Louis K. Wagner, PhD
Marsha D. McNeese, MD
M. Victoria Marx, MD[2]
Edward L. Siegel, MD

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Abbreviation:
TIPS = transjugular intrahepatic portosystemic shunt

[1] From the Departments of Radiology, University of Texas–Houston Health Science Center Medical School, 6431 Fannin St, Houston, TX 77030 (L.K.W.); the M.D. Anderson Cancer Center, Houston, Tex (M.D.M.); the University of Michigan, Ann Arbor (M.V.M.); and the University of Kansas, Kansas City (E.L.S.). Received December 21, 1998; revision requested March 2, 1999; revision received April 14; accepted June 10. **Address reprint requests to** L.K.W. (e-mail: *Louis.K.Wagner@uth.tmc.edu*).

[2] Current address: Department of Radiology, University of Southern California, Los Angeles.

[3] **. Multiple body systems

Author contributions:
Guarantors of integrity of entire study, L.K.W., M.D.M., M.V.M., E.L.S.; study concepts, L.K.W., M.D.M., M.V.M.; study design, L.K.W.; definition of intellectual content, L.K.W., M.D.M., M.V.M.; literature research, L.K.W., M.D.M., M.V.M.; clinical studies, L.K.W., M.D.M., M.V.M., E.L.S.; data acquisition, L.K.W., E.L.S.; data analysis, L.K.W., M.D.M., M.V.M., E.L.S.; manuscript preparation and editing, L.K.W., M.D.M., M.V.M.; manuscript review, L.K.W., M.D.M., M.V.M., E.L.S.

Severe Skin Reactions from Interventional Fluoroscopy: Case Report and Review of the Literature[1]

Some patients with certain preexisting health conditions may be at elevated risk for unusually intense radiation-induced skin reactions and late tissue damage from high-dose interventional procedures. The authors present a case report of a patient with mixed connective tissue disease and non–insulin-dependent diabetes mellitus who developed an unusual complication after placement of a transjugular intrahepatic portosystemic shunt. On the basis of a review of the literature, the following experiences may help identify patients at increased risk: previous high-dose procedures, connective tissue disease, diabetes mellitus, and homozygosity for ataxia telangiectasia.

In the 1990s, a major increase in high-dose fluoroscopically guided interventional procedures occurred in medicine. These procedures include cardiac radiofrequency ablation, coronary artery angioplasty and stent placement, neuroembolization, and transjugular intrahepatic portosystemic shunt (TIPS) placement. Such procedures tend to be long and involve fluoroscopy in a single area of anatomy for a prolonged time—frequently for longer than 30 minutes and occasionally for more than 1 hour. In addition, the need for multiple sequential sessions of treatment can occur. Because of the high skin doses that can be generated in the course of these interventions, some procedures have resulted in early (less than 2 months after exposure) and/or late (2 months or more after exposure) skin reactions, including necrosis in some cases (1–11). In all cases of skin reactions, the doses are thought to have been high, and the severity of some reactions has required use of skin grafts or myocutaneous flaps for treatment.

The occurrence of severe skin injuries is rare relative to the number of procedures performed each year. Approximately 40 injuries were reported to the United States Food and Drug Administration in 1994 (4). Wolff and Heinrich (1) report nine cases in Germany. Approximately 14 other cases have been reported in the literature (2,3,5–11), and personal communications (Wolff D, written communication, 1998) indicate several others.

In radiation oncology, some patients with preexisting conditions are at higher risk for exaggerated radiation responses that do not occur in patients with healthy skin. The most fundamental factor that increases a patient's risk for adverse response is a previous high dose from an earlier treatment, but other medical conditions such as homozygosity for the ataxia telangiectasia gene are known to sensitize patients to ionizing radiation, so much so that this condition is considered a contraindication to radiation therapy. A review of the literature suggests that patients with certain types of connective tissue disease and types I or II diabetes mellitus may be at elevated risk for unusual reactions. We present a case report and a literature review on the issues that add to the evidence of a potentiated response.

