Deep Vein Thrombosis and Haemolytic Anaemia in a Case of Overlap Syndrome

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Case Report

A 47 years old female patient with seropositive rheumatoid arthritis of 18 years duration presented with the complaints of high grade fever, pain abdomen, loose motions and progressively increasing swelling of right lower limb of 3 days duration. She had been treated for tuberculous lymphadenitis 4 years ago. She gave a history of Raynaud's phenomenon for the last 1 year. On examination she had malar rash, toxic look, puffy hands, cutaneous rash and petechiae all over body and alopecia. Right lower limb was markedly swollen, warm and red with pitting oedema. She was febrile (103°F), pulse 110/min. regular, BP 130/80 mm Hg. She was thoroughly investigated after initiating preliminary treatment.

I) Haematological profile

Hb 4.9 gm% (initially 9.4gm%)

TLC 24,400/mm^3

DLC P_{66} L_{19} E_4 M_1 myelocyte$_1$, metamyelocytes$_9$.

ESR 65 mm/Ist hour

Platelets 1.05 lakhs/mm^3

Reticulocytes 7%

Blood group B positive

Peripheral smear showed anisopoikilocytosis, elliptocytes, polychromasia with spherocytes, leucocytosis with neutrophilia.

Nucleated RBCs were 34/100 WBCs.

tRBC 2.09 million/mm^3

PCV 15.5%

MCV 74.5 fl

MCH 23.2 pg

MCH 31.2

Serum Fe 82 ug/dl

TIBC 359 ug/dl

Coomb's test (Direct and Indirect) Negative

RBC fragility test 0.31 gm/dl (N 0.40-045 g/dl)

Prothrombin time control 12 sec. Patient's 17 sec.

II) Routine & Biochemistry

Urine examination showed occasional RBCs, Albumin 1 +, Sugar nil

FBS 67 mg%

PPBS 114 mg%

Serum creatinine 1 mg%

BUN 10.2 mg%

Serum uric acid 5.1 mg%

Serum total proteins 6.7 gm%

Serum albumin 2.9 gm%

Serum globulin 3.8 gm%

A/G Ratio 0.75 : 1

AST 23 IU

ALT 9 IU

Serum alkaline phosphatase 76 U/L

CPK 94 IU/L

Urinary Protein 240 mg%

CCr 41.9 ml/min.

ECG - Normal

LDH - 450 Units/ml (Normal 110-240 units/ml Gay Bower's method)

III) Scanning

X-Ray right wrist joint AP view showed erosions.

Ultrasound abdomen was normal.

Duplex scan of veins of both lower limbs with colour flow mapping showed thrombosis of right femoral vein, patent and dilated right popliteal vein while right iliac vein was normal (see photograph).

IV) Immunology

HBsAg Negative (0.093 mg/ml)

VDRL Non-reactive

CRP Positive 24 IU/ml

RF strongly positive (320 IU/ml)

ANA positive

ds DNA 552 IU/ml (Normal < 250 IU/ml)

cANCA/PR3 ANCA (Elisa): 1.20 U/ml (Normal 0.0-7.0 U/ml)

pANCA/MPO ANCA (Elisa): 2.20 U/ml (Normal 0.00-7.0 U/ml)

IgG to Sm (Smith) antigen (Elisa): 2.20 U/ml (Normal 0-10 U/ml)

IgM Anticardiolipin antibodies : 4.80 MPL - U/ml (Normal 0-6)

IgG Anticardiolipin antibodies : 5.70 GPL - U/ml (Normal 0-12)

IgG anti RNP (Elisa): 3 EU/ml (Normal 0-20)

Lupus anticoagulant (LA)/Dilute Russel's viper venom time

Control 24.70 sec (Normal 24-27 sec)

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Patient 25.90 sec (Normal 24-27 sec)

Patient + Standard Human Plasma = 24.20 sec (Normal 24-40 sec)

