ITP, Early Presentation of Thymoma

Abbasi[1] M., Karimi[2] B.
[1]Department of internal medicine, school of medicine, Hamadan university of medical sciences & Health services, Hamadan Iran.
[2]Medical student, school of medicine, Hamadan university of medical sciences & health services, Hamadan, Iran.
Department of Internal medicine , School of Medicine, Hamadan university of Medical Sciences & Health Services, Hamadan, Iran.

Abstract
Mediastinal neoplasms are uncommon tumors that can occur at any age but are most common through the fifth decades of life.
A wide variety of systemic disorders are associated with 71% of thymomas. The symptoms of these associated disorders often lead to the original discovery of the mediastinal tumor.
A 35-year-old female with petechia and purpura was admitted to Sina hospital of the city of Hamadan in 5/6/2000. the serum platelet count was 4000/microliter. After the primary evaluations Idiopathic Thrombocytopenic Purpura (ITP) was diagnosed and after corticosteroid therapy serum platelet count increased. After 2 month she was admitted to the neurology ward of our hospital with diagnosis of cerebro vascular accident (CVA). In brain computed tomography (CT) scan a hyperdense lesion was reported that reveald hemorrhage in the temporoparietal region. The platelet count was 154000/microliter at this time which suggests the idea that some suppressive antibodies in the serum might lead to platelet disfunction. Two years later she was admitted to Shariati hospital with fatigue, left lid ptosis, speech disorder, bifacial weakness, diplopia and muscle force = 4/5. Myasthenia gravis was diagnosed and in the chest CT scan a density associated with thymus was reported. Thymectomy was performed for the patient and report of the pathologist was thymoma. After adjuvant radiotherapy serum platelet count increased and myasthenia gravis was improved and all of the patient's signs and symptoms resolved.
ITP must be considered as one of the paraneoplastic symptoms of thymoma.

Keywords: Thymoma/purpura, Thrombocytopenic, Idiopathic/Paraneoplastic syndromes

Introduction
Mediastinal neoplasms are uncommon tumors that can occur at any age but are most common through the fifth decades of life.[1, 4]
A wide variety systemic disorders are associated with 71% of thymomas. The symptoms of these associated disorders often lead to the original discovery of the mediastinal tumor. Autoimmune diseases such as Myasthenia gravis, Systemic lupus erythematosus, Polymyositis, Sjogren's syndrome, Myocarditis, Ulcerative colitis, Hashimoto's thyroiditis, Rheumatoid arthritis, Sarcoidosis and Scleroderma and Endocrine disorders such as Hyperthyroidism, Hyperparathyroidism, Addison's disease and Panhypopituitarism are most common.[5, 6]
Blood disorders such as Red cell aplasia, Hypogammaglobulinemia, T-cell deficiency syndrome, Erythrocytosis, Pancytopenia, Megakaryocytopenia, T-cell lymphocytosis and Pernicious anemia also have been noted.[7]
Thrombocytopenia is caused by one of three mechanisms: decreased bone marrow production, increased splenic sequestration or accelerated destruction of platelets. The most common causes of immunologic thrombocytopenia are viral or bacterial infections, drugs and a chronic autoimmune disorder referred to as idiopathic thrombocytopenic purpura (ITP).Patients with immunologic thrombocytopenia do not usually have splenomegaly and have an increased number of bone marrow megakaryocytes.[8]
In this article we report a 35-year-old woman that was admitted to our hospital with petechia and purpura how was followed for four years.

Patient presentation
A 35-year-old woman was admitted to the internal medicine ward of Sina hospital in Hamadan with petechia and purpura on 5/6/2000.
Some laboratory tests that were done for the patient are as follow:
WBC= 5100, ESR= 13, Bil. Direct= 0.21 mg/dl, Hb= 15 mg/dl, PT= 14, Bil. Total= 0.64 mg/dl, Hct= 45 ,PTT= 35 , SGOT= 27, Platelet= 4000/microliter, CRP= Negative, SGPT= 27
Bone marrow biopsy report is:

Cellularity= 55% and myeloid to erithroid ratio is 2:1 and erythroid is active and normoblasts have increased and hemoglobin in their cytoplasm has decreased. Myeloid is active and eosinophils have increased and megaloblastic changes in neutrophils is observed. Plasma cells are 2% and megakaryocyte production is hyperactive and there is no malignant change in bone marrow.

Abdomen and pelvic ultrasound was done and there was no problem in their report, so she was regarded suffering from ITP.

Corticosteroid was recommended for the patient and serum platelet count increased to 507000/microliter. Then the patient was discharged with good condition.

Two months later the patient came back while complaints or having a headache in the left part of the head also vertigo, vomiting and memory disorder.

Vital signs were:

Blood Pressure= 105 / 60 mmHg (supine in right hand) Pulse Rate= 84/minute

Respiratory Rate= 20/minute, Tempreature = 37.7 ºC, GCS=15/15

In brain computed tomography (CT) scan a hyperdense legion was distinguished in the left temporoparietal region which reveald hemorrhage in the brain. Serum platelet count was 154000/microliter at this time. The Patient was discharged after one week in a good condition.

