Systemic Mastocytosis in a Patient With Polycythemia Vera Treated With Radioactive Phosphorus

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Systemic mastocytosis occurred as a fatal event in a patient with long-standing polycythemia vera. The patient had been treated over the course of 21 yr with radioactive phosphorus. Possible relationships between mastocytosis and polycythemia vera, and also between mastocytosis and treatment with ionizing radiation, are discussed. Histopathologic and electron microscopic findings are illustrated. Difficulties in establishing the diagnosis of mast cell disease in this setting are also described.

POLYCYTHEMIA VERA occasionally terminates with the occurrence of acute leukemia. The frequency of this lethal transformation has been reported to be increased in patients with polycythemia vera treated with ionizing radiation, in most instances in the form of radioactive phosphorus (32P). An increased incidence of other neoplasms in these patients has not been noted.

The patient to be described received superficial x-ray therapy to the skin for psoriasis as an adolescent. Polycythemia vera developed during early adult life and was successfully controlled with 32P for 21 yr. Within 6 wk of the last dose of 32P, progressive pancytopenia appeared, and a year later the patient died with a disseminated mast cell neoplasm. This type of mast cell disease has not been reported in association with polycythemia vera or after radiation exposure. In rare instances, more benign mastocytosis in the form of urticaria pigmentosa has preceded the appearance of polycythemia vera.

Possible relationships of mastocytosis to polycythemia vera and treatment with radiation are discussed. Difficulties encountered in establishing the diagnosis of mast cell disease are also described.

CASE REPORT

The patient was 49 yr at the time of his admission to the Johns Hopkins Hospital. At age 15 yr, he had developed skin changes felt clinically to be typical of psoriasis, although biopsy was not obtained. The lesions improved following six or seven treatments with local radiation at age 17. At age 27, he noted the insidious onset of malaise, weight loss, headache, bleeding gums, and flushed appearance. Approximately 1 yr after the onset of these symptoms he was admitted to Sinai Hospital in Baltimore, where he was observed to have a plethoric appearance, suffusion of the conjunctivae, venous engorgement, mild psoriatic skin changes, and a spleen palpable 2 cm from the left costal margin. The bone marrow biopsy was hypercellular with a marked increase in mast cells. A histamine release test was positive.

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below the left costal margin. Laboratory data included a hematocrit of 79%, a white blood cell count of 19,600/cu mm, a platelet count markedly elevated as estimated on the peripheral smear, an erythrocyte sedimentation rate of 0 mm/hr, and a reticulocyte count of 1.0%. Blood volume studies were not performed. Arterial oxygen saturation at rest was 96%.

The patient was thought to have polycythemia vera. After venesection he received 6.65 mCi of \( ^{32} \text{P} \) intravenously. In the ensuing 21 yr, the patient’s erythrocytosis and symptoms were controlled with 11 injections of \( ^{32} \text{P} \), with a total dose of 74.5 mCi (Fig. 1). The final dose of 7.0 mCi was administered 14 mo prior to his admission, at which time the patient appeared to be in robust health, with a hematocrit of 50%.

During the 4 mo following that treatment, he developed progressive pancytopenia with a hematocrit nadir of 18%, white blood cell count of 1100/cu mm, and platelet count of 57,000/cu mm. Five months following the last dose of \( ^{32} \text{P} \), the patient was admitted to Sinai Hospital with fever and continued pancytopenia. A leftward shift in marrow granulopoiesis and the appearance of blasts and immature granulocytes in the peripheral blood suggested an early stage of transformation to granulocytic leukemia. Recovery from \( ^{32} \text{P} \)-induced marrow aplasia was also considered. The patient was transfused, anabolic steroids (oxymethalone, 150 mg/day) and later prednisone (20 mg/day) were begun. Over the next 7 mo, pancytopenia and a stable transfusion requirement persisted.

