Nephrol Dial Transplant (1998) 13: 3275–3281

Nephrology
Dialysis
Transplantation

Letters

Professor Mollie McGeown

Sir,
What a pleasure to read James Douglas's Laudatio for Professor Mollie McGeown.

Her's is a life that many of us can use as a role model.

I think that James Douglas missed one more of Mollie's greatest contributions; the number of young physicians who came to her to be trained.

I pride myself in being one of the many physicians who came from all over the world to be trained at her unit and to be inspired by her personality.

It is with great pride that I mention that I am the fourth in a series of Greek Nephrologists, trained in the Belfast City Hospital under Mollie McGeown.

Her hard work, her dedication to patients, her acceptance of only scientific facts in research and in patient management, and her humane approach continue to affect us. In some ways we have tried to transfer these principles to our own students so that Mollie's tradition will continue for many years to come.

On behalf of all her students, I would like to express publicly my gratitude for all she has done for us.

Division of Nephrology
University of Toronto
The Toronto Hospital
Western Division
Toronto M5T 2S8
Ontario
Canada

D. G. Oreopoulos, MD

Minimal change nephrosis and antiphospholipid antibodies: coincidental or associated?

Sir,
Thrombotic complications of the nephrotic state occur with membranous nephropathy and to a lesser extent with minimal change disease [1]. The primary antiphospholipid syndrome (APS), also characterized by thromboembolic events, has an ever increasing list of associated conditions [2]. A patient with recurrent thromboembolic episodes and who had antiphospholipid antibodies is reported here.

Case A 37-year-old male who presented with right-sided pleuritic chest pain was found to have high blood pressure and a pleural rub located in the right inframammary region. Chest skiagram revealed a wedge-shaped opacity in the right midzone associated with a right pleural effusion. Two days later, the patient had an episode of streaky haemoptysis. Urinalysis revealed protein 3+, pus cells 4–6/hpf; RBCs and eosinophils were absent. The 24-h urine protein excretion was found to be 1.56 g/day. Other investigation results were as follows: Hb 140 g/l, total leukocyte count 12.5 cells $\times 10^9$, BUN 13.56 mmol/l, Cr 74.26 μmol/l. Within the next 5 days, the patient developed nausea, vomiting and anorexia. BUN and creatinine increased to 22.64 mmol/l and 502.99 μmol/l respectively. Renal histology revealed 10 glomeruli (negative IF microscopy) and tubules with markedly vacuolated, swollen epithelial cells suggesting a biopsy of minimal change lesion. The patient received thrice a week haemodialysis but had no functional recovery by the end of the third week. In the next week, he suddenly developed backache, loin pain and oedema of the right lower limb over 5–6 h with no macroscopic haematuria. Re-evaluation revealed: urine protein 3+, pus cells 30–50/hpf, RBCs 20–25/hpf. The 24-h protein excretion had increased to 5 g/day. BUN levels were 13.21 mmol/l and serum creatinine 495.04 μmol/l. A duplex doppler sonographic study demonstrated an extensive thrombus involving the inferior vena cava, right common and external iliac, common and superficial femoral veins. Coagulation studies revealed: PT 20/26 s, PTTK 10/12 s; Protein C 83% (normal 70–140%), antithrombin III 125% (normal 80–120%), fibrinogen 2.51 g/l (normal 1.50–3.0 g/l). ANA and antibodies to double stranded DNA were absent, cholesterol 7.43 μmol/l. Heparin infusion and commencement of oral anticoagulants (warfarin) [INR $\geq$ 2.5] followed intravenous urokinase administered through a right jugular catheter. The patient gradually improved following initiation of steroid therapy with no further dialysis requirement after 1 month of steroids. Repeat duplex doppler sonography revealed that the thrombus in the IVC was persistent with partial resolution of the thrombus in the lower limb vessels. Warfarin was continued (INR of 3) along with aspirin and dipyridamole. Partial remission induced by steroids (12 weeks), converted to complete following an 8-week course of cyclophosphamide (2 mg/kg/day).

Two months later, thrombosis of the deep veins of the right lower extremity recurred, despite optimal warfarin therapy. Proteinuria was noted to be 2.5 g/day with serum albumin of 35 g/l. Anticardiolipin antibodies (ELISA) were present. (aCL IgG: 10.00 GPL units (>5 GPL significant), aCL IgM: 4.10 MPL units (>3 MPL significant). Steroids for 12 weeks (2 mg/kg on alternate days along with heparin (followed by oral anticoagulants)) were started simultaneously. Oral anticoagulant therapy was continued for 2 years after disappearance of aCL. Remission, obtained by the eighth week of steroid therapy, was maintained over the last 3 years.

Discussion Haemoptysis followed by rapidly progressive renal failure preceded detection of extensive thrombus in the venous system. Renal failure was related to the renal vein thrombosis associated with the steroid resistant MCNS. Coagulation profile (PT, PTTK, antithrombin III, Protein C, and fibrinogen) was within normal limits. Thrombosis recurred despite optimal high intensity warfarin therapy and in the absence of a severe nephrotic syndrome. The presence of APA was detected on screening.

Membranous nephropathy [4], but not MCNS, has been described in association with primary APS existing independently but acting synergistically could have produced recurrent thromboembolism in a manner similar to the hypothesized role of factor V Leiden mutation [5]. On the other hand, MCNS could have been one of the manifestations of primary APS. Increased circulating CD5+B cells [6], immune complex vasculitis [7], platelet and other cells functional derangement have been found in primary APS [8]. Immunologic abnormalities—cellular, humoral (lymphokines) described in the pathogenesis of MCNS [9], could explain the

MCNS in primary APS. This hypothesis warrants further investigation.

