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Review article/ *Articolo di revisione*

The timing from tuberculosis infection to cavitation

Il timing della tubercolosi, dall'infezione alla cavitazione polmonare

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Summary

Background. In Italy, a low risk country, reported tuberculosis cases among migrants have increased from 39.4% in 2004 to 63% in 2013 to 66.2% in 2017. Some physicians, particularly the youngest, deal poorly with epidemiology, pathogenesis and symptoms of pulmonary tuberculosis and sometimes misdiagnose tuberculosis for nontuberculous pneumonia. One of the reasons could be the lack of recognition of the time between tubercular infection and symptoms appearing. In the current medical literature, the pathological stages occurring from infection to active pulmonary disease are only partially known.

Objectives. The aims of the present study are: 1) to give a review of the current medical literature in the topic and 2) to offer to doctors, particularly those involved in the first aid to migrant population from high tuberculosis risk countries, useful data to better understand the concrete risk of pulmonary tuberculosis infectiousness during the time of its pathogenesis.

Method. Historical studies, animal models (particularly the macaques' models) and mathematical simulations related to the evolution of pulmonary lesions after tuberculosis infection were reviewed. Definitions of tubercular granuloma and cavitation and hypotheses about their formation were also summarized. Moreover, a very rare event today, the clinical evolution, accompanied by radiological documentation, without treatment, of a case of pulmonary tuberculosis from the stadium immediately subsequent the granuloma's formation until cavitation, through the stage of nodular lesion, not excavated yet contagious, is reported.

Conclusion. The period during which pulmonary tuberculosis evolves from the Ghon focus to pulmonary consolidation/cavitation may exceed 12-18 months.

Key words: LTBI, pulmonary TB, TB management, TB monitoring, TB natural history, TB timing

Riassunto

Background. *In Italia, paese a basso rischio, i casi di tubercolosi tra i migranti sono aumentati dal 39,4% nel 2004 al 63% nel 2013 fino al 66,2% nel 2017. Alcuni medici, soprattutto i più giovani, hanno poca familiarità con l'epidemiologia, la patogenesi e i sintomi della tubercolosi polmonare e talvolta possono scambiare una tubercolosi con una polmonite non tubercolare. Una delle ragioni potrebbe essere la mancata conoscenza del tempo che trascorre tra l'infezione e la comparsa dei sintomi. D'altronde, le tappe patogenetiche che conducono dall'infezione alla malattia attiva sono parzialmente note.*

Obiettivi. *Obiettivi dello studio sono: 1) proporre una review della letteratura sull'argomento e 2) offrire ai medici, specialmente a quelli impegnati nel primo soccorso ai migranti provenienti dai Paesi ad elevato rischio tubercolare, informazioni utili per comprendere meglio il rischio concreto di contagio durante le tappe seguite dalla patogenesi tubercolare.*

Metodo. *Review di studi storici, modelli animali (in particolare il macaco) e simulazioni matematiche relative alla evoluzione delle lesioni polmonari conseguenti all'infezione tubercolare. Definizione di granuloma e caverna tubercolare e sintesi delle ipotesi sulla loro formazione. Inoltre, sono descritte l'epidemiologia e la clinica, con relative immagini radiologiche, di un malato di tubercolosi polmonare documentata, come raramente ac-*

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Conflict of interest statement
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cade, dallo stadio immediatamente successivo alla formazione del granuloma tubercolare fino alla formazione della caverna tubercolare attraverso lo stadio di lesione nodulare, non escavata ma contagiosa.
Conclusioni. *L'intervallo durante il quale la tubercolosi polmonare evolve dal focolaio di Ghon fino al consolidamento parenchimale e alla cavitazione può superare 12-18 mesi.*

Parole chiave: LTBI, TB polmonare, gestione TB, monitoraggio TB, storia naturale TB, timing TB

Introduction

Background

Tuberculosis (TB) is an airborne infection transmitted between humans. Its natural history begins with the exposure of a susceptible host to an infectious case of pulmonary TB. Yet, only 30% of contacts will develop a TB infection. Indeed, most infections remain clinically latent carrying a risk for disease reactivation; it is widely accepted that approximately 10% of infected individuals will progress to TB whereas the rest will likely harbor the organism for the rest of their life [1].

