Mod Rheumatol (2006) 16:109–112
DOI 10.1007/s10165-006-0465-7

CASE REPORT

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A case of systemic lupus erythematosus complicated by pure red cell aplasia and idiopathic portal hypertension after thymectomy

Received: August 17, 2005 / Accepted: February 21, 2006

Abstract We describe a 49-year-old woman who presented in 2002 with pure red cell aplasia (PRCA), systemic lupus erythematosus (SLE), and idiopathic portal hypertension (IPH) that developed following a thymectomy. She underwent a thymectomy at 40 years of age to treat myasthenia gravis. PRCA developed 3 years after the thymectomy and she was successfully treated with cyclosporin. Systemic lupus erythematosus and IPH were diagnosed 6 years later. We conclude that immunological dysfunction resulting from the thymectomy contributed significantly to the subsequent development of PRCA, SLE, and IPH in this patient. This is the first report to describe this extremely rare occurrence.

Key words Idiopathic portal hypertension (IPH) · Pure red cell aplasia (PRCA) · Systemic lupus erythematosus (SLE) · Thymectomy

Introduction

Thymectomy is a recognized treatment for autoimmune diseases, including myasthenia gravis (MG) and pure red cell aplasia (PRCA) associated with thymoma. However, thymectomy can also induce a variety of autoimmune disorders. We describe a case in which PRCA, systemic lupus erythematosus (SLE), and idiopathic portal hypertension (IPH) developed after thymectomy.

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Case report

In 1986, a 33-year-old-woman was diagnosed with MG and subsequently underwent a thymectomy in 1993. In 1996, she was admitted to the Department of Hematology at Fukushima Medical University Hospital for investigation of severe anemia. Bone marrow aspiration demonstrated marked red cell hypoplasia with slightly elevated granulopoiesis and megakaryopoiesis, thereby establishing a diagnosis of PRCA. She has been successfully treated with cyclosporin A since then. In 2001, she had a hematoemesis. Esophagogastroduodenoscopy revealed esophageal varices, but no bleeding point was identified.

In 2002, she was admitted to our department with polyarthritis and renal dysfunction. Physical examination revealed fine bibasal crackles and 2-finger-breadth hepatomegaly. She gave a history of Raynaud's phenomenon but no skin rash was evident. Her right ankle joint was swollen.

Laboratory tests revealed an increased erythrocyte sedimentation rate of 120 mm in 1 h, a decreased white blood cell count of 1900/mm^3, hemoglobin of 9.9 g/dl and platelet count of 131000/mm^3. The levels of aspartate transaminase (AST), alanine transaminase (ALT), and lactate dehydrogenase (LDH) were normal. The level of urea nitrogen was 31 mg/dl, creatinine 1.2 mg/dl, and β_2-microglobulin 11.3 μg/dl. The levels of C3 (59 mg/dl) and C4 (10 mg/dl) were low whilst the Coomb's test was negative. Antinuclear antibodies were positive (1 in 20480 dilution) with homogeneous and speckled patterns. The levels of anti-DNA antibodies (19.8 IU/ml), anti-Sm antibodies (56.7 IU/ml), and anti-U1 RNP antibodies (159.1 IU/ml) were elevated. Anticardiolipin antibodies for β2-glycoprotein I and the lupus anticoagulant were negative. The indocyanine green load test was 8%. The levels of KL-6 (657 U/ml) and SP-D (174.1 ng/ml) were high. Urinalysis showed significant proteinuria (0.6 g/day) together with 10–19 red blood cells/field, and hyaline and granular casts. The creatinine clearance was significantly reduced at 27 ml/min. Chest X-ray and computed tomography revealed ground-glass shadowing affecting both lower lobes.

The patient was diagnosed as having SLE according to the 1997 American Collage of Rheumatology revised criteria for classification of systemic lupus erythematosus (SLE), on the basis of the presence of arthritis, proteinuria, leukopenia, positive anti-DNA antibodies, and a high titer of antinuclear antibodies. A renal biopsy was performed and histological examination established a diagnosis of lupus nephritis (WHO class IIIc). Mixed connective tissue disease was not diagnosed in the patient according to the Japanese criteria for mixed connective tissue disease.

