

Liver and biliary

Role of plasmapheresis in primary biliary cirrhosis

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SUMMARY Five patients with primary biliary cirrhosis and prolonged cholestasis underwent intensive plasmapheresis. The indications for plasmapheresis included intractable pruritus or hypercholesterolemia and xanthomatous neuropathy. Patients noted a rapid improvement of pruritus and fatigue which was sustained as long as plasmapheresis was continued. Cholesterol levels were lowered an average of 10.3 mmol/l and xanthomata were reduced in three of four patients. Two patients with painful neuropathy caused by xanthomata experienced relief of this symptom. The liver and spleen size were not affected by plasmapheresis, and activities of aminotransferases, alkaline phosphatase and titres of mitochondrial antibody remained unchanged. We conclude that plasmapheresis has a role in the therapeutic management of patients with advanced primary biliary cirrhosis who are disabled by the complications of pruritus, xanthomatous neuropathy, or hypercholesterolemia with xanthoma formation.

The treatment of primary biliary cirrhosis is directed at relief of symptoms. Complications of the disease are the result of prolonged cholestasis: pruritus, jaundice, hypercholesterolemia with xanthoma, and xanthomatous neuropathy, fat malabsorption, and osteopenia. Therapy is not effective for the hypercholesterolemia, and the pruritus, which responds early to the bile salt-sequestering resin, cholestyramine, may with time become refractory to such therapy. Based on prior reports of the efficacy of plasmapheresis in hypercholesterolemia,^{1,2} xanthomatous neuropathy,² and pruritus,^{3,4} we undertook a study of plasma exchange in five patients with primary biliary cirrhosis to answer the following questions: (1) can plasmapheresis effect sustained lowering of serum cholesterol levels with improvement of xanthomas and painful xanthomatous neuropathy? (2) can plasmapheresis relieve pruritus unresponsive to cholestyramine? and (3) can plasmapheresis improve the laboratory parameters of liver disease?

Methods

PATIENTS

Five patients with primary biliary cirrhosis were studied, four women and one man, with a mean age

of 44 years. The mean duration of disease was 10 years. The diagnosis of primary biliary cirrhosis was based on the following criteria: (1) alkaline phosphatase more than twice upper limit of normal, (2) the presence of mitochondrial antibody in the serum, (3) a compatible histologic appearance of a liver biopsy specimen, (4) normal extrahepatic bile ducts by endoscopic retrograde or operative cholangiography. The indications for initiation of plasmapheresis included intractable pruritus (five), and hypercholesterolemia (five) with xanthoma formation (four) and/or xanthomatous neuropathy (two). Additional findings which were noted before plasmapheresis included jaundice (five), hepatomegaly (three), fatigability (four), nausea (five), Sjögren's syndrome (four), and Raynaud's phenomenon (one). All patients had advanced disease at stage III or IV.⁵ The administration and dosage of other medications were held constant during the study period. All patients were receiving colchicine (four) and/or penicillamine (three).

TECHNIQUE

Plasmapheresis was performed using the Haemonetics Model 30 blood cell separator, using standard plasmapheresis technique. At each visit, 500-2000 ml of plasma was removed during a two to three hour session and replaced with 1000 ml of normal saline and 5% albumin. Patients underwent apheresis three times a week for the first two to

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three weeks until a clinical response was noted. Maintenance plasmapheresis was continued at one to two week intervals. A questionnaire was administered to patients before initiation of plasmapheresis, and every three months to assess the presence of pruritus, fatigability, dryness of the eyes or mouth, Raynaud's phenomenon, nausea and vomiting. Clinical scoring was as follows: 0 = absent, +1 = mild, +2 = moderate, +3 = severe, and +4 = disabling. The following physical findings were evaluated: hepatomegaly, splenomegaly, xanthomata, and peripheral neuropathy. Laboratory parameters including automated chemistry screen, immunoglobulins and mitochondrial antibody were studied serially. Immune complexes were estimated using a solid phase C1q-binding assay.

Results

Patients underwent plasmapheresis a mean of 63 times during a mean study period of 26 months (range, 20–37 months). An average of 95 litres was exchanged per patient during the study period. The clinical results of plasmapheresis are presented in Table 1. All patients experienced marked relief of pruritus, less fatigability accompanied by an improved sense of well-being, and a reduction in nausea. Xanthomatous neuropathy was relieved in both patients with this symptom. In addition, all four patients with Sjögren's syndrome had an improvement and Raynaud's phenomenon was improved in the one patient so affected. Xanthomata were reduced in three of four patients, but liver and spleen size were not affected.

The serum cholesterol level was most significantly affected by plasmapheresis, reduced by a mean of 10.3 mmol/l (range, 5.7–16.7 mmol/l) (Table 2).

