PARANEOPLASTIC ERYTHRODERMA IN A LUNG CANCER PATIENT

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Summary

Paraneoplastic syndromes are rare clinical findings affecting different parts of the body as a result of circulating substances synthetized by different tumors. Lung cancer can be accompanied by various paraneoplastic syndromes, including endocrine, neurologic, rheumatologic, hematologic and dermatologic syndromes. Cutaneous paraneoplastic syndromes are a category of skin diseases that can be related to an internal neoplasm. Erythroderma is characterized by a generalized redness of the skin, which can be caused by a range of conditions such as psoriasis, allergies, drug eruptions, but also systemic diseases like hematological malignancies and, rarely, solid tumors. We report on the case of an 80-year-old woman with a cutaneous paraneoplastic syndrome represented by erythroderma as a result of lung cancer.

Key words: *erythroderma, paraneoplastic syndromes, lung cancer*

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Introduction

Paraneoplastic disorders encompass signs and symptoms which appear as a result of damage to different organs caused by a remote malignancy.[1,2] Although these are not the clinical expression of metastases, they are connected to the primary disease and do follow the course of the malignancy, in a manner that the removal of the tumor will invariably lead to the healing of the paraneoplastic syndrome; however, a relapse of the cancer will be accompanied by the afore mentioned syndrome. The severity of these syndromes does not correspond to the tumor stage. Various tumors associate paraneoplastic syndromes not only through their ability to secrete substances rich in peptides, cytokines and hormones, but also through an immune cross-reaction between normal and tumoral cells. Tumors that most frequently associate paraneoplastic disorders include lung cancers, breast tumors, gynecologic malignancies and tumors of the hematopoietic and lymphoid tissues.[3]

It has been shown that about 2–20% of patients suffering from cancer are also affected by paraneoplastic syndromes, prevalence which is likely to increase since the life expectancy of these patients tends to be longer due to the continual improvement of diagnostic methods. These disorders can affect both genders regardless of race, with no predilection reported so far.[4] Paraneoplastic syndromes usually display later

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in life, the average age of onset being 66 years, with younger individuals rarely experiencing such effects.[5]

Clinical case

We report the case of an 80-year-old female patient from the urban area who addresses the dermatology department for a generalized erythematous eruption with a purplish-brown tint, accompanied by intense pruritus. The patient states that the lesions had first occurred 6 months prior to the presentation and that she had followed a treatment based on oral corticosteroids with a slight improvement of the eruption. However, when reducing the dose, the lesions returned to their initial intensity, which prompted her visit to the clinic. Family history was insignificant and previous medical history only revealed a hip replacement surgery.

Clinical examination revealed an erythematous purplish eruption with a generalized distribution, sparing the calves (*Fig 1, Fig 2*). The intensity was greater in the cleavage, posterior torso paravertebral and dorsal sides of the hands, with well-defined limits of the dorsal palmar junction. The eruption was accompanied by intense pruritus. On lung auscultation, a modified vesicular murmur could be detected. Moreover, the patient had developed dysphonia several months before presentation.

The blood analysis only showed a minimal increase in ESR while the biopsy revealed marked epidermal atrophy with pigmentation of the basal layer accompanied by moderate dermal oedema and a mild lymphocytic inflammatory cell infiltrate (*Fig 3, Fig 4*).

Since the eruption showed no further improvement under local and systemic corticotherapy and the skin biopsy ruled out both eczema and lymphoma, a paraneoplastic cause was suspected. The chest X-ray that was later performed showed an opacity in the posterior basal segment of the left lower lobe, bilateral opaque subclavicular micronodules and no pleural effusion (*Fig 5, Fig 6*). The patient was referred for a pulmonary consultation and at the pulmonologist's recommendation a CT scan was then executed.

