International Journal of Research in Medical and Clinical Science
Volume 2, Issue 1, 2024, PP: 01-05
www.journalserapublications.com

Case Report

Paraneoplastic Erythema Annulare Centrifuge in an 86-Year-Old Woman With Metastatic Colon Adenocarcinoma

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Abstract

The objective of this review is to alert different medical professionals to cutaneous signs and symptoms that can help in the diagnosis of an underlying malignancy. There is a wide spectrum of annular skin lesions that may be related to systemic malignant diseases such as erythema gyratum repens or necrolytic migratory erythema. Other skin lesions, however, do not always indicate malignancy but allow it to be suspected, this is the case of erythema annulare centrifuge, generalized granuloma annulare, subacute cutaneous lupus erythematosus , mucinosis erythematosa reticulata and pityriasis rotunda. In this article we focus preferentially on annular skin lesions, more specifically on erythema annulare centrifuge. We present the clinical case of an 86-year-old woman with metastatic colon adenocarcinoma and paraneoplastic erythema annulare centrifuge.

Keywords: Erythema annulare centrifuge, colon adenocarcinoma, cutaneous signs paraneoplastic.

Case Report

We present a case of an 86-year-old woman who was admitted for microcytic and hypochromic anemia with a hemoglobin of 6.2 g/ dL for study in the Geriatrics service. Her functional and cognitive situation was excellent (Lawton 8, Katz A, Barthel 100, FAC 5, MNA 14). Among her personal history, we highlight high blood pressure, Diabetes Mellitus type 2 treated with oral antibiotics (HbA1c 7.4%), anticoagulated Atrial Fibrillation with acenocoumarol withdrawn due to anemia. The patient was hemodynamically stable and afebrile, without lymphadenopathy, without constitutional syndrome and the rectal examination showed no alterations.

Upon admission, she was hemodynamically stable, with physical examination without relevant findings, except at the skin level where an annular and erythematous skin lesion was observed in the right supraclavicular region of two weeks of evolution, 8 cm in diameter, slightly scaly, with three concentric erythematous rings suggesting the clinical diagnosis of erythema annulare centrifuge (EAC) (Figure 1). No other skin lesions were evident. The blood test showed leukocytosis with neutrophilia and lymphopenia and anaemia microcytic and hypochromic under treatment with oral iron. In the imaging tests, after performing an abdominopelvic CT with intravenous contrast in the arterial and portal phases, hypodense liver lesions, both liquid and solid, were observed, which were reported as multiple liver metastatic lesions as well as the presence of hepatic cysts. Exploration of the rest of the abdominopelvic organs did not allow identification of the primary tumor. The study was expanded through an upper digestive endoscopy and a colonoscopy, observing at the level of the esophagus at 35 cm a 2 mm esophageal polypoid lesion (squamous cell micropapilloma) while the stomach and duodenum do not show pathological alterations.

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Colonoscopy allowed us to observe, at the level of the right colon distal to the ileocecal valve, without reaching it, an ulcerated lesion that reaches one third of the circumference of the colon, with a friable appearance that suggested a malignant neoplasm and which was reported after the pathological anatomy analysis as "fragments of Adenocarcinoma, colorectal type, with poorly differentiated areas, with mucinous component (10-15%)".

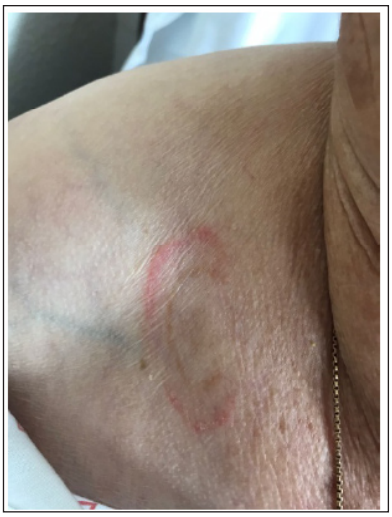

Figure 1. *Erythema annulare centrifuge : annular skin lesion and erythematous, slightly scaly, 8 cm in diameter maximum, in the right supraclavicular region.*

DISCUSSION

The skin is the most accessible organ in a medical examination, where the first easy and affordable approach is simple observation with the help - if possible - of a dermatoscope; being able to provide very valuable information in many systemic diseases. In fact, the skin may show the first guiding symptom in 1% of patients with internal neoplasms. There are different mechanisms by which these skin lesions occur, from a direct invasion of the skin by the malignant tumor itself and/or by metastatic dissemination to indirect mechanisms that induce the appearance of these skin lesions that are not related to the primitive tumor (paraneoplastic syndromes). Furthermore, there is a wide variety of nonstrictly paraneoplastic skin processes that in a certain context suggest the presence of a malignancy or that have a greater risk of developing it throughout life.

T. Colcott Fox (1849-1916) first introduced the term "figurative erythema" in 1889. Depending on the clinical pattern, figurative erythemas are annular, circinate, concentric, polycyclic or arcuate . The most important figurative erythema annulare are erythema annulare centrifugus (EAC), erythema marginatum, erythema gyratum repens erythema migrans, erythema chronicum migrans and pediatric erythema annulare.

We will focus on erythema annulare centrifuge (EAC) uncommon inflammatory hypersensitivity reaction characterized by annular or polycyclic plaques with central clearing and peripheral scale, caused by cutaneous or systemic infection, malignant neoplasms, drugs and various autoimmune diseases, as well as pregnancy among other factors (1). It was Jean Darier (1856-1938) who proposed the term erythema annulare centrifuge (EAC) in 1916.

