Clinical Perspective

Radiographic Appearance of Pulmonary Tuberculosis: Dogma Disproved

Anna Rozenshtein
Frank Hao
Michael T. Starc
Gregory D. N. Pearson

OBJECTIVE. The purpose of this article is to review the origins of the classic teaching on pulmonary tuberculosis, its evolution in the modern literature, and the evidence that led to its demise.

CONCLUSION. Use of molecular epidemiologic techniques that entail DNA fingerprinting has led to the discovery that the radiographic appearance of pulmonary tuberculosis does not depend on the time since infection. It has been confirmed that the upper lobe cavitary disease typical in adults is the disease of the immunocompetent host, whereas lower lung zone disease, adenopathy, and effusions, which are uncommon in adults, are the hallmarks of tuberculosis in an immunocompromised host.

G
enerations of physicians have been taught that pulmonary reactivation tuberculosis can be differentiated from the primary lung infection on the basis of radiographic appearance. According to the classic teaching, upper lobe cavitary disease was believed to be the hallmark of reactivation of latent infection, whereas lower lung zone disease, adenopathy, and effusions were believed to indicate recent infection [1–4]. Compelling evidence has accumulated against the classic teaching, but like all dogma it is proving resistant to change. Of the 11 popular radiology textbooks [5–15] for sale at the 2012 annual meeting of the Society of Thoracic Radiology, only two [5, 6] clearly stated that there is no difference in the radiographic appearances of reactivation and primary tuberculosis.

In this article we review the origins of the classic teaching, the evolution of the classic teaching in the modern literature, and the evidence that led to the demise of this teaching. Our purposes are to promote new understanding of the radiographic appearance of tuberculosis and to place the classic teaching in the pantheon of grand old theories of interest primarily to medical historians.

Classical Teaching Meets the AIDS Epidemic

By convention, tuberculosis is classified as primary if the onset of clinical disease falls within 1 year of the initial infection and as reactivation if the disease onset is more than 1 year after the initial exposure. Because the prevalence of tuberculosis was high throughout much of history, and thus most individuals were exposed and presumably infected in childhood, the classic teaching held that children commonly presented with primary disease but that adults usually presented with reactivation of a latent infection. Because lower lobe disease, adenopathy, and pleural effusions (Fig. 1), which are common in children, are unusual in adults, this pattern became known as atypical disease [3, 4]. On the other hand, the upper lobe disease observed in most adults [1, 2] became known as typical reactivation tuberculosis (Fig. 2). This observation was explained by the linear pathogenesis model, whereby a droplet laden with bacilli inhaled into the alveoli entered the lymphatic system and remained dormant. Later, at some point in time dependent on the host’s immunologic state, reactivation of the dormant infection was thought to occur preferentially in the upper lung zones as the result of decreased lymphatic drainage and increased partial oxygen pressures [16, 17]. As late as 2008 this model provided support for the classic teaching [18–22].

With the advent of molecular epidemiology in the 1990s, the classic view was increasingly questioned. In 1997 Jones and colleagues [23] proposed and in 2005 Geng and colleagues [24] confirmed that the radiographic appearance of tuberculosis is independent of the time since infection. Instead,
Radiographic Appearance of Pulmonary Tuberculosis

cavitary upper lobe disease is usually seen in an infected immunocompetent host, whereas immunocompromised patients usually present with lower lung zone disease, adenopathy, and effusions. This change in understanding resulted from research on HIV.

The AIDS epidemic of the 1980s and 1990s coincided with a dramatic increase in cases of active tuberculosis in the United States. In 1989 Selwyn and colleagues [25] reported that in the general population, latent infection with tuberculosis carried a 10% lifetime risk of reactivation, whereas in patients with concomitant untreated HIV infection, the risk of reactivation was 10% per year. However, patients with HIV infection more often than not had atypical manifestations of tuberculosis, that is, lower lung zone disease and adenopathy [26, 27]. The high rate of active tuberculosis has been linked to the loss of γ-interferon, an important cytokine that is normally produced by CD4+ T cells depleted by HIV [28]. Therefore, the atypical presentation of tuberculosis in patients with HIV infection was initially believed to be due to the increased susceptibility and more rapid progression of primary tuberculosis in this population [29, 30].

