

# Cutaneous Features of Neurofibromatosis


## ABSTRACT

Neurofibromatosis type 1 (NF1) is a multisystem genetic disorder that is characterized by café-au-lait spots, axillary or inguinal freckles, cutaneous neurofibromas, and skeletal dysplasias. Currently, there are no curative therapies for NF1 but medical therapies, including systemic sirolimus, have opened the door for significant medical advances in the treatment of NF1. Management of NF1 has been focused on routine examinations looking out for potential complications of NF1. However, many patients with NF1 are missed and may not be diagnosed early. The following review article will provide an overview of select common and uncommon cutaneous features of NF1 to help the practitioner recognize, diagnose and treat patients with NF1.


*KEYWORDS:* Neurofibromatosis type 1, café-au-lait spots, axillary freckles, inguinal freckles, cutaneous neurofibromas

## INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal dominant, multisystem genetic disorder that affects the human nervous system. It is one of the most common single gene disorder that affects approximately one in 3,500 births.[1] Clinical diagnosis of NF1 requires the presence of at least 2 out of the following 7 criteria:

1. Six or more café-au-lait spots or hyperpigmented macules > 5 mm (prepubertal) or > 15 mm (postpubertal)
2. Axillary or inguinal freckles
3. Two or more typical neurofibromas or one plexiform neurofibroma
4. Optic nerve glioma
5. Two or more iris hamartomas, often identified only through slit-lamp examination by an ophthalmologist
6. Sphenoid dysplasia or typical long-bone abnormalities such as pseudarthrosis
7. First-degree relative with NF1


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NF1 affects each person differently, even those from the same family, and it is difficult to predict the severity or progression of NF1. For the caregiver, the presentation of cutaneous features of NF1 can be a source of anxiety. For the physician, it can be a source of frustration as diagnosis can often be challenging and prognosis can be difficult to predict. The purpose of this review article is to provide a brief overview to assist practitioners with early identification, care, and management of common as well as uncommon cutaneous features of NF1.

## COMMON CUTANEOUS FEATURES

### *Café-au-lait Spots*

Café-au-lait spots are usually the earliest findings of the common cutaneous features of NF1 (Figure 1). These are macules that have light tan to dark brown color with well-demarcated smooth border. To fulfill the diagnostic criteria of NF1, patients need six or more > 5 mm (prepubertal) or > 15 mm (postpubertal) macules. These macules are very frequently seen in the general population; however, only < 1% of the general population have multiple café-au-lait spots.[2] These macules are often the first sign of NF1 and occur in 99% of NF1 patients within the first year of life.[3] These may be present at birth or may appear over time, frequently increasing in size and number throughout childhood, and become less obvious in adulthood.

