Tuberous Sclerosis Alliance

SKIN (DERMATOLOGICAL) FEATURES OF TSC

Most people with tuberous sclerosis complex (TSC) have changes in their skin. There may be light colored spots, called hypomelanotic macules, and bumps on the skin of several different types (angiofibromas, cephalic fibrous plaques, shagreen patches, and ungual fibromas). In combination, these skin features are found only in TSC, and they are often used to diagnose TSC especially in young patients.

Some TSC skin features may appear at birth. Others develop later in childhood or even in adulthood. Most people with TSC eventually have at least one skin feature, and many will have several (Darling et al., 2010; Northrup et al., 2013). Currently, there is no way to predict how many TSC skin features will develop during childhood, but they tend to remain stable during adulthood.

The presence of the skin features of TSC is highly variable from one individual with TSC to the next, even within one family. Some people have TSC skin changes that are hardly noticeable. Others may have growth on the skin that cause pain or bleed easily. In addition, tumors on the skin tend to occur in cosmetically important areas of the body such as the face. In such situations there are a variety of different treatments that can be used. The skin changes in TSC is due to uncontrolled cell proliferation resulted from underlying genetic mutation(s), a similar process that may affect the other organ systems of the body. However it is not unclear why one individual will have them and another will not. Ongoing research will help to shed light on the cause of the various skin features and treatment options.

Hypomelanotic Macules (Figure 1A)

Most people with TSC have hypomelanotic macules (hypo, meaning less than normal; melanotic, referring to the pigment of skin). These may be present at birth, increase during early childhood and usually persist throughout life. Sometimes hypomelanotic macules become less obvious in adulthood, and may even disappear. Hypomelanotic macules are usually the size of a thumbprint or larger. They are also referred to as ash-leaf spots when they are oval at one end and pointed at the other, resembling the leaf of the European mountain ash tree. Hypomelanotic macules can be scattered anywhere on the skin, but they are most common on the trunk, limbs and buttocks. Involvement of the scalp may result in a white patch of hair.

During infancy or in people with very fair skin, hypomelanotic macules are only visible with the use of a Wood's lamp. This is a special ultraviolet light that makes macules stand out against the surrounding normal skin.

The number of hypomelanotic macules may vary from 1 to more than 100. In order to be useful for making a diagnosis, the individual should have 3 or more hypomelanotic macules. This is one of the major features in the diagnostic criteria for TSC (Roach et al., 1998; Northrup et al., 2013). Fewer than 3 hypomelanotic macules do not count towards

making a diagnosis because one or two hypomelanotic macules are common in the general population, occurring in about 5% of children. Sometimes numerous small macules may be present in TSC (especially on the arms and legs). These may resemble confetti, and these are a minor criterion for diagnosis.

There are normal numbers of pigment (melanin)-producing cells in the hypomelanotic macules, but they are unable to produce sufficient amounts of pigment to create normal skin tone. This results in an area of skin that is lighter than the surrounding skin. The decreased pigment also means that these areas are more susceptible to sun burn. Individuals with TSC should be careful about sun exposure and use a broad-spectrum sunscreen. These sunscreens protect against UVA and UVB and have a sun protection factor (SPF) of at least 30. Sunscreen should be applied to all areas exposed to the sun, since tanning of surrounding skin will only make the hypomelanotic macules more apparent.

Currently, treatments for hypomelanotic macules attempt to conceal the spots and do not permanently restore the normal skin color. One treatment option is to use a sunless tanning lotion that contains dihyoxyacetone (DHA) as the active ingredient. These work by temporarily dyeing the top layers of the skin. Another option is to apply concealing creams that are matched to the person's skin color. The resource section at the end of this information sheet provides a list of companies that provide these products. A new treatment using topical rapamycin cream has also shown to be effective in a recent case report (Wataya-Kaneda M et al., 2012).