Close contacts with Latent Tuberculosis Infection (LTBI) are at particularly high risk of reactivation. Their level of risk of progression differs according to age group: in those aged < 14 years, the risk accrues within 150 days whereas in those aged ≥ 15 years, the risk is more evenly distributed, with approximately one-half of the total risk accruing within the first 227 days [2].

Among HIV-infected patients without antiretroviral therapy, recently acquired tuberculosis infection can progress more rapidly to cause TB, as documented in the 80s by Di Perri who examined a nosocomial outbreak of TB among 18 HIV-infected inpatients, 7 of whom *had* active disease within 60 days of exposure to the index case [3]. In 1992, Daley reported a TB outbreak occurred in an HIV housing facility in San Francisco during which 11 (36.7%) of the 30 HIV^+ residents exposed to *Mycobacterium tuberculosis* (Mtb) were infected and developed active TB within the first 6 months from TB infection [4].

Unfortunately, none of the tests currently available can accurately predict future progression. The largest study to evaluate Interferon Gamma Release Assays (IGRAs) and Tuberculin Skin Tests (TSTs), the UK PREDICT TB cohort study, recently showed that in a low-incidence setting among TB contacts and migrants from high TB risk countries positive predictive values are only 3-4% [5]. It means that only 3-4% of those positive progresses to active TB after infection. The PREDICT study also indicated that IGRAs were more sensitive and specific than TST 10 mm. Partially in contrast to this result, Auguste has lately documented among recent arrivals from high-endemic countries that TST 10 mm and 15 mm had lower sensitivity, but higher specificity compared to IGRAs and TST 5 mm in predicting future progression. In any case, no test globally outperformed the other [6].

In Italy, a low risk country, reported tuberculosis cases among migrants have increased from 39.4% in 2004 to 63% in 2013 [7] and to 66.2% in 2017 [8]. Some physicians, particularly the youngest, deal poorly with epidemiology, pathogenesis and symptoms of pulmonary tuberculosis and sometimes misdiagnose tuberculosis for nontuberculous pneumonia, due to lack of knowledge about the disease, which has been eliminated from the studies in medical schools for years, as reported in the 1st edition of the "Estates General of Tuberculosis", held in Rome in 2011.

Aims of the study

The aims of the present study are to give a review of the current medical literature in the topic and to offer to doctors, particularly the youngest involved in the first aid to migrant population, useful data to better understand the concrete risk of pulmonary TB infectiousness during the time of its pathogenesis.

Data from scientific literature

Historical studies

In TB, the precise duration and activity of the infection and the timing and pathological stages occurring from infection to active pulmonary disease are only partially known from available scientific literature. This had already been pointed out in the 70s by Morrison who suggested that the time of consolidation/collapse in relation to the primary infection usually occurs within a few months following the infection [9]. In addition, in the 70s, Ferebee found that 14% of 129 TST-positive close contacts of Philippine patients with cavitating disease who received placebo developed chest radiograph abnormalities within 2 years [10]. Furthermore, a study published in 1968 by Myers et al. examined 3,192 students of three private hospital schools of nursing in Minnesota assigned to care of persons with communicable TB. 21 out of those students had tuberculin conversion while in school and underwent chest roentgenogram about twice a year thereafter. Among them, 14 (66.7%) developed active pulmonary disease within 2 years, while the remaining developed the disease within 4 to 18 years (Fig. 1). None of the 21 students showed pulmonary cavitations [11].

