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Case Report

Response to Chemotherapy of Paraneoplastic Erythroderma in a Patient with Ovarian Cancer

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REZUMAT

Răspunsul la chimioterapie al eritrodermiei paraneoplazice la o pacientă cu neoplasm ovarian

Introducere: Eritrodermia poate fi secundară unei serii de afecțiuni cutanate, reacții postmedicamentoase, infecții si neoplazii interne. În absența tratamentului etiologic specific, leziunile cutanate au în general o evoluție nefavorabila, prin urmare identificarea cauzei eritrodermei este esențială.

Caz clinic: Prezentăm cazul unei paciente în vârstă de 51 ani care s-a prezentat în clinica noastră pentru eritrodermie de etiologie necunoscută în evoluție de 6 luni. Investigații extensive pentru elucidarea cauzei eritrodermiei a dus la stabilirea diagnosticului de carcinom papilar seros ovarian stâng invaziv în epiploon, peritoneul parietal și peretele vezicii urinare, stadiul pT2c pN0 cM0, FIGO IIC. După intervenția chirurgicală, pacienta a urmat multiple linii de chimioterapie. Examinarea prin tomografie computerizată a întregului corp, măsurarea nivelurilor serice ale makerilor tumorali și reevaluarea dermatologica au fost efectuate la interval de 3 luni.

Rezultate: Evoluția manifestărilor cutanate a fost paralelă cu cea a neoplaziei subjacente. Cele mai bune rezultate au fost obținute în cursul terapiei cu carboplatin plus gemcitabină paclitaxel plus carboplatin.

Concluzii: Diagnosticul de eritrodermie paraneoplazică este susținut de evoluția paralelă a carcinomului ovarian și a leziunilor cutanate. Screeningul pentru neoplazii interne trebuie practicat în toate cazurile de eritrodermie de etiologie necunoscută.

Cuvinte cheie: eritrodermie, cancer ovarian, chimioterapie

ABSTRACT

Background: Erythroderma may be secondary to several skin diseases, drug reactions, infections, and internal malignancies. Skin lesions usually have an unfavorable course until the underlying disease is treated, therefore a thorough search for the cause of erythroderma is mandatory.

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Case report: We present the case of a 51-year-old female patient who presented with an erythroderma of unknown etiology of 6 months duration. Extensive screening for the cause of erythroderma lead to the diagnosis of left ovarian papillary serous carcinoma invasive to the epiploon, parietal peritoneum and the wall of the urinary bladder, stage IIC FIGO, pT2c pN0 cM0. The patient underwent surgery, followed by multiple lines of chemotherapy. Whole body computed tomography scan, measurement of serum levels of tumoral markers and dermatologic reevaluation were performed every 3 months.
Results: The course of skin lesions paralleled that of the subjacent malignancy and was most favorable under platinum plus gemcitabinum and platinum plus taxanes based chemotherapy that also best controlled the neoplastic process.
Conclusion: The parallel evolution of the ovarian carcinoma and cutaneous lesions firmly supports the diagnosis of paraneoplastic erythroderma in our patient. Screening for internal neoplasia should be performed in all cases of erythroderma of unknown etiology.

Key words: erythroderma, ovarian cancer, chemotherapy

BACKGROUND

Erythroderma is an uncommon potentially fatal skin disorder first described by Hebra in 1868. Erythroderma is a definitive term that refers to generalized erythema and desquamation affecting > 90% of the body surface. It usually occurs in individuals older than 40, except when the subjacent disease is atopic dermatitis, seborrheic dermatitis or hereditary ichthyosis [1,2]. Erythroderma represents a reaction pattern, a maximal form of skin irritation that may be secondary to certain cutaneous diseases, drug reactions, infections, solid or hematological malignancies, and other conditions. In the absence of a suggestive history, the clinical and histopathologic distinction between the underlying causes is often problematic and determining the specific etiology is very challenging, an important proportion of cases being classified as idiopathic erythroderma.

Paraneoplastic erythroderma can predate, occur simultaneously with or follow the detection of an internal malignancy (breast cancer, gastric cancer, colon cancer, gallbladder cancer, small cell lung cancer, head and neck cancer, lymphoma [3-5]). Ovarian cancer is rarely associated with erythroderma.

CASE REPORT

We present the case of a 51 year old female patient who was admitted to our clinic for erythroderma of unknown etiology of 6 months duration, with no previous dermatological disorder. Skin lesions first appeared on the abdominal area. The patient was diagnosed with contact dermatitis and treated with local and oral corticosteroids, oral H1 antihistamines and emollients. The rash extended upon tapering of systemic corticoid doses, the lesions generalized and the course of the disease was marked by multiple exacerbations. A skin biopsy was performed, but the histopathologic findings were nonspecific.

