Cutaneous Manifestations of Pulmonary Disease

Jennifer Rullán, Rachelle E. Seijo-Montes, Annie Vaillant, and Néstor P. Sánchez

The recognition and correct elucidation of the cutaneous signs of diseases that primarily affect the pulmonary system may assist the clinician in diagnosis and estimation of prognosis. This chapter describes selected pulmonary diseases with distinctive cutaneous findings. Often times in medicine, findings on the skin may prove very helpful in exposing an underlying systemic condition. Pulmonary conditions can be particularly life threatening, and early detection and treatment may impact the course of a patient's life. In all fields of medicine, especially internal medicine, pneumology, nephrology, pediatrics, and dermatology, physicians can enhance their clinical proficiency by better understanding the rare and common cutaneous manifestations of pulmonary diseases such as sarcoidosis, tuberculosis, Birt–Hogg–Dubé syndrome (BHDS), and cystic fibrosis.

Sarcoidosis

The variable, multi-systemic disease of sarcoidosis was first described by Jonathan Hutchinson from England in 1875. Shortly after, in 1877, he described a patient with cutaneous sarcoidosis [1–3]. In 1899, the Norwegian dermatologist Caesar Boeck from Norway was accredited for the word "sarcoidosis" and the histopathologic description of skin nodules characterized by "epithelioid cells with large pale nuclei and also a few giant cells" which he called "multiple benign sarcoid of the skin" [4, 5]. The etiology remains uncertain; however, several genetic polymorphisms are associated with an increased risk of developing sarcoidosis, suggesting that genetic susceptibility to sarcoidosis is probably polygenic [6]. Environmental factors may also modify the susceptibility to sarcoidosis. The pathogenesis of this condition involves a T-helper-1-mediated immune response to environmental antigens in a genetically susceptible host [6]. The characteristic histologic feature of the non-infectious, non-caseating granulomas of sarcoidosis are the epithelioid tubercles (macrophages faced with chronic cytokine stimulation differentiate into epithelioid cells) that are "naked," in other words, there are few to no plasma cells or lymphocytes associated with the granuloma [5, 7].

Pulmonary disease occurs in up to 90% of sarcoid patients, of which 90% are associated with hilar and/or paratracheal lymphadenopathy. Fibrosis with bronchiolectasis (dilatation of the bronchioles) and honeycombing of the lung parenchyma occurs in 25% of patients and is the most common mechanism responsible for pulmonary hypertension in these patients [5, 7]. Although the lung is the most common organ affected by the disease, there have been reports of skin involvement in approximately 25–35% of the patients [5, 8, 9]. Cutaneous sarcoidosis can represent a diagnostic challenge due to its widely variable morphologies; hence, it is often known as one of the great imitators in dermatology [10]. The presence of cutaneous manifestations in sarcoidosis has shown significantly decreased time to diagnosis and can provide relevant prognostic implications. The importance of taking into account cutaneous sarcoidosis in the clinical differential diagnosis of a given skin lesion depends on the systemic involvement and the convenience of the skin as a tissue source for histologic analysis [9, 11].

The cutaneous lesions of sarcoidosis are classified in one of two ways: either specific, because of the presence of the hallmark naked sarcoid granulomas upon histologic evaluation, or nonspecific, because of the absence of such granulomas [9]. Specific lesions occur in 16% of patients and are associated with a poor prognosis or a chronic form of the disease [3, 12]. The most common specific lesions of cutaneous sarcoidosis include lupus pernio, infiltrated plaques, macular and papular lesions, and subcutaneous nodules [13]. Other such lesions include scar sarcoidosis, alopecia, ulcerative lesions, and

J. Rullán (✉) • R.E. Seijo-Montes • N.P. Sánchez
Department of Dermatology, University of Puerto Rico School of Medicine, Medical Sciences Campus, San Juan, Puerto Rico
e-mail: rullanmed@yahoo.com

A. Vaillant
Department of Obstetrics and Gynecology, San Juan City Hospital, Medical Sciences Campus, San Juan, Puerto Rico

N.P. Sánchez (ed.), *Atlas of Dermatology in Internal Medicine*,
DOI 10.1007/978-1-4614-0688-4_2,

hypopigmented patches. Patients with nonspecific lesions tend to have a good prognosis since these are mostly associated with an acute form of sarcoidosis. The most common nonspecific lesion is erythema nodosum. Other forms include nail, mucosal, and childhood sarcoidosis [9].

Specific Sarcoidosis

Lupus Pernio (Besnier–Boeck–Schaumann Disease)

The classic specific lesion of sarcoidosis is lupus pernio, first described in 1889 by Besnier [14]. It is characterized by relatively symmetric, violaceous, shiny, indurated, smooth, and doughy plaques and papules. The term "lupus" was used originally to describe lesions with an eroded appearance and the term "pernio" is used to describe the inflammation caused upon exposure to the cold [14]. The violaceous color has often been described as having a cyanotic hue as that seen in frostbite. It is frequently found on the nose (especially the alar rim), earlobes, cheeks, and sometimes the fingers, areas primarily affected by cold weather (Fig. 1). It occurs more commonly in women and in patients with black skin [3, 11, 12, 15]. This persistent lesion is not painful and does not disturb the epidermis causing ulceration; however, the lesions are disfiguring and may erode into the underlying cartilage and bone. Even a small amount of little papules on the nose may be associated with granulomatous dissemination into the nasal mucosa and upper respiratory tract, resulting in ulcerations, masses, or even serious airway obstruction [16]. Lupus pernio is associated with the chronic form of sarcoidosis and extra-pulmonary involvement [5, 9, 12, 16, 17].

Lupus Pernio patients have lung involvement in 75% of the cases and upper respiratory tract involvement 50% of the time [7]. In addition, patients with lupus pernio have increased occurrence of lytic and cystic bone lesions underlying affected skin areas, especially the hands and feet, chronic uveitis, and fibrotic sarcoid in the kidneys and lacrimal glands [7, 18].

Papules, Macules, Nodules, and Plaques

Granulomatous infiltrates of the skin most commonly present as persistent papules, nodules, or plaques. Papules, nodules, and maculopapular eruptions, as a group, are the most common cutaneous manifestations of sarcoidosis (Fig. 2) [3]. They may be red-brown or yellow-brown with an erythematous base, or violaceous in color and the surface is smooth due to the lack of epidermal involvement [1, 12]. They are most commonly found on the face, specifically the eyelids, periorbital area, and nasolabial folds, but are also common in other areas of the body such as the trunk, extremities, nape of the neck, and upper back [5, 9, 19]. Diascopy, a procedure used to study the lesions by compressing a slide against them, reveals blanching, and a yellowish brown or "apple-jelly" color, which is characteristic of sarcoidal skin [9, 13].

Papules can evolve into plaques. Some plaques may show hyperpigmentation with scales and they commonly form an annular configuration with central clearing (Figs. 3 and 4). When the plaques contain telangiectasias, or dilated blood vessels near the surface of the skin, it is called angiolupoid sarcoidosis [7, 19]. Sarcoid plaques are usually distributed symmetrically and bilaterally [8, 9]. It is important for a physician to be able to distinguish the presence of plaques because they are more likely to be associated with a chronic form of the disease [9, 13]. Since these lesions are often elevated and crusted, they are more likely than papules to resolve with scarring [9, 13, 19]. A rare variant of the sarcoid plaques that

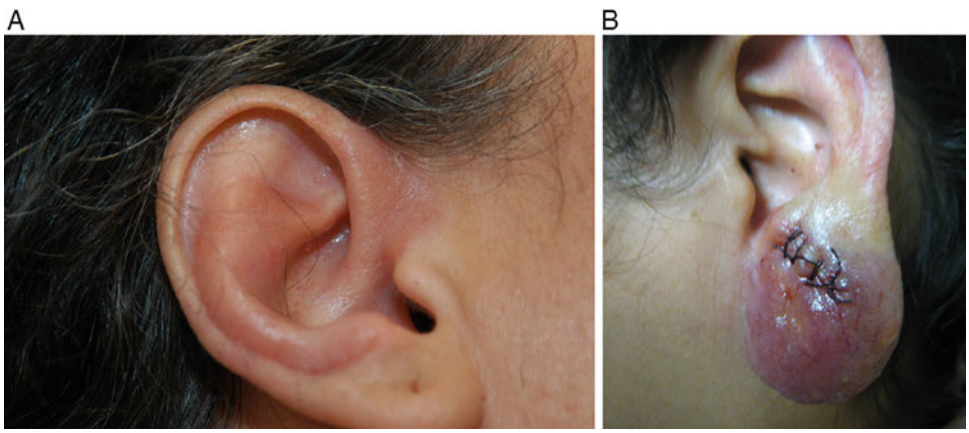

Fig. 1 (**a**, **b**) Lupus pernio. The cyanotic hue is characteristic. The earlobes, nose, and cheeks are affected areas most prone to perniosis. It may be disfiguring and destructive (origin of name lupus)

presents with scaly lesions on the knees and elbows is called psoriasiform plaques. It can be distinguished from true psoriasis by the fact that they heal with scarring [9, 13].