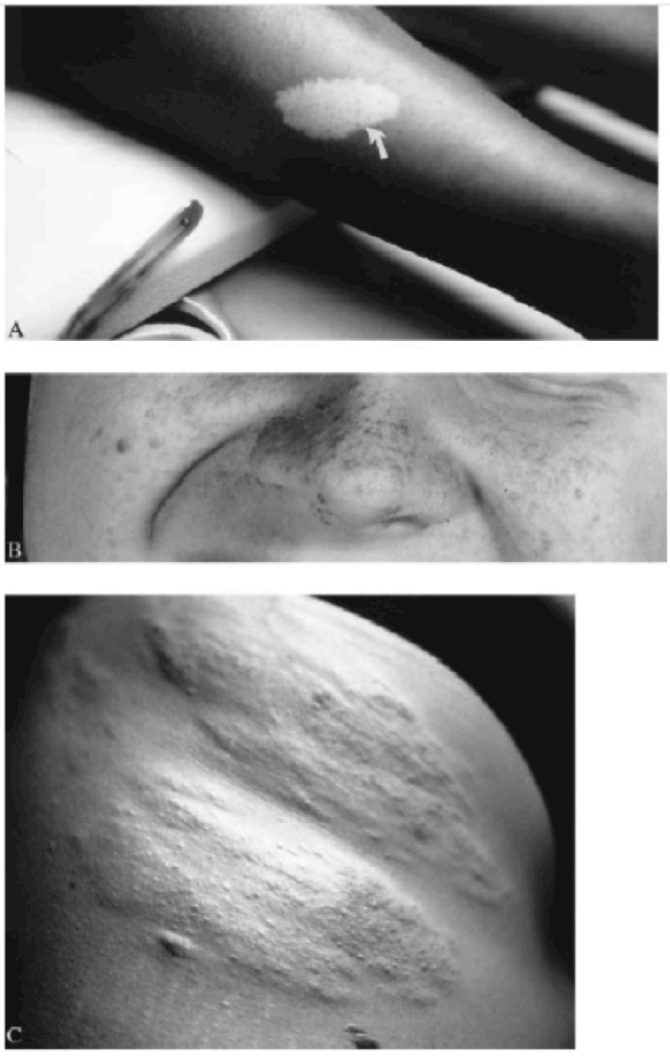


Figure 1. Classic cutaneous manifestations of tuberous sclerosis include (A) hypomelanotic macule (ash-leaf spot) (arrows), (B) facial angiofibromas. (C) Shagreen patch. Figures 1A and 1C reprinted from Roach ES, Semin Neurol 1988; 8:83–96, with permission. Figure 1B reprinted from Roach ES, Delgado MR, Derm Clin 1995;13:151–161, with permission.

Angiofibromas (Figure 1B)

Angiofibromas are found in a majority of individuals with TSC over 5 years of age (Webb et al., 1996). These small bumps are usually scattered on the central face, especially on the nose and cheeks, and sometimes on the forehead, eyelids, and chin. They are often clustered in the grooves at the side of the nose. Angiofibromas are typically smaller than a peppercorn, but they can grow

larger. They may be skin-colored, pink, or red. In darkly pigmented individuals they may be reddish brown or dark brown. People with TSC usually have multiple angiofibromas, and some individuals may have hundreds. Individual with three or more facial angiofibroma meets one of the major diagnostic criteria for TSC.

Angiofibromas may begin in early childhood as flat red "spots" on the face, or a diffuse redness of the cheeks. The redness is due to increased blood vessels in the skin. They later become elevated due to increased amounts of fibrous tissue. Fibrous tissue is similar to what is found in a scar. Angiofibromas are overgrowths of normal skin components (hamartomas), and they do not become cancers. None of the skin features in TSC become cancers. However recent study has shown that sun exposure can cause additional genetic mutation in facial angiofibromas, suggesting that sun protection may reduce the number and severity of angiofibromas (Tyburczy ME et al., 2013)

Treatment of Angiofibromas

Angiofibromas may be treated for several reasons. They may bleed with minimal or no trauma. Bleeding can be stopped by applying pressure to the area of bleeding, but treatment lessens the likelihood of repeated episodes of bleeding. Rarely, angiofibromas become large enough to block vision or impair breathing through the nose, and these problems may necessitate treatment. Angiofibromas can have adverse effects on appearance and self-image, prompting some to avoid social situations. Treatments reduce the impact of angiofibromas on the person's life. A variety of surgical approaches can be used to treat angiofibromas, including the use of lasers. There is evidence that medical treatments may also be effective. Many studies recently have shown that topical rapamycin treatment can be promising for the treatment for angiofibroma. When treatment is started while angiofibromas are small, it will likely reduce the need for laser treatment in the future. A large scale clinical trial investigating the effectiveness of this medication is currently underway (www.clinicaltrials.gov).

A vascular (blood vessel) laser is used to treat the flat red spots. This type of laser is designed to destroy blood vessels with low risk of scarring. This laser treatment can either be performed in the office as an outpatient procedure (if the treatment area is small or if the individual with TSC is cooperative) or in an ambulatory surgical center should the patient requires sedation. Treatment usually takes 5-20 minutes. It causes moderate discomfort if performed using only topical anesthetics but is pain-free when using sedation. Following the treatment, there is rarely any discomfort and usually no wound to care for except protection from sun and trauma is usually recommended. The full effect of a given treatment can be judged 6 to 8 weeks later. If a lesion does not disappear, it can be retreated. Although there is no limit to the number of treatments that can be performed, generally speaking, if no noticeable improvement is apparent after two treatments, one has to reassess either (1) the nature of the lesion that is being treated; (2) the choice of laser; or (3) the laser setting used. There is no age restriction for vascular laser treatment, but it appears that greater success is obtained when treatment is started early in childhood while the lesions are still flat. It may be that early treatment decreases the development of raised lesions later in life.

