Chapter 15

CUTANEOUS TUBERCULOSIS

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INTRODUCTION

Just as systemic tuberculosis can be protean and diverse in its clinical manifestations, so tuberculosis of the skin is also highly variable in its clinical appearance, significance, and prognosis. Five factors that are important for the clinical presentation of cutaneous tuberculosis are (1) the pathogenicity of the organism, (2) its antibiotic resistance profile, (3) the portal of infection, (4) the immune status of the host, particularly the presence or absence of acquired immunodeficiency syndrome (AIDS) secondary to infection with human immunodeficiency virus (HIV), and (5) various local factors in the skin (eg, relative vascularity, trauma, lymphatic drainage, and proximity to lymph nodes).

The incidence of tuberculosis in the United States has been increasing since 1984 owing to the following factors:

- immigration of previously infected people from developing countries,[1]
- increasing homelessness and malnutrition,[2]
- worsening urban economic and social environments,[3]
- increased drug resistance,[4]
- the relaxation, reduction, or elimination of tuberculosis-control programs over the past two decades,[3]
- physicians who have not treated their patients in accordance with recommended treatment guidelines,[5]
- the increasing prevalence of AIDS.[6]

At present, the incidence of tuberculosis in the United States is approximately 10.5/100,000/y,[7] (up 15% since 1990), the largest group being 25 to 44 years of age—a group likely to have children in their households who are at risk of becoming infected.[8]

The worldwide incidence of tuberculosis in 1990 was estimated by the World Health Organization (WHO) to be 7.5 million cases, with the greatest number occurring in Southeast Asia and the western Pacific regions with 4.9 million cases, followed by India with 2.1 million, then China with 1.3 million, and Indonesia with 0.4 million.[9] This incidence is anticipated to climb by 58% to 11.9 million cases per year by the year 2005.[9] The rate of incidence of tuberculosis in the developing countries of the world is much greater: approximately 500/100,000/y.[10] These same factors that have led to the increases in the United States are operative worldwide. Of especially great alarm has been the progressive increase in numbers of strains of tuberculosis that are resistant to multiple antibiotics[11,12] as well as the rampant spread of such strains in AIDS-infected patients.[6,12,13]

Since 1984, the incidence of extrapulmonary tuberculosis has increased at an even faster rate than that of pulmonary tuberculosis[14,15] and is considered a diagnostic criterion in the case definition for AIDS.[16] Because immunocompromised individuals are at increased risk for extrapulmonary tuberculosis, dermatologists are renewing their historic role in the diagnosis of cutaneous lesions of tuberculosis.

From the military standpoint, the risk of tuberculosis exposure virtually worldwide has increased dramatically since the end of the Vietnam conflict. The continued rise toward a worldwide pandemic of tuberculosis, AIDS-associated tuberculosis, and drug-resistant tuberculosis portends a perilous future for troops who deploy to any underdeveloped country. Vigorous surveillance for tuberculosis, coupled with comprehensive drug treatment and aggressive public health programs will be essential to ensure that our military forces do not fall victim to this age-old malady.

HISTORY

Unless otherwise noted, the general history of the study of tuberculosis up to the time of Robert Koch is quoted from Baldwin's "Tuberculosis: History and Etiology," a chapter in Osler, McCrac, and Funk's *Modern Medicine: Its Theory and Practice*, originally published in 1925.[17] The discussion of the contributions of Robert Koch is quoted from Neisser's "Chronic Infectious Diseases of the Skin," a chapter in Ziemssen's *Handbook of Diseases of the Skin*, originally published in German in 1885.[18]

Material relating to tuberculosis in the military in this chapter is quoted from Long's "Tuberculosis in the Army," published in 1963,[19] and Guiton and Barrett's "Tuberculosis," published in 1982,[20] both of which are chapters in official histories published by the U.S. Army Medical Department. The infor-

mation contained in these sources is essentially unavailable elsewhere.

Tuberculosis In Antiquity

Pulmonary tuberculosis (also called consumption and phthisis) has existed from very remote times. It transcends all other maladies in the total number of its victims and the cost to society in civilized countries. Tuberculosis was a disease familiar to the most ancient civilizations, judging from the inscriptions on Babylonian tablets, which represent the earliest human records.[17] Pathological evidence of tuberculosis of the spine has been found in Neolithic burial sites in Heidelberg, Germany. Bone lesions have also been recognized in the mummified body of a priest of Ammon, exhumed from a tomb of the 21st Egyptian Dynasty, 1000 BC.[21]

Hippocrates (460–376 BC) first gave an intelligent description of phthisis, although empyema and *phyma* (abscess of the lung), were included. Otherwise, his portrayal of the symptoms of consumption was unsurpassed for many centuries. The Hippocratic school believed in the curability of phthisis in all stages and the benefits of a change of residence. Contagion was mentioned by Isocrates. Aristotle, a contemporary of Hippocrates, notes that it was a general belief among the Greeks of his day that phthisis was contagious. Celsus (30 BC) wrote of the disease in three forms: atrophy, cachexia, and ulceration. Aretaeus (AD 50) gave a very clear description of the disease and differentiated it from empyema. He believed in the efficacy of sea voyages and country air. Pliny lauded pine forests for their healing powers.[17(p267)]

Galen (AD 131–201) considered the disease an ulceration that should be treated by measures designed to dry the secretion. He therefore sent patients to the high land of Phrygia. In other details, the conceptions of the disease held by Galen were like those of Hippocrates; nor was any further light shed on the nature of consumption for 1,400 years, when anatomical study began.[17(p267)]

Observations During the 4th Through 19th Centuries

[*A clue to the prevalence of tuberculosis in different periods of European history is found in the accounts of the ceremony of the "touch" performed by French and English monarchs to cure the swollen glands that occurred in the necks of those suffering from scrofula. Ever since Clovis in the 5th century, the kings of France were believed to receive from God this healing power at the time of their anointment. Edward the Confessor had also claimed it for the English kings in the 11th century. The first act of Henry of Navarre, when he entered Paris as Henry IV in 1594, was to touch 600 scrofulous persons. The 17th century seemed to be the heyday for touching, as well as for deaths from pulmonary consumption. In England, the largest number of persons applying to be touched was recorded in 1684, when many of them were trampled to death in attempting to reach the hand of the king.*[21]*—JWS*]

Sylvius (1614–1672) was the first to indicate the connection between tuberculous nodules and phthisis. He regarded these nodules as enlarged lymph glands in the lung, analogous to scrofula, and on the scrofulous constitution depended the inheritance of phthisis. He gave a careful description of the symptoms and believed in contagion. Morton, (1689) whose celebrated book [on phthisis] was widely known among English physicians, brought the tubercle prominently to attention as the true cause of phthisis. He also believed in the hereditary predisposition to and contagious nature of tuberculosis. Morgagni (1682–1771) was uncertain that tubercles and glands were identical, and thought that phthisis could originate from other things; he regarded it as extremely infectious, and refrained from doing autopsies on consumptives.[17(pp267–268)]

The teachings of Benjamin Rush exerted a powerful influence on American medicine in Revolutionary times. In his *Thoughts upon the Causes and Cure of Pulmonary Consumption* (1783), he regarded tuberculosis as a disease of debility and considered tubercles to be the result of hypersecretion from the bronchial vessels. He believed in contagion at first, but doubted it later in his life. Stark described the miliary tubercles, and near the end of the 18th century, Reid (1785) and Baillie (1794) completed the description. Most noteworthy is the work of Gaspard Laurent Bayle (1810), who is justly named as the founder of correct teaching about tuberculosis. He studied miliary tubercles in all stages, and laid great stress on their varying degrees of opacity.[17(p268)]

Réné Laennec (1819), whose work soon followed Bayle's, summarized and simplified the knowledge thus far gained. He recognized the unity of all phthisis as tuberculosis, and scrofula as tuberculosis of lymph glands; his ideas in general as to causation and infection were distinctly modern, and his descriptions of the tubercle and its transformation toward ulceration are unsurpassed.[3(p268)]

During this period, America was represented but meagerly until 1834, when Samuel Morton, of Philadelphia, published the first pathological studies on consumption. He was a student of Laennec, and his conclusions as to the nature of tubercles were fairly accurate; they were ascribed to altered secretion and not to inflammation. Samuel Morton's work on *Pulmonary Consumption* found much favor in America, and included excellent therapeutic advice as to open-air life and exercise.[17(p268)]

English, American, and German physicians accepted the probability of infection under special conditions, but the strongest opinions were held by the Latin races [*Mediterranean peoples—JWS*], among whom the disease was said to be more virulent. The influence of Valsalva and Morgagni was certainly most potent in causing fear in Italy. The first recorded inoculations were by Kortum (1789), which, like some of those of his successors, were fortunately unsuccessful, since they were partly on humans including themselves. The strife over the question of the danger of inoculation of scrofula with vaccination led to these first attempts.[17(p268)]

Virchow (1847–1850) classified scrofula and tuberculosis entirely apart, restricting the latter term to the miliary form and considering it a form of lymphoma due

to an unknown diathesis; caseation was a nonspecific process. Hence, the idea of unity in tuberculous diseases received a serious rebuff despite the important discovery by Buhl (in 1857) that miliary tubercles were most often associated with preexisting caseous foci, from which he thought the specific poison originated. The microscopical studies brought out valuable data, but withal much confusion.[17(p369)]

Jean Antoine Villemin presented his important communication, *On the Cause and Nature of Tuberculosis and the Inoculation of the Same from Man to Rabbit*, in December 1865. His conclusions were positive: (1) Tuberculosis is a specific affection. (2) It has its origin in an inoculable agent. (3) The inoculation from man to rabbits is very successful. (4) Tuberculosis pertains, therefore, to the virulent diseases, and should be classed with variola, scarlatina, syphilis, or, better still, with glanders. Villemin covered a wide field in his inoculations, employing fragments of lung tubercle, sputum, blood, scrofulous gland, and perlsucht or bovine tubercle, with positive results in nearly all cases. His conclusions excited widespread discussion and experimentation. A new era in microbiology was founded about the same time by [Louis] Pasteur.[17(p269)]

The contest over the specificity of the giant cell, the importance of which was emphasized by Langhans (1868), was settled in the negative. Tubercles were studied in all the tissues hitherto unassociated with the conception of tuberculosis, as fungous joints, carious bones, and lupus, by Koster (1873) and Friedländer (1873). The development and spread of miliary tubercles were traced to venous infection by Weigert (1879–1892). The pathway of infection was already inferred by the many feeding and inhalation experiments, so that, with the rapidly developing investigation of bacteria caused by Pasteur's discoveries, search was being made for a specific living organism. E. Klebs (1877) was the first to observe actual transference of the virus by artificial culture on egg albumin through several generations before inoculation, but he did not recognize the bacillus; instead, he found a motile organism, *Monas tuberculosum*, which he presumed to be the contagium vivum. Aufrecht (1881) and Baumgarten (1882), working independent of Koch, described bacilli in the center of the tubercles, which, owing to lack of culture and staining methods, were not positively identified as the infective agents. The actual achievement was due to [the German physician] Robert Koch, whose demonstration [in 1882] of the causative relation of the tubercle bacillus to tuberculosis[22] was so complete that but little of importance has been added since.[17(p269)]

The Contributions of Robert Koch

[*Because Koch's contributions were so brilliant and of such great importance, albeit published in German, the following historical review of his work is reproduced verbatim from the account of his work written in 1885 by Professor Albert L. S. Neisser (1855–1916), the dermatologist from Breslau, Germany, now Poland.—JWS*]

At the present time, tuberculosis, and with it scrofulosis, is the best-known chronic infectious disease of man, and the only one demonstrated with certainty.[18(p275)]

Villemin was the first to class tuberculosis as an inoculable infectious disease, but his doctrine failed to secure universal recognition. Further inoculation experiments were made by different savants in the most variable manner. The experimenters introduced the material into the animals from all possible points, so that the following result was rendered certain. If tuberculous material be transferred to an (appropriate) organism, there is developed in it, in a typical manner, a tuberculosis which sometimes remains more local, at other times spreads through the body generally. Only specific tuberculous material is capable of communicating this disease. Nontuberculous matters, or those deprived of their infectious quality, never produce tuberculosis. It was shown at the same time that the "predisposition" of some classes of animals was variable as regards the receptivity for the disease.[18(p275)]

Klebs described a form of micrococcus as peculiar to tuberculosis and cultivated it. In the same way, Schüller has reported experiments in cultivation and inoculations with its result. A landmark has been furnished also by the interesting experiments made by Deutschmann, who by leaving at rest inoculable tuberculous pus, separated it into a light wine-yellow serum inactive in inoculation, and a thick, tenacious sediment which produced tubercle. Recently, Damsch, in Ebstein's clinic, has been able to demonstrate tuberculosis of the urinary passages in the living, by successful inoculations into the anterior chamber of the eye of rabbits. Aufrecht alone has described microscopically specific bacteria in the tissues, without having been able to gain general recognitions of his results.[18(p275)]

But the credit of having finally elucidated the nature of tuberculosis belongs to Robert Koch, who furnished the incontrovertible proof that a specific bacillus is the cause of tuberculosis and of scrofulosis.[18(p275)]

The proof consisted, first, in the demonstration of a parasitic microorganism in tuberculous neoplasms. For this a new staining process had to be invented since alkaline solutions alone were appropriate. The method originally devised by Koch was very soon modified by Ehrlich, who found the alkalinizing factor in aniline oil (or, according to Ziehl, in carbolic acid). His procedure is as follows: the sections are warmed, then stained in a mixture of a concentrated alcoholic-fuchsin or gentian-violet solution and an aqueous solution of anilin oil (carbolic acid solution) for several hours, or for a short time if heated. The sections are then freed from excess color by alcohol or water washing, then immersed in a solution of one part of officinal sulphuric (or nitric) acid with two or three parts of distilled water. The deep blue (or red) color gives place at once to a faint yellow, the stain being bleached in all parts of the tissue. The bacilli, however, retain the color and may now be recognized under comparatively low power. It is better to further stain the background with anilin brown or methylene

blue, because then the blue (or red) bacilli can be more easily distinguished. The preparations, after having been dehydrated in alcohol, are rendered transparent in oil of cloves and preserved in Canada balsam. The preparations are not always permanent, the color of the bacilli gradually fading, probably because the acid is not thoroughly washed out. The gentian preparations are certainly more constant in their color than the fuchsin preparations. The color keeps best when the specimens (dry preparations) are not enclosed in Canada balsam, but are directly examined in oil of cedar (with homogeneous immersion).[18(pp275–276)]

The bacteria rendered visible by this method have a rod shape, hence are bacilli. Their length corresponds about to one-fourth to one-half the diameter of a red blood corpuscle. Their breadth differs according to the method employed; Koch's original methylene blue results in exceedingly slender bacilli, while Ehrlich's and Baumgarten's method additionally colors the sheath enclosing the bacillus. Characteristic of the tubercle bacilli, in Koch's older method, is their rejection of the anilin brown staining after they have already taken the methylene blue. In Ehrlich's method, the tubercle bacilli retain the tint present in the anilin oil and are not decolored by acid or subsequent methylene blue staining.[18(p276)]

Bacilli are aggregated in great numbers wherever the tuberculous process is of recent inception and in rapid progress—forming closely packed groups often arranged in intracellular bundles. There are also numerous free bacilli, especially at the border of large cheesy patches where they are present in large free swarms. After the pinnacle of the tubercular eruption has been passed, the bacilli become sparser and can be seen only as isolated, often faintly colored, probably dying or dead formations. If giant cells are present, the bacilli are most numerous within them. Here, too, those with bacilli are the more recent, those without them the older cells in which the bacilli originally present have died or have passed into a subsequent dormant state. Besides the ordinary bacillus forms, we find others with two to four oval spores which are placed at regular intervals along the bacillus [*producing the pathognomonic "beaded" appearance of this distinctive mycobacterium—JWS*].[18(p276)]

Subsequent examinations, wherever made, confirmed the correctness of Koch's statement as to the constant presence and the diagnostic value of these bacilli in tuberculous infections.