Approximately 13 mo after the final dose of \( ^{32} \text{P} \), the patient was again admitted to Sinai with fever, cough, nausea, vomiting, and the appearance of dark urine. Splenomegaly was noted at that time. During the hospital course, the patient developed a transient left pleural effusion, and marked hepatosplenomegaly with abnormal liver function tests. Oxymethalone was discontinued. Prednisone was increased to 80 mg/day and tapered rapidly thereafter. Increased numbers of immature granulocytes appeared in the peripheral smear (5%, blasts, 31%, myelocytes, and 30%, juveniles), associated with the appearance of nucleated red blood cells (27/100 WBC), and poikilocytosis of mature red cells. Bone marrow examination again showed immaturity of the granulocytic series and diminished erythropoiesis. Clumps of mast cells and basophils were noted. The patient’s general condition deteriorated, and gastrointestinal bleeding occurred. Androgen therapy was resumed. Antituberculous therapy was begun empirically.

After 1 mo hospitalization, the patient was transferred to the Johns Hopkins Hospital for further evaluation. On admission, he appeared acutely ill and deeply icteric, with a liver span of 17 cm. The spleen was now palpable 13 cm below the left costal margin. No skin lesions, bone tenderness, or palpable adenopathy were noted. Further tests to rule out tumor, infection, Budd-Chiari syndrome, biliary obstruction, and hepatitis were unrevealing. Bone marrow biopsy again showed immaturity of the granulocytic series and diminished erythropoiesis. Clumps of mast cells and basophils were noted. The patient’s thrombocytopenia worsened and gastrointestinal bleeding persisted. On the ninth day of hospitalization, an exploratory laparotomy was performed with splenectomy and wedge biopsy of the liver. Despite splerectomy and platelet transfusions, the platelet count remained less than 20,000/cu mm. The immediate postoperative period was complicated by moderate upper
gastrointestinal bleeding and pulmonary infiltrates. On the fifth postoperative day the patient became obtunded and developed fever, hypotension, and tachycardia. He was treated with blood, platelets, and parenteral fluid in addition to high-dose steroids. Antibiotics were continued. The patient continued to deteriorate and died following a massive upper gastrointestinal hemorrhage on the sixth postoperative day.

**PATHOLOGY**

**Surgical Specimens**

The spleen weighed 1710 g and was very firm; the cut surface was pale in appearance with numerous fresh infarcts. No tumor nodules were seen.

On histologic section (all material fixed in 15%, aqueous formalin), the normal architecture was effaced by interlacing fibrous bands. A diffuse cellular infiltrate was present throughout the fibrous tissue, in areas forming discrete nests among the surrounding fibrous bands (Fig. 2). The nuclei of the cells were generally round or oval with finely stippled chromatin, which often margined along the nuclear membrane. Nucleoli were not prominent. Occasional binucleate and multinucleate cells were seen. Mitotic figures were rare. In the majority of cells, the cytoplasm varied from clear to lightly eosinophilic. Occasional cells exhibited a densely granular cytoplasm and stained positively with Alcian blue and the periodic acid Schiff reagent. With toluidine blue the granules stained metachromatically, and a light granular metachromasia was noted in many of the remaining cells and background (Fig. 3), identifying the process as mast cell infiltration. Similar cells were noted in the liver biopsy and abdominal lymph nodes, without significant fibrosis or architectural distortion. A bone marrow biopsy obtained during this hospitalization showed numerous mast cells, a finding not present in the marrow biopsy done 7 mo before.

Small fragments of splenic tissue from the outer edge of material originally fixed in 15%, aqueous formalin were obtained for electron microscopy. As expected from the light microscopic findings, most cells contained only a small number of electron-dense granules, and only a few heavily granulated cells were present (Fig. 4). Many granules were bounded by a well-defined limiting
membrane. The matrices of the granules were, in general, uniformly fine to coarsely granular. Rare intragranular lamellar structures were seen.

Occasional megakaryocytes and aggregates of nucleated red blood cells were identified in the sections of spleen, liver, and lymph nodes examined.