Two years later she was admitted to Shariati hospital in Tehran with these signs and symptoms: fatigue, left lid ptosis, speech disorder, bifacial weakness, horizontal diplopia, normal pupil size and normal fondoscopy and force of neck flexors and lower and upper limb muscle were 4/5. Babinski's sign was downward and Tensilon test was positive.

Myasthenia gravis was diagnosed for the patient and Mestinon 60mg Q6h was recommended to her.

Some laboratory tests that were done for the patient at this time are below:

Plt= 242000/microliter	**ESR= 15**	**LDH= 305**
WBC= 9200	**FBS= 101**	**CPK= 40**
Hb=15 mg/dl	**BUN= 12 RA factor= (-)**	
Hct= 44.8	**Cr= 0.7**	**ANA= (-)**
MCV= 44.8	**SGOT= 13**	**T_4= 7.8**
SGPT= 11	**T_3= 123**	**TSH= 0.6**

In thorax computed tomograpgy scan a density associated with thymus was seen and thymectomy was performed. Pathological findings showed: thymoma, predominantly epithelial cells with foci of invasion to perithymic fat and right pleura.

Anterior and posterior radiotherapy with Cobalt and with appropriate margine in 23 courses were done for the patient and the amount of radiation was 4600 rad.

After this treatment, serum platelet count was normal and myasthenia gravis was improved and all of patient's signs and symptoms were resolved and now she is in a good condition.

Disscussion

Myasthenia gravis is the most common autoimmune disorder, occurring in 30% to 50% of patients with thymomas. Younger women and older men are usually affected, with a female to male ratio of 2:1. Symptoms begin insidiously and result from the production of antibodies to the postsynaptic nicotinic acetylcholine receptor at the myoneural junction. Occular symptoms are the most frequent initial complaint, eventually progressing to generalized weakness in 80 %. The rule of the thymus in myasthenia remains unclear, but autosensitization of T-lymphocytes to acetylcholine receptor proteins or an unknown action of thymic hormones remain possibilities. Pathologic changes in the thymus are noted in approximately 70 % of patients with myasthenia gravis. Thymomas are identified in only about 15 % of patients with myasthenia gravis. [9, 10]

Pure red cell aplasia is considered an autoimmune disorder and is found in approximately 5 % of patients with thymomas, Of the patients with red cell aplasia, 30% to 50% have associated thymomas. 96% of the patients affected are older than 40 years of age. Examination of the bone marrow reveals an absence of erythroid precursors and in 30% an associated decrease in platelet and leukocyte number. But pure thrombocytopenia isn't noted. Thymectomy has produced remission in 38% of patients. The pathologic basis of these responses are poorly understood.[7, 11]

In this reported patient, platelet number increased after corticosteroid therapy but hemorrhagic CVA occurred during the illness that can suggest suppressive autoantibodies in the serum produced during the process of disease might disturb platelet function. Thymectomy had a good effect on platelet count and after adjuvant radiotherapy myasthenia gravis was improved and all of the patient's signs and symptoms resolved.

Kabayashi and his colleagues have reported a 64-year-old woman who developed aplastic anemia and idiopathic thrombocytopenic purpura with antibody to platelet glycoprotein IIb/III a 4 years following a resection of malignant thymoma. The life span of platelets was markedly decreased to 3.07 h and the test for antiplatelet glycoprotein IIb/III a antibody was positive. He believes that apastic anemia in this patient may have been induced by some suppressive activity in the serum. Splenectomy followed by an administration of cyclosporine effectively restored peripheral blood count.[11]

Matsuge has reported a 62-year-old female with chest and right shoulder pain. The chest computed tomography showed a large anterior mediastinum mass with pleural effusion and thymoma was suspected by percutaneus aspiration biopsy. Serum platelet count was 7.0×10^4/microliter. After evaluations, they diagnosed ITP for the patient. After giving her intravenous high dose gammaglobulin, her platelet count increased to normal. Pathological findings showed hematoma in the thymus and a small thymoma. After the operation, her platelet count has not been changed to normal but remained at a lower level. He believes though myasthenia gravis improved after total thymectomy, but ITP coud not improve. [12]

Otto believes that most important prognostic determinations of the thymomas are the gross findings at operation (equal to the presence or absence of gross invasion of adjacent tissue) and the presence or absence of the thymoma-associated systemic disease particulary myasthenia gravis. 40.3 percent of patients he has reported have had a thymoma associated systemic disease. The most common presenting symptoms were related to myasthenia gravis (26.3 %). The 5 year survival rate was 90 percent for non-invasive thymomas without myasthenia gravis and 50 percent for invasive thymomas. The 5 year survival rate for patients with myasthenia gravis and encapsulated (non-invasive) thymomas was approximately 60 percent whereas that for invasive thymomas with myasthenia gravis was 40 percent. He suggests that the primary form of therapy for all thymomas is the surgical exicision. In a case with invasive and/or metastasing thymomas post operative radiation and adjuvanted chemotherapy is indicated but in most series the longterm results of this form of therapy are discouraging. [13]