Case Report

A 61-year-old, pale, obese white man (height, 5 feet 10 inches [178 cm]; weight, 230 lb [104 kg]) presented with hematemesis and melena. His previous medical history included pancytopenia secondary to aplastic anemia, non–insulin-dependent diabetes mellitus, polycystic kidney disease, and atherosclerotic coronary artery disease. The patient also reported a history of lupus erythematosus,

with associated Sjogren syndrome. However, the diagnosis of either of these conditions was uncertain. (Tests for Sjogren syndrome proved positive 8 months after this presentation for hematemesis. Tests performed 10 months later were positive for antinuclear antibody patterns and levels consistent with mixed connective tissue disease.) The patient was previously treated for seborrheic dermatitis. The patient had no history of alcohol consumption, was a previous smoker, and had undergone multiple hernia repairs and a parotidectomy for a benign tumor. Physical examination revealed several telangiectases on the thorax. The patient was hospitalized for 1 week. Diagnoses included gastrointestinal bleeding secondary to esophageal varices and hepatic cirrhosis of unknown origin. It was noted that the patient's rheumatoid factor was significantly elevated at 320.

One month later, the patient was again hospitalized for hematemesis. During this stay, the patient underwent celiac and superior mesenteric angiography, hepatic venography, and transjugular liver biopsy. These studies revealed patent mesenteric and portal veins, prominent esophageal varices, elevation of hepatic vein wedge pressure, and tortuous hepatic arterial branches consistent with cirrhosis. The biopsy revealed only nonspecific hepatic fibrosis.

Three weeks after the angiographic and biopsy procedures, the patient was seen in the dermatology clinic with 2–3-week symptoms of an intensely pruritic area on his back to the right of the midline. Physical examination revealed a clustered papular red eruption, slightly excoriated, at approximately the T4–T12 area. There were no vesicles or pustules. The assessment was contact dermatitis.

Six months later, the patient had recurrent hematemesis and returned to the hospital. Because of the cirrhosis, portal hypertension, and recurrent variceal bleeding, creation of a portosystemic shunt was recommended. The patient was evaluated at vascular surgery, but was considered a poor surgical candidate. Consequently, he was referred to the interventional radiology department to undergo a TIPS procedure. The procedure was performed 4 days later.

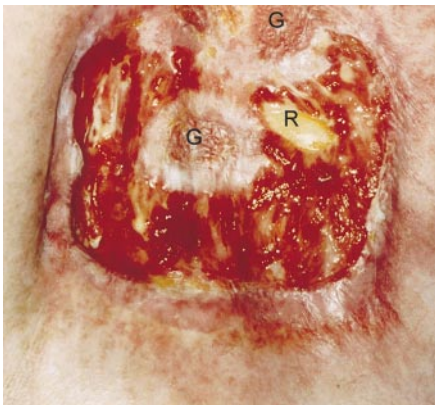
The procedure proved to be difficult, requiring multiple catheter and wire exchanges and sequential angioplasties. The procedure was technically successful and resulted in a portosystemic gradient of 6 mm Hg. The procedure lasted nearly 5 hours. High-dose fluoroscopy was available but was used during only initial puncture of the portal vein and deployment of the stent.

On the following day, the patient was evaluated in the dermatology department for a warm pruritic erythematous area of about 10 × 15 cm located on the back to the right of the midline. At this time, it was noted that erythema had been present for "several" weeks. The area was never tender and became less itchy with time. (It was noted that the patient also had a seborrheic dermatitis on his face, and it is not clear from the notes whether the patient was describing a "several weeks" rash on his back, which was initially reported 6 months earlier, or the rash on his face.) The patient was treated and released from the hospital the next day.

The patient returned 2 weeks later for his persistent rash. The lesion progressed over a protracted course. At 6 weeks, vesiculation and an eroded area of about 10 × 7 cm with yellow purulent material that drained centrally were noted. At 5½ months, the affected area was about 15 × 12 cm with an ulceration of 10 × 7 cm. Repeated attempts at grafting were unsuccessful. Ribs were exposed at 6 months. The status of the wound at 13 months is shown in the Figure.