Subcutaneous Nodules (Darier–Roussy)

The first documented case of subcutaneous sarcoidosis was in 1904 by Darrier and Roussy [20, 21]. It encompasses 12.0% of the specific lesions of sarcoidosis and it occurs in 1.4–6.0% of patients who have systemic disease [9, 13, 22]. The peak incidence occurs during the fourth decade of age. The pathology of subcutaneous nodules are restricted to the subcutaneous tissue and does not affect the epidermis. These lesions can be painless or tender, firm, mobile, and the nodules vary from about 0.5 to 2.0 cm in diameter (Fig. 5) [19]. They are mostly found on the extremities, specifically the forearms, but may also be found on the trunk and face with a symmetric distribution. When the forearms are affected, the dorsum of the hand and the fingers tend to swell in a fusiform pattern [13, 20–22].

These skin lesions are the only subset of sarcoidosis frequently (80%) associated with systemic disease, particularly bilateral hilar adenopathy. Despite the associated systemic disease, it usually resolves within several months and is not associated with a chronic fibrotic disease [3, 9, 13, 21, 23, 24]. Subcutaneous sarcoidosis has a consistent clinicopathologic presentation and usually appears at the beginning of the disease. The confirmatory diagnosis requires the detection of pannicular (fat lobules) sarcoid or epitheliod granulomas with minimal lymphocytic inflammation and minimal septal involvement (Fig. 6) [21, 24, 25].

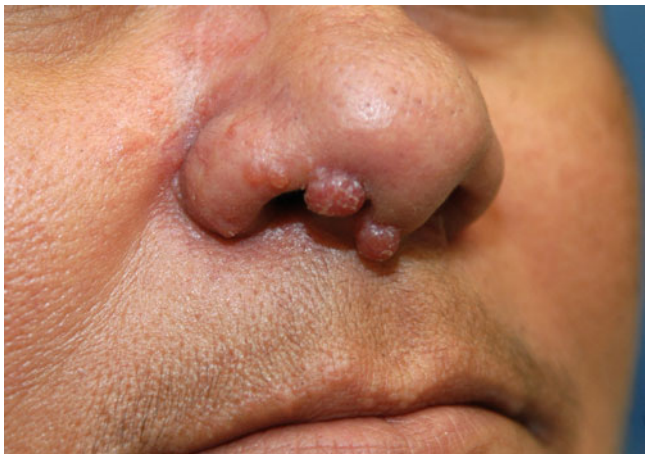

Fig. 2 Sarcoidosis: papules and nodules. *Red-brown* nodules occur predominantly around the nose

Scar Sarcoidosis

Scar sarcoidosis was first described in 1899 by Caesar Boeck. It frequently presents in West Africans [26, 27]. Scar sarcoidosis shows characteristic granulomatous invasion of previously traumatized skin or areas with imbedded foreign material, such as tattoos [3, 5, 23]. It often occurs with other cutaneous manifestations; however, it tends to occur near the beginning of the onset of sarcoidosis when the presence of pulmonary involvement may have not yet begun [13, 26]. Particular attention should be given to sites on the body such as areas for venipuncture access, previous Mantoux test sites,

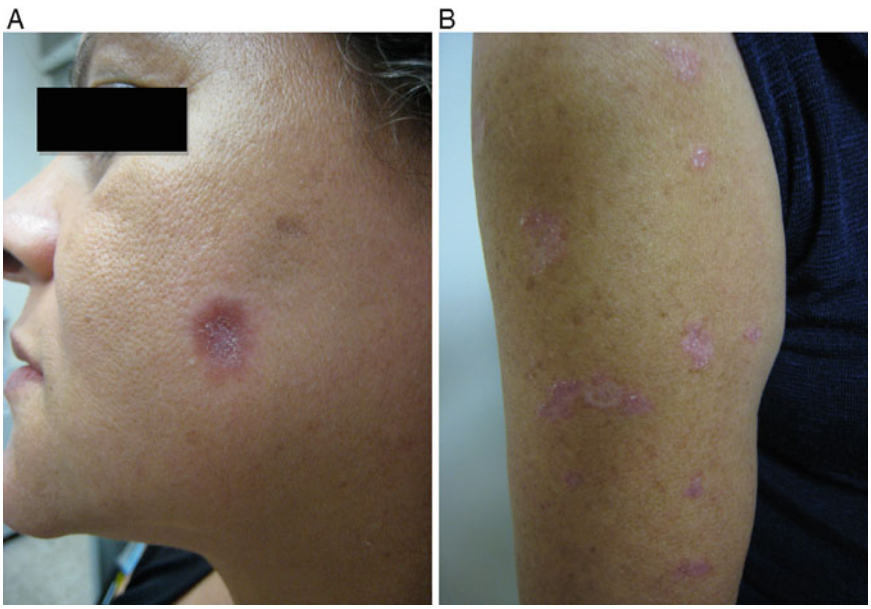

Fig. 3 (**a**, **b**) Sarcoidosis: annular plaques. Plaques with an annular configuration and central clearing affecting the face and arms

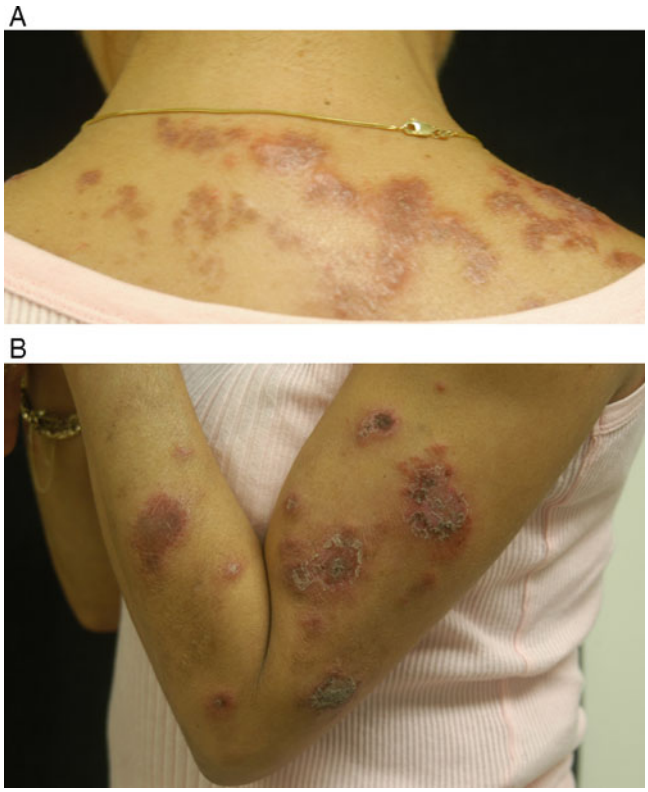

Fig. 4 (**a**, **b**) Sarcoidosis: plaques. A patient presenting with widespread *red-brown* plaques occurring on the bilateral extremities. The trunk is a common site. Most of these patients have pulmonary involvement, lymphadenopathy, and splenomegaly

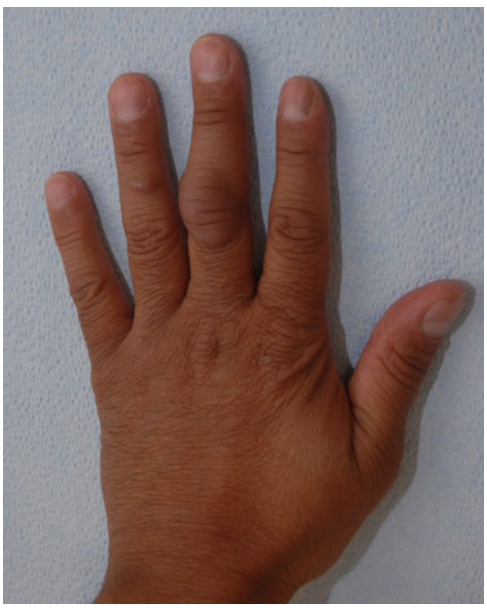

Fig. 5 Sarcoidosis: subcutaneous nodules (Darier–Roussy)

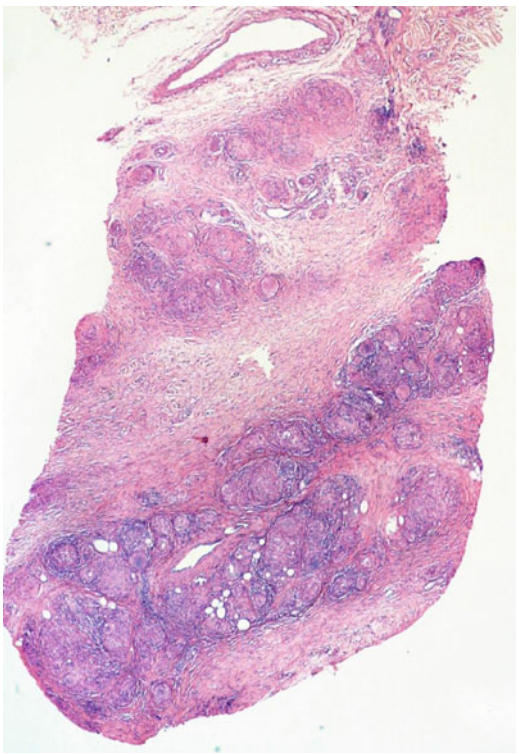

Fig. 6 Histopathology of Darier–Roussy. Sarcoid granulomas in the inferior dermis and subcutaneous tissue

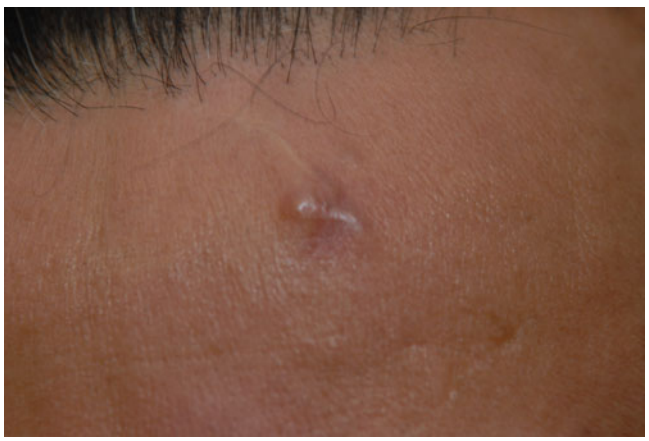

Fig. 7 Sarcoidosis associated with a scar. Granulomatous invasion of old scar tissue is particularly characteristic

healed herpes zoster dermatomes, tattoos, post-cutaneous laser surgery areas, post-consecutive botox injection areas, and injury scars [26, 28, 29]. The old scars, often atrophic and hypopigmented, evolve into elevated, purple or red lesions with associated new nodules or plaques (Fig. 7) [3, 9, 13, 19, 23].