In the 1990s, however, a growing body of evidence suggested that tuberculosis manifests itself differently in an immunosuppressed host irrespective of the time since the initial infection. In 1993, Jones and colleagues [31] reported that the radiographic pattern of tuberculosis in HIV-positive patients correlated with the stage of HIV infection. For example, patients with CD4 counts greater than 354 cells/µL usually had upper lobe disease. As CD4 counts declined, cavitation occurred less frequently. Pleural effusions were seen at CD4 counts greater than 200 cells/µL, but mediastinal adenopathy was most frequently seen at CD4 counts less than 200 cells/µL.

Two years later, Post et al. [32] found that the radiographic appearance of tuberculosis could be used as a predictor of CD4 count. The positive predictive value (PPV) of apical disease for CD4 counts greater than 200 cells/µL was 78%, the PPV of lower lung zone disease for CD4 counts less than 200 cells/µL was 84%, and the PPV of adenopathy for CD4 counts less than 200 cells/µL was 89%.

Molecular Epidemiology and Radiographic Appearance

The newly discovered association between pulmonary tuberculosis and the immune status of the host called into question the accepted relation between radiographic appearance and time since infection. At the same time, advances in molecular epidemiology—DNA fingerprinting with restriction fragment length polymorphisms—provided a powerful new epidemiologic tool [33–35] as an alternative to seroconversion. The technique involves extraction of the Mycobacte-
rium tuberculosis DNA, digestion with the restriction enzyme PvuII, electrophoresis, and hybridization by Southern blotting, allowing generation of a so-called DNA fingerprint. Tuberculosis strains were classified as clustered when genetically identical strains were recovered from two or more patients and as unique if found in only one person. Clustered cases were observed in miniepidemics and correlated with primary disease; unique cases correlated with reactivation of latent infections [36]. A single molecular strain isolated from two or more people, who also happened to be related in space and time, could be accurately characterized as primary disease. On the other hand, unique molecular isolates were more likely to be cases of reactivation tuberculosis [36].

DNA fingerprinting was used to study the epidemiology of tuberculosis in several large urban areas. In June 1994, the New England Journal of Medicine published the results of two studies on the transmission of tuberculosis. Alland et al. [37] examined 104 adult patients in New York City and found 35 clustered strains. Small et al. [38] examined 473 patients in San Francisco and found 191 clustered strains. Contrary to previous teaching, in both urban centers only approximately one third of newly diagnosed adult cases of tuberculosis were due to primary disease; the others were due to reactivation [37, 38].

The classic teaching had come into question. In 1997 Jones and colleagues [23] examined a group of 103 patients with tuberculosis. They used molecular epidemiologic techniques to look for correlations with radiographic findings in patients with primary and reactivation disease and found no difference. A review of their results is instructive. In the HIV-negative group 24 of 28 (86%) patients with reactivation disease (unique isolates) and 24 of 30 (80%) patients with primary tuberculosis (clustered cases) presented with upper lung zone disease. Only two had the classic pattern of primary infection. In the HIV-positive group the opposite was true: 10 of 16 (63%) patients with primary disease and 10 of 16 (63%) patients with reactivation had the atypical pattern of primary disease. The authors concluded that the radiographic appearance of tuberculosis was not determined by the time since infection but by the state of the immune system. These results were supported by findings of a follow-up study published in 2005 by Geng and colleagues [24], who used similar techniques to examine 456 patients, 54% with HIV infection, who presented with tuberculosis in New York City between 1990 and 1999. Their study was powered at 95% to detect a 15% difference between study populations. Although there was overlap in radiographic appearance in the two groups, presumably related to differences in patient disease susceptibility and the virulence of the different M. tuberculosis strains, the investigators found that cluster status, which allowed them to differentiate recently acquired from remotely acquired tuberculosis, was not a significant predictor of radiographic appearance [24]. Although the virulent properties of the tuberculosis strains seen in the 1960s and the disease patterns in the affected host could theoretically be different from those seen 50 years later, Geng and colleagues proved that time since infection is not predictive of the radiographic appearance of tuberculosis in either patients with or patients without symptoms of HIV infection.