The subsequent CT scan revealed a nodular process that occupied the area inferior to the left oblique fissure. The process had spikes in its contour along with an intensely irregular shape

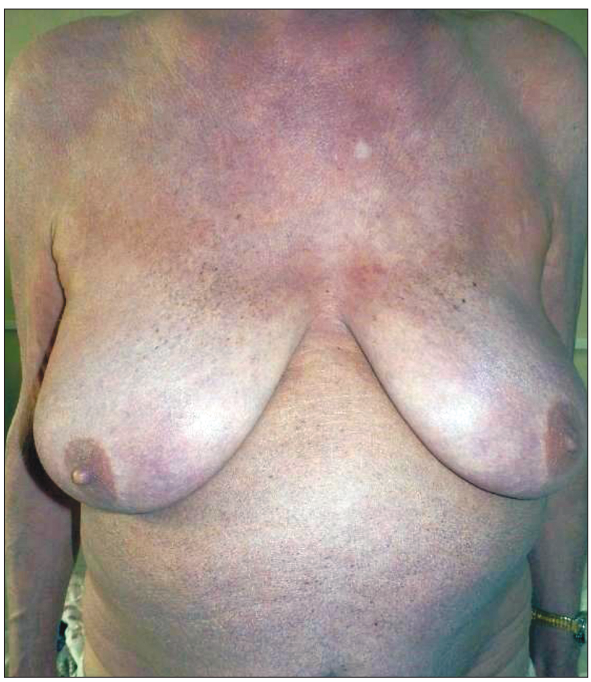

Fig. 1. Clinical aspect. Erythematous eruption

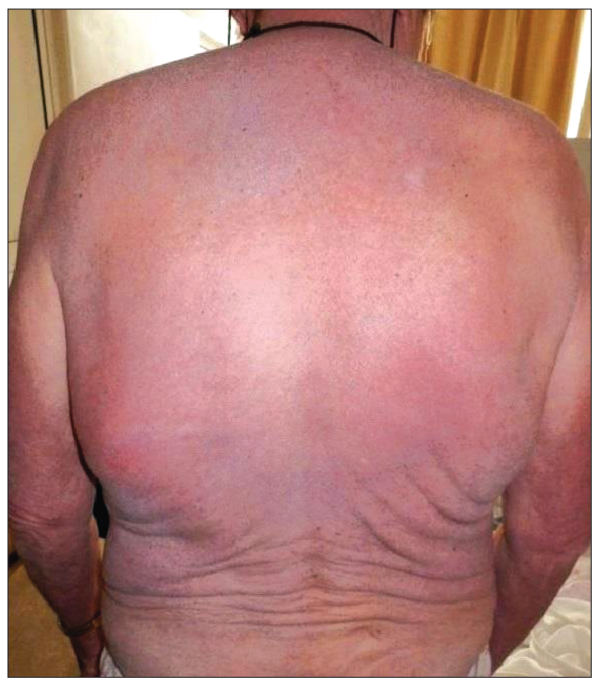

Fig. 2. Clinical aspect. Erythematous eruption

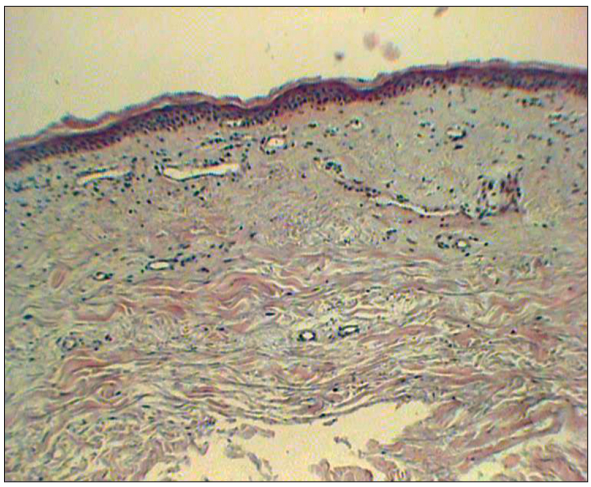

Fig. 3. Histopathological aspect, 10X, 4X. Epidermal atrophy, diffuse lymphocytic infiltration, pigmentation in the bottom layer