But even this did not satisfy Koch himself. He said:

> It does not follow, however, from this coincidence of tuberculous affliction with bacilli that both phenomena stand in causal relation to each other, though no slight degree of probability for this assumption is furnished by the fact that the bacilli are found chiefly wherever the tuberculous process is in its inception or progress, disappearing where the disease comes to a standstill.[4(p276)]
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> In order to prove that tuberculosis is a parasitic disease caused by the immigration of the bacilli and is originally due to their growth and increase, the bacilli must be isolated from the body and cultivated in pure fluids until they are freed from any possibly still adhering morbid product derived from the animal organism, and finally, by the introduction of the isolated bacilli into animals, the same morbid picture of tuberculosis must be produced which experience has shown us to result from inoculation with tuberculous matters of natural origin.[18(p276–277)]

This task Koch has performed in a brilliant and absolutely irrefutable manner.

The cultivations were made in sterilized, coagulated blood serum. They were distinguished by an exceedingly slow growth which proceeds only at a temperature of 37° to 38°C; they form minute compact scales which can be easily detached in toto and by appropriate examination are shown to consist only of the well known, extremely delicate bacilli. The cultivations yielded corresponding results, whether the matter was derived from animal or human tuberculosis; they were continued for months outside of the animal body, by successive transfer from serum to serum.[18(p277)]

But in every case inoculations of healthy animals with the cultivation yielded a positive and constantly uniform result—a typical inoculation tuberculosis of the animal.[18(p277)]

In guinea pigs, the inguinal glands swelled after 2 weeks. The inoculation sites on the abdomen changed into an ulcer, and the animals emaciated. After 32 to 35 days the animals were killed. They all exhibited intense tuberculosis of the spleen, liver, and lungs; the inguinal glands were greatly swollen and cheesy, the bronchial glands were only slightly swollen.[18(p277)]

In the same way rabbits, rats, cats, dogs, etc., were successfully inoculated. The experiments with rats and dogs are especially interesting because these animals have otherwise shown themselves uncommonly resistant toward inoculations of tuberculosis.[18(p277)]

The result of the experiments is independent of the point of inoculation: subcutaneous connective tissue, anterior chamber of the eye, abdominal cavity, direct introduction into the blood current, etc. It is necessary, owing to their exceeding slow growth, that the infectious matters be brought to a spot where, protected from external injury, the bacilli have the opportunity to increase and penetrate into the tissues, otherwise the bacilli are eliminated before they secure a habitat.[18(p277)]

> Small shallow cutaneous incisions are no wounds appropriate to the invasion of bacteria. Similar conditions will be requisite to ensure the adherence of the bacilli which have reached the lungs. Probably, factors favorable to the retention of the bacilli, such as stagnating secretions, denudation of the mucosa of its protective epithelium, etc., will be of assistance in effecting the infection.[18(p277)]

Furthermore, it appeared that the rapidity of the course of inoculated tuberculosis, as well as its extent and spread over the several organs, is dependent upon the larger or smaller quantity of infectious matter introduced. The

picture of acute miliary tuberculosis occurred only when the body was at once overwhelmed, as it were, by a large quantity of infectious organisms. Otherwise, when but few bacilli are inoculated, the processes are of slow development or circumscribed locally (nodules on the iris, opacity of the cornea, affections of the lymphatic glands), which are very much later succeeded by general infection, unless the disease terminates altogether with the local process.[18(p277))]

[*In 1882, only 2 years after the discovery of Mycobacterium tuberculosis, Robert Koch found the tubercle bacillus in the lesions of lupus vulgaris. This revelation gave rise to the concept of "localized tuberculosis of the skin." Sir Jonathan Hutchinson accepted the bacillary origin of lupus, in contrast to that of leprosy, and in a series of lectures in 1888, used the term "apple jelly nodule" to describe their peculiar transparency. Paul Gerson Unna later introduced the use of the diascope, which is particularly useful in the diagnosis of lupus vulgaris.*[23]

In 1891, Koch recognized the reactivity of the skin to inoculation of virulent or killed tubercle bacilli when the host had had previous tuberculosis. In 1906, the Viennese pediatrician Clemens von Pirquet perceived that this reactivity to killed or heated bacilli after the development of a primary tuberculous complex was a tuberculosis specific allergy.[24] *In 1907, Charles Mantoux introduced the Mantoux skin test, the standard method for determining previous exposure to tuberculosis. Since that time, the tuberculin skin test has been one of the most important methods of diagnosis of infection as well as for determining the cellular immune status (anergic, normal, hyperergic) of the host.—JSW*]

Tuberculosis in the Military

Tuberculosis has been a problem since antiquity and for centuries was a principal cause of death in men of military age. Records of hospital admissions and medical discharges from military service for tuberculosis have been maintained by the U.S. Army since the Civil War. During that conflict, there were 13,499 tuberculosis admissions and 5,286 deaths from the disease among white soldiers. The mean annual rate of discharge for tuberculosis was 8.6 per 1,000 in white troops and 3.1 per 1,000 in black troops. However, in neither the Civil War nor the Spanish-American War was the disease frequent enough to prompt any unusual comment in the analyses recording the medical aspects of military operations.[20(p214)]

Tuberculosis in World War I

During World War I, men with tuberculosis were detected and excluded from military service almost entirely on the basis of the physical examination, as roentgenology was in its infancy and screening skin testing resources were not available. There were 22,812 disability separations because of tuberculosis during the war, or 5.52 per 1,000 strength per annum. The disease was the leading cause of disability separation, accounting for 11.1% of the total. Further, the full magnitude of the problem did not become evident until several years after the war. Goldberg (1941) calculated that the approximate expenditure by the Veterans Administration for service-connected tuberculosis from the close of World War I through 1940 was $1,186,000,000. The number of hospitalized tuberculosis beneficiaries peaked in 1922 at 44,591.[20(p215)]

Tuberculosis in World War II

At the beginning of World War II, the Office of The Surgeon General recognized that drastic revision of the physical standards in the existing Mobilization Regulations was necessary because of technical developments in tuberculosis control. In April 1939, a chest X-ray examination was required before applicants could be commissioned. As early as 1940, routine screening chest X-ray examinations for all inductees were considered, but they were not made a mandatory part of all physical examinations at induction stations until 3 June 1941. While approximately 10 million men had chest X-ray examinations, about 1 million were inducted without them.[20(p215)]

The average incidence rate of tuberculosis for World War II from 7 December 1942 to 14 August 1945 was 1.2 per 1,000 per annum. Tuberculosis accounted for 1.9% of all discharges for disability from disease between 1942 and 1945, ranking 13th on the list. Among Americans who had been prisoners of war, the rates were higher. Prisoners from the European theater had an incidence five to seven times that of the U.S. Army in general. Statistics on those returned from the Pacific area were more difficult to obtain, but a special study of repatriated prisoners at West Coast debarkation hospitals, directed by The Surgeon General, showed that 2.7% of 3,742 individuals studied with chest X-ray examinations had evidence of active pulmonary tuberculosis.[20(p215)]

Extrapulmonic forms of tuberculosis were rare. A total number of 140 cases of cutaneous tuberculosis were reported by the U.S. Army between 1942 and 1945, or 0.01 case per 1,000 per year (ie, less than 1% of patients with systemic tuberculosis).[19(p369)]

The semiannual report of the senior consultant in tuberculosis in the European theater, dated 3 July 1945, called attention to an excessive and steadily rising prevalence of all forms of tuberculosis in nurses for the 3½ years of the war. The mean rate for the 3½ years was 3.8 times as high as the general tuberculosis admission rate for troops in the theater.…[I]n analyzing the responsible factors, [the report] called attention to the carelessness in technique that develops in times of strain and stressed the failure of medical officers to maintain proper measures, designed to prevent spread of the disease in hospitals.[19(pp342–343)]

In the final weeks of the war in Germany, Allied troops overran a large number of the notorious concentration camps in which the German government imprisoned political nonconformists, Jews, nationals of surrounding states, and others who had offended the Nazi Party. These camps included Auschwitz, Buchenwald,

Nordhausen, Dachau, Belsen, and many others. Thousands of dead were found in the camps at the time of their liberation, and many more thousands were sick and dying. Among the latter were hundreds of persons with advanced tuberculosis, who constituted an immediate problem for the evacuation hospitals of the advancing armies.[19(p349)]

A vivid description of conditions at the Dachau concentration camp, and the extent of tuberculosis in hospitalized inmates of that camp, has been given by Piatt.[25] He made a statistical analysis of 2,267 roentgenograms of the chest of patients removed from the concentration camp hospital and examined by X ray on admission to the receiving and evacuation section of the 127th Evacuation Hospital. In only 45.3% of the films was no abnormality discovered. Tuberculosis, pneumonia, and heart disease were the chief abnormalities. Six hundred twenty-six definite cases of tuberculosis, or 27.6% of the total number examined, were detected. In more than half of these, the disease was bilateral, and in four fifths of the cases, the process was either moderately or far advanced. In addition to definite tuberculosis, there were 94 patients (4.1% of the total) with pleural effusion, probably tuberculous in origin. There were five cases of miliary tuberculosis.[19(p350)]

Piatt, among others, expressed the view that the incidence of tuberculosis in Europe would increase appreciably in the years to come as a result of the return of numerous persons with undiagnosed active disease from concentration camps to their homes.[19(p350)]

Tuberculosis in the Korean and Vietnam Conflicts

While specific incidence rates are not available for the Korean conflict, tuberculosis continued to be a problem for the U.S. Army, as reflected by the approximately 600 admissions per year to Fitzsimons General Hospital during that period.[20(p215)]

Rightful concern was expressed about the exposure of American troops in Vietnam to a population with a high tuberculosis infection rate. The conflict in Vietnam placed an estimated 500,000 American military personnel annually in varying degrees of contact with a highly infected population. In 1968, a chest X-ray survey by Siegler, et al, of Vietnamese civilians showed that 31.7% [of the population] over the age of 15 had definite radiologic evidence of active pulmonary tuberculosis. Another study demonstrated that nearly 100 percent of the adult population was tuberculin skin test positive.[20(p216)]

Among U.S. troops, approximately 95% had had no previous exposure to tuberculosis and were tuberculin-negative on arrival in Vietnam. Data from the 20th Preventive Medicine Unit indicated that only 6.2% of 901 first-time personnel were tuberculin positive on entering the country, whereas 13.7% of 190 personnel who had served a previous tour in Vietnam were positive. In the first-tour group, breakdown by race showed that 3.2% of whites, 7.4% of blacks, 9.1% of Orientals, and 15.6% of Spanish-surnamed persons were tuberculin positive; a similar racial distribution was noted in the group with previous tours in Vietnam.[20(p216)]

The clinical course of tuberculosis was apparently no different in U.S. servicemen in Vietnam than it was in patients in the United States. Extrapulmonary forms and pleural effusion were uncommon.[20(p218)]

[*Currently, from a military perspective, the incidence of tuberculosis is highest in Africa, where estimates run 165 cases per 100,000 population. In Asia, the estimated incidence is 110 per 100,000. Because the population in Asia is much larger than Africa's, however, the total number of cases in Asia is thought to be 3.7 times greater. In the western Pacific, the highest rates occur in the Solomon Islands, the Philippines, and South Korea, and the lowest in Australia, New Zealand, and Japan. Some third-world countries may have incidences approaching 500 cases per 100,000 population.*[8] *—JWS*]

EPIDEMIOLOGY

An estimated 1.7 billion people are infected with *Mycobacterium tuberculosis*: approximately one of three living persons.[26] In 1982, WHO estimated that of the 10 million new cases of tuberculosis that occur each year worldwide, 4 to 5 million are highly infectious, smear-positive cases, and approximately 3 million cases prove fatal.[27] In 1990, WHO estimated an incidence of 7.5 million cases of tuberculosis and 2.5 million deaths. HIV infection was considered responsible for 116,000 deaths (4.2%).[9] Case-fatality rates were estimated at 15% for those receiving treatment and 55% for those receiving no treatment.[27] For the decade 1990 through 1999, 30 million deaths (12.3 million in Southeast Asia, 6 million in sub-Saharan Africa) are anticipated from tuberculosis, with approximately 10% expected to be associated with HIV.[27]

Although in most areas of the world the incidence of tuberculosis is anticipated to decline or remain stable, the incidence rates in Africa are anticipated to rise by some additional 10 cases per 100,000 population per year through 2005, primarily because of the HIV epidemic.[9]

In the United States, the large influx of immigrants from Southeast Asia and Haiti and the growing numbers of homeless—up to 50% of whom are infected with tuberculosis[26]—have posed a new threat to a previously well-administered tuberculosis-control program. More than 20% of the new cases in the United States occur among the foreign-

born,[28] virtually all of whom are from resource-poor countries with high rates of tuberculosis. For example, in 1988, not only did Asians and Pacific Islanders have the highest incidence of tuberculosis in the United States, with 49.6/100,000 (compared to 26.7/100,000 for blacks and 5.7/100,000 for whites), but in addition, 93.6% of those affected were foreign-born.[29] Selected incarcerated populations are at even greater risk for developing tuberculosis. For example, the incidence of tuberculosis in New York state prisons between 1980 and 1990 was 134/100,000—almost 14-fold higher than the national average.[26]

In the United States from 1963 through 1986, the incidence of pulmonary tuberculosis declined at an average annual rate of 5.0%; however, the incidence of extrapulmonic tuberculosis declined only 0.9% annually. Immigrants from developing areas, particularly from Africa, India, tropical America, and Southeast Asia, have been a major source of these extrapulmonary forms. In the United States in 1986, only 17.5% of all cases of tuberculosis were extrapulmonic, but of those, 71.2% of patients belonged to racial ethnic minorities or were foreign-born.[30] (Likewise, of patients with pulmonic tuberculosis, 63% belonged to racial ethnic minorities or were foreign-born.[30])

As might have been expected, some of the most dreadful epidemics of tuberculosis have occurred in populations who had had little or no previous contact with the disease:

- Scrofula and pulmonary tuberculosis were extremely rare among native Pacific Islanders before contact with European immigrants; however, within a few decades, tuberculosis was the cause of 40% of all deaths in New Caledonia and Hawaii.
- The highest mortality rate on record (9,000/100,000) occurred among the Indians of the Qu'Appelle Valley Reservation in Western Canada.
- Tuberculosis was both fulminant and rampant in the Senegalese troops and Capetown men who were brought to France during World War I. Large numbers of these soldiers succumbed to what was then called "galloping consumption."[21]

Cutaneous tuberculosis is also found worldwide with higher frequency in the cooler latitudes. However, fewer than 1% of all cases of tuberculosis are expected to have cutaneous manifestations.[19] Nonetheless, with the sharp increases in AIDS, cutaneous forms of tuberculosis such as miliary tuberculosis,[31,32] tuberculous abscesses,[33] and scrofuloderma[34] are beginning to be reported among AIDS patients. Infection with *M tuberculosis* can occur from contact with contaminated bodily fluids, secretions or discharges, or through direct contact with diseased skin. Modes of transmission for infection include (*a*) respiratory, (*b*) gastrointestinal (from unpasteurized milk from infected animals), (*c*) genitourinary (through sexual intercourse), and (*d*) inoculation through skin or mucous membranes (eg, the conjunctiva). Sources of infection include humans, cattle, swine, dogs and cats, monkeys, and laboratory bacteriological cultures. Exogenous iatrogenic inoculation has occurred in laboratory workers.[35]

Social and economic conditions are important factors in the incidence and prevalence of tuberculosis. Extreme youth, old age, poverty, overcrowding, and inadequate hygiene and nutrition increase the risk of infection, as does immunosuppression during the course of pregnancy, diabetes, sarcoidosis, leukemia, and lymphoma. Increased genetic susceptibility is associated with HLA-B_W15 antigen. Treatment with cytostatic medications or systemic glucocorticosteroids can also increase the risk of acquisition or reactivation of pulmonary tuberculosis.

