Myasthenia Gravis in a Patient with Chronic Myeloid Leukemia Treated by Busulfan

By Meir Djaldetti, Jack Pinkhas, Andre de Vries, Edna Kott, Henry Joshua and Leah Dollberg

The alkylating agent busulfan used widely in the treatment of chronic myeloid leukemia may cause side effects of peculiar nature, such as Addison-like syndrome1,4 and interstitial pulmonary fibrosis.5,6 We recently observed a patient with chronic myeloid leukemia who subsequent to busulfan treatment developed myasthenia gravis.

Case Report

P.M., a seventy year old Polish-born male clerk, was referred to the Hematology Clinic in September 1963. Examination in another medical service in 1961 had revealed moderate hepatosplenomegaly, a platelet count of 900,000 per cu.mm. with normal red and white blood cell counts, and megakaryocytic hyperplasia in bone marrow with excessive platelet production and hyperplasia of the white cell series with a shift to the left but without blast cells. The diagnosis of primary thrombocythemia was made, and the possibility of transformation to myeloid leukemia was raised, but no specific treatment was prescribed.

Examination in our clinic in 1963 revealed hepatosplenomegaly, the spleen being palpated 6 cm. and the liver 2 cm. below the costal margin, both firm and nontender. Several enlarged nontender lymph glands of diameter up to 2 cm. were palpated in the neck and the axillae. The hemoglobin was 12.6 Gm. per cent, RBC 4,000,000 per cu.mm., hematocrit 40 per cent, reticulocyte count 0.1 per cent, and WBC 10,000 per cu.mm. with polymorphonuclei65 per cent, band forms 4 per cent, eosinophils 4 per cent, blast cells 3 per cent, lymphocytes 24 per cent. The platelet count was 1,000,000 per cu.mm., bleeding time 6 min., clotting time 5 min., clot retraction normal, ESR (Westergren) 13 mm. in the first hour and 20 mm. in the second. The serum B12 level was 1250 mcg per ml., urea 42 mg. per cent, uric acid 6.5 mg. per cent. LE cells were not found. A sternal bone marrow biopsy smear was similar to the examination in 1961, except for the presence of a few blast cells. Leukocyte alkaline phosphatase staining showed a zero score. The clinical and hematologic findings were considered consistent with chronic myeloid leukemia. The patient refused treatment. In September 1964, his hemoglobin was 12.6 Gm. per cent, WBC 16,500 per cu.mm., with a normal differential count. The platelet count was 300,000 per cu.mm. The spleen, liver, and lymph glands were essentially unchanged since the previous examination.
Tomographic examination of the mediastinum repeated on December 5 showed a soft shadow 4 mm. Myasthenia gravis for a period of 3 to 5 months became more impaired, and marked cyanosis appeared. Exploration of the mediastinum revealed a mass of fatty tissue, measuring 3 by 6 cm., in the thymus region. Histologic examination of the excirpated mass revealed fatty tissue with involuted thymic remnants, consisting of a few islands of epithelial cells, round thymocytes, and an occasional Hassal body. No signs of thymic hyperplasia were seen. This picture of thymic rests did not differ from that found in normal subjects of this age. Two weeks after surgery, the patient experienced gradual improvement of his muscle weakness and the drug dosage could be gradually reduced.

In July 1965, while still on busulfan treatment, the patient felt increasing weakness. The liver and spleen were not palpable and no enlarged lymphnodes were found. Blood examination showed hemoglobin 12.3 Gm. per cent, WBC 5,700 per cu.mm. with a normal differential count and a platelet count of 71,000 per cu.mm. Busulfan was discontinued, during the 9 months period of treatment a total dose of 540 mg. having been administered. In the next month, his weakness became more pronounced, and in September 1965, i.e., two months after discontinuation of busulfan treatment, he experienced diplopia and severe muscular weakness of the limbs. Within a few days the weakness became extreme, and he was unable to perform even the slightest limb movement. At the same time, he had difficulty with mastication and closure of the mouth, and respiratory movement became impaired. He was hospitalized in poor general condition and showing marked weight loss. No pigmentation of skin or mucosa was found. The liver was palpated 1 cm. below the costal margin; the spleen was not felt and no enlargement of lymph glands was noted. The respiration was shallow and there was bilateral ptosis and poor function of the orbicularis oculi muscles. The eyelids could be easily retracted. The rectilateral muscles were paralyzed. Motor weakness of the limbs, more pronounced on the right side and more obvious in the proximal parts of the limbs, was noted. Repeated exercise of the limbs led to marked muscular fatigue. The patient was unable to change from prone to recumbent position. The tendon reflexes were brisk. A Tensilon test was positive after intravenous injection of 10 mg. Tensilon, the diplopia, and the weakness of the ocular and limb muscles disappeared for a period of 3 to 4 min. Myasthenia gravis was diagnosed.