Department of Nephrology
Seth G.S. Medical College
and K.E.M. Hospital
Bombay
India

Vipul Chimanlal Chitalia
Alan Fernandes Almeida
Murali Krishnan
Sandeep K Chauhan
Prakash P Khetan

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Response of mean reticulocyte haemoglobin content to intravenous iron therapy in haemodialysis patients

Sir,

Iron deficiency is a major cause of sub-optimal response to human recombinant erythropoietin (rhEpo) therapy in haemodialysis patients [1]. This can be reversed by intravenous (i.v.) iron [2–4]. Successful treatment however, necessitates the reliable detection of iron deficiency and subsequent monitoring of response to therapy in haemodialysis patients. Mean reticulocyte haemoglobin content (CHr) focuses on new red cells released by the bone marrow. It allows the identification of poorly haemoglobinised reticulocytes in advance of any change in the red cell population. In a small preliminary uncontrolled study, we examined the response of mean reticulocyte haemoglobin content to i.v. iron therapy in haemodialysis patient on rhEpo therapy.

Patients and methods: 16 patients, 12 male and 4 female, mean age 62.1 years (range 26–78 years) with end stage renal disease on regular haemodialysis were followed prospectively over 84 days in a longitudinal study. Mean duration of their dialysis was 35 months (range 12–131 months). Patients with factors known to be associated with potential rhEpo resistance were excluded from the study. Dialysis was performed via a.v. fistula or dual lumen subclavian catheters using Cobe C3 version 15 monitors, bicarbonate buffered dialysis with Gambro GFE cuprophane dialysers. Patients received maintenance subcutaneous rhEpo at a median dose of 4000 units per week having been previously titrated to maintain a haemoglobin concentration of 10 g/dl.

Blood samples were drawn prior to commencement of a dialysis session, 10 ml lithium heparin for measurement of serum ferritin (SF) and transferrin saturation (TS) and 5 ml EDTA for measurement of haemoglobin concentration and CHr. Haemoglobin and CHr were measured by standard laboratory methods and using a Bayer automated Technicon H-3 analyser respectively [5,6].

Patients were given 200 mg i.v. iron (iron dextran 50 mg/ml) during each of the first seven consecutive dialysis sessions. This was administered via a syringe driver in the last hour of dialysis through the venous bubble trap port of the dialysis circuit. This was given as an initial test dose administered in the first 30 min with regular observations and the remainder over the next 30 min.

Results are given as means $\pm$ standard error of the mean. The student *t*-test was used to examine for significance over time. A P value of <0.05 was considered to be statistically significant.

Results: the mean haematological and biochemical parameters of the study group prior to i.v. iron therapy were aluminum 1.38 μmol/l (range 0.75–2.46 μmol/l), parathyroid hormone 125.6 pmol/l (13–365 pmol/l), serum folate 24.4 μg/l (5.4–43.3 μg/l) and vitamin B_{12} 629.6 ng/l (389–1296 ng/l).

No patient experienced any major adverse reaction to i.v. iron. The mean haemoglobin concentration rose from 10.21 ± 0.3 g/dl at baseline to 10.53 ± 0.36 g/dl ($P=0.035$), 4 weeks after i.v. iron therapy. After 12 weeks it had decreased to 10.15 ± 0.27 g/dl.

CHr over the period of investigation was normally distributed with a mean of 28.27 ± 0.27 pg. It rose significantly from 28.3 ± 0.57 pg to a peak concentration of 30.2 ± 0.5 pg ($P=0.01$) at 14 days after commencement of iron therapy before returning to a value not dissimilar from the baseline concentration (28.4 ± 0.51 pg) after 8 weeks. After 12 weeks it had dropped to 23.6 ± 0.4 pg ($P<0.05$). SF rose significantly from 24 ± 2.7 to 185.3 ± 19.4 μg/l ($P<0.001$) 28 days after commencement of iron therapy, reaching a maximum concentration of 217 ± 24.8 μg/l after 8 weeks. Changes in TS followed a similar pattern to CHr, reaching a maximum after 14 days before dropping to $24.3 \pm 3\%$ after 12 weeks ($P<0.005$), (Figure 1). In comparing CHr to the red blood cell haemoglobin content (MCH), the ratio of CHr to MCH was <1 in 94% of cases at baseline, 63% after iron therapy, and 100% after 12 weeks.

Comments: concerns remain about the accuracy of current tests to diagnose iron deficiency in dialysis patients [7]. Iron metabolism can be determined by the quantification of iron stores (SF), measurement of iron circulating in plasma (TS) or the assessment of iron uptake or utilization by the marrow and its incorporation into the proliferating erythroblasts (CHr). SF and TS provide limited information regarding iron availability to the newly formed red blood cells [6] while CHr gives an estimate of available iron for the erythroid tissue.

A decrease in CHr is a sensitive early marker of iron deficiency [5,6]. Fishbane *et al.* [8,9] have suggested that a CHr that is less than the MCH is indicative of the acute onset of iron deficiency.

In this study i.v. iron therapy produced an increase in haemoglobin concentration. This suggests a degree of iron deficiency or at least deficiency of utilizable iron for erythropoiesis. The subsequent drop in haemoglobin with continued rhEpo therapy is also suggestive of an exhaustion of utilizable iron despite sufficient stores (normal SF) and need for further i.v. iron therapy. There was a rise in CHr after i.v. iron suggesting increased iron availability for haemoglobin production. The subsequent decline paralleling the decline in both haemoglobin and TS may reinforce the idea of an exhaustion of available iron for erythropoiesis and the need for further iron therapy. In this study initial iron therapy was only sufficient in 37% of patients to produce a