CASE REPORT

Disseminated intravascular coagulation and a negative D-dimer test

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ABSTRACT

The diagnosis of disseminated intravascular coagulation (DIC) requires the presence of a fibrin-related marker. D-dimer is frequently used in clinical practice as a fibrin-related marker. We present a case of paraneoplastic DIC with a false-negative D-dimer test. Repeating the test using a different D-dimer assay as well as the measurement of other fibrinolysis markers confirmed the diagnosis of DIC.

KEYWORDS

D-dimer, disseminated intravascular coagulation

BACKGROUND

Disseminated intravascular coagulation (DIC) is characterised by systemic activation of blood coagulation, which occurs under a variety of clinical conditions including sepsis, trauma, malignancy and obstetric disorders.[1,2] The diagnosis of DIC suffers from the lack of a true gold standard. A scoring system for DIC in critically ill patients has been devised by the International Society of Thrombosis and Haemostasis (ISTH).[2,3] This scoring system is based on an underlying disorder known to be associated with DIC, a diminished platelet count, a prolonged prothrombin time (PT), a low fibrinogen level, and the presence of a fibrin-related marker.[2,3] Routinely, a D-dimer assay is used as a fibrin-related marker. Various D-dimer assays are commercially available. The selection of a D-dimer assay for the routine clinical practice is not only based on its performance, but also on its costs and efficacy.[4,5] We report here a case in which a negative D-dimer test failed to initially confirm the diagnosis of DIC.

CASE REPORT

A 73-year-old male was admitted because of a spontaneous large haematoma on his chest. Twelve months earlier a transdiaphragmatic resection of the oesophagogastric junction was performed because of a stage T3N0M0 undifferentiated adenocarcinoma. The resected specimen demonstrated edges microscopically free of tumour and two negative lymph nodes.

Physical examination revealed a slim male with a WHO performance status of 3 with a normal body temperature and blood pressure. A large haematoma of approximately 15 x 15 cm was seen on the right side of the chest. Smaller haematomas, but no petechiae, were present on his legs.

Laboratory examination showed normocytic anaemia with normal leucocyte and platelet counts (*table 1*). Liver enzymes were normal. In addition, clotting times (APTT and PT) were prolonged and the fibrinogen concentration was lowered. A repeated measurement of D-dimers (CARDIAC D-dimer, Roche, Germany) was normal (<0.5 mg /l).

A computed tomography (CT) scan showed multiple enlarged lymph nodes in the mediastinum and in the retroperitoneal space. A single lesion suspicious for a metastasis was found in the left lobe of the liver. Because of the coagulation disorders a biopsy could not be safely performed. The most likely diagnosis was a relapse of the previous carcinoma of the oesophagogastric junction.

Because the coagulation tests did not fulfil the criteria for DIC, we performed additional tests. A mixing assay with 50% normal donor plasma *in vitro* demonstrated a normalisation in the clotting time, excluding the presence of a coagulation inhibitor in the patient's plasma. Hyperfibrinogenolysis as a cause of lowered fibrinogen concentration was confirmed by the presence of increased fibrin/fibrinogen degradation products (FDP) (*table 1*). Because isolated hyperfibrinogenolysis is very rare we measured the

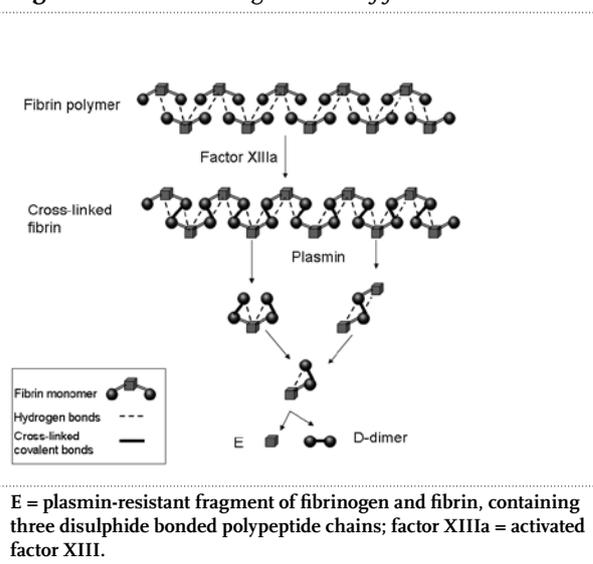| **Table 1.** *Biochemical parameters of the presented case and reference values*		
	Measured value	**Reference value**
Haemoglobin	6.1 mmol/l	8.5-11.0 mmol/l
Leucocytes	6.9 x 10⁹/l	4.3-10 x 10⁹/l
Platelets	160 x 10⁹/l	150-400 x 10⁹/l
Activated partial thromboplastin time	39 sec	<32 sec
Prothrombin time	22 sec	8-11 sec
Fibrinogen	0.3 g/l	2.0-4.0 g/l
D-dimer (CARDIAC D-dimer)	0.26 mg/l; 0.46 mg/l[*]	<0.5 mg/l
Antithrombin activity	64%	80-120%
Plasminogen activity[‡]	63%	80-120%
α-2-antiplasmin activity[‡]	29%	80-120%
Fibrin/fibrinogen degradation products[#]	160 ng/l	<10 ng/l
Lactate dehydrogenase	440 E/l	<450 E/l
Bilirubin	15 μmol/l	<17 μmol/l
Carcinoembryonic antigen	13 μmol/l	<5 μmol/l