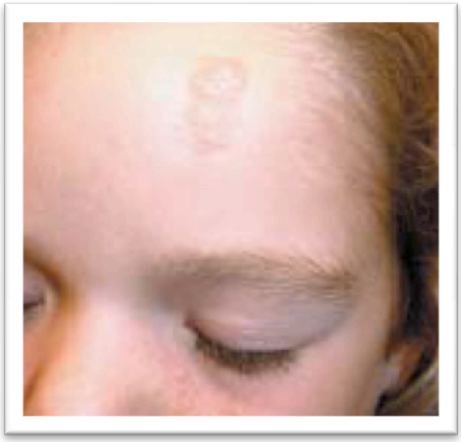
For individuals with angiofibromas that are elevated above skin level, an ablative laser is commonly used, such as carbon dioxide (CO_2) or erbium: YAG laser, sometimes in combination with a vascular laser. A new approach is to use a combination of

electrosurgery, pulsed-dye laser treatment, and ablative fractional resurfacing (Weiss and Geronemus, 2010). Other treatments include photodynamic therapy, surgical excision, dermabrasion, or cryosurgery. Removal is quick using these methods, but the scarring and changes in pigmentation that may result are permanent. Seek a physician who is experienced in these procedures. Either plastic surgeons or dermatologists generally perform laser surgery.

Treatment with an ablative laser is usually performed as single-day surgery in a hospital or surgery center, with the patient under general anesthesia and under the supervision of an anesthesiologist. Prophylatic antiviral treatment sometimes are needed before the surgery to prevent wound infection. There is typically minimal postoperative pain when the face is treated with liberal application of topical emollient ointments. Clear and detailed pre- and post-operative instructions are very important, and careful attention to wound care is necessary for optimal skin healing. The patient should be sure the physician addresses these issues with him or her.

Raised facial angiofibromas can be treated at any age. There may be a rapid growth phase of the facial angiofibromas during puberty, so it is suggested that the child be seen and evaluated for treatment before puberty begins. Reoccurrence is the greatest problem associated with removal of facial angiofibromas. As a result, laser surgery may need to be repeated. There have been multiple reports on the treatment of facial angiofibromas in children using topical rapamycin. This may provide an alternative to the current approach in the management of angiofibromas in the future. This treatment has not been officially approved by the food and drug administration (FDA), therefore is only available at special compounding pharmacy when prescribed by dermatolgists.

Cephalic Fibrous Plaques (previous known as forehead fibrous plaques)

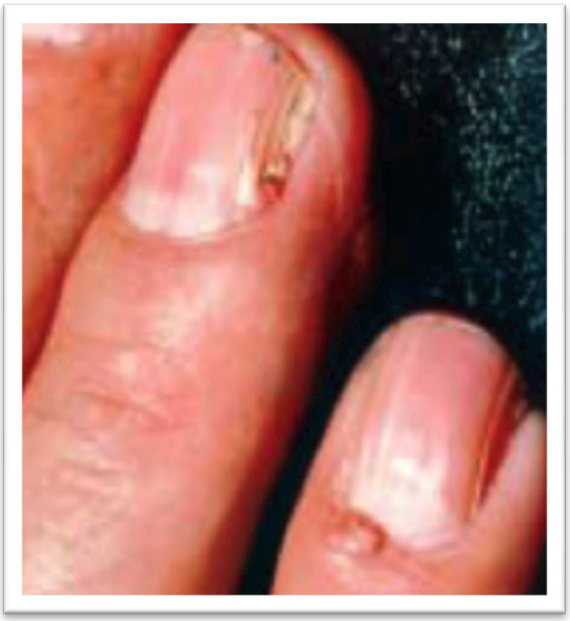


The fibrous plaque is similar to an angiofibroma but is a larger area of elevated pink skin. It is usually found on the forehead, but fibrous plaques may also occur on the cheeks or scalp. These skin lesions can be surgically removed, but, because of the resultant scar, it is advisable to discuss the benefits and risks of surgery with a plastic surgeon or dermatologist before making that decision.

Shagreen Patch (Figure 1C)

The shagreen patch is an area of thickened, elevated pebbly skin (like an orange peel) usually found on the lower back. It can be single or multiple. Sometimes the shagreen patch is located elsewhere on the back or on the buttocks or upper thighs. It consists of an excess amount of fibrous tissue, similar to that found in scars. The shagreen patch usually does not cause problems, but if it does it can be treated by surgical excision.

