Chapter 9: Dermatologic Issues

Introduction

Skin abnormalities, such as altered skin pigmentation either overall or in spots, can be the presenting symptoms of Fanconi anemia (FA). Other skin abnormalities may emerge as patients with FA become adults. Patients who undergo hematopoietic stem cell transplants can develop skin abnormalities if the transplanted donor cells attack the recipient's body (graft versus host disease, GvHD). The risk of developing skin cancer appears to be increased for adult patients with FA, making early education on sun protection and skin cancer prevention essential.

Good to Know

To protect against all forms of skin cancers, providers should recommend:

- Applying sunscreen, wearing protective clothing, or avoiding sun exposure altogether. These precautions apply for children age 6 months and older. For babies under 6 months of age, try to keep out of direct sunlight and dress in protective clothing, a hat with a brim, and sunglasses. If sunscreen is needed, only apply a small amount and wash off after use.
- Using sunscreens that contain physical blockers (zinc oxide and titanium oxide)
- Performing annual skin exams for patients age 18 and older. For all patients who have received bone marrow transplants, yearly skin exams should be performed regardless of age. More frequent exams are needed if skin malignancies are detected.
- Performing skin biopsies of suspicious lesions
- Maintaining adequate vitamin D levels, by taking vitamin D supplements if necessary, particularly in young adults

This chapter will describe the most common skin problems that affect patients with FA:

- *Pigmentation changes*
- *Sweet's syndrome*
- *Warts*
- *Basal or squamous cell carcinoma*
- *Actinic keratosis*
- *Melanoma*

This chapter will also describe how certain therapies for FA, such as androgen therapy or hematopoietic stem cell transplantation (HSCT), can affect a patient's skin. Therefore, a patient's clinical care team should include a **dermatologist** to evaluate any problems related to the skin.

Skin Appearance on Initial Diagnosis

Pigmentation changes

Changes to pigment, the substance that gives the skin its color, are the skin abnormalities most commonly associated with a diagnosis of FA. A patient with FA can develop both hyper- (increased) pigmentation or hypo- (decreased) pigmentation, typically in sun-exposed areas [2]. Hyper- and hypopigmented patches of skin can appear on the neck, trunk, and tops of hands and feet; they can also appear on under arms, genitals, hand palms, or foot soles. Differently colored areas of skin often overlap and can create a freckly appearance: raindrop-like, light-colored patches of skin scattered over darker areas. Some patients also appear to have a dusky or shadow-like skin tone, most notably in joint areas, lower extremities, and on the neck. Smooth-bordered, tan patches of skin (café au lait macules) are also common on young patients with FA.

A diagnosis of FA should be considered in young children with distinct skin discoloration and accompanying disorders but can only be confirmed by blood tests (described in *Chapter 2*). While some patients with FA develop skin abnormalities, others do not, and abnormalities that develop are not unique to individuals with FA. The hypopigmented patches in patients with FA are also found in syndromes such as neurofibromatosis and tuberous sclerosis. Café au lait patches of skin are a relatively common birthmark, and also can appear in multiple locations on patients with neurofibromatosis. For cosmetic appearances, some hyperpigmented lesions such as café au lait macules may be removed by laser treatments.

Sweet's syndrome

Patients with FA may develop Sweet's syndrome (SS), also called acute neutrophilic dermatosis, which presents as painful red plaques or nodules on the skin (Figure 1). As many as 12% of all patients with FA develop SS, according to one institution's experience [3]. The syndrome frequently develops many years after a patient has been diagnosed with FA. A fever typically accompanies the red skin plaques or nodules, and similar lesions may be present in a patient's bones, lungs, or gastrointestinal tract.

SS lesions are often mistaken for sites of active infection and treated as such. Providers should consider the possibility of SS in patients with FA who have painful red skin lesions that do not respond to antibiotics. Because patients with FA can develop SS lesions below the skin, radiographic imaging may be necessary to diagnose the condition. Of note, patients with FA who develop SS also tend to have a high incidence of myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML) which either precedes or follows shortly after the diagnosis of SS. When SS is diagnosed along with characteristic hematologic or skeletal abnormalities, providers should consider a diagnosis of FA. Patients with FA who develop SS should undergo a bone marrow aspiration and biopsy to evaluate the possibility of evolution to MDS or AML.

