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Case Reports

Are there still other asbestos-related malignancies to be discovered?

Case-report of Mycosis fungoides in a patient with occupational asbestos exposure

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Abstract

Mycosis fungoides is one of the most common forms of cutaneous T-cell lymphoma. Its diagnosis is sometimes challenging and quite difficult for the physician, because its onset clinical appearance is similar to other skin diseases. Although there are a few hypotheses about mycosis fungoides' etiology, they aren't fully understood and still need confirmation. We report the case of a 68 years old patient diagnosed with mycosis fungoides, who has been exposed to asbestos fibers. This case is one of the few reported cases of association between asbestos and mycosis fungoides. There is no data exploring the causal relation between asbestos exposure and mycosis fungoides but common biological mechanisms could represent an argument. If occupational exposure to asbestos will be confirmed in larger studies, a new research-field of asbestos-related diseases needs to be opened.

Keywords: *mycosis fungoides, asbestos, immunity dysregulation*

Introduction

Mycosis fungoides, is one of the most common forms of cutaneous non-Hodgkin's T-cell lymphoma, first described by the French dermatologist Jean-Louis-Mark Alibert. It amounts to nearly 50 % of the total cutaneous lymphomas [1,2] and it affects patients aged between 55 and 60 years old and twice more men than women [3]. Clinically, it presents with a slow evolution, going through 4 stages: patch stage, plaque stage, tumor stage and visceral involvement stage [4]. It is the typical clinical evolution pattern, named "Alibert-Bazin syndrome" that defines mycosis fungoides according to the Classification WHO-EORTC [5]. In the early stages of the disease, the histopathology features show CD4+ T-cells infiltration and CD8+ reactive T-cells, in the presence of a dominant Th1 cytokine pattern: interferon gamma (IFγ), interleukins (IL): IL12 and IL-2. In more advanced stages it is followed by a gradual increase in CD4+ T-cells and a switch to Th-2 immune profile with production of proinflammatory cytokines: IL4, IL5, IL13 and IL10 both in peripheral blood and skin, thus the gradual loss of immune response through CD8 arm is being matched by the disease progression [6, 7]. The diagnosis of mycosis fungoides can be sometimes difficult because its clinical onset and histopathology features show minimal cutaneous

inflammation that needs to be differentiated from other skin lesions, such as psoriasis, atopic dermatitis or chronic eczema [2, 8]. Mycosis fungoides' etiology remains mostly unknown, although there are some theories involving the genetic component, the vitamin D deficiency, the viral exposure and the chronic antigenic stimulation. Mycosis fungoides has also been reported after organ transplantation and the mycosis fungoides' geographical distribution suggests that occupational exposure may play a role [9]. The results of a multicentered European case-control study between 1995 and 1997, on seven rare cancers, including mycosis fungoides, showed that some occupational factors were associated to the onset of mycosis fungoides. Workers in glass, paper and pulp industries, pottery, and ceramic factories carried the highest risk to develop mycosis fungoides [10]. The most associations were made with the following occupational exposures: aromatic hydrocarbons, hydrazine, halogenated hydrocarbons, formaldehyde and mustard gas [11, 12].

Over the last decades, there were studies suggesting a causal relation between asbestos exposure and the development of lympho-proliferative disorders [13] and a study published in USA highlighted development of mycosis fungoides' in two patients with prolonged exposure to asbestos [14].

We report the case of a patient with a 30 years history of occupational exposure to asbestos fibers who developed mycosis fungoides.

Clinical case

We present a case of a 68 years old woman, from an urban environment, non-smoker, retired at the age term. She worked in an asbestos-cement factory for 33 full years and was exposed to high levels asbestos fibers. The first admission of the patient in the Clinic of Occupational Diseases took place in 2013 for effort dyspnea, weather-changes dependent joint pains and cutaneous rash. On clinical examination, the patient presented on her abdominal area and thighs, brown patches with irregular outline and variable size, not painful, slightly itchy, some of them with a plaque aspect (Figure 1-3) . At that time, the patient had no lymphadenopathy or hepatosplenomegaly. A standard chest X-ray was performed which indicated bilateral basal reticulo-nodular micro opacities and bilateral latero-thoracic, anterior left and basal right pleural plaques. The radiological examination was completed with a thoracic computed tomography scan that confirmed the presence of interstitial fibrosis and bilateral pachypleuritis with parcel distribution. The Pneumoconiosis medical board established the diagnosis of Asbestosis (2t, hi according to ILO2011 Classification) and latero-thoracic bilateral pleural plaques. A skin biopsy was performed from one of the plaque lesions. The following elements were described: parakeratosis and intense spongiosis. The HP diagnostic established was: mycosis fungoides-poikiloderma atrophicans vascular-plaque stage. The treatment indications consisted of UVA phototherapy and topical corticosteroids.