Alopecia

Sarcoidal alopecia is a type of secondary scarring alopecia [30]. It tends to commence on the fronto-parietal area and progress into the scalp as an atrophic, red, and scaly plaque of alopecia. It can easily be confused with cutaneous discoid lupus erythematosus because it also presents as an erythematous, scaly, and atrophic plaque of alopecia [30, 31]. A biopsy is needed in such situations to differentiate between these two conditions histopathologically. These lesions present in various morphologies including macular lesions, scaly plaques, and infiltrated nodules [9]. The few cases reported mostly involve African-American women, of which, also tend to have other cutaneous manifestations. Physicians should carefully evaluate the patient to rule out systemic sarcoidosis after the diagnosis of scalp sarcoidosis is established [30, 32].

Ichthyosiform Sarcoidosis

An acquired ichthyosis secondary to sarcoidosis was first described by Braverman in 1981 [33]. Ichthyosis refers to dry and scaly skin due to a defect in keratinization. The classic presentation of this rare manifestation of sarcoidosis is nontender, adherent, pigmented, polygonal scales on the anterior lower limbs [33, 34]. Histopathology reveals the specific naked granuloma and ichthyosis vulgaris changes of the epidermis, such as compact orthokeratosis and a decrease or absence of the granular layer [34]. This subtype of sarcoidosis is significant due to its high association with systemic disease, where over 95% of reported cases have systemic involvement [33, 34].

Hypopigmentation

The first report of sarcoidosis hypopigmented macules was in 1963 by Thomas et al. [35, 36]. Oftentimes, sarcoidosis on black or dark skin only presents with hypopigmented papules, macules, or dermal nodules. They are most often found on the extremities. Since it may be the presenting sign of the disease, it is important to recognize these lesions and rule out similar clinical presentations seen in vitiligo, pinta, post-inflammatory changes, and pityriasis versicolor [35, 36]. A biopsy showing dermal sarcoid granulomas is always confirmatory [9, 36]. The mechanism of action remains controversial; however, a nutritional deficiency in melanocytes, a fixation artifact, or an increased susceptibility to damage of the mitochondria of melanocytes are postulated hypotheses [36–38].

Nonspecific Sarcoidosis

Erythema Nodosum

Erythema nodosum (EN) is the most common nonspecific cutaneous eruption of sarcoidosis [18]. It occurs in about 10% of patients with sarcoidosis and usually resolves spontaneously within 6 weeks [5, 9, 39]. It is a painful disorder of the subcutaneous fat. The characteristic lesion is a tender, erythematous, poorly delineated subcutaneous nodule usually distributed in a symmetric pattern. The main causes of EN include idiopathic (55%), streptococcal pharyngitis (48%), sarcoidosis (25%), drugs (10%), pregnancy (5%), and enteropathies (4%) [40]. EN lesions typically occur on the anterior tibial surface, but can also be present on the extensor surface of the forearms, the thighs, and the trunk [3, 8, 40]. The nodules can vary from 1 to 10 cm in diameter. The essential histologic features are those of a septal panniculitis where there is intense inflammation of the deep dermis and fibrous septum with relative sparing of the fat lobules, without evidence of vasculitis [9, 40].

In the 1950s, Lofgren and Lundback discovered the association between EN and bilateral hilar lymphadenopathy, now referred to as Löfgren's syndrome [3]. Löfgren's syndrome encompasses sarcoidosis with hilar adenopathy, polyarthritis, and EN. Other symptoms may include fever or ocular involvement. This syndrome, similar to the EN sarcoid patients, has a good prognosis due to the association with an acute or transient form of the disease [3, 8, 9, 13, 40].

Other

Nail, Mucosal, and Childhood Sarcoidosis

Some of the most unusual manifestations of sarcoidosis are those lesions involving in the nails or mucosa, as well as presenting with disease manifestations as a child. Nail sarcoidosis findings include clubbing, subungual hyperkeratosis, brittleness, pitting, discoloration, and onycholysis. Nail involvement is indicative of the chronic form of the disease and is considered a specific lesion because of the presence of the hallmark non-caseating granulomas upon histologic examination [2, 7, 9].

Mucosal sarcoidosis presents as granulomatous lesions affecting the oral, nasal, anal, and, less frequently, the genital mucosa. The most common presentation is nodules of the buccal mucosa, gingival tissue, tongue, lips, hard palate, and salivary glands [7, 9].

Sarcoidosis is uncommon in adolescents and children. In the case of children ranging from 9 to 15 years, the disease presents with the same lesions adults exhibit, except erythema

nodosum and lupus pernio. In children younger than 6 years, sarcoidosis has the characteristic triad presentation of skin lesions, arthritis, and uveitis. The first manifestation is cutaneous: erythematous maculopapular rash on the extremities which later becomes generalized. The pulmonary manifestations are rare, but when present, include stage one changes on chest radiographs (bilateral hilar lymphadenopathy without infiltration). Childhood sarcoidosis can be easily confused with polyarticular rheumatoid juvenile arthritis and Blau's syndrome (however Blau's syndrome does not involve the lung), so it is important for the physician to carefully distinguish between the three [7, 9].

Treatment

The first-line treatment of choice is corticosteroids, either in the topical, intralesional, or oral from. The cutaneous lesions in sarcoidosis are not life threatening and the therapeutic regimen should be dependent and adjusted according to the progression and severity of the disease. The most mutilated skin lesions should be injected with triamcinolone acetonide weekly. The traditional treatment of systemic disease is oral prednisone at a dose of 1 mg/kg/day for 4–6 weeks, usually 20–40 mg in daily divided doses, followed by tapering of the dose over the following months. The alternate day use of prednisone for maintenance therapy has proven to be just as effective as the daily dose regimen [9, 12, 21].

Chronic skin lesions tend to respond well to chloroquine (250–500 mg/day) and hydroxychloroquine (200–400 mg/day) antimalarial drugs, but one must be cautious for serious side effects such as retinopathy and blindness. Chloroquine can also be used intralesionally once a month. Other treatment options include the following: methotrexate (15 mg/week), thalidomide (50–300 mg/day), infliximab and allopurinol (100–300 mg/day), to mention a few [9, 12, 21].

Lupus pernio and disfiguring skin plaques have been treated successfully in some patients with laser treatments such as pulsed-dye and the CO_2 laser, however, as with all medications, not all patients respond the same. Cosmetic options should be taken into consideration due to the social and psychological impact such cutaneous lesions can have on a patient [16, 41].

Tuberculosis

Théophile Laennec, from France, especially known for his invention of the stethoscope, can also be recognized for his elucidation of the pathogenesis and the description of the physical findings in pulmonary disease of tuberculosis at the beginning of the nineteenth century (1819). Laennec described a "prosecutor wart" in 1826, the first reported example of cutaneous tuberculosis [42, 43]. The German physician and scientist, Dr. Robert Koch, discovered the etiology of tuberculosis, the infectious bacillus bacteria. He was awarded a Nobel Prize for his discovery in 1905 and became known as the "father of bacteriology" [44].

Tuberculosis presents a significant public health issue with 8–9 million new infections annually. The World Health Organization estimates that approximately one-third of the world's population is affected, and claims about 3 million lives a year [45]. TB has become the most common cause of death in AIDS-infected patients and is considered a true AIDS-defining illness in patients infected with human immunodeficiency virus (HIV) by the Center for Disease Control (CDC) [46, 47]. An estimated 15 million people are co-infected with HIV and *Mycobacterium tuberculosis*, and 6,00,000 of the 3 million HIV deaths in 2003 were specifically ascribed to TB [45, 48].

