A CASE OF LATE ONSET GAUCHER DISEASE WITH SEVERE PULMONARY INVOLVEMENT AND CONCURRENT TUBERCULOSIS

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SUMMARY: Gaucher Disease is the most common of the storage diseases characterized by deficiency of the enzyme glucocerebrosidase and thus accumulation of glucocerebroside in lysosomal macrophages resulting in multiple organomegalies and functional abnormalities. The absence of the enzyme or its cofactors is a genetically inherited (autosomal recessive) abnormality and multiple mutations are being discovered recently. The disease manifests itself in 3 distinct clinical forms with different prognosis. Diagnosis is best made by detection of B-glucosidase activity in leucocytes but usually it is done by recognition of typical Gaucher cells in the bone marrow microscopically. Many organ systems are reported to be involved in Gaucher disease. Though pulmonary involvement is rarely encountered, it reflects a poor prognosis resulting in death in many of the patients. We describe a case of Gaucher disease of late onset with outstanding pulmonary symptoms causing death in a short period of time. An interesting feature of this case was the coexistence of tuberculosis, discovered at the postmortem examination involving multiple tissues. This coexistence was not only rare but it was also conflicting with the reports underlining the genetic resistance of Gaucher patients against tuberculosis. Thus one must consider coexisting diseases together with Gaucher's disease when pulmonary involvement is concerned.

Key Words: Gaucher disease, tuberculosis.

INTRODUCTION

Gaucher disease is a lysosomal storage disorder first described by Gaucher in 1882 (1). The disease is an uncommon one, especially severe forms are rarely seen while milder forms are relatively common especially in Ashkenazi Jewish population (2). The disease has three forms differing in clinical course and type of organ involvement. Type 1 the relatively benign adult form which is sometimes even coincidentally recognized, goes without neurological involvement. Type 2 is the infantile form having a malignant course with neurological involvement, death usually occurring before the age of 2. Type 3, the juvenile form which has a later onset of neurological involvement and a longer course than type 2 (3).

The underlying pathology is deficiency of the enzyme glucocerocidase (glucosylceramidase) which is necessary for the lysosomal degradation of glycolipids (2, 4). The result is the accumulation of insoluble glucocerebroside in lysosomes of macrophages thus giving rise to organ enlargements recognized clinically. The deficiency is some times not in the enzyme itself but in cofactors that are required for the catalytic function of glucocerebrosidase (2).

From the genetic point of view, the disease is inher-

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ited autosomally recessive. The gene for glucocerebrosidase is located on chromosome 1 in the region q21. There is also a pseudogene 95% homologous to the functional gene which is transcribed but not translated into glucocerebrosidase because of deletion (2). A number of mutations cause the disease and patients have different clinical features. A mutation at cDNA nucleotide 1226 is largely responsible especially in Jewish population. Another common mutation is a nucleotide insertion at cDNA 84. The fact that there are sometimes discordances between genotypes and clinical symptoms reflects that there are still some factors affecting the severity of the disease that we do not know.

Clinically the disease manifests itself by multiple organ enlargements and neurological symptoms (2-6). Bone marrow involvement is frequently encountered resulting in anemia or thrombocytopenia. Diagnosis of the disease is usually made by microscopic examination of the bone marrow. The detection of leucocyte acid B-glucosidase activity is a precise method but it is not yet routinely used at every center (2, 7). Polymerase chain reaction is also helpful in detecting mutations at 84, 1226 and 1448 and thus, also in genetic counseling of the disease (4). Rises of serum acid phosphates and angiotensin converting enzyme levels are supporting findings (2, 8, 9).

Other than symptomatic measures like splenectomy, splenic embolization real therapy consists of replacement of the enzyme glucocerebridase (2, 5,10). Allogeneic bone marrow transplantation is still not settled because of known risks (2,10). Future goal is gene transfer therapy (2).

The case that we would like to present is a late onset Gaucher disease without neurological symptoms with features like hepato-splenomegaly and bone marrow involvement and severe pulmonary involvement resulting in death in a short period of time. A very striking feature was the postmortem detection of tuberculosis (Tb) in spleen and liver tissues together with Gaucher cells. Patients with Gaucher disease is believed to have a special resistance to Tb, though this concept was proposed for Ashkenazi Jews (11). When we reviewed the literature although we found some reports about pulmonary involvement which is known to be quite rare in the adult form (2, 3,12), we did not notice any report about Gaucher disease and tuberculosis.

CASE REPORT

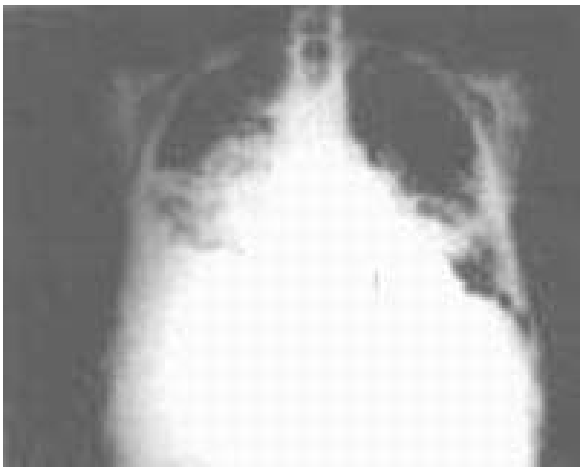
A 47 year old woman was admitted to the Çukurova University Oncology department with complaints of fatigue and dyspnea. The history revealed episodes of epistaxis repeating almost every 10 days for the last 2 years. The patient also complained about low blood pressure and dizziness for the last year. During the last two months she had increasing abdominal pain for which she consulted a physician who told her that her spleen was enlarged. She had lost 20 kg of weight during the preceding year. One month before admission, dyspnea on exertion and cough productive of white sputum especially on supine position started.

