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Review

Inactive Fibrotic Lesions Versus Pulmonary Tuberculosis With Negative Bacteriology☆

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ABSTRACT

This article analyzes the concept of inactive fibrotic lesions of presumed tuberculous origin (old healed tuberculosis), defined by radiological characteristics and a positive tuberculin skin test (TST), and we examine the evidence-based foundation for the indication of treatment of latent tuberculosis infection in these cases. We explore the risk of reactivation in older and recent literature, and the problems raised by the differential diagnosis with active tuberculosis with negative bacteriology. We also analyze data on the prevalence of fibrotic lesions in the recent literature. We examine the possible role of Interferon Gamma Release Assays (IGRAs) versus TST and other molecular antigen detection techniques in sputum that can aid in establishing the diagnosis and we discuss the current indications for chemoprophylaxis and the different options available. We propose diagnostic guidelines and therapeutic algorithms based on risk stratification by age and other factors in the management of radiological lesions that raise a differential diagnosis between fibrotic lesions and active pulmonary tuberculosis with negative bacteriology.

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Lesiones fibróticas inactivas versus tuberculosis pulmonar con bacteriología negativa

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RESUMEN

El presente artículo analiza el concepto de lesiones fibróticas inactivas de presumible origen tuberculoso *(old healed tuberculosis)*, su definición por sus características radiológicas y la presencia de prueba de la tuberculina (TST) positiva. Se revisa el fundamento basado en la evidencia de la indicación de tratamiento de infección tuberculosa latente en estos casos, el riesgo de reactivación en la literatura antigua y reciente, así como los problemas que plantea el diagnóstico diferencial con la tuberculosis activa con bacteriología negativa. Se consideran los datos sobre prevalencia de lesiones fibróticas en la literatura reciente. Se analiza el posible papel de las técnicas de *Interferon Gamma Release Assay* (IGRA) versus TST, así como otras técnicas moleculares de detección antigénica en esputo que pueden ayudar a hacer el diagnóstico. Se analizan las actuales indicaciones de quimioprofilaxis, las diferentes opciones y se proponen algoritmos diagnósticos y terapéuticos basados en la estratificación del riesgo según la edad y otros factores, para manejar las lesiones radiológicas que plantean diagnóstico diferencial entre lesión fibrótica inactiva y tuberculosis pulmonar con bacteriología negativa.

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Introduction

Fibrotic lesions or scars, also known as old healed tuberculosis, are a common finding on chest X-rays and are universally accepted as an indication for treatment of latent tuberculous infection (TLTI).[1,2] However, little information is available in the recent literature on the statistics of TLTI in fibrotic lesions, and references generally cite the major studies performed in the 1970s[3,4] and

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publications from the International Union against Tuberculosis (IUAT)[5] and Styblo et al.,[6] dating from the 1980s.

Fibrotic scars are defined as lesions on chest X-ray larger than 5 mm suggestive of old untreated pulmonary tuberculosis (PT) in patients without a previous diagnosis of PT. They are generally described as "well-defined" or "radiologically dense", and consist of nodules, fibrosis-like linear images with or without retraction and bronchiectasis in the upper lobes and with no evidence of alveolar component and/or cavitations. Calcified primary complex, localized pleural thickening and/or isolated lateral costophrenic angle blunting have also been described, but these may be considered less significant and are excluded from some definitions.[7,8]

Most authors require a transverse induration on tuberculin skin testing (TST) of at least 5 mm for the diagnosis of fibrotic lesions,[1,5] although neither TST nor Interferon Gamma Release Assay (IGRA) is 100% sensitive.[9] In our setting, up to 23% of the cases with negative TST have had PT confirmed with positive smear or culture (13% in the population with no risk factors, 60% in the HIV-infected population).[10]

Stable radiological findings over a period of 1 year were required as a criterion for diagnosis by the IUAT in 1982,[5] although the American Thoracic Society (ATS) declared in 2003 that 3 months' stability on X-ray was sufficient if sputum cultures were negative and there were no clinical symptoms.[11]

Images suggestive of PT on X-ray, whether known and/or treated, are not considered fibrotic lesions but rather "post-PT sequelae", although at times no distinction is made between the two concepts,[6,12] which can lead to some confusion.

Fibrotic lesions are important for 3 reasons:

(1) There is a risk of reactivation PT in the future.
(2) Misdiagnosis of fibrotic lesions can mask smear-negative active PT, and there is a risk of starting single-agent TLTI that may lead to acquired resistance or failure to treat. Conversely, misdiagnosis of fibrotic lesions as active PT may lead to the administration of unnecessary and potentially toxic medications.
(3) Fibrotic lesions on X-rays are not always indicative of tuberculosis (TB) and may be confounded with other unrelated disease entities that may present with the same radiological patterns.

