrinogen level and fibrin/ogen degradation products (FDP)

occurrence of a chronic DIC of low intensity has been assumed. Since there was no severe bleeding, anticoagulant treatment was omitted.

Discussion

The possible causes of increased fibrinogen turnover in rhabdomyosarcoma are (i) fibrin deposits in the tumour, as observed in carcinoma patients [11]; (ii) increased fibrinogen consumption in consequence of DIC [3] or (iii) hyperfibrinolysis [16]. The last possibility had to be omitted since no increased fibrinolytic activity was found.

Among the coagulation activating triggering factors, thromboplastic substances released by the tumour and/or endothelial damages of tumour vessels or vessels damaged by metastases should be considered [1, 14, 16, 17].

If the fibrinogen plasma concentration is stable, production and degradation are in equilibrium, the absolute catabolic rate points to the grade of synthesis. In our patient the plasma fibrinogen level was uniformly high throughout the observation period, while ACR was fourfold the normal and so suggested a compensatory increase of fibrinogen synthesis. The liver disposes of extremely large reserves: a fivefold increase of fibrinogen synthesis has been observed in experimental chronic DIC [11]. In humans, no correlation has been found between fibrinogen level and turnover [9, 13].

Although an increase of fibrinolytic activity was not observed, the concentration of FDP was higher than normal. This might be attributed to an inability of the RES to eliminate the FDP accumulated in consequence of the large amount of decomposed fibrinogen, despite a normal fibrinolytic activity. The increased fibrinogen production might be interpreted by the continuous rise of the FDP level. According to some authors, fibrinogen fragments and degradation products are involved as substrates in the synthesis of the new molecule [6, 18]. Other authors assume that FDP stimulates fibrinogen synthesis in the liver and neutralizes the operon inhibiting repressor that regulates hepatocyte function [2].

In the literature available, four reports on rhabdomyosarcoma associated with haemorrhage have been found. Lechner and Moran [12] reported the first observation; although at that time DIC was not yet known, it seems most probable that DIC was the cause of the fatal gastrointestinal haemorrhage. Merskey et al. [14] reported two cases, and Eldor et al. [4] a patient showing clinical and laboratory signs suggestive of subacute DIC. To our knowledge, no report has been published on rhabdomyosarcoma associated with chronic DIC.

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