Her family history revealed hypertension and cerebrovascular disease in old age, and she had 4 children.

Physical examination disclosed a cachectic, pale woman weighing 38 kg 1.55 m tall. Her pulse rate was 120/min, respiratory rate 35/min and fever 37.5°C. There was no lymphadenopathy. Pleural fraction rub was heard bilaterally, rales were prominent at the end of inspiration especially at the bases. Heart sounds were normal and rhythmic. Liver was palpated 10 cm below the right costal margin with a total dullness of 20 cm, the spleen was extending the left costal margin 20 cm reaching the right inguinal region. No neurological deficit was detected.

Laboratory tests revealed a hematocrit 15.2%, leucocytes ranging between 1.400 and 3.700/mm^3, platelet count was between 60.000 and 100.000/mm^3. The erythrocyte sedimentation rate was 150/mm/hr. In the peripheral blood smear, basophilic stippling, anisocytosis, poikilocytosis and tear drop erythrocytes were noticed. Bun was 70 mg/dl, creatinine 2.4 mg/dl, the electrolytes were between normal ranges, total protein was 7.0 gr/dl while albumin was 2.0 gr/dl. In the protein electrophoresis albumin constituted 41.5%, α1 3.1%, α2 7.9%, β5.3% and τ41.9%. There was a monoclonal peak in the t region. Serum acid phosphates values were 24.6 BU on admission while it rose to 158.9 BU on the 7th hospital day. Serum iron value was 17 mcg/dl with TIBC 502 mcg/dl. Blood, urine, faces and sputum cultures revealed no bacteria, and cultures of blood in Novy-MacNeal-Nicolle (NNN) medium gave negative results for Leishmania. Tests for Salmonella. Brucella and Infectious Mnonucleosis also gave negative results. In the bone marrow examination, Gaucher cells were recognized microscopically.

Figure 1: An x-ray of the lungs re- vealing bilateral patchy infiltrations.



A chest x-ray revealed diffuse interstitial involvement, with bilateral patchy infiltration (Figure 1). Abdominal ultrasonography disclosed homogenous hepatosplenomegaly. In the electrocardiogram no abnormality other than sinus tachycardia was noticed. Echocardiogram was evaluated as normal.

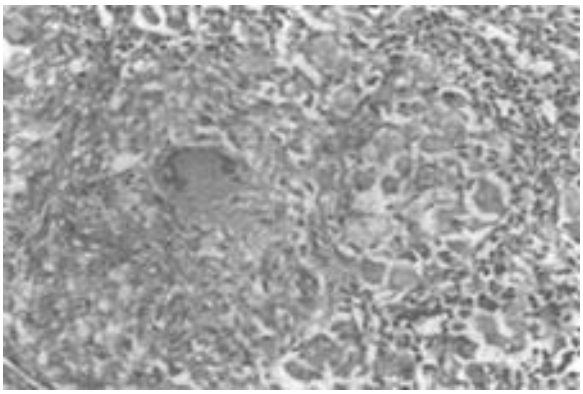
While on the hospital the patient had fever rising up to 38°C. She showed respiratory symptoms which never improved but got even worse despite supportive therapy. Blood gas analysis disclosed hypoxia with PO2 50-70%, PCO2 37.6-45%. The patient's condition deteriorated progressively and death ensued on the 8th hospital day with symptoms of respiratory failure. Postmortem liver and spleen biopsies were taken which were evaluated as Gaucher disease and tuberculosis histopathologically (Figure 2). Lung biopsy could not be taken for technical reasons but as far as the patient's clinical status and roentgenographic findings are concerned we believed that pulmonary tuberculosis was most probably present.

DISCUSSION

Our patient as a 47 year old cachectic woman with predominant pulmonary symptoms and hepatosplenomegaly, with laboratory findings like monoclonal gammopathy, hypoalbuminemia, iron deficiency, high ESR, BUN and creatinine values, implied malignancy at first. Respiratory symptoms were attributed to heart failure and perhaps some concomitant infection. The presence of Gaucher cells in the bone marrow was surprising for us because of the low incidence of Gaucher Disease at such an old age. We also searched for multiple myeloma because of the high incidence of these two diseases occurring together (2,13). But there was no evidence of MM in the bone marrow and laboratory analysis.

As for pulmonary findings, in a developing country like Turkey a physician generally feels obliged to rule out tuberculosis first because of the relatively high incidence. Although the roentgenographic appearance was not typical for Tb, (bilateral and rapidly progressive lesions) we still searched for acid fast bacilli in the sputum and took cultures for Lowenstein-Jensen medium. These analysis

Figure 2: A section of spleen tissue revealing Gaucher cells and granulomas consisting of epithelioid lymphocytes, lymphocytes and giant Langhans cells. (375 X Hematoxilen Eosin).



gave negative results, leaving the possibility of pulmonary involvement of Gaucher which is known to be rare especially in adults. Unfortunately the patient's clinical condition did not permit for proper diagnosis and therapy before death. Despite the fact that we could not demonstrate bacillus Tuberculosis in any of the specimens for accurate diagnosis, histological findings pertaining to Tb provided definite criteria for diagnosis. Another possibility was a granulomatous process accompanying Gaucher's disease, but we could not find any supporting report on this. Thus Tb was considered as a definite diagnosis concurrent with Gaucher in our patient. It is therefore suggested that in Gaucher patients presenting with pulmonary findings, clinician should not take Gaucher for granted but search for other diseases as well.

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