Wars usually bring into sharp focus the inadequacy of hereditary resistance and immunity when environmental stress, malnutrition, and hygienic conditions become too formidable. Tuberculosis mortality increased suddenly and dramatically in Paris during the siege by the Prussian Army in 1871. Similarly, it increased everywhere in Europe within a few months after two world wars began—even in countries that did not take a direct part in the conflict and where food was never scarce.[21]

Once tuberculosis is established in the host, spread to the skin may occur by contiguous extension of underlying lymph nodes or osseous lesions, from hematogenous or lymphatic dissemination, or through secondary exogenous inoculation.

An epidemiological analysis published in 1990[36] reviewed 400 cases of tuberculosis with skin manifestations seen in hospitals in Poland over the past 25 years. Of these, 268 (67%) had tuberculosis of the skin and 132 (33%) had tuberculids (which are discussed later in this chapter). The investigator noted that the prevalence of skin tuberculosis was 5.8-fold lower during the period 1983 through 1987 than it had been during the period 1963 through 1967. The frequency of the different forms of tuberculosis were as follows: lupus vulgaris (57.5%), scrofuloderma (35.4%), verrucous tuberculosis (4.5%), and

ulcerative tuberculosis (2.6%). The male-to-female ratio was 1:2.05. Women were more likely to have lupus vulgaris or scrofuloderma, while men more frequently had verrucous or ulcerative tuberculosis. The young more frequently had scrofuloderma and the elderly more frequently had lupus vulgaris.

In western Algeria, 45 cases of cutaneous tuberculosis were diagnosed from March 1981 through December 1987. Both sexes were equally represented. The different forms of tuberculosis were seen in the following frequency: lupus vulgaris (28.8%), scrofuloderma (28.8%), specific adenitis (13.3%), verrucous tuberculosis (13.3%), tuberculous gumma (13.9%), and ulcerative tuberculosis (2.2%). The tuberculin skin test was positive in 86% of the cases.[37]

BACTERIOLOGY

The bacterium *M tuberculosis* measures 2.5 to 3.5 μm in length by 0.3 to 0.6 μm in width. This slightly curved, sporeless, motile, obligate aerobic, Gram-positive bacterium is acid-, alkali-, and alcohol-fast. It has a high lipid content and a slow growth rate. Its peptidoglycan skeleton contains approximately 30 different antigenic substances, of which the most important is the tuberculoprotein, the active component of tuberculin, which is the agent used for intradermal testing for delayed hypersensitivity. Within the cell wall of *M tuberculosis* may lie all of the elements associated with tuberculosis, including the factors responsible for caseation and other features of hypersensitization, the antigens responsible for humoral immunity, the agents of toxicity, and, indeed, the very antigens implicated in protective immunity.[38]

There are two types of *M tuberculosis*—human and bovine—but apparently no clinical difference between infections caused by either type. Bacille bilié de Calmette-Guérin (BCG) is an attenuated strain of the bovine form that is used for vaccination in many parts of the world. In a prospective series of 70 patients with cutaneous tuberculosis that was published in 1989,[39] researchers were able to culture *M tuberculosis* (using a concentration procedure from biopsy tissue homogenates inoculated on Lowenstein-Jensen medium) from 24 of 70 (34.03%) of their patients overall**:** from 4 of 30 (13.3%) patients with lupus vulgaris, 3 of 7 (42.85%) patients with verrucous tuberculosis, and 17 of 33 (51.05%) patients with scrofuloderma.

Tubercle bacilli grow in 3 to 4 weeks when cultured on Lowenstein-Jensen medium. In contrast, guinea pig inoculation requires 6 to 7 weeks for confirmation.

HISTOPATHOLOGY

The histopathological inflammatory reactions to *M tuberculosis* can be organized along an immunopathological spectrum, as can be done with leprosy. A sequence from nonnecrotic epithelioid cell granulomas with no acid-fast bacilli (high-immune), through necrotic epithelioid granulomas with some acid-fast bacilli, to necrosis with abundant acid-fast bacilli (low-immune) can be arranged. Lupus vulgaris typifies the high-immune pole; tuberculosis cutis orificialis and acute miliary tuberculosis, the low-immune pole.

A similar immunopathological spectrum has been devised for cutaneous tuberculosis, extending from lupus vulgaris toward scrofuloderma through tuberculosis verrucosa cutis.[40]

In the classic case, the hallmark of the histopathological diagnosis of cutaneous tuberculosis is the presence of tuberculous or tuberculoid granulomata. However, the diagnosis may be missed if one searches solely for the classic tuberculoid granulomata.[41] Seven additional patterns of inflammation have been described[42]:

- Classic tuberculoid granulomas, which consist of typical granulomas with Langhans'-type giant cells. A peripheral cuff of inflammatory cells, predominantly lymphocytes, surrounds the giant cells. Caseation necrosis may or may not be present (Figure 15-1).
- Abscess formation, which consists of acute or chronic (or a mixture of both) inflammatory cells with variable degrees of necrosis. The amount of fibrosis varies during the healing phase. Giant cells are present in some cases only.
- Diffuse infiltration of histiocytes, in which the infiltrate is composed primarily of histiocytes; few other types of inflammatory cells are present. Only a few well-formed granulomas are seen. Necrosis is universal.

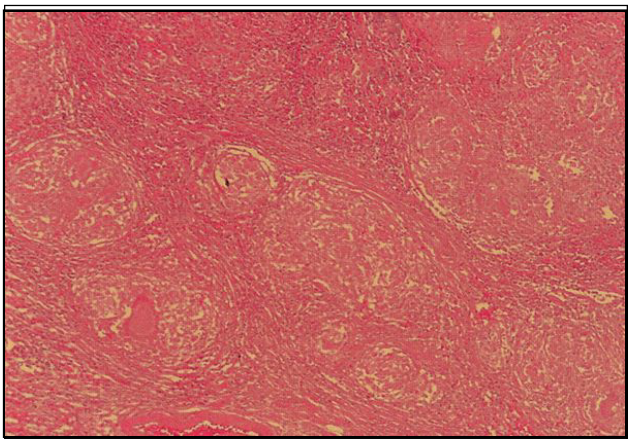

Fig. 15-1. Classic tuberculoid granuloma, seen on low-power magnification. Note foci of caseation necrosis and Langhans'-type giant cells.

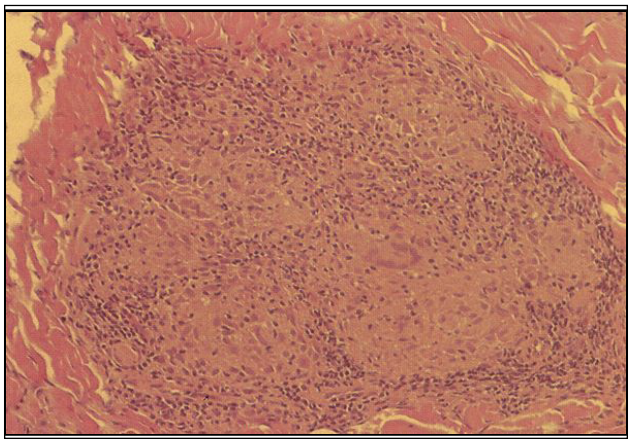

Fig. 15-2. Lupus vulgaris, seen on medium-power magnification. In this sarcoidal-type granuloma, the peripheral rim of lymphocytes, which is typical of lupus vulgaris, helps to differentiate it from sarcoidosis.

- Panniculitis, which is unusual in that both septae and lobules are involved. The infiltrate may be an acute inflammation, a chronic inflammation, or both. Abscess formation may occur as well as necrosis. Phlebitis can be found rarely. One reported case[42] exhibited acid-fast bacilli in the vascular endothelium.
- Nonspecific chronic inflammation, which includes sheets or scattered clusters of chronic inflammatory cells consisting predominantly of lymphocytes and histiocytes. However, other cell types, including plasma cells and eosinophils, can be seen. Giant cells are absent in this pattern.
- Sarcoidal granulomas, which are classically described as "naked" granulomas, due to the absence of peripheral inflammatory cuffing of the granulomas by lymphocytes. The granulomas in this pattern consist primarily of Langhans'-type giant cells with little or no lymphocytic cuffing. Necrosis is minimal or absent. Lamellar calcifications identical to Schaumann bodies are sometimes present (Figure 15-2).
- Rheumatoid-like nodules, the hallmark of which is the presence in the dermis or subcutaneous tissue, or both, of central necrosis surrounded by palisading histiocytes. A mild, chronic, inflammatory infiltrate may be present, and giant cells are occasionally seen.

Several points must be emphasized when considering these patterns of inflammation: (1) The patterns do not correlate with either a specific mycobacterium or a specific clinical presentation. In fact, subsequent biopsies in the same patient may show a different pattern. (2) These patterns are not pure but represent a spectrum of changes; the patterns may be seen in any combination. (3) Patients with mycobacterial infections do not always present with tuberculoid granulomas, nor does the presence of tuberculoid granulomas necessarily indicate cutaneous tuberculosis. Infections (eg, syphilis) and noninfectious granulomas (eg, zirconium granuloma) may give identical histological patterns.

The sections that follow give the clinical presentations of diseases caused by *M tuberculosis*. The histological descriptions given are those most commonly encountered for each of the clinical entities; however, the general patterns given above must be kept in mind.

CLASSIFICATION

Numerous attempts have been made to classify cutaneous tuberculosis based on clinical morphology, etiology, the immune status of the host, and so forth. Morphologic classification is unsatisfactory because similarly appearing skin lesions can have multiple causes and can differ histologically. Classifications based on etiology or immune status are not helpful clinically. Confusion abounds

regarding chronic, reactivation, and reinfection tuberculosis; however, the complexities of cutaneous tuberculosis can be classified and the general pathogenesis described (Table 15-1 and Figure 15-3).

Primary Inoculation Tuberculosis

Primary inoculation tuberculosis is also called tuberculous chancre, cutaneous primary complex, and tuberculosis primaria cutis.[43] This infection with the tubercle bacillus develops as a result of inoculation of *M tuberculosis* into the skin or mucosa of a nonimmune host. (Immunity can be conferred by previous infection or BCG immunization.) An initial negative reaction to purified protein derivative of tuberculin (PPD) reflects the host's absent immunity.

Epidemiology

Inoculation tuberculosis accounts for only 5% of total primary tuberculosis; the majority of patients have (*a*) respiratory exposure with the subsequent formation of a Ghon complex or (*b*) gastrointestinal exposure.[44] Because *M tuberculosis* cannot penetrate intact human skin, some sort of injury must be present for an infection to be established. Portals of entry often include such minor injuries as abrasions, puncture wounds, hangnails, and pyodermas. Overall, children are most frequently affected with primary inoculation tuberculosis, with the face and exposed extremities being sites of predilection. (The most famous example of inoculation tuberculosis, the "prosector's wart," albeit a secondary or reinfection tuberculosis, was frequently acquired by pathologists in years past from handling tuberculous lungs or other tissues without protective gloves at the autopsy table.) Tuberculous chancres have also followed *b'rit milah* (ritual circumcision), cardiopulmonary resuscitation, tattoos, inoculations and injections for immunization or therapy, ear piercing, venipuncture, misinoculation of laboratory animals, and sexual intercourse. Inoculation can also occur in the mucous membranes of the oral cavity after tooth extraction, in the tonsils from ingesting nonpasteurized milk, or in the ocular conjunctiva during ocular surgery.[43,44] Recently, primary inoculation tuberculosis has been reported following a needlestick injury from a patient with AIDS and undiagnosed tuberculosis.[45]

TABLE 15-1

CLASSIFICATION OF CUTANEOUS TUBERCULOSIS

Stage	Source	Mode	Histology	Course	Disease	Immunity	Bacilli
Primary	Exogenous	Inoculation	Nonspecific	Localized	Chancre	Developing	+++
			TB specific	Localized	Primary TB complex	Good	+?
			TB specific	Localized	Lupus vulgaris	Moderate	++
			TB specific	Progressive	TB fungosa serpiginosa	Poor	+++
			TB specific	Generalized	Miliary TB	Poor	+++
Secondary	Exogenous	Reinoculation	TB specific	Localized	TB verrucosa cutis	Good	+/–
			TB specific	Progressive	TB cutis orificialis	Poor	+++
	Endogenous	Contiguous	TB specific	Localized	Lupus vulgaris	Moderate	++
			TB specific	Localized	Scrofuloderma	Poor	+++
		Autoinoculation	TB specific	Localized	TB verrucosa cutis	Good	+/–
			TB specific	Progressive	TB cutis orificialis	Poor	+++
		Hematogenous	TB specific	Localized	Lupus vulgaris	Moderate	+++
			TB specific	Localized	Gumma (subcutaneous abscess)	Moderate	++
			TB specific	Localized	Ulcerative TB	Moderate	++
			TB specific	Progressive	TB fungosa serpiginosa	Poor	+++
			TB specific	Progressive	TB cutis orificialis	Poor	+++
			TB specific	Generalized	Miliary TB	Poor	+++
Tuberculid	Endogenous	Hematogenous	Variable	Localized	Erythema induratum	Moderate-to-good	–/+
			Variable	Scattered crops	Papulonecrotic tuberculid	Moderate-to-good	–/+
			Variable	Generalized	Lichen scrofulosorum	Moderate-to-good	–/+

+++: numerous bacilli: ++: some bacilli; +/–: bacilli rarely found; –/+: unusual to find bacilli; +?: variable, depending on time course

