A new cryopathic syndrome

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SUMMARY One case of a syndrome simulating a systemic disease is reported. An HLA-B₈ patient presented with apparent toxoplasmosis, retinal vein occlusion, autoantibodies against cephalin, contact factors and lipoproteins, immune complexes, rheumatoid factor, and cryoprecipitate. A representation of the immunological mechanisms involved is proposed.

A circulating anticoagulant has already been found in certain normal and pathological conditions: after childbirth, in apparently healthy elderly subjects, in women after parturition, after surgery, in infections, and in malignant and some other diseases such as haemophilia, systemic lupus erythematosus, rheumatoid arthritis, bullous dermatosis, regional enteritis, and hepatic disorders.¹ The association of circulating anticoagulant with biological false-positive reactions for syphilis was reported by Frick, in 1955,² in systemic collagen disease. This circulating anticoagulant is a protein found in the immunoglobulin fraction. Two years later, Laurell and Nilsson³ reported two cases with circulating anticoagulant, false-positive syphilis reactions, and an associated hypergammaglobulinaemia. In 1969, Glueck *et al.*⁴ described hyperlipoproteinaemia, dysglobulinaemia, and a coagulation defect with systemic lupus erythematosus, and M'Seffar *et al.*, in 1978,⁵ reported the association of cryoprotein, immune complexes, and rheumatoid factor in connective tissue diseases.

Toxoplasma infection may be associated with abnormal biological test results such as circulating anticoagulant, false-positive reactions for syphilis, hypergammaglobulinaemia with cryoprecipitate, hyperlipidaemia, immune complexes, and rheumatoid factor and then mimics a systemic disease. We report an HLA-B₈ patient with toxoplasmosis, autoimmune abnormalities, and retinal vein occlusion. The problem of this unusual association is reviewed in the light of recent knowledge of immunological mechanisms.

Material and methods

CASE REPORT

A 50-year-old Caucasian woman was admitted to hospital in November 1977 because of rapidly failing vision. For one year she had had severe left occipital and frontal headaches. The fundus of the right eye was normal, but on the left side the veins were congested and a discrete papillar haemorrhage was visualised. For six months the erythrocyte sedimentation rate had been 34 mm/h. Two months before admission the patient experienced intermittent unilateral blurring of vision. There was a history of goitre but no other relevant history. The patient had not received oestrogen preparations and manifested no cold intolerance. There was a cat in the house but no culture of the pet's faeces had been made. Physical examination of this patient was normal except for a firm thyroid nodule. An electrocardiogram demonstrated a few premature auricular beats. Radiological screening, cerebral and thyroid scans, and bone marrow examination were all normal. Ocular examination showed an abnormal fundus of the left eye with retinal vein occlusion and a visual acuity of 4/200 from 180/200.

Laboratory findings

Urinary, haematological, and ionic values were normal. Total serum proteins were 7.3 g/dl with 54.1% albumin, 2.7% α_1 , 6.8% α_2 , 9.5% β , and 26.9% γ globulins. Quantitative determination of immunoglobulins gave 2.250 mg/100 ml (22.5 g/l) IgG ($N < 17.2$ g/l), 1100 mg/100 ml (11 g/l) IgM ($N < 2.8$ g/l), and 145 mg/100 ml (1.45 g/l) IgA ($N < 3.95$ g/l). Serum immunoelectrophoresis

Table 1 Ophthalmological and laboratory findings

Date	Left eye	Left visual acuity	ESR	APTT	VDRL	RF
2 Nov '76	Discrete venous congestion and a disc haemorrhage					
26 Sept '77	Important venous congestion, cross sign	180	110			
17 Oct '77	Extensive venous congestion, retinal haemorrhages, congested disc	60	110	180		
4 Nov '77	Disc oedematous		110	180	1:64	
9 Nov '77	Extensive retinal haemorrhages, macula haemorrhage					
12 Dec '77	First haemorrhage of vitreous	4	93	155		1:7968
31 Jan '78	Oedematous papilla	12	90	150		
13 Mar '78	Oedematous papilla	25	68	150		
18 Apr '78	Retinal oedema		62	120	1:16	
30 May '78	Neovascularisation of papilla	33	38	90		1:56
12 Sept '78	Oedematous papilla	25	29	85		
7 Nov '78	Second haemorrhage of vitreous	8		65	1:4	
11 Dec '78	Clarification of vitreous	12		31	1:4	
24 Jan '79			25	25		
26 Feb '79		10	18	27	1:1	
Normal		200/200	<20 mm/h	<50*	<1:1	<1:56

ESR = erythrocyte sedimentation rate; APTT = activated partial thromboplastin time; VDRL = Venereal Disease Research Laboratory; RF = rheumatoid factor.

showed polyclonal precipitin arcs with human anti-IgG and anti-IgM antisera. SGOT was 12 IU/l ($N < 20$), SGPT 50 IU/l ($N < 17$), and gamma-glutamyl transferase 82 IU/l ($N < 25$). Fluorescent treponema antibody was negative and treponema pallidum haemagglutination was non-specific. The other pathological results with the associated ophthalmological findings are detailed in Table 1.