Tuberculosis was a major problem in the late nineteenth century but declined due to improved hygiene, improved living standards, use of BCG immunization, and the introduction of chemotherapy [49]. However, there has been a resurgence of TB since the 1980s, for which, the Centers for Disease Control and Prevention attributes to several factors, including HIV infection, TB among foreign-born immigrants, the rise of drug-resistant TB, and the decline of TB control programs [48, 50]. In developing countries, contributing issues include shortages of healthcare facilities with appropriate diagnostic equipment, reduced access to treatment, and poor treatment compliance among patients who often resort to traditional medicine [51]. The global incidence of TB is increasing at a rate of 1.1% per year, fueled primarily by countries in sub-Saharan Africa and the former Soviet Union [52]. In addition, the recent FDA approval of biologic therapies for plaque psoriasis and other autoimmune diseases has introduced dermatologists into the management and screening of TB infections. Biologic agents, especially etanercept, infliximab, alefacept, efalizumab, and adalimumab, are known to cause reactivation TB due to the suppression of the cell-mediated immune response [48]. The ability to detect tuberculosis of the skin will serve as a valuable skill in the rapid detection and realization of therapy for physicians of the twenty-first century.

The disease primarily affects the lungs due to the transmission via droplets of respiratory secretions. Since TB-causing bacteria are obligate aerobes, they are able to remain suspended in the air for hours (droplet nuclei) and survive in well-ventilated alveoli [53]. Pulmonary macrophages swallow up the TB organisms in the alveolar spaces and then migrate to draining regional lymph nodes to initiate a cell-mediated immune response to contain the infection. The introduction of TB into the lungs is asymptomatic in the majority of patients and without radiographic changes, but later develops into a chronic non-productive cough. The primary disease may also present with constitutional symptoms such as fever, weight loss, night sweats, anorexia, and malaise

Table 1 Cutaneous manifestations of tuberculosis

Disease	Infection	Clinical presentation	Dermatopathology	Culture
True cutaneous TB				
Lupus vulgaris	H,L,C, BCG vaccine, direct	Types: Plaque, hypertrophic, ulcerative, or painless papulonodule that ulcerates with adenopathy	+/– Tuberculoid granuloma	+/– (Direct+)
Scrofuloderma	C	Nodule over affected lymph node, ulcerates	Necrosis, abscess, bacilli	+
Miliary TB	H	Copious discrete pinpoint papules	Microabscesses, many bacilli	+
Orificial TB	Auto-inoculation	Nodules, painful punched-out ulcers	Tuberculoid granuloma, many bacilli	+
TB chancre	D (exogenous)	Painless papulonodule, ulcerates, adenopathy	Acute inflammation, reaction granuloma, many bacilli	+
TB verrucosa cutis	D (exogenous)	Papule, verrucous plaque with soft center	Tuberculoid granuloma	+/–
Tuberculids				
Lichen scrofulosorum	H	Perifollicular lichenoid papules in clusters on the trunk, heals without scarring	Tuberculoid granuloma in papillary dermis	–
Erythema induratum of Bazin	H	Indurated, ulcerated erythematous nodules of calf veins healing with atrophic scars	Tuberculoid granuloma, lobular panniculitis	–
Papulonecrotic tuberculid	H	Small papules, crust, ulcerates	Wedge-shaped necrosis	–
Nodular tuberculid	H	1–2 cm nodules, non-ulcerating, red-blue in color, lower extremities	Granulomatous vasculitis at the junction of the dermis and subcutaneous fat	–

Derived from Tables I, II, and III in Cutaneous tuberculosis diagnosis and treatment. Am J Clin Dermatol 2002;3:319–28
H Hematogenous, *L* lymphatic, *C* contiguous, *D* direct, + positive, – negative, +/– may or may not be present

[54, 55]. Primary infections are traditionally characterized by any pneumonic infiltrate (granuloma) in the middle or lower lung zones (Ghon focus), especially a circular shape, associated with an ipsilateral hilar or mediastinal adenopathy, together known as the primary complex. A reactivation of TB, in contrast, classically has cavitary lesions in the upper lobes of the lung [48].

Systemic involvement in tuberculosis is commonly associated with cutaneous TB. The incidence of skin tuberculosis is gradually rising in both developing and developed countries parallel to systemic TB. It remains to be one of the most elusive and more difficult diseases to diagnose [56]. The incidence of systemic tuberculosis in children is around 26% and up to 35% in adults [57, 58]. Extra-pulmonary manifestations of TB account for approximately 13.7% of cases, and this percent may be much higher in patients co-infected with HIV [47]. Cutaneous manifestations of TB are very rare and only represent 1.5% of all extra-pulmonary forms of TB [42, 59, 60]. Several published studies have revealed that cutaneous TB is best diagnosed using a comprehensive work up of the patient in which histologic study of the skin biopsy specimen is most essential [61]. Skin lesions are distinguished by whether *M. tuberculosis* is revealed upon acid-fast bacilli (AFB) stains, culture, or polymerase chain reaction (PCR). Lesions that in fact demonstrate the presence of *M. tuberculosis* are classified as true cutaneous tuberculosis. True cutaneous tuberculosis can be acquired exogenously or endogenously and includes such lesions as tuberculous chancre, tuberculosis verrucosa cutis (TVC), lupus vulgaris (LV), scrofuloderma, miliary tuberculosis, orificial tuberculosis, and gummatous tuberculosis. Tuberculids, on the other hand, do not reveal *M. tuberculosis* on AFB stains, culture, or PCR and are defined as cutaneous hypersensitivity reactions to an underlying focus of tuberculosis [42]. The tuberculids include lichen scrofulosorum, erythema induratum of Bazin (EIB), tuberculonecrotic tuberculid, and nodular tuberculid [49, 59].

Cutaneous lesions of tuberculosis can also be attributed to another strain of bacteria, specifically *M. bovis*, or even by the BCG vaccine which is an attenuated form of the former [49]. The major difference is that *M. bovis* infection is spread from animals to humans, most frequently through infected milk products [62] (Table 1).

True Cutaneous Tuberculosis

Endogenously Acquired Disease

Lupus Vulgaris

LV is the most common form of cutaneous tuberculosis in most countries, especially in India and Africa [63–66]. Up to 40% of LV cases are associated with lymphadenitis and up to 20% involve the lungs and bones [65]. Its pathogenesis is multifactorial: direct inoculation, BCG vaccination, contiguous, lymphatic, and hematogenous route of infection [49, 65].

The lesions may present in a variety of morphologies including the classic plaque or keratotic type (gelatinous), the hypertrophic form (tumor-like soft nodule), the ulcerative form (necrosis), and the vegetative form (papule with ulceration and necrosis). The plaque form is the most common form of LV, accounting for 32% of cases [42, 57]. It initially presents as asymptomatic, flat, red-brown papules and plaques. It progresses into slowly expanding skin-colored or erythematous plaques with deep tiny nodules arising near the margins of the plaque. On diascopy, the nodules are seen as yellow-brown macules (the characteristic "apple-jelly" color). The expanding plaque has an atrophic center with a raised red-brown border, occasionally with scaling [67]. The ulcerative form is the most destructive and deforming of all LV lesions because the underlying tissue becomes ulcerated and necrotic, leaving behind an atrophic scar. It can be especially destructive, if the auricular or nasal cartilage is involved. Finally, the vegetative form is similar to the ulcerative form in that it is characterized by necrosis and ulceration; however, there is minimal scarring left behind [49, 59]. After many decades with the disease, squamous cell carcinoma may develop in the lupus vulgaris lesion [67, 68].

The areas in the body where these lesions appear vary among different places in the world. In Western countries, LV is most commonly seen on the neck and face, especially the nose and cheeks, and rarely involves the mucous membranes [69]. In the tropics and developing countries, on the other hand, where kids play without protective clothing, it occurs most often on the lower extremities and buttocks [42, 49].

As a consequence of the developed antibodies due to previous exposure to the organism, LV is exceptionally chronic with a slow and destructive progression. It occurs in patients with moderate to high immunity against *M. tuberculosis*, as evidenced by a strongly positive tuberculin test [70]. Since lupus vulgaris is a paucibacillary form of tuberculous infection, the culture is often negative and the diagnosis is mainly based on the histopathological appearance and the response to chemotherapy [59].

The histopathologic examination shows the hallmark tubercles, which consist of accumulations of epithelioid histiocytes with Langerhans giant cells and varying amount of caseation necrosis in the center [71]. A significant finding also includes fibrosis of the dermis due to the chronic long-standing course with intermittent episodes of healing. Neither caseation necrosis nor tuberculoid granulomas are pathognomonic because deep fungal infections, syphilis, and leprosy can show similar histological features. It is the additional clinical criteria that is helpful in the differential diagnosis, such as the soft texture of the lesions, the brownish-red color, the slow progression, and the apple-jelly nodules revealed by diascopy [71].

Scrofuloderma

Scrofuloderma, also known as tuberculosis cutis colliquativa, arises from the extension of underlying tubercle bacilli from an infected lymph node, bone, joint, or epididymis to the overlying skin in patients with a weak immune response [69, 72, 73]. This is the most common cutaneous TB in children and it is more common in girls than in boys [42, 57, 66, 69]. It has been postulated that the consumption of unboiled/unpasteurized milk is a common occurrence around the world that leads to the *M. bovis* infestation of the cervical lymph nodes [49, 66, 69, 72, 73].

Scrofuloderma initially presents as a red-brown profound nodule overlying the site of the deeper infection. The nodule becomes indurated and forms an abscess. Over a period of months, it begins to ulcerate, eventually forming the hallmark sinus tracts that drain watery, purulent, or caseous material [49, 60, 72].The ulcers are shallow with undermined blue-colored borders. Healing forms an elongated scar or keloid, the characteristic puckered scar [49, 59, 60].