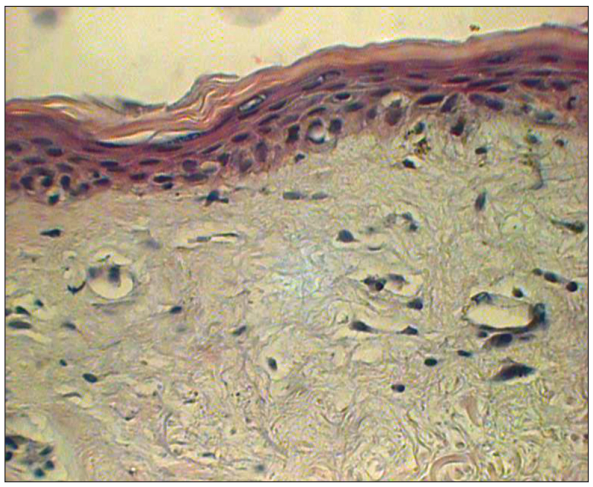

Fig. 4. Histopathological aspect, 10X, 4X. Epidermal atrophy, diffuse lymphocytic infiltration, pigmentation in the bottom layer

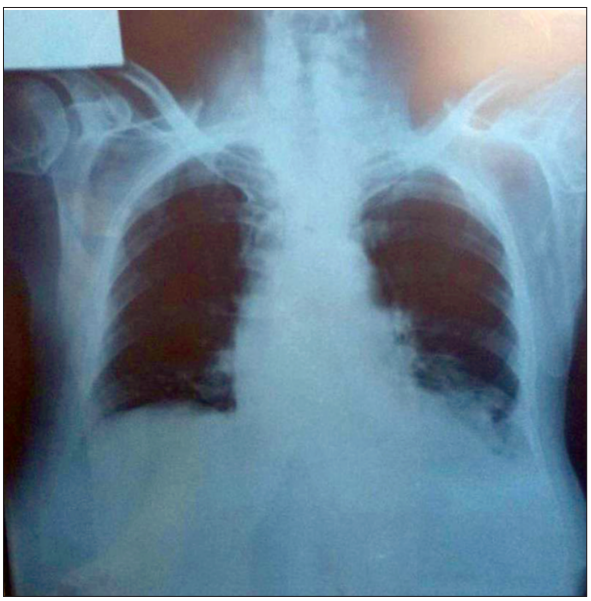

Fig. 5. Chest X-ray, PA and LAT view. Opacity in the posterior basal segment of the left lower lobe and bilateral opaque subclavicular micronodules

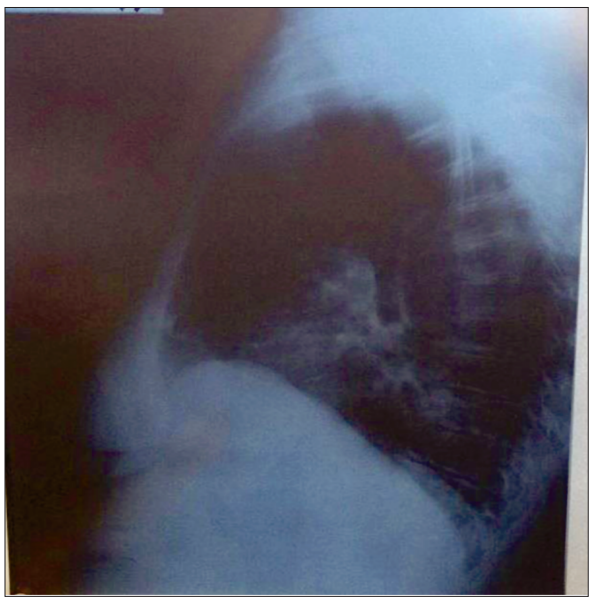

Fig. 6. Chest X-ray, PA and LAT view. Opacity in the posterior basal segment of the left lower lobe and bilateral opaque subclavicular micronodules