Over the course of the 6 months after the TIPS procedure, the patient underwent additional radiologic procedures including computed tomography of the abdomen with and without contrast material, a TIPS catheterization, and a TIPS revision with placement of a new stent and portal venous sampling.

During more than 5 years of follow-up after the initial TIPS procedure, the patient experienced no further episodes of variceal bleeding, but the wound required intensive medical and surgical attention including use of hyperbaric oxygen and resection of at least one rib. Within the past year, the wound has been successfully covered, and daily dressings are no longer necessary.



Photograph of affected area at about 13 months after the TIPS procedure. *G* = graft, *R* = exposed rib.

Discussion

Case Report

The timing of the patient's symptoms and the location of the erythema after the initial angiographic procedure (6 months before the TIPS procedure) suggest strongly that the fluoroscopic radiation was the cause of the patient's first symptom of pruritic dermatitis. The main radiation-induced erythema effect is known to commence about 1 week after irradiation, and it peaks at about 3 weeks (12). This time course matches identically the patient's recollection of the course of its development after angiography. This location on the skin also corresponds to the location of the entrance x-ray beam. It therefore seems reasonable to suspect that the radiation from the procedure played some role in the dermatitis. If so, then either the radiation dose was excessive or the patient's skin was hypersensitive to the radiation that was delivered.

The absorbed skin dose from angiography and biopsy for a properly functioning machine would not likely exceed the 6 Gy that is listed as the common threshold for this phase of radiation-induced erythema. It is known that radiation outputs from machines can malfunction (6), but there are no indications that this was the case. The machine was inspected annually by a physicist, but output data are not available. Unfortunately, data on the output of the equipment and details of the procedure are not sufficient to be definitive on this issue.

The TIPS procedure delivered a high dose to the skin of the patient, as is evident from the patient's size and the duration and difficulty of the procedure. There was no record of the fluoroscopy on time, and an accurate estimate of the skin dose is not possible. On the basis of data in 25 cases from one of our facilities (University of Michigan), fluoroscopy time during a TIPS procedure ranges from 18%–30% of total procedure time (average, 24%). Therefore, the fluoroscopy on time for a 5-hour procedure would be expected to be in the range of 60–90 minutes. At a maximum rate of roughly 90 mGy/min, the skin dose would be expected to be on the order of 5–8 Gy. (This takes into account the maximum compliance exposure rate of a high-level control unit manufactured before 1994 and a source-to-skin distance of about 60

cm.) The skin-dose rate in the high-level mode has been measured at about 310 mGy/min. In a retrospective worst-case reconstruction of the procedure (L.K.W., E.L.S.), with phantom studies in a large patient and incorporation of high-dose-rate fluoroscopy and geometry, the maximum expected dose would be about 12 Gy.

We reviewed records of 25 other patients who underwent TIPS procedures at the same facility during an interval of 18 months before and 2 months after this procedure. Twenty-one of these patients were alive at more than 9 months after the procedure, and 20 had undergone follow-up procedures. Eight patients underwent procedures that lasted more than 5 hours, and one patient, a large man, underwent two procedures 7 months apart that lasted a total of 12¼ hours. This patient lived 4 years longer and never developed a skin problem. One patient who underwent a procedure lasting less than 4 hours developed a nonsymptomatic discoloration of the skin that was detected at physical examination several months after the procedure. This patient also happened to be diabetic, with type II diabetes mellitus, and this may explain the reaction. No other dermatologic changes are known for the other patients.

A dose of 12 Gy would be expected to result in some long-term skin changes, but the observed reaction is much greater than expected for reactions from healthy skin (12). Some authors (2,3) have reported skin changes with such doses, but they do not approach the severity of this case. We caution, however, that this is a retrospective maximum estimate of skin dose, and the possibility of higher doses due to unknown circumstances (eg, machine malfunction) cannot be ruled out.

