Polymyositis Associated with Thymoma and the Subsequent Development of Pure Red Cell Aplasia

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A 53-year-old woman with polymyositis associated with thymoma subsequently developed pure red cell aplasia (PRCA). She was hospitalized because of fever and muscle weakness, and diagnosed as having polymyositis by muscle biopsy. Remarkable clinical improvement followed administration of prednisolone. Progressive anemia became evident, however, while prednisolone was being tapered. Erythroid aplasia and the presence of thymoma confirmed the diagnosis of PRCA. Further examinations revealed that cytotoxic T cells may play an important role in the pathogenesis of this case.

(Internal Medicine 34: 569–573, 1995)

Key words: combined autoimmune disease, cytotoxic T cells

Introduction

A wide spectrum of diseases associated with thymoma have been well documented (1–4). They include myasthenia gravis, pure red cell aplasia (PRCA), secondary hypogammaglobulinemia and polymyositis. The precise relationship between thymoma and the associated disorders remains obscure, but an abnormality of the immune system has been strongly implicated as a prominent etiologic factor.

The present report describes an unusual case with the combination of polymyositis, thymoma and PRCA. Of particular interest is the possibility that cytotoxic T cells may play an important role in its pathogenesis.

Case Report

A 53-year-old woman was admitted to our hospital in January 1992 because of fever and progressive muscle weakness. The patient had been well until late December 1991, when an abrupt onset of high fever of up to 39°C occurred, accompanied by general malaise and diffuse muscle weakness.

She had been admitted to another hospital because of non-A, non-B, non-C acute hepatitis for three months in 1989, which subsequently improved without specific treatment. It should be noted that the liver biopsy specimen was most suggestive of

autoimmune hepatitis. Family history was non-contributory.

Physical examination on admission showed an acutely ill woman unable to stand unaided due to marked proximal muscle weakness. Pulse rate was 96/min, temperature 37.8°C and blood pressure 124/60 mmHg. Her height was 158 cm, and weight 41.0 kg. There was no sign of anemia. No skin lesions or lymphadenopathy was noted. Eye movements were normal, and no ptosis of the lids was evident. There was no dysarthria or dysphagia. Chest, heart and abdomen were not remarkable. Muscles of the extremities were indurated, slightly enlarged, moderately tender and markedly weak. Muscle weakness was most obvious in the proximal lower limbs. Neither sensory disturbance nor pathological reflex was found.

Laboratory data on admission are shown in Table 1. There was evidence of mild anemia, but the reticulocyte count was within the normal limits (1.2%). Serum muscle enzymes such as creatine kinase (CK) and aldolase were markedly elevated. The liver function tests were all within normal limits. Serological markers for hepatitis A, B and C virus were all negative. Antinuclear antibodies (ANA) were positive at a titer of 1:40, with a speckled pattern. Although there had been no clinical signs or electromyographic evidence suggesting myasthenia gravis, anti-acetylcholine receptor antibodies (Ach-R Ab) were detected at high titers. Other autoantibodies including anti-Jo1 antibodies (Jo-1 Ab) were all negative. Electromyographic

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Received for publication January 20, 1994; Accepted for publication February 14, 1995

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Table 1. Laboratory Data on Admission

Peripheral Blood:		Creatine kinase	3,460IU
RBC	3.83×10 ⁶ /μl	Aldolase	11.0IU
Hemoglobin	11.2g/dl	s-Myoglobin	3,268.2ng/ml
Hematocrit	35.1%	u-Myoglobin	129.2ng/ml
WBC	5,020/μl	TTT	20.4K.U.
Band	16.0%	ZTT	23.9K.U.
Segment	69.0%	Total cholesterol	146mg/dl
Lymphocyte	14.0%	BUN	22mg/dl
Monocyte	1.0%	Creatinine	0.6mg/dl
Platelet	385×10 ³ /μl	Serological Exam:	
Reticulocyte	1.2%	CRP	21.5mg/dl
ESR:	58mm/h	RF	26U/ml
Urinalysis:	n.p.	ANA	40× (speckled)
Blood Chemistry:		Anti-DNA Ab	(-)
Total protein	6.6g/dl	Anti-Sm Ab	(-)
Albumin	3.1g/dl	Anti-RNP Ab	(-)
α ₁ -globulin	6.6%	Anti-Jo1 Ab	(-)
α ₂ -globulin	13.2%	Anti-PM1 Ab	(-)
β-globulin	7.3%	Anti-AchR Ab	78nmol/l
γ-globulin	25.5%	IgG	2450mg/dl
Total bilirubin	0.2mg/dl	IgA	102mg/dl
AST	267IU	IgM	179mg/dl
ALT	292IU	C ₃	94mg/dl
LDH	1,663IU	C ₄	18mg/dl
ALP	95IU	CH ₅₀	43.7U/ml
γ-GTP	71IU	CD4/CD8	0.86

