Case Study

Ms. P is a 46-year-old female who visited a walk-in clinic with a two-to-three week history of flu-like symptoms that included a fever higher than 38.5°C (102°F), chills, and night sweats. She also was experiencing anorexia and fatigue and reported a 15-pound weight loss. She added that her children had been sick with the flu during this time. She was placed on a seven-day course of antibiotics and told to return to the clinic after completion of the antibiotics. One week later, the symptoms persisted and she developed shortness of breath and increasing fatigue. At the clinic, a chest x-ray and complete blood count were performed. An elevated white blood count (109,000/mm³) prompted the physician to immediately refer her to an oncologist in the area. She then was transferred to the medical center with a tentative diagnosis of acute myeloid leukemia.

During the hospital admission interview, Ms. P denied any significant past medical history other than knee surgery 10 years prior and scarlet fever as a child. Her mother died of lung cancer at age 67, and her father had died of a cerebral vascular accident at age 72. She had no known allergies and was only taking ibuprofen as needed. Noted on Ms. P’s right elbow. Tape from a previous IV site had been removed near this area, so it was first thought to be a reaction to the tape. However, subcutaneous nodules were discovered on the lower extremities. The following day, lesions were seen over the tunnel track of Ms. P’s central venous catheter. Although only one set of blood cultures had grown gram-positive, coagulase-negative Staphylococcus, the recommendation of the infectious disease service was to start vancomycin. Ms. P’s laboratory reports included the following results: white blood count = 109,000/mm³; blast cells = 86%; hemoglobin = 8.1 g/dL; platelets = 116,000/mm³; lactic dehydrogenase = 1,103 IU/L; uric acid = 15.9 mg/dL.

Pathologic analysis of leukemia cells was positive for Auer rods. A bone marrow biopsy was performed, and a diagnosis of acute myeloid leukemia, French, American, British classification subtype of M2, acute myelogenous leukemia, was confirmed. On day two, as part of a standard treatment course, induction chemotherapy was initiated with a “3 + 7” regimen consisting of an IV push anthracycline daily for three days with seven days of continuous infusion cytarabine. Per the institution’s leukemic protocol, Ms. P also was started on infection prophylaxis with fluconazole and acyclovir. A course of oral allopurinol and IV fluids with sodium bicarbonate was initiated to alkalinize the urine and reduce the risk of tumor lysis syndrome.

On day three, Ms. P developed a temperature spike of more than 39.0°C. Empirically, metronidazole hydrochloride was started, although cultures were negative. Over the course of the next two days, the fever persisted and IV antibiotic coverage was switched to amphotericin B. On day five, she developed diarrhea. Her stool then was tested for Clostridium difficile toxins. On day seven, the fever returned and was persistently above 38.5°C, with a temperature spike of more than 39.0°C. Empirically, amphotericin B was started, although cultures were negative. Over the course of the next two days, the fever persisted and IV antibiotics were started. On physical examination, a 4 x 4 cm erythematous area tender to palpation was noted on Ms. P’s right elbow. Tape from a previous IV site had been removed near this area, so it was first thought to be a reaction to the tape. However, subcutaneous nodules were discovered on the lower extremities. The following day, lesions were seen over the tunnel track of Ms. P’s central venous catheter. Although only one set of blood cultures had grown gram-positive, coagulase-negative Staphylococcus, the recommendation of the infectious disease service was to start vancomycin. Ms. P’s laboratory reports included the following results: white blood count = 400 cells/mm³; bands = 2%; segmented neutrophils = 12%; lymphocytes = 85%; no blasts; and absolute neutrophil count (ANC) = 56.

What clinical condition could best describe these lesions, seen in the photos, based on the patient’s diagnosis, physical findings, and diagnostic test results?

Carol White, RN, MSN, AOCN®, is an advanced practice nurse in hematology/oncology at Loyola University Medical Center, Foster McGaw Hospital, in Maywood, IL. This article was written in memory of Ms. P, who graciously allowed the publication of these pictures to further educate oncology nurses.
TABLE 1. DRUG RASH MANIFESTATIONS AND NURSING CONSIDERATIONS