COAGULATION STUDIES

The recalcification, prothrombin, thrombin and activated partial thromboplastin (APTT) clotting times, fibrinogen and fibrin degradation products measurements, and quantitative assays for factors II, V, VII, VIII, IX, X, XI, and XII were performed according to previously described methods.⁶ Factor VIII—RA was measured by rocket electrophoresis.⁷ A circulating anticoagulant against factors participating in the intrinsic clotting pathway was first detected by determination of APTT measured on a mixture of normal plasma (0.9 ml) and various dilutions of the patient's plasma (0.1 ml). The dilutions prepared with barbital saline buffer (pH 7.35) varied from 1/2 to 1/160. These tests were performed after a 4-hour incubation at 37°C. To demonstrate the specificity of the inhibitor, assays of factors V, VIII, IX, X, XI, and XII were performed on mixtures of normal plasma and dilutions of patient's plasma. Detection of an inhibitor of the contact phase of blood coagulation was according to Zucker *et al.*⁸ The inhibitory effect was quantified by comparing the clotting time of the patient's plasma with a dilution curve of contact factors. Neutralisa-

tion of the circulating anticoagulant was performed using rabbit anti-human μ chain and γ chain antisera (Dako, Copenhagen).⁹

IMMUNOFLUORESCENCE STUDY

In order to identify the patient's antibodies, these were coupled with fluorescein isothiocyanate, and a direct fluorescence test was performed on formol Toxoplasma.

Electron microscopy

The cryoprecipitate was treated as previously described.¹⁰

Immunochemical analysis

Blood was drawn with a warmed syringe and allowed to clot at 37°C. The serum was stored at 4°C for 24 hours. The cryoprecipitate was isolated by centrifugation (2000 rpm) for 30 minutes at 4°C, washed twice with saline, lyophilised, and stored at -20°C. Electrophoresis, immunoelectrophoresis, and immunofixation were performed according to the usual methods.

Immunology

Patient's plasma was submitted to ultracentrifugation to detect the antilipoprotein activity of immunoglobulins. The antibody activity of the immunoglobulin fraction (density (d) < 1.021) was tested by double-immunodiffusion (Ouchterlony) in 1% agar gel plates against the lipoprotein fraction ($d < 1.019$, $1.019 < d < 1.063$, and $1.063 < d < 1.21$).

FAT	Specific IgM	SFDT	IC	EBV-VCA antibodies	Cholesterol		Triglycerides		Treatment
					mmol/l	mg%	mmol/l	mg%	
					12.0	462	2.12	186	
				1:256	11.0	425			
					10.5	406	2.44	216	Chlorambucil 5 mg/day
:2560	1:160	>1:4000	++		8.7	336	3.76	233	Plasmapheresis
		>1:4000							Prednisolone 50 mg/day
		>1:4000							Trimethoprim 320 mg/day
		>1:4000							Sulphamethoxazole 1.6 g/day
:1280		>1:4000	16.3		7.6	294	1.20	160	
:512			8.7						
.256									
					6.96	269	1.58	140	
					6.52	252	1.13	100	Spiramycin 2 g/day
							0.85	75	
	<1:1	1:2000	18	1:64					
	<1:1	1:300			6.08	236	0.88	77	
:64	<1:1	≤1:100	<9.8% TC	1:8	3.87	150	0.51	40	
					8.8	340	1.93	170	

FAT = indirect fluorescent antibody test; SFDT = Sabin Feldman dye test; IC = immune complexes; TC = total count; EBV-VCA = Epstein Barr virus capsid antigens.

Lipid analysis

Lipid extraction of the cryoprecipitate was performed with chloroform-methanol (2:1) and then thin-layer chromatography (TLC) of the neutral lipids in ether-hexane-acetic acid (20:80:1) and of phospholipids in chloroform-methanol-water (65:25:4). Spots corresponding to cholesterol esters, triglycerides, free fatty acids, free cholesterol, lecithin, sphingomyelin, and lysolecithin were revealed by iodine vapour.