RBC: red blood cell, WBC: white blood cell, ESR: erythrocyte sedimentation rate, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyltranspeptidase, TTT: thymol turbidity test, ZTT: zinc sulfate turbidity test, BUN: blood urea nitrogen, CRP: C-reactive protein, RF: rheumatoid factor, ANA: antinuclear antibody.

study showed a myogenic pattern. A neostigmine test was negative. A quadriceps muscle biopsy, performed five days after admission, was characteristic of acute myositis; diffuse infiltration of lymphocytes was present where muscle fibers showed the most severe degenerative changes (Fig. 1).

The patient was diagnosed as having polymyositis, and steroid therapy was started. Remarkable clinical improvement followed administration of prednisolone at an initial dosage of 80 mg daily (Fig. 2a). Serum CK returned to normal levels in about one month, accompanied by a gradual improvement in muscle strength.

Four months after admission, in May 1992, when prednisolone was tapered to 15 mg daily, progressive anemia became evident. Laboratory studies showed normochromic normocytic anemia with a reticulocyte count of 0.0% (Table 2). Coombs tests, both direct and indirect, were negative. Serum erythropoietin showed a grossly elevated value of 390 mM/ml. Serum haptoglobin was within the normal range. The bone marrow aspirate revealed mildly hypocellular marrow with adequate numbers of megakaryocytes and granulocyte precursors, but

virtually complete absence of erythroblasts. The computed tomographic (CT) scan of the chest revealed an anterior mediastinal tumor, with an appearance suggestive of thymoma.

Under the clinical diagnosis of PRCA with thymoma, a thoracotomy was performed in July 1992, and an unencapsulated tumor weighing about 40 g was removed from the anterior mediastinum. The tumor was histologically characteristic of thymoma of the lymphoepithelial type; it was predominantly composed of lymphoid cells with some epithelial elements (Fig. 1c). These findings confirmed the diagnosis of PRCA with thymoma developing in the course of the therapy for polymyositis.

The clinical course of the patient before and after thymectomy is shown in Fig. 2b. Despite the removal of thymoma, the patient continued to show an absence of reticulocytes. A repeat bone marrow study did not show any evidence of red cell precursors. Approximately six weeks post-thymectomy, immunosuppression with prednisolone (initially 60 mg daily) and cyclophosphamide (100 mg daily) was started, resulting in later remission of PRCA in October 1992.

Immunological findings

Immunohistochemical staining of a biopsy specimen from the right quadriceps muscle revealed that diffusely infiltrating lymphocytes were strongly positive for the T-lineage antigen UCHL-1 detected by the monoclonal antibody UCHL-1 (Fig. 1b) and that they were negative for the B-lineage antigen L-26 detected by the monoclonal antibody L-26. The resected thymoma was also immunohistochemically positive for UCHL-1 (Fig. 1d).

Lymphocyte surface marker studies by means of one- and two-color flow cytometry were performed on cells isolated from the patient's peripheral blood, bone marrow and thymoma (Table 3). The CD4/CD8 ratio was markedly reduced in the bone marrow. A striking increase was observed in a population of cytotoxic T lymphocytes bearing CD11⁻CD8⁺ antigens not only in the peripheral blood but also in the bone marrow and thymoma. Furthermore, numbers of activated suppressor/cytotoxic T lymphocytes bearing HLA-DR⁺CD8⁺ antigens were elevated in the peripheral blood and bone marrow. These immunological findings suggest that cytotoxic T cells might play an important role in the pathogenesis of this case.

