Acral Erythema Secondary to High-Dose Cytosine Arabinoside With Pain Worsened by Cyclosporine Infusions

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Acral erythema after high-dose cytosine arabinoside (Ara-C) has been described as a painful, sharply demarcated, and intense erythema of the palms and soles. This phenomenon occurred and is described in three out of three allogeneic bone marrow transplant (BMT) recipients who received high-dose Ara-C and total-body irradiation for conditioning therapy *via* the same protocol. These patients also received cyclosporine and methotrexate as prophylaxis for acute graft-*versus*-host disease. Two of the three patients experienced an increase in the pain associated with acral erythema during cyclosporine infusions and required large doses of narcotic analgesics. Since alcohol intensifies the pain of stomatitis and cyclosporine is manufactured in an alcohol base, the high alcohol content is suspect as the causative factor for this adverse reaction/drug interaction.

Cancer 63:2482–2485, 1989.

A DISTINCTIVE RASH, termed acral erythema, has been described in patients receiving high-dose chemotherapy for acute myelogenous leukemia.[1] This rash is characterized by a painful, sharply demarcated, and intense erythema of the palms and fingers and the soles of the feet, followed by bullae formation, desquamation, and healing. A number of authors have reported similar cases of toxic erythema secondary to hydroxyurea,[2] fluorouracil,[3,4] methotrexate,[5] mercaptopurine,[6] mitotane,[7] cytosine arabinoside (Ara-C),[8,9] and combination chemotherapy.[1,10] In one case, however, a patient with acute myelogenous leukemia experienced painful palmar-plantar erythema who had not received chemotherapy.[11] In other cases, the reaction has occurred after a combination of chemotherapy with total-body irradiation (TBI) in bone marrow transplant (BMT).[12] The cause of erythema is unknown, but appears to be multifactorial.

We have noted a particularly high frequency of acral erythema at our institution in patients receiving high-dose Ara-C, methotrexate, and TBI. In addition, we have seen a worsening of the pain temporally associated with acral erythema in patients who also received cyclosporine in BMT.

Cyclosporine is often used as prophylaxis against acute graft-*versus*-host disease (aGVHD) in bone marrow transplant patients. A number of leukemia patients have received allogeneic BMT at our institution under several different protocols. Treatment for these protocols usually involves high-dose chemoirradiation therapy followed by marrow transplantation. Acute graft-versus-host disease often develops after allogeneic transplantation and is a complication which limits the survival rate from the procedure. One BMT protocol at our institution addresses the following: (1) the toxicity of high-dose Ara-C and TBI, (2) efficacy of cyclosporine and methotrexate as prophylaxis against aGVHD, and (3) the efficacy of high-dose steroids in the treatment of aGVHD. Treatment involves conditioning chemotherapy with Ara-C 3 g/m^2 body surface area (BSA) intravenously (IV) over 1 hour every 12 hours for 12 doses, followed by TBI 1200 rad administered as 200 rad twice daily for 3 days and human leukocyte antigen (HLA)-identical, mixed lymphocyte culture

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The authors thank Elliott F. Winton, MD, Associate Professor of Medicine (Hematology/Oncology), and L. Thompson Heffner, MD, Associate Professor of Medicine (Hematology/Oncology), for reviewing this manuscript.

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Accepted for publication November 28, 1988.

(MLC)-compatible sibling marrow. The regimen used for aGVHD prophylaxis includes methotrexate 15 mg/m^2 BSA IV on day 1 posttransplant and 10 mg/m^2 BSA on days 3, 6, and 11. Cyclosporine is given at a dose of 1.5 mg/kg IV every 12 hours beginning 24 hours before transplant and continuing until gastrointestinal toxicity subsides. Then the drug is administered orally at a dose of 6.25 mg/kg every 12 hours until day 50; at day 50, the dose is tapered by 50% per week and the drug is discontinued on or before day 180. If renal toxicity develops or cyclosporine (radioimmunoassay [RIA], whole blood) levels are greater than or equal to 850 ng/ml, cyclosporine doses are adjusted using a medical management protocol for cyclosporine in BMT recipients.

To date, three patients have been placed on this BMT protocol. In each case, patients developed acral erythema. In two cases, the pain from the acral erythema was worsened significantly when cyclosporine infusion began, and both patients required large doses of narcotic analgesics to ease the pain.

Case Reports

Case 1

A 41-year-old woman with acute lymphoblastic leukemia diagnosed in 1983 was admitted to the Hematology Service on April 13, 1987 for an allogeneic BMT. The conditioning regimen was begun on April 15, 9 days before BMT. The aGVHD prophylaxis was begun on April 23 per protocol. Because the patient died 30 days posttransplant, oral cyclosporine was never given. Allogeneic bone marrow was transplanted on April 24, 1987.