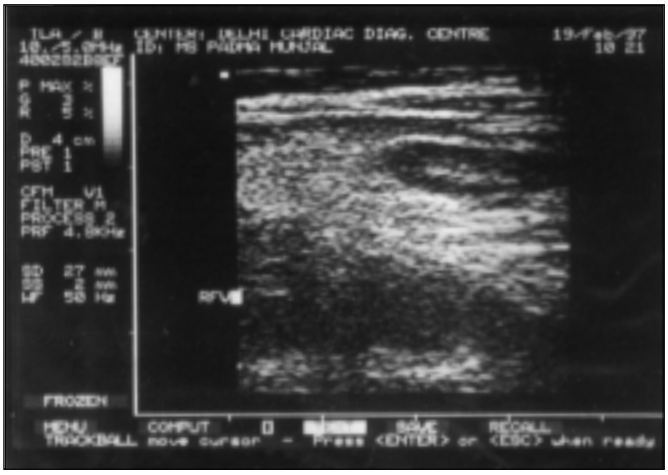

Fig. 1 : Duplex scan showing thrombosis of right femoral vein.

V) Skin Biopsy : From cheek showed leucocytoclastic vasculitis in the upper and mid dermis. The epidermis was unremarkable. The skin biopsy from back was also unremarkable except for increase in sebaceous glands in the dermis. This was suggestive of hypersensitivity vasculitis.

Discussion

Q. What is an overlap syndrome ?

A. Some patients develop the full blown clinical picture of a definite connective tissue disease but others may present manifestations of more than 1 definite connective tissue disease. The latter have been referred to as having overlap syndrome. It has been stated that as many as 25% of all patients with connective tissue disease will have overlap features[1]. The various overlap syndromes include co-existent rheumatoid arthritis (RA) and systemic sclerosis (SSc)[2]; overlap of RA and systemic lupus erythematosus (SLE)[3]; co-existent SSc and SLE[4]; SSc and polymyosits[5]; and dermatomyositis (DM) and SLE[6].

Q. What is mixed connective tissue disease (MCTD) ?

A. In 1972, Sharp *et al*[7], described an apparently distinct overlap syndrome, which they called mixed connective tissue disease (MCTD). The clinical characteristics of the patients with MCTD included a combination of features similar to those of SLE, Ssc and PM. Most of these abnormalities were responsive to corticosteroid therapy and the disease was reported to have a favourable prognosis. The hallmark of this syndrome was the detection of high titres of antibodies against the nuclear ribonucleoprotein fraction of extractive nuclear antigen. (i.e., anti-nRNP antibodies). MCTD was thought to represent a distinct rheumatic disease, with patients having a combination of arthralgias, swollen hands, Raynaud's phenomenon, oesophageal dysfunction and myositis but lacking cerebral, pulmonary, or renal involvement. It has since become clear that many patients have nRNP antibodies but lack these particular clinical features. In addition, other patients have these clinical features but lack this antibody specifically and many patients who initially seem to fit this classification eventually develop scleroderma (usually) or SLE (occassionally).

MCTD has remained, since then, a controversial clinical entity. Table I shows the various classification criteria for MCTD viz. Sharp criteria, Alarcon-Segovia criteria, Kasuhawa criteria and Kahn criteria. The co-existence of several sets of classification criteria for MCTD indicates how difficult it is to give a precise definition of the disease. Some authors, like Sharp, consider MCTD a distinct clinical entity within the overlap syndromes and regard as essential, the presence of high titres of antibodies to nRNP for the diagnosis of MCTD. Others, like Lazaro et al[8]; have concluded that antibodies to nRNP do not identify a particular subgroup within the overlap syndromes and that MCTD doesn't appear to be a distinct entity.

Q. Is the presence of nRNP antibodies essential for the diagnosis of MCTD ?

A. For some time, it was thought that once present, antibodies to nRNP persisted for a long time usually irrespective of treatment[9]. Now it is known that these antibodies can appear or disappear during the course of disease[10,11]. Furthermore, it has been shown that the production of antibodies can switch from nRNP to Sm (Smith's antibodies) or vice versa[12].

Q. Does MCTD exist in India ?

A. In a study, 1000 consecutive patients with systemic connective tissue diseases were screened clinically and serologically to determine the existence of

MCTD in Indian population. After completion only 3 patients could be diagnosed as having MCTD using the standard diagnostic criteria. The results of this study point to MCTD existing but it appears to be very rare entity in the Indian population[13].