and was measuring about 46/40 mm in its maximal axial diameter. The lesion was also accompanied by small satellite nodules, the largest of which was located in the left lower lobe, measuring 12 mm in diameter. Micronodules could also be detected in the right pulmonary lobes. Left hilar lymph node enlargement was also present and the largest lymphadenopathy was situated infracarinally, measuring 38/22 mm. Isolated axillary lymph node enlargement was also present, with the largest lymph node measuring 10 mm in diameter. No pleural or pericardial effusion could be detected (*Fig 7*). With this result, the pulmonologist was able to establish the diagnosis of lung cancer.

During hospitalization, the patient was treated with systemic and topical corticosteroids,

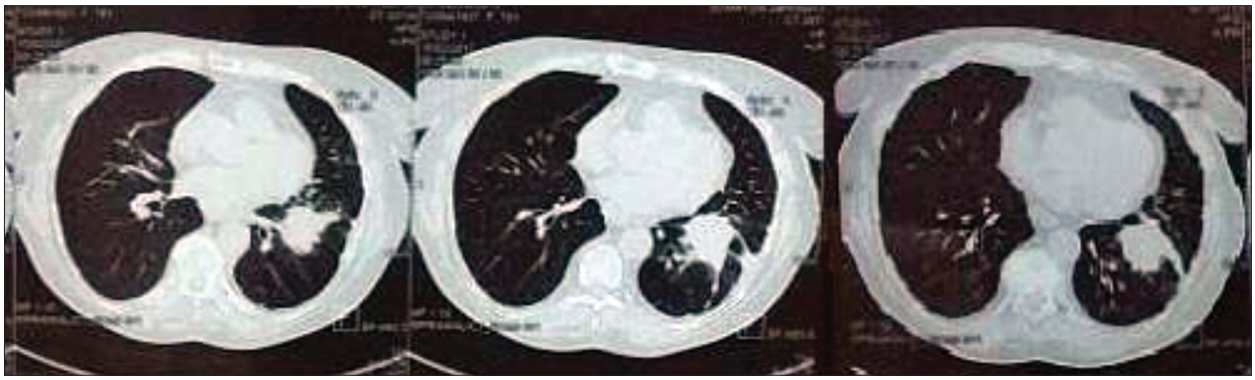

Fig. 7. CT scan. Tumoral process in the lower lobe of the left lung

with minimal improvement of the skin lesions. Afterwards, the patient refused any and all treatment for the tumor and was eventually lost to follow-up.

Discussions

Paraneoplastic disorders are remote effects produced by certain cancers, which can be attributed neither to local invasion nor to metastasis. While seldom lethal, these effects can sometimes dominate the clinical picture.[8] They were first mentioned in 1890 by a French specialist, M. Auchè, who reported the involvement of the peripheral nervous system in neoplastic patients.[9]

The most common paraneoplastic disorders are represented by endocrine syndromes (Cushing syndrome, inappropriate antidiuresis, hypercalcemia, hypocalcemia), neurologic and neuromuscular syndromes (sensory neuropathy and encephalomyeloneuritis, limbic encephalitis, peripheral neuropathies), hematologic syndromes (erythrocytosis, anemia), the hypercoagulable state (venous thrombosis, disseminated intravascular coagulation) and cutaneous syndromes.[8]

Paraneoplastic dermatoses encompass a wide group of cutaneous and mucocutaneous disorders which are related to an internal malignancy in the sense that, although dependent on its evolution, they are not directly linked to the tumor. Paraneoplastic dermatoses can be classified, according to specificity and the frequency of association to certain cancers, in obligate, facultative and exceptional paraneoplastic dermatoses.[5]