More recently, Guwatudde studied 1,206 Ugandan household contacts of 302 TB index cases and found that

19 out of 25 contacts with incident active pulmonary TB developed active disease within 2 years (the median time to diagnosis of incident tuberculosis was 16 months) while the remaining contacts developed the disease between 28 and 56 months. Approximately half of the incident cases occurred in HIV-infected individuals, and 20% occurred in subjects < 15 years of age [12]. However, Guwatudde and colleagues did not report whether characteristics such as age, HIV status, or radiological and clinical features were associated with a shorter or longer time interval to active disease, nor if and how many of the 25 patients both HIV^+ and HIV^- had developed a cavitary TB. Anyway, it is generally believed that HIV-infected patients with TB rarely show a cavitary pulmonary disease [13]. Nevertheless, in 2018, Patterson has documented by chest X-ray the presence of cavitations in 25% (4 subjects) of 16 HIV^+ newly diagnosed TB patients compared to 52.9% (9 subjects) of 17 HIV^- newly diagnosed TB patients [14]. The apparent contradiction of the data reported above is resolved by the widely shared consideration that among HIV-infected patients with pulmonary TB, the likelihood of cavitation is correlated with the CD4 count. In general, HIV-infected patients with CD4 > 350 cells/μl show typically upper lobe infiltrates and cavitations, while those with CD4 < 200 cells/μl do not, so much so that a cavitary lesion in patients with CD4 counts of less than 200 should prompt a search for other etiologies [15].

Infectiousness of respiratory TB

TB patients with pulmonary cavity, which contains up to 1.000.000.000 of mycobacteria, are the principal source of disease transmission compared with those with noncavitary disease. Also, Endobronchial TB (EBTB) is a highly infectious disease even if the yield of sputum positivity for Mtb is not as high as in parenchymal involvement. More in detail, mycobacteria are isolated in 16-53% of EBTB patients in relation to which one of the seven categories of EBTB [16] the patient shows, being the granular forms more often positive to acid fast bacilli in sputum examination while the fibrostenotic forms regularly negative [17-19]. The granuloma is a pauci bacillary lesion. Actually, much of the literature assumes that mycobacteria reside within granulomas. However, multiple studies found that granulomas are sterile after 5 years [20].

Owing to the paucity of data on the evolution of parenchymal lesion in humans, the time elapsed since infection and the exact mechanisms resulting in pulmonary cavitation are poorly understood. So that, our current knowledge of natural history of TB and

