Metastatic Angiosarcoma with Thrombocytopenia and Intratumoral Indium-111-Platelet Deposition

Michael A. Arcomano, Barry L. Shulkin, Neil A. Petry, and Richard L. Wahl

Department of Internal Medicine, Division of Nuclear Medicine, University of Michigan Medical Center, Ann Arbor, Michigan

A 66-yr-old woman with cutaneous angiosarcoma of the face presented with thrombocytopenia and metastases to the skeleton. Scintigraphic imaging with ^{111}In-oxine-labeled autologous platelets demonstrated localization of radiolabeled platelets at sites of metastatic tumor. This imaging study suggests intratumoral destruction of platelets by the metastases of the malignant vascular tumor as the cause of the patient's thrombocytopenia.

J Nucl Med 1991; 32:2278–2280

Patients with malignancy can develop thrombocytopenia in association with tumors. The mechanisms of thrombocytopenia include decreased platelet production, accelerated destruction, and sequestration (*1*). Decreased production may be due to bone marrow failure following radiation or chemotherapy, and infiltration by tumor cells. Accelerated destruction of platelets can be immune mediated, as occurs with lymphomas or by disseminated intravascular coagulation. Sequestration may occur with massive splenic enlargement. Scintigraphy with ^{111}In-labeled platelets has been used to define the mechanism of thrombocytopenia in selected patients and thus to direct therapy, which may include or preclude removal of the site of destruction. We studied a patient with angiosarcoma of the face, skeletal metastases, and thrombocytopenia to evaluate the role of the spleen and possible benefits of splenectomy.

CASE REPORT

A 66-yr-old woman was admitted to the University of Michigan Hospitals for further evaluation of thrombocytopenia and for possible splenectomy.

Two years earlier, the patient had noted right-sided facial discoloration. This had been treated with Retin-A cream and antibiotics without improvement. Two and one-half months prior to admission, she was admitted to an outlying hospital with gastrointestinal bleeding and received transfusion therapy. Physical examination revealed bluish discoloration of the dorsum of the nose and right side of the face. Petechiae and ecchymoses were present on the abdomen and extremities. The platelet count was 10,000/mm^3. Prothrombin (PT) and partial thromboplastin time (PTT) were normal. A CT scan of the chest showed multiple pulmonary nodules in both lung fields, suggestive of pulmonary hemorrhage. The patient also complained of pain in the right shoulder, left sacroiliac region, and left hip. Radiographs depicted two lytic lesions in the scapula and sclerosis of the left humeral head and left ilium. A bone marrow biopsy of the left sacroiliac region demonstrated increased numbers of megakarocytes and slightly increased cellularity. Immune thrombocytopenia was suspected and prednisone therapy initiated.

After discharge from the hospital, biopsy of the right cheek and nose was performed. There were irregular vascular spaces lined by atypical endothelial cells in the upper dermis, deep dermis, and subcutaneous adipose tissue consistent with well-differentiated angiosarcoma. Iliac crest bone marrow aspiration and biopsy again demonstrated increased numbers of megakaryocytes and erythrocyte precursors, with no evidence of metastatic tumor.

At the time of admission to the University of Michigan Hospitals, there was bluish discoloration of the dorsum of the patient's nose and right malar region. Cutaneous petechiae and lower extremity edema were present. Laboratory studies included WBC 23,100/mm^3, platelets 57,000/mm^3, PT 12.2 sec (normal 11.1–12.5), PTT 18.7 sec (normal 20.3–29.8), fibrinogen 328 mg/dl (normal 150–350), and fibrin split products 8 μg/ml (normal <8). Direct and indirect immunofluorescence assays for platelet-associated IgG were negative. Plain films showed partial resolution of the multiple lung nodules with several residual ill-defined nodular areas in the left mid-lung, small areas of sclerosis in the right humeral head, fractures of two right ribs, and sclerosis adjacent to the left SI joint.

The patient's course was complicated by pulmonary thromboembolism. Scintigraphy with ^{111}In-oxine-labeled autologous platelets was performed five days later to evaluate the possible benefit of splenectomy in managing the thrombocytopenia. The platelets were radiolabeled as previously described (*2*). Indium-111-platelets (510 μCi) were injected intravenously. Whole-body images (approximately 230,000 counts per image) were obtained in the anterior and posterior projections at 1 hr, 24 hr, and 48 hr postinjection using a large field of view gamma camera and a medium-energy collimator interfaced to a portable computer.

Images obtained at 1 hr and later following injection showed localization of radiolabeled platelets at multiple abnormal sites within the axial and appendicular skeleton, including the skull, proximal humeri, ribs, vertebrae, pelvis, and femurs (Fig. 1A).

Received March 13, 1991; revision accepted July 11, 1991.