Obligate paraneoplastic dermatoses are cutaneous disorders which are almost constantly associated with certain malignancies. Pertaining to this category are the following cutaneous afflictions: acrokeratosis Bazex (upper airways carcinomas), acanthosis nigricans (gastric adenocarcinoma, bronchogenic carcinoma), tripe palms (gastric adenocarcinoma, bronchogenic carcinoma), florid cutaneous papillomatosis (gastric adenocarcinoma), hypertrophic osteoarthropathy (bronchogenic carcinoma), necrolytic migratory erythema (glucagonoma), erythema gyratum repens (bronchogenic carcinomas), paraneoplastic pemphigus (lymphoma, leukemia), acquired hypertrichosis lanuginosa (various carcinomas).[6, 7]

Facultative paraneoplastic disorders involve syndromes which are rather frequently but not constantly associated with various neoplasms. These are represented by nail clubbing (bronchogenic carcinoma), the sign of Leser-Trélat (gastric carcinoma, bronchogenic carcinoma), acquired ichthyosis (Hodgkin disease), pityriasis rotunda (hepatocellular carcinoma), acquired palmar filiform hyperkeratosis (various solid tumors), dermatomyositis (leukemia, lymphoma), erythroderma (lymphoma, various tumors), Sweet syndrome (leukemia, lymphoma), pyoderma gangrenosum (leukemia, lymphoma), yellow nail syndrome (breast cancer), erythromelalgia (myeloproliferative neoplasms), multicentric reticulohistiocytosis (lymphoma), palmar fasciitis and polyarthritis syndrome (ovarian cancer), generalized pruritus

without skin lesions (Hodgkin disease, lymphoma). [6, 7]

Exceptional paraneoplastic disorders are syndromes that are infrequently associated with an internal malignancy. Such are the cases of bullous pemphigoid (solid tumors), acquired epidermolysis bullosa (lymphoma), linear IgA dermatosis (Hodgkin lymphoma), Raynaud syndrome (lymphomas, solid tumors), sclerodermiform syndrome (lymphomas), chronic urticaria (ovarian cancer, lymphoma), vitiligo (melanoma), eczema craquelé (gastric adenocarcinoma), erythema annulare centrifugum (bronchogenic carcinoma).[6, 7]

While most neoplasms are capable of associating various paraneoplastic phenomena, it has been shown that lung tumors most commonly associate this type of disorders[10], with almost 10% of lung cancer patients also suffering from a paraneoplastic effect.[11] No connection has been demonstrated between the severity of the paraneoplastic syndromes and the extent of the primary tumor. Occasionally, these disorders will develop before the detection of the malignancy, while in other cases they may appear in the late stages of the disease or as a sign of relapse.

A broad range of paraneoplastic disorders has been shown to be associated with bronchogenic carcinoma, the most frequent of which are endocrine, neurologic and skeletal effects. Endocrine syndromes include humoral hypercalcemia of malignancy, syndrome of inappropriate antidiuretic hormone production, Cushing's syndrome, gynecomastia, hypoglycemia, hypercalcitonemia, hyperthyroidism and carcinoid syndrome. Neurologic syndromes found in lung malignancies can be divided into two subgroups, namely syndromes of the central nervous system and syndromes of the peripheral nervous system. Examples of pathological conditions pertaining to the first category are encephalomyelitis, necrotizing myelopathy, limbic encephalitis and cancer associated retinopathy. Examples of pathological conditions related to the peripheral nervous system are subacute sensory neuropathy, autonomic neuropathies, chronic gastrointestinal pseudo-obstruction, Guillan-Barré syndrome, brachial neuritis, myasthenia gravis, Eaton-Lambert myasthenic syndrome. Skeletal syndromes include hypertrophic osteoarthropathy and digital clubbing. [1, 12]