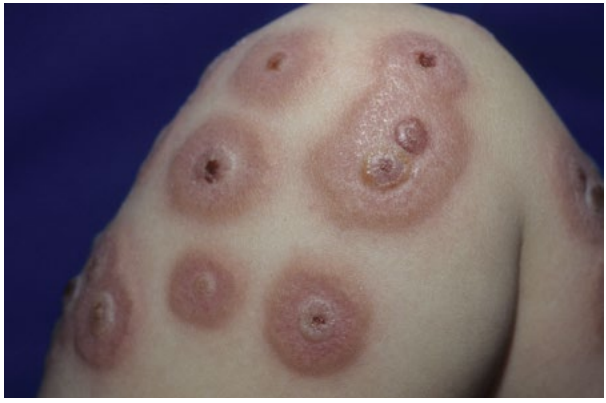

Figure 1. A patient with Sweet's syndrome.

Types of Skin Growths Associated with FA

Ultraviolet radiation, DNA damage, and FA
Ultraviolet radiation from the sun has different subtypes: UVA causes premature aging and wrinkling of the skin; UVB induces DNA damage and is the major source of skin cancer. Individuals with FA have a decreased ability to repair the types of DNA damage induced by UVB (double-strand breaks) and therefore have increased potential vulnerability to the damaging effects of UVB [4]. Three types of skin cancer are discussed below.

Basal and squamous cell carcinomas and verruca vulgaris (warts)
The relative risk of developing cutaneous basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) is unknown, although cases of these cancers in individuals of relatively young ages have been reported to the Fanconi Anemia Research Fund.

Basal cell carcinoma is the most common type of skin cancer in the general population and accounts for over 80% of cases. BCC can look like a shiny, waxy, pearly, red or pink bump, but can have other appearances. It almost never metastasizes but grows locally, can be disfiguring, and must be removed.

Squamous cell carcinoma is more aggressive than BCC and can metastasize, especially when on the head and neck. It appears as red, thick, scaly, tender patches of skin. Individuals who are immunocompromised, including anyone post-transplant, are at greatly increased risk of SCC. Actinic keratosis, another type of skin lesion, presents as flat pink or red scaly patches and may progress to SCC.

Warts occur when keratinocytes (the main non-pigmented cells that make up skin) proliferate. Most warts are initiated by human papillomavirus (HPV). FA has been associated with the occurrence of unusual numbers of warts and may signal a decrease or abnormality in cell-mediated immunity [(1)].

Scaly raised growths in patients with FA may be warts, BCC, SCC, actinic keratosis, or other types of lesions. In a young patient with FA, multiple scaly lesions are likely to be warts and can be frozen off using cryotherapy or treated topically. In an older adolescent or adult, providers should perform a biopsy to determine whether the lesion is related to BCC, SCC, or actinic keratosis.

Dermatologists usually use surgery to remove skin cancers. In addition, photodynamic therapy (PDT) can be used to treat BCC, SCC, and actinic keratosis. PDT uses a drug called a photosensitizing agent and a specific type of light to kill cancer cells. Other therapies include use of a topical chemotherapy such as 5FU to kill cancer cells, and topical drugs that stimulate the immune system to kill cancer and precancerous lesions. Although individual patients have received these treatments without apparent problems, the overall tolerability of these treatments in patients with FA has not been well-studied.

Melanoma

Melanomas are the most dangerous and deadly form of the common skin cancers. The majority are black or brown, are often multicolored, can have irregular edges, and are asymmetrical. They are highly aggressive, and must be removed immediately before they metastasize. Stem cell transplant recipients may have an increased number of melanocytic nevi, or moles, including irregular moles on limbs, fingers, ears, or other acral locations [(8)]. A dermatologist should evaluate notable changes in the size, shape, or color of

preexisting moles, and new moles that are growing rapidly, are asymmetric, or are uneven in color. Whether there is an increased risk of developing melanoma in patients with FA is not known. However, immune compromise and damage from solar radiation are both risk factors for melanoma and these may be of increased relevance in FA. Thus, it is reasonable for providers to conduct annual full body skin examinations for all or any of the common skin cancers beginning at age 18.

Skin Cancer Prevention

Given that the ultraviolet rays from the sun act as an immunosuppressant and patients with FA may be immunosuppressed (especially for at least a year after HSCT), skin protection or sun avoidance should be implemented from an early age. Skin protection should include protective hats and clothing and sunscreen. Sunscreens that contain physical blockers such as zinc oxide and titanium oxide are effective. The SPF must be at least 30 (50 or higher is often recommended in immunocompromised patients), and should be reapplied every 1-2 hours. Recommended products that provide broad-spectrum UV coverage are Neutrogena (helioplex), La Roche Posay, and Blue Lizard (zinc oxide). Skin is the sole source of vitamin D synthesis and sunscreen prevents this process. Diet and vitamin D supplements can provide adequate amounts of vitamin D.