On admission, the routine tests (blood cells count, liver and renal function, inflammatory markers) were normal. The abdominal and pelvis computer tomography performed scans were normal. Based on the patient's medical history, the skin lesions have developed 10 years ago, being initially located on her distal part of the body in patches. The lesions gradually evolved in size and extension developing into cutaneous plaques on certain areas. Until 2013, the patient used inconsistently topical corticosteroid ointments. On her last admission from March 2018, compared to previous admissions, the skin lesions had evolved to cover more than 20% of the body surface, their aspect consisting of slightly brown macules, moderately atrophic with regular outline and variable size, alternating with papules.We mention that between 2013 and 2018 the patient was given UVA phototherapy and she was treated with topical corticosteroids, simultaneously. A new dermatological exam, was performed and the following treatment was reinitiated: UVA-UVB phototherapy, topical corticosteroid ointment and a new treatment was added: oral retinoid, calcineurin inhibitors and skin moisturizers. The pulmonary lesions remained unchanged since the initial presentation (2013).

Discussion

We present the case of a patient diagnosed with mycosis fungoides with a 33 years history of asbestos exposure and documented asbestosis. In comparison with other reported cases, the malignant disorder was independent of other malignant diseases induced by asbestos. Proven the carcinogenicity of asbestos, we considered that exposure to asbestos could be a cause that cannot be excluded.

We have started from the idea that the etiology of mycosis fungoides has largely remained unknown and that all the environmental factors have been proposed. There are studies suggesting that many patients with mycosis fungoides have a chemical

occupational exposure [10-12]. On the other hand, the carcinogenicity of asbestos exposure has been proven and all the asbestos varieties were classified as human carcinogens (group I) from IARC [15,16].