Abdominal ultrasonography and computed tomography revealed a dilated portal tract and splenomegaly but no evidence of liver cirrhosis. Magnetic resonance imaging showed normal parenchyma and no nodules. Portal, splenic, and mesenteric veins were patent on magnetic resonance angiographic imaging whilst esophagogastric varices were identified at esophagogastroduodenoscopy. A liver biopsy was performed, and histological examination revealed normal liver parenchyma with no fibrosis and normal vessels in the portal area. These findings established a diagnosis of IPH according to the 2004 general rules for the study of portal hypertension by the Japanese Society of Portal Hypertension.

The patient received endoscopic injection sclerotherapy for the esophagogastric varices. After the therapy, she was treated with 40 mg/day of prednisolone, which increased the white blood cell count, decreased the titer of anti-DNA antibodies, and resulted in complete resolution of the proteinuria and pulmonary shadowing. She was discharged with no symptoms. The clinical course of this patient is illustrated in Fig. 1.

Discussion

Thymoma-associated autoimmune diseases such as MG, PRCA, polymyositis, and SLE have been well documented.[1] The prevalence of SLE in patients with MG has been reported to be 0.2%–2.7%.[2] A recent report states that SLE developed before thymectomy in 17 of the 28 patients with both SLE and MG, with the remaining 11 patients (39%) developing SLE after the thymectomy.[3] Table 1 shows the clinical characteristics of the 21 patients, including our case (2 men and 19 women), in whom SLE developed after thymectomy.[3–16] Their ages ranged from 11 to 66 years (mean, 40.4 years) with SLE developing from

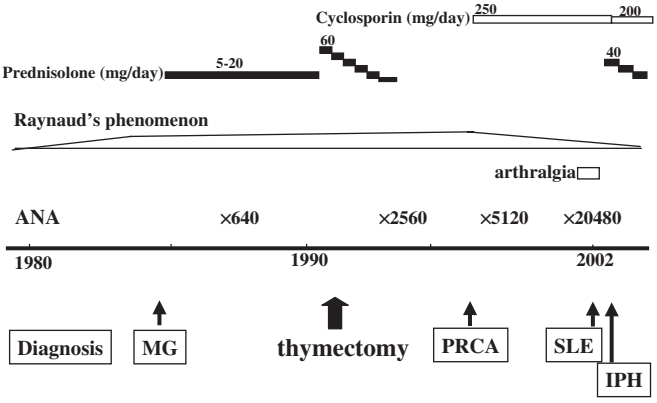

Fig. 1. Course of treatment. *MG*, myasthenia gravis; *PRCA*, pure red cell aplasia; *SLE*, systemic lupus erythematosus; IPH, idiopathic portal hypertension; *ANA*, antinuclear antibodies

Table 1. Clinical characteristics of 21 patients in whom systemic lupus erythematosus developed after thymectomy

First author[Ref.]	Age (years)/sex	Interval	Lesion		Other autoimmunological disease
Alarcon-Segovia[4]	32/F	6 years	Arthritis		MG
	11/F	3 years	Arthritis		UC
Petersen[5]	37/F	8 years	Arthritis		MG
Kennes[6]	27/F	8 years	Arthritis		MG
Calabrese[7]	21/M	3 years	Arthritis	Nephritis	MG
Claudy[8]	55/M	Unknown		Dermatitis	
				Nephritis	
Steven[9]	49/F	16 months	Arthritis	Nephritis	
	48/F	Unknown	Arthritis	Cardiac	
Goldman[10]	34/F	9 years		Optic neuritis	MG
				Transverse myelitis	
Ohnishi[11]	41/F	5 years	Arthritis	Pleuritis	MG
Ogawa[12]	49/F	Unknown	Arthritis	Nephritis	
Vaiopoulos[3]	37/F	7 years	Arthritis		MG
Rosman[13]	38/F	4 years	Arthritis		SS
Mevorach[14]	66/F	3 months	Arthritis	Vasculitis	
				Pleuritis	
	49/F	3 years	Arthritis		MG
	61/F	5 years		Pleuritis	
	26/F	2 years		Dermatitis	MG
Zandman-Goddard[15]	48/F	2 months		Serositis	
			Arthritis	Dermatitis	
Park[16]	36/F	3 months	Arthritis		MG
	34/F	13 years	Arthritis	Dermatitis	MG
Present case	49/F	11 years	Arthritis	Nephritis	MG, PRCA, IPH