Paraneoplastic dermatological disorders most commonly encountered in lung cancer patients include acrokeratosis Bazex, acanthosis nigricans, tripe palms, the sign of Leser-Trélat and erythema gyratum repens. [1]

Acrokeratosis paraneoplastica or Bazex syndrome is always associated with a malignancy, most often located in the upper aerodigestive tract or in the lungs.[13] Among the histological types of lung cancer, squamous cell carcinoma most commonly associates Bazex syndrome, followed by adenocarcinoma. [14] Acrokeratosis paraneoplastica is almost exclusively observed in male patients around the age of 55 who report alcohol and cigarette abuse in the past. The lesions are erythemato-squamous, psoriasiform: poorly defined plaques of purplish-red color, covered in scales of various thickness and adhesiveness, nonpruritic and painless. The topography is limited to the extremities, nasal ridge and ears. Treatment of the malignancy greatly improves the cutaneous lesions. Although the pathophysiology of the syndrome is still not clear, attributing a role to growth factors is currently taken into consideration. [6]

Acanthosis nigricans is a condition that can be divided into two groups: malignant or paraneoplastic acanthosis nigricans and benign acanthosis nigricans, which can be idiopathic, familial, drug induced (nicotinic acid) or associated with hyperinsulinemia.[15] All adult patients with new-onset acanthosis nigricans, regardless of gender, should go through a detailed examination for internal malignancy. Although gastric adenocarcinomas most frequently associate acanthosis nigricans, representing 55-61% of all adenocarcinomas that associate this syndrome, a significant number of non-small-cell lung carcinoma cases associating acanthosis nigricans has also been reported.[16] The most important clinical aspect of acanthosis nigricans is represented by gray plaques that slowly darken to an almost black color, located in the axilla, inner thighs, anogenital region, folds of skin behind the elbows and knees and the back of the neck. Papillomas and seborrheic keratoses are

also typical in paraneoplastic acanthosis nigricans.[6] The pathogenesis of paraneoplastic acanthosis nigricans, although unclear, is believed to involve an increased level of *transforming growth factor* (TGF) targeting the epidermal tissue via *epidermal growth factor receptor* (EGFR). [17]

Tripe palms is also known as palmar hyperkeratosis, acanthosis palmaris or acquired pachydermatoglyphia and it is defined by a yellowish thickening of the palms and soles which leads to pronounced dermatoglyphics.[6] Studies show that most cases of tripe palms, specifically 94%, are related to cancer[18], prompting medical specialists to do a detailed examination for internal malignancies when encountering this ailment. In 77% of cases acanthosis palmaris was observed in association with acanthosis nigricans. The most commonly observed underlying cancer in patients with palmar hyperkeratosis alone was bronchogenic carcinoma, adding to a total of 53% of cases, while patients that associated acanthosis palmaris and acanthosis nigricans most often suffered from gastric cancer (35% of cases) followed by bronchogenic carcinoma (11% of cases).[6,18] The pathophysiology of tripe palms is still not clear, but it is thought to involve the proliferative effects of TGF-α secreted by the tumor. [6, 19]

The sign of Leser-Trélat expresses the sudden onset of multiple seborrheic keratoses or the rapid increase in number and size of preexisting ones. This syndrome is sometimes associated with other paraneoplastic diseases, such as acanthosis nigricans.[6] Gastric adenocarcinomas seem to associate the sign of Leser-Trélat most frequently[16], followed by non-small-cell lung carcinomas.[20] The pathogenesis of this syndrome is poorly understood, with a role being attributed to mutations of FGF3 and PIK3CA.[21]

Erythema gyratum repens is a rare dermatosis that usually accompanies intrathoracic neoplasms, although it has also been reported in the absence of any detectable malignancy. [22]