**Autopsy**

At autopsy large numbers of mast cells were again noted in the liver, thoracic and abdominal lymph nodes, and bone marrow. No skin lesions were seen, and random sections of skin showed no increase in the number of mast cells. The kidneys were the only other organs involved by the process, with scattered collections of mast cells in the cortices, predominantly in perivascular locations.

Other major findings included a severe acute bronchopneumonia, with associated fibrinous pleuritis and bilateral pleural effusion. Two penetrating duodenal ulcers measuring 2 and 1.3 cm, respectively, the latter containing a grossly eroded arterial branch in its bed, were present. The stomach and intestine contained a large amount of fresh and altered blood.

The liver weighed 2780 g. In addition to the mast cell infiltrate and extramedullary hematopoiesis, multiple areas of centrilobular necrosis were present, consistent with the terminal hypotension.

The bone marrow was diffusely hypercellular, and approximately 30%, 40%, of the cells were mast cells. The metachromatic staining seen in marrow touch preparations was greatly attenuated in decalcified histologic sections obtained from adjacent bone. No anatomic evidence of significant chronic pulmonary disease, or other neoplastic, renal, or cardiac lesions usually associated with secondary polycythemia was noted.

Permission to examine the head and neck organs was not granted.
DISCUSSION

Erythroid hyperplasia is considered the hallmark of polycythemia vera. The majority of patients with polycythemia vera at some time during their course will also exhibit increased activity of the granulocytic and megakaryocytic series, differentiating polycythemia vera from other forms of erythrocytosis.\(^2\)\(^,\)\(^10\) The disease has thus been characterized as a “panmyelosis,”\(^1\)\(^2\) and, in fact, one of the causes of death in these patients is transformation into acute leukemia.\(^1\)\(^1\) The relationship of this transformation to treatment with radiation, primarily in the form of radioactive phosphorus, has been a subject of much debate.

Lawrence et al.\(^1\)\(^2\) have postulated that the occurrence of leukemia or a “leukemia-like state” is the result of a natural progression of the basic disease process in polycythemia vera. They have suggested that leukemic transformation has become more prevalent because of the increased survival time in patients treated with \(^32\)P. Israels,\(^1\)\(^3\) citing experience with nonradioactive methods of treatment, has averred that acute leukemia is not a natural complication of the disease process. Modan and Lilienfeld,\(^1\) in a large multicenter study, have concluded that leukemic transformation is chiefly due to radiation therapy. They have noted, however, that the frequency of leukemia has been higher than expected when compared to that seen in patients without polycythemia vera.
who have had similar amounts of radiation exposure and felt that patients with polycythemia vera may also have an increased susceptibility to the development of leukemia. The patient presented would have been considered at high risk of developing leukemia on the basis of both longer than average survival for this disorder and larger total dose of $^{32}$P.

Another common cause of death in patients with polycythemia vera is the development of myeloid metaplasia and myelofibrosis. Silverstein, in a series of 207 patients with polycythemia vera from the Mayo Clinic, has noted an approximate fourfold increase in the incidence of “postpolycythemia myeloid metaplasia” in patients treated with $^{32}$P, compared to those treated by other means. Modan and Lilienfeld, however, have not noted an increase in the development of myeloid metaplasia in their patients treated with radiation compared to those not so treated. Wasserman considers myeloid metaplasia and myelofibrosis an autochthonous part of polycythemia vera, and reports that in his cases of long duration these changes have almost invariably been present in some degree. The appearance of these changes, in addition to osteosclerosis, have led him to speculate that the initial growth stimulus causing polycythemia vera is directed at the primitive mesenchymal cell, with proliferation not only of hematologic but also of nonhematologic connective tissue elements as well.