The newer studies had limitations. There was overlap in radiographic appearance between the groups with and without HIV, at least in part related to patient immune status and the virulence of the individual strain. Molecular fingerprinting has limitations. Some unique isolates could represent recent infection from an unknown and possibly distant source. In each cluster, one case could represent reactivation, and others could represent infections that occurred before the 1-year window of primary tuberculosis. There are also issues of interpretation. When in a minority of cases DNA isolates had similar but not identical patterns, reactivation could not be definitively differentiated from primary tuberculosis because genetic divergence could happen in the process of disease transmission [39]. The limitations notwithstanding, by 2005 there was compelling evidence that radiographic appearance cannot be used to differentiate primary from reactivation tuberculosis.

Origins of the Classic Teaching

When new data are incompatible with a generally held notion taught to generations of physicians, it is instructive to examine the origins of the original belief. We started by looking at reference textbooks in search of source articles. Many texts offered no citations, as if this truth were self-evident, and others commonly quoted four articles from the 1960s through the 1980s [1–3, 40]. Each of these works used a different definition of primary and reactivation disease, and none provided strong evidence in support of the classic teaching. For example, in the 1983 case series of patients with primary tuberculosis described by Choyke and colleagues [1], only 64% of patients had documented recent seroconversion. The others were so classified on the basis of radiographic features (lymphadenopathy and pleural effusions) or clinical manifestations. This method had been popularized earlier by Stead and colleagues [40], who in 1968 reported a series of 37 cases of primary tuberculosis in which eight (22%) were included solely on the basis of lymphadenopathy and parenchymal disease in the lower lung zones. Moreover, their definition of primary tuberculosis was elastic: only 30% of their patients with documented tuberculin conversion became ill within 1 year of infection, 40% within 2 years, and 65% within 9 years. This means that one third of their patients with documented seroconversion did not have disease close enough to the time of infection to meet the consensus definition of primary disease. Furthermore, the authors admitted to excluding any patient if “the disease involved the apical or posterior segment of the upper lobe because these are segments so commonly involved in the postprimary stage of infection.” Woodring et al. [2] referenced Choyke et al. [1] in discussing the radiographic manifestations of tuberculosis and presented data of their own showing considerable overlap between primary and reactivation disease, grouping adults with children. Weber et al. [3] reported on the findings of primary tuberculosis in childhood, and thus their findings are of limited value to our discussion.

Stead and colleagues [40] explained their reliance on radiographic appearance to differentiate primary disease from reactivation because several authors had reported mid and lower lung zone disease with adenopathy or pleural effusions as common in primary tuberculosis and rare in postprimary (so-called reinfection-type) tuberculosis. Analysis of those publications identified three English-language articles [41–43] relevant to the radiographic appearance of tuberculosis. In 1944 Frostad [41] published data on a population of 3336 Norwegian students who underwent periodic testing with tuberculin over 10 years in the 1930s. In his introduction, Frostad referred to a body of German language literature by “Assmann, Redeker and Walter, Fraenning, Lydittin, Eckert, Kayser-Petersen, Ulrici, and others” that “showed that tuberculosis originating in the apex of the lung was an infrequent occurrence.” We reviewed Frostad’s raw data in a yellowed foldout—the 1940s equivalent of a 21st century computer

Rozenshtein et al.
spreadsheet. Of 48 adult patients with proven active pulmonary tuberculosis within 12 months of the last negative tuberculin skin test result, 25 (52%) were noted to have upper lung zone disease and 23 (48%) to have lower lung zone disease. These findings are incompatible with the assertion that apical disease is infrequent in primary infection. The distribution in the pediatric population was even less supportive: of the 28 children (younger than 14 years) who had active tuberculosis within 12 months since infection 23 (82%) had upper lobe disease and six (18%) had lower lobe disease. The rates of adenopathy and pleural effusion were not reported.