Laboratory examinations showed hemoglobin 11.1 Gm. per cent, RBC 3,700,000 per cu.mm., WBC 9,200 per cu.mm., with polymorphonuclear neutrophils 64 per cent, band forms 5 per cent, eosinophils 5 per cent, lymphocytes 22 per cent, monocytes 4 per cent. The platelet count was 20,000 per cu.mm. A sternal bone marrow aspiration biopsy showed moderate granulocytic hyperplasia with a shift to the left but no blasts. The megakaryocytic and red cell series were slightly hypoplastic. The leukocyte alkaline phosphatase showed a subnormal score—24. Routine liver function tests, blood urea and electrolytes, and excretion of 17-ketosteroids and 17-hydroxysteroids in the urine were normal. Total serum protein was 5.9 Gm. per cent of which albumin was 3.2 Gm. per cent. The paper-electrophoretic pattern indicated a slight decrease of gamma globulin and a slight increase of alpha-2-globulin. A Sia test and search for LE cells were negative. Using the indirect staining method in which antihuman globulin rabbit serum conjugated with fluorescein-thiocyanate was incubated with human rectus abdominis muscle and with human thymic tissue pretreated with patient’s serum, no antimuscle or antithymus antibodies were demonstrated. Serum aldolase and creatine phosphokinase were normal, before and after exercise. Anteroposterior x-ray of the chest was normal, but tomographic examination of the mediastinum revealed a soft shadow, 4 by 5 cm., localized in the thymus area.

Treatment with Prostigmin 60 mg. per day, Mestinon 240 mg. per day, and atropine 1.5 mg. per day was started. The muscle weakness, however, did not improve. X-ray irradiation over the thymus area was started on November 11, 1965, and a total of 1000 r was given in 5 sessions. Again, no improvement in the muscle weakness was achieved. Tomographic examination of the mediastinum repeated on December 5 showed the shadow in the thymic area to have disappeared. During the next few weeks, the patient’s condition deteriorated, he became unable to move and speak, swallowing became difficult, breathing became more impaired, and marked cyanosis appeared. Exploration of the mediastinum through vertical sternotomy, performed on December 20, 1965, revealed a mass of fatty tissue appearance, measuring 3 by 6 cm., in the thymus region. Histologic examination of the excirpated mass revealed fatty tissue with involuted thymic remnants, consisting of a few islands of epithelial cells, round thymocytes, and an occasional Hassal body. No signs of thymic hyperplasia were seen. This picture of thymic rests did not differ from that found in normal subjects of this age. Two weeks after surgery, the patient experienced gradual improvement of his muscle weakness and the drug dosage could be gradually reduced.

Patient now agreed to treatment, and busulfan, 4 mg. per day, was started, with a subsequent dose of 2 mg. per day.

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reduced. Two months after surgery the patient was discharged in a fair condition, while on small doses of Prostigmin and Mestinon.

Follow-up examination in the clinic revealed that the diplopia had disappeared within five months after operation. Patient then experienced only rare episodes of slight weakness. In June 1967, he felt fairly well, moved around easily, was able to talk freely and without fatigue, and had returned to work as a clerk. He still took daily 15 mg. of Prostigmin, not daring to stop taking the drug, although he did not experience muscle or general weakness. Physical examination was normal. Blood examination at that time showed hemoglobin 14.0 Gm. per cent, RBC 5,000,000 per cu.mm., WBC 6,800 per cu.mm. with a normal differential count, and a platelet count of 61,000 per cu.mm. The leukocyte alkaline phosphatase score was 30, the serum B12 level 550 uug. per ml. A sternal aspiration biopsy smear was normal. The chromosome pattern of the peripheral and bone marrow leukocytes was normal. It was judged that the patient was in remission from his leukemia, as well as from the myasthenia.

COMMENTS

The diagnosis of chronic myeloid leukemia in this patient appears well established on the basis of the findings of lymph gland enlargement and hepatosplenomegaly, leukocytosis, presence of blast cells in the peripheral blood and bone marrow, thrombocytosis, low leukocyte alkaline phosphatase score, and elevated serum B12 level.

The unusual feature of the course of patient’s disease was the appearance of severe muscular weakness, clinically characteristic for myasthenia gravis, with involvement of ocular, limb, respiratory, masticatory, and pharyngeal muscles, and a positive response to Tensilon. The patient’s muscular condition could be clearly differentiated from two other disorders in which excessive weakness is a prominent feature: the Addisonian-like syndrome associated with busulfan treatment, and a myasthenic reaction complicating malignant disease, as seen in the Eaton-Lambert syndrome.