For reprints contact: Barry L. Shulkin, MD, Pediatric Nuclear Medicine, MCHC F3313-0229, University of Michigan Medical Center, Ann Arbor, MI 48109-0229.

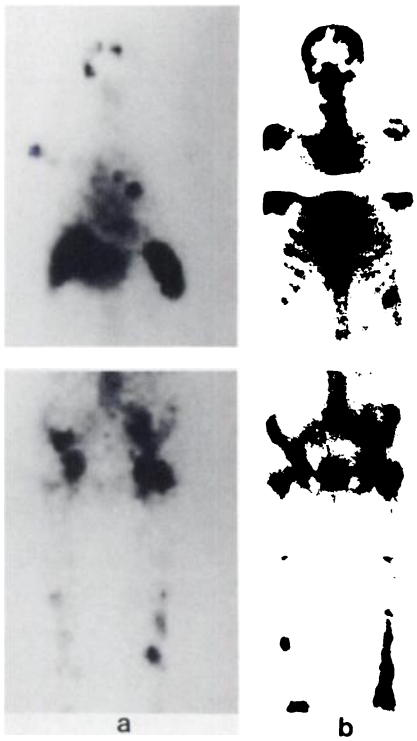

FIGURE 1. (A) Anterior whole-body image acquired 24 hr following the intravenous injection of 510 μCi ^{111}In-autologous platelets. Abnormal focal accumulations are evident in the skull, both shoulders, the spine, pelvis, femurs, and tibia. Activity in the liver and spleen is normal. (B) Anterior images obtained 3 hr after administration of 25 mCi ^{99m}Tc-MDP. Abnormal uptake is present in the skull, right shoulder, left hip, both femurs and tibia. More lesions are depicted by platelet scintigraphy than by bone scanning. It is likely that many of the lesions seen on ^{111}In-platelet scintigraphy not visualized on bone scanning represent soft-tissue metastases.

Platelet recovery 15 min postinjection was only 15% (normal 55% to 72%) (*3*), suggestive of very rapid destruction or sequestration of the injected platelets. To further localize and determine the significance of the focal platelet accumulations, skeletal scintigraphy was performed one week later. Images acquired following administration of 25 mCi ^{99m}Tc-MDP showed multiple abnormal sites of uptake, corresponding to many of the lesions identified by the ^{111}In-platelet study and consistent with metastatic disease (Fig. 1B). Radiographs demonstrated sclerotic and lytic lesions in the left femoral neck, left iliac wing, and right acetabulum. To obtain a cytologic diagnosis of the skeletal lesions, a bone marrow aspirate and biopsy of the right iliac crest were done. The bone marrow was normocellular with a slight increase in megakaryocytes but no evidence for neoplastic cells. A rib needle aspiration under fluoroscopy guidance was also negative for malignancy.

Shortly after discharge, the patient fell at home and was readmitted with a pathologic fracture of the left femoral neck (this area had been previously noted to have intense uptake of ^{111}In-platelets and ^{99m}Tc-MDP). A left hip hemiarthroplasty was placed. Microscopic examination of the surgical specimen revealed irregularly shaped blood vessels lined by plump endothelial type cells containing cytologically atypical nuclei, consistent with metastatic angiosarcoma.

Palliative therapy for the thrombocytopenia was attempted using glucocorticoids, platelet transfusions, and 800 rads to the lower body. The platelet count failed to rise above 80,000 and, approximately 3 mo later, the patient died from pulmonary hemorrhage.

DISCUSSION

The cause of this patient's thrombocytopenia was, from the evidence presented here, the destruction of platelets in the metastatic lesions resulting from her primary cancer. The rapid disappearance of ^{111}In-labeled autologous platelets from the circulation and localization to sites of metastatic involvement identified multiple sites of tumor involvement not previously suspected. Subsequent radionuclide imaging with ^{99m}Tc-MDP showed that many of the abnormal accumulations identified by the platelet study lie within bone. However, ^{111}In-platelet imaging identified more abnormal foci than bone scanning, particularly in the pelvis. It seems likely that lesions identified by ^{111}In-platelet scanning, but not by bone scintigraphy, represent soft tissue metastases. Normal activity within the liver and spleen exonerated these organs from major roles in platelet destruction. Furthermore, the results of the ^{111}In-platelet study spared the patient an unnecessary splenectomy in the management of her illness. It is of interest that the primary tumor, the cutaneous facial lesion, did not accumulate platelets and was not involved in platelet destruction. The reasons for the lack of platelet trapping by the primary tumor are unclear.

Indium-111-labeled platelet scintigraphy has been investigated in a substantial variety of clinical situations but the technique has failed to gain widespread clinical application. The principal uses have been the assessment of allograft rejection, thrombogenecity of prosthetic grafts, and evaluation of thrombocytopenia (*4–6*). Indium-111-platelets have been useful in identifying hemangiomatous destruction of platelets in patients with Kasabach-Merritt syndrome (*7–10*).