Q. When is the term "undifferentiated connective tissue disease" (UCTD) used ?

A. Patient with features of a connective tissue disease like joint pains, Raynaud's phenomenon, fever but who cannot be categorised into a discrete entity like SLE or SSc are sometimes labelled as UCTD[14]. It is not unusual to see the evolution over many years, of features more commonly associated with another connective tissue disease. This propensity for evolution and transition between connective tissue diseases has been said to occur in about 25% of patients. Overlapping sometimes occurs concurrently, but more commonly it is the dimension of time that allows one syndrome to take on the features of another[15]. Figure 2 shows the evolution of UCTD.

Q. What is the diagnosis in this case ?

A. This case had features of rheumatoid arthritis i.e., arthritis of more than 3 joints especially of hand joints which was symmetric, rheumatoid factor was strongly positive and X-Ray of wrist joints showed erosions. She also had features of SLE in the form of malar rash, haemolytic anaemia, alopecia,

Table I : Classification criteria for mixed connective tissue disease (MCTD)

Sharp Criteria	Alarcon-Segovia Criteria	Kasukawa Criteria	Kahn Criteria
Major criteria 1. Severe myositis 2. Lung involvement: DLCO<70% and/or pulmonary hypertension and/or proliferative vascular lesions on biopsy 3. Raynaud or oesophageal hypomotility 4. Swollen hands or sclerodactyly 5. Anti-ENA ≥ 1:10,000 with anti-RNP + and anti-Sm- Minor criteria 1. Alopecia 2. Leukopenia < 4000 3. Anaemia 4. Pleuritis 5. Pericarditis 6. Arthritis 7. Trigeminal neuralgia 8. Malar rash 9. Thrombocytopenia 10. Mild myositis 11. History of swollen hands MCTD certain 4 major criteria, no anti-Sm, anti-UI-RNP>1:4000 MCTD probable 3 major criteria, and no anti-Sm, or 2 major criteria and 1 minor criterion, anti-UI-RNP>1:1000	1. Serologic criteria Anti-RNP at Haemagglutination titer > 1:1600 2. Clinical criteria a. swollen hands b. synovitis c. biologically or histologically proven myositis d. Raynaud's e. acrosclerosis with or without promimal systemic sclerosis MCTD if Criterion 1 present AND at least 3 clinical criteria (if a, d, and e are present, b or c are required as well)	1. Common symptoms a. Raynaud's b. Swollen fingers 2. Anti-RNP Ab 3. Symptoms A. of SLE: a. polyarthritis b. adenopathies c. malar rash d. pericarditis or pleuritis e. leukopenia or thrombocytopenia B. of SSc: a. sclerodactyly b. pulmonary fibrosis or restrictive change of lung or reduced DLCO c. hypomotility or oesophageal dialation C. of polymyositis a. muscle weakness b. elevated muscle enzymes c. myogenic signs on EMG MCTD if Presence of at least 1 of the 2 common symptoms AND Anti-RNP Ab + AND Presence of at least 1 sign of at least 2 of the following CTD: SLE, SSc, PM.	1. Serologic criteria Presence of high titer anti-RNP corresponding to speckled ANA at titer ≥ 1:2000 2. Clinical criteria a. Raynaud's b. synovitis c. myositis d. swollen fingers MCTD if Serologic Criteria + AND Raynaud's phenomenon AND at least 2 of the 3 following signs synovitis, myositis, swollen fingers

vasculitis, venous thrombosis, positive ANA and dsDNA. She also had a history of Raynaud's phenomenon which was the only clinical evidence suggestive of systemic sclerosis. Hence this case fits into the diagnosis of overlap syndrome.

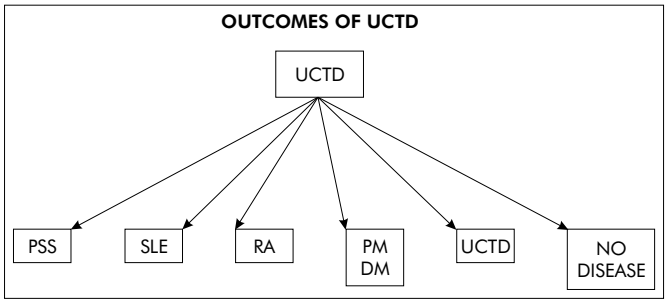

Figure 2 : The evolution of UCTD[16].