The patient presented to our clinic for generalized erythema and scalling with small islets of unaffected skin on the posterior torso and shins (**Fig. 1**).

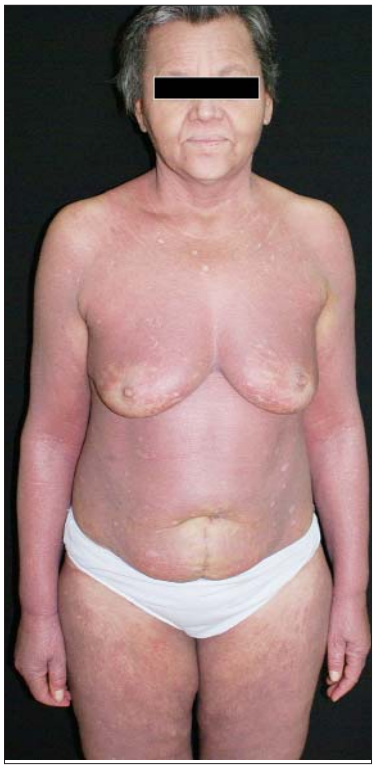

Figure 1. Erythema and scalling affecting > 90% of the body surface

Laboratory work-up showed important eosinophilia (22.9%, normal values <7%), increased lactate dehydrogenase level (1094 U/l, normal value < 220 U/l), inflammatory syndrome (erythrocyte sedimentation rate = 67 mm/h, normal value < 20 mm/h; C reactive protein=18.8 mg/l, normal value < 5 mg/l), and a high serum immunoglobulin (Ig) E level (1019 UI/ml, normal value <100 UI/ml). Abdominal ultrasound indicated the presence of a left ovarian tumor. Computer tomograph scan confirmed the existence of a large left ovarian tumor (10.5/9.2/10cm) and subdiaphragmatic adenopathy. CA 125 value was 91.7 UI/ml (normal values < 35 UI/ml). A new skin biopsy was performed and the histopathologic exam showed an interface dermatitis.

The patient was referred to a gynecology specialist. Intraoperatory examination revealed left ovarian tumor invasive to the epiploon, parietal peritoneum and the wall of the urinary bladder and total hysterectomy with bilateral adnexectomy, inguinal lymph node dissection and omentectomy was performed. The histopathologic and imunohistochemical diagnosis was G3 papillary serous ovarian carcinoma (ER+80%, PGR+90%, Ki 67+60%), pT2c pN0 cM0 stage IIC.

The oncology specialist initiated treatment with paclitaxel 175mg/m2 IV and carboplatin AUC6 day 1, every 3 weeks. After 3 cycles of chemotherapy, the patient experienced significant improvement of the skin lesions and well circumscribed areas of normal skin appeared on the patient's torso. Topical treatment consisted of intermediate-strength topical steroids and emollients. However, the skin lesions gradually worsened.

After 6 cycles of paclitaxel and carboplatin, the values of tumoral markers were within normal limits, but positron emission tomography showed the presence of multiple peritoneal, supra- and subdiaphragmatic lymph node metastases. Surgical reintervention, consisting of omentectomy, pelvic, right prerenal, and right subdiaphragmatic peritonectomy with diaphragm parcelar resection, right pleurostomy and left external iliac and interaortocaval lymphadenectomy was performed. Histopathologic exam of the peritoneal nodules and epiploon revealed the presence of G3 papillary serous carcinoma. The oncology tumor board initiated second line therapy with topotecan 1.5 mg/m2/ dayIV, days 1-5, every 21 days for 6 cycles.

CT scan showed disease progression, with increase in the number and size of peritoneal and retroperitoneal lymph nodes metastases.The medical oncologist decided to stop treatment with topotecan and to start administration of liposomal doxorubicin 50 mg/m2 IV, every 28 days. After the fourth cycle of treatment with liposomal doxorubicin, the patient presented with grade III oral mucositis. Whole body CT scan described the appearance of a pleural metastasis, an increase in CA125 level and the bone MRI scan showed T9 bone metastases. The skin lesions showed no improvement and the tumor board concluded that during the course of the illness, the paraneoplastic skin lesions only improved under platinum based chemotherapy. Therefore, treatment with gemcitabine 1000mg/m2 IV days 1,8 and carboplatin AUC4 IV day 1 plus zoledronic acid 4mg day 8, every 21 days was initiated and after 10 cycles the CT scan showed a partial response for the first time in 2 years of chemotherapy. The course of skin lesions paralleled that of the subjacent malignancy and significant improvement of the cutaneous manifestations was observed upon dermatologic reassessment (**Fig. 2**).