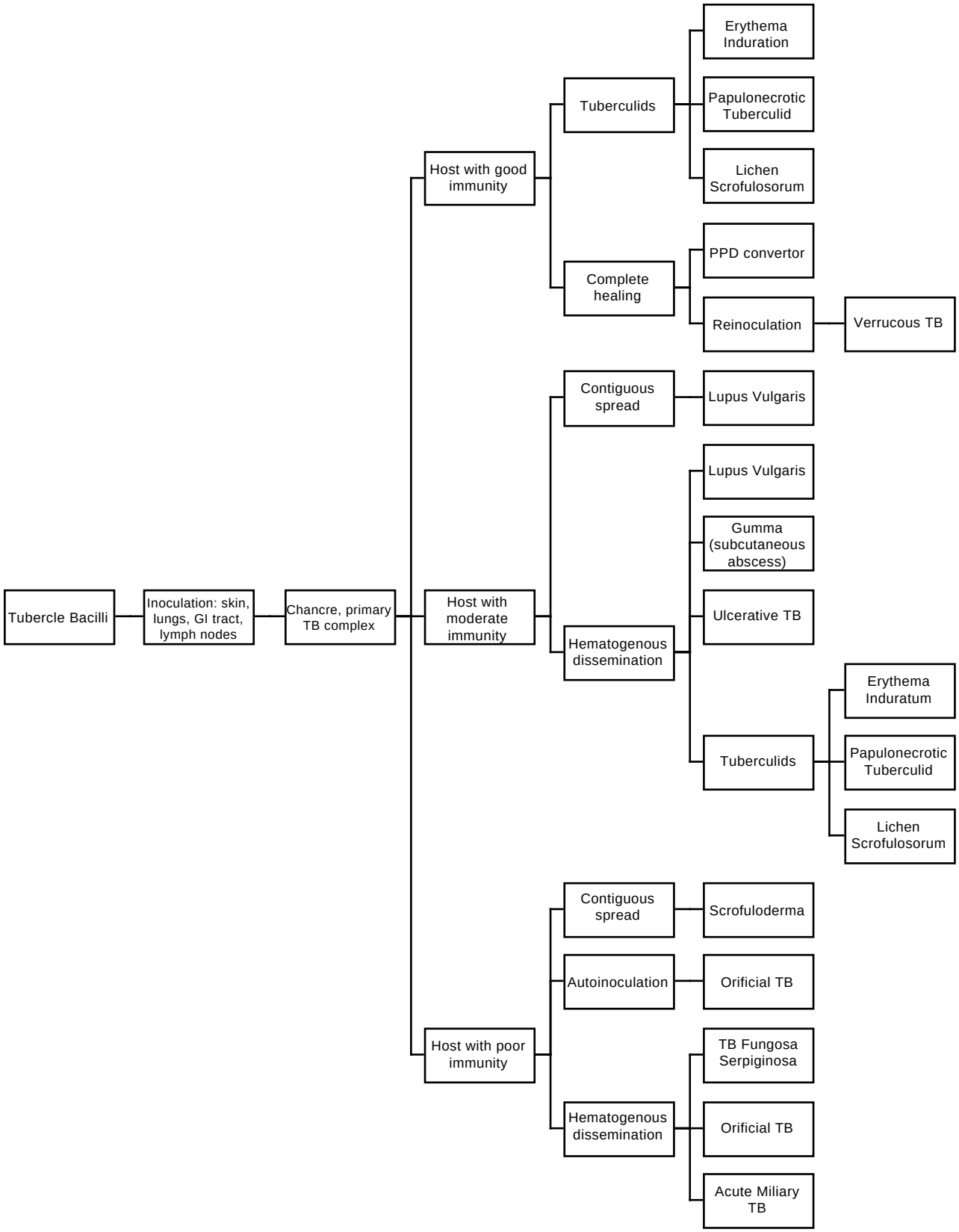

Fig. 15-3. General pathogenesis of cutaneous tuberculosis

Clinical Features

After an incubation period of 3 to 4 weeks following inoculation, a small inflammatory papule develops, which quickly breaks down into an indolent, firm, nontender, sharply delimited ulcer with no tendency for spontaneous healing for several weeks (Figures 15-4 and 15-5). After 3 to 8 weeks, tubercle bacilli reach the regional nodes, producing a painless lymphadenitis. This ulceroglandular complex is the prototype of primary inoculation tuberculosis, the skin analog to the primary pulmonary Ghon complex. The PPD usually becomes positive following the development of lymphadenopathy, although early treatment may prevent conversion.

Laboratory and Histological Features

Tuberculin testing is negative early in the course of disease. Conversion will usually occur at the time that lymphadenopathy becomes apparent.

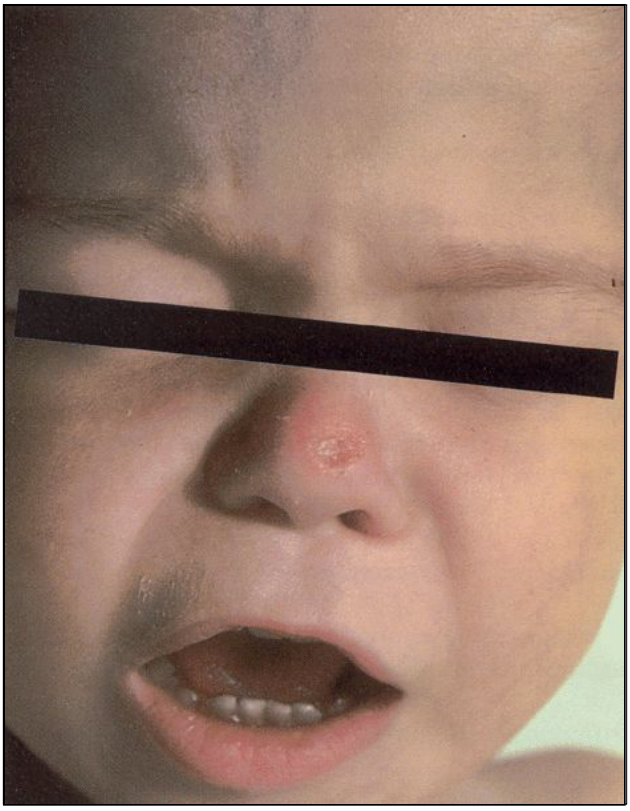

Fig. 15-4. A painless, well-circumscribed ulcer of primary inoculation tuberculosis is seen on the nose of a child.

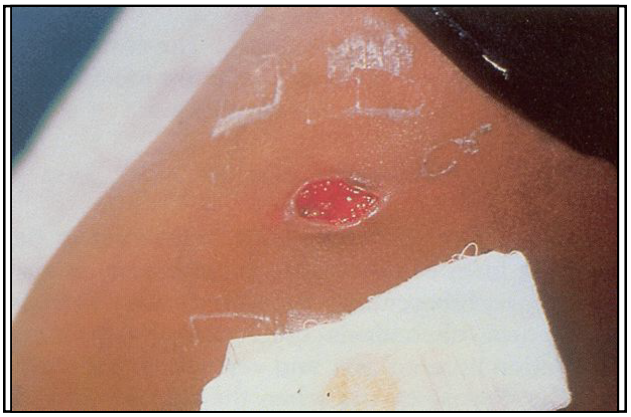

Fig. 15-5. A well-circumscribed, indolent, nontender, clean ulcer (1.5 x 3.0 cm) of primary inoculation tuberculosis is seen on the right lateral thigh of a child.

The earliest histological sign of primary inoculation tuberculosis is that of an acute neutrophilic reaction with areas of necrosis, ulceration, and the presence of numerous tubercle bacilli. After 3 to 6 weeks, immunity usually develops and the infiltrate becomes granulomatous. Epithelioid cells, Langhans'-type giant cells, and a peripheral rim of lymphocytes are present. Caseation necrosis may develop with a subsequent decrease in the number of tubercle bacilli. Changes in the lymph nodes are similar.

Course and Prognosis

After 1 to 3 months, the primary lesion usually heals with scarring. Rarely, the condition may last up to 1 year. In patients with poor immunity and large bacterial load, acute miliary tuberculosis can develop, with a fatal course. Usually, however, satisfactory host immunity with a high degree of tuberculin sensitivity result. Nonetheless, latent foci of infection can later reactivate locally or shed organisms hematogenously to distant sites. By these mechanisms, lupus vulgaris or even tuberculosis verrucosa cutis may develop as late sequelae of primary inoculation tuberculosis. Regional lymph nodes may liquefy, producing scrofuloderma. In as many as 10% of patients, erythema nodosum may develop as a nonspecific hypersensitivity reaction.

Differential Diagnosis

The differential diagnosis of primary inoculation tuberculosis includes primary syphilis, tularemia, cat-scratch disease, sporotrichosis, and other

ulceroglandular infectious diseases. Dark-field microscopy can confirm syphilis. The clinical setting and culture of lesional tissue are most useful for distinguishing the other conditions.

Tuberculosis Verrucosa Cutis

Tuberculosis verrucosa cutis, a verrucous (ie, wartlike) form of reinfection tuberculosis, is also called warty tuberculosis, prosector's wart, verruca necrogenica, tuberculosis cutis verruca, postprimary inoculation tuberculosis, and verrucous tuberculosis. The disease occurs when the skin of a previously infected or BCG-immunized (sensitized) host, who possesses a moderate or high degree of immunity, is subjected to exogenous reinfection with tubercle bacilli.

Epidemiology

Reinoculation occurs at sites of minor abrasions or wounds. In the past, tuberculosis verrucosa cutis was an important occupational hazard for physicians, pathologists, medical students, laboratory attendants, and so forth, who were infected by tuberculous patients or by autopsy material. Veterinarians, farmers, and butchers are likewise susceptible to infection from tuberculous cattle. Autoinoculation from tuberculous sputum rarely occurs.

Clinical Features

The initial lesion of tuberculosis verrucosa cutis is a painless, dusky red, firm papule or papulopustule that expands peripherally and is surrounded by an inflammatory halo that develops at the site of inoculation. It quickly develops a verrucous keratotic surface. By gradual, irregular, centrifugal expansion and growth, along with spontaneous central resolution, a polycyclic, serpiginous, or annular plaque with a warty, advancing border and central area of atrophy develops (Figure 15-6). Areas of softening, especially in the center, may be present. Pus and keratinous material may be expressed from the fissures in the warty areas. Lesions occur on areas exposed to trauma. Hands and fingers are most common sites in the West, but the lower extremities are affected most frequently in the East. The classic lesion is solitary, but multiple lesions also occur. Lymphadenopathy is characteristically absent. Lymph node enlargement, when present, may be the result of secondary infection. The lesions rarely ulcerate, and spontaneous involution may occur over months to years.

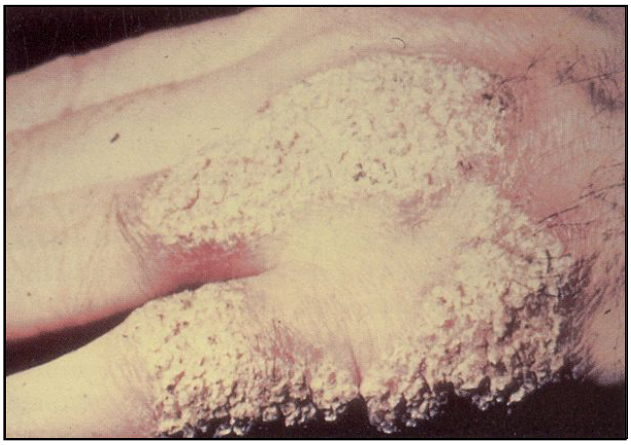

Fig. 15-6. Tuberculosis verrucosa cutis on the dorsal surface of the left hand, demonstrating a large, warty-appearing plaque with central clearing

Some of the documented unusual clinical presentations of tuberculosis verrucosa cutis are perianal ulcerations from gastrointestinal inoculation, sclerotic masses, fungating granulomas, disseminated tuberculosis with cutaneous and pulmonary involvement in an immunocompetent patient, and multifocal guttate tuberculosis verrucosa cutis.[43]

Laboratory and Histological Features

Tuberculin testing usually shows a moderate-to-marked positive reaction.

Hyperkeratosis, hypergranulosis, acanthosis, and papillomatosis of the epidermis are present in tuberculosis verrucosa cutis. Abscesses form at the dermo–epidermal junction and in the superficial dermis. Variable numbers of tuberculoid granulomas with a modest amount of caseous necrosis and a few acid-fast bacilli are seen in the mid-dermis. With time, marked fibrosis occurs.

Course and Prognosis

Lesions may evolve and last for years or even decades. Overall, the prognosis is good.

Differential Diagnosis

The differential diagnosis of tuberculosis verrucosa cutis includes iododerma and bromoderma, chronic vegetative pyoderma, squamous cell carcinoma, verrucous carcinoma, North American blastomycosis, chromoblastomycosis, verrucous

atypical mycobacterial infection, verrucous lupus vulgaris, and tertiary syphilis. Consequently, biopsy, culture, and macroscopic and microscopical examination for aggregated colonies of organisms (ie, grains) in exudates, when present, help to distinguish among these entities.

Miliary Tuberculosis of the Skin

Miliary tuberculosis of the skin, a rare form of acute or subacute cutaneous tuberculosis, is also called tuberculosis cutis miliaris disseminata, tuberculosis cutis miliaris acuta generalisata, and disseminated miliary tuberculosis of the skin. This disease occurs primarily in infants or children and is caused by hematogenous dissemination of *M tuberculosis* from an internal focus of disease, usually pulmonary or meningeal, often following infections that reduce the host immune response (eg, measles). Tuberculin sensitivity is usually absent and bacterial load very high.

In the United States during the period 1963 through 1986, of the 22,506 cases of tuberculosis reported, 289 cases (0.01%) were of miliary tuberculosis.[30] Several cases associated with AIDS have been reported.[31,32,46]

Clinical Features

Disseminated lesions occur on all parts of the body with predilection for trunk, thighs, buttocks, and genitalia. The mucous membranes of the mouth can also be affected. The primary lesions erupt as discrete, pinhead-sized, bluish red–to–brownish red macules or papules, often with a hint of purpura. They may be capped with minute vesicles, which soon burst and desiccate to form crusts. The lesions are often densely packed. Other forms of lesions may accompany the eruption, including macules, large pustular lesions, ulcerations, subcutaneous nodules, and purpuric lesions. All of these lesions are bacteria rich.

Laboratory and Histological Features

Tuberculin testing is almost always negative.

The characteristic features of miliary tuberculosis of the skin are (*a*) focal areas of necrosis and (*b*) abscess formation containing numerous tubercle bacilli. These may be surrounded by a zone of macrophages. Bacilli may also be found intravascularly. If and when immunity develops, lymphocytic cuffing of the vessels and tubercles can be seen.

Course and Prognosis

The general prognosis of miliary tuberculosis of the skin is poor: it is usually a harbinger of death due to overwhelming infection. However, with aggressive therapy, a few survive. In patients whose internal manifestations do not prove fatal, spontaneous healing occurs with significant scarring as a sequela.

Differential Diagnosis

The differential diagnosis includes Letterer-Siwe syndrome, pityriasis lichenoides acute et varioliformis, secondary syphilis, and drug reactions. The Venereal Disease Research Laboratory test (VDRL, with prozone check) and biopsy are definitive.

Scrofuloderma

Scrofuloderma, a subacute form of tuberculosis that occurs in patients who have already evolved through a primary tuberculous complex, is also called tuberculosis colliquativa cutis and tuberculous gumma. The disease usually originates as a tuberculous process of the subcutaneous tissues leading to the formation of cold abscesses and then secondary breakdown of the overlying skin. The tuberculous foci are commonly in the lymph nodes, bones and joints, and epididymis.

Epidemiology

In earlier times, scrofuloderma was common in children—80% following an oral or tonsillar primary inoculation of bovine tuberculosis from infected milk.[24] The elderly are also susceptible, particularly when their immune defenses are compromised. True tuberculous lymphadenitis is becoming less common in children and is more often due to atypical mycobacteria: *M avium*, *M intracellulare*, or *M scrofulaceum*.[43] Scrofuloderma occurs rarely from the introduction of exogenous tubercle bacilli into the subcutis by trauma, or by injections into individuals with previous latent or manifest tuberculosis.