Another factor to consider is the skin reaction after hepatic arteriography and biopsy 6 months before the TIPS procedure. The suggestion by the patient that remnants of that skin rash were lingering at the TIPS procedure implies that the skin may not have recovered completely from the previous dermatitis. This may have reduced the tolerance of the skin at the time of the TIPS procedure, as radiation damage is cumulative.

An alternative explanation is that the patient was hypersensitive to the fluoroscopic x rays because of his connective tissue disease and diabetes.

Literature Review

It is well known that tissue tolerance to radiation is reduced by previous treatments that may have delivered a high dose to healthy tissue. This also holds true for interventional radiology, in which a previous treatment may have delivered a high dose to specific skin areas. Even though the time between treatments permits the skin to recover somewhat from the exposure, recovery from high doses may not be complete, resulting in reduced tolerance of the skin for future procedures. Several authors cited injuries in patients who underwent multiple interventional procedures (1–3; Wolff D, written communication, 1998). Some patients were unaware of the changes because they were located in an area the patient could not see, and the skin condition did not cause any symptoms. These unnoticed changes included hypo- and hyperpigmentation and telangiectasia. As in radiation therapy, a patient's medical history should be reviewed for previous high-dose procedures that may have altered tolerance to radiation. A physical examination of such patients is warranted to identify any skin changes, with the intention of managing any further procedures to avoid irradiation of the same area.

Unusual radiation-related complications, including some that involve skin reactions, have been anecdotally reported (13–21) after cancer therapy in patients with a history of rheumatoid arthritis; discoid or systemic lupus erythematosus; scleroderma (progressive systemic sclerosis); calcinosis, Raynaud syndrome, esophageal hypomotility, sclerodactyly, and telangiectasia (the CREST syndrome); or mixed connective tissue disease. All these diseases involve the connective tissues and are collectively referred to as collagen vascular disease. Two reports have systematically investigated the relationship between complications and these diseases (22,23).

In 1993, Ross and co-workers (22) performed a matched-pair study of acute and late radiation complications after radiation therapy in 61 patients with collagen vascular disease (39 with rheumatoid arthritis, 13 with systemic lupus erythematosus, four with scleroderma, four with dermatomyositis, and one with polymyositis). The authors reported a slight, but not statistically significant, increase in complications among patients with collagen vascular disease. However, some patients were followed up for less than 3 months, and most of the patients had rheumatoid arthritis. In a larger study (23), findings suggest that patients with rheumatoid arthritis may not be at higher risk for complications and that long-term complications are a factor to consider.

In 1997, Morris and Powell (23) reported acute and late radiation toxicity in 209 patients with collagen vascular disease (131 with rheumatoid arthritis, 78 with nonrheumatoid arthritis). They found acute toxicity of at least grade 3 in 10% of irradiated sites, which is within the range of normal. Acute effects included skin reactions. There was no difference in overall acute effects between patients with rheumatoid arthritis and those with nonrheumatoid arthritis collagen vascular disease. Among patients with severe acute effects, however, there was an association with severe late effects. Also, significant late effects were seen at standard doses in patients other than those with rheumatoid arthritis, suggesting an increased radiosensitivity in patients with systemic lupus erythematosus, scleroderma, or mixed connective tissue disease. There was no evidence that diabetes, hypertension, symptomatic atherosclerosis, recent tobacco use, or simultaneous treatment with chemotherapy increased risk. Of 36 patients treated with electrons or orthovoltage, no significant late morbidity was observed. This observation is important in that it suggests that intense skin reactions in individuals with collagen vascular disease are not common. Late effects in sensitive patients included small bowel obstruction, xerostomia, dysphagia, fibrosis, necrosis, and telangiectasia.

In 1999, Herold and coauthors (24) reported the cases of 121 patients with type I or II diabetes mellitus who underwent three-dimensional conformal radiation therapy for prostate cancer. When compared with 823 patients without diabetes who underwent the same treatment, the diabetic patients had a statistically significant increase in late grade 2 genitourinary and gastrointestinal complications (the number of patients with grade 3 or 4 severities was small in the sample population). After 5 years, the diabetic patients demonstrated a 34% actuarial rate of grade 2–4 complications, whereas nondiabetic patients demonstrated a 23% actuarial rate.