Discussion

The association of PRCA with thymoma has been well documented (5). It has been estimated that approximately 50% of patients with PRCA have a thymic tumor. The association of polymyositis with thymoma has also been reported although it is relatively rare. There are 17 reported cases of polymyositis with thymoma in the literature (Table 4) (6-20). The association of polymyositis with PRCA is very unusual. To our knowledge, only one case has been reported (21). Therefore, this is an extremely rare case in which polymyositis, thymoma and PRCA were combined.

The close relationship between thymoma and myasthenia

Figure 1. Biopsy specimen from the right quadriceps muscle showed diffuse infiltration of lymphocytes and severe degenerative changes of muscle fibers (HE stain) (a). Immunostaining using monoclonal antibodies revealed the diffusely infiltrating lymphocytes to be strongly positive for UCHL-1 (b). An unencapsulated tumor, surgically removed from the anterior mediastinum, was histologically characteristic of thymoma of the lymphoepithelial type (HE stain) (c). Immunohistochemical staining showed infiltration of numerous UCHL-1-positive mature T lymphocytes (d) (a, c: $\times 100$, b, d: $\times 200$).

Figure 2. The clinical course of the patient after the onset of polymyositis. Remarkable clinical improvement followed administration of prednisolone at an initial dosage of 80 mg daily (a). The clinical course of the patient before and after the onset of pure red cell aplasia (b).

gravis, particularly in the presence of thymoma, has long been noted (6-20). It has been commented that some patients with

polymyositis might have myasthenic features and some patients with myasthenia gravis have histological lesions of polymyositis. Of 17 reported cases of polymyositis with thymoma listed in Table 4, 16 had concurrent myasthenia gravis. In the present case, there were no clinical symptoms or electromyographic evidence suggestive of myasthenia gravis, and muscle weakness was unresponsive to anticholinesterase agents. However, anti-acetylcholine receptor antibodies (ACh-R Ab) were detected at high titers. In accordance with the improvement of polymyositis, there is a gradual decrease in the titer of ACh-R Ab.

Polymyositis is generally accepted as being an autoimmune disorder. A cell-mediated immune reaction to muscle plays an important role in its pathogenesis. Similarly, it is suggested that PRCA may be caused by an immunological process, because of its frequent association with thymoma and successful responses to thymectomy and immunosuppressive agents (22). Several

Table 2. Laboratory Data after the Onset of PRCA

Peripheral Blood:		s-Erythropoietin:	390mM/ml*
RBC	2.59×10 ⁶ /μl	s-rG-CSF:	<30pg/ml**
Hemoglobin	7.2g/dl	anti-Erythropoietin Ab:	(-)
Hematocrit	22.6%	Bone Marrow:	
WBC	6,120/μl	Nucleated cell count	58,000/μl
Band	3.0%	Megakaryocytes	10/μl
Segment	40.0%	Erythroid	0%
Lymphocyte	53.0%	Myeloid	85.9%
Monocyte	4.0%	Lymphoid	10.3%
Platelet	175×10 ³ /μl		
Reticulocyte	0%		

*normal value 8-36, **normal value <30.

Table 3. Lymphocyte Surface Marker Studies Using Flow Cytometry after the Onset of PRCA (July 3, 1992)

Peripheral blood		Bone marrow		Thymoma	
CD3	91.7%	CD3	n.e.	CD4 ⁺ CD8 ⁺	33.0%
CD4	26.9%	CD4	5.9%	CD4 ⁺ CD8 ⁻	16.6%
CD8	55.0%	CD8	49.2%	CD4 ⁻ CD8 ⁺	37.4%
CD4/CD8	0.49	CD4/CD8	0.12	CD4/CD8	0.44
CD11 ⁻ CD8 ⁺	46.3%	CD11 ⁻ CD8 ⁺	42.2%	CD11 ⁻ CD8 ⁺	57.7%
CD8 ⁺ HLA-DR ⁺	6.7%	CD8 ⁺ HLA-DR ⁺	19.7%	CD8 ⁺ HLA-DR ⁺	0.98%

n.e.: not examined.