DISCUSSION

Ovarian cancers are the ninth most common cancers in women, accounting for approximately 3%

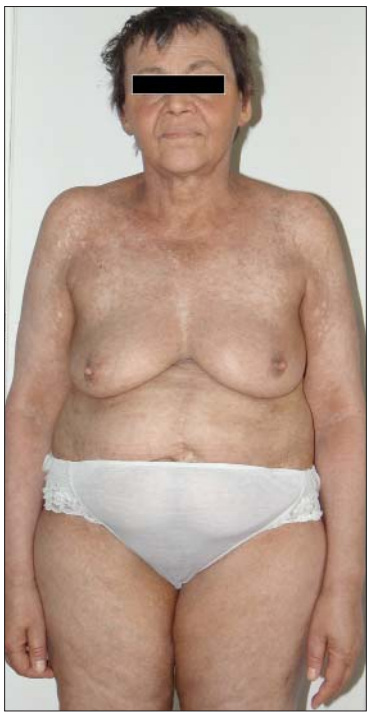

Figure 2. Significant improvement of skin lesions, residual hyperpigmentation

of all new malignancies in women and are frequently diagnosed in an advanced stage [6]. Ovarian cancer can be associated with several paraneoplastic syndromes, including nervous system disorders (cerebellar degeneration, polyneuritis), connective tissue disorders (dermatomyositis, systemic lupus erythematosus), hematologic disorders (hemolytic anemia, disseminated intravascular coagulation), cutaneous disorders (acanthosis nigricans) and nephrotic syndrome, all with a poor prognosis [7,8]. Paraneoplastic erythroderma is rarely associated with ovarian cancer. Nevertheless, it can be the presenting sign of an ovarian neoplasm and should alert the clinician towards the possibility of internal malignancy.

The exact mechanism of occurrence of paraneoplastic erythroderma is not clear. It is thought to develop as a response to hormones or other active substances, like cytokines (interleukin 1, 2, 8) and cellular adhesion molecules (vascular cell adhesion molecule-1, intercellular adhesion molecule-1, E-selectin, P-selectin) released by cancer cells [9-11]. These substances induce skin infiltration with immune cells, resulting in a significant increase in the turnover rate of the epidermis, with consecutive erythema and scalling that affects more than 90% of the body surface and impairment of skin barrier function and thermoregulation [9-11]. Interestingly, ovarian carcinoma is known to represent one of the more immunogenic tumors [12].

For our patient, the parallel course of the ovarian carcinoma and cutaneous lesions firmly supports the diagnosis of paraneoplastic erythroderma, that proved a veritable cutaneous marker for the evolution of the internal neoplasia. The skin lesions showed a partial response after the taxanes/carboplatinum based chemotherapy, but the PET -CT scan evaluation after 6 cycles described progression of the distant metastases. After the tumor board meeting, the patient underwent second and third line therapy with no clinical or biological improvement, although patients who progress on two consecutive therapy regimens without evidence of clinical benefits have diminised likelihood of benefitting from additional therapy. The decision to offer additional combination regimens was made on a highly individual basis: the patient's ECOG 1, the partial response of the skin lesions and the decrease of the CA 125 marker after paclitaxel/ carboplatinum based chemotherapy.

After almost 2 years from the paraneoplastic erythroderma diagnosis and chemotherapy treatment, the patient responded to gemcitabine/ carboplatin combination therapy. After 10 cycles, the CT scan was within normal limits (except the T9 bone metastases) and the course of skin lesions paralleled that of the subjacent malignancy.

The patient will continue treatment with zoledronic acid and hormonal therapy and will be evaluated every 3 months by a dermatologist and by a medical oncologist (physical exam, CA 125 tumor marker, CBC, chemistry profile, chest, abdominal, pelvic CT scan).

CONCLUSIONS

Erythroderma is a rare manifestation of ovarian cancer. The parallel course of the ovarian carcinoma and cutaneous lesions in our patient firmly supports the diagnosis of paraneoplastic erythroderma, that proved a veritable cutaneous marker for the evolution of the internal neoplasia. Screening for underlying malignancy should be performed in all cases of erythroderma of unknown etiology.

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