Clinical Features

Patients with the initial lesion present with a firm, subcutaneous or deep cutaneous swelling or nodule, which is freely movable initially but soon firmly attaches to the skin and later ulcerates. The

ulcers tend to have bluish, undermined edges and soft, granulating floors. Watery, purulent, or caseous discharge may exude from the sinuses.

Cervical lymph nodes are infected most commonly on the side of the neck where the primary tuberculous complex was located (Figures 15-7 and 15-8). In the neck, the tonsillar, submandibular, preauricular, postauricular, occipital, and supraclavicular lymph nodes are usually implicated. The parasternal, axillary, inguinal (Figure 15-9), and epitrochlear nodes are potential sites, as well. In adults who have scrofuloderma, multiple lesions may form through hematogenous dissemination, especially on the trunk and pubic and buttock regions. Patients with lesions on the buttocks present with liquefying abscesses, fistulae, and purulent drainage resembling hidradenitis suppurativa.[24] Occasionally, discharging sinuses may occur over areas normally devoid of nodes. Over weeks to months the nodes enlarge, turn livid red, suppurate, then perforate with resultant ulceration and fistula formation. Over time, multiple fistulae form; severe, cordlike scarring bridges the ulcerations.

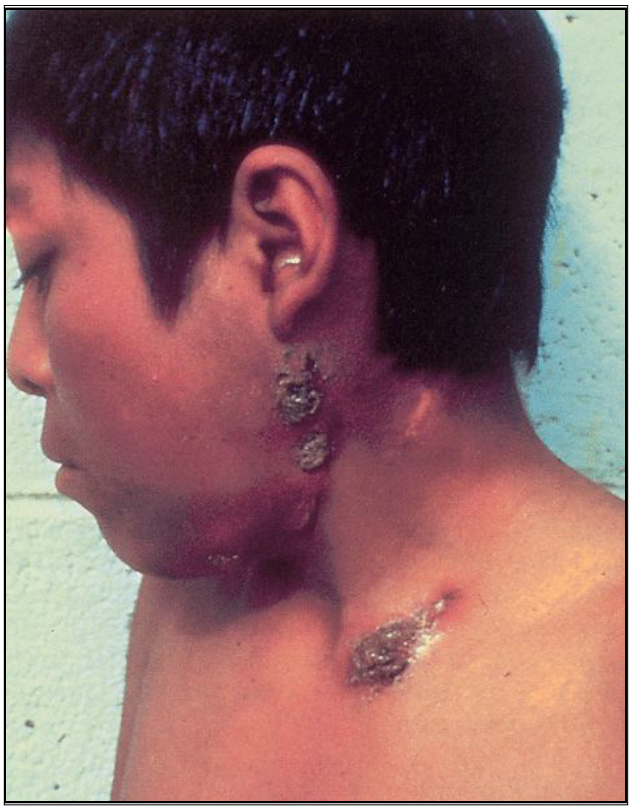

Fig. 15-7. Scrofuloderma of the left cervical lymph nodes in a Central American adolescent male. Note the enlarged lymph nodes immediately inferior to the mandible and the multiple, perforating sinus tracts.

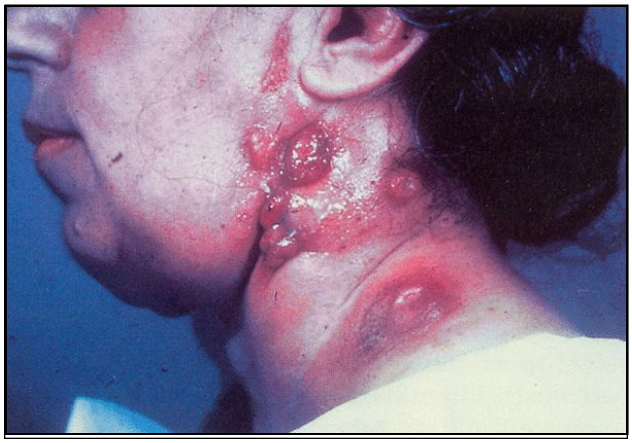

Fig. 15-8. Scrofuloderma of long-standing duration in the neck. Note the boggy, edematous skin surrounding a number of perforating sinus tracts.

Spontaneous healing does occur, but it takes years before it is completed. Cordlike keloidal scars and localized recurrences are characteristic.

Laboratory and Histopathological Features

Tuberculin sensitivity is usually marked. Massive ulcers and abscesses form in the center of the lesion. Tuberculoid structures with marked caseation necrosis are present in the lower dermis and at the periphery of the ulcerations or abscesses. Epithelioid cells form the major component. A

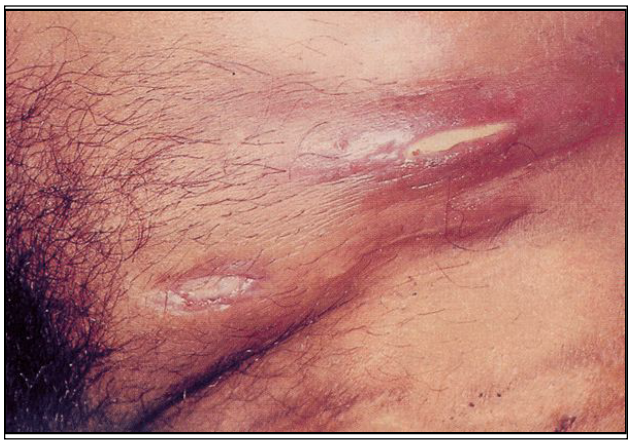

Fig. 15-9. Scrofuloderma of the left inguinal lymph nodes showing subcutaneous swelling and purulent ulceration

large number of giant cells are present. Acid-fast bacilli are easily identified. As the lesion ages, caseation necrosis occurs and the number of organisms decreases. Occasionally, granuloma formation may not be apparent and the sections may only show a nonspecific, chronic, inflammatory infiltrate.

Course and Prognosis

Scrofuloderma is usually associated with manifest tuberculosis elsewhere in the body, usually in the lungs and occasionally in the abdomen. Lupus vulgaris may occur at the site, in the vicinity, or in the scar of scrofuloderma. Malignant change in the form of an epithelioma can occur, and the very infrequent association of cutaneous tuberculosis with systemic amyloidosis was reported in a case of scrofuloderma.[43]

Differential Diagnosis

The differential diagnosis includes tertiary syphilis, deep fungi (eg, sporotrichosis, actinomycosis, severe acne conglobata, hidradenitis suppurativa), and chronic granulomatous disease. Biopsy and culture are the definitive tests for the diagnosis.

Tuberculosis Cutis Orificialis

Tuberculosis cutis orificialis is also called orificial tuberculosis and tuberculosis ulcerosa cutis et mucosae. Orificial tuberculosis is the tuberculosis of the mucous membranes and the skin of the orifices, resulting from autoinoculation of the tubercle bacilli in patients with advanced visceral tuberculosis. Its occurrence by lymphatic or hematogenous extension is rare.

Epidemiology

Tuberculosis cutis orificialis affects men more often than women and is most prevalent in middle-aged or older individuals. The underlying disease is advanced pulmonary, intestinal, or genitourinary tuberculosis. At a traumatized site, bacilli that are shed from these foci become inoculated into the mucocutaneous areas of the orifices.

Clinical and Diagnostic Features

Ulcerative lesions of tuberculosis cutis orificialis occur in the oral cavity and the perineal or perirectal areas. The tongue—particularly its tip and lateral margins—is the site most commonly affected in the mouth. Other sites in the mouth are the soft and hard palate, lips, and in a tooth socket after extraction. In a patient with intestinal tuberculosis, the area on and around the anus is involved; with genitourinary tuberculosis, the vulva, glans, penis, and urinary meatus are involved. The lesion consists of a small, yellowish or reddish nodule that rapidly breaks down to form an exquisitely painful, shallow ulcer with bluish, undermined edges. The surrounding mucosa is swollen and the ulcer is covered by pseudomembranous material. Ulcers do not heal spontaneously and are signs of a poor prognosis.[43]

Cutaneous hypersensitivity to tuberculin in these patients is controversial; however, there is an absolute consensus that such patients ultimately develop anergy.

Histologically, in most cases, tuberculoid infiltrates with pronounced necrosis are found deep in the dermis. Acid-fast bacilli are easy to demonstrate. Ulceration and edema are the rule.

Lupus Vulgaris

Lupus vulgaris, also called tuberculosis cutis luposa, is a reinfection tuberculosis of the skin occurring in previously sensitized individuals who have a high degree of tuberculin sensitivity. The disease may have protean and dramatic clinical presentations. Hypersensitivity to tuberculin is high, although immunity is low to moderate.

Epidemiology

Lupus vulgaris is not only the most frequent type of cutaneous tuberculosis, it also has the greatest potential for disfigurement. Worldwide, approximately 50,000 new cases are diagnosed each year, and women tend to be affected twice as commonly as men.[24] Patients are usually tuberculin positive.

As many as two thirds of patients with lupus vulgaris are found to have visceral foci of tuberculosis. Of these, 40% have tuberculous adenitis or involvement of the mucous membranes, and 10% to 20% have pulmonary, bone, or joint tuberculosis.[43]

Pathogenesis

Lupus vulgaris is a cutaneous form of postprimary tuberculosis. Because it may develop in the site of primary inoculation tuberculosis, in the scar of scrofuloderma, or after BCG immunization (particularly after multiple BCG vaccinations), it is likely that lupus vulgaris arises from a latent focus of

tuberculosis that is triggered into activity by later trauma or injury. Alternatively, the disease can arise from the perforation of tuberculous abscesses into the skin or from endogenous dermal inoculation of tubercle bacilli (via lymphatic or hematogenous metastasis) from a reactivated focus in an internal organ.

Clinical Features

In western countries, lupus vulgaris is most common on the face, especially the nose and cheeks, followed by the ears, the extensor surfaces of the extremities, the buttocks, and the breasts. However, in India and many developing nations, the lower extremities, especially the buttocks, are the primary site of involvement. It is exceedingly rare for the mucous membranes to be involved.

The initial lesions are usually solitary. Occasionally, two or more foci can occur. Rarely, in the case of a preceding period of anergy, disseminated lesions may occur, resulting in lupus vulgaris postexanthematicus.

Clinically, the earliest lesion appears as small, brownish red papules of soft gelatinous consistency, often resembling a small hemangioma. On diascopy, the characteristic translucent, apple jelly–colored lupoid infiltrates may be demonstrable (Figure 15-10), although they are rarely seen in the tropics because of the natural dark color of the skin of the indigenous populations. From these small granulomas, the various forms of lupus vulgaris develop over the course of years.

As the lesions enlarge, caseation necrosis proceeds, resulting in softening of the lesions. Probing with a blunt instrument at this stage may cause lesions to perforate. With time, the lesions become more infiltrated, elevated, and brown. They grow by peripheral extension and are accompanied by

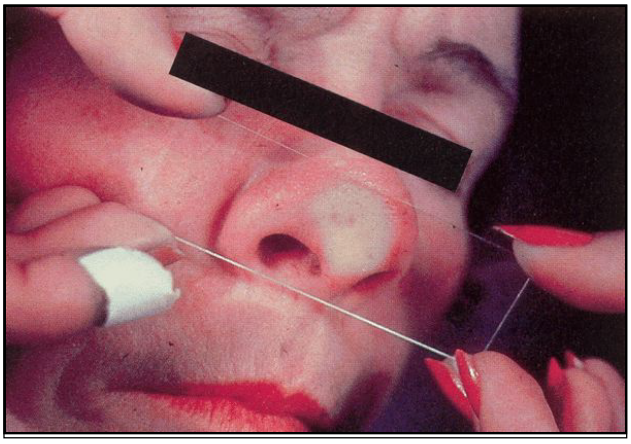

Fig. 15-10. The lesions of lupus vulgaris on this patient's nose show the characteristic apple jelly–colored papules on diascopy.

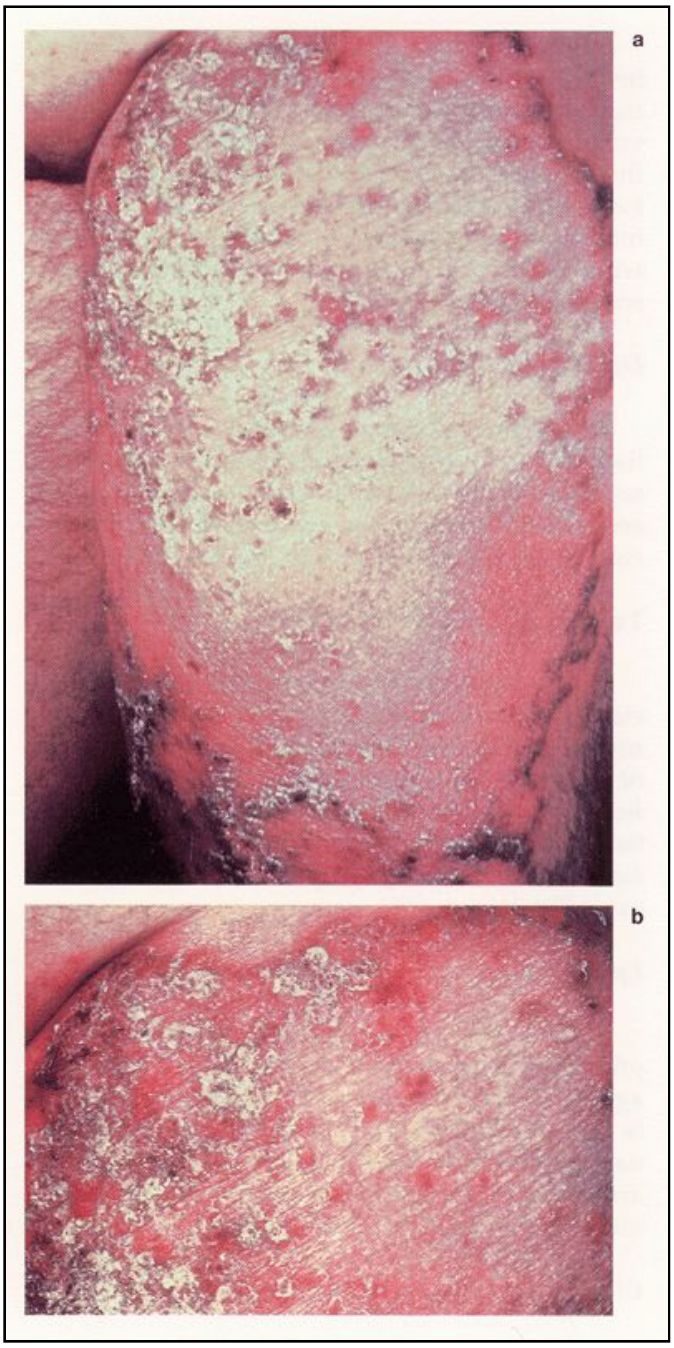

Fig. 15-11. (**a**) An extensive plaque of lupus vulgaris can be seen on the patient's thigh. (**b**) A closer view of same patient shows an active border, relative central clearing, and new papules in previously cleared areas.

central atrophy or scarring (Figures 15-11 and 15-12). The reactivation of nodules within previously atrophic or scarred areas (ie, fresh papules may appear in old areas) is characteristic of the disease. A few sentinel lupus nodules may be present at the periphery on the normal skin. Lesions are usually asymptomatic.