Results

COAGULATION

The first haemostatic profile revealed an extension of

the APTT and a nearly normal prothrombin time (Table 2). Two plasmaphereses carried out within a four-day interval yielded a slight but transient improvement of the coagulation tests. Prolonged clotting times returned rapidly, and corticosteroid therapy was tried for one week without success. Intravascular coagulation disease was ruled out by the low level of fibrin degradation products (<10 mg/l).

Tests were performed to detect a circulating anti-coagulant inhibitory effect against several clotting factors. Mixtures of dilutions of the patient's plasma and of control plasma yielded a prolonged clotting time in APTT, thrombin time, and V, VIII, IX, X, and XI factor assays. Clotting times were markedly pro-

Table 2 Coagulation tests

	Plasmapheresis				Methylprednisolone		Sulphamethoxazole trimethoprim				Normal range
	4 Nov '77		8 Nov '77		30 Nov '77 7 Dec '77		14 Dec '77 19 Apr '78		4 Oct '78		
	Before	After	Before	After	Before	After					
Platelet count (10 ⁹ /l)	324	190	225	219							150-350
Activated partial thromboplastin time (s)	180	97	106	75	158	>240	100	80	50		25- 55
Prothrombin time (s)	13	14.8	16.7	16.5	>38	>38	14.2	14.8	13.4		11.4
Thrombin time (s)	23	22	22.4	24	>120	>120	19.8	19.8	20.8		18- 22
Fibrinogen (g/l)		1.6	2.3	1.7	1.8	1.9	2.6	3.1	2.7		2.0-4.0
FDP (mg/l)						<10					20
Factor levels (%)											
II		65	70	65	35	45	95	97	95		60-130
V		50	40	30	10	25	25	35	100		
VII + X		85	90	85	25	30	85	>100	100		
X		55		35	40	<10	45	35	45		70-130
VIII						0		24	65		50-150
IX						0		87	95		60-160
XI						0		50	70		63-136
XII						0		54	80		22-253
VIII-related antigen				125					130		70-130

longed when tests were performed with low dilutions of the patient's plasma and they returned to normal with high dilutions (Table 3). Incubation of the patient's plasma for 4 hours at 37°C did not alter the results. Prolongation of the clotting times was more obvious when tests were performed after storage of the patient's plasma for 24 hours at -20°C. The patient's plasma inhibited 98% of the contact products. This inhibitory activity was present immediately and also after 15-minutes' incubation. It was already detected by using contact products at a dilution of 1/2 (Table 4).

The anticoagulant effect disappeared completely after neutralisation with anti-IgM serum and partially after anti-IgG serum. The long APTT obtained with the patient's plasma (108 seconds 2/10) returned to a normal value (56 seconds 4/10) after neutralisation of the plasma with anti-IgM serum and to a better one (75 seconds 4/10) after neutralisation with anti-IgG serum. The neutralisation of the anticoagulant by anti-IgM serum resulted in normal factors VIII, IX, XI, and XII assays.

During the subsequent six months, the potency of this inhibitor decreased during sulphamethoxazole-trimethoprim treatment, and the anticoagulant was no longer detectable 11 months after the beginning of treatment.

IMMUNOFLUORESCENCE

The direct fluorescent-antibody test for *T. gondii* was positive at a 1/2 dilution of the patient's immunoglobulins.

ELECTRON MICROSCOPY

The cryoprecipitate presented a fibrillar ultra-structure and a proteinaceous appearance (Fig. 1).

CHEMISTRY AND IMMUNOCHEMISTRY

The serum was viscous and formed large gel-like lumps at room temperature. The cryoprecipitate was 690 mg/100 ml. Cryoprecipitate treated with alkylating or reduction agents did not react when tested against various antisera. On agar gel electrophoresis the solubilised cryoprecipitate showed one band of γ -mobility (stained with Coomassie Brilliant Blue FF) and another of β -mobility (stained with Fad Red B). Chloroform-methanol extracts of the cryoprecipitate showed the presence of 5% of lipids. Thin-layer chromatography of neutral lipids and phospholipids showed patterns similar to those of a normal plasma but the number of washings excluded the possibility of contamination by plasma. On double-diffusion plates (Fig. 2), patient's plasma immunoglobulins prepared by ultracentrifugation ($d < 1.021$) reacted with patient's plasma VLDL +