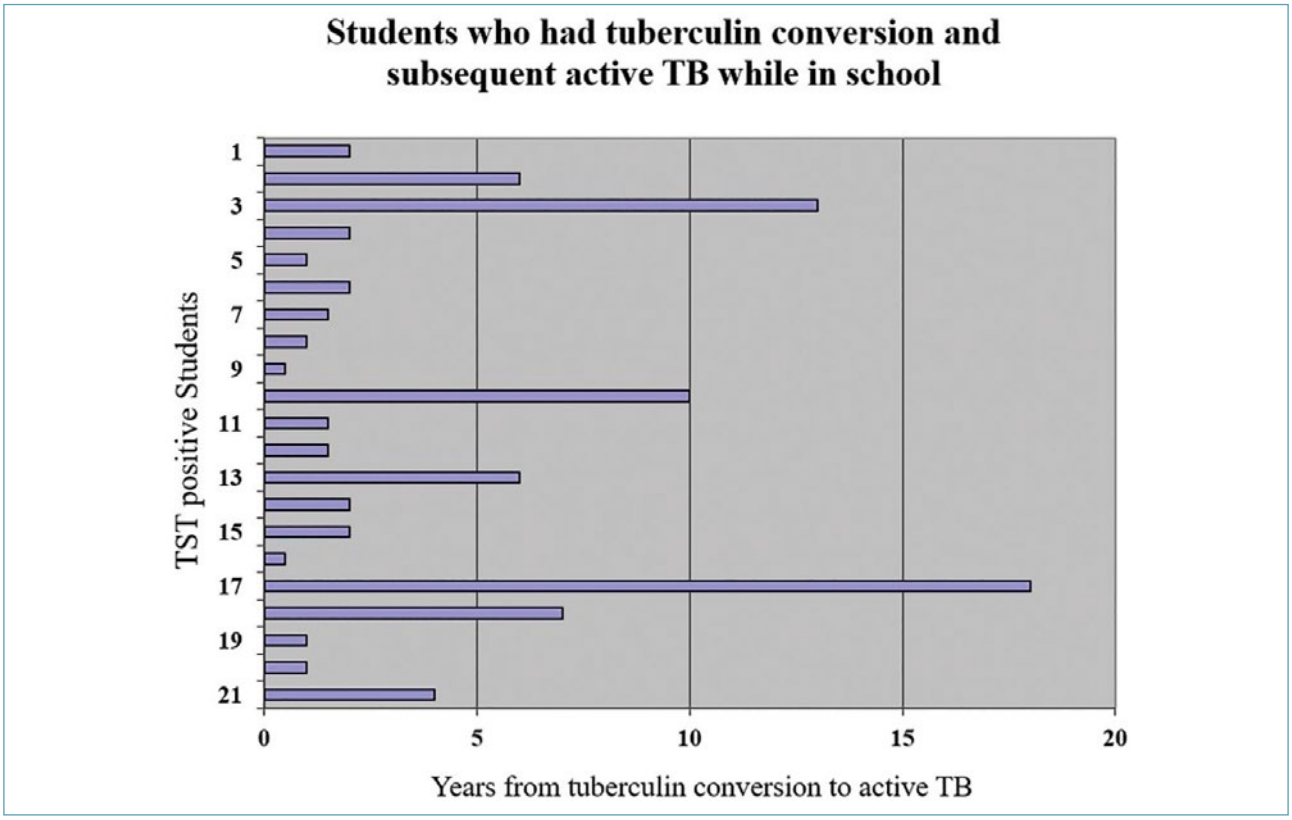

Figure 1. 66.7% of students studied by Myers et al. assigned to care of persons with communicable tuberculosis had active TB within 2 years after tuberculin conversion.

pathogenesis of cavitation stems also from animal models, microbiology and mathematical models [21-23].

Animal models

Macaques are excellent models for clinical translational research on TB, as these animals share with humans clinical and histopathological manifestations of TB [24]; indeed, they may develop either rapid-onset disease, or active-chronic disease, resembling that seen in humans [25].

Zhang studied 24 monkeys inoculated via bronchoscope with low (25 Colony-Forming Unit [CFU]), or high doses (100 to 500 CFU) of virulent strains and in this setting the monkeys'chest X-ray displayed nodular infiltrates or patches between 4 to 12 weeks after inoculation [24].

Capuano monitored for 15 to 20 months 17 monkeys inoculated via bronchoscope with low (25 CFU) doses of a virulent strain, and observed that five of the monkeys had an abnormal chest radiograph from 3 to 10 months post-infection; interestingly, one monkey that had negative chest radiographs at 2 month post-infection, at the 8 month follow-up developed a cavitary lesion in the right lobe, which spread to the left lobe 2 weeks later [25]. Unfortunately, experimental settings mimic only partially natural infection (monkey to monkey transmission) as the animals are generally inoculated by bronchoscopy with low (16-25 CFU) or high (100-500 CFU) doses of virulent strains and are only monitored for a short time (about 16 months) before they are sacrificed.

Nevertheless, Mätz-Rensing was able to study the natural Mtb infection in a colony of 26 adult rhesus monkeys of different ages and sexes, living in a closed, long-term facility of the *Max Planck Institute* of Tübingen, Germany, that were accidentally infected by a human TB patient. The index monkey had become symptomatic (coughing) 5 months before its TB was confirmed by necropsy examination (caseous granulomas in the lung, spleen and liver) and microbiological studies. Ten of the remaining 25 asymptomatic animals were infected and their radiological examination revealed pulmonary lesions of different size, shape and density, without cavities. 1-2 months later, also these ten animals were sacrificed, and their necropsy described within their lungs firm yellow-white or grey nodules, ranged from pinpoint to several millimeters in diameter, which were coalescing. However, no cavitation was described. Unfortunately, the short course of the TB disease of all infected monkeys, before their necropsy, did not allow us to know the timing of disease progression [26].