[*]**Second measurement after 24 hours by CARDIAC D-dimer. [‡]Chromogenic assay (amidolytic method), Dade Behring, Germany, external blood tests by Sanquin Diagnostiek. [#] Latex agglutination assay, Thrombo-Wellcotest, Remel, USA, external blood tests by Sanquin Diagnostiek.**

presence of fibrin degradation by another D-dimer assay (VIDAS, bioMerieux, France). This assay demonstrated a D-dimer value of 3.02 mg/l (normal <0.5 mg/l). In addition, antithrombin activity, plasminogen activity and α-2-antiplasmin activity were decreased (*table 1*). With this, the diagnosis of paraneoplastic DIC was established. Because of the patient's poor performance status, there were no therapeutic options for the metastatic disease and empirical treatment with tranexaminic acid was initiated.

DISCUSSION

The DIC score according to the recommendations of the ISTH includes a fibrin-related marker in order to differentiate DIC from other conditions associated with a lowered platelet count or prolonged clotting times.[1-3] Fibrin is the product of fibrinogen interaction with thrombin, and its structure is stabilised by cross-linkage between the γ-chains catalysed by activated factor XIII. Intravascular formation of fibrin induces its concomitant proteolysis by plasmin, which results in degradation products with a wide range of molecular weights carrying various numbers of cross-linked D-domains, called D-dimers (*figure 1*).[6,7]

Applying the DIC score criteria to the presented case means that a normal D-dimer would result in 3 points (2 points for marked prolongation of prothrombin time, 1 point for lowered fibrinogen concentration). According to ISTH criteria, a score ≥5 points is compatible with the diagnosis of DIC.[3] An elevated D-dimer would have correctly identified the diagnosis of DIC by increasing the score to 5 points.

Currently, more than 30 D-dimer immunoassays based on more than 20 different D-dimer-specific antibodies are

Figure 1. *Schematic degradation of fibrin to D-dimers[6]*

E = plasmin-resistant fragment of fibrinogen and fibrin, containing three disulphide bonded polypeptide chains; factor XIIIa = activated factor XIII.

available, but an international standard is lacking.[4,5] The performance of different D-dimer assays has been assessed predominantly in venous thromboembolic events (VTE), and varies due to differences in monoclonal antibodies, assay technology and calibration. The enzyme-linked immunosorbent assays (e.g. ELISA, VIDAS, bioMerieux) and the latex-based immunoassays (e.g. Tinaquant, Roche) are highly sensitive (>95%) with a high negative likelihood ratio for VTE at a cut-off value of 0.5 mg/l.[4,5] The use of these D-dimer assays in routine clinical practice may be hampered by the long turnaround time or the specially required equipment.[4,5] New rapid assays have been developed in order to increase the efficacy for the emergency situations. CARDIAC D-dimer assay (Roche)

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uses whole blood instead of plasma and is measured on a reflectometer device producing a quantitative result in ten minutes.[8,9] CARDIAC D-dimer has similar high sensitivity and thus negative predictive values for VTE as the Tinaquant and ELISA immunoassays.[8,9]

The performance of D-dimer assays for the diagnosis of DIC has not been so thoroughly evaluated. As many current D-dimer assays are optimised for exclusion of VTE, their measuring range may be too narrow for the diagnosis of DIC.[4] In addition, the recommendations of the ISTH do not specify the fibrin-related marker. So for the diagnosis of DIC, fibrin/fibrinogen degradation products (FDPs) or soluble fibrin may be used as 'fibrin-related markers' too.[10,11] More specialised tests measure the generation of thrombin and have a high sensitivity and specificity for DIC, but they are not generally available for the routine clinical practice.[1,3,11]

The presence of DIC in severe illness has important therapeutic and prognostic implications.[1,12] The management of DIC requires the treatment of the underlying disorder and supportive measures for the coagulopathy. Although in the presented case there were no therapeutic options, the management of other malignancies, such as acute promyelocytic leukaemia, benefits from rapid and reliable diagnosis of paraneoplastic DIC. Because D-dimer is routinely used as a fibrin-related marker, clinicians should be aware of the heterogeneity of the assays that measure D-dimer. Intensive collaboration between clinicians and clinical chemists is required when a clinical suspicion of DIC is not confirmed by a D-dimer test, because other fibrin-related marker tests may be employed.

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