

Acral Erythema associated with Irradiated Blood Transfusion in Myelodysplastic Syndrome: A Case Report

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Citation

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Abstract

Acral erythema (AE) is a known chemotherapy-induced adverse cutaneous reaction that has been described in association with a number of different chemotherapeutic agents. The most common agents implicated in this reaction are cytarabine, doxorubicin, and fluorouracil. This disorder has also been described in association with graft versus host disease (GVHD) related to solid organ and bone marrow transplantation. An association with blood transfusion has only been described in transfusion-related GVHD. The skin reaction consists of painful intense macular erythema of palms and soles. It may be followed by blister formation and skin necrosis and usually heals uneventfully with desquamation of the skin. We describe a case of an 88 year old female with myelodysplastic syndrome (MDS) who presented with red, swollen and painful macular rash on both palms and soles after receiving leukocyte depleted, irradiated packed red blood cells 2 days prior. We found no description in the medical literature of AE to be associated with blood transfusion in the absence of GVHD.

INTRODUCTION

Acral erythema (AE), also known as hand-foot syndrome, palmo-planta erythrodyesthesia, and toxic erythema of palms and soles, was first reported by Zuehlk in 1974 in association with mitotane therapy [1]. Several chemotherapy-induced clinical and histologic changes of the area have been reported in the past decade because of new chemotherapeutic drugs, better recognition of histologic reaction patterns, and the prescription of higher dosages by oncologists. Since then, AE has been described as a side effect of many chemotherapeutic agents. Drugs implicated most commonly include doxorubicin [2], methotrexate [3], 5-fluorouracil [4], cytosine arabinoside [5], and hydroxyurea [6]. A distinctive acral erythema has been depicted in patients with myelogenous leukemia, subsequent to blood transfusions and intensive chemotherapy with cytarabine [5]. Other reports have also linked AE to GVHD related to bone marrow and solid organ transplantation [7]. Prior association of AE association with blood transfusion was only described in the setting of transfusion related GVHD [8,9]. We report a case of AE associated with irradiated blood transfusion in the absence of GVHD.

CASE REPORT

An 88-year-old Caucasian female with a history of transfusion dependent myelodysplastic syndrome (MDS) of

8 months duration presented with red, swollen and painful intense macular erythema of the palms and soles. Since the diagnosis of MDS, the patient received 10 units of irradiated, leukocyte-depleted packed red cells with no complications or adverse events. Benadryl was routinely administered prior to transfusion to prevent transfusion reactions. The patient had a history of coronary artery disease, and her angina was occasionally exacerbated with worsening of anemia. She was on extended release metoprolol, isosorbide dinitrate, and enteric coated aspirin for angina and hypertension. No new medications were started before this presentation and she had no known drug or food allergies. She was given 2 units of irradiated, leukocyte depleted, packed red blood cell transfusion two days prior to admission without premedication with benadryl to avoid sedation. After transfusion of the second unit, she developed fever, acral tingling, pruritis, burning sensation and pain followed by a rash only in the acral area (Figures 1 and 2). Physical examination revealed a temperature of 38.5°C, pulse 96 per minute, respiratory rate 18 per minute and blood pressure of 146/46 mm/Hg. Both palms were red, edematous, and tender with erythema extending up to the forearms. There was marked tenderness, erythema and edema of both feet, with turbid bullae on the soles. The skin lesions progressed to necrosis in some areas. The remainder of the physical examination was unremarkable, except for radiologically

Acral Erythema associated with Irradiated Blood Transfusion in Myelodysplastic Syndrome: A Case Report

persistent (clinically not significant) bilateral lung infiltrates due to a recently treated bacterial pneumonia. Laboratory tests showed pancytopenia with a platelet count of 13,000 and neutropenia with a white blood cell count of 1,200. The consulting dermatologist attributed the skin rash to an unusual reaction to transfusion resembling the necrolytic acral erythema of chemotherapy.

Figure 1

Figure 1. Bilateral erythematous rash of the palms



Figure 2

Figure 2. Dusky, red erythematous plaques are present bilaterally on the plantar aspect of the feet and toes. Arrows are pointing to necrotic lesions.



The patient was treated symptomatically with cool water soaks and 1% hydrocortisone cream. Fever subsided promptly. The rash healed over the next two weeks with desquamation of the skin. Subsequent transfusions using multiple units of washed, irradiated red blood cells were given and did not produce any similar reactions. . However,

a month later, after an ordinary (non-wash leukodepleted product) blood transfusion the patient developed a severe asthma-like attack (presumably due to transfusion related acute lung injury, TRALI) which did not respond to any clinical interventions. Four days later the patient died of cardiopulmonary failure due to complications of her refractory MDS, and TRALI.