Microbiology

Microbiology testing shows that Mtb and other pathogenic mycobacteria grow very slow. Doubling times of 24-96 hours have been reported for Mtb, and this is in striking contrast for example with *Escherichia coli (E. coli)*, which has a doubling time as low as 20 minutes = 1/288 of Mtb doubling time [27]. By analogy, assuming the *E. coli* timing from infection to pneumonia is about 2 days [28], the analogous timing for Mtb would be 2 days x 288 = 576 days = about 17 months.

Mathematical simulations

Based on mathematical simulations, bacterial levels in the lung during active TB keep growing up to 104 by the end of the 7th month. After this time, Mtb continues its replication up to 107 by the end of 13th month then its growing lasts for a further 600 days [22].

Definitions

The granuloma, hallmark of TB infection, is: "*a highly organized structure consisting of many immune cell types (e.g. macrophages, neutrophils, natural killer cells and T- and B-cells) that surround a caseous necrotic core of Mtb-infected alveolar macrophages. The granuloma is traditionally thought to be host-protective by sequestering and preventing dissemination of Mtb proliferation and spread*" [29].

The pulmonary cavitation, hallmark of TB disease, is: "*a process by which normal pulmonary tissue is obliterated, becoming gas-filled spaces or cavities in the lung. This process initially involves caseous necrosis of lipid pneumonia lesions, producing caseous pneumonia. During caseation, alveolar cells and septa are destroyed along with neighbouring vessels and bronchi. Cavities form when these regions of caseous pneumonia liquefy, fragment and are released upon coughing*" [29].

Hypotheses on granuloma and cavity formation

Granuloma formation

The results of *in vitro* experiments and data from animal and mathematical models suggested that inhaled mycobacteria are first phagocytosed by resting (i.e. inactivated) alveolar macrophages which are unable to clear them because Mtb has evolved mechanisms for evading killing by its host macrophages. Thus, the maturation of the mycobacterial phagosome is blocked, Mtb replicates in an intracellular niche within macrophages, so evading detection by humoral immunity, with a doubling time of 24/96 hours [30]. At this point, macrophages, which are now defined "infected", start producing and secreting antimicrobial peptides, cytokines (like tumor necrosis factor (TNF)-α,

interleukin (IL)-1β, IL-12, and IL-6) and chemokines, able to create, all around the site, a gravitational field that direct other cells, particularly T lymphocytes, to areas of greater cytokines concentration so leading to the formation of granuloma. The concentration gradient of cytokines is not achieved correctly if macrophages do not secrete TNF-α. When the bacteria inside the macrophage reach the number of 20, the macrophage can explode, and the escaping bacteria are taken up by other alveolar macrophages and by dendritic cells. Dendritic cells are mobile cells whose task is to migrate to the nearest lymph nodes where they present Mtb antigens to the T naïve cells so transforming them in activated CD4+ which produce cytokines, principally interferon-γ (IFN-γ), the main activator of macrophages, that in conjunction with TNF-α and IL-12 drive the host immune responses into Th1 polarization. At this point, Mantoux test is still negative. Mathematical models had showed that, in the granuloma formation, the fastest process is diffusion of chemokine, then T cell movement (2 μm/min) and macrophage movement (1 μm/min) [30]. It means that T cell speed should be about 0.12 mm/hour, that is 2.88 mm/die. For this reason, Mtb specific T-cells can reach the lung only 14-21 days after the infection starts [31] depending on how far the nearest lymph nodes are from the site of granuloma formation. Production of TNFα and IFN-γ by T-CD4+ stimulates killing activities by macrophages. T-cells complete granuloma formation by forming the lymphocytic cuff surrounding it [32]. Only after their arrival to the parenchyma the Mantoux test become positive. Once formed, the granuloma contains the mycobacteria and prevents spreading, but at the same time serves as a site of replication and persistence for Mtb [33]. In non-human primates, the typical time frame for the entire process of the development of a granuloma is from 14 to 100 days [30].

