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SHORT COMMUNICATION

Erythema Annulare Centrifugum Associated with Ovarian Cancer

Aleksandra Batycka-Baran, Magdalena Żychowska, Wojciech Baran, Jacek C. Szepietowski and Joanna Maj

Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Chałubinskiego 1, 50-368 Wroclaw, Poland. E-mail: aleksandra.batycka-baran@umed.wroc.pl

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Erythema annulare centrifugum (EAC) is an inflammatory skin condition, classified as a variant of figurate or gyrate erythema. It manifests with annular, erythematous macules, papules and plaques. The aetiopathogenesis of EAC is not fully understood; it is currently regarded as a hypersensitivity reaction to multiple factors, such as infections, medications, food components or even some pregnancy-related factors (1–3). However, EAC may also less commonly represent a paraneoplastic syndrome associated with occult malignancy. To the best of our knowledge the case described here is the first report of EAC associated with ovarian cancer.

CASE REPORT

A 70-year-old woman presented with 3-year history of recurrent, annular and erythematous lesions with peripheral scaling located symmetrically in the inguinal region and on the upper-inner area of the thighs. Despite several negative mycological examinations, the skin lesions had been treated repeatedly with oral and topical antimycotics with no clinical response. The medical history revealed colon cancer in 2004, with complete resection, subsequent ileostomy and adjuvant chemotherapy and radiotherapy. The patient had been under regular oncological surveillance with no recurrence of colon cancer. Recent serum levels of carcinoembryonic antigen (CEA) and transabdominal ultrasonography showed no abnormalities. In addition, patient had hyperuricaemia, arterial hypertension, chronic venous insufficiency and biliary lithiasis. Dermatological examination revealed well-demarcated, annular erythematous macules and plaques with scale on the inner part of the raised border (Fig. 1A). The lesions were located symmetrically in the inguinal and upper-inner regions of the thighs. The course of disease was chronic and recurrent. Some lesions disappeared spontaneously with no treatment, while similar annular skin changes occurred in the adjacent skin. The patient reported mild pruritus (visual analogue scale (VAS) score=2 points). Routine laboratory test showed elevated serum levels of uric acid, low-density lipoprotein (LDL) cholesterol, D-dimer, prolonged prothrombin and activated partial thromboplastin time (APTT) with no other abnormalities. Direct mycological examination and culture were negative. Antinuclear antibodies (ANA) and serological tests for diagnosis of borreliosis were negative. The biopsy was taken from the raised border of the skin lesions. Histological examination revealed dermal perivascular lymphohistiocytic infiltrates with epidermal hyperplasia, spongiosis and hyperkeratosis (Fig. 1B, C). Direct immunofluorescence was negative. After establishing a diagnosis of EAC, further extended tests were performed. Additional work-up displayed highly elevated level of ovarian tumour biomarker CA-125. Transvaginal ultrasonography revealed cystic tumour within the left ovary. The patient was referred to the department of gynaecology for surgery. The tumour was completely excised with subsequent chemotherapy. Histological examination revealed serous papillary adenocarcinoma G2. The skin lesions gradually resolved within several weeks after gynaecological surgery and there was no recurrence of skin lesions during 12 months' follow-up.

DISCUSSION

Two types of EAC are traditionally distinguished in the literature: a superficial type with trailing scale on the inner border of the erythematous lesions and a deep type with infiltrated non-scaly plaques. The skin lesions in the current case appeared to possess the features of both types. Most researchers agree that EAC is not a specific clinicopathological entity, but clinical reaction pattern with unknown aetiopathogenesis (3). The condition is considered to be a reactive erythema associated with various bacterial, viral or fungal infections, medications (e.g. hydroxychloroquine, cimetidine, spironolactone,

