Respiratory Distress and Hypoxemia in Systemic Mastocytosis*

William A. Kaye, M.D.;** and Michael A. Passero, M.D., F.C.C.P.†

A 25-year-old woman with documented mastocytosis developed hypoxemia with pruritus, diarrhea, headache, and hypotension on two separate occasions. The hypoxemia appeared to be related to a massive release of histamine. Resolution of the patient's symptoms was accompanied by the return of her arterial oxygen tension to normal levels.

Systemic mastocytosis is characterized by the abnormal infiltration of mast cells from tissue into the skin (urticaria pigmentosa), bone, bone marrow, liver, spleen, and lymph nodes. In a study of 31 patients with systemic mastocytosis, Demis1 noted a high incidence of associated symptoms, such as flushing, tachycardia, shock, pruritus, gastrointestinal symptoms, headache, and weakness. Respiratory distress in systemic mastocytosis is unusual and is estimated to occur in not more than 3 percent of the patients.1 To our knowledge, documented hypoxemia has not been previously described. We report the findings in a patient who on two occasions developed reversible hypoxemia without wheezing that was associated with exacerbations of her mastocytosis.

CASE REPORT

A 25-year-old woman was admitted to Roger Williams General Hospital, Providence, RI, with shortness of breath and hypoxemia. When she was 17 years old, systemic mastocytosis had been diagnosed on the basis of diffuse hyperpigmented macules, dermatographia, and a bone survey. The patient also described occasional throbbing headaches accompanied by intense pruritus, rhinorrhea, diarrhea, and vomiting. Three days prior to admission, a sore throat, headache, nausea, vomiting, and diarrhea developed. The findings from physical examination were unremarkable, except for fever and diffuse hyperpigmented macules covering most of the patient's body. She was treated with aspirin and suppositories of trimethobenzamide.

Three hours later, the patient developed shortness of breath and tightness in the chest. Her temperature was 30°C (102.2° F). Darier's sign (localized urticaria and pruritus secondary to degranulation of mast cells after stroking of the skin) was absent. The lungs were clear to auscultation, and a grade 2/6 systolic ejection murmur was present. Laboratory studies disclosed the following data: white blood cell count, 14,600/cu mm; hematocrit reading, 38 percent; partial thromboplastin time, 70 seconds; and prothrombin time, 15.3 seconds. Analysis of arterial blood gas levels with the patient breathing room air revealed that the arterial pressure (PAO2) was 55 mm Hg, the arterial carbon dioxide tension (PA CO2) was 25 mm Hg, and the arterial pH was 7.48. The chest x-ray film and lung scan were normal.

Therapy with acetaminophen and prochlorperazine was given. The patient's blood pressure fell to 100/0 mm Hg, and shaking chills developed. On repeat determination, the white blood cell count was 9,900/cu mm; and repeat studies of arterial blood gas levels with the patient breathing room air showed an arterial pH of 7.56, a PA CO2 of 32 mm Hg, and a PAO2 of 65 mm Hg. The hematocrit reading fell to 33 percent. Cephazolin, gentamicin, and diphenhydramine were administered, and over the next 12 hours the patient's condition dramatically improved. Examination of the stool, urine, and a gastric aspirate showed occult blood. A test for disseminated intravascular coagulation was negative.

By the third day of hospitalization, the prothrombin time and partial thromboplastin time were normal. A culture of material from the throat grew β-hemolytic streptococci. On the fifth day of hospitalization, while the patient was asymptomatic, arterial blood gas levels with the patient breathing room air were as follows: pH, 7.46; PAO2, 57 mm Hg; and PA CO2, 37 mm Hg. The serum level of histamine and the urinary level of 5-hydroxyindoleacetic acid were normal. Tests of pulmonary function showed a value of 72 percent for the ratio of the forced inspiratory volume in one second over the forced vital capacity (FEV1/FVC) and a value of 87 percent for the forced expiratory flow over the middle half of the FVC (formerly maximal midexpiratory flow); other values for pulmonary function were normal. A liver and spleen scan showed diffuse hepatomegaly.

Three months later, the patient was treated with diphenhydramine, meperidine (Demerol) hydrochloride, and scopo- lamine before surgery for extraction of a tooth. Twenty-four hours after surgery, fever, hypotension, tachycardia, headache, rhinorrhea, vomiting, and diarrhea developed. Arterial blood gas levels with the patient receiving supplemental oxygen at 3 L/min by nasal cannula showed an arterial pH of 7.48, a PAO2 of 55 mm Hg, and a PA CO2 of 37 mm Hg. The patient's lungs were clear, and the chest x-ray film was normal. She recovered without further therapy.