Cavity formation

Mtb generally has the highest prevalence of cavities among people with pulmonary disease of any infection [34]. The established paradigm of cavity formation was developed by Dannenberg in the late 20th century. He considered the caseating granuloma as the characteristic TB lesion which encounters liquefactive necrosis, leaving behind a cavity during active disease. However, this paradigm principally derives from classical experiments in the rabbit model of *Mycobacterium bovis* infection, in which large tubercles develop and then rupture into the airways [35]. Hunter, instead, pointed out that pre-antibiotic era researchers had documented that all human Mtb granulomas, once formed, did not undergo erosion and necrosis and that human studies had suggested that cavities originate, rather, from lipid pneumonia. After he directly examined the slides from autopsies of adults who died of untreated pulmonary TB during the preantibiotic era, he developed a different paradigm according to which, during the post primary TB, the lesions progress as an endogenous lipid pneumonia, not as a caseating granuloma, that undergo caseous necrosis whose necrotic tissue may either soften, fissure and coughed up leaving a cavity or harden producing fibrocaseous TB [36,37].

Although the precise immune mechanisms underlying cavities formation are not fully understood, normal immunity should play a significant role. In fact, as underlined above, humans suffering from AIDS develop cavities when their CD4 count is > 350 cells/μl while they usually do not when their CD4 count is < 200 cells/μl [15]; reports about cases presenting the tuberculosis-associated Immune Reconstitution Inflammatory Syndrome (IRIS) have described patients with advanced HIV/TB and minimal initial radiographic lung involvement who develop massive pulmonary infiltrates or lung cavitations after the Antiretroviral Therapy (ART) had restored their immunity [38] (the IRIS typically occurs within the first few weeks and up to 3 months after ART is initiated). Nevertheless, diverse autoimmune phenomena occur in human TB (for example, autoantibodies are detected in 40% of TB patients); erythema nodosum occurs in TB and autoimmune diseases; sarcoidosis, an autoimmune disease, resembles TB (their histologies characterized by well-organized granulomas formed from activated macrophages are similar, also the location of lesions in the upper lobes and the tendency to affect other organs are similar). Based on the above-mentioned characteristics of HIV/TB coinfection and similarities between autommunity and TB, Elkington, in 2016, has hypothesized that the cavity could be the result of an autoimmune inflammation due to inappropriate host responses to self-antigens induced by mycobacteria [39].

Case study

Here we report the precise timing from infection to parenchymal disease and cavitation in an untreated immunocompetent adult patient. Between August 2009 and May 2010, a 36-year-old Italian man with a 15-pack year smoking history had daily contacts at work with an unknown case of pulmonary TB, a 25-year-old man from Romania [40]. Of note, in February 2009, the 36-year-old man had undergone a routine Mantoux test, which was negative. In August 2010, the 25-year-old

Romanian man was diagnosed with active TB, therefore the Italian man underwent again a Mantoux test, which was positive, Ø = 22 mm. His chest X-ray showed a 5 mm irregular nodule in the right upper lobe without hilar enlargement (Fig. 2). Due to the complete lack of symptoms, and contrary to what had been previously agreed upon, he decided not to undergo a chest CT and medical surveillance. Ten months later, in June 2011, he was referred to the Urology Unit due to a twisting of his spermatic cord. A routine chest X-ray described "nodular opacities in the right upper lobe" (Fig. 3). Despite this finding, once the testicular torsion was solved the patient was discharged and no further investigation was suggested.

In March 2012, nineteen months after the initial chest X-ray, the patient was admitted to our Respiratory Unit due to persistent fever, cough, night sweats and progressive weight loss that had been evolving over several weeks.

Physical examination revealed a skinny and suffering man but was otherwise unremarkable. The chest X-ray revealed bilateral infiltrates with several cavitary lesions suggestive of active TB (Fig. 4).

CT of the chest revealed pulmonary consolidations with cavities and a "tree-in-bud pattern" (Fig. 5).

