Perspective

Lung cancer screening and prevention in a still endemic region for granulomatous disease: Brazil

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Abstract: The aim of this article is to give a perspective on how to perform lung cancer screening in places with high incidence of granulomatous diseases (GDs). Regarding improvements in diagnosis and treatments, TB remains one of the major health problems to be faced in Brazil and worldwide. The aspect of the primary complex is the same as that of the indeterminate pulmonary nodule, which may increase the rate of "positive" findings during a screening program. The multidisciplinary team is able to differentiate such nodules from those with greater suspicion, especially when analyzing the whole set of computed tomography (CT) findings associated with the "positive" pulmonary nodule. Considering the lung cancer importance in the depicted epidemiological profile, primary and secondary prevention are fundamental to change the actual scenario. For secondary prevention, periodic lung cancer screening may be useful. In Brazil, there are major concerns that in heavy smokers many benign nodules might be found secondary to GD, leading to unnecessary diagnostic testing and surgical intervention. It is important to emphasize that low-dose CT (LDCT) examinations performed in people from regions with high prevalence of GD may be interpreted by radiologists with experience seeing its most common findings, such as scars at the apex of the lungs, presence of pleural thickening and occurrence of multiple micro nodules. In the experience of our group, with the accomplishment of LDCT screening in about 800 asymptomatic individuals, active tuberculosis (TB) was diagnosed in only three cases, where the radiological suspicion aroused in the absence of significant symptoms. In this scenario, it seems to be feasible to engage asymptomatic high-risk persons for cancer screening in large-scale programs within areas with high prevalence of GDs. Benefits of case-finding in both circumstances of benign transmission able disease or lethal cancer type outweigh most of the harms encountered.

Keywords: Lung cancer; screening; prevention; granulomatous disease (GD)

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Introduction

The main goal of early disease detection is simple, but extremely important. A program of primary cancer prevention aims to protect individuals from the disease by eliminating risk factors such as smoking, obesity or environmental toxins. Meanwhile, an early detection process, also called secondary prevention, is designed to discover and cure diseases at asymptomatic, subclinical stages (1). As a secondary prevention tool, lung computed tomography (CT) screening has been proved a significant asset for decreasing cancer mortality in the United States and it is being used in many other countries (2).

During the last decade, increased availability of low-dose CT (LDCT) has facilitated interest in lung cancer screening worldwide (3). Many regions in the world, including Latin America, are shifting the epidemiology scenario from infectious diseases to chronic conditions, turning cancer their number one population killer.

The proportion of new cancer cases diagnosed in less

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developed countries, including some countries in Latin America, is projected to increase to more than 60% of the world total during this decade. This is especially due to the increasing trends in cancer rates and expected increases in life expectancy (4-6).

Nevertheless, some of these countries still face health problems with infectious lung diseases. Despite advances in diagnosis, prevention methods and greater understanding of treatment failure reasons, tuberculosis (TB) remains common throughout Latin America (7)

These unique characteristics of Latin America patients certainly affect the diagnostic evaluation of pulmonary nodules. However, the great majority of the studies on screening for lung cancer are from countries where the incidence of TB is minimal, with less than ten cases per hundred thousand inhabitants (8,9).

The aim of this article is to give a perspective on how to perform lung cancer screening in places with high incidence of granulomatous diseases (GDs).

GD (TB) in Brazil

Regarding the improvements in diagnosis and treatments, TB remains one of the major health problems to be faced in Brazil and worldwide. According to the World Health Organization (WHO), Brazil is among the 30 countries of the world with the worst situation of TB and TB/human immunodeficiency virus (HIV) cases. In 2015, more than 81,000 TB cases were notified, resulting in an incidence rate of 41 per 100,000 inhabitants. Additionally, the underreporting rate is estimated to be 13%.

TB is caused by lung contamination with small aerobic non-motile bacillus which are transmitted by 1–5 μm diameter droplets, but not all individuals exposed to TB will get infected. In approximately 90% contaminated individuals, the infection only presents at subclinical level, or becoming a latent infection. These individuals are asymptomatic and noncontagious, but they could present radiographic signs of stable fibronodular changes, such as nodular opacities in the apical and upper lung zones, partially calcified granulomas or enlarged mediastinal lymph nodes (10,11).