Application of the lessons of radiation therapy to fluoroscopically guided interventional procedures is confounded by the differences in radiation application. Radiation therapy delivers treatment in modest fractionated doses with beam energies designed to spare the skin from injury. Healthy tissues at greatest risk due to high doses are usually located well below the skin. Even though the skin is not always the organ involved in the reported complication, the data are relevant to interventional procedures because the implication is that the presence of connective tissue disease and diabetes compromises the tissues that receive the high doses. The use of skin-sparing tech-

niques and fractionated regimens may be reasons why radiation therapy has produced adverse events on only a sporadic scale. Interventional procedures, on the other hand, use beams with no skin-sparing quality, and the doses can be delivered at a high level in a single fraction, or in a few fractions when repeated procedures are necessary. For these reasons, skin is the organ at greatest risk. Thresholds for deterministic skin effects are established for healthy skin, but data on thresholds for skin in patients with active connective tissue disease or diabetes have not been reported, to our knowledge. Exaggerated and intense reactions after high-dose interventional procedures may be more frequent in diabetic patients or in patients with connective tissue disease, particularly systemic lupus erythematosus, scleroderma, or mixed connective tissue disease. The patient in this case report had mixed connective tissue disease and non–insulin-dependent diabetes mellitus, which supports this hypothesis.

Another factor that might explain the infrequency of unusually severe events in radiation therapy might be related to the activity of the disease at the time of radiation exposure. Patients with connective tissue disease are known to have periods when the disease is more active than at other times, which may affect radiosensitivity.

We recommend that patients with a history of skin rashes and telangiectasia be carefully screened for connective tissue disease before a potentially prolonged interventional procedure is attempted that requires the use of fluoroscopy at a single anatomic location. Patients with known or suspected lupus erythematosus, scleroderma, ataxia telangiectasia, or mixed connective tissue disease and those with diabetes mellitus or evidence of skin damage from an earlier procedure should be advised of the possibility for an adverse skin reaction if their procedure may require a high skin dose. If an interventional procedure is attempted, difficult procedures that are not terminated early may result in severe skin reactions in a small number of patients. The use of radioprotectants has been recommended by some authors (3) to reduce the likelihood of skin damage. To our knowledge, however, the effectiveness of these agents has not been verified.

When a procedure is required in a patient with a positive history for elevated risk, a reasonable benchmark for the operator is to assess the risk-to-benefit ratio after each absorbed-dose interval of 3 Gy before continuing. In lieu of real-time dose monitoring, we suggest the assessment be made after each 30-minute interval of on-time fluoroscopy to a single skin entrance site. For all patients in whom multiple sequential procedures are required to accomplish the therapeutic goal, attempts to vary the skin entrance site should be considered (eg, anteroposterior vs posteroanterior beam geometry). Patients with a history of connective tissue disease should be followed up with serial physical examinations of the skin entrance site in order to detect injury. If injury is suspected or detected, early interdisciplinary management that includes representation from the operator's discipline (ie, radiology or cardiology), dermatology, and plastic surgery is recommended.

In summary, (*a*) the ability of skin to tolerate high-dose interventional irradiation may be compromised by previous high-dose procedures, connective tissue disease, diabetes mellitus, or homozygosity for ataxia telangiectasia. (*b*) Large patients are at greatest risk because their size will require high fluoroscopic outputs, and the geometry of the examination in a large patient will additionally cause doses to be elevated due to proximity of the skin to the x-ray source. (*c*) Candidates for high-dose interventional procedures should undergo screening for previous high-dose procedures, history of skin rashes, connective tissue disease, diabetes mellitus, or ataxia telangiectasia. (*d*) Patients with a positive history of previous high-dose procedures should be physically examined for skin changes. (*e*) Candidates positive for diabetes mellitus, connective tissue disease, homozygosity for ataxia telangiectasia, or radiation-induced skin changes should be advised about potential elevated risk. (*f*) A concerted effort should be made to avoid irradiation of skin sites with preexisting radiation-induced changes.

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