The presence of scrofuloderma suggests a systemic TB infection, especially pulmonary involvement [49, 59, 66, 69]. The incidence of systemic involvement in adults with scrofuloderma is 35% [58].The most commonly affected area is the neck, but may also occur on the axillae, chest, or groin [66, 69, 72–74]. At times, lupus vulgaris may arise from scrofuloderma. This form of cutaneous TB may take several years to spontaneously heal [49, 59, 71].

Gummatous TB is another cutaneous tuberculosis lesion, indistinguishable from scrofuloderma. It is also referred to as metastatic tuberculous abscesses that arise on the trunk, extremities, or head [46, 47, 49, 54, 59, 74]. It occurs after dissemination of an active infection, usually in seasons of low immunologic resistance, as occurs with undernourished children or immunosuppressed patients.

Acute Miliary Tuberculosis

Acute miliary tuberculosis is the extensive dissemination of *M. tuberculosis* due to hematogenous spread. It is a rare presentation encompassing 1–3% of all TB cases. The internal focus of the active disease most commonly originates from the lungs. This rare form of TB has become increasingly common among HIV-infected patients. The first documented case that presented with cutaneous findings was reported in 1990 in an AIDS patient [75]. Patients with acute miliary TB usually have a serious systemic infection, especially those with AIDS because of their extreme $CD4^+$ T cell depletion. As a result, they have a poor prognosis, with many cases leading to death [49, 59].

The cutaneous manifestations consists of widespread discrete blue-red to brown-colored papules, pustules, purpura, and uncommonly, umbilicated vesicles [49, 60, 71–73]. The vesicles may either rupture or dry with a crust that later develops into an ulcer. By the fourth week, the lesions are usually healed with remaining white atrophic scars that have a surrounding brown halo [49, 71, 72]. Histology confirms the diagnosis, revealing multiple microabscesses with neutrophils and numerous AFB organisms surrounded by macrophages and giant cells [49, 60].

Orificial Tuberculosis

Orificial tuberculosis, also known as tuberculosis cutis orificialis, is an atypical manifestation of TB that usually occurs in patients with advanced infection of the lungs, intestine, or genito-urinary tract. Recognizing this cutaneous lesion is significant because it indicates advanced internal disease and poor prognosis. It presents as red- or yellow-colored nodules that ulcerate around the mucosal orifices, such as on the lips, inside the mouth, or on the anogenital region. These painful ulcers have an irregular circular shape, with an undermined border and a shallow, punched-out, and granulomatous appearance. It spreads to infect the mucosa or orificial skin by means of autoinoculation, where an active infection drains to the nearest orifice [49, 59]. An active TB infection of the lungs and pharynx tends to manifest in the mouth, whereas infection of the intestines manifests in the anus orifice [49, 59, 60, 74]. Perianal tuberculosis is believed to be a consequence of auto-inoculation from swallowed bacilli-containing sputum through defects in the perianal mucosa [71].

Exogenously Acquired Disease

Tuberculous Chancre

The tuberculous chancre, also known as the primary inoculation tuberculosis, is seen following primary infection with *M. tuberculosis*, in other words, the patient is nonsensitized or non-immune (initially negative purified protein derivative test) [49, 59, 60]. It accounts for 1–2% of cutaneous TB [46, 47, 49, 54, 59]. The tubercle bacilli cannot penetrate intact skin, thus only after the patient suffers some sort of skin trauma or minor abrasion can the organism infiltrate and cause infection. It has also been reported to occur post-mouth-to-mouth resuscitation, jail-house tattooing, circumcision, piercings, and in health care workers [49, 72].

The chancre appears 2–4 weeks after inoculation as a reddish-brown papulonodular lesion, which quickly grows and erodes [49, 59]. The resultant shallow ulcer is painless, with an indurated granular base. The borders of the ulcer are well defined, blue-red in color, and have an undermined appearance. Sometimes the border has scattered pustules and the edge may have an adherent crust on the surface [68, 71, 72, 76]. When the chancre is coupled with regional lymphadenopathy, usually 3–8 weeks after inoculation, it accounts for what is known as primary tuberculous complex [71]. These lesions appear primarily on the face and extremities and are able to heal without treatment after several months, but may leave an atrophic scar. Treating this condition with anti-tuberculous medications can not only prevent scarring, but can also avoid the evolution of these lesions into Tuberculosis Verrucosa Cutis (TVC), lupus vulgaris, or scrofuloderma [49, 59, 72, 73]. Histologically, it initially reveals nonspecific inflammation and later, after the development of adenopathy, a granulomatous pattern with scattered bacilli can be seen [62, 72].

After the bacilli Calmette-Guerin (BCG) vaccination, a sore may persist, on the upper outer arm, which imitates the TB chancre, but is referred to as a BCG granuloma. It tends to occur 2–6 weeks after vaccination. It appears as a small solitary brown nodule or papule that ulcerates, scabs, and heals as a scar [62, 72].

Tuberculosis Verrucosa Cutis

TVC results from a reinfection with *M. tuberculosis* or *M. bovis* by direct inoculation (through abrasions or wounds). Unlike the chancre, these patients are previously sensitized and have strongly positive PPD's; therefore, BCG vaccination would be futile [49, 74, 77]. Since this cutaneous manifestation entails reinfection, it occurs most often in those who have occupational exposure, such as physicians (especially pathologists or forensic scientists), other medical personnel, or butchers [49, 62, 68]. This cutaneous variant of TB occurs in patients with strong cell-mediated immunity.

The lesion first appears as a small, solitary, asymptomatic, and reddish-brown papule that progresses into a large, irregular verrucous plaque [49, 60]. The margins are firm while the center is soft, and there is a surrounding erythematous border. There are deep fissures on the surface which often expel pus [49, 59]. TVC is found most commonly on the lower limbs and buttocks in eastern countries and on the dorsal hands in western countries [77]. There have been cases where it appears on the face or around the anus [74]. They persist for several years (slow growing and chronic in nature), but they eventually heal spontaneously with an atrophic scar [49, 77].

Histology reveals hyperkeratosis and papillomatosis of the epidermis. The dermis contains tuberculoid granulomas with necrosis and occasional acid-fast bacilli [49, 60].

Tuberculids

Tuberculids are due to an immune response to the antigenic component of *M. tuberculosis*, often described as a hypersensitivity reaction. They are characterized by negative smears and cultures, but strong positive PPD reactivity. No bacilli are seen in the lesions due to the rapid destruction in the skin by the high immune system of the patient [49, 78, 79]. The skin lesions are numerous and distributed symmetrically. In 1896, Jean Darier introduced the term tuberculid to designate papular and nodular skin outbreaks that spontaneously involute and recur in individuals with a previous history of active TB [49, 79]. Histologically, all tuberculids share a granulomatous inflammation, necrosis, and vasculitis [49].

Lichen Scrofulosorum

Lichen scrofulosorum (LS) has been reported as the most common form of tuberculids and the most common cutaneous manifestation of TB in children. It was first described by Hebra in 1868 and it accounts for about 8% of all patients with cutaneous tuberculosis. This form of cutaneous TB is associated with the infection of the lungs, lymph nodes, or bones [42, 49, 74, 80, 81]. The lesions of LS usually appear on the trunk and proximal extremities as asymptomatic, lichenoid, firm follicular, and parafollicular papules. Micropustules and central adherent crust may also be present, but scaling is minimal or absent. Lesions may coalesce to form annular or discoid plaques [82]. The papules have a yellow-brown or pink color [7, 42, 49, 60, 78]. Upon histologic evaluation, there is evidence of dermal non-caseating granulomas around the hair follicles and sweat ducts. These lesions heal spontaneously without scarring after several months [49, 59, 74]. Lichen scrofulosorum needs to be differentiated from similar follicular disorders such as keratosis pilaris, lichen spinulosus, lichen nitidus, pityriasis rubra pilaris, and lichenoid sarcoidosis [42].

Erythema Induratum of Bazin

EIB, also known as nodular vasculitis, was first described in 1861 by Ernest Bazin [83, 84]. About 15% of EIB cases are associated with lung disease [85]. This form of cutaneous TB is one of the most common types of tuberculids among patients, the typical patient being a middle-aged woman with fatty or heavy legs characterized by some degree of venous insufficiency [65, 79, 86, 87]. It describes a tuberculid response manifesting with flares of indurated violaceous nodules of the calves that tend to ulcerate and then recur every 3–4 months [79, 88, 89]. The lesions appear bilaterally on the posterior calves, or, in rare occasions on the thighs or arms [49, 59]. There are four common histologic findings involving the deep subcutaneous fat including septal panniculitis, fat tissue necrosis, vasculitis, and caseating granulomas [74, 89]. Healing usually occurs spontaneously after several months with postinflammatory hyperpigmentation and atrophic scarring. The differential diagnosis for such lesions includes nodular vasculitis, perniosis, polyarteritis nodosa, and erythema nodosum [88].