**Figure 1:** Light brown macules and patches with well-demarcated smooth borders.

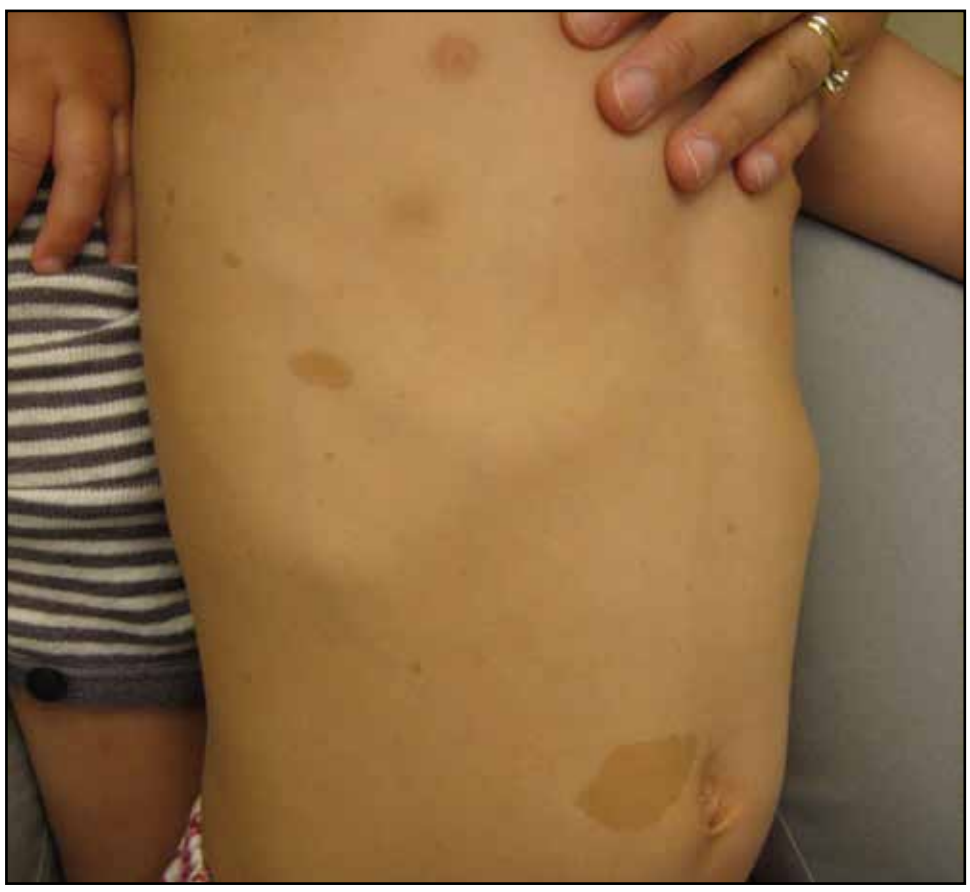
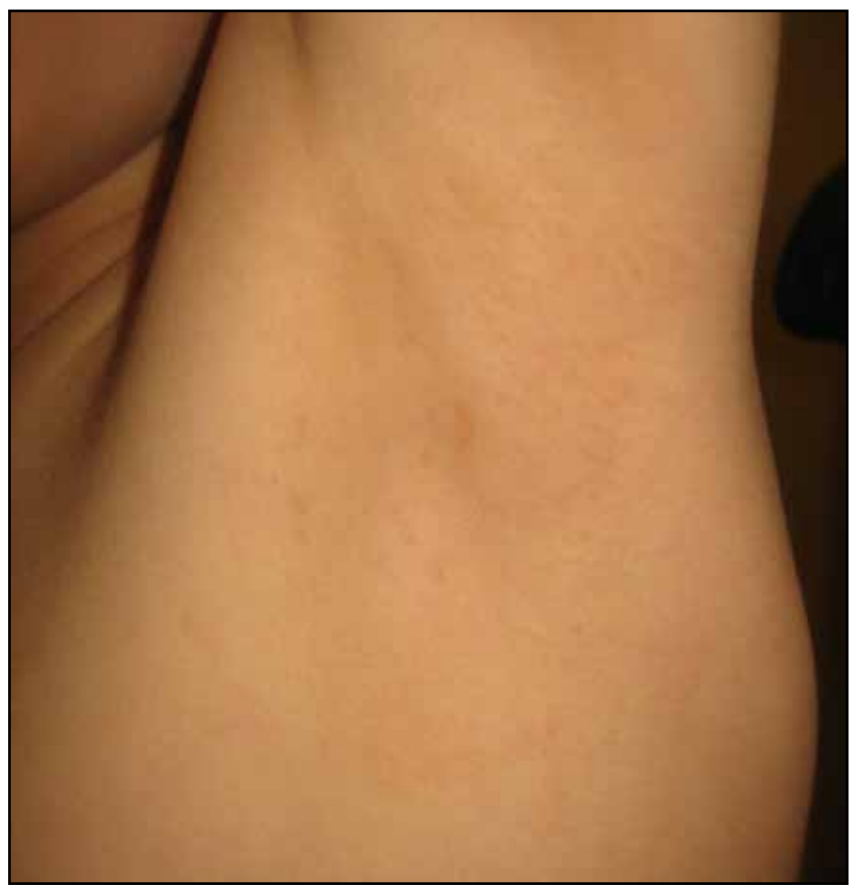