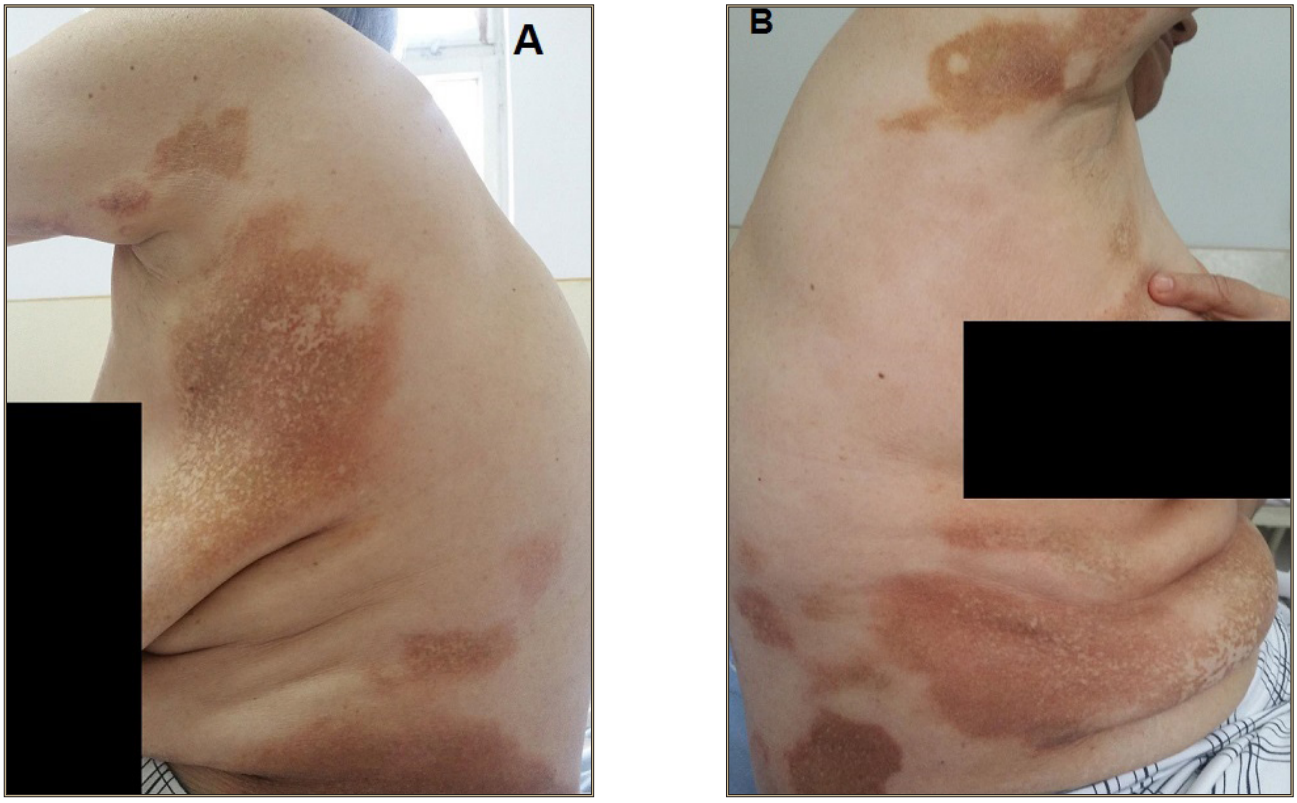

Figure 1. Mycosis fungoides on the lateral chest wall of the patient; A (left side), B (right side).

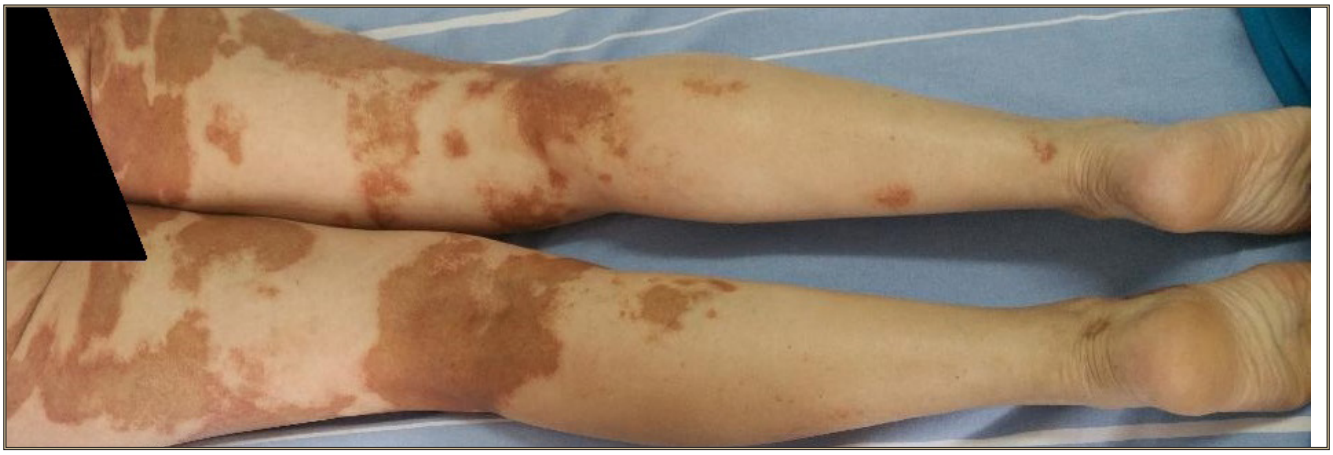

Figure 2. Posterior view of the lower limbs.