DISCUSSION

Demis1 reviewed 113 cases of systemic mastocytosis and found only six patients with respiratory symptoms. Dyspnea appears to be the most common respiratory symptom,2 and wheezing has been described by several authors. Mutter et al3 described a 58-year-old man with wheezing during exacerbations of his mastocytosis. At autopsy, he had extensive peribronchial and alveolar infiltration by mast cells. Stutzman et al4 reported the findings in a 60-year-old man with systemic mastocytosis who developed a chronic cough, exertional dyspnea, and occasional expiratory wheezes. These authors theorized that these symptoms might be related to long-term effects of histamine or serotonin (or both).

We interpreted the development of dyspnea, headache, pruritus, diarrhea, hypotension, and tachycardia in our patient to be consistent with systemic mastocytosis. We believe that the development of hypoxemia was related to a massive release of histamine from mast cells. Human mast cells contain histamine,5 but there is no evidence that they contain serotonin. Patients with urtica- caria pigmentosa and mastocytosis frequently have ele-
vated concentrations of histamine in the urine and serum, while the serum level of serotonin and the urinary level of 5-hydroxyindoleacetic acid in these patients are normal.4,5

Histamine's effect on pulmonary function has been investigated in laboratory animals and man. Using unanesthetized sheep, Brigham et al6 demonstrated that intravenous administration of histamine significantly lowers the levels of oxygen in the blood and increases the pulmonary lymph flow, the pulmonary vascular permeability, total lung water, and the pulmonary vascular resistance. Pretreatment with diphenhydramine reduced the histamine-induced drop in the PaO2 and prevented the increase in the pulmonary lymph and the total lung water.

In man the effect of histamine appears to be a function of dose and the baseline respiratory status. Patients with bronchitis, emphysema, and asthma appear to be sensitive to intravenous administration of histamine. Intravenously administered doses of 0.02 to 0.03 mg of histamine significantly decreased the vital capacity and caused bronchoconstriction.7 The same doses in healthy volunteers did not produce these abnormalities. Intravenous administration of histamine has also been shown to increase closing volumes and the respiratory system resistance and to decrease the vital capacity, the FEV1, the FEV1/FVC expressed as a percent,8 and the pulmonary compliance.9

In this patient, further studies were not done to distinguish between possible mechanisms of hypoxemia induced by histamine. These mechanisms include increased airway resistance and increased closing volume, which may result in areas of decreased ventilation vs perfusion or perhaps an intrapulmonary shunt. Additionally, histamine may alter the permeability of capillaries, with resultant "subclinical" pulmonary edema, also creating ventilation-perfusion abnormalities. Finally, in the presence of shock or hypotension, a decreased cardiac output might result in a fall in the oxygen tension of mixed venous blood, thus contributing to a low PaO2.

It is important to emphasize that our patient's two episodes were probably precipitated in part by use of aspirin, meperidine hydrochloride, and scopolamine, which are known to cause exacerbations of this disease. Opiates, derivatives of strychnine, d-tubocurarine, gallamine, decamethonium, and dextran are histamine-releasing agents to be avoided in these patients.5,10

REFERENCES
8 Newball HH, Keiser HR: Relative effects of bradycin and histamine on the respiratory system of man. J Appl Physiol 35:552, 1973

MB Isoenzyme of Creatine Phosphokinase*

Indicator of Ischemia in Coronary Arterial Disease

Alon Marmor, M.D.; Shlomo Keidar, M.D.; Ehud Grenadier, M.D.; and Avraham Palant, M.D.

After undergoing a stress test that showed abnormal findings, a patient with severe coronary arterial disease had an elevated concentration of the MB isoenzyme of creatine phosphokinase, in the presence of normal levels of creatine phosphokinase and myoglobin in the serum.

It is well known that an elevated concentration of the MB isoenzyme of creatine phosphokinase in the presence of an elevated concentration of total creatine phosphokinase is an unquestionable indicator of myocardial necrosis.1 Recently,2,3 the appearance of the MB form of creatine phosphokinase was reported in the presence of a normal level of total creatine phosphokinase in the early stages of myocardial infarction.

To the best of our knowledge, there has been no report of the finding of the MB isoenzyme in patients with acute coronary ischemia. The following case report is presented because it is a unique instance in which an elevated concentration of the MB isoenzyme of creatine phosphokinase was detected after abnormal findings on a stress test in a patient with severe coronary heart disease.

CASE REPORT

A 53-year-old white man was admitted with a year-long history of anginal pain related to effort. During the four weeks before admission, the patient noted frequent episodes of anginal pain occurring with mild effort. Treatment with nitroglycerin and propranolol (propranolol; up to 330 mg/day) did not relieve his symptoms. The findings from physical examination, an electrocardio-

*From the Department of Cardiology, Lady Davis Carmel Hospital, Haifa, Israel.

Reprint requests: Dr. Palant, Carmel Hospital, Haifa, Israel.