Chapter 33
Tuberous Sclerosis

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33.1 Introduction

Tuberous sclerosis or tuberous sclerosis complex (TSC) is a genetic disorder that classically causes skin changes, intellectual disability, and seizures. This relatively common condition often involves the face with angiofibromas (adenoma sebaceum) that in the earliest stages may be misinterpreted as acne lesions. Variable expressivity complicates the diagnosis and epidemiology of this autosomal dominant disorder. Current treatment focuses on mechanical removal of the angiofibromas. Recently, topical or systemic IL-2 inhibitors like rapamycin have also shown promise as a therapy [1].

33.2 Background

TSC is caused by a mutation in either the *TSC1* or *TSC2* genes with resultant loss of cell growth control. While TSC is an autosomal dominant disorder, the majority of cases are not inherited. Instead, 65–85 % arise from spontaneous mutations [2]. The two genes are distinct in location and function but produce nearly indistinguishable clinical presentation. Mutations in *TSC2* are found in more than half of the total number of patients. In about one fifth of patients, no mutation is identified in either of the *TSC1* or *TSC2* genes [3]. The range of prevalence estimates vary widely from 1 in 5,800 to 1 in 25,000 in the Caucasian population [4, 5].

The biological roles of hamartin (the protein product of *TSC1*) and tuberin (the protein product of *TSC2*) have been fairly well defined. They form a multimeric

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complex that functions in the mTOR pathway. The mTOR pathway plays an important role in cell growth and proliferation hence its effect on cell growth. The loss of function of either gene leads to increased activation of this pathway. The TSC complex interacts with Rheb, a member of the RAS subfamily, and stimulates conversion of Rheb to its inactive form. Loss of function TSC complex mutation leads to an increase in active Rheb, which in turn increases downstream mTOR expression.

33.3 Clinical Presentation

Presentation for TSC in the skin varies widely from a few subtle angiofibromas to diffuse angiofibromatosis with shagreen patches and ash-leaf macules, with clinical manifestations depending largely on the genetic expression in a given patient. Ash-leaf macules and shagreen patches are more likely to be present either at birth or shortly thereafter. Angiofibromas, however, may appear at any time but most often appear in late childhood or early adolescence frequently appearing much like the papules of acne vulgaris. Angiofibromas are several millimeter in diameter, fleshy pink to red papules. These can occur singly or in clusters of hundreds often in a malar distribution (Fig. 33.1). Koenen tumors are subungual fibromas that are pathognomonic for TSC (Fig. 33.2). Ash-leaf macules are hypopigmented macules that generally have a single broad side that tapers into a narrow tip, while shagreen patches are hamartomas of connective tissue that are typically raised, irregularly shaped, and firmer than surrounding tissue.

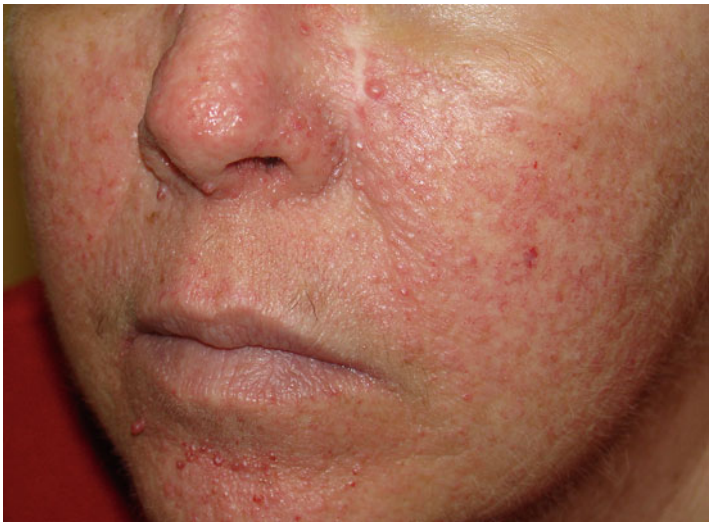

Fig. 33.1 Thousands of angiofibromas cover the face of a patient with Tuberous Sclerosis (Photo credit: Joshua A. Zeichner, M.D.)