DISCUSSION

There is no known mechanism of AE, although it appears to be dose dependent when occurring as a result of chemotherapy. There is no age, sex or racial predilection for susceptibility to this reaction. One hypothesis is that it is a direct toxic effect of the chemotherapeutic agent on the skin in acral areas [10]. Another explanation may be that the most common cause of acral cyanosis is vascular spasm which can be induced by several drugs. The skin in the acral areas has unique anatomical features that include thick stratum corneum, rapidly dividing epidermis, absence of sebaceous glands, absence of hair follicles, and high concentration of eccrine glands.

Other features also include presence of arteriovenous anastomoses known as Sucquet-Hoyer canals which are surrounded by specialized smooth muscle (glomus) cells that serve as sphincters enabling blood to bypass the capillaries, thereby accelerating blood flow to acral sites, increasing the temperature of those areas. This has led to the hypothesis that there could be an increased accumulation of toxic chemotherapeutic substances in the acral area compared to the rest of the skin. However, studies have failed to provide support for this hypothesis [11]. Diminished elimination of methotrexate has been associated with increased eccrine secretion [12]. In that particular study, the occurrence of eosinophilia and a strongly positive drug lymphocyte stimulation test during an episode of AE suggested a potential allergic mechanism.

The histopathology of AE is nonspecific. Histological findings have been described to include mild spongiosis of the epidermis, vacuolar degeneration of the basal layer, scattered necrotic and dyskeratotic keratinocytes, and mild to moderate epidermal atypia with cellular enlargement, nuclear pleomorphism, and multinucleation [13]. Dermal changes include dilated blood vessels, papillary edema, and sparse superficial perivascular lymphohistiocytic infiltration [13]. Our patient was immunocompromised, elderly and fragile, thus punch biopsy of the affected skin was avoided.

Acral Erythema associated with Irradiated Blood Transfusion in Myelodysplastic Syndrome: A Case Report

AE also has been described in association with acute GVHD in the setting of organ and bone marrow transplantation as well as transfusion-associated GVHD complicating non-irradiated blood products, and may be the earliest and only manifestation of the disease. When associated with GVHD, it is usually accompanied by other symptoms such as nausea and vomiting, intractable diarrhea and a rise in serum bilirubin [14], which were not present in our patient.

Cutaneous reactions to blood transfusion have been described in the setting of anaphylactic and anaphylactoid reactions [15]. Most frequently, they occur alone as an allergic reaction to transfusion. The most common finding is an intensely pruritic localized or disseminated urticarial eruption. In addition, it has been noted that reactions that included skin rash also tend to be associated with prepared blood stored for a longer period of time. In a prospective study by Frewin et al, patients who developed anaphylactoid reactions demonstrated higher mean plasma histamine levels in the transfused blood, compared with the non-anaphylactoid group, suggesting that high plasma histamine concentration in the transfused blood may readily contribute to the occurrence of a skin rash [16]. Our patient did not manifest any anaphylaxis or anaphylactoid reactions associated with any previous transfusions; however, she was not pretreated with benadryl for this transfusion.

We attribute the AE in our case to a possible immune mediated allergic reaction to the transfused blood or the products of cellular breakdown and nuclear damage secondary to irradiation that manifested only in the acral areas due to the unique histology of that skin region. It could be speculated that immunoglobulin (Ig)E antibodies against donor plasma constituents and vasoactive or complement-activating factors in the blood products may be involved in this reaction. It also could be considered that the myelodysplastic syndrome in our elderly patient created a pathophysiologic background that contributed favorably to the mechanism in the development of the AE. Moreover, our patient's death was related to blood transfusion; dyspnea and a fatal asthma-like attack that developed within 6 hours of transfusion support a diagnosis of transfusion-related acute lung injury (TRALI). This condition, recognized in the early 1970's and referred to as non-cardiogenic pulmonary edema (NCPE), was reported to the FDA as leading cause of transfusion-related fatalities from 2001-2003.

To our knowledge, the case presented here is the first to describe an association between irradiated blood transfusion

and acral erythema in a patient with MDS in the absence of GVHD, malignancy, or chemotherapy, and may be added to the long list of etiologies of this disease. Physicians should be aware of the rare possibility of occurrences of acral erythema in patients who undergo repeated blood transfusions, especially in similar clinical situations.

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