These 3 points are discussed below.

Risk of Reactivation of Fibrotic Lesions

In the IUAT study published in 1982 with 28 000 participants over a 5-year follow-up, the annual risk of reactivation of TB was 0.286%, subdivided into 0.232% and 0.426% depending on whether lesions were smaller or larger than 2 cm,[2] respectively, on chest X-ray.[5] In Rotterdam in 1984, Styblo et al.[6] found an annual reactivation rate of 0.103% in 2895 fibrotic lesions monitored for 3 years. In USA reports from the 1970s, annual reactivation rates as high as 0.9% were recorded in a 5-year follow-up of 1992 cases.[4] In 2004, Horsburgh[13] published a metaanalysis of cohort studies performed in the USA between 1949 and 2003, stratifying the reactivation risk of subjects with positive TST. In old healed tuberculosis, he found a lifetime risk ranging from 66% in patients under 5 years of age with TST of 15 mm or over, to 6% in patients over the age of 65 with TST between 5 and 9 mm. The same author subsequently analyzed the reactivation rates of latent tuberculosis infection (LTI) in the USA, based on cases of PT confirmed by smear or culture not included in molecular clustering studies (cases attributed to endogenous reactivation and not recent transmission). He concluded that reactivation rates had fallen due to the almost total disappearance of fibrotic lesions in the USA-born population.[14]

No direct data on the current prevalence of fibrotic lesions in Spain are available. The results of widespread X-ray campaigns for the eradication of TB carried out between 1965 and 1973, revealing a prevalence of 5% in the general population,[7] are no longer applicable, given the obvious improvement in the epidemiological situation since that time. However, it seems that prevalence may be as high as 13.8% among groups of poverty-stricken individuals and others that rely on social services.[15] There are no systematic worldwide data on the country-specific prevalence of fibrotic lesions in the general population; available data are partial and derived from population reviews. For example, the radiological screening of 13 379 Ethiopian immigrants in Israel found 257 (1.9%) patients with fibrotic lesions, of whom 15 (5.8%) developed active PT within one year.[16] In an Indian study of 726 healthcare workers, 334 TST- and/or IGRA-positive subjects underwent radiological screening; 169 (23.2%) had calcified nodules and 37 (5%) had other lesions consistent with fibrotic scarring.[12] These high rates are likely to be associated with the epidemiological situation in those countries, since the available partial data suggest that fibrotic lesions are more prevalent in areas with a high endemic presence of TB.

The risk of reactivation of fibrotic lesions depends on a series of factors, these being:

(1) The maturity of the lesions: according to the IUAT study,[5] the risk in the untreated placebo group fell progressively over 5 years of follow-up compared to the first year.
(2) The lifetime risk of reactivation of fibrotic lesions diminishes significantly with age.[13] Lesions are more likely to be old in the elderly, and given their reduced life expectancy there is less likelihood of reactivation. Conversely, in young subjects, lesions are more probably recent and this, along with longer life expectancy, leads to a higher risk of reactivation. In children, the concept of fibrotic scarring is complicated, since lesions can be presumed not to be old, and with the exception of some very specific cases, they should be diagnosed as active PT and treated accordingly.
(3) TST induration diameter is correlated with a greater risk of reactivation, particularly if it is larger than 15 mm.[13]
(4) If conversion is recent and there is no old radiological evidence, the chances of the images corresponding to active PT are higher; however, conversion is an independent risk factor in itself.[13,17,18]
(5) The more extensive the scarring, the greater the bacillary load of the initial tuberculosis. The surface of the lesions on X-ray and the risk of reactivation are also statistically correlated.[5] Lesions with cavitation, non-calcified adenopathies and/or pleural effusion should not be assumed to be fibrotic, even if smear or culture results are negative, as there is a strong possibility that they indicate active tuberculosis.
(6) Recent contact is a predictor of increased risk for active PT, irrespective of the presence or absence of fibrotic lesions on chest X-ray.[13,17,18]
(7) HIV infection is one of the most important immunosuppressive factors for the development of PT.[2] Others (transplantation, corticosteroid treatment, anticancer chemotherapy, diabetes, etc.) may also be highly significant from a clinical point of view. After HIV infection, anti-TNF treatment is the most significant risk factor for LTI reactivation and may be associated with forms of disseminated tuberculosis.[19] Post-transplantation immunosuppression is a major clinical concern in view of the high morbidity and mortality of TB in graft recipients. According to some guidelines, untreated fibrotic lesions in a donor lung could be a contraindication for transplantation.[20]

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