Piccoto has described a patient who developed generalized autoimmune myasthenia gravis six years after the spontaneous remission of a Stiffman syndrome. He also suffered from chronic active hepatitis and had radiological evidence of a thymoma. Anti-nicotinic acetylcholine receptor antibodies, anti-nuclear, anti-DNA, anti-mitochondrial and anti-skeletal muscle antibodies were found in his serum. Piccoto believes a relationship between thymoma and the neurological syndromes could be considered. [14]

Eralp has surveyed the therapeutic outcome and prognostic factors in 36 patients with respectable thymoma. The median age was 45 years (ranging from 19 to 72 years). Myasthenia gravis was observed in 28 patients (77.7%). The most frequent histologic subtype was epithelial (n=21, 58.3%), followed by the lymphocytic type (n=6, 16.7%). The majority of the patients (n=32, 88.9%) had completely respectable disease, wherease 2 patients had microscopic and 2 more patients had macroscopic residual disease after surgery. After a median follow up period of 39 months, 5 patients (16.1%) experienced recurrence. The results of this study suggest that adjuvant radiotherapy may provide survival benefits in patients with respectable thymoma, regardless of surgical margins.[15, 16]

References:

1- Davis RD, Oldham HN, Sabiston DC. Primary cysts and neoplasms of the mediastinum: recent changes in clinical presentation, methods of diagnosis, mamagement and results. Ann Thorac Surg 1987; 44: 229.

2- Cohen AJ, Thompson L, Edwards FH, Bellamy RF. Primary cysts and tumors of the mediastinum. Ann Thorac Surg 1991; 51: 378.

3- Azarow KS, Pearl RH, Zurcher R, Edwards FH, Cohen AJ. Primary mediastinal masses: a comparison of adult and pediatric populations. J Thorac Cardiovasc Surg 1993; 106: 67.

4- Mullen B, Richardson JD. Primary anterior mediastinal tumors in children and adults. Ann Thorac Surg 1986; 42: 338.

5- Souadjian JV, Enriquez P, Silverstein MN, et al. The spectrum of diseases associated with thymoma. Arch Intern Med 1974; 134: 374.

6- Marchevsky AM, Kaneko M. Surgical pathology of the mediastinum. New York: Raven press, 1984: 58.

7- Masaoka A, Hashimoto T, Shibata K, Yamakowa Y, Nakamae K. Thymomas associated with pure red cell aplasia: histology and follow up studies. Cancer 1989; 64: 1872.
8- Robert I. Handin, Disorders of hemostasis in: Braunwald E, Fauci A, Kasper D, Hauser S, Longo D, Jameson J, editors: Harrison's principles of internal medicine. 15 th ed. NewYork: Mcgraw-Hill; 2001: 745– 62.
9- Berrich-Akin S, Morel E, Raimond F, et al. The role of the thymus in myasthenia gravis: immunohistological and immunological studies in 115 cases. Ann N Y Acad Sci 1987; 505: 51.
10- Palmisani MT, Evoli A, Batocchi AP, Provenzano C, Torali P. Myasthenia gravis associated with thymoma: Clinical Characteristics and long term outcome. Eur Neurol 1993; 34: 78.
11- Kobayashi H, Kitano K, Ishida F, et al. Aplastic anemia and idiopathic thrombocytopenia purpura with antibody to platelet glycoprotein IIb/III a following resection of malignant thymoma. Acta Haematol. 1993; 90(1): 42-5.
12- Matsuge S, Hosokawa Y, Murakami Y, Satoh K. Thymoma with idiopathic thrombocytopenic purpura preceded by mediastinal hemorrhage; report of a case. Kyobu Geka. 2002 sep; 55(10): 899-902.
13- Otto HF. A comparative clinical and pathological study on the classification and prognostic features of 57 thymomas. II. prognostic features. Z Krebsforsch Klim Onkol Cancer Res Clin oncol. 1978 Jan 26; 91(1): 103–15.
14- Piccolo G, Martino G, Moglia A, Arrigo A, Cosi V. Autoimmune myasthenia gravis with thymoma following the spontaneous of Stiff– man syndrome. Ital J Weurol Sci. 1990 Apr; 11(2): 177– 80.
15- Eralp Y, Aydiner A, Kizir A, et al. Resectable thymoma: treatment outcome and prognostic factors in the late adolescent and adult age group. Cancer invest. 2003; 21(5): 735 43.
16- Haniuda M, Marimoto M, Nishimura H, et al. Adjuvant radiotherapy after complete resection of thymoma. Ann Thorac Surg 1992; 54: 311.
17- Gattenlohner S, Brabletz T, Schultz A, et al. Cloning of a c DNA coding for the acetylcholine receptor alpha–subunit from a thymoma associated with myasthenia gravis. Thymus 1994; 23 (2): 103– 13.
18- Schergna E, Bracco F. Prognosis of myasthenia gravis. Riv Pathol Nerv Ment. 1976 Jun; 97 (3): 160– 9.
19- Fagiolo E, Terenzi CT. Enhanced IL-10 production in vitro by monocytes in autoimmune haemolytic anemia. Immunol invest 1999 Sep– Dec; 28 (5– 6): 347– 52.