Several clinical variants are seen:

- Lupus vulgaris exfoliativus is characterized by plaques with a psoriatic scale. Over time, serpiginous or polycyclic configurations may develop with central clearing and atrophy. Large plaques will have both (*a*) active scaly and (*b*) scarred and/or atrophic nonscaly areas.[47]
- Lupus vulgaris verrucosus results from a wartlike pseudoepitheliomatous hyperplasia of the epidermis.
- Lupus vulgaris ulcerosus forms when massive necrosis occurs within the tuberculous granulomas. This ulcerative variant may be accompanied by deep destruction of underlying tissues and cartilage.
- Lupus vegetans (also called lupus papillomatosus) is a vegetative form of lupus vulgaris that often occurs in regions of erosive or ulcerative disease.
- Lupus vulgaris postexanthematicus is a disseminated papular or nodular form that usually arises during a period of anergy or waning immunity (eg, following measles).
- Lupus vulgaris of the mucous membranes is a rare and special form of lupus vulgaris arising in the mucous membranes by direct extension of skin lupus to the buccal, nasal, or conjunctival mucosa. This form can be highly destructive and disfiguring.

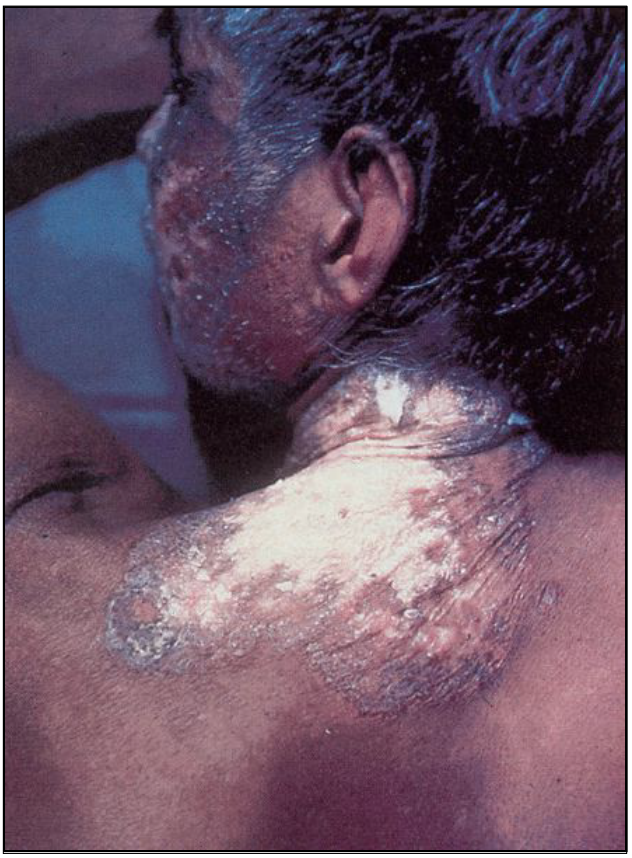

Fig. 15-12. Lupus vulgaris on the neck and back. Scarring with severe hypopigmentation and an active, advancing margin, especially over the left scapula, can be seen.

Laboratory Features

Bacilli in lupus vulgaris are few and sparse. Inoculated guinea pigs usually succumb to disseminated tuberculosis at the anticipated time when inoculated with lesional tissue. Tuberculin testing is usually positive. The recent use of polymerase chain reaction (PCR) techniques to diagnose the presence of *M tuberculosis* deoxyribonucleic acid (DNA) in formalin-fixed, paraffin-embedded tissue within approximately 2 days promises to greatly facilitate the diagnosis of this and other forms of cutaneous tuberculosis.[48]

Diagnosis of the internal focus of tuberculosis may be aided by modern methods such as sonography, computerized tomography, and magnetic resonance imaging.

Histological Features

The most prominent histological feature of lupus vulgaris is the presence of granulomas, usually in the upper dermis, composed of epithelioid cells, Langhans'-type giant cells, mononuclear cells, and a peripheral zone of lymphocytes. Epithelioid cells and lymphocytes predominate. Caseation necrosis is uncommon and minimal. Bacilli are difficult to find. Secondary epidermal changes (eg, atrophy, ulceration, acanthosis, or pseudoepitheliomatous hyperplasia) may be present. Occasionally, squamous cell carcinoma may be present. Foreign-body granulomas may develop. Occasionally, the necrosis and ulceration are accompanied by nonspecific inflammatory infiltrates, which may mask the tuberculous character of the disease.

Course and Prognosis

Lupus vulgaris can be a very protean, destructive disease. In the absence of treatment, it may progress slowly over years or even decades. Because of its relatively slow progression, the disease is usually present for more than 5 years before a definitive diagnosis is made. Yet, the lesions remain essentially noncontagious (although the underlying organ tuberculosis may be quite contagious). Severe scarring and disfigurement of cosmetic areas may occur (eg, ectropion, distortion of the mouth, or destruction of the nose). Where scarring encompasses an entire lower extremity, distal elephantiasis can develop. The most critical areas where severe mutilation can result tend to be the face, hands, and feet.

Patients with pulmonary tuberculosis in combination with lupus vulgaris have a 4- to 10-fold higher mortality rate than patients with pulmonary tuberculosis alone.[49]

Long-standing lupus vulgaris can be complicated by the development of squamous cell carcinoma. Other tumors are exceedingly rare during the course of lupus vulgaris but can include basal cell carcinoma, sarcoma, and Hodgkin's disease.

Tuberculids such as lichen scrofulosorum and papulonecrotic tuberculid can be seen in conjunction with lupus vulgaris.

Differential Diagnosis

Although the presence of apple jelly nodules is characteristic of lupus vulgaris, it is not pathognomonic. Other diseases with similar lupoid infiltrates that look like apple jelly nodules include lupoid leishmaniasis, sarcoidosis, lupoid rosacea, lupus erythematodes lupoide, pseudolymphoma of the skin, chronic granulomatous disease, and Spitz nevi. The real identification of a lupoid infiltrate as lupus vulgaris is done with a blunt probe, which easily breaks through the overlying epidermis into the nodule due to the caseous necrosis present in the lesions. Biopsy with special stains for organisms and culture are important diagnostic procedures to differentiate these other lupoid conditions.

Other Rare Forms of Cutaneous Tuberculosis

Tuberculous Gumma

Tuberculous gumma (also called metastatic tuberculous abscess) is a rare form of tuberculosis that results from hematogenous spread from a primary focus of infection during periods of bacillemia and lowered resistance.[50] The disease usually occurs in malnourished children, and immunodeficient or immunosuppressed patients. The lesions are single or multiple, cold, subcutaneous nodules, which liquefy into nontender abscesses and perforate the skin, forming ulcers and sinus tracts. Tuberculin sensitivity is modest. Occasionally, the lesions mimic the lymphatic spread of sporotrichosis. With the spread of HIV infection, atypical forms of many infectious diseases are being seen, including tuberculosis. Several cases of isolated subcutaneous abscesses arising through hematogenous spread have been reported, two of which follow.

Case 1.—A 58-year-old, immunocompetent male presented with a 9-month history of several disseminated subcutaneous ulcerative nodules, fever, and weight loss associated with pulmonary tuberculosis. Large skin biopsies grew *M tuberculosis* in 6 to 8 days, whereas sputum samples and smaller biopsies grew out in 4 weeks. These lesions seemed to represent a type of hematogenous dissemination intermediate between classic cold abscesses (gumma) and acute miliary tuberculosis of the skin.[51]

Even in areas where tuberculosis is endemic, ulcerative forms are extremely rare and are often misdiagnosed because the physician has a low index of suspicion.

Case 2.—A 19-year-old Filipino male presented with (*a*) a 2-month history of persistent, dry cough; general malaise; and 7-kg weight loss, despite good appetite; and (*b*) a 5-month history of an enlarging, painful, purulent ulcer 4- x 8-cm in diameter, in the midlumbar area; and a nonfluctuant, 4-cm swelling involving the sternum. The ulcer was well demarcated, with a violaceous, slightly heaped-up border; an undermined edge; and a scant, light brown, cheesy, purulent discharge. Histological examination showed early granuloma formations. No organisms were identified. Roentgenograms of the chest showed bilateral, upper-lobe, nodular densities without definite hilar lymphadenopathy. A solitary lytic lesion was present in the sternum, consistent with osteomyelitis. Culture from bronchial washings and from tissue biopsy grew *M tuberculosis* in 2 and 6 weeks, respectively. PPD was strongly positive at 27-mm induration and 55-mm erythema (such hypersensitivity is consistent with the negative acid-fast stains since a higher degree of immunity is presumed). Triple drug therapy with isoniazid (isonicotinic acid hydrazide [INH]), rifampin, and ethambutol cleared the ulcer in 5 months. Therapy was continued for 1 year.[52]

Such ulcerated tuberculous gummas usually arise in adolescents, and are found on the extremities; occasionally on the trunk; and often in the presence of silent, deep foci of tuberculosis. These gummas

result from secondary breakdown of subcutaneous cold abscesses.

Tuberculosis Fungosa Serpiginosa

Tuberculosis fungosa serpiginosa is a very rare, chronic form of skin tuberculosis that occurs in anergic, elderly individuals via endogenous or exogenous inoculation. Patients with this disease present with thick, papillomatous, vegetative, noncornified plaques (commonly in the axilla or on the backs of the hands) that resemble a chronic, vegetative pyoderma. The lesions are notable for fissures and fistulae with serous or purulent exudate. The lesions and exudates are bacillary rich. Tuberculin sensitivity is absent. With peripheral extension and central healing, annular and serpiginous lesions are formed.

Iatrogenic Immunization Tuberculosis

Tuberculosis infection—ranging from primary inoculation complex to scrofuloderma, lupus vulgaris, or acute miliary tuberculosis—can also result from BCG immunization.[50,53] Since the BCG immunization organism is an attenuated *M tuberculosis bovis*, it can behave as a virulent opportunistic pathogen where immunity is depressed or lacking. With the worldwide increase in AIDS, the potential for such iatrogenic disease is growing.

Tuberculous Mastitis

Patients with this rare form of tuberculosis involving the breast present with a nontender, cold abscess. Diagnosis depends on microbiologic and histological investigations.

DIAGNOSIS

Diagnosis of cutaneous tuberculosis certainly requires (*a*) evidence of the tubercle bacilli either in the smear or in tissue sections or (*b*) its recovery in vitro (Exhibit 15-1). Various workers have tried but failed to demonstrate the bacilli in the histological sections of the usual variants of cutaneous tuberculosis using the routine acid-fast staining. Fluorescent staining with auramine or rhodamine is more effective; the results in lupus vulgaris, however, are still disappointing. Thus, the absolute diagnosis can be established only when the bacilli are isolated. Unfortunately, however, most investigators report a low incidence of positive culture growths in cutaneous tuberculosis.

The immunological diagnosis may be established in pulmonary tuberculosis by the tuberculin test, enzyme-linked immunosorbent assays for antibody to PPD and to *M tuberculosis* antigen 6, and specific tests using monoclonal-antibody and recombinant-DNA techniques. These latter two techniques might be employed in the diagnosis of cutaneous tuberculosis in the future.

One group of investigators,[39] utilizing the Mantoux test (ie, an intradermal injection of 0.1 mL of tuberculin [10 tuberculin units/0.1 mL]) in a prospective study of 70 patients with cutaneous tuberculosis (lupus vulgaris, verrucous tuberculosis, and scrofuloderma only), noted that all patients were moderately to highly reactive.

However, the most promising and exciting new technique for the rapid diagnosis of tuberculosis is the use of the PCR for the detection of *M tuberculosis*–specific DNA fragments. This amplification technique yields millions of copies of tuberculosis-specific target nucleotide sequences. The particular

EXHIBIT 15-1

CRITERIA FOR THE DIAGNOSIS OF CUTANEOUS TUBERCULOSIS

Absolute Criteria

- Culture
- Guinea pig inoculation
- Positive polymerase chain reaction to *Mycobacterium tuberculosis* complex

Relative Criteria

- Compatible history and skin examination
- Active, visceral tuberculosis
- Positive tuberculin-purified protein derivative reaction
- Positive enzyme-linked immunosorbent assay for antibody to purified protein derivative of tuberculin reaction or to *M tuberculosis* antigen 6
- Compatible histopathology
- Acid-fast bacilli in lesion
- Fluorescent staining of *M tuberculosis* organisms with auramine or rhodamine
- Response to specific tuberculosis therapy

assay having the greatest promise, due to its high sensitivity and specificity, is based on detection of a putative insertion sequence IS6110. This is usually present in 6 to 15 copies in most strains of *M tuberculosis*. Unlike other PCR-based assays, this method does not require hybridization of the PCR product to DNA probes, thus simplifying the test for routine clinical use. Other primer–probe sequences in use include ribosomal RNA, the DNA sequence mtp40, DNA encoding on a 38-kilodalton or 65-kilodalton protein, and MPB64.[26]

Because PCR reactions can be performed on formalin-fixed, paraffin-embedded sections, they hold great promise for the diagnosis of extrapulmonary tuberculosis, especially of the cutaneous type. Not only has *M tuberculosis*–complex DNA been demonstrated in paraffin-embedded sections taken from proven cases of lupus vulgaris,[54] scrofuloderma,[55] and several other types of cutaneous tuberculosis,[56] but such probes have also been used to diagnose several tuberculid reactions as being truly tuberculous in origin,[57] allowing for a quicker diagnosis and treatment of the underlying systemic tuberculosis.[58] Turnaround time for the diagnosis takes only a few days, in contrast to the weeks required for culture and identification or inoculation.

TREATMENT

As in tuberculosis of other organs, chemotherapy is the treatment of choice for cutaneous tuberculosis (Table 15-2). The only exception is the occasional use of cryosurgery or electrocautery for destroying small lupus nodules within scarred areas.[43]

Of great importance, especially in the Third World, has been the development of short-course, four-agent chemotherapy regimens for 6 months.[59] Treatment of smear-positive or culture-positive pulmonary or extrapulmonary tuberculosis is essentially identical. For the four-agent regimen, an initial combination of isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin is given daily for 2 months. Subsequently, a 4-month course of isoniazid and rifampin is given. However, due to the increasing number of patients with single or multiple drug resistance, cure rates may drop as much as 20% to 25% for each drug the mutant bacilli are able to resist.[10] Resistance rates in New York City for one drug are as high as 33%, for two drugs, 26%. One study[60] found resistance to isoniazid to be 25%; rifampin, 20%; isoniazid-rifampin, 16%; and isoniazid-rifampin-streptomycin-ethambutol resistance, 13%. The virulence of this modern plague is accentuated in that the case-fatality rate exceeds 50% for patients with multidrug-resistant diseases, and approaches 90% for patients with HIV infection. The extent of the problem is illustrated by conditions in Manila, where as many as 80% of patients who present for treatment of tuberculosis are resistant to at least one, if not to several, drugs.[10]

Nosocomial outbreaks of multidrug-resistant organisms have been devastating. In a survey of outbreaks in hospitals and prisons in New York and Florida,[61] 96% of patients had underlying HIV infection. The case-fatality rate was 72% to 89%, with death occurring in 4 to 19 weeks following diagnosis, despite aggressive multidrug therapy. Six of eight hospital staff who became infected with these resistant organisms were also positive for HIV; four have died.