However, the findings of previous TB infection are extremely variable and can mimic several other infectious or inflammatory diseases, with local or diffuse pattern. Currently, two major frameworks exist around the discussion of the role of the granuloma in TB pathogenesis and treatment. The granuloma is either considered a critical component of the protective cellular immune response, serving a vital role in pathogen containment, or is considered detrimental, contributing to the clinical manifestations of active TB disease and persistence of *Mycobacterium tuberculosis* (Mtb) (12).

The aspect of the primary complex in early stages is exactly the same as that of the indeterminate pulmonary nodule (13). In regions with a high prevalence of histoplasmosis, such as the "histoplasma belt", the occurrence of the pulmonary nodule may also increase the rate of "positive" findings during a screening program.

The multidisciplinary team trained in such regions is generally able to differentiate such nodules from those with greater suspicion, especially when analyzing the set of CT findings associated with the pulmonary nodule under analysis.

The local guidelines for the diagnosis of TB include the investigation of individuals with history of suggestive symptoms, positive epidemiology (including those exposed to the bacillus in the family environment) or vulnerable populations such as imprisoned people or HIV patients (14).

In suspected TB cases, there is recommendation for image testing, sensitivity skin tests (PPD), sputum examination and/or collection of polymerase chain reaction (PCR) or adenosine deaminase (ADA) from body fluids. Active search or screening is not recommended on asymptomatic individuals.

The workup of patients with high suspicion of TB should be made in accordance with the precepts currently established by the WHO (15). The definitive diagnosis of TB occurs by identifying the Mtb into a biological sample through smear microscopy, culture or molecular methods. The samples generally referred for Mtb searching are sputum, bronchial lavage, bronchoalveolar lavage (BAL) and other respiratory tract related fluids. Blood, biochemical and radiological examinations can aid in diagnosis by directing the physician to more specific tests (16,17).

In patients who cannot spontaneously emit sputum it may be necessary to use induction by inhaling hypertonic saline solution, bronchofibroscopy (BFC) with bronchial lavage LB and BAL, collection of sputum after BFC and to the performance of gastric aspirate (18).

Smoking and primary prevention

The number of current smokers in Brazil has been showing a significant drop in the last decades due to countless actions developed based on the National Tobacco Control

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Policy. In 1989, an estimated 35% of the population over 18 years old were composed by current smokers. An expressive reduction in these numbers was observed by the year of 2003, when the percentage was 22.4%. A subsequent decrease was observed in 2008 and 2013 with 18.5% and 14.7% respective rates. The most recent data, from 2016, shows a total percentage of current smokers aged 18 years old or more in Brazil as 10.2%; 12.7% among men and 8.0% among women. This percentage corresponds to more than 14 million Brazilian citizens. Furthermore, about 26 million people are former smokers, who still exhibit elevated risk compared to never smokers as this risk never returns to baseline (19-21).

Therefore, despite the relative decrease of current smokers in the population, millions continue to smoke and thus are at a higher risk for lung cancer and other tobacco related diseases. Data from WHO indicated that in 2004 around 16% of all deaths of people aged 30 or older could be related to tobacco use in the Americas (22).

Lung cancer numbers and stage presentation

The overall estimate for 2015 was >500,000 new cancer cases in Brazil. Lung cancer is the most common cause of cancer death worldwide and second most common in both genders in Brazil, following breast and prostate casualties. In 2016, data from the Brazilian National Cancer Institute (INCA) estimated 17,330 new cases of lung cancer among men and 10,890 new cases among women (23).

The diagnosis of lung cancer is often at advanced stage, since patients may be asymptomatic with early stage lung cancer, and up to 60% of patients have local advanced or metastatic disease at the time of diagnosis. Stage I or II NSCLC is diagnosed in less than 15% of patients in most public or private institutions (24).

Survival is closely associated with staging at the time of diagnosis, with a 5-year survival of only 6% for patients with distant disease presented on initial diagnosis, compared with 85% for patients with stage IA disease (25).

Considering the lung cancer importance in the depicted epidemiological profile, which is similar to many other regions in the world, primary and secondary prevention are fundamental to change the actual scenario.