In conclusion, this study demonstrated the localization of ^{111}In-platelets to metastatic deposits in a patient with widespread angiosarcoma, and showed that the spleen did not contribute to the associated thrombocytopenia, sparing the patient an unnecessary splenectomy. This suggests that ^{111}In-platelets may be useful in the evaluation of thrombocytopenic patients with malignancies in whom splenectomy is considered.

ACKNOWLEDGMENT

The authors thank Joyce Stafford for secretarial expertise.

REFERENCES

1. Bitran JD, Ultmann JE. The paraneoplastic syndromes. In: Kelley WN, ed. *Textbook of internal medicine.* Philadelphia, PA: J.B. Lippincott Co., 1989:1352–1357.
2. Thakur ML, Welch ML, Joist JH, Coleman RE. Indium-111 labeled platelets: studies on preparation and evaluation of in vitro and in vivo function. *Thrombosis Res* 1976;9:345–357.
3. International Committee for Standardization in Hematology, Panel on Diagnostic Applications of Radionuclides. Recommended method for indium-111-platelet survival studies. *J Nucl Med* 1988;29:564–566.
4. Catafau AM, Lomena FJ, Ricart MJ, et al. Indium-111-labeled platelets in monitoring human pancreatic transplants. *J Nucl Med* 1989;30:1470–1475.
5. Wakefield TW, Shulkin BL, Fellows EP, Petry NA, Spaulding SA, Stanley JC. Platelet reactivity in human aortic grafts: a prospective randomzied

study of platelet adherence and release products in dacron and ePFTE conduits. *J Vasc Surg* 1989;9(2):234–243.
6. Castle VP, Shulkin BL, Coates G, Andrew M. The use of indium-111-oxine platelet scintigraphy and survival studies in pediatric patients with thrombocytopenia. *J Nucl Med* 1989;30:1819–1824.
7. Warrell RP, Kempin SJ, Benua RS, Reiman RE, Young CW. Intratumoral consumption of indium-111-labeled platelets in a patient with hemangiomatosis and intravascular consumption (Kasabach-Merritt syndrome). *Cancer* 1983;52:2256–2260.
8. Sondel PM, Ritter BS, Wilson DG, Lieberman LM. Use of ^{111}In-platelet scans in the detection and treatment of Kasabach-Merritt syndrome. *J Pediatr* 1984;104:87–89.
9. Schmidt RP, Lentle BC. Hemangioma with consumptive coagulopathy (Kasabach-Merritt syndrome). Detection by indium-111-oxine-labeled platelets. *Clin Nucl Med* 1984;9:389–391.
10. Shulkin BL, Argenta LC, Cho KY, Castle VP. Kasabach-Merritt syndrome: treatment with epsilon aminocaproic acid and assessment by indium-111-platelet scintigraphy. *J Pediatr* 1990;11:746–749.

(continued from p. 2265)

SELF-STUDY TEST
Radiobiology and Radiation Protection

ANSWERS

ITEMS 1–5: Effects of Acute Whole-Body Radiation Exposure

ANSWERS: 1, T; 2, F; 3, T; 4, F; 5, F

In general, whole-body doses over 100 rads have significant effects on immune system responsiveness. A whole-body exposure of 100 rads will reduce the peripheral blood lymphocyte count by about 50%. In fact, the immunosuppressive properties of whole-body radiation have been used to prevent rejection of transplanted organs.

The dose in humans that produces permanent sterilization is about 500–600 rads. Such an effect is highly unlikely from a whole-body radiation exposure because a dose of this magnitude is likely to be lethal before sterility is manifest. In males, doses as low as 15–30 rads markedly reduce the sperm count at about 8 wk after exposure. The sperm count slowly recovers over the next several months. At doses above 100–150 rads, the sperm count begins to fall earlier, and after falling practically to zero may recover, but very slowly.

Even with high doses of radiation the likelihood of radiation-induced cancer in an irradiated individual is small. For a whole-body dose of 100 rads the lifetime risk of radiation-induced fatal cancer is about 1%. The risk of radiation-induced genetic effects in the offspring of such irradiated individuals would be quite small. In fact, the study of 18,946 children born to parents who were A-bomb survivors (with a mean dose of 117 rads received jointly by the two parents) showed no statistically significant increase in stillbirths, congenital defects, premature death, and abnormal blood proteins.

Epilation and bleeding of gums would be quite unlikely after a dose of 100 rads; these effects generally occur after doses of about 400 rads.