Table 3 Inhibitory activity against coagulation factors

	APTT (s)	TT (s)	Factor V (s)	Factor X (s)	Factor VIII %	Factor IX %	Factor XI %	Factor XII %
Control plasma	42	20.4	22.5	27	95	115	100	100
Patient's plasma	>120	>120	>40	>120	Inc	Inc	Inc	Inc
Mixtures of 9 parts of control plasma and 1 part of patient's diluted plasma					1 part of control plasma and 1 part of patient's diluted plasma			
Dilution 1/ 2	225	>120						
1/ 4	225	>120						
1/ 8	95	63						
1/ 10	65	43	40	108				
1/ 20	53	35	34	90	25	32	23	24
1/ 40	49	26	21	31	30	37	28	34
1/ 80	45	23	19.8	29				
1/160	42	22.8	19.8	27				
1/400					63	45	46	48
					51	56	46	52

Inc = incoagulable.

Table 4 Inhibition of contact products by the patient's serum

	Barbital buffer				Normal serum				Patient's serum											
Dilution of contact products	1/2		1/2		1/4		1/8		1/16		1/32		1/64		1/128		1/2		1/8	
Incubation time (min)	0	15	0	15	0	15	0	15	0	15	0	15	0	15	0	15	0	15	0	15
Clotting time (s)	81	83	81	83	114	122	160	157	177	172	195	188	215	212	232	236	248	235	243	240
Contact products (%)	100		100		50		25		12.5		6.2		3.1		1.5		1.5		1.5

Fig. 1 Electron micrograph of cryoprecipitate. Original magnification $\times 50\,000$. Calibration bar $0.2\ \mu\text{m}$.

Fig. 2 Double-diffusion in agar of concentrated plasma IgM in centre well and plasma lipoprotein fractions in exterior wells: (a) VLDL + IDL; (b) LDL; (c) HDL; (d) normal serum.

IDL ($d < 1.019$) and LDL ($1.019 < d < 1.063$). No reaction was visualised with HDL.

Discussion

Three groups of aetiological factors, abnormal blood flow patterns, vessel wall, and blood constituents (Virchow triad), are commonly considered in retinal vein occlusion.¹¹ In the present case, hypergammaglobulinaemia with cryoprecipitate, hyperlipidaemia, and activation of the extrinsic pathway of blood coagulation acted to cause a stagnation thrombosis (Fig. 3B). Since 1961, cryopathies have usually been referred to according to Ritzmann's classification.¹² In our patient, classical criteria for cryofibrinogenaemia (elevated levels of α_1 -antitrypsin and hyperfibrinogenaemia) and cryoglobulin

Fig. 3 Schematic representation of possible immunological mechanisms leading to retinal vein occlusion.

(A) *Toxoplasma gondii* is digested by resting macrophages which produce antigens activating B-lymphocytes (1) and responder T-lymphocytes (2). Activated immunocompetent B-lymphocytes mature to plasma cells (3), which produce immunoglobulins inducing negative feedback on immunocompetent B-lymphocytes. Responder T-lymphocytes secrete lymphokines, transforming resting macrophages into activated macrophages (5). Interaction of activated macrophages, complement, and immunoglobulins leads to destruction of *T. gondii* with release of *Toxoplasma* and cellular debris (6). This damaged cell debris may act as immunosuppressive products and stimulate suppressor T-lymphocytes (7), which block the reaction of responder T-lymphocytes (8).

(B) Phospholipid glycoprotein complex from damaged cells activates factor VII and thus the extrinsic pathway of blood coagulation (9). Lipoproteins as new antigenic determinants generate responder T-lymphocytes, leading to T and B cell cooperation (10) with production of different autoantibodies (11), one against cephalin (positive VDRL), one against contact products (circulating anticoagulant), and one against lipoprotein constituting lipoprotein autoantibody immune complex with cryoprecipitation (12), lipoprotein lipase inhibition, and hyperlipidaemia (13). Activated coagulation, hyperlipidaemia, and cryoprecipitate cause retinal vein occlusion.