**Figure 2:** Tan-colored macules in the axilla.



## Axillary and Inguinal Freckling

Axillary and inguinal freckling (Figure 2) is the most specific criteria for NF1. Axillary and inguinal freckles, their size ranging from 1 to 3 mm, are rarely present at birth, but appear during childhood through adolescence. The etiology of the freckling is unknown and is unrelated to sun exposure even though their appearance is similar to that of solar-induced freckling.

## Cutaneous Neurofibromas (dermal, subcutaneous, and plexiform)

Cutaneous neurofibromas are another diagnostic criteria of NF1. They can be seen in any parts of the body with a wide variation in their shape and size. There are three different types of cutaneous neurofibromas as follows: dermal, subcutaneous, and plexiform neurofibromas (PNs). Dermal neurofibromas are dome-shaped, soft, fleshy, skin-colored tumors (Figure 3), whereas subcutaneous neurofibromas are firm and nodular. Dermal neurofibromas may appear initially as small papules on the upper body including face, whereas subcutaneous neurofibromas may be detected only through palpation. Dermal neurofibromas usually appear in the 2nd decade of life. In contrast, plexiform neurofibromas (PNs) (Figure 4) are more of diffuse growths that may be associated with overlying hyperpigmentation or hypertrichosis. PNs usually are present at birth. PNs can be deeply invasive and in 8-12% of NF1 patients, this has the potential to be malignant. Rapid growth, bony erosion, and persistent pain of PNs are rare symptoms in PN and suggestive of malignant transformation.[4] In general, cutaneous neurofibromas usually become apparent over time and may continue to grow in size as well as number throughout life. Puberty and pregnancy are associated with these changes of pre-existing lesions.[5]

**Figure 3:** Skin-coloured nodules on the palms in an adult with neurofibromatosis type 1

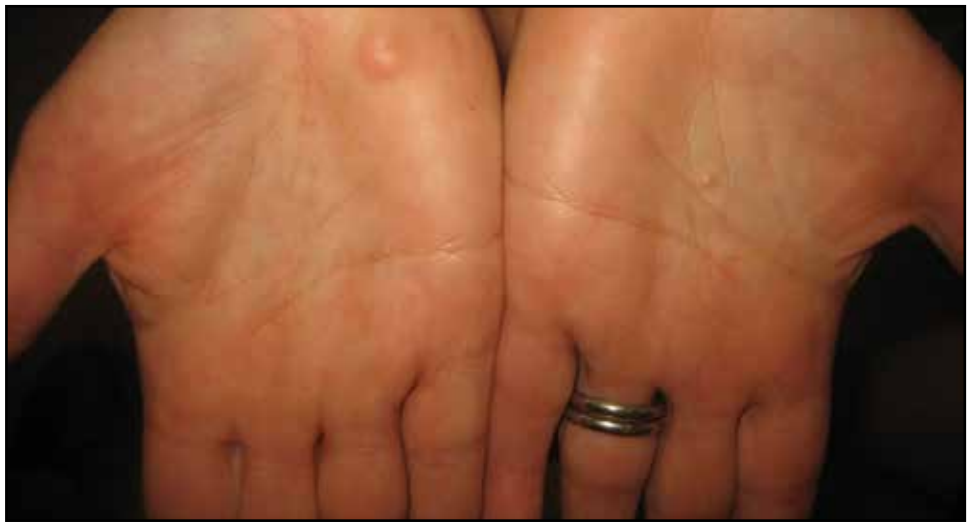
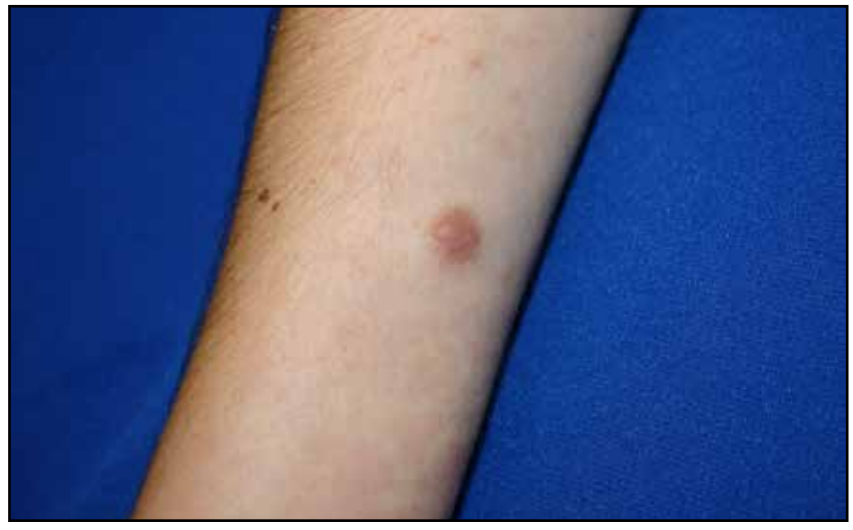