ITEMS 6–10: Nonstochastic Effects

ANSWERS: 6, T; 7, F; 8, T; 9, T; 10, F

Nonstochastic effects of radiation are those for which the severity, rather than the probability, of an effect varies with the dose, and for which a threshold may occur. Nonstochastic effects of radiation include nonmalignant damage to the skin, cell depletion of the bone marrow, induction of cataracts, and gonadal cell damage leading to impaired fertility. Because the thresholds for these effects are well above the dose equivalent limits for occupational exposure, these nonstochastic effects can be prevented.

Stochastic effects (carcinogenesis) appear to saturate at high doses—the likely explanation for this phenomenon is cell killing. Many nonstochastic effects, on the other hand, specifically occur as a result of cell killing.

ITEMS 11–14: Genetically Significant Dose

ANSWERS: 11, F; 12, F; 13, F; 14, T

The genetically significant dose (GSD) is *not* the dose of radiation each person receives from birth to death and is *not* the dose of radiation that can be shown to lead to a genetic death. Rather, the GSD is an index of the presumed genetic impact of radiation exposure on the population. The GSD is defined as the dose that, if received by every member of the population, would be expected to produce the same total genetic injury to the population as is produced by the actual doses received by various individuals. The GSD for medical radiations is calculated from the frequency of the particular examination in a certain age group of the population, the corresponding gonadal doses and the appropriate weighting factors that take into account the expectancy of offspring in the population. Because the presumed genetic injury is *only* associated with the offspring of irradiated individuals, estimation of GSD from the gonadal doses received by these individuals requires that these doses be weighted for the probability of offspring, i.e., not only must there be gonadal radiation, there must be a probability of offspring for it to have a genetic effect. A nuclear medicine procedure resulting in gonadal radiation exposure to a 70-yr-old woman would not contribute to the GSD because the probability of offspring is nil. The annual contributions to the GSD from background, diagnostic radiology, and nuclear medicine procedures in the U.S. are: 82, 20, and 2–4 mrems/yr, respectively. confirm the diagnosis of fish tapeworm infestation.

Reference

1. Mettler FA, Williams AG, Apar JA, Kelsey CA. Estimation of the genetically significant dose from nuclear medicine examinations in the United States: 1980. *Health Phys* 1986;51:377–379.

ITEMS 15–19: Genetic "Doubling Dose"

Answers: 15, T; 16, F; 17, F; 18, T; 19, F

By definition, the doubling dose is the amount of radiation that would be expected to add as many new mutations as occur spontaneously. Thus, the higher the doubling dose, the lower would be the risk of mutation from any particular radiation dose. The doubling dose is the reciprocal of the relative mutation risk, the fraction by which each added rad of radiation dose would increase the mutation rate above the spontaneous level. Thus, a relative mutation rate of 0.01/rad, a risk of 1/100 per rad, would give a doubling dose of 100 rads. A doubling dose would not double the incidence of mutations in the next generation but would require several generations to be fully expressed, i.e., to reach a new equilibrium. This is because elevations in radiation dose must persist over many generations to result in a new and higher mutation burden in the gene pool of the population. Mutant genes are eliminated from the population faster as the number of mutant genes in the population increases. Eventually (after perhaps ten or more generations) a balance will occur between the rate of increase and elimination of mutations and a new "equilibrium" will be established.

The BEIR-1980 estimate of a doubling dose of 50–250 rads was obtained from data on mice because no genetic effects have been observed in humans.

References

1. Searle AG. Hereditary damage. *Radiat Environ Biophys* 1979;17:41–46.
2. Selby PB. Genetic effects of low-level irradiation. In: Fullerton GD, Kopp DT, Waggener RG, Webster EW, eds. *Biological Risks of Medical Irradiation.* Medical Physics Monograph No. 5. New York: American Institute of Physics, 1980:1–20.

ITEMS 20–24: Genetic Effects of Radiation

ANSWERS: 20, T; 21, F; 22, F; 23, F; 24, T

Mutations are almost always detrimental to the organism. Any gene, presumably, is the bearer of some bit of valuable genetic information, a particular command that must be executed if the cell is to function properly. In its mutated form the gene's "action" will be missing.

Because there is no direct evidence in humans of radiation-induced genetic damage (even in the progeny of the A-bomb survivors) it has been necessary to rely on animal studies to estimate the risk to humans. Animal studies have revealed that the type and magnitude of the genetic effect depends on: (1) the stage of germ cell development at irradiation (immature germ cells appear to be capable of repair, whereas, in mature germ cells there is little or no repair); (2) dose rate (lower dose rates and fractionation produce fewer mutations); and (3) the interval between exposure and conception (it has been observed that avoiding conception for a time interval after irradiation greatly reduces the production of mutations).

Note: For further in-depth information, please refer to the syllabus pages included at the beginning of *Nuclear Medicine Self-Study Program I: Part I.*