Smear microscopy was positive for Acid-Fast Bacilli (AFB), while the culture on Lowenstein-Jensen medium and the drug susceptibility test identified a mycobacterium

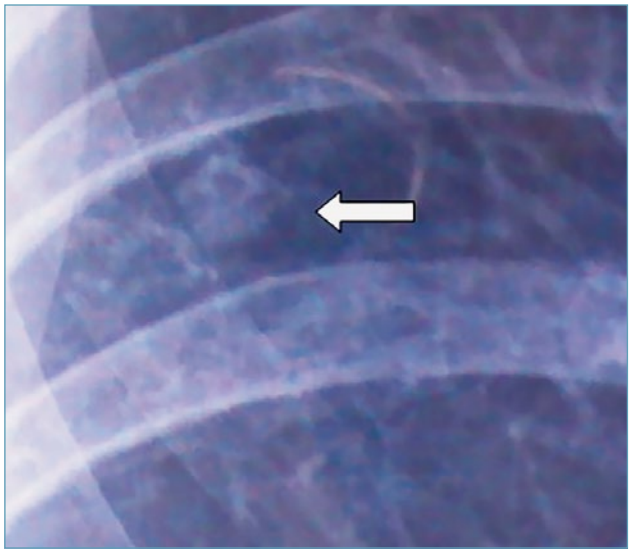

Figure 2. Chest X-ray showing a 5 mm irregular nodule in the right upper lobe.

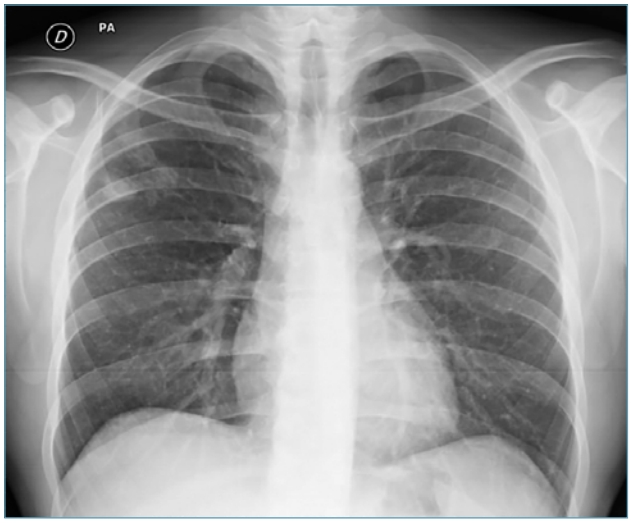

Figure 3. Chest X-ray showing nodular opacities in the right upper lobe.

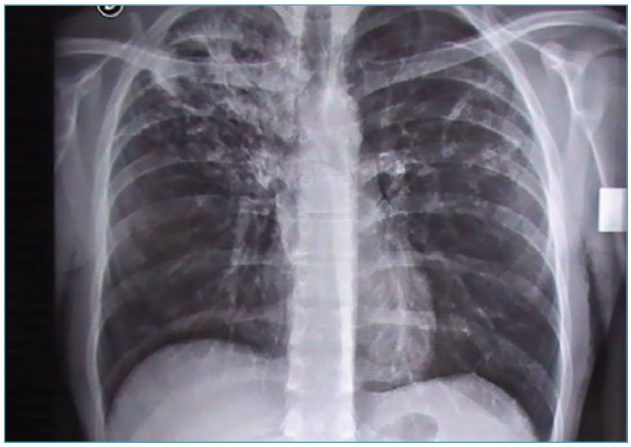

Figure 4. Chest X-ray showing bilateral infiltrates with several cavitary lesions suggestive of active tuberculosis.