The Addisonian-like syndrome developing consequent to busulfan therapy is characterized by generalized pronounced weakness, pigmentation, anorexia, and weight loss, with absence of laboratory or biochemical evidence of adrenal insufficiency. This complication of busulfan treatment appears usually after prolonged periods of administration and high total dosage, varying in the reported cases from 820 to 5,710 mg. In our patient, who received a total of 540 mg. of busulfan during a period of nine months, the prominent feature was not general weakness but specifically muscle weakness; moreover, he had no pigmentation and no anorexia, his weight loss being rather explained by insufficient food intake due to the difficulty in mastication. A myasthenic reaction complicating malignant disease appeared improbable in our patient in view of the aggravation of his muscle fatigue following repeated exercise, the brisk tendon reflexes, and the positive Tensilon test.

Consistent with myasthenia gravis in this patient was the enlarged thymus, the irradiation and subsequent removal of which was followed by remission of his muscular condition. Histologically, the removed mass showed only involuted thymic remnants. The establishment of the exact nature of the thymic enlargement was rendered difficult by the preoperative irradiation. A malignant thymoma appeared improbable since these tumors generally are not destroyed by the radiation dosage applied in this patient. Leukemic infiltration
of the thymus seemed improbable in view of the presence of the retrosternal mass at the time of clinical and hematologic remission, and the complete absence of leukemic cells on histologic examination. Thymic hyperplasia, responding to irradiation, appeared the most reasonable assumption.

Three possibilities may be considered in the etiology of the myasthenia gravis in this patient with chronic myeloid leukemia: independent disorder, sequel to the leukemia, or reaction to busulfan treatment. While an independent disorder cannot be excluded, the other two etiologic possibilities deserve comment.

The coincidence of myasthenia gravis and disorders of hematopoietic system is known. The association of pernicious anemia and myasthenia gravis has been reported by Simpson and by Howard et al., who observed this combination in four and eleven patients, respectively. In only one of the patients reported by the latter authors was a thymoma found. Although autoantibodies are found in both pernicious anemia and myasthenia gravis, mainly against gastric parietal cells and intrinsic factor in the former and against muscle and thymic tissue in the latter, and gastric antibodies have been found in some patients with myasthenia gravis, their significance in the etiology of the combined syndromes has not been finally established. The combination of benign thymoma, hypoplastic anemia, and myasthenia gravis has been described in a few patients. Interestingly, in one of these, monocytic leukemia developed after thymectomy. To our knowledge, however, the development of myasthenia gravis in the course of chronic myeloid leukemia, as observed in our patient, has not been mentioned in the literature.

Finally, the development of myasthenia gravis as a reaction to busulfan therapy, possibly through the intermediary of an autoimmune reaction, must be considered. An autoimmune mechanism has been implicated in the causation of interstitial pulmonary fibrosis following busulfan administration by Oliver et al. and Leak et al. In analogy to the negative results of the search for antibodies in a considerable percentage of cases of myasthenia gravis, the lack of finding of antimuscle and of antithymus antibodies in our patient does not preclude the assumption of an autoimmune process in the explanation of his muscle syndrome. Whether busulfan may have engendered an autoimmune reaction by affecting primarily the thymus or the muscles, or both, remains speculative.

Summary

Myasthenia gravis and roentgenologic evidence of a mass in the anterior mediastinum appeared in a patient with chronic myeloid leukemia following busulfan treatment.

X-ray irradiation of the thymic area and subsequent surgical removal of the anterior mediastinal mass were followed by remission from the myasthenia gravis. Histologic examination of the mass showed involuted thymic remnants without evidence of leukemic infiltration or of malignant thymoma.

The possible etiology of the myasthenia gravis in this patient, with special reference to a busulfan-induced autoimmune process, is discussed.
SUMMARIO IN INTERLINGUA

Myasthenia grave e evidentia roentgenologic de un massa in le mediastino anterior appareva in un patiente con chronic leucemia myeloide post tractamento a busulfano.

Irradiation a radios X del area thyrnic e le subsequente excision chirurgic del massa antero-mediastinal esseva sequite de remission del myasthenia grave. Le examine histologic del massa monstrava involutionate residuos de thymo sin evidentia de infiltration leucemic o de thymoma maligne.

Es commentate le possibile etiologia del myasthenia grave in iste patiente, con referentia particular al processo autoimmun inducite per busulfano.

REFERENCES


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