The eruption consists of 2 to 3 cm wide erythematous concentric strips that create a lacy aspect, generally respecting the face, scalp and extremities. These lesions are constantly shifting, leaving behind a thin desquamation. Occasionally pruritus is reported. [6] A review that included 49 cases of erythema gyratum repens showed that 84% of the cases were related to an internal malignancy, with bronchogenic carcinoma being the most common cancer that associated this syndrome. [23] The pathophysiology involved in this syndrome is still unclear, although an immune mechanism is taken into consideration since complement and immunoglobulin deposits were detected in the basal membrane of both healthy and affected skin. [24]

Erythroderma or exfoliative dermatitis is characterized by erythema and scaling affecting at least 90% of the body surface.[25] It may be accompanied by other symptoms like fever, chills and pruritus. It is most often caused by an exacerbation of a previous dermatologic disease like atopic dermatitis, psoriasis or a drug reaction. The most common drugs that can be related to erythroderma are antibiotics (penicillin, sulfonamides), allopurinol, dapsone, calcium channel blockers, cimetidine, gold salts and lithium.[26] Although infrequent, a malignant tumor can be detected in about 10% of erythroderma cases.[6] It has been shown that liver, colon, breast, prostate and thyroid cancer most often associate erythroderma as a paraneoplastic cutaneous manifestation, while erythroderma related to lung cancer is actually a very rare finding.[27] The mechanisms related to the pathophysiology of exfoliative dermatitis caused by internal malignancies are still insufficiently understood, although they are believed to be of an immune nature. Thus, an accelerated epidermal turnover occurs as a result of the lymphocytic infiltrate that is caused by a complex interaction between signaling proteins such as interleukins 1, 2, 8 and cell adhesion molecules like *vascular cell adhesion molecule* (VCAM) and *intercellular adhesion molecule* (ICAM). [28] However, an immune response brought about by the tumor cells or an antigenic cross-reaction between carcinoma and the tegument are also taken into consideration.[29]

Paraneoplastic erythroderma is a very rare indicator of lung cancer, with only a handful of such cases having been described in the literature. Gupta et al described the case of a

53-year-old male patient admitted for erythema, thickening and scaling of the skin associated with intense pruritus with 3 month duration. Clinical and paraclinical investigations have led to the diagnosis of lung cancer in the right lower lobe. [30] Adramanantena et al presented the case of an 81-year-old male patient who was admitted with general malaise and erythroderma. After being diagnosed with lung cancer, chemotherapy was instituted and there was a favorable tumoral response along with the fading of erythroderma. However, the tumor relapse was announced by the recurrence of erythroderma 2 months after the completion of chemotherapy.[31]

A rare association of multiple paraneoplastic cutaneous disorders: erythroderma, acquired ichthyosis and palmo-plantar keratoderma was reported in a 56-year-old male patient, who was diagnosed with non-small cell lung cancer. After a left pneumonectomy, all cutaneous manifestations ceased. Still, the tumor recurrence occured a year later and the outcome was fatal.[32] Similarly to the case we are describing, Chirag et al presented the case of a 55-year-old male patient admitted for erythroderma with 7 month duration. The patient had no response to corticotherapy and therefore the suspicion of an internal malignancy led to the diagnosis of squamous cell lung cancer. [33]

In the case we are reporting, the patient presented for a generalized erythematous eruption accompanied by intense pruritus that had occurred 6 months prior to the presentation. Taking into account the clinical aspects, the lack of response to corticotherapy and the histopathological findings, we went looking for collaboration with the pneumologist. Following further investigation it was found that the patient was in fact suffering from lung cancer so that ultimately, the diagnosis of paraneoplastic erythroderma was established.

Conclusion

This case aims to underline the importance of recognizing dermatological syndromes and establish their causes. Whenever the etiology is unclear, further examination for internal malignancies should always be performed, since it might lead to an earlier diagnosis that could contribute to a better outcome. Paraneoplastic erythroderma is a very rare tell-tale sign of lung cancer that nevertheless should not be overlooked, especially in cases resistant to conventional treatment.

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Conflict of interest
NONE DECLARED

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