Table 4. Reported Cases of Polymyositis with Thymoma

Case	Author	Ref. no.	Year	Sex/Age	Complications	After thymectomy
1	Klein et al	(6)	1964	F/61	MG	No response
2				F/56	MG	No response
3	Souadjian et al	(7)	1969	F/65	MG	Remission
4	Canquet et al	(8)	1974	F/60	MG	(-)
5	Namba et al	(9)	1974	F/57	MG	(-)
6	Reznik et al	(10)	1974	F/37	MG	(-)
7				M/52	MG	(-)
8	Hopf et al	(11)	1977	F/44	MG	(-)
9				F/66	MG	(-)
10	Akatsuka et al	(12)	1977	M/33	MG	(-)
11	Ketz et al	(13)	1979	F/57	MG	No response
12	Weiller et al	(14)	1984	F/51	MG	Remission
13	Lane et al	(15)	1984	F/35	MG	Remission
14	Shimada et al	(17)	1989	F/37	MG	Remission
15	Marc'hadour et al	(18)	1989	F/67	Hashimoto thyroiditis	(-)
16	Funabashi et al	(19)	1989	M/37	SLE and MG	(-)
17	Boeckel et al	(20)	1990	M/22	MG	(-)
18	The present case		1992	F/53	PRCA	No response

MG: myasthenia gravis, (-): thymectomy was not performed.

authors have documented the existence of serum inhibitors to erythropoiesis, which were thought to be antibodies against erythropoietin or erythroblasts (23). Other reports have shown that inhibition of erythropoiesis can be caused by suppressor/cytotoxic T lymphocytes (24).

In the present case, immunohistochemical staining of the muscle and thymoma showed infiltration of numerous UCHL-1-positive mature T lymphocytes. Furthermore, lymphocyte surface marker studies revealed a striking increase in the population of cytotoxic T lymphocytes bearing CD11⁺CD8⁺ antigens in the patient's peripheral blood, bone marrow and thymoma. Antibody against erythropoietin was negative. Although we could not investigate the lymphocyte subsets in muscle, it is likely that massive infiltration of T lymphocytes, probably cytotoxic T lymphocytes, could be responsible for destruction of the muscle. These immunological findings strongly suggest that cytotoxic T cells might play a central role in the pathogenesis of this case.

It might be of interest to investigate the clonality of these proliferating T cells by means of TcR gene rearrangement analysis, but this was not possible in the present case. Although it is unlikely that clonal expansion of the unique TcR (TcR α/β) positive cytotoxic T lymphocytes is induced, these analyses may suggest that a common target molecule is involved in the pathogenesis of this interesting case.

The relationship between thymoma and associated disease is still unknown. Since removal of the thymoma does not affect the course of the disease in many instances, including the present case, it is unlikely that the thymoma itself produces the associated disease. There may be an autoimmune process causing a primary disturbance, which stimulates the thymic epithelium to undergo hyperplasia or neoplasia. An unknown immunological abnormality might cause the activation of cytotoxic T lymphocytes and lead to the onset of thymoma and polymyositis followed by PRCA.