Q. Why were ANCA antibodies tested in this case?

A. ANCA antibodies were tested to rule out the possibility of Wegener's granulomatosis in view of the presence of vasculitis in this case.

Q. Why was antibodies against Smith antigen (Anti-Sm) tested ?

A. Anti-Sm antibodies were tested since they are specific for SLE.

Q. What was the significance of testing Anticardiolipin/Antiphospholipid antibodies in this case ?

A. Presence of anticardiolipin antibodies increases the risk of venous or arterial thrombosis. It is also associated with the presence of lupus anticoagulant and false positive VDRL. The presence of antiphospholipid antibodies has been well described in SLE[17] and MCTD[18]. In our case, aCL antibodies were in the normal range. In a study[18] of 48 patients, only 15% patients of MCTD had positive aCL.

Q. What was the cause of petechiae in this case?

A. The cause of petechiae in this case was proven by skin biopsy from cheek which showed the presence of hypersensitivity vasculitis. This was one of the unique findings of the case. Hypersensitivity vasculitis has been described with RA, SLE and Sjogren's syndrome but rarely in overlap syndrome.

Q. What was the probable cause of deep vein thrombosis (DVT) in the absence of aCL antibodies?

A. Inflammatory knee joint effusion in patients of RA is known to produce acute DVT. The effusion results in baker's cyst which in concert with the local inflammation induces acute DVT[19]. This explanation may also hold true for UCTD.

Q. This patient also had haemolytic anaemia. In association with DVT, can there be a single mechanism accounting for both DVT and haemolytic anaemia ?

A. This patient had severe (Coomb's negative) haemolytic anaemia with raised nucleated RBCs, and mild thrombocytopenia. The negative Coomb's test rules out Evan's syndrome and absence of severe renal involvement and normal coagulation profile makes haemolytic uraemic syndrome also improbable. Thrombotic thrombocytopenic purpura (TTP) is one disease which can explain the presence of DVT, haemolytic anaemia and thrombocytopenia. TTP produces thrombi in arterioles, capillaries and venules. The thrombus formation triggered by unknown stimuli is supposed to be caused either by primary intravascular platelet agglutination with secondary vascular injury or primary endothelial damage followed by platelet adhesion or by the simultaneous occurence of both processes. The thrombus formation can be promoted by increased platelet and endothelial reactivity and decreased proteolysis and prostacyclin synthesis. In autoimmune diseases, TTP is probably the result of immune vasculopathy leading to platelet aggregation. This vasculopathy may be mediated by antiendothelial antibodies, circulating immune complexes or other humoral factors that can damage the endothelium[20].

Q. What is the prognosis in the patients of MCTD/overlap syndrome ?

A. In the original description of MCTD, it was claimed that MCTD had a benign prognosis and responded to small doses of corticosteroids. The presence of renal disease, vasculitis, neurological involvement, pulmonary involvement, TTP, etc., can prove fatal. Hence, a guarded prognosis is appropriate. A review of many series of MCTD

patients shows that 13% of patient were dead within 12 years[21].

Table II

Problems	Treatments
Fatigue, arthralgias, myalgias	NSAIDs, antimalarials, low dose prednisone (≤ 10 mg day)
Arthritis	NSAIDs, antimalarials, gold, methotrexate
Pleurisy	NSAIDs, short course of prednisone, about 20 mg/day
Aseptic meningitis	Discontinue NSAIDs, short course of high-dose prednisone, about 60 mg/day
Myositis	Acute onset/severe - prednisone, 60-100 mg/day Chronic/low grade - prednisone, 10-30 mg/day
Membranous glomerulo-nephropathy	Trial of prednisone, 15-60 mg/day
Nephrotic syndrome	Trial of steroids, may require dialysis/transplantation
Raynaud's phenomenon	Keep warm, avoid finger trauma. Nifedipine as tolerated. Pentoxifylline in case of potential digital gangrene
Acute-onset digital gangrene	Intra-arterial prostacycline
Myocarditis	Trial of steroids and cyclophosphamide; avoid digoxin
Asymptomatic pulmonary hypertension	Trial of steroids and cyclophos-phamide
Symptomatic pulmonary hypertension	Trial of intravenous prostacycline and angiotensin-converting enzyme inhibitors. Heart-lung transplantation
Vascular headache	Trial of propranolol or alternate-day aspirin, 350 mg
Dysphagia	Trial of prednisone, 15-30 mg/day
Heartburn	Raise head end of bed, discontinue smoking, avoid caffeine H2 antagonists, proton pump blockers Metoclopramide
Trigeminal neuropathy	None