Pain and erythema of palms and soles began on day 1 post-BMT (9 days after initiation of high dose Ara-C) and 2 days after the last dose of TBI. Bullae formation was noted on palms and soles 5 days after the onset of symptoms. Desquamation of these areas was noted 13 days after onset and reepithelialization was evident at 18 days after onset of symptoms.

Four days after BMT, the patient complained of an intense and unbearable pain of the palms of hands and the soles of feet during the 2-hour to 4-hour cyclosporine infusion. The infusion was stopped and the pain went away. Thirty minutes later, the cyclosporine infusion was restarted and the pain returned even though the patient had been pretreated with 25 mg IV meperidine. The infusion was lengthened to 6 hours but this made no difference and only extended the duration of pain.

Oxycodone/acetaminophen was ineffective at relieving the pain during the cyclosporine infusion as was meperidine 25 to 50 mg IV every 2 hours as needed. In order to alleviate the pain during the cyclosporine infusion, the patient was pretreated with 5 mg methadone 30 minutes to 1 hour before infusion and placed on a patient-controlled analgesia (PCA) pump which delivered 2 mg morphine sulfate every 30 minutes for up to 4 hours. The patient used an average of 8 mg per 4-hour cyclosporine infusion.

During the period after BMT, the patient experienced mild diarrhea, nausea, vomiting, and anorexia consistent with chemoirradiation. Liver function studies were within normal limits, with the exception of the day before death (day 19). Total bilirubin ranged from 0.2 to 0.6 mg/dl on days 0 to 18.

Case 2

An 18-year-old man diagnosed in August 1986 with acute lymphoblastic leukemia was admitted on February 2, 1987 to the Hematology service for an allogeneic BMT. Conditioning chemotherapy was begun with high-dose Ara-C on February 4 (9 days before BMT) and TBI on February 10. Allogeneic bone marrow was transplanted on February 13, 1987. Intravenous methotrexate and cyclosporine were begun 1 day before BMT. The cyclosporine regimen was changed on March 20 to an oral dosage.

After the last dose of TBI and before BMT (February 13), the patient began to complain of mild tingling in the palms of his hands. Both palms were erythematous, but the soles of feet were not involved. Six days after the onset of symptoms, fluid-filled vesicles were noted over the pressure areas of fingers and palmar surfaces of the hands. Eleven days after onset, bullae ruptured; 12 days after onset, peeling began. Reepithelialization was noted on day 14 (February 27) with slow but continued improvement over the next 2 weeks.

Three days after the onset of symptoms (February 10), the patient complained that the cyclosporine intensified the pain in his palms during the infusion period. He described it as, "It feels like someone is sticking a thousand needles in my palms."

Meperidine 75 mg IV every 3 hours with methadone 5 mg every 6 hours relieved the pain, but tolerance soon developed. Meperidine 100 mg every 2 hours as well as meperidine 25 mg every 30 minutes *via* PCA pump was inadequate in controlling the intense pain and burning experienced during the cyclosporine infusions. Methadone 7.5 mg before cyclosporine infusion, morphine 2 mg every 15 minutes *via* PCA pump, and ice water soaks were required to alleviate the pain experienced during cyclosporine infusion. From February 19 to February 25, the patient received, *via* PCA pump, 58.3 mg morphine per day, and during February 18 to February 19, the patient received meperidine 500 mg/day with methadone 10 mg on February 18 and 27.5 mg on February 19. The PCA pump was discontinued on February 25. Methadone 5 mg every 6 hours and morphine sulfate 6 mg IV every 4 to 6 hours, as needed, continued to control pain. Narcotics were then tapered.

During the period after BMT, the patient experienced one episode of diarrhea and mild nausea and vomiting. Total bilirubin ranged from a low of 0.2 to a high of 1.3 mg/dl over 35 days.

Case 3

A 34-year-old woman with Philadelphia chromosome negative chronic granulocytic leukemia (CGL) diagnosed in April 1979 was admitted on January 11, 1987 for an allogeneic BMT.

Conditioning chemotherapy was promptly started 9 days before BMT with high-dose Ara-C. The first dose was 6 g, but all subsequent doses were 5.76 g. The TBI, intravenous methotrexate, and cyclosporine were begun per protocol. On February

19, the regimen was changed to cyclosporine 375 mg orally every 12 hours. The harvested bone marrow was transplanted on January 23.