EAC is characterized histologically by the presence of a dense perivascular infiltrate composed of lymphocytes, histiocytes , and occasional eosinophils . As a result of the well-demarcated distribution that tightly wraps around blood vessels, the infiltrate has been described as a "coat-sleeve" pattern. It is considered a hypersensitivity reaction to a variety of antigens and is associated with multiple underlying causes, including malignancy. Although a specific etiology has not yet been elucidated, it is likely that this form of EAC occurs due to cytokine and/or antigen stimulation of an underlying malignancy. It is mainly associated with lymphoproliferative disorders and rarely with solid tumors.

There are 2 distinct histologic patterns of EAC: superficial type and deep type. It tends to spread centrifugally while developing a central clearing. The most common locations are the trunk and proximal extremities. Individual lesions last from several days to weeks and may resolve spontaneously. EAC can appear at any age with a peak incidence in middle adulthood and without differences between sexes. Kim KJ et al (2) retrospectively studied 76 patients (24 men and 42 women) who had been diagnosed with EAC by clinical and histopathological examination. The mean age was 39.7 years and the mean disease duration was 2.8 years. The lower extremities, particularly the thigh, were the most frequently affected locations. The most common clinical manifestation was large (>1 cm), scaly, erythematous and indurated plaques. Forty-eight patients (72%) had combined diseases including fungal skin infection (48%), such as tinea pedis , other skin diseases (18%), internal malignancies (13%), and other systemic diseases (21%).

Erythema annular centrifugum (EAC) is more likely to be associated with lymphoproliferative malignancies such as lymphomas and leukemias (3-9). But the association with other solid neoplasms has also been documented (10, 11). There are multiple and very varied skin signs that can lead to suspicion of a possible internal neoplasia (Table 1).

Table 1. *Different skin signs to suspect a possible internal neoplasia.*

Erythema, Facial Edema And Flushing	Carcinoid syndrome (12), Pheochromocytoma (13), Superior vena cava syndrome, Mastocytosis (14), Dermatomyositis (15), Systemic lupus erythematosus (16), Bloom's syndrome (17), Rothomund-Thomson syndrome (18).
Hyperpigmentation	EctopicACTHproductionsyndrome(19),Hemochromatosis (20), POEMS Syndrome (21), Metastatic melanoma (22), Acanthosis nigricans (23), Hodgkin and non- Hodgkin leukemias and lymphomas (24), Melanotic macules and papules of perianal and genital distribution (25), Cronkhite-Canada syndrome (26), Peutz-Jeghers syndrome (27).
Annular Lesions	Erythema gyratum repens , Necrolytic migratory erythema (28, 29,30).
And Other Annular Lesions	Erythema annulare centrifuge, Generalized granuloma annulare, Subacute cutaneous lupus erythematosus, Mucinosis erythematosa reticulata and Pityriasis rotunda.
Erythematosquamous And Hyperkeratotic Lesions	Acrokeratosis Bazex paraneoplastic disease, Small plaque parapsoriasis, Pityriasis rubra pilaris, Superficial disseminated porokeratosis and Keratoderma palmoplantar (30).
Dermatosis With Skin Thickening And Induration	Primary systemic amyloidosis, Scleromyxedema, Scleroedema, Systemic sclerosis or scleroderma, Pachydermoperiostosis or Secondary hypertrophic osteopathy (30).
Vascular Lesions	Telangiectasias, Purpura and ecchymosis, Cutaneous ischemia, Vasculitis, Thrombophlebitis, Livedo reticularis and Palmar erythema (30).
Other Injuries	Erosive and blistering lesions, Inflammatory papules and nodules, Xerosis, Ichthyosis, Exfoliative dermatitis (erythroderma), Pruritus and prurigo, Hirsutism and hypertrichosis, Hyperhidrosis and anhidrosis, Skin tumors, Oral alterations and nail alterations .

Referring to our clinical case (86-year-old woman diagnosed with right colon adenocarcinoma in stage IV and paraneoplastic annular erythema centrifuge) we will focus specifically on the differential diagnosis of annular cutaneous lesions that can be included as cutaneous alerts of systemic diseases. Pitchoford et al (11) presented the case of erythema annulare centrifuge (EAC) associated with adenocarcinoma colorectal metastatic.

These annular lesions can be very varied and can be related to systemic malignancies, such as classic paraneoplastic syndromes such as erythema gyratum repens or necrolytic migratory erythema. Other skin

lesions, not always indicative of malignancy, allow it to be suspected, such as erythema annulare centrifuge (31), generalized granuloma annulare, subacute cutaneous lupus erythematosus, mucinosis erythematosa reticulata and pityriasis rotunda. The differential diagnosis for EAC includes other annular erythematous lesions (32). It is important to rule out entities such as Lyme borreliosis , lupus erythematosus , and an underlying tumor or annular metastasis. Other lesions to include in the differential diagnosis of EAC would be: Erythema chronicum migrans, Annular subacute cutaneous lupus erythematosus, Annular urticaria, Erythema multiforme, Tinea corporis , Annular psoriasis and Mycosis fungoids.

Conclusion

Annular skin lesions may be related to systemic malignancies, such as classic paraneoplastic syndromes, for example erythema gyratum repens or necrolytic migratory erythema. Other skin lesions that are not always indicative of malignancy, allow them to be suspected, as is the case with erythema annulare centrifugus. Although the Erythema annular centrifugum (EAC) is more likely to be associated with lymphoproliferative malignancies such as lymphomas and leukemias; the association with other solid neoplasms has also been documented. In our case, erythema annulare centrifuge was associated with metastatic right colon adenocarcinoma in an 86-year-old woman.

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Cite this article: Lucia Cameselle-Cortizo, Daniel Pérez-Soto. *Paraneoplastic Erythema Annulare Centrifuge in an 86-Year-Old Woman With Metastatic Colon Adenocarcinoma. International Journal of Research in Medical and Clinical Sciences. 2024;2(1): 01-05.*