Three years after Frostad’s publication, Poulsen [42] published his account of a 1945 epidemic of tuberculosis in an isolated community on the Faroe Islands. Owing to frequent outbreaks of tuberculosis in this fishing community, mandatory examination for tuberculosis was begun in 1939. Six years later a documented cluster of seroconversions followed by clinical illness in 17 patients was traced to a single source. In this group 13 (76%) had right hilar enlargement, three (18%) had a pleural effusion, three (18%) had a basilar or perihilar infiltrate, and one (6%) had right upper lobe disease. Poulsen’s data were difficult to generalize to the general population, however, because of the small sample size and the unique characteristics of the cohort. Many of the patients were related, and the infection was unusually virulent: three (18%) patients had meningitis, an uncommon complication of tuberculosis.

It is noteworthy that U.S. data on the radiographic appearance of confirmed primary tuberculosis were available when Stead et al. [40] were writing their work. In 1965 Alpert and Levison [44] published an account of an epidemic of tuberculosis in a medical school. Of their 25 patients, all with primary disease, eight (32%) had cavitary lesions thought then to be the hallmark of reactivation disease, and nine had pleural effusions. They did not comment on lobar distribution or adenopathy. In 1968, the same year Stead et al. published their results, Hardy and Schmidek [45] reported on an epidemic of tuberculosis aboard a U.S. Navy heavy cruiser. Among the 25 previously healthy young men with active tuberculosis documented with sputum smears, sputum cultures, or pleural biopsy, 16 patients had pulmonary involvement. Of these, 13 (81%) had upper lobe disease, one (6%) had lower lobe disease, and two (13%) had pleural effusions.

Epilogue

Review of the seminal work on the radiographic appearance of tuberculosis shows that the classic teaching was not based on strong epidemiologic data in large representative populations. Although authors have frequently divided patients into those having typical and those having atypical patterns, the definitions varied, and when patient findings have been available for review, it becomes clear that there is often considerable overlap in individual patients. It appears that Frostad [41] was wrongly handed the paternity of the dogma, which appears to have been based on the works of other authors publishing primarily in the German literature. Gedde-Dahl [43] made his observations in an impoverished population in which high rates of tuberculosis were attributed to malnutrition, a well-known cause of immunocompromise [46–48]. Poulsen [42] reported an outbreak of tuberculosis caused by a single strain in a small genetically homogeneous group. Although at the time of Poulsen’s publication, variation in virulence among M. tuberculosis strain may not have been widely known, it was accepted that genetic susceptibility plays an important part in the development of active tuberculosis [49].

It is intriguing that despite the presence of contradictory data on U.S. adults, the dogma was accepted wholesale. We speculate that the ability to differentiate primary and reactivation tuberculosis was critical to clinical management. Reactivation disease requires that close contacts of the index patient undergo screening for conversion. If no cases of conversion are found, treatment of the index patient prevents further spread. Discovery of a case of primary tuberculosis, on the other hand, necessitates a search for the source of infection: treatment of the index patient is insufficient to contain an epidemic because the person who infected the index patient may still be infecting others. In the years after World War II, tuberculosis posed a major public health threat to rebuilding communities with limited medical resources. Using readily available and relatively inexpensive chest radiography to attempt to differentiate a possible epidemic from an isolated case of infection was attractive. This may be why all evidence that did not fit the classic teaching was ignored, and the dogma survived into the 21st century.

The physicist Max Planck [50] wrote, “A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it.” It has been 20 years since the first papers disproving the classic tuberculosis dogma were published. It is time to put it to rest.

References


41. Frostad S. Tuberculosis incipiens: a clinical roentgenological investigation on the earliest forms of pulmonary tuberculosis with special view to its relation to the primary infection. Copenhagen, Denmark: Munksgaard, 1944


45. Hardy MA, Schmidek HH. Epidemiology of tuberculosis aboard a ship. JAMA 1968; 203:175–179