On February 5, 13 days post-BMT, small blisters were noted on the lateral aspects of both hands and feet, believed to be secondary to high-dose Ara-C therapy. Two days prior, on February 3, a PCA pump with morphine sulfate 1 mg/ml was begun for severe mucositis and pharyngitis. The 4-hour limit was adjusted according to the physician's discretion regarding patient need. Morphine doses averaged approximately 16 mg/8-hour shift. The lesions on the hands and feet continued to improve and a dermatology consult stated no skin biopsy was indicated.

No increase in pain of the hands/feet lesions was noted during the cyclosporine infusion; however, the PCA morphine pump was begun before the noting of the dermatologic lesions.

The patient experienced no diarrhea with mild nausea and vomiting. Total bilirubin ranged from 0.3 to 2.3 mg/dl over 53 days. The high of 2.3 mg/dl was transient and occurred as the acral erythema was resolving.

Discussion

In each of the above case reports, acral erythema was the final diagnosis, although aGVHD and radiation dermatitis were considered. The dermatologic component of aGVHD, for example, usually is manifest as an erythematous, maculopapular rash not associated with nodules or bullae. Also, most cases of aGVHD develop from 7 to 20 days after BMT.[13-15] Acute graft-*versus*-host disease is more highly suspected if liver function values are increasing or are increased.[15,16] Of the three cases reported, liver function tests were not significantly changed from baseline throughout the first month except in one case. In Case 1, the total bilirubin increased from <1.0 to 4.0 mg/dl beginning 4 to 5 days before death.

In addition, aGVHD is associated with gastrointestinal toxicity. Nausea, vomiting and diarrhea are characteristic signs. Cases 1 and 3 were significant for diarrhea, but Case 2 had essentially no documented diarrheal episodes. Although nausea was present in all three cases, it could have resulted from the high-dose chemoirradiation.

Radiation dermatitis is a well-documented phenomenon which may manifest in one of several ways. A transient, faint erythema sometimes appears during the first week of therapy, and is probably due to capillary dilation and an increased vascular permeability. There is almost immediate inhibition of mitotic activity in the germinal cells of the epidermis, hair follicles, and sebaceous glands. Epilation is manifest usually during the second week of radiation therapy and is obvious by the end of the third week. Dry skin results from suppression of sebaceous glands and is usually permanent. By the third or fourth week, a typical erythema appears, sharply localized to the radiation field. The skin is red, edematous, warm, and variably tender. Blood vessels in the upper dermis are dilated and one might visualize small foci of hemorrhage. If the total dose does not exceed 3000 rad, the erythema phase will be followed by "dry desquamation" characterized by pruritis and scaling, and often by increase in melanin pigmentation in the basal layer.[17]

In our case studies, the severe acral erythema occurred almost immediately after the chemotherapy and TBI conditioning regimen, and signs of reepithelialization were evident within 14 to 21 days. We attribute the acral erythema to chemotherapy administration, but believe that the TBI may have played an additive role in the severity of the dermatologic reactions observed. We have noted other cases in our institution of acute myelogenous leukemia patients receiving high-dose Ara-C without TBI who experienced a less severe acral erythema.

Also in two of the three cases described above, we noted an increase in the pain secondary to acral erythema during cyclosporine infusion. Cyclosporine is administered orally and intravenously. Both dosage forms are formulated in an alcohol and oil base. The IV dosage form contains 32.9% v/v alcohol and the oral form contains 12.5% by volume. Products with a high alcohol content are known to increase the pain of stomatitis. The acral and palmar-plantar erythema has been described as a painful, blistered, edematous dermatologic reaction associated with high-dose Ara-C infusions. It follows that the high alcohol content of cyclosporine may increase the irritation and pain associated with this adverse effect.

This speculation is particularly attractive in light of Case 1. When the cyclosporine infusion was stopped, the pain decreased and when restarted, the intensification of pain recurred. Whether the alcohol content was directly related to the pain is difficult to determine, but in this case, increased pain appears to be specifically related to cyclosporine administration.

In summary, our case reports seem to indicate that high-dose Ara-C with TBI, in some patients, results in acral erythema. In two of three cases, increased pain was clearly noted when cyclosporine was infused. The pain subsided when the infusion was stopped and returned when it was restarted. In addition, pain was effectively controlled with the use of a PCA infusion device, allowing for patient control. Other possible methods for controlling the severe pain include the use of cold water soaks, pretreatment with narcotics, decreasing the infusion rate for cyclosporine, and increasing the dilution of the cyclosporine infusion. Other studies are needed, and more patients on protocol should be followed to establish the incidence of adverse effects or risk factors associated with the adverse effects.

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