Papulonecrotic Tuberculid

Papulonecrotic tuberculid presents as multiple, painless, and scattered pustular or necrotizing papules on the extensor aspects of the extremities and buttocks of children or adolescents. These dusky-red papules become necrotic and leave behind a hyperpigmented atrophic scar or may even progress to lupus vulgaris [89]. These lesions occasionally coexist with EIB [79]. Histologic examination reveals the presence of vasculitis and wedge-shaped areas of necrosis or infarction [59, 71].

Nodular Tuberculid

Nodular tuberculid, the fourth and most recent adoption to the tuberculid family, was described in 1997 in Japan by Hara as a nodular thickening along the course of the veins [89–91]. The nodules are 1 and 2 cm in diameter, non-ulcerating, red-blue in color, and predominately occur on the lower extremities [89]. Nodular tuberculid has a characteristic histological pattern: a granulomatous vasculitis at the junction of the dermis and subcutaneous fat, between the superficial papulonecrotic tuberculid (papillary dermis) and the deep EIB (subcutaneous fat) [89, 91]. It has been previously called "nodular granulomatous phlebitis" and has remarkable similarities with superficial migratory thrombophlebitis.

Treatment

The treatment regimens used for pulmonary tuberculosis are sufficient for treating cutaneous tuberculosis because the bacillary load is much smaller in cutaneous tuberculosis than in pulmonary tuberculosis [49]. The Centers for Disease Control and Prevention recommends a two phase treatment schedule: an intense initial phase with isoniazid, rifampin, pyrazinamide and either ethambutol or streptomycin for 8 weeks and a final continuation stage of isoniazid and rifampin for 16 weeks. The initial phase is meant to quickly destroy a large number of living organisms and the second maintenance phase is meant to kill the remaining persistent organisms [60, 71]. The treatment should be continued for at least 2 months after the cutaneous lesions have entirely regressed due to the fact that viable organisms can be cultured from clinically healed lesions. Surgical excision is a useful adjunct to the management in scrofuloderma and the localized lesions of verrucosa cutis and lupus vulgaris [71, 81]. Lupoid nodules in areas of scar tissue can be eliminated with electrocautery or cryotherapy [49, 73].

Birt–Hogg–Dubé Syndrome

BHDS was first described in 1977 by the Canadian physicians Birt, Hogg, and Dubé [92, 93]. BHDS is a rare, autosomal dominant predisposition to the development of benign skin tumors, lung cysts, and spontaneous pneumothorax. Also, there is a strong association with renal cancers, often multiple and bilateral, and detected at a median age of 51 [94]. BHDS is caused by a mutation of the folliculin gene (FLCN) whose product is a novel protein with tumor suppressor

effects [94]. The folliculin gene lies within the chromosome band 17p11.2. This genodermatosis is characterized by a large spectrum of mutations and clinical heterogeneity. It is thought to be associated with colonic neoplastic polyps, medullary carcinoma of the thyroid, and connective tissue nevi. Eighty-four percent of BHDS patients have lung cysts on CT imaging and 38% of patients have a history of pneumothorax. The skin lesions usually develop during the third or fourth decades of life. The three skin lesions originally described in the BHDS include fibrofolliculomas, trichodiscomas, and acrochordons (skin tags). Ninety percent of families with BHDS had individuals with multiple histologically confirmed fibrofolliculomas [95]. All these three associated skin lesions are small, firm, papular, and painless. There can be several to over a hundred papules that develop gradually over the scalp, face, neck, upper chest, back, popliteal fossa, and antecubital fossa. It is important to be able to recognize these three benign skin lesions associated with this syndrome as it may aid in a more rapid detection of renal carcinoma or a spontaneous pneumothorax, ensuing in possible better prognosis and decreased mortality [92, 93, 95].

Fibrofolliculoma

A fibrofolliculoma is a benign tumor developing from the hair follicle. They are small, flesh, or pale yellow-colored papules measuring 2–4 mm in diameter. Histologically, they are circumscribed proliferations of collagen and fibroblasts that surround the distorted hair follicles. The inside of the hair follicle is packed with keratinous debris or a hair shaft, appearing as a dilated cyst. This is surrounded by abundant loose connective tissue full of elastic fibers, fine collagen, and numerous vessels [7, 19, 96].

Trichodiscomas

Trichodiscomas cannot be distinguished from fibrofolliculomas based on clinical inspection. Both are 2–4 mm, white or flesh colored, smooth, and dome-shaped papules. A trichodiscoma, however, is a benign tumor or hamartoma of the hair disk, which is now considered a non-existent structure. Trichodiscomas are today considered to be fibrofolliculomas or perifollicular fibromas. In the superficial dermis there is a loose myxoid stroma and spindle cell proliferation [93, 95, 96].

Acrochordons

Acrochordons are also known as skin tags, cutaneous papilloma, soft fibromas, and fibroepithelial polyps. Acrochordons are tiny raised or pedunculated pigmented soft papules, with a tan or brown color. Most acrochordons in BHDS are smaller than usual, about 1–2 mm in diameter. The polyps are histologically characterized by mature keratinizing squamous epithelium overlying a fibrovascular core with papillomatosis and hyperkeratosis [93, 95, 96].

Cystic Fibrosis

Cystic fibrosis is an autosomal recessive disorder reported in 1/1,500 live births in Northern American and Northern European Caucasian populations [97]. The mutated gene, called the cystic fibrosis transmembrane conductance regulator (CFTR), is the reason for the abnormal ion transport. Approximately 90% of children with cystic fibrosis present with classic pulmonary or gastrointestinal symptoms, such as cough, dyspnea, or steatorrhea [98]. The cutaneous manifestations that have been reported are nonspecific, yet may be important initial presentations which include: wrinkling, cutaneous vasculitis, and cystic fibrosis nutrient deficiency dermatitis (CFNDD) or an acrodermatitis enteropathica-like eruption.

Premature skin wrinkling subsequent to water exposure is a primary consequence of cystic fibrosis. It is due to the increased concentration of electrolytes in the sweat, creating an aquagenic skin wrinkling effect [97, 99–101]. It presents clinically as poorly demarcated edematous white papules and plaques of the palms and soles that develop after exposure to water.

The vasculitis, a secondary sequela, most commonly presents with a recurrent macular purpura that progresses to palpable purpura on the lower extremities [97, 102–105]. Urticarial vasculitis and bullae secondary to vasculitis have also been reported [102, 103, 106, 107]. Intermittent arthralgias have been associated with such skin lesions [102, 105, 108]. In these patients, vasculitic dermatoses are associated with exacerbations of pulmonary symptoms [23]. The mechanism of action of such vasculitic lesions has been shown to be due to antigens from bacteria, antibiotics, and from pancreatic enzyme supplements because they lead to increased circulating immune complexes [102, 104, 107, 109–111].

Rarely, cystic fibrosis may present with CFNDD, a primary and secondary sequela, presenting at 2 weeks to 6 months of age. The skin involvement commences in the perineum, perioral, and periorbital regions as erythematous papules that subsequently spread to the extremities over weeks to months and progress to desquamating plaques [97, 98, 112–116]. This cutaneous manifestation is typically coexistent with failure to thrive, hypoproteinemia, and edema prior to any pulmonary manifestations [117–120]. It can be differentiated from acrodermatitis enteropathica due to the normal mucous membranes and nails, and the lack of involvement of the skin folds [97, 112–114].