Factors leading to multidrug resistance include monotherapy, erratic drug ingestion, omission of one of more of the prescribed chemotherapeutic agents, suboptimal dosage, poor drug absorption, insufficient number of active chemotherapeutic agents in a regimen, cavitary disease, and HIV infection.[60,61,62] In one study[62] of HIV-infected individuals, the median survival time for those with AIDS was 1.5 months versus 14.8 months for those without AIDS. Various social factors that contribute to these factors include homelessness, joblessness, intravenous drug addiction, alcoholism, and other forms of irresponsible behavior that place a low priority on taking multiple medications daily for prolonged periods.[60]

Recommendations for multidrug resistance change continually. As of September 1993, suggested approaches for treatment include the following[62]:

1. Patients in communities where the risk of single-drug resistance is greater than 2% should be placed on four-drug chemotherapy: isoniazid, rifampin, pyrazinamide, and ethambutol, until the results of drug sensitivity testing are available (2–5 wk, optimally).
2. In high-risk urban areas such as New York City, where many patients show resistance to two or more agents, at least five drugs are necessary.
3. For patients in high-risk areas with HIV infection or AIDS, six-drug chemotherapy, based on local patterns of resistance, may

TABLE 15-2

TUBERCULOSIS TREATMENT: DRUGS, DOSES, AND SIDE EFFECTS

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*Not available in the United States
PO denotes administration via oral route; IM, intramuscular route; ? denotes not known
Sources: Adapted with permission from (1) Kastrup EK, Olin BR, Connell SI. *Drug Facts and Comparisons*. St. Louis, Mo: Facts & Comparisons; 1988: 1534. (2) Sehgal V, Wagh S. Cutaneous tuberculosis: Current concepts. *Int J Dermatol*. 1990;29:246. (3) Iseman MD. Treatment of multidrug-resistant tuberculosis. *N Engl J Med*. 1993;329:787.

be indicated until the results of antibiotic susceptibility testing are known.

4. Drug dosages and optimal timing of administration need to be determined for each patient to achieve maximal serum concentrations in the targeted ranges without serious side effects. In addition, care should be taken to assess proper absorption of antituberculosis agents in patients with AIDS, as they commonly malabsorb these drugs.

The optimal duration of therapy has not been determined. Generally, extrapulmonic tuberculosis is treated for the time being as pulmonic. However, with miliary tuberculosis or tuberculosis of the meninges or skeleton, longer courses are required.[26] Patients with pulmonary tuberculosis whose organisms are resistant to all or most of the first-line chemotherapeutic agents are treated with oral medications for 24 months following conversion of the sputum cultures from positive to negative. Of those who convert, as many as 20% may relapse after therapy is discontinued.[62]

Turning back the clock to the preantibiotic era in selective patients with cavitary pulmonic tuberculosis may be beneficial. Iatrogenic induction of pneumothorax or pneumoperitoneum, or surgical crushing of the phrenic nerve to collapse diseased lobes (because *M tuberculosis*, being an obligate aerobe, perishes in anaerobic environments), has been of some aid in difficult cases.[10] Similarly, where economically feasible, presurgical chemotherapy and hyperalimentation combined with pneumonectomy or lobectomy, reinforced with a muscular flap to secure the bronchial stump, has saved several severely afflicted patients. Experience with the latter for multidrug-resistant pulmonary tuberculosis at National Jewish Center in Denver, Colorado, has been most gratifying: 49 of 50 long-term survivors have consistently had negative sputum smears and tuberculosis cultures.[62]

PREVENTION

The approach to the prevention of active tuberculosis varies from country to country. In developed countries such as the United States, where drug resistance is relatively low, two forms of isoniazid prophylaxis have been effective tools. First, in patients who meet the criteria for use, a 6- to 12-month course of isoniazid (300 mg / d in adults, 5-10 mg / kg / d in children) can reduce the development of active disease by 75%. Second, a multidrug prophylaxis with isoniazid, streptomycin, rifampin, and pyrazinamide for 8 weeks resulted in an 81.5% reduction in the incidence of bacteriologically proven tuberculosis—a prophylactic course as effective as 12 months of isoniazid alone.[59]

In developing countries, where tuberculosis morbidity and mortality are much greater, disease prevention is most desirable. BCG vaccination against tuberculosis, which is relatively safe, inexpensive, and easy to use in the field, has been used for many years. Large-scale epidemiological studies have been attempted, but the interpretation of their results has been hampered by the biological variability of available BCG vaccines, difficulties in case ascertainment and confirmation, and the necessity for long-term follow-up. Measured efficacy of current vaccines in preventing tuberculosis ranges from nil to 80%.[28] Vaccination apparently does not prevent infection but shows definite protection against the development of miliary tuberculosis and meningitis, especially when given to infants and children.[28] Consequently, BCG immunization should be given as early in life as possible in areas of high prevalence. However, it does not seem to prevent reactivation of latent infections.

One of the probable reasons for the failure of BCG vaccination is that immunosuppressive factors present in mycobacterial polysaccharides depress cell-mediated immunity during active infection through (*a*) decreased expression of human lymphocyte antigens–D-group related (HLA-DR) determinants and (*b*) increased production of interleukin-1. The consequences of these immunosuppressive circuits are (*a*) depression of tuberculin-induced blastogenesis, (*b*) production of interleukin-2, and (*c*) generation of interleukin-2 receptors (ie, natural infection with *M tuberculosis* or with BCG may cause immunosuppression).[63]

Thus, worldwide control of tuberculosis appears improbable unless an effective vaccine is developed. One approach is to identify virulence factors and, through the use of transposon-mediated gene inactivation, produce mutants that lack these factors. Such a strategy can provide important information regarding the specific antigens that are important to the host for protection. Genetic deletion

or modification of these virulence factors provides insight into both the mechanisms of pathogenesis and the possibilities for the development of live attenuated vaccines. Alternatively, individual antigens identified as important for protection by antibodies and T cells could be used to generate a vaccine. Current investigation centers on genetic engineering techniques to modify and optimize the antigenic determinants on the tubercle bacillus to avoid down-regulating the immune system.

TUBERCULOSIS AND ACQUIRED IMMUNODEFICIENCY SYNDROME

The elimination of tuberculosis in countries where it is highly prevalent, particularly Africa, may be seriously impeded by patients with AIDS and persons infected with HIV. It is inevitable that the number of cases of tuberculosis will increase in those countries with large numbers of patients with AIDS. Indeed, as AIDS increases exponentially in Africa, tuberculosis continues to keep pace with it. Many of these patients will succumb rapidly to their disease, but not before they infect family members, friends, coworkers, and others with drug-resistant organisms. Infection with *M tuberculosis* tends to occur early in the course of AIDS, often preceding the diagnosis of AIDS by several months. This is in contrast to infections with an atypical opportunistic organism such as *M avium–intracellulare,* which tends to occur later when immunosuppression is more profound.[64]

Along with the increase in the number of patients who have both AIDS and tuberculosis, developing countries face serious epidemiological problems in the chemotherapy for tuberculosis. Why? Because poor countries tend to rely on intramuscular streptomycin as part of their drug regimens instead of the more expensive oral alternative, pyrazinamide. In primitive environments, keeping syringes sterile to prevent the transmission of AIDS presents a challenge to native public health services. Disposable syringes are not the answer due to their cost and the potential for reutilization.[65]

A different problem concerns BCG vaccination for tuberculosis or leprosy in children in countries with a high prevalence of AIDS: the BCG organism may become a pathogen in children infected with AIDS.[65]

TUBERCULOSIS CONTROL IN REFUGEE CAMPS

Tuberculosis management in refugees and other displaced persons in temporary settlements poses a great challenge to the military or to other organizations that coordinate and provide care and resettlement. Although we might suspect that the incidence, morbidity, and mortality of tuberculosis might be worse in war zones, where malnutrition and physical and emotional stress may be at their worst, recent evidence from Thailand's experience with Kampuchean refugees and Pakistan's experience with Afghan refugees suggests that the incidence of tuberculosis in refugees is similar to that in their respective countries of origin.[66]

Initial attention to basic needs (nutritional rehabilitation, immunization, water supply, and sanitation) is paramount. This can be followed by treatment of the most infectious patients: those with active, smear-positive tuberculosis. Without treatment, 30% to 50% of these individuals will die of their disease, having first spread their bacilli to many others in the cramped refugee camps.[66]

Case-finding is one of the first tasks. Sputum samples should be checked on the spot for acid-fast bacilli in any patient presenting with (*a*) a history of 3 weeks of cough or chest pain or (*b*) hematemesis or significant weight loss. Those whose sputum tests are negative for acid-fast bacilli should be rechecked on two consecutive mornings and observed if suspicion remains, but they should not be treated at this point. Treatment should be initiated for those whose sputum tests are positive for acid-fast bacilli, and additional cases should be sought among family members and close contacts. Among contacts, children are notorious for having sputum that tests negative; consequently, if they have symptoms and signs compatible with tuberculosis, they should be treated as well. Tuberculin sensitivity is a poor predictor of active tuberculosis in child contacts of known cases.

Basically, however, a rational choice for the patient with tubercle bacilli that are fully susceptible to drugs lies between these extremes:

- a 12-month course of isoniazid combined with thiacetazone (not available in the United States, due to the high frequency of side

effects seen especially among some Asians), preferably supplemented by streptomycin for the first 2 months, which is a very inexpensive regimen; and
- a 6-month course of isoniazid combined with rifampicin (supplemented with pyrazinamide, with or without streptomycin for the first 2 mo), which is an expensive regimen.

Whichever course is selected, patients being treated should be monitored to ensure compliance with the treatment regimen, lest interruption of treatment lead to drug resistance. This may require retention of the individual in a medical patient-holding facility.

Chemoprophylaxis with isoniazid does not play any significant role for tuberculosis control in a temporary refugee settlement with a high incidence of disease. BCG immunization for infants and small children is still recommended to slow hematogenous spread of tubercle bacilli and the resultant miliary and meningeal tuberculosis.

THE TUBERCULIDS

The term *tuberculid* denotes a symmetrical, generalized exanthem in the skin of a tuberculous patient due to an allergic or hypersensitivity reaction to the tubercle bacillus or one of its constituent parts.

In 1896, Jean Darier reported that patients with tuberculids have the following key findings[67]:

- a positive tuberculin skin test,
- tuberculous involvement of lymph nodes or internal viscera or both,
- absence of tubercle bacilli from skin biopsy and culture, and
- skin lesions that heal on remission of the tuberculous infection.

In the modern era, rapid resolution of the skin lesions invariably follows the institution of antituberculous antibiotic therapy.[67]

Tuberculids usually result from hematogenous spread of mycobacteria in an individual with a moderate or high degree of immunity (ie, the fluctuation in the immunological state of the patient determines the development and the features of the eruption). Histologically, the morphologic changes in the skin have a tuberculous character. Stasis, skin temperature, and the relative blood supply are responsible for the pattern of the disease.

Tuberculids have always been rare, even when tuberculosis was common. Today, they are so infrequent that some authorities question whether they ever existed. However, their appearance after the injection of tuberculin, after BCG prophylaxis, or during the chemotherapy of active tuberculosis remains the best evidence of their existence. Historically, tuberculids encompassed a host of conditions, including erythema induratum, papulonecrotic tuberculid, and lichen scrofulosorum.[68] Of 400 cases of tuberculosis with skin manifestations seen in hospitals in Poland during the period 1963 through 1987,[36] 268 (67%) had tuberculosis of the skin, 113 (28%) had pseudotuberculids, and only 19 patients (5%) had true tuberculids. Of the population with true tuberculids, 13 (68%) had erythema induratum and 6 (32%) had papulonecrotic tuberculid. No cases of lichen scrofulosorum were seen.[36]

Erythema Induratum

Erythema induratum (also called Bazin's disease, tuberculosum, tuberculosis cutis indurativa, nodose tuberculid) is a chronic condition associated with past or active tuberculosis. The disease is characterized by inflammatory cutaneous and subcutaneous nodules that have a tendency to ulceration and scarring. It typically occurs on the backs of women's legs and is believed to be an allergic or hypersensitivity reaction to the tubercle bacillus. Although in recent decades, many investigators have denied its tuberculous origin and have preferred the name nodular vasculitis, others have vigorously defended it.[68] Therefore, the term erythema induratum should be reserved for those cases in which components of tubercle bacilli are causative.

Epidemiology

In earlier times when the morbidity of tuberculosis was greater, erythema induratum was frequently seen. Today, however, it is rarely diagnosed, its incidence paralleling the decline of tuberculosis seen in most industrialized countries. The disease tends to favor teenaged or middle-aged women, especially those with plump extremities and minor

peripheral circulatory disturbances such as cold feet, erythrocyanosis, or cutis marmorata.

Etiology and Pathogenesis

The tuberculous cause of erythema induratum was generally accepted until the discovery of the tubercle bacillus and the development of Koch's three postulates for the diagnosis of tuberculosis: (1) isolation, (2) culture, and (3) the transfer of the bacillus. However, tubercle bacilli have only rarely been cultured out of the lesions of erythema induratum. Additionally, the degree of tuberculin sensitivity has been variable and the response to antituberculous therapy inconsistent. Nonetheless, researchers[68] argued strongly in 1989 for a connection between tuberculosis and erythema induratum, after studying a large series of patients who (*a*) had strong personal or family histories of tuberculosis, (*b*) were extremely tuberculin sensitive, and (*c*) had complete resolution of skin lesions after adequate antituberculosis therapy.

The pathogenic premises for erythema induratum and papulonecrotic tuberculid are the same: a tuberculous stimulus is initiated through either (*a*) hematogenous dissemination of a few tubercle bacilli or (*b*) dissemination of tubercle antigen into a cooled extremity with disturbed circulation. The ensuing hypersensitivity reaction, if immune-complex mediated, may be the cause of cases that show histological changes consistent with nodular vasculitis; if cell mediated, they may cause the cases that show the classic tuberculous histology. In support of the latter, researchers[69] reporting in 1990 found Leu-1^+, Leu-3^+, and HLA-DR^+ mononuclear cells (ie, helper T cells) within the lesions, in the absence of immunoglobulin or C3 deposition—thus suggesting a cell-mediated immune response to tuberculous antigen. Further, they noted one patient in whom satellite nodules of erythema induratum developed in the periphery of a PPD skin test, supporting the concept that the lesions of this tuberculid can indeed be produced by tuberculous antigen alone. Recently, the PCR has been applied to seven patients with erythema induratum. Five of seven patients were positive for *M tuberculosis* complex DNA, providing direct molecular confirmation for this long-debated association of tuberculosis and chronic nodular eruptions of the lower legs.[56]

Clinical Features

The eruption of erythema induratum is usually symmetric, and typically affects the calves of pubertal or adult women. Rarely are the pretibial areas affected. The lesions arise in small numbers as moderately tender, pea- to cherry-sized lesions, often platelike, firm, well circumscribed, and elastic. After some months, these lesions customarily regress, especially in the summer. Frequently, the larger lesions will turn livid red, liquefy centrally, ulcerate through the skin, and form ulcerations or fistulae. The ulcers tend to be ragged, irregular, and shallow. The oily or crusted ulceration can remain for months, but has little or no associated pain. An exhaustive search for a deep focus of tuberculosis is necessary, especially in countries where tuberculosis is prevalent.[70]

Laboratory Features

Patients with erythema induratum are usually highly sensitive to PPD, with intradermal Mantoux test results strongly positive (ie, 20-mm induration/40-mm erythema, or +++) using the weaker 1:10,000 dilution (1 unit PPD). (Note: subcutaneous injection frequently will give a false-negative reaction, and initial skin testing with more concentrated preparations may result in ulceration.) Bacterial cultures are customarily negative.