MG, myasthenia gravis; UC, ulcerative colitis; SS, Sjögren's syndrome; PRCA, pure red cell aplasia; IPH, idiopathic portal hypertension

2 months to 13 years (mean, 4.9 years) after thymectomy. Polyarthritis was the most common manifestation of SLE, and there were no life-threatening disease manifestations. The other autoimmune complications were MG in 12 patients and ulcerative colitis (UC) in 1. To our knowledge, there has been no previous report describing the development of three autoimmune diseases after thymectomy, namely, SLE, PRCA, and IPH.

In this patient, PRCA developed 3 years after thymectomy. Pure red cell aplasia is characterized by a normochromic normocytic anemia and reticulocytopenia, with aplasia or severe hypoplasia of the red cell line associated with normal white cell and megakaryocyte precursors in the bone marrow.[17] Pure red cell aplasia has a high association with thymoma; thymectomy is a recognized treatment for such PRCA patients and results in remission in about 30%.[18] On the other hand, PRCA can also develop after thymectomy.

Systemic lupus erythematosus is rarely associated with PRCA. Habib et al. reported 24 patients with SLE and PRCA, and the clinical and laboratory features of these patients were similar to those of SLE patients without PRCA except for a lower incidence of pleuritis[19] Pure red cell aplasia was diagnosed before the onset of SLE in 12 patients. Three of those patients had thymomas, but whether SLE and PRCA were associated with thymectomy was not mentioned.

Idiopathic portal hypertension also developed after thymectomy in our patient. Liver involvement in SLE is relatively common and occurs in about 20% of patients with SLE.[20] A wide variety of hepatic abnormalities have been described including cirrhosis, chronic active and persistent hepatitis, granulomatous hepatitis, steatosis, nodular regenerative hyperplasia, and autoimmune hepatitis.[20–22] In our patient, the diagnosis of IPH was made because these related diseases were excluded by the imaging and histological examination. Idiopathic portal hypertension is clinically characterized by portal hypertension, splenomegaly, and pancytopenia in the absence of evidence of cirrhosis, blood disease, parasites in the hepatobiliary system, or occlusion of the hepatic and portal veins.[23] The etiology of IPH is unknown but autoimmunity is considered to be one of the causes, since autoantibodies and a reduced autologous mixed lymphocyte reaction are observed in patients with IPH.[23] The presence of lupus anticoagulant or anticardiolipin antibodies, immune-complex mediated small vessel vasculitis, or microthromboembolism in the portal vein have been implicated in portal hypertension in patients with SLE,[24,25] but it is unknown whether IPH is associated with thymectomy.

Thymectomy can induce various autoimmune diseases. In animal models, thymectomy in neonatal New Zealand black × New Zealand white F_1-crossed (NZB × NZW) mice accelerated the autoimmune process, possibly as a result of the elimination of a population of thymic T-suppressor cells.[26] Furthermore, reconstitution of these mice with young syngeneic thymic grafts retarded the development of autoimmunity.

In humans, long-term thymectomized patients with MG exhibited a mild T-cell lymphopenia and a polyclonal increase in serum IgM and IgG associated with the presence of autoantibodies, including anti-dsDNA and anticardiolipin antibodies, which may increase the risk of developing systemic autoimmune diseases such as SLE and PRCA.[27] Although anticardiolipin antibodies or lupus anticoagulant were negative in our patient, there is a possibility that the immunological dysfunction induced by thymectomy contributed to the development of not only SLE and PRCA but also IPH.

In summary, we conclude that the immunological dysfunction caused by thymectomy contributed largely to the development of PRCA, SLE, and IPH in our patient. This is the first report to describe this extremely rare occurrence.

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