References

1. Sharma OP. Sarcoidosis: a historical perspective. Clin Dermatol. 2007;25:232–41.
2. Hutchison J. Case of a livid papillary psoriasis. In: Hutchison J, editor. Illustrations of clinical surgery. London: J & A Churchill; 1877. p. 42.
3. Rose A, Tielker M, Knox K. Hepatic, ocular, and cutaneous sarcoidosis. Clin Chest Med. 2008;29:509–24.
4. Boeck C. Multiple benign sarcoid of the skin. J Cutan Genitourin Dis. 1899;17:543–50.
5. Iannuzzi M, Rybicki B, Teirstein A. Medical progress sarcoidosis. N Engl J Med. 2007;357:2153–65.
6. Ali MM, Atwan AA, González ML. Cutaneous sarcoidosis: updates in the pathogenesis. Eur Acad Dermatol Venereol. 2010;24:747–55.
7. Howard A, White CR. Non-infectious granulomas. In: Bolognia JL, Jorizzo JL, Rapini RP, et al., editors. Dermatology. Philadelphia: Elsevier; 2003. p. 1455–60.
8. Katta R. Cutaneous sarcoidosis: a dermatologic masquerader. Am Fam Physician. 2002;65:1581–4.
9. Fernandez-Faith E, McDonnell J. Cutaneous sarcoidosis: differential diagnosis. Clin Dermatol. 2007;25:276–87.
10. Kannan S, Simpson GL, Sheehan DJ, et al. Giant verrucous nodules in a patient with tuberculosis. Am J Dermatopathol. 2009;31:591–3.
11. Judson M, Thompson B, Rabin D, et al. The diagnostic pathway to sarcoidosis. Chest. 2003;123:406–12.
12. Marchell R, Judson M. Chronic cutaneous lesions of sarcoidosis. Clin Dermatol. 2007;25:295–302.
13. Rosenberg B. Ichthyosiform sarcoidosis. Dermatology Online Journal. http://dermatology.cdlib.org. Accessed 3 Nov 2008.
14. Stedman TL. Stedman's medical dictionary. 24th ed. Baltimore: Williams & Wilkins; 1982. p. 813.
15. Edmondstone W, Wilson A. Sarcoidosis in Caucasians, Blacks and Asians in London. Br J Dis Chest. 1985;79:27–36.
16. Yanardag H, Pamuk O, Pamuk G. Lupus pernio in sarcoidosis: clinical features and treatment outcomes of 14 patients. J Clin Rheumatol. 2003;9:72–6.
17. Judson M, Thompson B, Rabin D, et al. The diagnostic pathway to sarcoidosis. Chest. 2003;123(2):406–12.
18. Lodha S, Sanchez M, Prystowsky S. Sarcoidosis of the skin: a review for the pulmonologist. Chest. 2009;136:583–96.
19. English J, Patel P, Greer K. Sarcoidosis. J Am Acad Dermatol. 2001;44:725–43.
20. Darier J, Roussy G. Un cas de tumeurs benignes multiples (Sarcoidessouscutanées ou tuberculides nodulaires hypodermique). Ann Dermatol Syphiligr. 1904;5:144–9.
21. Marcoval J, Moreno A, Mana J, Peyri J. Subcutaneous sarcoidosis. Dermatol Clin. 2008;26:553–6.
22. Vainsencher D, Winkelmann R. Subcutaneous sarcoidosis. Arch Dermatol. 1984;120:1029–31.
23. Mana J, Marcoval J, Graells J, et al. Cutaneous involvement in sarcoidosis. Relationship to systemic disease. Arch Dermatol. 1997;122:882–8.
24. Ahmed L, Harshad S. Subcutaneous sarcoidosis: is it a specific subset of cutaneous sarcoidosis frequently associated with systemic disease? J Am Acad Dermatol. 2006;54:55–60.
25. Requena L, Sanchez Y. Panniculitis. Part II. Mostly lobular panniculitis. J Am Acad Dermatol. 2001;45:325–61.
26. Mehta V, Balachandran C, Mathew M. Scar sarcoidosis sparing a surgical scar. Dermatology Online Journal. http://dermatology.cdlib.org. Accessed 10 Nov 2008.
27. Minus H, Grimes P. Cutaneous manifestations of sarcoidosis in blacks. Cutis. 1983;32:361–3.
28. Selim A, Ehrsam E, Atassi M, Khachemoune A. Scar sarcoidosis: a case report and brief review. Cutis. 2006;78:418–22.
29. Ahbib S, Lachapelle J, Marot L. Sarcoidal granulomas following injections of botulic toxin A (Botox) for corrections of wrinkles. Ann Dermatol Venereol. 2006;133:43–5.
30. Henderson C, Lafleur L, Sontheimer R. Sarcoidal alopecia as a mimic of discoid lupus erythematous. J Am Acad Dermatol. 2008;59:143–5.
31. Douri R, Chawaf A, Alreface B. Cicatricial alopecia due to sarcoidosis. Dermatology Online Journal. http://dermatology.cdlib.org. Accessed 10 Nov 2008.
32. Katta R, Nelson B, Chen D, Roenigk H. Sarcoidosis of the scalp: A case series and review of the literature. J Am Acad Dermatol. 2000;42:690–2.
33. Cather J, Cohen P. Ichthyosiform sarcoidosis. J Am Acad Dermatol. 1999;40:862–5.
34. Rosenberg B. Ichthyosiform sarcoisis. Dermatology Online Journal. http://dermatology.cdlib.org. Accessed 10 Nov 2008.
35. Patterson J, Fitzwater J. Case report. Hypopigmented sarcoidosis. J Tenn Med Assoc. 1978;71:662–4.
36. Thomas RH, McKee P, Black M. Hypopigmented sarcoidosis. J R Soc Med. 1981;72:921–3.
37. Breathmach A. Branched cells in the epidermis: an overview. J Invest Dermatol. 1980;75:6–11.
38. Clayton R, Breathnach A, Martin B, Feiwel M. Hypopigmented sarcoidosis in the negro. Report of eight cases with ultrastructural observations. Br J Dermatol. 1977;96:118–27.
39. James D. Erythema nodosum. Br Med J. 1961;1:853–7.
40. Schwartz R, Nervi S. Erythema nodosum: a sign of systemic disease. Am Fam Physician. 2007;75:695–700.
41. Rosell A, Garcia-Arranz G, Romero N, et al. Lupus pernio with involvement of nasal cavity and maxillary sinus. ORL J Otorhinolaryngol Relat Spec. 1998;60:236–9.
42. Vashisht P, Sahoo B, Khurana N, Reddy B. Cutaneous tuberculosis in children and adolescents: a clinicohistological study. J Eur Acad Dermatol Venereol. 2007;21:40–7.
43. Marmelzat W. Laennac and the 'prosecutor's wart'. Arch Dermatol. 1962;86:546–51.
44. Daniel TM. The history of tuberculosis. Respir Med. 2006;100:1862–70.
45. World Health Organization. Global tuberculosis control – surveillance, planning, financing. WHO report 2005. Geneva: World Health Organization; 2005. p. 1–247.
46. Valadas E, Antunes F. Tuberculosis, a re-emergent disease. Eur J Radiol. 2005;55:154–7.
47. Aaron L, Saadoun D, Calatroni I, et al. Tuberculosis in HIV-infected patients: a comprehensive review. Clin Microbiol Infect. 2004;10:388–98.
48. Hernandez C, Cetner A, Jordan J, et al. Tuberculosis in the age of biologic therapy. J Am Acad Dermatol. 2008;59:363–80.
49. Barbagallo J, Tager P, Ingleton R, et al. Cutaneous tuberculosis: diagnosis and treatment. Am J Clin Dermatol. 2002;3:319–28.
50. McKenna MT, McCray E, Onorato I. The epidemiology of tuberculosis among foreign-born persons in the United States, 1986 to 1993. N Engl J Med. 1995;332:1071–6.
51. Morrone A, Dassoni F, Pajno MC, et al. Ulcers of the face and neck in a woman with pulmonary tuberculosis: presentation of a clinical case. Rural Remote Health. 2010;10:1485.
52. Kaufmann SH. New issues in tuberculosis. Ann Rheum Dis. 2004;63:50–6.
53. American Thoracic Society. Diagnostic standards and classification of tuberculosis in adults and children. Am J Respir Crit Care Med. 2000;161:1376–95.
54. Harries A, Dye C. Tuberculosis. Ann Trop Med Parasitol. 2006;100:415–41.