Lung cancer screening

For secondary prevention of lung cancer, periodic lung cancer screening may be useful. Notably, the National Lung Cancer Screening Trial (NLST) demonstrated a 20% reduction in mortality with LDCT screening, and guidelines now endorse annual LDCT for those at increased risk (9). However, despite the very significant findings of the NLST, lung cancer screening is still under considerable discussion in Europe and it is also not well structured in Latin America and other under developing countries.

There are major concerns that in heavy smoker populations, living or borne in areas with high incidence of GD, many benign nodules might be found, leading to unnecessary diagnostic testing and surgical intervention (26). Furthermore, given income inequalities and the weak health infrastructure of developing countries, often options are indeed limited. Alternatively, local initiatives are emerging to promote changes within the private and public health systems, aiming to provide better quality of care and enhanced access to primary and secondary prevention on the topic of lung cancer.

In this scenario, the first Brazilian early lung cancer detection program (BRELT1) was the first program for lung cancer screening in a Latin America country, launched in in 2013, with the goal of recruiting one thousand persons at high risk for lung cancer for LDCT screening. The inclusion and exclusion criteria were based on NLST trial (9) and the management of CT findings was based on the NCCN Guidelines Lung Cancer Screening (27) and the Fleischer Society (28).

Proper planning, from the definition of the objectives of the program, led to the targeting of actions, setting parameters for performance analysis of the organizational structure, identification of critical points, stimulation of multidisciplinary and interdisciplinary performance and better utilization of physical, technological and human resources.

Lung cancer, despite being one of the most lethal tumors, until recently lacked a clear mandate to conduct population screening. So, to implement such a program, a significant change in organizational structure and local culture is required to engage high risk population and health organizations. The medical community should be well informed of the potential risks and benefits of lung cancer screening to serve as advocates and ambassadors of prevention programs. Studies have been conducted to better understand the relationship between smoking cessation programs and cancer screening; however, it is important that primary prevention should be associated with early detection programs.

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Analysis of the suspect pulmonary node

The current pulmonary nodule analysis algorithms take into account size, location, presence of spicules, pulmonary emphysema and patient risk factors. In screening programs, all individuals are part of a high-risk group for pulmonary neoplasia, and the Lung RADSTM classification is the most commonly applied (29).

The findings related to benign disease, such as calcification or other chronic sequelae, help defining the Lung RADSTM classification, allowing its decrease on specific cases. Cases classified as Lung RADSTM 4 by an experienced radiologic team would complement investigation with PET-CT or biopsy or be accompanied with LDCT in shorter than 1-year period.

It is important to emphasize that LDCT examinations performed in people from regions with a high prevalence of GD may be interpreted by radiologists with experience seeing the most common findings in these regions, such as scars at the apex of the lungs, presence of pleural thickening and occurrence of multiple micro nodules. It is important to note that these findings do not exclude the possibility of lung cancer concomitantly or into other pulmonary parenchyma regions altered by TB.

In the experience of our group, with the accomplishment of LDCT in about 800 asymptomatic individuals, active TB was diagnosed in only three cases, where the radiological suspicion aroused in the absence of significant symptoms (30).

LDCT screening is not recommended for the searching of active TB cases, so cases with suggestive symptoms should be investigated outside structured screening programs, or they should be tagged when entered the program with remarkable respiratory symptoms (fever, cough, hemoptysis, night sweats, etc.)

The follow-up of patients with findings compatible with previous TB infection represents an additional challenge to the screening program, since such findings could be accompanied for longer time under the false premise of being benign scars, delaying the approach of malignant cases.

Conclusions

One of the greatest challenges of modern medicine, with the growing demand for high-cost technology, is finding ways to provide the benefit to a greater number of persons without exponentially increasing costs.

In this scenario, it seems to be feasible to engage asymptomatic high-risk persons for cancer screening in large-scale programs within areas with high prevalence of GDs. Benefits of case-finding in both circumstances of benign transmission able disease or lethal cancer type outweigh most of the harms encountered.

Automation of services and provision of screening services with lower cost personnel (non-medical consultations, less frequent visits, etc.) may be feasible forms of population preventive healthcare in the future.

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Footnote

Conflicts of Interest: Ricardo Sales dos Santos: invited speaker of MSD, Brystol and Johnson & Johnson.

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