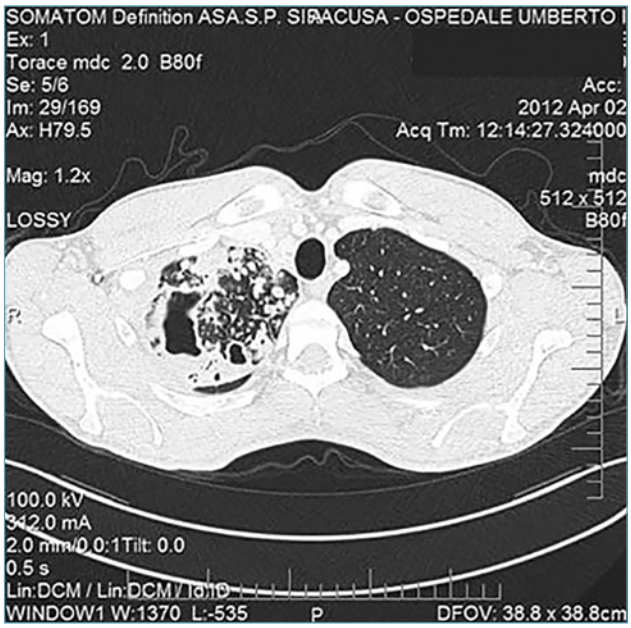

Figure 5. CT of the chest revealed pulmonary consolidations with cavities and a "tree-in-bud pattern".

tuberculosis complex sensitive to all first line drugs. HIV test was negative.

Discussion

TB infection is usually asymptomatic [11]. Some patients develop concomitant symptoms, such as erythema nodosum in the lower limbs and phlyctenulosis, but the majority of them do not. The Ghon focus, the initial TB lesion, is generally not detectable on the chest X-ray as it often resolves spontaneously. Sometimes, the Ghon focus may be easily identified radiographically when calcified [41].

TB disease occurs predominantly as a reactivation of a Latent TB Infection. In addition, patients with TB are usually pauci- or asymptomatic. Accordingly, the infectiousness of asymptomatic patients may persist for months before they are eventually diagnosed, and their contacts checked for the risk of infection [42]. Therefore, it is crucial that doctors involved in the diagnosis and care of TB patients are aware of the highly variable timing from infection to parenchymal disease and cavitation.

According to historical and microbiological studies and mathematical simulations, the estimate "TB timing" ranges, from several months to 1-2 years or more. Hunter has hypothesized that mycobacteria need a time of 1 to 2 years to asymptomatically obstruct bronchioles to physically isolate a lobule of lung and then accumulate within its alveoli mycobacterial antigens and host lipids in preparation for a sudden necrotizing reaction to produce a cavity of sufficient size to mediate transmission of infection to new hosts [43]. At the TC examination, this obstructive lobular pneumonia is visible as a characteristic centrilobular tree-in-bud [44] which has histopathologically interpreted as a result of obstruction of the terminal or respiratory bronchioles where the "buds" are foci of pneumonia in the alveoli of the obstructed ducts [45]. Similarly, in our TB patient the timing from evolutive Ghon focus to symptomatic pulmonary disease was approximately nineteen months, thus confirming a recent TB timing model [46]. We believe that our patient was infected by his work colleague because he had no previous evidence of infection and other possible sources of infection were reasonably excluded. Indeed, he lived in a low-endemic setting.

After the infection, the patient became the index case of a new infection/disease chain. In fact, the Mantoux tests of several of his family members turned out to be positive, while his 2-year-old daughter and his 4-year-old nephew had also radiographic evidence of active disease (hilar enlargement and pulmonary consolidation accompanied by AFB positivity, respectively). The aforementioned mathematical model estimates TB infectiousness as zero at the start of the active period, increasing thereafter as a linear function of time for the first nine months of disease (i.e., as bacillary burden grows), and stable thereafter at the maximum level until the individual is diagnosed and treated, or dies. Therefore, according to this model, our patient's 2-year-old daughter and 4-year-old nephew might have been infected when the patient was asymptomatic and before he developed lung cavitation.

Conclusions

Our case report suggests that 1) the period during which pulmonary TB evolves from the Ghon focus to pulmonary consolidation/cavitation may exceed 12-18 months; 2) young children are at a high risk of rapid progression from infection to disease; and 3) doctor's specific education and training in fighting TB needs to improve substantially.

Many obstacles still weighed heavily upon TB monitoring and management. Indeed, the 1st edition of the Estates General of Tuberculosis, held in 2011 in the Senate of Italian Republic, stated that the first critical issue in tuberculosis control is the "lack of preparation of doctors in terms of the disease itself, which has been removed from medical school for years" [47].

Strict contact tracing and use of preventive chemotherapy are important ways to reduce TB-related suffering of contacts, thus avoiding the seed of the epidemic for the next generation.

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