Medications and Treatments that Affect the Skin

Androgen therapy

Androgen therapy (see *Chapter 7*) can increase hair growth in both men and women. Laser treatment may remove unwanted hair, but it is unlikely to have a lasting effect if androgen therapy continues. The risks of laser hair removal are discomfort, temporary pigment changes, and scarring. Laser hair removal has not been associated with an increase in the risk of skin malignancy.

Hematopoietic stem cell transplantation

GvHD

Graft-versus-host disease (GvHD) may occur in patients with FA. GvHD is thought to result primarily from the reaction of donor T-cells (a type of white blood cell) to the patient's skin. New strategies to deplete or inactivate T-cells before or after HSCT have greatly decreased the occurrence of GvHD in FA patients (see *Chapter 11* and [5, 6, 7]).

As GvHD's clinical manifestations and histological features closely resemble other conditions seen in post-transplant patients, providers, usually the hematologist or transplant physician, must take care to prioritize the recognition and management of cutaneous GvHD. Treatment for cutaneous GvHD may include the use of topical steroids. GvHD prevention and treatment is discussed in detail in *Chapter 11*.

Skin Cancer

While all stem cell transplant recipients are generally at risk for nonmelanoma and melanoma skin cancer, patients with FA may be at heightened risk, due to their decreased ability to repair damaged DNA [9,10]. Skin cancer may also behave more aggressively in this population [11]. Risk factors in the general population for nonmelanoma skin cancer include a history of chronic GvHD, prolonged immunosuppression, use of the anti-fungal medication voriconazole (see below), and a history of total body irradiation (particularly greater than 14 grays). Risk factors for melanoma include previous treatment with certain alkylating and antimitotic chemotherapies and radiation. Fortunately, most of these risk factors are minimized in the current routine approach to FA transplantation.

Voriconazole (anti-fungal)

Voriconazole can increase the skin's sensitivity to sunlight. Voricanozole has been implicated in SCC in transplant patients in the general population when used for over 12 months [12]. Due to the increased risk of skin cancers from voriconazole, the use of other anti-fungals should be discussed with a patient's hematologist and transplant team.

Vitiligo

Stem cell transplant recipients may develop localized or generalized loss of skin or hair color [7]. The cause of this condition is unclear, though it may be more common in patients with a history of acute or chronic GvHD. These patients should be particularly careful to protect their skin from the sun or to avoid sun exposure altogether.

Chapter Committee

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References

1. Johansson E, Niemi KM, Siimes M, Pyrhonen S (1982) Fanconi's anemia: Tumor-like warts, hyperpigmentation associated with deranged keratinocytes, and depressed cell-mediated immunity. Arch Derm 118:249-252.
2. Rao GA (2008) Fanconi's anemia. In J Derm Ven Lep 74:398-399.
3. Giulino L, et al. (2011) Sweet syndrome in patients with Fanconi anemia: association with extracutaneous manifestations and progression of haematological disease. *Br J Haematol* 154:278-281.
4. Romick-Rosendale LE, Lui VW, Grandis JR, Wells SI (2013) The Fanconi anemia pathway: Repairing the link between DNA damage and squamous cell carcinoma. *Mut Res* 743-744:78-88.
5. Filipovich, AH, *et al*. (2005) National Institutes of Health consensus development project on criteria for clinical trials in chronic Graft-versus-Host Disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transpl* 11:945-955.
6. Andrews ML, Robertson I, Weedon D (1997) Cutaneous manifestations of chronic graft-versus-host disease. *Anstral J Dermatol* 38:53-64.
7. Sanli H, *et al.* (2008) Vitiligo after hematopoietic cell transplantation: six cases and review of the literature. *Dermatol* 216:349-354.
8. Green A, et al. (1993) Melanocytic naevi and melanoma in survivors of childhood cancer. *Br J Cancer* 67:1053-1057.
9. Leisenring W, *et al.* (2006) Nonmelanoma skin and mucosal cancers after hematopoietic cell transplantation. *J Clin Oncol*. 24:1119-1126.
10. Bhatia S, *et al*. (1996) Malignant neoplasms following bone marrow transplantation. *Blood* 87:3633-3639.
11. Curtis RE, *et al.* (2005) Impact of chronic GvHD therapy on the development of squamous-cell cancers after hematopoietic stem-cell transplantation: an international case-control study. *Blood*. 105:3802-3811.
12. Cowen EW, *et al.* (2010) Chronic phototoxicity and aggressive squamous cell carcinoma of the skin in children and adults during treatment with voriconazole. *J Am Acad Dermatol*. 62:31-37.