A relationship between asbestos exposure and lympho-proliferative disorders development has been suggested [17]. Asbestos is a generic name used for a naturally hydrated silica group of Mg, Fe, Na, Ca, and Al, characterized by a filamentous crystalline structure. There are 6 types of silica classified as asbestos which were divided according to their chemical composition and geological formation, in two mineralogical groups: serpentine mineral represented by chrysotile and amphiboles, where we included the following: crocidolite, amosite, actinolite, anthophyllite and tremolite [18, 19], that can penetrate into the organism through the respiratory, digestive and cutaneous pathways [18]. Although not all the mechanisms through which the asbestos induces toxic effects in the body were elucidated,

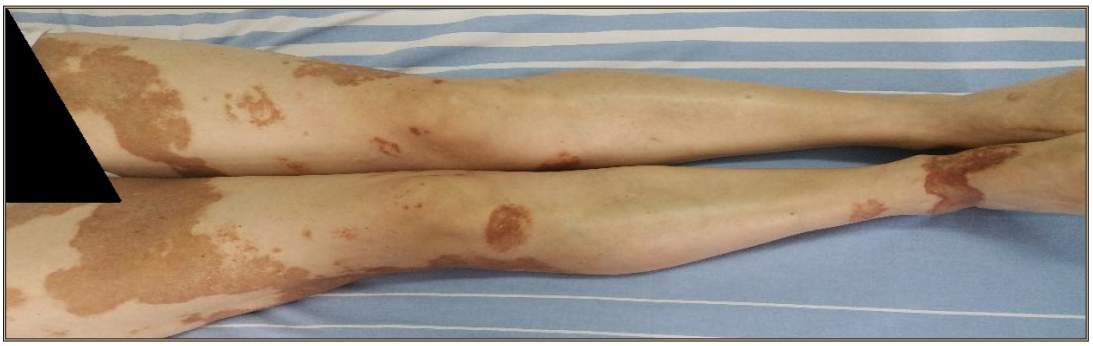

Figure 3. Anterior view of the lower limbs.

it is known that its biological effects are due to the direct interaction between asbestos and different body macromolecules (proteins, cell membrane lipids, DNA, RNA) or to the cytokine release mediated by the macrophages [18]. This interaction is considered to be part of the cytotoxic and genotoxic activities. Recent experimental studies revealed a certain role of asbestos exposure in immunological disregulation through a decrease in the normal antitumor activity, of the immunocompetent cells to kill tumoral cells. Asbestos exposure affects the NK cells, by down-regulating the activity receptors on the NK cells and decreasing the granzyme A and perforin levels, that lead to a decrease in tumor cells apoptosis. A decrease in suppressor T-cells' function (CD8) and in the cytotoxic cells differentiation, that affects the antitumor immune defense mechanisms has been proven [20-22]. The association between asbestos exposure and lymphoproliferative diseases has been previously reported [13, 23]. To the best of our knowledge, there are only two other cases of asbestos exposure and mycosis fungoides association reported in the literature. The ones reported in US by Chirinos and Geskin developed mesothelioma [14]. In our patient, asbestosis and mycosis fungoides were diagnosed on the first admission, but we don't have a clear documentation if one preceded the other.

Regarding the molecular pathogenesis of mycosis fungoides, many uncertainties are also present One hypothesis is that it arises from antigen-stimulated T memory helper cells, but the antigen remains unknown [24]. The antigen stimulation hypothesis suggests that mycosis fungoides could develop after a persistent chronic exogenous antigen stimulation. Chronic stimulation leads to the activation of T helper cells, followed by proinflammatory cytokines release and chronic inflammation, that will finally lead to a clonal malignant T-cell with continuous expansion [24, 25]. Impaired skin reactivity to antigens was also described from asbestos exposure [26], but, on the present experimental data, we cannot assign it to the MF development.

We are aware that a potential relation between cutaneous lympho-proliferative disorders and asbestos needs further epidemiological data gathering which is not an easy task since mycosis fungoides occurs only in 3.6-5.6 per million individuals [27].

Conclusion

Although there is not enough information regarding the asbestos exposure leading to mycosis fungoides development, by analyzing the asbestos effects and the pathogenic mechanism of MF, we cannot disregard that the chronic inflammation or the genomic interactions caused by asbestos exposure, and the advanced age (> 55 years) could lead to a lympho-proliferative disorder. Also, we cannot exclude the possibility that the disease could have developed independently. Therefore, we propose that amongst other risk factors the occupational exposure to asbestos should also be taken into consideration when interpreting the risk of developing mycosis fungoides.

A detailed occupational and non-occupational history of asbestos exposure in patients with mycosis fungoides could clarify the strengths of the association. In order to establish if there is an immunological dysregulation or a direct toxic effect of the asbestos exposure that could determine the mycosis fungoides development, additional investigations are required.

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