The tissue mast cell is also considered a derivative of the primitive mesenchymal cell, and mast cell tumors have been classified among the reticuloendothelial neoplasms. Although the development of mastocytosis in patients with preexisting polycythemia vera has not, to our knowledge, been recorded, isolated cases of the opposite sequence have been reported. In each instance, the patient has presented with long-standing cutaneous mastocytosis (urticaria pigmentosa), with the subsequent appearance of polycythemia vera. Brink and Marshall in their report view the concurrence of the two disorders as evidence of the close relationship of the reticuloendothelial system and the hematopoietic system. Diamond and Gross have considered their case as evidence suggesting a stimulus to the “multipotential reticulum cells,” with initial proliferation of mast cells and later of the erythroid series.

Further evidence of the relationship of mast cells to the hematopoietic system is found in a review of 26 fatal cases of mastocytosis from the literature by Sagher and Even-Paz. Twenty-one of these patients had proven systemic mastocytosis (i.e., tissue confirmation of pathologic increase of mast cells in other than cutaneous sites). Of these 21, at least 5 terminated with mast cell leukemia, and 3 died with hemocytoblastic, myeloid, and monocytic leukemia, respectively. An additional three who did not develop elevated white cell counts had the appearance of a significant percentage of tissue mast cells in the peripheral blood prior to their demise.

It is also of interest that the distribution of therapeutically administered $^{32}$P is primarily to the organs involved by mast cell disease in this patient, i.e., bone marrow, liver, spleen, and lymph nodes. Selye reviews the conflicting results of studies on the effects of ionizing radiation on the mast cell in animals and in man. He remarks that repeated exposure to ionizing radiation may be associated with a marked rise in the mast cell count in various tissues. No cases
of mast cell neoplasms associated with radiation have been noted, however. The sequence of events in this case raises the possibility of induction of mastocytosis by long-term treatment with ionizing radiation.

Certain diagnostic difficulties arose in identifying the terminal process in this patient as mast cell in nature, in particular differentiating it from the "myeloid metaplasia with myelofibrosis syndrome" occurring in patients with polycythemia vera. This patient presented many of the clinical and laboratory features seen in the syndrome, including increasing hepatosplenomegaly, a leukoerythroblastic blood picture with prominent poikilocytosis, anemia, extramedullary hematopoiesis, and increase in reticulin fibers on bone marrow biopsy. The absence of skin lesions and some of the more specific histamine-related symptoms such as flushing, dermographism, tachycardia unassociated with hemorrhage, etc., further obscured the diagnosis. Although an increase in the number of mast cells was noted in the aspirated marrow smear, this has not been uncommon in association with a variety of disorders, in particular anemia and splenomegaly due to various causes. Because of sparse granularity of the mast cells in the bone marrow biopsy, these were initially difficult to recognize among the immature marrow elements. In hematoxylin- and eosin-stained sections, recognition of the occasional well-granulated cells led to the establishment of the diagnosis by use of appropriate special stains.

The sparse granularity of the mast cells may have been due to a number of

Fig. 5. Touch preparation from fresh resected spleen demonstrating large number of metachromatically staining granules in mast cells and background. Toluidine blue. ¥ 1500.
factors, in particular in this case, the use of routine aqueous fixatives. Mast cell granules are quite water soluble in certain species, although in man they are said to be less so. In this case, however, there was marked decrease in granularity of the cells in sections of spleen fixed in aqueous formalin when compared to touch preparations from the fresh spleen also stained with toluidine blue (Fig. 5). This patient also received prednisone during much of his final course, and the use of adrenal corticoids has been associated with mast cell disruption and degranulation in both man and animals.

In summary, this patient presented with a long history of polycythemia vera treated with radioactive phosphorus and died with a disseminated mast cell neoplasm. Diagnosis of the latter disorder was a source of difficulty. Because this has been the first such reported case, the concurrence of the two disorders may represent coincidence. The possibility is raised, however, that this may represent proliferation of another cell line of an already hyperstimulated primitive mesenchyme, either as a result of the basic nature of polycythemia vera, of long-term treatment with ionizing radiation, or both.

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