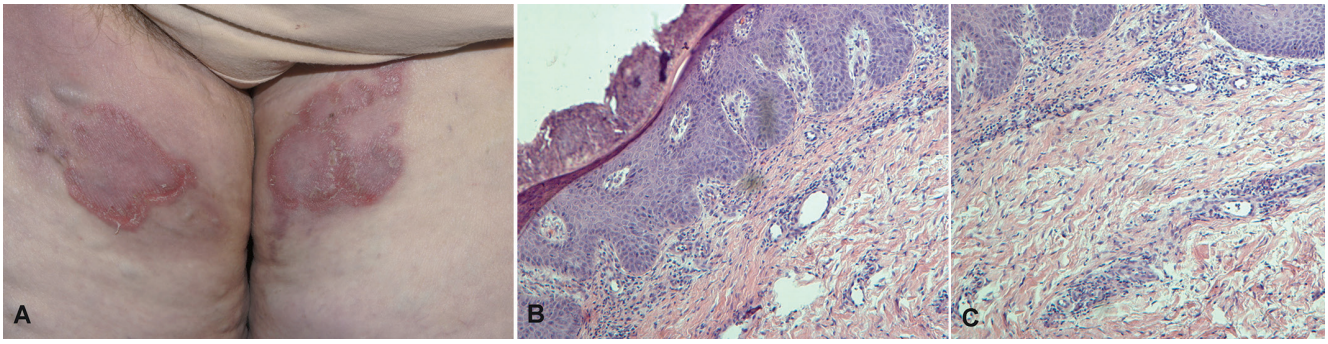

Fig. 1. (A) Annular, erythematous macules and plaques with scale on the inner part of the raised border, located on the upper area of the thighs. (B) Superficial dermal perivascular lymphohistiocytic infiltrates with epidermal hyperplasia, spongiosis and hyperkeratosis (haematoxylin and eosin (H&E) × 100). (C) Superficial and deep dermal perivascular lymphohistiocytic infiltrates (H&E× 100).

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interferon α2a plus ribavirin, ustekinumab, rituximab), endocrinological disorders or trigger factors. In many cases the exact underlying cause is difficult to establish and immunosuppressive medications are commonly given (1–3). However, it should be pointed out that searching for the underlying condition should be the first step in the management of EAC.

Furthermore, published data point to the possibility of EAC being a paraneoplastic syndrome. In 2012, Chodkiewicz & Cohen (4) introduced the term "paraneoplastic erythema annulare centrifugum eruption" (PEACE). So far, only a few cases of underlying neoplasms have been reported. Most of the cases were lymphoproliferative malignancies, e.g. acute myeloblastic leukaemia, chronic lymphocytic leukaemia, Hodgkin's disease, mantle B-cell non-Hodgkin's lymphoma, CD30 positive anaplastic large cell lymphoma or myeloma (5–10). Solid tumours diagnosed in patients with EAC include prostate adenocarcinoma, non-small cell lung cancer, breast cancer and malignant carcinoid tumour of the bronchus (11–14). So far there have been no reports of EAC associated with ovarian malignancy. The aetiopathogenesis of PEACE is unknown; however, it is speculated to be the result of release of cytokines or other tumour-related factors (4). In our case, the patient did not report EAC associated with previous colon cancer. It is worth mentioning, that PEACE often precedes the onset of the malignancy. In most of the reported cases, as well as in our patient, the diagnosis of EAC led to the detection of the occult malignancy. Carlesimo et al. (5) presented a case of persistent EAC that occurred 7 years before the onset of mantle B-cell non-Hodgkin's lymphoma. Reactive EAC associated with infections or stress tends to resolve spontaneously within 1–2 weeks. In cases associated with underlying malignancy, the lesions either do not disappear spontaneously or reappear after a short time. PEACE usually does not respond to anti-inflammatory or immunosuppressive therapy, but resolves after treatment of the underlying condition. Moreover, the relapse of EAC after treatment of the malignancy may be associated with relapse of the neoplasm. In one case, the occurrence of EAC was associated with the activation of breast carcinoma, operated on 10 years prior to the appearance of the skin lesions (13). Therefore, it should be pointed out that patients with persistent, chronic or recurrent EAC should be examined extensively, as skin lesions may be an early sign of occult neoplasm. In our patient, the skin lesions were misdiagnosed for several years as a fungal infection. Correct diagnosis enabled the detection of an underlying ovarian cancer. We present this case to highlight the possibility of PEACE and the necessity of thorough work-up in patients with persistent, chronic EAC.

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