**Figure 4:** Small soft, fleshy, erythematous tumor with irregular surface.



## UNCOMMON CUTANEOUS FEATURES

### *Juvenile Xanthogranuloma*

Juvenile xanthogranuloma (JXG) is a rare, usually benign and self-limiting condition composed of single or multiple papulo-nodular lesions ranging from 1 to 20 mm (Figure 5). It has an orange-tan color and occurs most often in the skin of the head, neck, as well as trunk but can also occur in any parts of the body including the eye. The most common ocular presentation involves the iris. It may present as diffuse or localized tumors that can lead to heterochromia, uveitis, spontaneous hyphema, secondary glaucoma, and eventually blindness.[6] These can be seen in 4% of children and in 5-10% of all population[6] but the prevalence can be as high as 18.2% in patients with NF1.[7] They require prompt ophthalmology and dermatology consultations for management.

It has been reported and debated that JXG, NF1, and juvenile myelomonocytic leukemia (JMML) are associated with each other. In consensus, physicians should be aware of presenting features of JMML such as hepatosplenomegaly, lymphadenopathy, pallor, and petechiae. Routine screening in NF1 patients is not recommended.

### *Nevus Anemicus*

Nevus anemicus is a congenital, hypo-pigmented, well-demarcated and asymptomatic macule or patch that is caused by the increased sensitivity of blood vessels to catecholamine (Figure 6). Nevus anemicus is often recognized in NF1 patients; however, it may be coincidental due to lack of correlation studies. They are usually found on the upper body however they may occur in any parts of the body. Nevus anemicus can be distinguished from vitiligo and hypochromic nevi by applying pressure with a glass slide to the lesion as well as to an adjacent unaffected area. With this method, it should become indistinguishable from the