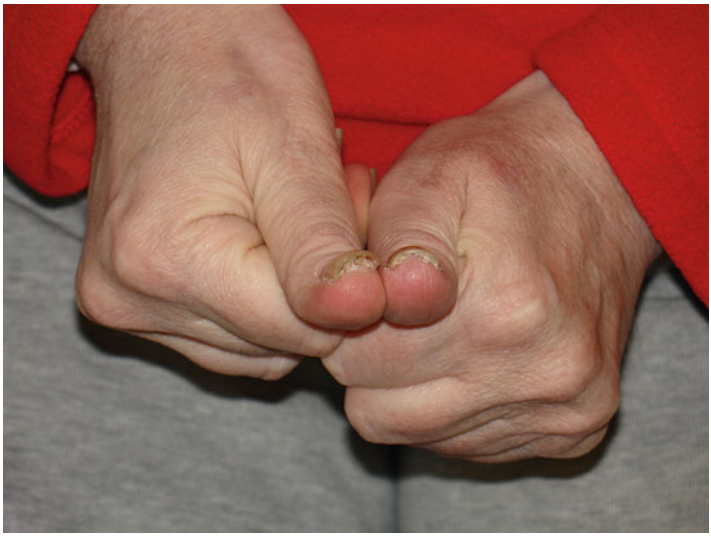

Fig. 33.2 Reddish to flesh-colored, smooth, firm subungual papules. Koenen tumors may also appear in a periungual distribution, emerging along the nail folds (Photo credit: Joshua A. Zeichner, M.D.)

In addition to the multiple skin findings, TSC also has effects on internal organ systems as well. The presence of skin changes should prompt a more thorough work-up to examine for possible renal lesions, neurologic findings, and pulmonary manifestations. Sequelae from internal organ involvement can cause serious morbidity and mortality [6].

33.4 Work-Up

Diagnosis of TSC is based upon diagnostic criteria and therefore cannot simply be made upon any one clinical finding such as the presence of angiofibromas. Diagnosis of TSC requires associated lesions of two or more organ systems or at least two different lesions in the same organ to confirm diagnosis [7]. In fact, some of the so-called pathognomonic features such as intellectual disability and epilepsy are so common in the general population that they are not specific enough to contribute to diagnosis [8]. For this reason a list of criteria was set forth to establish consensus as to a reliable and consistent method of diagnosis [9]. Complete diagnosis and the evaluation of TSC go beyond the scope of this text; however, one or more angiofibromas, without other appropriate findings, do not suffice for diagnosis nor does it imply a work-up for TSC is warranted. Angiofibromas occur in over 90 % of individuals with TSC. However, a variant of angiofibromas occur commonly in the general population and are known as fibrous papules of the nose or simply fibrous papules. These may occur singly or multiply but only rarely in as high numbers or as diffusely as is manifest in the angiofibromas of TSC [10].

33.5 Treatment

The treatment of TSC depends on the patient's clinical status and radiologic findings. Diagnosis and treatment should include appropriate referral to a TSC clinic if possible with adequate follow-up and screening. Cutaneous lesions can be monitored or treated depending on patient preference and overall status using mechanical removal or Argon and /or CO2 laser technologies. More inexpensively, radiofrequency ablation, chemical peel, and dermabrasion may also be effective [11, 12].

With the discovery of the role of the TSC complex in the mTOR pathway, utilization of mTOR inhibitors was identified as a potential treatment of all tumors in TSC patients. One mTOR inhibitor is sirolimus, also known as rapamycin, an immunosuppressant FDA-approved for use in transplant patients. Sirolimus has shown promise in clinical trials both systemically and topically for the treatment of angiofibromas [13, 14]. This therapeutic strategy appears to inhibit angiogenesis by decreasing production of vascular endothelial growth factor [15]. Ongoing clinical trials are underway to study sirolimus as an effective and safe for mainstream treatment.

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