Ungual Fibromas



Ungual fibromas are fibrous growths that are located around the fingernails or toenails (Aldrich et al., 2010). They are called subungual fibromas when they arise from beneath the nail and periungual fibromas when they arise from around the nail. Ungual fibromas may distort the nail by causing a groove or by pushing the nail up from the nail bed causing infection and bleeding. On the toes, ungual fibromas can be painful when wearing shoes. Ungual fibroma may occur after incidental trauma. More than two ungual fibromas however is considered as one of the major diagnostic criterion for TSC. Ungual fibromas can be removed by surgical excision. This may be combined with CO_2 laser removal to maximize effectiveness while limiting scarring and damage to the nail. Ungual fibromas may recur.

Dental Pits

Dental enamel pits can be a nonspecific finding. However the diagnosis of TSC should be considered when there are three or more dental enamel pits noted especially in children. Since many of the oral manifestations of TSC occur in young children; baseline oral evaluation is recommended as early as six month of age or at time of diagnosis. For the majority of TSC patients, regular exam every 6 months is recommended. Patients with special needs and difficulty maintaining oral hygiene may benefit from routine exam every 3 months.

Gingival Cysts

Because of the risk of bone cyst formation in the jaw, panoramic radiographic evaluation is recommended by age 6-7 years or earlier for asymmetry, asymptomatic swelling, or delayed or abnormal tooth eruption sequence.

Gingival Fibromas

Gingival fibromas are fibrous nodular growths involving the gingiva (gums) of the mouth. They can cause bleeding or, rarely, problems with eating. Gingival fibromas may occur more frequently in individuals with epilepsy who are taking phenytoin, an antiepileptic drug that causes gingival overgrowth. Although the diagnosis of TSC should be considered, when there are more than two gingival fibromas are noted especially in children. The finding can be nonspecific, therefore is considered as one of the minor diagnostic criterion. Gingival fibromas may be surgically removed by dermatologists, dentists or oral surgeons.

Soft Fibromas (Skin Tags)

Some individuals with TSC may have soft, baglike growths on the neck, trunk, armpits, or groin. They may also have smooth skin-colored bumps on the neck, armpits, and near the flexure of the limbs. If these fibromas are large they can be surgically removed. They may bleed excessively if they are torn off the skin, so an individual with TSC should always have a physician remove the fibroma.

Medical Treatment for TSC Skin Lesions

New medical treatments for TSC are being tested that may supplement current surgical approaches for treatment. These treatments are based on studies of people with TSC taking sirolimus (rapamycin), or drugs that are similar to sirolimus, for internal tumors. Several studies have reported that these drugs appear to reduce the size and redness of angiofibromas. However, these drugs have the potential for serious side effects, so they would not usually be used for treating only the skin. However, a form of the medicine applied topically to the skin, instead of being taken internally, may retain effectiveness while having fewer side effects (Haemel et al., 2010; Koenig et al., 2012; Wheless and Almoazen, 2013). Preliminary study has shown that the medication is rarely absorped to a measurable amount in the blood stream when applied to a limited area. Recurrence is also expected when the treatment is discontinued. There are ongoing clinical trials investigating the use of topical formulations of mTOR inhibitor drugs such as sirolimus which may provide a more cost-effective treatment for those affected. For information on clinical trials, see www.clinicaltrials.gov or http://www.tsalliance.org/pages.aspx?content=332.

Health Insurance Coverage for Skin Treatments in TSC

The willingness of health insurance companies to cover the cost of treatment is quite variable. Be sure to check with your health insurance company before consulting with your doctor. If your health insurance company refuses to cover the removal of facial angiofibromas, or any of the skin features of TSC, you may simply be talking to someone who considers this a cosmetic procedure and who does not understand the nature of the disease. Very often a letter from your doctor will help educate your health insurance company about TSC and the nature of the skin features of the disease, after which the insurance company will often agree to cover the costs of the procedure.

A sample letter for you to use to educate your health insurance provider is available at http://www.tsalliance.org/documents/Medical%20necessity%20letter%20for%20dermatological%20procedures%20with%20references.pdf. This letter can be tailored by your physician for your individual needs. If you are denied coverage by the insurance company, you have the right to appeal their decision. Ask the company specifically why the coverage has been denied—it may be that they are denying the coverage thinking it is cosmetic surgery, or it may be that this type of surgery is not covered by your insurance plan.

Summary

Although most skin features of TSC are not curable, an experienced physician can control or remove the lesions with favorable results. Additionally, with continued research about medications that specifically inhibit the proliferation of blood vessel and fibrous tissue in

TSC, the future looks bright for new, more effective treatments for the skin manifestations of this disease.

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Resources

There are cosmetics available to cover hypomelanotic macules and facial angiofibromas. The following are a few of the cosmetic lines that can be contacted for more information:

Clinique
1-800-419-4041
www.clinique.com

Covermark
1-800-524-1120
www.cm-beauty.com/

Dermablend
Phone: 1-800-662-8011
www.dermablend.com

Linda Seidel
Phone: 1-800-590-5335
www.lindaseidel.com

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