**Figure 5:** A single orange-tan colored papulo-nodular lesion consistent with a juvenile xanthogranuloma.

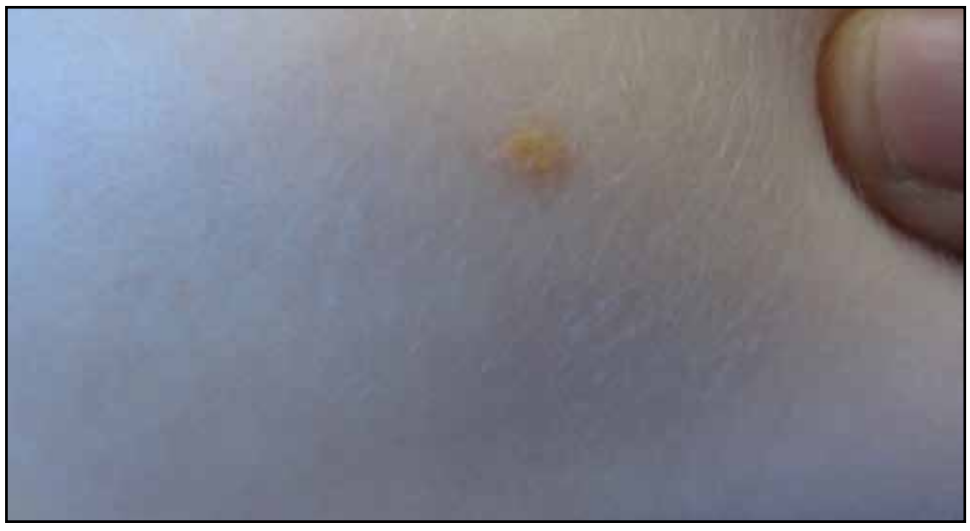
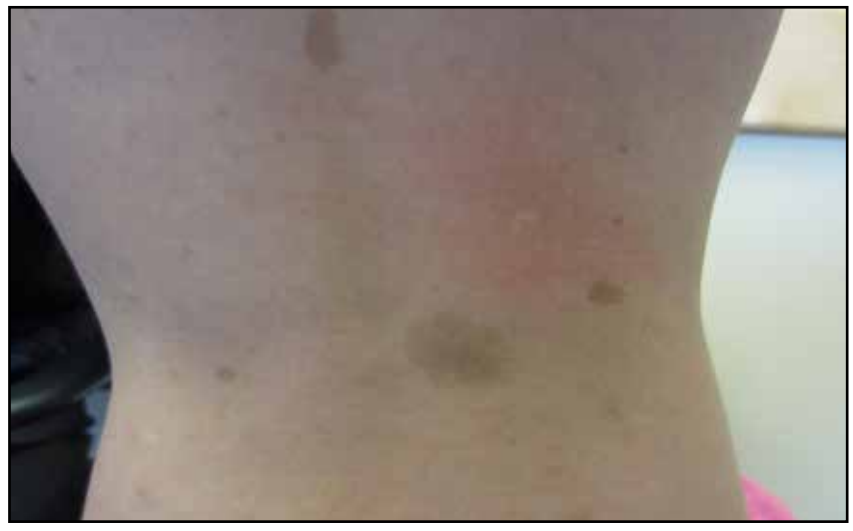


**Figure 6:** Hypoperfused, well-demarcated macules consistent with nevus anemicus.



## SUMMARY OF KEY POINTS

1. Clinical diagnosis of NF1 requires the presence of at least 2 out of the 7 criteria.
2. Not all patients with café-au-lait spots will have NF1.
3. Axillary and inguinal freckling are the most specific criteria for NF1.
4. Three different types of cutaneous neurofibromas are dermal, subcutaneous, and plexiform neurofibromas (PNs). PNs can become malignant.
5. Juvenile xanthogranuloma and nevus anemicus are uncommon associated cutaneous features of NF1.

surrounding skin, unlike vitiligo and hypochromic nevi. Treatment is not required. However, camouflage makeup may be recommended to the patient who is bothered by its cosmetic appearance.

## SUMMARY

Neurofibromatosis type 1 (NF1) is a genetic disorder that affects multiple systems. It is very important to recognize the common and uncommon features of NF1 in order to differentiate it from other similar disorders. This allows for prompt and appropriate referrals leading to optimal management. The annual examinations should focus on blood pressure, assessment of skin, visual acuity checks, ophthalmological evaluations, and looking for any bone abnormalities. In general, physicians should play an active role in educating caregivers and put emphasis on routine exams looking out for rare cutaneous manifestations of NF1 to prevent potential complications.

## REFERNCES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## CLINICAL PEARLS

NF1 is a genetic disorder and there is no cure.

Patients should be routinely monitored for rare complications and annual exam should include BP measurement, skin and bone abnormality assessment, visual acuity checks, and ophthalmological evaluations.

Not all Cafe-au-lait spots require specialist referral however early recognition and prompt referral is essential.

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