Histopathology

Often it is necessary to obtain many biopsies to obtain a definitive diagnosis because there are variations from biopsy to biopsy and within different areas of the same biopsy. In the earliest stages, a distinctive inflammation occurs in the vessel wall (usually a vein, but this disease can also involve the arterioles) with lymphocytic and plasma cell infiltration, and with thickening of the adventitia and media, sometimes with proliferation of the endothelium even to the point of occluding the lumen. A variable perivascular infiltrate is the rule at this stage. A septal panniculitis is present, which may overflow into the fat lobules. In many cases, the infiltrate is tuberculoid throughout[71]; in others, it is more banal. Fat necrosis and a foreign-body giant cell reaction may be present. A lobular granulomatous reaction in the damaged fatty tissue leads to *Wucher* (ie, proliferating) atrophy, wherein normal fat tissue disappears and is replaced by fibroblasts and macrophages.[71,72] Older lesions may progress to caseation and liquefaction. Later, fibrosis occurs. Caseation is always a late feature and may be seen at biopsy in only 50% of cases.[73]

Course

Erythema induratum may wax and wane for many years, with worsening in the colder months. New nodules may form, while older nodules and ulcerations may show only a slight tendency to heal. Altogether, a good prognosis can be expected if no general disease is found. Careful investigations can reveal, in a large proportion of cases, active tuberculosis in an organ or the indication of past tuberculosis.

Differential Diagnosis

It is important to distinguish erythema induratum from other conditions affecting the legs. Erythema nodosum predominantly affects the pretibial area and consists of tender, erythematous nodules that do not ulcerate. Other conditions to distinguish include subcutaneous lipogranulomatosis (Rothmann-Makai disease), which has a different histology (nodular vasculitis/cutaneous periarteritis nodosa) that can also be present with tuberculosis; the gummas of tertiary syphilis, which tend to be asymmetrically located; and nodular pernio, which has an even greater seasonal predilection, a more subacute course, and only occurs on the cold-exposed acral regions. In every case, histological examination is useful.

Treatment

Combination four-agent antituberculous therapy given for 6 months is most important in treating erythema induratum, as one- or two-drug chemotherapy may frequently prove inadequate—especially with the increasing antibiotic resistance to INH and rifampin currently being seen.[59,74] Simple measures to prevent cold exposure to the legs, and general measures to improve the peripheral circulation are believed by some investigators[24,75] to be important. The indiscriminate use of corticosteroids for the treatment of nodular vasculitis, which mimics erythema induratum, may be harmful.

Papulonecrotic Tuberculid

Papulonecrotic tuberculid (also called tuberculosis cutis papulonecrotica) is clinically characterized as a recurrent, chronic, symmetric eruption of necrotizing skin papules that appear in crops. The lesions tend to heal with varioliform scarring, and occur in patients with active or past tuberculosis. The disease may be thought of as a reaction pattern reflecting a normal protective immune response in a host with tuberculosis.

Pathogenesis

As a rule, bacteria are difficult to demonstrate in the lesions of papulonecrotic tuberculid by acid-fast staining of tissue sections, culture, or guinea pig inoculation. But occasionally these investigations prove fruitful. A tuberculous etiology is not in question because

- a large number of cases have an associated deep focus of tuberculosis,
- tuberculin skin testing is almost always positive, and
- patients respond rapidly to antituberculous therapy.

However, rather than direct metastatic spread of infectious organisms (as is seen in miliary tuberculosis), some investigators[76] believe the mechanism of spread in papulonecrotic tuberculid is an Arthus reaction followed by a delayed hypersensitivity reaction to mycobacteria in the skin tissue; in other words, a focus of tuberculosis is believed to release mycobacteria into the circulation periodically, where they are opsonized by immunoglobulins and complement-forming circulating immune complexes. These complexes then lodge in the walls of slow-flowing capillaries in the skin. Phagocytosis of opsonized bacilli and the resultant destruction of neutrophils release proteolytic enzymes, which subsequently necrose and destroy the vessels. Presumably, the ensuing mononuclear cell response then destroys the bacilli. Other investigators[77] suggest that the primary insult is either (*a*) nonspecific or (*b*) a subacute lymphohistiocytic vasculitis with thrombosis and destruction of small dermal vessels, leading to an infarctive lesion with coagulative necrosis of the overlying dermal tissue.

Most recently, as in erythema induratum, PCR studies have detected *M tuberculosis* complex DNA in lesions of papulonecrotic tuberculid, suggesting the presence of at least partially intact bacilli within the skin.[57,78]

Epidemiology

Girls and young women seem to be more susceptible than men to this particular condition. Papulonecrotic tuberculid is vanishingly rare in the industrialized world.[79] It occurred in 10 of 222 cases of tuberculosis in South Vietnam and only 9 times in

a 15-year period in the clinic at the Osaka University School of Medicine in Japan.[67] Rarely, it follows BCG vaccination.

Clinical Findings

Typically, symmetrical, loosely disseminated, grouped eruptions of papulonecrotic lesions arise in crops, particularly on the extensor surfaces of the arms and legs, with predilection for the elbows, knees, backs of the hands, and dorsal surfaces of the feet (Figure 15-13), as well as on the lower trunk and buttock region. The genital region is usually spared. The eruption tends to worsen in the winter and fade in the summer months. The lesions begin as pinhead-to-pea-sized papules or small nodules and, over the course of approximately 2 weeks, may become pustular, vesicular, pemphigoid-like, hemorrhagic, and necrotic. After another 3 to 6 weeks, the lesions heal with varioliform scars. Rarely, crateriform ulcerations occur. With recurrent crops, fresh papules and old scars frequently appear side by side. This results in a characteristic polymorphous clinical picture. The total number of lesions in any given patient is highly variable. Itching and burning sensations in the lesions may occasionally be present.

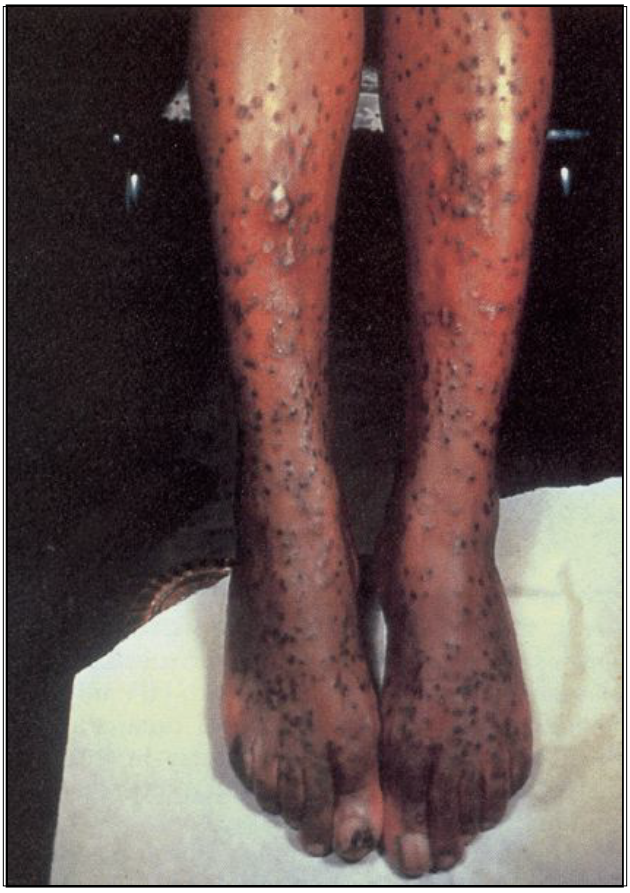

Fig. 15-13. Papulonecrotic tuberculid on the legs of an elderly woman with active pulmonary tuberculosis.

Laboratory and Histopathological Findings

Patients often have an exceedingly heightened sensitivity to tuberculin, with positive intradermal reactions to PPD in dilutions of 10^{-8} to 10^{-9}.

A leukocytoclastic vasculitis is present early on. Later, wedge-shaped necrosis develops, representing a microinfarct. Epithelioid and giant cells are often seen at the periphery of the necrotic zone. However, well-formed granulomas are not identified. Blood vessel involvement is a key feature, being granulomatous, necrotizing (with fibrin present in the walls and lumen), and sometimes obliterative (ie, leading to thrombosis and complete occlusion of the vascular channels).

Course

The disease may last for years or even decades with recurrent crops of ulcerations and consequent varioliform scarring.

Differential Diagnosis

Differentiation from other papulonecrotic processes is necessary. Such entities may include leukocytoclastic vasculitis, pityriasis lichenoides et varioliformis acuta (Mucha-Habermann), lymphomatoid papulosis, acne necrotica, secondary syphilis (rarely), and prurigo simplex–neurotic excoriations. In all cases, biopsy and tuberculin skin testing are extremely helpful.

Treatment

Definitive therapy for tuberculosis with four-drug therapy is indicated.[59,74] Occasionally, this is combined with systemic glucocorticosteroids in moderate doses in exceptionally extensive cases.

Lichen Scrofulosorum

Lichen scrofulosorum (also called tuberculosis cutis lichenoides) is a very rare, but distinctive, lichenoid tuberculid. The disease, which was originally recognized by Ferdinand von Hebra in 1860,[80] occurs predominantly in children and adolescents

who have either primary complex of tuberculosis or a secondary organ tuberculosis.

Clinical Features

In lichen scrofulosorum, the sites of predilection are the sides of the trunk. The exanthem is very discrete and consists of symmetrically arranged groups of tiny papules—often in elongated, oval arrangements parallel to the skin relaxation lines (lines of Langer). The primary lesion is a white, pale yellow-brown, pale red, or skin-colored follicular or perifollicular soft acuminate papule, which may carry a fine scale on its summit. Rarely, a small vesicle may be seen. Occasionally, the small, pointed, agminated papules are more polygonal and resemble lichen ruber acuminatus (a form of lichen planus). On diascopy, the distinct yellow-tone tuberculous character of the infiltrate is easy to miss due to its minimal size. In addition, because the eruption is asymptomatic, it may be overlooked.

Course

After a few months, lichen scrofulosorum eruptions customarily resolve spontaneously without scarring. Recurrences are possible. If central vesicle or pustule formation progresses to an acneform or necrotic picture, then transformation to papulonecrotic tuberculid is assumed to have occurred.

Laboratory and Histopathological Features

The Mantoux skin test for tuberculosis is almost uniformly positive. *M tuberculosis* can occasionally be cultured from the lesions.[81]

Typically in lichen scrofulosorum, tuberculoid granulomas with Langhans'-type giant cells are seen in the papillary dermis surrounding hair follicles and sweat ducts. Nonspecific inflammatory infiltrates may be mixed in with the tuberculous granulomas. Caseation necrosis is generally absent.

Differential Diagnosis

The differential diagnosis includes lichen nitidus, lichen planus, keratosis pilaris, lichenoid secondary syphilis, lichenoid drug eruption, lichenoid sarcoidosis, follicular eczemas, and lichen scorbutus (scurvy). A rare possibility, lichenoid syphiliticus (a small papular, grouped follicular or lichenoid syphilid), occurs during the course of tertiary syphilis.

Prognosis

In patients whose disease is due to tuberculin testing or BCG immunization, the prognosis is excellent. In other patients, the condition is associated with lymph node, osseous, pulmonary, or genitourinary tuberculosis. In patients with normal immunity and with chemotherapy, the prognosis is generally good.

Treatment

The spontaneous resolution of the condition in most patients is no contraindication for treatment because lichen scrofulosorum is a harbinger of internal tuberculosis. Consequently, chemotherapy for the underlying systemic tuberculosis is indicated and usually clears the skin manifestations in a matter of weeks; in contrast, the internal disease may require 6 months or more of therapy.[24,59,75]

SUMMARY

Tuberculosis is an infectious disease caused by the bacterium *Mycobacterium tuberculosis*. Estimated to be present in one third of all humans, tuberculosis is again increasing in incidence, particularly in sub-Saharan Africa, due, in part, to the AIDS epidemic. More alarming has been the progressive increase in multidrug-resistant strains, particularly among AIDS patients. Cases of extrapulmonic tuberculosis—and especially cutaneous tuberculosis—are again being seen in western Europe and in the United States as a result of the immigration of peoples from countries with high prevalence of tuberculosis. Although cutaneous lesions are present in fewer than 1% of all tuberculosis patients, most cutaneous tuberculosis reflects more serious underlying systemic tuberculosis and can be seen in patients presenting with HIV infection. Therefore, prompt recognition of tuberculosis of the skin is important, as any delay in treatment may contribute to further spread of disease in the community.

Patients with cutaneous tuberculosis present with diverse forms ranging from single, smooth papules to disseminated, eruptive papules; verrucous or vegetative plaques; single or multiple ulcerations; or extensive sinus tracts. The form of the disease

depends on the virulence of the strain, the immune status of the host, the portal of entry, the mode of internal spread, and the adequacy of initial treatment. Acute miliary tuberculosis, particularly in patients who are highly immunosuppressed (eg, those with AIDS), is generally a harbinger of death due to overwhelming infection. Scrofuloderma and lupus vulgaris are much more common and are seen in patients who are less immunosuppressed. Tuberculosis verrucosa cutis is a highly localized form of cutaneous tuberculosis that is seen in patients who are immunocompetent.

The clinical diagnosis of cutaneous tuberculosis is suggested by the presence of apple jelly–colored dermal infiltrates. Definitive diagnosis requires that the organisms be (*a*) recovered and (*b*) identified by either bacterial culture or guinea pig inoculation, or by demonstration of the presence of *M tuberculosis* via PCR assays for specific DNA sequences. Compatible histopathology consisting of granulomatous infiltrates with caseation necrosis and the presence of acid-fast bacilli in tissue sections are both suggestive, but are by no means pathognomonic of tuberculosis.

Tuberculosis can be accompanied by a variety of hypersensitivity reactions to the bacillus or one of its constituent parts. These autosensitization reactions are commonly called tuberculids. Recent use of PCR assays for certain *M tuberculosis*–complex DNA segments have suggested that the tuberculid skin lesions contain sizable bacterial fragments of whole organisms.

The treatment of systemic tuberculosis has become much more complicated during the 1990s. Administering four-agent chemotherapy for 6 months is standard initial therapy where the incidence of drug resistance is very low. However, with the rapid rise of multidrug-resistant strains—especially in the HIV-infected population—intensive and innovative chemotherapy protocols based on antibiotic sensitivities need to be custom tailored to each patient. The treatment of cutaneous tuberculosis in most cases is the same as for pulmonary tuberculosis, as lesions in the skin often represent hematogenously or lymphatically dispersed disease from internal foci of infection. Rarely will tuberculosis in the skin be confirmed as strictly a cutaneous disease.

Militarily, tuberculosis is a serious and growing health threat in most areas of the world, especially in Africa, Asia, and the Pacific. With the increased emphasis on peacekeeping forces, disaster relief, and so forth, military personnel are increasingly involved with refugees in distant, third-world areas where tuberculosis (and HIV) may have very high prevalence and incidence. Thus, the likelihood of exposure is greater. When coupled with the possibility that HIV-positive military personnel could be present, whose natural resistance to the organism may be significantly compromised, the stage is set for serious, highly infectious, life-threatening disease. Therefore, intensive tuberculosis screening, aggressive treatment, and comprehensive public-health measures are mandatory for protecting the health of military personnel who are deployed to these areas.

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