This reduction was sustained with continued plasma exchange. The alkaline phosphatase and aminotransferase activities, bilirubin, and mitochondrial antibody titres were not affected by plasmapheresis. Bilirubin concentrations dropped 20–40% immediately after each treatment but were back to pretreatment levels within a week. Over the entire period of study the gradual rise of bilirubin expected did not occur. Immune complexes were detected in two patients studied for their presence, and were cleared by plasmapheresis.

Discussion

The aetiology of primary biliary cirrhosis is unknown but is thought to involve an immunologic derangement. The presence of circulating autoantibodies in greater than 90% of patients and the frequent coexistence of Sjögren's syndrome, Raynaud's phenomenon, and thyroiditis,⁶ have raised the question of autoimmune origin. No specific therapy for the disease exists.

Treatment currently is directed at alleviating symptoms. The most troublesome symptom is pruritus, which usually responds to cholestyramine.⁷ Some patients with advanced disease, however, become refractory to this drug as cholestasis becomes more severe. Also troublesome is the severe hypercholesterolemia which occurs, with its sequelae of xanthomata, painful xanthomatous neuropathy,⁸ and possibly accelerated atherosclerosis.⁹ Fatigability may also be severe and no therapy improves this.

Our study confirms a previous report¹⁰ that plasmapheresis has a role in the palliative management of primary biliary cirrhosis when complicated by these symptoms. Patients experience a dramatically improved sense of well-being, relief of

Table 1 *Signs and symptoms*

	Patients									
	RF		SD		MD		AR		CG	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Fatigue	3+	1+	2+	1+	0	0	2+	1+	2+	1+
Pruritus	3+	0	3+	1+	3+	0	3+	1+	3+	1+
Nausea	1+	0	1+	0	3+	0	1+	0	1+	0
Sjögren's syndrome	2+	0	1+	0	0	0	2+	0	1+	0
Raynauds phenomenon	0	0	0	0	0	0	0	0	3+	0
Liver size (cm)	18	13	10	10	11	11	16	14	16	16
Spleen size (cm below costal margin)	4	6	0	1	1	1	5	7	0	0
Xanthomata	3+	0	2+	2+	0	0	3+	1+	2+	0
Painful neuropathy	0	0	0	0	0	0	3+	0	4+	0
Duration of therapy (months)		22		28		18		26		37

Table 2 Laboratory data

	Patients									
	RF		SD		MD		AR		CG	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
AST (nl, 1-50 U/l)	186	137	102	131	108	72	68	74	114	137
AST (nl, 1-53 U/l)	180	114	157	156	185	90	88	67	88	113
Alkaline phosphatase (nl, 30-90 U/l)	1273	1004	425	682	978	1255	1025	846	942	835
Total bilirubin ($\mu\text{mol/l}$)	274	222	274	222	325	239	205	239	85	68
IgM (g/l)	8	3.4	7.2	10.5	2.7	4.3	1.6	7.6	10	11.2
Mitochondrial antibody (titre)	1:320	1:320	1:160	1:160	1:160	1:320	1:80	1:320	1:80	1:640
Cholesterol (mmol/l)	14.7	9	22.9	7.4	11.3	4.5	15.7	9.1	25.3	8.6

pruritus, resorption of xanthomata, and elimination of the pain caused by xanthomatous neuropathy, accompanied by a reduction in serum cholesterol. Additionally, the symptoms of Sjögren's syndrome and Raynaud's phenomenon appear to be reduced.

The mechanism of these effects is removal from the body of cholesterol and bile salts (or other pruritogens) which are normally excreted *via* the bile. Relief of the Sjögren's or Raynaud's symptoms may depend upon removal of other substances – for example, immune complexes, but this is not clear. The effect of plasmapheresis on liver function and on the long term prognosis of primary biliary cirrhosis cannot be assessed from this study. If immune aberrations are aetiologic as suggested by Sherlock¹¹ and others,¹² long term apheresis, by removing autoantibodies or immune complexes, could possibly alter the basic disease mechanism; this remains to be shown. What does seem clear is that chronic plasmapheresis has a role in improving the quality of life for patients with primary biliary cirrhosis with intractable pruritus and/or the complications of protracted hypercholesterolemia. The rate of progression of the disease seems to be slowed as life expectancy is otherwise very short in patients with primary biliary cirrhosis and extreme rises in bilirubin.¹³

Over a three year period encompassing 317 procedures, we have found plasmapheresis to be a safe therapeutic modality. Mild urticaria and transient hypotension have occurred several times but always with rapid response to fluids, albumin, and adrenaline. In contrast, Rubenstein¹⁴ recently reported three cases of anaphylaxis in 22 patients receiving therapeutic plasma exchange, manifested by urticaria, bronchospasm, and hypotension. Fatal pulmonary microvascular occlusion developed in an additional patient after an apheresis procedure. Thus, caution must be exercised, and patients closely followed after initiating plasmapheresis.

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