Q. How to manage a case of MCTD/UCTD/ Overlap Syndrome ?

A. The management is governed not by the diagnosis but by the extent and type of organ involvement.

An approach that makes good sense is to suggest the safest therapies that may be empirically given to patients suffering from the component disease manifestations of UCTD. Table 2 shows the prevailing guidelines for managing MCTD[15].

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BOOK REVIEW

MONOGRAPH : RECENT CONCEPTS IN STROKE

Publisher : Indian College of Physicians (ICP), an academic wing of API.

Editor-in-chief : BC Bansal

Executive Editor : AK Agarwal

Exclusive Distributors : Jaypee Brothers Medical Publication (P) Ltd. Delhi, Bangalore, Chennai, Calcutta, Mumbai

Price : Rs.300/-

Congratulations to Prof. BC Bansal for bringing out a much needed down to earth book on stroke. With the slogan of brain attack for Cerebro-Vascular Disease it has become esential to keep the treating physicians updated on the various aspects. I have not come across any Indian author who has brought out the ground realities for managing the condition. The book gives a panoramic view without missing the essential details. He has mustered a formidable team of national and international faculty to give us an authoritative book.

He commences with anatomy and physiology, surveys the epidemiology, covers prevention of stroke and describes their various types. The management whether of ischemic or haemorrhage stroke is fully covered. This is the part where controversies are abundant. However, with up to date references the reader has to make his own decisions. The part written by G. Arjundas and Deepak Arjundas is full of clear cut guidelines but the chapter by Prof. Charles Warlow tells us that we are still on thin ice and our anchor of management is still judicious critical care Again the management of intra cerebral bleed stroke is promising but has to stand the test of statistical analysis. Thrombolysis, both intravenous and arterial, has been discussed and is a new avenue. However, to make it a reality, the need for a well oiled back up and educating the public and our profession is essential. Re-vascularisation of the carotid artery by surgery and angioplasty and stenting is becoming available at various centres in the country and we have been given proper guidelines for selection of the cases. Prof. Sen Gupta has pointed out the importance of the selection of the cases for aneurysm surgery and their transportation to the centres where such surgery is possible. The imaging of the stroke patients is important for their management and covers MRA and CT angiography. The subject is brought to a topical conclusion by covering the rehabilitation aspects also.

The book gives a comprehensive updated information and critical analysis of the problems of stroke. The extensive references are a help to dig deeper into the subject.

Prof Bansal has been a teacher all his life and the book is another commendable step in that direction.

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Deep vein thrombosis, or DVT, is a blood clot that forms in a vein deep in the body. Most deep vein clots occur in the lower leg or thigh. If the vein swells, the condition is called thrombophlebitis. A deep vein thrombosis can break loose and cause a serious problem in the lung, called a pulmonary embolism. Sitting still for a long time can make you more likely to get a DVT. Some medicines and disorders that increase your risk for blood clots can also lead to DVTs. Deep vein thrombosis can develop if you have certain medical conditions that affect how your blood clots. It can also happen if you don't move for a long time, such as after surgery or an accident, or when you're confined to bed. Deep vein thrombosis can be very serious because blood clots in your veins can break loose, travel through your bloodstream and lodge in your lungs, blocking blood flow (pulmonary embolism). Products & Services.Â Pulmonary embolism occurs when a blood clot gets lodged in an artery in the lung, blocking blood flow to part of the lung. Blood clots most often originate in the legs and travel up through the right side of the heart and into the lungs. A serious complication associated with deep vein thrombosis is pulmonary embolism. Pulmonary embolism.