<table>
<thead>
<tr>
<th>DRUG</th>
<th>INCIDENCE/CHARACTERISTICS</th>
<th>NURSING CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>&gt;10%: flushing and erythematous or maculopapular rash of neck, face, and chest (red neck or red man syndrome) because histamine release with rapid IV infusion</td>
<td>Establish baseline renal function and adjust the dose as needed. Establish baseline renal function and adjust the dose as needed. Infuse over at least one hour, and monitor the patient for the first five minutes with the initial dose. Instruct the patient to call with any signs or symptoms of itching, rash, wheezing, or chest tightness. At first complaint, stop the infusion immediately and notify the physician. Symptomatic treatment may include antihistamines, corticosteroids, and IV fluids. With subsequent doses, healthcare professionals may need to premedicate patients with a steroid and/or antihistamine and give vancomycin at a slower rate. Maintain comfort measures and skin care as prescribed (e.g., antihistamine for itching, nonperfumed creams for moisturizing, topical steroid creams to reduce inflammation).</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>1%–10%: rash, usually pruritic maculopapular; exfoliative, urticarial, or purpuric lesions; Stevens-Johnson syndrome; toxic epidermal necrolysis</td>
<td>Establish baseline renal function and uric acid level. Establish baseline renal function and uric acid level. Based on chemotherapy and tumor lysis potential, administer allopurinol 24–48 hours prior to start of therapy, along with IV fluids as prophylaxis for tumor lysis syndrome. Document any drug rash history with past treatments and/or medications. Document any drugs the patient is taking currently that could interact with allopurinol (a higher incidence of rash is reported when used in conjunction with ampicillin or amoxicillin). Notify a physician at the first sign of a rash and obtain the order to discontinue the etiologic agent. Document the onset, characteristics, and duration of the rash. Continue comfort measures and skin care as prescribed (see above).</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>1%–10%: itching, urticaria, maculopapular rash with or without fever, freckling, pain, erythema, skin sloughing of the palmar and plantar surfaces</td>
<td>Assess and document baseline skin condition prior to initiation of therapy. May occur with high-dose therapy; consider corticosteroids as premedication to prevent rash. Continue comfort measures with analgesics, topical steroid creams, diphenhydramine hydrochloride.</td>
</tr>
<tr>
<td>Imipenem/cilastatin sodium</td>
<td>1%–5%: urticaria, pruritis, rash (maculopapular or erythematous), flushing, cyanosis, facial edema, skin texture changes, angioedema, Stevens-Johnson syndrome, and exfoliative skin reactions</td>
<td>Establish any history of drug allergies, especially cephalosporins and penicillin (partial cross-reactivity). Establish any history of drug allergies, especially cephalosporins and penicillin (partial cross-reactivity). Assess and document baseline skin condition prior to starting the drug. Instruct the patient to report any itching, rash, or skin changes. Discuss discontinuation of the agent with a physician if a patient reports any of the above. Continue comfort measures and skin care as discussed above.</td>
</tr>
</tbody>
</table>

Discussion

Reviewing Ms. P’s course, the following etiologies were considered.

- Drug rash
- Leukemic cutis
- Infection/septic emboli
- Neutrophilic dermatosis (Sweet’s syndrome)

In considering drug rash as the cause of Ms. P’s dermatologic problems, a review of the drugs that most likely caused the reaction consisted of allopurinol, cytarabine, imipenem/cilastatin sodium, and vancomycin (see Table 1). Ms. P had completed a short course of allopurinol approximately three days before the first appearance of the skin lesions, so allopurinol was not the suspected cause of her symptoms. A rash from cytarabine usually is seen when high doses (>1–3 g/m²) are given; however, it still may cause a rash in low doses (Wilkes, Ingwersen, & Barton-Burke, 2000). Erythema, rash, itching, and skin sloughing of the palmar and plantar surfaces may occur with high-dose therapy (Solimando, Bressler, Kintzel, & Geraci, 2000), but the cytarabine had been completed for several days prior to the first eruptions. A rash with imipenem/cilastatin sodium is less common, with 1%–5% of patients reporting a rash (Solimando et al.; Wilkes et al.). The description of drug rash as a “symmetric erythematous rash” (Murphy-Ende, 2000, p. 85), however, did not fit Ms. P’s clinical picture. Typical cutaneous manifestations associated with vancomycin are red man syndrome, a generalized erythoderma caused by histamine release with rapid IV infusion. The upper chest, neck, and face are the areas most commonly affected (Wilkes et al.). Because these agents were not suspected in causing Ms. P’s symptoms, the infectious disease service recommended continuing both antibi-otics.

When considering leukemic infiltration of the skin as a possible cause, the most notable reason to rule this out was Ms. P’s low white blood count at the time of the appearance of the lesions. In most instances of leukemic cutis, infiltration is seen at the time of diagnosis, most commonly in M4 (myelomonocytic) or M5 (monocytic) leukemias or chronic myeloid leukemia in blast...
transformation when the white blood count is high (Wujcik, 1997). Although a high white blood count may cause infiltration into soft tissue and Ms. P did present with gingival hypertrophy that was a function of a white blood count higher than 100,000 cells/mm³, she had no other evidence of soft tissue infiltration at the time of diagnosis. However, this did remain a differential diagnosis until otherwise ruled out with a tissue biopsy, although it seemed a less likely source of the problem.

Infectious disease (ID) physicians strongly suspected the tunneled central venous catheter as the infectious source and recommended removal of the catheter, as the fever had continued despite the addition of vancomycin. The catheter was removed and the tip sent for culture and sensitivity. The fever persisted, new lesions continued to erupt, and all cultures remained negative. Simultaneously with the ID consult was a dermatology consult. Dermatologists were less convinced of either an infection or tumor as the source of the rash. Several areas of the affected skin were biopsied. The final pathology report confirmed the working diagnosis of Sweet’s syndrome resulting from the presence of neutrophilic infiltrate in the biopsy specimens. This paraneoplastic syndrome has been linked to both hematologic and solid tumors and particularly to acute myelogenous leukemia (Camp-Sorrell & Hawkins, 2000).