(thermal reversibility) were absent. Two families of serum IgM were considered, one with IgM antibodies directed against *Toxoplasma gondii* (Fig. 3A) and the other with IgM autoantibodies (Fig. 3B) against cephalin, contact factors, lipoproteins, and/or membranes. IgM autoantibodies against cephalin (positive VDRL) involved phospholipid antigens.¹³ Circulating anticoagulants can be regarded as a real autoantibody¹⁴ and are thought to be anti-thromboplastin.² In the case of Laurell and Nilsson³, both serum antithromboplastin activity and non-specific Wassermann reactions were directed against lipids: thromboplastin and cardiolipin. The attack of thrombosis without bleeding and the nature of the coagulation's inhibitor (IgM) are characteristic of an interfering inhibitor similar to those in autoimmune disease¹ and in chlorpromazine-treated patients with inhibition of the contact activation phase.⁸ Autoantibodies against lipoproteins may be important in

the pathology of dyslipidaemias, malignancies (Table 5), and hepatitis.¹⁵ In Table 5, the patient's autoantibody against lipoprotein is compared to that in other reported cases. According to Kodama,¹⁶ activity of such autoantibodies is directed against the lipid haptens (phospholipid groups) and not against the protein moiety of lipoprotein groups.¹⁶ Autoantibody against lipoprotein shares two characteristics reported in the literature: cryoprecipitation as lipoprotein-autoantibody immune complexes¹⁶ and inhibition of lipoprotein lipase activity with production of hyperlipidaemia.¹⁷ It seems possible that, in our patient, all three IgM autoantibodies (anti-cephalin, anti-contact products, and anti-lipoprotein) were similar or even identical. Another interesting problem is the role of circulating complexes 'which not always were the pathogenic cause of disease'.¹⁸ In a few cases, specific protozoa have been identified in human diseases with immune

Table 5 Laboratory findings of autoantibodies against lipoproteins (survey of the literature)

Reference	(No.)	Disease	Fredrickson classification	Cholesterol		Triglycerides		Riesen's type	Autoantibody	Lipoproteins as antigens	Lipoprotein antigenic fraction
				mmol/l	mg %	mmol/l	mg %				
1962 Kayden <i>et al.</i>	(23)	Xanthomatosis	II	Increased				2a			LDL
1965 Lewis and Page	(24)	Xanthomatosis	II	32.3	1250	23.7	2100	2a	M IgA	β	
1966 Beaumont	(25)	Xanthomatosis with myeloma								β	
1966 Lewis <i>et al.</i>	(26)	Lymphoma		5.12	198	1.78	158	2a	M IgA	α - β	
1967 Aubert <i>et al.</i>	(27)	Xanthomatosis with myeloma						3a	M IgM	β	VLDL
1969 Beaumont	(28)	Xanthomatosis	Iib	29	1120	15.25	1350	2a	M IgA	β -pré β	
1972 Kodama <i>et al.</i>	(29)	Xanthomatosis	Iib	9.31	360	4.52	400	2a	M IgG	α - β	
1972 Nosedá <i>et al.</i>	(30)	Acne profunda, arthritis	Hypo β	7.29	282	5.29	468	2a	M IgG	α - β -pré β	
1974 Cooper <i>et al.</i>	(13)	Lymphoma	lipoproteinaemia	2.04	79	1.05	93	3b	Poly IgG	β	
1976 Beaumont <i>et al.</i>	(31)	Macroglobulinaemia	Iib	1.97	76			3a	M IgM		
1977 Kodama	(16)	Xanthomatosis	IV	8.79	340	2.15	190	2a	M IgM		LDL
This study		Toxoplasmosis	Iib					2b	Poly IgG	α - β	
				11.3	425	2.63	233	2b	Poly IgM	β -pré β	VLDL, LDL

M = monoclonal; Poly = polyclonal; VLDL = very low density lipoproteins; LDL = low density lipoproteins; HDL = high density lipoproteins.

complexes.¹⁹ According to the criteria of de Meuter *et al.*,²⁰ our patient was infected with *T. gondii*, but no Toxoplasma antigen was found in the cryoprecipitate. Lipoprotein antigens may be non-specific as damaged cell debris or serum lipoproteins. *T. gondii* is a parasite which eludes the immune response by adaptation to macrophages, may be found in haematological diseases and immunodepressed patients, and frequently causes retinochoroiditis but seldom other ocular lesions.²¹ These genetic (HLA-B₈), biological (autoantibodies), and clinical (retinal vein thrombosis) patterns are commonly associated with autoimmune disease. According to Eddleston,²² HLA-B₈ was implicated in a defect of 'suppressor'-cell activity which would usually switch off autoantibody production in autoimmune diseases.²² In conclusion, the association of toxoplasmosis with retinal vein occlusion found in our HLA-B₈ patient has not been reported previously. Chemotherapy resulted in correction of the coagulation disorders, restitution of partial visual acuity, and a return to normal of the hyperlipidaemia and other biological parameters. However, the 18-month follow-up period is not yet sufficient to exclude an associated malignancy.

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