55. Chesnutt MS, Prendergast TJ. Pulmonary tuberculosis. In: McPhee SJ, Papadakis MA, Tierney LM, editors. Current medical diagnosis and treatment 2007. New York: McGraw-Hill; 2007. p. 260–8.
56. Sahin N, Aydin NE, Senol M, et al. Longstanding skin ulcers due to Mycobacterium tuberculosis in a healthy man. Trop Biomed. 2010;27:120–4.
57. Pandhi D, Reddy B, Chowdhary S, Khurana N. Cutaneous tuberculosis in Indian children: the importance of screening for involvement of internal organs. J Eur Acad Dermatol Venereol. 2004;18:546–51.
58. Yates V, Pormedero L. Cutaneous tuberculosis in Blackburn district (UK): a 15-year prospective series. Br J Dermatol. 1996;136:483–9.
59. MacGregor R. Cutaneous tuberculosis. Clin Dermatol. 1995; 13:245–55.
60. Sethuraman G, Ramesh V, Raman M, Sharma V. Skin tuberculosis in children: learning from India. Dermatol Clin. 2008;26:285–94.
61. Ranawaka RR, Abeygunasekara PH, Perera E, et al. Letter: Clinico-histopathological correlation and the treatment response of 20 patients with cutaneous tuberculosis. Dermatol Online J. 2010;16:13.
62. Ara M, Pharm C, Baselga C, et al. Primary tuberculous chancre caused by Mycobacterium bovis after goring with a bull's horn. J Am Acad Dermatol. 2000;43:535–7.
63. Ramesh V, Misra R, Beena K, Mukherjee A. A study of cutaneous tuberculosis in children. Pediatr Dermatol. 1999;16:262–9.
64. Terranova M, Padovese V, Fornari U, Morrone A. Clinical and epidemiological study of cutaneous tuberculosis in Northern Ethiopia. Dermatology. 2008;217:89–93.
65. Ho CK, Ho MH, Chong LY. Cutaneous tuberculosis in Hong Kong: an update. Hong Kong Med J. 2006;12:272–7.
66. Kumar B, Muralidhar S. Cutaneous tuberculosis: A twenty-year prospective study. Int J Tuberc Lung Dis. 1999;3:494–500.
67. Lipsker D, Grosshans E. What is Lupus vulgaris in 2005? Dermatology. 2005;211:189–90.
68. Du Vivier A. Atlas of clinical dermatology: the skin and systemic disease. 3rd ed. Boston: Churchill Livingstone; 2002. p. 264–8, 391,509–13.
69. Kumar B, Rai R, Kaur I, et al. Childhood cutaneous tuberculosis: a study over 25 years from northern India. Int J Dermatol. 2001;40:26–32.
70. Morais P, Ferreira O, Nogueira A, et al. A nodulo-ulcerative lesion on the nose. Dermatol Online J. 2010;16:11.
71. Tappeiner G, Wolff K. Tuberculosis and other mycobacterial infections. In: Fitzpatrick TB, Freedberg IM, Eisen AZ, Wolff K, Austen KF, editors. Dermatology in general medicine. 5th ed. New York: McGraw-Hill; 2003. p. 1933–50.
72. Sehgal V, Wagh S. Cutaneous tuberculosis: current concepts. Int J Dermatol. 1990;28:355–62.
73. Sehgal V. Cutaneous tuberculosis. Dermatol Clin. 1994;12:645–53.
74. Bravo F, Gotuzzo E. Cutaneous tuberculosis. Clin Dermatol. 2007;25:173–80.
75. Stack R, Bickley L, Coppel I. Miliary tuberculosis presenting as skin lesions in a patient with acquired immunodeficiency syndrome. J Am Acad Dermatol. 1990;23:1031–5.
76. Sehgal VN, Wagh SA. Cutaneous tuberculosis. Current concepts. Int J Dermatol. 1990;29:237–52.
77. Erbagci S, Almila T, Nazan B, Erkilic S, Bayram A. Tuberculosis verrucosa cutis in a patient with long-standing generalized lichen planus: Improvement of lichen after antitubercular polychemotherapy. J Dermatolog Treat. 2006;17:314–8.
78. Sehgal V. Lichen scrofulosorum: current status. Int J Dermatol. 2005;44:521–3.
79. Mascaró J, Baselga E. Erythema induratum of Bazin. Dermatol Clin. 2008;26:439–45.
80. Hebra F. Lichen scrofulosorum. In: Fagge CH, Pye Smith PH, editors. Diseases of the skin. London: New Syndenham Society; 1868. p. 52.
81. Singal A. Lichen scrofulosorum: A prospective study of 39 patients. Int J Dermatol. 2005;44:489–93.
82. Kumar U, Sethuraman G, Verma P, et al. Psoriasiform type of lichen scrofulosorum. Pediatr Dermatol 2010. Dec 7. doi:10.1111/j.1525-1470.2010.01304X.
83. Bazin E. Leçons théoriques et cliniques sur la scrofule. 2nd ed. Paris: Delahaye; 1861.
84. Schneider J, Jordaan H, Geiger D, et al. Erythema induratum of Bazin. Am J Dermatopathol. 1995;17:350–6.
85. Shimizu A, Takahashi A, Negishi I, et al. The close association of lymphadenitis tuberculosa and erythema induratum of Bazin in Japanese patients. Dermatology. 2003;207:426–7.
86. Garcia-Rodriguez J, Monteagudo-Sanchez B, Marino-Callejo A. Cutaneous tuberculosis: a 15-year descriptive study. Enferm Infect Microbiol Clin. 2008;26:205–11.
87. Segura S, Pujol R, Trindade F, et al. Vasculitis in erythema induratum of Bazin: a histopathologic study of 101 biopsy specimens from 86 patients. J Am Acad Dermatol. 2008;59:839–51.
88. Heinemann C, Kaatz M, Elsner P. Erythema induratum of Bazin and Poncet's disease–successful treatment with antitubercular drugs. Eur Acad Dermatol Venereol. 2003;17:334–6.
89. Freidman P, Husain S, Grossman M. Nodular tuberculid in a patient with HIV. J Am Acad Dermatol. 2005;53:S154–6.
90. Hara K, Tsuzuki T, Takagi N, et al. Nodular granulomatous phlebitis of the skin: a fourth type of tuberculid. Histopathology. 1997;30:129–34.
91. Motswaledi H, Schulz E. Superficial thrombophlebitic tuberculide. Inter J Dermatol. 2006;45:1337–40.
92. Birt A, Hogg G, Dubé W. Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons. Arch Dermatol. 1977;113:1674–777.
93. Vincent A, Farley M, Chan E, James WD. Birt-Hogg-Dube syndrome: a review of the literature and the differential diagnosis of firm facial papules. J Am Acad Dermatol. 2003;49:698.
94. Stavrakoglou A, Dubrey SW, Dorkins H, et al. The Birt–Hogg–Dubé syndrome: dermatological features and internal malignancies. Q J Med. 2010;103:987–90.
95. Toro J, Wei M-H, Glenn G, Weinreich M, et al. BHD mutations, clinical and molecular genetic investigations of Birt-Hogg-Dubé syndrome: a new series of 50 families and a review of published reports. J Med Genet. 2008;45:321–31.
96. Gruson L. Birt-Hogg-Dube syndrome. Dermatol Online J. 2004;10(3):15–16. http://dermatology.cdlib.org. Accessed 10 Nov 2008.
97. Bernstein M, McCusker M, Grant-Kels J. Cutaneous manifestations of cystic fibrosis. Pediatr Dermatol. 2008;25:150–7.
98. Zedek D, Morrell D, Graham M, et al. Acrodermatitis enteropathica-like eruption and failure to thrive as presenting signs of cystic fibrosis. J Am Acad Dermatol. 2008;58:S5–8.
99. Franks A, Werth V. Cutaneous aspects of cardiopulmonary disease. In: Fitzpatrick TB, Freedberg IM, Eisen AZ, Wolff K, Austen KF, editors. Dermatology in general medicine. 5th ed. New York: McGraw-Hill; 2003. p. 1625–34.
100. Johns M. Skin wrinkling in cystic fibrosis. Med Biol Illus. 1975;25:205–10.
101. Katz K, Yan A, Turner M. Aquagenic wrinkling of the palms in patients with cystic fibrosis homozygous for the delta F508 CFTR mutation. Arch Dermatol. 2005;141:621–4.
102. Fradin M, Kalb R, Grossman M. Recurrent cutaneous vasculitis in cystic fibrosis. Pediatr Dermatol. 1987;4:108–11.
103. Garty B, Scanlin T, Goldsmith D, et al. Cutaneous manifestations of cystic fibrosis: possible role of cryoglobulins. Br J Dermatol. 1989;121:655–8.

104. Soter N, Mihm M, Colten H. Cutaneous necrotizing venulitis in patients with cystic fibrosis. J Pediatr Scand. 1979; 95:197–201.
105. Schidlow D, Goldsmith D, Palmer J, et al. Arthritis in cystic fibrosis. Arch Dis Child. 1984;59:377–9.
106. John E, Medenis R, Rao S. Cutaneous necrotizing venulitis in patients with cystic fibrosis. J Pediatr. 1980;97:505.
107. Finnegan M, Hinchcliffe J, Russel-Jones D, et al. Vasculitis complicating cystic fibrosis. Q J Med. 1989;72:609–21.
108. Schidlow D, Panitch H, Saeri N, et al. Purpuric rashes in cystic fibrosis. Am J Dis Child. 1989;143:1030–2.
109. Abman S, Ogle J, Harbeck R, et al. Early bacteriologic, immunologic, and clinical course of young infants with cystic fibrosis identified by neonatal screening. J Pediatr. 1991;119:211–7.
110. Disis M, McDonald T, Colombo J, et al. Circulating immune complexes in cystic fibrosis and their correlation to clinical parameters. Pediatr Res. 1986;20:385–90.
111. Hodson M, Beldon I, Batten J. Circulating immune complexes in patients with cystic fibrosis in relation to clinical features. Clin Allergy. 1985;15:363–70.
112. Crone J, Huber W, Eichler I, Granditsch G. Acrodermatitis enteropathica-like eruption as the presenting sign of cystic fibrosis-case report and review of literature. Eur J Pediatr. 2002;161: 475–8.
113. Patrizi A, Bianchi F, Neri I, Specchia F. Acrodermatitis enteropathica-like eruption as the presenting sign of cystic fibrosis. Pediatr Dermatol. 2003;20:187–8.
114. Hansen R, Lemen R, Revsin B. Cystic fibrosis manifesting with acrodermatitis enteropathica-like eruption. Association with essential fatty acids and zinc deficiencies. Arch Dermatol. 1983;119:51–5.
115. Darmstadt G, McGuire J, Ziboh V. Malnutrition-associated rash of cystic fibrosis. Pediatr Dermatol. 2000;17:337–47.
116. Darmstadt GL, Schmidt CP, Wechsler DS, et al. Dermatitis as a presenting sign of cystic fibrosis [comment]. Arch Dermatol. 1992;128:1358–64.
117. Lovett A, Kokta V, Maari C. Diffuse dermatitis: An unexpected initial presentation of cystic fibrosis. J Am Acad Dermatol. 2008;58:S1–4.
118. Darmstadt GL, Schmidt CP, Wechslet DS, Tunnessen WW, Rosenstein BJ. Dermatitis as a presenting sign of cystic fibrosis. Arch Dermatol. 1992;128:1389–90.
119. Abman S, Accurso F, Bowman C. Persistent morbidity and mortality of protein calorie malnutrition in young infants with cystic fibrosis. J Pediatr Gastroenterol Nutr. 1975;5:393–6.
120. Muñiz A, Bartle S, Foster R. Edema, anemia, hypoproteinemia, and acrodermatitis enteropathica: an uncommon initial presentation of cystic fibrosis. Pediatr Emerg Care. 2004;20:112–4.

http://www.springer.com/978-1-4614-0687-7

Atlas of Dermatology in Internal Medicine
Sánchez, N.P. (Ed.)
2012, XIV, 148 p. 129 illus. in color., Softcover
ISBN: 978-1-4614-0687-7