References

- Good RA. Agammaglobulinemia: A provocative experiment of nature. *Bull Univ Minn Hosp Minn Med Found* **26**: 1, 1954.
- Clagett OT, Eaton LM. Thymic tumors in myasthenia gravis. *Surg Clin North Am* **23**: 1076, 1943.
- Souadjan JV, Enriquez P, Silverstein MN, Pepin JM. The spectrum of diseases with thymoma. *Arch Intern Med* **134**: 374, 1974.
- Hatakeyama S, Inui S. On a case of unusual triad: thymoma, giant-cell myocarditis and myasthenia gravis. *Bull Tokyo Med Dent Univ* **11**: 1, 1964.
- Jacobs EM, Hatter RVP, Pool JL, Ley AB. Benign thymoma and selective erythroid aplasia of the bone marrow. *Cancer* **12**: 47, 1959.
- Klein JJ, Gottlieb AJ, Mones RJ, Appel SH, Osserman KE. Thymoma and polymyositis. *Arch Intern Med* **113**: 142, 1964.
- Souadjan JV, Howell LP, Lambert EH. Thymoma with myopathy: Report of a case. *Minn Med* **52**: 595, 1969.
- Canquet R, Festal G, Deslignieres S, Pierres M, Lapresle J, Larouche C. Polymyosite a forme myasthenique, thymome, degeneration musculaire lisse. *Nouv Press Med* **3**: 743, 1974 (in French).
- Namba T, Brunner NG, Grob D. Idiopathic giant cell polymyositis. *Arch Neurol* **31**: 27, 1974.
- Reznik M. Deux cas de syndrome myasthenique avec thymome polymyosite myocardite et thyroidite. *J Neurol Sci* **22**: 341, 1974 (in French).
- Hopf HC, Thorwith V. Myasthenia-myositis-myopathy. in: *Myasthenia Gravis und Andere Storungen der Neuromuskularen Synapse*. Hertel von G, Martens HG, Ficker K, Schimrigle K, Eds. Thieme, Stuttgart, 1977, p.142.
- Akatsuka S, Torigata C. An autopsy case of malignant thymoma with polymyositis. *Nihon Rinsho* **35**: 212, 1977 (in Japanese).
- Ketz E, Fopp M, Weissert M, Bekier A. Polymyositis, myasthenic syndrome and thymoma in a patient with defective cell-mediated immunity. *Acta Neurol Belg* **79**: 469, 1979.
- Weiller PJ, Durand JM, Prince-Zucchelli MA, et al. L'association polymyosite, myasthenie, thymome. *Ann Med Interne* **135**: 299, 1984 (in French).
- Lane RJM, Hudgson P. Thymectomy in polymyositis. *Lancet* **626**: 1984.
- Sakuma H, Yoshida H, Kasukawa R, Satoh N, Yoshino K. An autopsy case with Good's syndrome and dermatomyositis. *Clin Rheumatol* **4**: 196, 1985.
- Shimada K, Koh CS, Tsukada N, Shoji S, Yanagisawa N. Detection of immune complexes in the sera and around the muscle fibers in a case with myasthenia gravis and polymyositis. *Clin Neurol* **29**: 432, 1989 (in Japanese).
- Marc'hadour FL, Ramos JM, Pasquier B, Pasquier D, Couderc P. Association d'un carcinome thymique, d'une thyroidite de Hashimoto et d'une polymyosite. *Ann Pathol* **9**: 355, 1989 (in French).
- Funabashi H, Igari Y, Kuroda M, et al. An autopsy case of a patient with myasthenia gravis who showed various symptoms of collagen diseases and complicated with malignant thymoma. *Rheumatology* **29**: 185, 1989.
- Boekel VV, Godoy JM, Menezes JMT. Associacao rara: polimiosite, miastenia grave e timoma. *Arq Neuro-Psiquiat (Sao Paulo)* **48**: 505, 1990 (in Spanish).
- Sanchez JAC, Fernandez JLD, Jesus RL. Aplasia pura de celulas rojas asociada a un cuadro de polimiositis. *Revista Clinica Española* **159**: 221, 1980 (in Spanish).
- Totterman TH, Nisell J, Killander A, Gahrton G, Lonnqvist B. Successful treatment of pure red-cell aplasia with cyclosporin. *Lancet* **693**: 1984.
- Marmont A, Peschle C, Sanguineti M, Condorelli M. Pure red cell aplasia (PRCA): response of three patients to cyclophosphamide and/or antilymphocyte globulin (ALG) and demonstration of two types of serum IgG inhibitors to erythropoiesis. *Blood* **45**: 247, 1975.
- Litwin SD, Zanjani ED. Lymphocytes suppressing both immunoglobulin production and erythroid differentiation in hypogammaglobulinemia. *Nature* **266**: 57, 1977.