Dr. Robert Sweet first identified Sweet’s syndrome in 1964 as an acute eruption of painful nodules and plaques in the skin, accompanied by fever. He documented a population of middle-aged women who developed the syndrome following upper respiratory infections (Sweet, 1964). In the mid-1980s, major and minor criteria were developed that established guidelines for diagnosis. Major criteria include the abrupt painful onset of red or purple plaques or nodules and neutrophilic infiltration of the dermis. Minor criteria include a prior fever or infection, arthralgia, conjunctivitis or underlying malignancy, leukocytosis, and good response to steroids (Su & Liu, 1986). At the Mayo Clinic, a fifth minor criterion was added: increased erythrocyte sedimentation rate. To confirm a diagnosis of Sweet’s syndrome, both major and two minor criteria must be met (Fett, Gibson, & Su, 1995).

Ms. P’s case fits the criteria except for leukocytosis, as her total white blood count was only 400 cells/mm³, with an ANC of 54 following completion of chemotherapy. However, in the early 1990s, a retrospective study at the Mayo Clinic was conducted on all patients diagnosed with Sweet’s syndrome over a 10-year period (48 cases). Fifty-six percent of the patients also were diagnosed with a hematologic or oncologic malignancy (Fett et al., 1995). Subsequent reports in the literature have documented that Sweet’s syndrome can be diagnosed in the presence of granulocytopenia (Aractingi et al., 1995; Conesa, Morales, Majado, Gonzalez, & Candeli, 1998; Probert, Ehmann, Al-Mondhriy, Ballard, & Helm, 1998; Starobinski & Salomon, 1998).

Skin lesions associated with Sweet’s syndrome in granulocytopenic patients appear approximately 12 days after the start of chemotherapy, when the leukocyte count is low. Although the mechanism of action is unclear, the connection between the previous high blast count and the developmental life span of clonal neutrophils may be the source of the eruptions. Theories have suggested that the neutrophils found on biopsy may have been leukemic precursors differentiating after chemotherapy (Aractingi et al., 1995; Fett et al., 1995). The associated fever is thought to be mediated by cytokine release, possibly interleukin-6 (Probert et al., 1998). In all of the case reports, patients who were given steroids responded with decreased pain, became afebrile, and their lesions began to fade. In Ms. P’s clinical course, the same was true. Once steroids were started, she became afebrile, her pain decreased, no new lesions appeared, and the old lesions began to fade.

Although this discussion may seem diagnostic and unrelated to nursing clinical practice, it may be of value when the nurse first encounters a patient newly diagnosed with leukemia. Understanding which subtypes of leukemia may manifest cutaneously will support nursing documentation of the thorough head-to-toe assessment, which the nurse completes on admission. Establishing the presence or absence of any rash, nodules, or oral lesions and describing the size, color, location, and presence or absence of pain will act as a comparison for future changes, as well as a guide for relevant questions during the history interview (Murphy-Ende, 2000). Throughout treatment, monitoring for changes will assist in educating the patient and family regarding the cause and focusing nursing care on the relief of symptoms. In Ms. P’s case, the continued pain, fever, and eruptions were both physically and psychologically draining. Ms. P and her family feared that the leukemia or some deadly infection was overwhelming any progress made with the chemotherapy. By understanding the process of the leukemic infiltration of the gums at diagnosis and then learning about Sweet’s syndrome, the staff was able to address the questions and concerns of Ms. P and her family throughout the course of treatment. Managing Ms. P’s symptoms while awaiting the final pathology report consisted of pain relief with analgesics and fever management with comfort measures (e.g., around-the-clock acetaminophen, cool cloths). These measures brought temporary relief of Ms. P’s symptoms. Once the steroids were started, her fevers subsided and her pain was more easily controlled. As the skin lesions began to fade, intense itching occurred. Symptom management included the use of diphenhydramine hydrochloride around the clock and hydrocortisone cream as needed for comfort. As the symptoms subsided, Ms. P and her family were able to regain their hope and concentrate on learning the tasks, such as central line care, that would be necessary prior to discharge.

In summary, Sweet’s syndrome, febrile acute neutrophilic dermatosis, has been associated in case reports with acute myeloid leukemias. Although linked most often to M4 and M5 leukemias, any patient with myeloid leukemia presenting with a high white blood count may develop this syndrome. However, at time of the eruptions, most of the patients are granulocytopenic. The infiltration of the neutrophils into the skin with the subsequent release of cytokines contributes to the signs and symptoms of Sweet’s syndrome.
and symptoms of fever, pain, erythematous eruptions, or purple plaques. The usual location of the lesions is on the arms or legs but can be anywhere on the body. Diagnosis is based not only on tissue biopsy and clinical conditions but also on the response to steroid administration, which is the treatment of choice. Detailed physical assessment and history taking by the nurse at initial diagnosis is important in establishing a baseline for comparison. Patient and family education regarding the disease process of leukemia, as well as Sweet’s syndrome, is important to alleviate fear.

References

Author Contact: Carol White, RN, MSN, AOCN®, can be reached at 243 N. Myrtle, Elmhurst, IL 60126 or at cwhite@lumc.edu